Genioglossus activity available via non-arousal mechanisms vs. that required for opening the airway in obstructive apnea patients

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Younes M, Loewen AH, Ostrowski M, Laprairie J, Maturino F, Hanly PJ. Genioglossus activity available via non-arousal mechanisms vs. that required for opening the airway in obstructive apnea patients. J Appl Physiol 112: 249–258, 2012. First published September 15, 2011; doi:10.1152/japplphysiol.00312.2011.—It is generally believed that reflex recruitment of pharyngeal dilator muscles is insufficient to open the airway of obstructive apnea (OSA) patients once it is closed and, therefore, that arousal is required. Yet arousal promotes recurrence of obstruction. There is no information about how much dilator [genioglossus (GG)] activation is required to open the airway (GG Opening Threshold) or about the capacity of reflex mechanisms to increase dilator activity before/without arousal (Non-Arousal Activation). The relationship between these two variables is important for ventilatory stability. We measured both variables in 32 OSA patients (apnea-hypopnea index 74 ± 42 events/h). GG activity was monitored while patients were on optimal continuous positive airway pressure (CPAP). Zopiclone was administered to delay arousal. Maximum GG activity (GGMAX) and airway closing pressure (PcCRT) were measured. During stable sleep CPAP was decreased to 1 cmH₂O to induce obstructive events and the dial-downs were maintained until the airway opened with or without arousal. GG activity at the instant of opening (GG Opening Threshold) was measured. GG Opening Threshold averaged only 10.4 ± 9.5% GGMAX and did not correlate with PcCRT (r = 0.04). Twenty-six patients had >3 openings without arousal, indicating that Non-Arousal Activation can exceed GG Opening Threshold in the majority of patients. GG activity reached before arousal in Arousal-Associated Openings was only 5.4 ± 4.6% GGMAX below GG Opening Threshold. We conclude that in most patients GG activity required to open the airway is modest and can be reached by non-arousal mechanisms. Arousals occur in most cases just before non-arousal mechanisms manage to increase activity above GG Opening Threshold. Measures to reduce GG Opening Threshold even slightly may help stabilize breathing in many patients.

GG opening threshold; ventilatory stability; control of upper airway dilators

IN OBSTRUCTIVE SLEEP APNEA (OSA) the development of an obstructive upper airway event is associated with progressive worsening of blood gas tensions and increased respiratory muscle output (respiratory drive), which, in the presence of an obstructed airway, is associated with progressively more negative pharyngeal pressure (41, 45). Stimulated respiratory drive activity and the negative intrathoracic/pharyngeal pressure developed during an obstructive apnea are potent arousal stimuli (3, 11, 23) and once a certain level of these stimuli is reached (Arousal Threshold), the patient arouses, dilator activity increases, and the airway opens (45). The same stimuli (respiratory drive and negative pharyngeal pressure) can also activate the dilators via non- arousal (i.e., reflex) mechanisms (13, 29, 33, 38–40, 50, 51). Several studies have shown that dilator activity in patients with OSA does increase progressively in the course of obstructive events prior to arousal (4, 6, 20, 21, 28, 38, 41, 45). This indicates that these muscles can be activated through non-arousal mechanisms in OSA patients. In some early studies (e.g., 45) the arousal-associated increase in dilator activity was noted to be quite large relative to the increase in activity prior to arousal. This has led to the enduring notion that non-arousal mechanisms are too weak to open the airway and, by extension, that upper airway opening requires arousal (43, 45).

More recently, several lines of evidence were introduced that cast doubt about the “incompetence” of non-arousal mechanisms (52–54, 56). The main conclusions from these studies are that 1) most OSA patients are capable of opening the airway via non-arousal mechanisms if only arousal does not interrupt the evolution of these mechanisms, 2) in most patients arousals occur with fairly small changes in blood gas tensions that can be safely exceeded, and 3) most importantly, arousal is associated with a ventilatory overshoot that promotes recurrence of the obstruction.

The idea that large increases in dilator activity are needed to open the airway in OSA patients is based on limited, qualitative observations of relatively large increases in activity associated with arousal near the time of opening. There is in fact no information on how much dilator activation is required to open the airway in these patients with or without arousal, and the large arousal-associated increases may simply represent a response overshoot, well in excess of the level required for opening. There is also no information on the capacity of non-arousal mechanisms to increase dilator activity, particularly if arousal is delayed. The relationship between these two variables (Opening Threshold and Capacity of non-arousal mechanisms) in individual patients should be of considerable interest as it determines the potential of therapeutic measures that increase Arousal Threshold or decrease Opening Threshold to stabilize breathing.

In this study we measured the activity of a dilator muscle [genioglossus (GG)] at the moment of upper airway opening (GG Opening Threshold) as well as the highest activation that could be produced by non-arousal mechanisms in OSA patients. Two interventions were used to increase arousal threshold, thereby making it possible to unmask the real potential of non-arousal mechanisms. First, obstructions were induced from a stable baseline on continuous positive airway pressure (CPAP) that allowed patients to progress into deeper sleep before the obstruction was induced by dial-down of CPAP. Second, we administered a therapeutic dose of zopiclone.
METHODS

Patient Recruitment

Patients referred to the Sleep Center for evaluation of OSA were screened with ambulatory monitoring [Remmers Sleep Recorder model 4.2, Saga Tech Electronic, Calgary, Canada (18, 49)]. Patients who had a respiratory disturbance index >15 events/h and who did not have any of the exclusion criteria, were invited to participate. Exclusion criteria included significant comorbidities (dialysis-dependent renal failure, congestive heart failure, severe COPD, previous stroke), obesity-hypoventilation syndrome, pregnancy, use of sedatives or antidepressants, or use of antiplatelet or anticoagulant medication or medications that reduce the metabolism of zopiclone. The Conjoint Health Research Ethics Board at the University of Calgary approved the study protocol, and all subjects gave written informed consent to participate.

Polysomnography

Patients underwent attended polysomnography in the sleep laboratory on two separate nights, a diagnostic study and the research study. With three exceptions (17, 27, and 65 days), the research study was done within 10 days of the diagnostic study. The patient did not receive treatment for OSA during the interval.

The diagnosis and severity of OSA was confirmed by overnight, attended polysomnography using standard polysomnography equipment (30). Registered technologists scored respiratory events using the Chicago criteria (1). Sleep and arousals were scored using standard criteria (2, 44). AHI, average and minimum O2 saturation, and number of respiratory events with arousal were calculated for the supine and lateral positions during non-rapid eye movement (NREM) sleep.

During the research study monitoring was identical to that used for diagnostic polysomnography with the addition of GG monitoring and the dial-down set-up that has been described previously (30, 56). GG electrodes were inserted to measure GG activity [EMG (29, 32), see acknowledgment]. Two sterile stainless steel, Teflon-coated, 25-gauge wires, threaded through 25-gauge needles, were inserted into the floor of the mouth, one on each side, 3 mm from the midline. The needles were advanced ~15 mm below the surface and were subsequently withdrawn. The external ends of the wires were connected to an amplifier (Grass, Quincy, MA) with a common ground. The raw signal was band-pass filtered (30–500 Hz) and displayed on the computer screen. The patient was asked to perform several maneuvers to determine maximum GG activity (GGMAX). These included tongue protrusion, swallowing, and maximally pushing the tongue against the front upper or lower teeth.

CPAP was then applied via nasal mask connected to a special ventilator, described previously (52, 53, 57), which allowed reduction of CPAP to 1.0 cmH2O. Flow was recorded from a pneumotachograph in the hose of the ventilator and mask pressure was recorded from a side port in the mask. Airway CO2 was monitored at the nares and after zopiclone in a subset of patients and found no significant difference (31).

The following interventions were carried out during stable NREM sleep.

**Intervention 1.** Three-breath dial-downs of CPAP to different pressures. These maneuvers were done to determine the near-passive mechanical properties of the pharynx (5, 42, 46).

**Intervention 2.** Long dial-downs of CPAP to 1 cmH2O to determine the level of GG activity at the time of upper airway opening (GG Opening Threshold) and the highest level of activity that can be reached without arousal. These dial-downs induced obstructive hypopneas or apneas. The dial-down was maintained until the upper airway opened, as indicated by a sudden increase in inspiratory flow (Figs. 1 and 2).

**Intervention 3.** In 20 of the 31 patients, ventilation was stimulated by reducing FIO2, and/or increasing FICO2 for 30 to 120 s while the patient was on optimal CPAP, and this was followed by brief (3 breath) dial-downs to 1 cmH2O during which the inspired gas was air. These interventions were alternated with intervention 2 in these patients and were designed to study the response of GG to ventilatory stimulation during CPAP application and in response to sudden induction of an obstructive event (breath 1 of the dial-down). The results of this investigation were reported separately (31). In some of these interventions, with chemical preloading, the upper airway opened early, during one of the three dial-down breaths, as opposed to the more delayed opening that occurs following the long dial-downs from air breathing. Measurements of GG activity at the time of opening in these breaths are included in this report and will help determine whether the number of obstructed breaths preceding airway opening affects GG opening threshold.

**Analysis**

The flow signal was corrected for leaks as described previously (56). Leak levels were subtracted from the flow signal to obtain patient flow.

The raw GG signal was rectified and two moving averages (MA) were digitally obtained (centered 200 and 500 ms). The MA signal was calibrated and is expressed in volts. The 200-ms moving average was used except where the signal was choppy (usually at low levels of activity). The highest moving average value associated with maximum voluntary maneuvers done at the beginning of the study was noted (GGMAX).

**Determination of Closing Pressure from Data Collected in Intervention 1**

Breaths with flow limitation during the dial-downs were identified by their characteristic flow contour (8, 14, 34). Maximum flow during flow-limited breaths was plotted against the corresponding dial-down pressure and a linear regression was performed (5, 46, 52). Regression analysis was performed from data obtained during the second breath of the dial-down to minimize the effect of viscoelastic behavior of the pharynx on the closing pressure (PCRIT estimate) (5, 52). The intercept on the pressure axis is reported as P_{CRIT}. In eight patients there was only mild hypopnea during the second breath of the dial-down (flow >50% flow on CPAP) and the intercept was less than ~1 cmH2O or was difficult to determine with confidence (confidence interval of the intercept greater than ±1.0 cmH2O). In these patients we report flow at 1 cmH2O instead of P_{CRIT}.

**Determination of GG Opening Threshold**

Baseline GG activity was determined from average peak activity on CPAP during the 30 s preceding the dial-down. The moving average of GG activity was measured at the point of upper airway opening (Figs. 1 and 2) and was expressed as %GGMAX after subtracting baseline activity on CPAP prior to the dial-down. The reported values therefore represent the increase in GG activity, above baseline activity, required to open the airway. Each opening event was classified as occurring with or independent of arousal as follows. A senior PSG technologist (MO) determined whether an arousal occurred following...
the dial-down and, if so, determined its time of onset to the nearest 0.1 s. The onset of arousal was identified from the first indication of a high-frequency shift in any of the three EEG electrodes (2 central electrodes and 1 occipital electrode). The 3-s rule was waived so that briefer (>1.5 s) high-frequency shifts, excluding spindles, were considered as arousals. K complexes were ignored unless associated with a high-frequency shift that is not a spindle. An opening event was deemed to have occurred independent of arousal if there was no arousal noted throughout (e.g., Fig. 1) or 1) opening occurred at least 0.5 s before the onset of arousal and 2) there was evidence of progressive increase in GG activity prior to the opening event such that the activity in the breath in which the airway opened appears as a natural progression of the preceding recruitment pattern (e.g., Fig. 2A). Some events could not be classified, either because arousal started too soon (within 0.5 s) after opening or the increase in high-frequency content was equivocal or there was an abrupt large increase in GG activity at the time of opening with no prior recruitment. Such events were not used in comparisons of GG opening threshold with and without arousal.

**Determination of the Highest GG Activity Reached Without Arousal**

For every opening event without arousal we measured the highest GG activity reached in the interval following opening but not later than the onset of arousal, if any, minus 1 s. This value could exceed the GG Opening Threshold because activity often continued to increase beyond the point of opening (Fig. 2, A and C). The average of the highest three such values in the entire file was considered the highest GG activity that was reached without arousal. We also measured the highest GG activity just before arousal in arousal-associated events (open arrows, Fig. 2, B and C). The difference between this value and GG Opening Threshold reflects how close the reflex mechanisms came to opening the airway in these cases.

The arousal-free rate of rise of peak GG activity in the vicinity of airway opening was determined from the difference in peak GG activity between the two breaths that are nearest airway opening and are also totally free of arousal (e.g., difference between B3 and B2 in Fig. 1 and difference between the two breaths with asterisks in Fig. 2A). It is expressed as %GGMAX per breath.

**Statistics**

All values are expressed as means ± SD unless otherwise indicated. Average GG Opening Threshold for all observations in each subject was calculated. Where observations with and without arousal (minimum 4 observations per category) were present in the same patient, average GG Opening Threshold was calculated separately for the two types and the results in participating subjects (i.e., those having observations in both categories) were compared using the paired t-test. Likewise, when enough opening events (minimum 4 observations) occurred early after the dial-down in the presence of prior ventilatory stimulation (intervention 3), average GG Opening Threshold was calculated separately for early and late opening events and the results in participating subjects were compared using the paired t-test.

**RESULTS**

Table 1 shows subject characteristics. Apnea-hypopnea index ranged from 6 to 133 events/h. In 24 patients, maximum flow at breath 2 of the dial-down was <25% of flow on CPAP, including 15 patients in whom flow was zero at the dial-down pressure of 1 cmH2O. In these patients, Pcrit ranged from −1.0 to 10.2 cmH2O (1.9 ± 2.8 cmH2O). In the remaining 8 patients, flow at 1 cmH2O was >50% of flow on CPAP (62 ± 13%). The data of these patients were included because in some of the long dial-downs flow continued to decrease reaching <25% flow on CPAP, including four patients in whom flow reached zero in some dial-downs.

Figure 1 illustrates an example of opening without arousal. The opening threshold here was 12% GGMAX. Figure 2 illustrates three other examples in which arousals were observed. In Fig. 2A, arousal started 1 s after opening and there was progressive recruitment prior to opening. This type of opening was attributed to nonarousal mechanisms (i.e., non-arousal-associated opening). In the remaining two examples, arousals began before opening, but in one case (Fig. 2B) there was
progressive recruitment prior to arousal, whereas in the other there was none. The same patient could display two or more of these patterns at different times. As reported previously (53), opening without or before arousal tended to occur more commonly in slow-wave sleep. Figure 2 also illustrates the wide range of GG opening thresholds (17, 25, and 4% GGMAX in Fig. 2, A, B, and C, respectively).

The shape of the rising phase of GG inspiratory activity in the absence of arousal varied considerably among patients but was consistent within patients. The most common pattern, seen in approximately half the patients, was upward concavity where the rate of rise is initially slow and accelerates later in inspiration (e.g., Figs. 1 and 2A). The inflection point occurred sooner as peak activity increased in the course of the obstructive event (Fig. 1). Other patterns included a nearly linear increase or downward concavity.

During complete apneas, flow occasionally appeared in the expiratory phase immediately preceding inspiratory upper airway opening (e.g., Fig. 2, A and B), indicating that in some cases opening occurs first during the expiratory phase. This phenomenon was invariably associated with an increase in expiratory (tonic) GG activity (Fig. 2, A and B) and/or evidence of expiratory muscle recruitment near end expiration (i.e., an increase in the rate of decline in one Respitrace signal near end expiration; Fig. 2A).

There were 20.0 ± 9.3 opening events per patient. Of these 12.1 ± 7.9 events/patient were arousal associated and 7.9 ± 6.9 were arousal unassociated. Of the latter category ~45% (3.6 ± 4.3 per patient) were totally free of arousal while in the

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>Age, yr</td>
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<tr>
<td>Body mass index</td>
<td>32.7 ± 6.3</td>
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<tr>
<td>Apnea-hypopnea index, events/h*</td>
<td>74 ± 42</td>
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<tr>
<td>Average SaO2, %</td>
<td>91.6 ± 4.2</td>
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<tr>
<td>%Time SaO2 &lt;90%*</td>
<td>10.7 ± 10.7</td>
</tr>
<tr>
<td>Optimal CPAP, cmH2O</td>
<td>11.3 ± 2.8</td>
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<tr>
<td>GGMAX, V</td>
<td>0.21 ± 0.09</td>
</tr>
<tr>
<td>Baseline GG activity on CPAP (%GGMAX)</td>
<td>2.8 ± 1.9</td>
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remainder (4.3 ± 4.6 per patient) arousal began 1.27 ± 0.48 s after airway opening.

Average GG activity on CPAP was 2.9 ± 1.7% GGMAX, consisting mainly of tonic activity (Figs. 1 and 2). The average GG Opening Threshold, after subtracting baseline activity on CPAP, was 10.4 ± 9.5% GGMAX (range 0.3 to 37.7% GGMAX). Individual values (with SD bars) are shown in Fig. 3. GG Opening Threshold in the eight patients with mild hypopneas during dial-downs (Fig. 3, open bars) was significantly lower than in the others (2.8 ± 2.3 vs. 12.9 ± 9.7% GGMAX, P < 0.005). However, even when opening occurred during breaths with flow limitation (as opposed to complete obstruction), GG activity had to increase above a certain level before flow became sensitive to GG activity. This is evident in Fig. 1 in the breaths preceding opening and in the first part of the breath in which the airway opened. Flow insensitivity to GG activity below a certain threshold was, however, not limited to breaths with severe flow limitation. In many cases it was also evident in breaths with mild flow limitation (Fig. 4).

Twenty patients had more than four openings in each of the arousal-associated and non-arousal-associated categories. The GG Opening Threshold was not significantly different between the two types of opening (12.4 ± 10.6 vs. 12.1 ± 11.6% GGMAX). Openings occurring shortly after dial-down following chemical loading (intervention 3; 9.9 ± 5.8 interventions per patient) had a slightly, but significantly, lower GG Opening Threshold than those following air breathing (10.6 ± 7.5 interventions per patient; 13.2 ± 11.3% GGMAX vs. 14.9 ± 12.3% GGMAX, P < 0.02 by paired t-test, n = 20 patients).

The relationship between GG Opening Threshold and P_{CRIT} in patients with a well-defined P_{CRIT} (> −1 cmH2O, n = 24) is shown in Fig. 5. There was no significant correlation between the two variables (r = 0.04).
in the vicinity of airway opening was 8.6 ± 5.2% GGMAX per breath (e.g., Figs. 1 and 24).

Apnea hypopnea index was >40 events/h in 24/32 patients. These included three of the eight patients with very mild mechanical abnormality. AHI was <22 events/h in the other eight patients. These included five of the eight patients with very low PCRIT and, also, very low GG Opening Threshold (0.3–4.6% GGMAX), and three others of whom two had very low GG Opening Threshold. Interestingly, the remaining patient had the second highest GG Opening Threshold but he also had very vigorous spontaneous recruitment (patient 2, Fig. 3 and corresponding points in Fig. 6 at an abscissa value of 35).

**DISCUSSION**

The main findings from the present study are as follows. 1) The GG activation required to open the airway (GG Opening Threshold) varies greatly among patients with OSA, but is generally low. 2) GG Opening Threshold is not correlated with the severity of the passive mechanical properties of the pharynx, as reflected by pharyngeal closing pressure. 3) In the majority of OSA patients non-arousal mechanisms are capable of increasing GG activity above the Opening Threshold if uninterrupted by arousal.

**GG Opening Threshold**

To our knowledge, this is the first time this variable has been measured. The results are remarkable in that in more than half the patients GG activity needs to increase by no more than 8% GGMAX to open the airway from a closed or severely narrowed position and in 85% of patients the necessary increase is <18% GGMAX (Fig. 3). The actual increase at the time of opening is often much greater than what is required (e.g., Figs. 1 and 2, A and C, and Fig. 6, open circles), thereby reflecting an overshoot response.

We used GGMAX as the reference value for expressing GG Opening Threshold. GGMAX is a voluntary maneuver and it may be argued that it is not a reliable reference. However, our highly experienced technologists took great care to ensure that each patient made his/her best effort and insisted on having three reproducible values. In early experiments we tried a variety of maneuvers including tongue protrusion, swallowing, deep breathing, sniffing, and finally settled with asking the subject to curl the tip of his tongue and push against the back of the lower incisors as hard as possible. This maneuver invariably produced the greatest level of activation. Nonetheless, in all subsequent experiments, we also measured activity during swallowing and this always resulted in much lower activity. Thus we believe that our GGMAX values truly reflected the patient’s best protrusive effort. Furthermore, since GGMAX can only be underestimated, had we underestimated GGMAX in these patients the GG Opening Threshold, which is already quite low, would be even lower. Thus any underestimation of GGMAX would not alter the conclusion that this threshold is very low in most patients.

As evident by the SD bars in Fig. 3, GG Opening Threshold varied little across the night in individual patients although the observations included openings with and without arousal and with and without prior ventilatory stimulation, which advanced the time of opening relative to the beginning of the obstructive event. There was no difference in the Opening Threshold between openings with and without arousal. This was somewhat surprising in that behavioral responses may be expected to involve more pharyngeal dilators than reflex responses (32). The lack of difference may reflect a dominant role of the tongue in effecting opening or that tongue activity is representative of collective activity of all muscles involved in upper airway opening regardless of their mechanism of activation. Alternatively, many of the arousals that existed at the time of opening may have been ineffectual in recruiting other dilators. In fact, many of these arousals barely met arousal criteria and may have simply reflected the high respiratory drive at the time. The Opening Threshold was slightly lower in openings occurring early in the dial-down following ventilatory stimulation (13.2 ± 11.3 vs. 14.9 ± 12.3% GGMAX, P < 0.02, n = 20 patients). This is likely due to the fact that airway collapsibility is less during the first 2–3 breaths after dial-down than later on (46, 52).

**Relation Between GG Opening Threshold and PCRIT**

The Opening Threshold in patients with mild hypopneas at the dial-down pressure of 1 cmH2O was, not surprisingly, much less than in patients who developed severe hypopneas or apneas (2.8 ± 2.3 vs. 12.9 ± 9.7% GGMAX, P < 0.005). What was surprising was the total lack of correlation between the Opening Threshold and PCRIT in the latter group (Fig. 5). Thus Opening Threshold was <7% GGMAX over a PCRIT range of −1 to +10 while ranging up to 38% GGMAX over a narrow PCRIT range (−1 to 4 cmH2O; Fig. 5). There are several possible reasons to explain how the required activation may vary so much at the same PCRIT.
A) Differences in tongue strength. A weaker muscle requires a greater degree of activation to generate the same force. There is much evidence to suggest that the upper airway dilators of OSA patients display abnormalities in histological and contractile properties, but there is controversy as to the clinical significance of these changes (see Refs. 10, 24 for review). It is possible that in some OSA patients there is tongue myopathy. However, regardless of the existence of pathology, the maximum force that can be generated by the tongue varies greatly among OSA patients and normal subjects [15 to 43 Newtons (37)]. Consequently, it is possible that individual differences in tongue strength account in part for differences in %GGMAX required to open the airway at the same PCRIT.

B) Site of obstruction. The site of obstruction varies among OSA patients from retro-palatal to retro-glossal (7, 15, 36, 47). It is possible that, for the same PCRIT, a retro-glossal obstruction can be more easily overcome than a retro-palatal obstruction, since the latter would be influenced only indirectly by tongue contraction.

C) Viscosity of pharyngeal secretions. Tenacious salivary secretions should make it more difficult to open the airway from a closed or significantly narrowed position. Surface tension of pharyngeal lining fluid varies among OSA patients and normal subjects [45 to 65 mN/m (26, 27)]. A lower surface tension is associated with a decrease in the intraluminal pressure required to reopen a closed pharyngeal airway in humans (25, 48) and reduction in the AHI (19, 26, 35). Thus it is possible that differences in the physical properties of pharyngeal secretions among OSA patients account in part for the differences in required activation at similar PCRIT.

D) Balance of forces/negative effort dependence. The increase in GG activity during obstructive episodes is associated with a greater negative pharyngeal pressure that tends to oppose opening (45). The latter is a consequence of increased respiratory drive. According to one construct (45), opening from a completely closed position can only occur when the dilating force produced by tongue activation exceeds the opposing force produced by negative pharyngeal pressure. It is possible that differences in pharyngeal anatomy or physical characteristics of the tongue alter the relationship between negative pharyngeal pressure and the collapsing backward force it exerts on the tongue. Such differences would translate into greater or lesser activity required to dislodge the tongue from a closed position. The situation is more complicated with flow limitation since, with classical flow limitation (e.g., in COPD), downstream pressure (negative pharyngeal pressure in this case) should not affect maximum flow and, by extension, any increase in dilating force at the site of obstruction should result in increased flow. This is not the case in pharyngeal flow limitation. It has been shown that maximum flow in the pharynx can decrease as pharyngeal pressure becomes more negative [Negative Effort Dependence (14, 17)]. The more prominent this negative effort dependence is, the more dilator activity would be required to increase flow. The magnitude of this negative effort dependence (slope of flow vs. negative pressure) varies considerably among patients (17) and, consequently, may contribute to the variability in GG Opening Threshold in hypopneas. It may also account for the fact that flow remains independent of GG activity until a threshold activity is reached (Figs. 1 and 4).

Capacity of Non-Arousal Mechanisms to Increase GG Activity

It has long been proposed that non-arousal (chemical and reflex) mechanisms are not sufficient to open the airway in OSA patients and that, by extension, arousal is necessary to restore adequate ventilation. This notion is based on the very frequent occurrence of arousal near [but not necessarily before or at (53)] the time of opening. More recently, it was pointed out that many OSA patients develop periods of stable breathing, from which it was implied that under some conditions dilator muscle activity can increase enough to maintain adequate airway patency via non-arousal mechanisms (52). This latter prediction was recently confirmed by Jordan et al. (20). Nonetheless, because stable breathing is observed only in some patients, and these patients have other periods in which there are recurrent events, the idea that non-arousal mechanisms are capable of restoring upper airway patency in OSA patients could not be generalized.

In this study, we used two interventions that increase arousal threshold, thereby giving non-arousal mechanisms a greater opportunity to evolve. First, obstructive events were induced during stable breathing and sleep while the patient was receiving optimal CPAP. This is not the case in untreated OSA where the patient usually has difficulty getting into deep sleep and obstructive events occur during light sleep and, hence a low arousal threshold. Second, we used zopiclone. With these interventions 26 of the 32 patients had several openings without arousal and in all of them GG activity had risen to exceed the Opening Threshold (Fig. 6). Despite these arousal-retarding interventions, arousals still occurred at the time of opening in an average 60% (range 0–100%) of observations, including six patients in whom all openings were associated with arousal. In patients in whom both arousal-associated and non-arousal-associated openings occurred (n = 26) it was clear that arousal interrupted the evolution of non-arousal mechanisms, which would otherwise have risen to open the airway (Fig. 6, compare solid and open symbols). In fact, peak GG activity just before arousal was only 5.4 ± 4.6% GGMAX below GG Opening Threshold. Given that the arousal-free rate of rise of peak GG activity in the vicinity of opening was 8.6 ± 5.2% GGMAX per breath (e.g., Figs. 1 and 2A), the activity required to open would have been reached spontaneously if arousal were delayed only a few seconds. Thus it can be concluded that in most OSA patients non-arousal mechanisms are capable of restoring upper airway patency if given the chance.

The excellent correlation between GG activity reached without arousal and the GG Opening Threshold (Fig. 6, open symbols; r² = 0.91) is of interest. Such a correlation is dictated by the fact that the stimulus for non-arousal responses will necessarily continue to increase so long as GG activity is below GG Opening Threshold. Furthermore, once the airway opens, the stimulus for these responses rapidly disappears, so that activity cannot increase much above the threshold. Some overshoot is unavoidable since it appears that the activity does not decline instantly upon airway opening (e.g., Figs. 1 and 2).

The reason for the different shapes of the rising phase of GG activity is not clear. Similar differences in shape have been described for diaphragmatic activity (58). Upward concavity of GG activity was very common during obstructive events (e.g., Fig. 1). Although this may reflect a predetermined central
pattern, it is possible that the increase in rate of rise later in inspiration may reflect a non-linear central response to negative pharyngeal pressure. This possibility is supported by the recent observation that activation of GG via the negative pressure reflex may not occur until a certain chemical drive threshold is reached (31). Since in the setting of airway obstruction chemical drive and negative pharyngeal pressure are correlated, it is possible that the increase in rate of rise later in inspiration occurs when a certain level of negative pharyngeal pressure, required to engage this reflex, is reached in the course of individual inspirations.

Mechanism(s) of Antecedent Expiratory Opening

As shown in Fig. 2, at times the airway opened first during expiration. Given the associated Respitrace pattern (Fig. 2A), it is likely this is due to recruitment of expiratory muscles with consequent increase in pharyngeal pressure. Expiratory muscles become active late in expiration when respiratory drive increases above a certain threshold (16). The expiratory opening is likely further facilitated by the progressive increase in expiratory (tonic) GG activity, which is often observed during sustained obstructions (22, 55). Clearly, since pharyngeal pressure is positive during expiration and negative during inspiration, expiratory opening would require less dilator activation than inspiratory opening. It is curious, however, that when expiratory opening occurs first, inspiratory opening follows soon after (e.g., Fig. 2, A and B). It is possible that the chemical drive threshold required to activate the expiratory muscles enough to open the airway during expiration is similar to the threshold required to activate the inspiratory GG activity enough to open the airway during inspiration. Alternatively, transiently forcing the airway to open during expiration makes it easier for the dilators to open the airway during the next inspiration.

Clinical Implications

The obvious clinical implication of these findings is that if arousals are sufficiently suppressed the airway will open spontaneously. Since arousals promote ventilatory overshoot (53), such an intervention may result in stable breathing. In fact, the potential use of sedatives in selected OSA cases has been considered (9, 12, 53, 54). However, in our experience, it is difficult to increase arousal threshold sufficiently with therapeutic doses of sedatives and, if such administration is not effective, oxygen desaturation and hyperventilation may be aggravated. Furthermore, the rationale for using sedatives is that they would allow chemical drive to increase to a higher level before arousal occurs (12, 53, 54). Because a higher chemical drive at the time of opening is, itself, destabilizing (54), the use of sedatives may simply exchange one destabilizing factor (arousal) for another one (higher chemical drive at opening). The current study points to another potential approach that does not have the problems of sedatives, namely strategies to reduce GG Opening Threshold. Such an intervention would achieve the same end result (reflex responses exceeding Opening Threshold without arousal) but without the side effects of sedatives andwithout the need to increase respiratory drive beyond the level reached with a normal arousal threshold (Fig. 7). The lack of correlation between GG Opening Threshold and Pcrit indicates that determinants of this Threshold are largely unknown and deserve further exploration. It is possible that some of these determinants may be amenable to manipulation. In this respect, it is worth noting that GG activity reached before arousal in arousal-associated openings (Fig. 6, solid dots) was only 5.4 ± 4.6% GMMAX below GG Opening Threshold, so that in many patients small reductions in GG Opening Threshold may achieve stability.

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GRANTS

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DISCLOSURES

Magdy Younes holds several patents related to improvements in mechanical ventilation and receives royalties from Respironics and Covidien for licenses to use these technologies. He has also received honoraria from both companies for teaching activities related to mechanical ventilation and from Respironics for acting as an expert witness in a legal case. He is the CEO and owner of YRT Limited, a Winnipeg research and development company involved in developing new technologies for the diagnosis and treatment of respiratory failure and sleep disorders. YRT is not undertaking any developments that would benefit from the outcome of this study. The research reported in this manuscript was exclusively supported by a grant from the Canadian Institutes of Health Research with no industrial contribution. Patrick Hanly received honoraria for scientific presentations sponsored by Respironics. Dr. Hanly is Director of the Sleep Medicine Program at the University of Calgary, which has received financial support from Respironics for trainees. Michele Ostrowski: consultant to YRT Ltd. (see disclosure of MY). John Laprairie: performed some sleep scoring work for YRT Ltd. (see disclosure of MY) and received payment from Respironics for performing and scoring some research studies. Andrea Leowen and Frances Maturino have no conflicts.

AUTHOR CONTRIBUTIONS

Author contributions: M.Y. and P.J.H. conception and design of research; M.Y., A.H.L., M.O., J.L., and F.M. performed experiments; M.Y., A.H.L., and M.O. analyzed data; M.Y. and P.J.H. interpreted results of experiments; M.Y.
prepared Figs.; M.Y. drafted manuscript; M.Y. and P.J.H. edited and revised manuscript; M.Y. approved final version of manuscript.

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