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The Effect of Gender on Compensatory Neuromuscular Response to Upper Airway Obstruction in Normal Subjects Under Midazolam General Anesthesia

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Abstract

Background—Upper airway patency may be compromised during sleep and anesthesia due to either anatomical alterations (mechanical properties) or disturbances in the neural control (compensatory neuromuscular responses). The pathophysiology of upper airway obstruction during anesthesia may differ between men and women. Recently, we reported that the upper airway mechanical properties were comparable to those found during natural non-rapid eye movement sleep, as evaluated by measurements of passive critical closing pressure (P_{CRIT}) and upstream resistance (R_{US}) during midazolam sedation. In this study, we compared the effects of gender on compensatory neuromuscular responses to upper airway obstruction during midazolam general anesthesia.

Method—Thirty-two subjects (14 men, 18 women) were studied. We constructed pressure-flow relationships to evaluate P_{CRIT} and R_{US} during midazolam anesthesia. The midazolam anesthesia was induced with an initial dose of midazolam (0.07 to 0.08 mg/kg bolus) and maintained by midazolam infusion (0.3 to 0.4 μg/kg/min), and the level of anesthesia was assessed by Ramsay score (level 5) and Observer's Assessment of Alertness/Sedation score (level 2). Polysomnographic and hemodynamic variables were monitored while nasal pressure (via mask), inspiratory air flow (via pneumotachograph) and genioglossal electromyograph (EMG_{GG}) were recorded. P_{CRIT} was obtained in both the passive condition, under conditions of decreased EMG_{GG} (passive P_{CRIT}), and in an active condition, whereas EMG_{GG} was increased (active P_{CRIT}). The difference between the active P_{CRIT} and passive P_{CRIT} ($\Delta P_{CRIT\ P\text{-}A}$) was calculated in each subject to determine the compensatory neuromuscular response.

Results—The difference between the active P_{CRIT} and passive P_{CRIT} ($\Delta P_{CRIT\ A\text{-}P}$) was significantly greater in women than in men (4.6 ± 2.8 cmH_2O and 2.2 ± 1.7 cmH_2O, respectively; $p<0.01$), suggesting greater compensatory neuromuscular response to upper airway obstruction independent of arousal.

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Conclusion—We demonstrate that the arousal-independent compensatory neuromuscular responses to upper airway obstruction during midazolam anesthesia were partially maintained in women, and that gender may be a major determinant of the strength of compensatory responses during anesthesia.

INTRODUCTION

Maintenance of upper airway patency is critical for spontaneous breathing during sedation and general anesthesia, whereby upper airway dilator muscle activity becomes significantly compromised in the absence of arousal responses.[1–3] It is well recognized clinically that there is an increased risk of apnea and hypopnea during deep sedation due to additional anesthesia administered in order to mitigate surgical stress or pain during procedures.[4] These transient changes from deep sedation to general anesthesia may cause further sustained upper airway obstruction, similar to the sleep-disordered breathing events that occur in patients with obstructive sleep apnea hypopnea syndrome.[5]

In the unconscious or sleep states, upper airway patency may be compromised due to anatomical alterations (i.e., mechanical properties) or disturbances in upper airway neural control (i.e., compensatory neuromuscular responses).[6] In previous studies, we have indicated that the hypotonic upper airway mechanical properties, evaluated by critical closing pressure (P_{CRIT}) and up-stream resistance (R_{US}), during natural non-rapid eye movement (REM) sleep are comparable to those measured during moderate midazolam sedation.[7,8] Moreover, we have shown[9] that defects in both upper airway mechanical properties and the compensatory neuromuscular responses to upper airway obstruction are necessary for the development of obstructive sleep apnea. The difference between P_{CRIT} under hypotonic conditions (passive P_{CRIT}) and following progressive increases in neuromuscular activity (active P_{CRIT}) is a measurement of the strength of dynamic compensatory neuromuscular responses to upper airway obstruction ($\Delta P_{CRIT\ A\text{-}P}$).[9]

The major risk factors for compromised upper airway patency during sleep (i.e., obesity, age, sex) may also play a role in collapse of the upper airway during general anesthesia. In healthy subjects and sleep apnea patients, we have recently shown differences in upper airway mechanical properties between men and women during sleep, independent of age and Body Mass Index (BMI).[10] During moderate sedation, men also appear to have greater dynamic negative airway pressure-dependent decreases in upper airway patency than women,[11] suggesting that there are gender differences in hypotonic upper airway mechanics. Nevertheless, it remains unclear whether men and women have differences in compensatory neuromuscular responses to upper airway obstruction during midazolam general anesthesia.

The aim of the present study was to quantify the magnitude of the effect of gender on the compensatory neuromuscular responses by assessing $\Delta P_{CRIT\ A\text{-}P}$ during midazolam general anesthesia. We hypothesized that women have greater compensatory neuromuscular responses to upper airway collapse than men during midazolam anesthesia.

MATERIALS AND METHODS

Subjects

Thirty-two healthy subjects (14 men , 18 women; Table 1) were recruited, and a detailed clinical history was obtained. Subjects were excluded if they were overweight or obese (BMI>25 kg/m^2); were frequent or excessive snorers (more than 3 times/wk); had abnormal sleep patterns or reported excessive daytime sleepiness (Epworth Sleepiness Score >10); had significant medical disease (cardiopulmonary pathology) or other clinical history (allergy to anesthesia); or reported tobacco use or chronic alcohol or drug use. Subjects were also excluded if they had

an anatomical deformation of the upper airway, such as retrognathia (assessed by lateral view and occlusial condition), as a normal range of overbite (2–3 mm) and overjet (2–3 mm). All subjects had to have a Mallampati score of I or II and a thyromental distance longer than 60 mm. The experimental protocol was approved by the Human Investigation Committee of the Nagasaki University School of Dentistry and written informed consent was obtained from all subjects.

Experimental Techniques

Polysomnographic Measurements—All subjects were placed supine in a dark and quiet room and the head, neck and mandible were kept in a constant neutral position throughout the study using a molded pillow, as previously described.[12] All subjects underwent routine hemodynamic monitoring (systolic and diastolic blood pressure, heart rate) and electrocardiogram, polysomnographic monitoring of sleep state, with bilateral electrooculograms, electroencephalograms (EEGs) and submental electromyograms (EMGs) to confirm steady-state anesthetic level. EEG signals were processed by the Bispectral Index (BIS) monitor (Aspect Medical Systems Inc., Natick, MA) in order to quantify the depth of anesthesia (Table 1). Oxygen saturation (SpO_2) was measured by finger pulse oximetry, and transcutaneous CO_2 ($TcCO_2$, Tina, TCM4, Radiometer, Tokyo, Japan) was monitored continuously. Both thoracic and abdominal movements were recorded by inductance plethysmography.

Respiratory Effort, Pressure and Flow—Respiratory effort was monitored via a Hyatt-type esophageal balloon (Ackrad Laboratories, Cranford, NJ) placed pernasally for monitoring esophageal pressure. The tip of the catheter was positioned 45 to 50 cm from the nares. Airflow was measured by a pneumo-tachometer (#3830, Hans Rudolph, Inc., Kansas City, MO, USA), and nasal pressure (P_N) was measured by a differential pressure transducer (#1100, Hans Rudolph, Inc., Kansas City, MO, USA), both connected to the mask. A variable pressure device (MAP/ResMed, Martinsreid, Germany) was used to deliver constant pressure in the nasal mask (P_N) over the range from −15 to +15 cm H_2O. These measurements were displayed and stored simultaneously on a computer using a data acquisition device (Embla A-10 with Somnologica, Medcare, Broomfield, CO, USA). Air leaks were prevented by applying surgical tape to the subject's mouth after the bio-calibrations and immediately before the commencement of data acquisition.

Experimental protocols

Anesthesia—Midazolam anesthesia was maintained by the same infusion method previously described.[8,13] Briefly, midazolam (~0.07 to 0.08 mg/kg) was initially injected at a rate of 0.5 mg/min until a steady-state of general anesthesia was attained. The behavioral responses as classified using the Ramsay scale (i.e., score 5 = sluggish response to a light glabellar tap or loud auditory stimulus) and Observer's Assessment of Alertness/Sedation (i.e., score 2 = Responsiveness: responds only after mild prodding; Speech: Not recognizable) were used to titrate the maintenance infusion rate of midazolam (range: 0.2 to 0.4 μg/kg/min; Table 1) for the assessment of upper airway patency and compensatory neuromuscular responses. At the conclusion of the measurements, the total time needed for the completion of the study was recorded. The midazolam infusion was then withdrawn and all subjects remained supine until spontaneous emergence.

Measurement of upper airway collapsibility

Assessment of passive P_{CRIT}—After reaching the maintenance level of anesthesia, P_N was initially set at atmospheric pressure, then gradually increased to a holding pressure (range: 0–8 cm H_2O) sufficient to abolish inspiratory airflow limitation, as previously described.[14,

[15] Thereafter, the P_N was rapidly changed from the holding pressure to a lower pressure for 5 successive breaths before being returned to the holding P_N ("*Passive state*"; Figure 1 and Figure 2 – top panels).

Assessment of active P_{CRIT}—We used a successive continuous pressure decrease method to produce transient hypoxia and hypercapnia under loaded breathing, similar to the method described in our previous study by Patil et al.[9] After obtaining a stable unobstructed breathing pattern at a positive holding pressure, P_N was then decreased by approximately 2 to 4 cmH_2O (producing a 40% to 50% reduction in $V_I max$) from holding pressure to produce flow-limited breaths associated with increased genioglossus EMG (EMG_{GG}) activity ("*Activated state*"; Figure 1 and Figure 2 – bottom panels). Once the activity of genioglossus EMG started to increase, associated with moderate SpO_2 desaturation (3–5%) as well as an increase in $TcCO_2$ (5–10 mmHg above baseline value), P_N was maintained for 5 minutes. Thereafter, P_N was decreased again by 2 cm H_2O in a stepwise fashion and maintained for 5 breaths at each P_N level until either obtaining zero flow or reaching a lower SpO_2 limit of 88% to 90%.

EMG_{GG} monitoring—EMG_{GG} was monitored (men, n = 10/14; women, n = 14/18), and the tonic and phasic EMG_{GG} activity was analyzed using the method described by Eastwood et al.[4,16] EMG_{GG} was measured using a pair of unipolar intramuscular electrodes referenced to a single ground, thus producing a bipolar recording. Two 25-gauge needles containing 0.05 mm diameter, teflon-coated, stainless steel wires were inserted perorally ~1.5–2.0 cm into the body of the genioglossus muscle at points 3 mm lateral to the frenulum and midway between the first mandibular incisor and the sublingual fold. The needles were removed, leaving the wires in place. The raw EMG_{GG} signal was amplified, bandpass filtered, and recorded at 200 Hz on the polysomnographic unit. *Post hoc*, the data were exported to analysis software (Chart 5.4.2, ADinstrument Pty Ltd, Bella Vista NSW, Australia), full-wave rectified, and integrated with a time constant of 100 ms.

Tonic activity of integrated EMG_{GG} activity (minimum EMG_{GG} value during expiration) was defined as the difference between electrical zero and end-expiratory activity during passive state and active state for each breath. Phasic activity of integrated EMG_{GG} was defined as the difference between end-expiratory and peak-inspiratory activity when P_N was decreased to near P_{CRIT} level (i.e., presence of marked flow limitation without complete airway collapse). Measurements were expressed as a percent change from the maximal value obtained during voluntary tongue protrusion against the upper incisors and forced swallows.

Data analysis

Upper airway pressure-flow relationship—Peak inspiratory airflow and corresponding mask pressure for each breath were analyzed at all levels of P_N and evaluated for the presence of inspiratory airflow limitation, as previously described.[15,17] Briefly, inspiratory flow limitation was defined as the presence of a plateau in inspiratory airflow in association with a continued decrease in esophageal pressure by at least 1 cm H_2O beyond the onset of the plateau. Flow limitation in the presence of an abdominal strain gauge was determined using the criterion of Hosselet et al.[18] Breaths associated with arousal were excluded from analyses. As reported previously,[19] the inspiratory pressure-flow relationship was analyzed by Least-squares linear regression and fitted by the following equation: $V_I max = (P_N - P_{CRIT}) / R_{US}$, where P_{CRIT} is the critical closing pressure (P_N at zero flow) and R_{US} is the resistance of the portion of the tube upstream from the site of collapse (Figure 3).

Magnitude of the Compensatory Neuromuscular Response ($\Delta P_{CRIT\ A\text{-}P}$)—The compensatory neuromuscular response to upper airway obstruction ($\Delta P_{CRIT\ A\text{-}P}$) is determined by the difference between passive P_{CRIT} and active P_{CRIT} in the following equation:

$$\text{active } P_{CRIT} = \text{passive } P_{CRIT} + \Delta P_{CRIT\ A-P} \quad [9]$$

where passive P_{CRIT} represents the hypotonic mechanical properties of the upper airway and active P_{CRIT} is the arithmetic sum of the mechanical properties and the compensatory neuromuscular responses.[9]

Statistical Analysis—All statistical analyses were performed using SPSS version 16.0 (SPSS, Inc., Chicago, IL, USA). The primary outcomes in the study including the passive P_{CRIT} and active P_{CRIT} were analyzed using General Linear Model (GLM) for repeated measures, with a *post hoc* protected Bonferroni adjustment test after confirmation of normal data distribution (test for skewness and kurtosis). Secondary outcomes included difference in R_{US} and difference between the active and passive P_{CRIT} ($\Delta P_{CRIT\ A-P}$), and tonic and peak phasic EMG_{GG} were statistically analyzed using the Mann-Whitney test because data were not normally distributed. Statistical significance was assumed for $P < 0.05$. The data are presented as mean ± standard deviation (SD) with 95% confidence intervals (95% CI), unless otherwise noted.

Due to technical failure of the intramuscular electrode placement, we were unable to obtain EMG_{GG} measurements in 4 female and 4 male subjects. Data from these subjects were included in the primary analysis of the gender differences in passive P_{CRIT}, active P_{CRIT} and $\Delta P_{CRIT\ A-P}$ measurements and in secondary analysis of R_{US}. There was no effect on the reported gender differences in the upper airway properties when these subjects were excluded from the analysis.

RESULTS

In 32 subjects (14 men, 18 women; Table 1) there was a significant difference in height and body weight between men and women but no difference in BMI values. In men the initial dose of midazolam administered was 4.8 ± 0.5 mg and the total dose was 6.2 ± 0.7 mg over 53.4 ± 7.4 minutes for the completed study (1.83 ± 0.23 μg/kg/min). In women the initial dose of midazolam was 3.9 ± 0.4 mg and the total dose was 5.0 ± 0.5 mg over 55.2 ± 5.9 minutes (1.82 ± 0.17 μg/kg/min). Although the initial and total doses of midazolam were larger in men than in women, the weight-adjusted doses were the same (Table 1).

There was no significant difference in BIS values between men (53.4 ± 4.3) and women (51.5 ± 4.6%) or between the passive (51.8 ± 6.3) and active (54.2 ± 9.3%) states (P=0.16). During steady-state anesthesia >85% of EEG power spectrum had frequencies in the <4Hz range (delta waves) for all subjects, i.e., comparable to EEG power spectrum of non-REM stage 3 to 4 sleep. During the passive state there was no significant increase of $TcCO_2$ from baseline (39.6 ± 6.4 mmHg) to passive level (41.7 ± 4.9 mmHg, P=0.13), whereas during the active state $TcCO_2$ increased from baseline (40.8 ± 5.1 mmHg) to the activated level (48.1 ± 4.9 mmHg; $p<0.05$). There were no changes in the SpO_2 during measurements in the passive state, whereas during the active state, the lowest value of SpO_2 decrease from a baseline of 97.2 ± 0.9% to 91.6 ± 1.8% ($p<0.05$).

The tonic EMG_{GG} activity significantly increased from 5.4 ± 1.8% in the passive state to 10.2 ± 2.3% in the active state ($p<0.01$) in men and from 7.2 ± 2.1% in the passive state to 10.2 ± 4.5% in the active state ($p<0.05$) in women. Similarly, peak phasic EMG_{GG} activity increased from the passive state (10.1 ± 2.5%) to the active state (14.4 ± 3.7 %; $P<0.01$) in men; and from the passive state (11.1 ± 4.4%) to the active state (16.9 ± 4.8%; $P<0.01$) in women. There

was no significant difference in the EMG_{GG} in any state between men and women (all P>0.3). (Fig 4)

The individual subjects' passive P_{CRIT} values are shown for both men and women (Tables 2A and 2B). The mean passive P_{CRIT} in women was significantly lower (more negative) than in men (−6.4 ± 3.8 cmH_2O and −3.8 ± 3.8 cmH_2O, respectively; P<0.05) (Figure 5); however, there was no difference in the R_{US} in the passive state (30.7 ± 19.2 cmH_2O and 36.0 ± 20.7 cmH_2O, respectively). Similarly, active P_{CRIT} was significantly decreased in women compared to men (−11.0 ± 4.5 cmH_2O and −6.0 ± 4.6 cmH_2O, respectively; p<0.05); however, there was no difference in the active R_{US} (32.6 ± 20.1 cmH_2O/ml/s and 38.5 ± 21.6 cmH_2O/ml/s, respectively). The $\Delta P_{CRIT\ A\text{-}P}$ was significantly larger in women than men (4.6 ± 2.8 cmH_2O and 2.2 ± 1.7 cmH_2O, respectively; p=0.007; Tables 2A and 2B).

DISCUSSION

The main findings of this study were that under midazolam anesthesia: 1) the mechanical upper airway properties were more collapsible in female subjects than in men, and 2) the strength of the compensatory neuromuscular responses ($\Delta P_{CRIT\ A\text{-}P}$) to upper airway obstruction was greater in women than in men.

Effect of Gender on Upper Airway Collapsibility

Mechanical Properties—We found a significant gender effect on the mechanical properties of the upper airway, as evaluated by measurements of the passive P_{CRIT}. The passive P_{CRIT} was lower in women (−6.4 ± 3.8 cmH_2O) than in men (−3.8 ± 3.8 cmH_2O) under midazolam anesthesia, and approximated the differences found by Norton et al.[11] during midazolam sedation and the passive P_{CRIT} values (2.6 cmH_2O) reported in our previous study[10] and in a smaller study cohort by Jordan et al.[20] during sleep. Norton et al. investigated the hypotonic upper airway mechanics during a moderate level of midazolam sedation and reported that men have increased dynamic pressures required to induce upper airway obstruction (a method similar yet not as sensitive as the passive P_{CRIT} method). In the current study men and women had approximately the same BMI and age, therefore the difference in upper airway mechanical properties may be related to other factors, i.e., pharyngeal size, changes in resting lung volume, surrounding soft tissue structures and fat distribution,[21,22] or female sex hormones. It has been shown that the pharynx is more elongated in men than in women,[23,24] leaving a larger region exposed to upper airway collapse. An elongated upper airway may be more vulnerable, especially with the depressed level of neuromuscular activity of dilator muscles under midazolam anesthesia. Deposition of truncal or central adiposity may be associated with decreased lung volumes and diminish sternomedial caudal traction on upper airway structures, and in turn compromise upper airway patency and increase P_{CRIT}.[25–29] It has also been suggested that the resting activity of the genioglossus muscle is higher in healthy women than in men during wakefulness[21] and higher in women in the luteal than the follicular menstrual phase.[23] Therefore, female sex hormones may play a role in determining upper airway mechanical properties, although it is still uncertain how the resting level of the genioglossus muscle alters upper airway collapsibility during sleep. Future research should examine the effect of menstrual hormones on upper airway patency in normal women during general anesthesia and sleep.

Compensatory Neuromuscular Responses to Upper Airway Collapse—We are not aware of any other study that examined the compensatory neuromuscular responses to upper airway collapse during anesthesia with midazolam or any other sedative hypnotic drugs. The magnitude of $\Delta P_{CRIT\ A\text{-}P}$ represents the contribution of the upper airway muscles to counterbalance intra- and extraluminal collapsing pressures. For example, a 5cm H_2O

$\Delta P_{CRIT\ A\text{-}P}$, due to increased neuromuscular activity, has the same stabilizing effect as applying 5 cm H_2O of continuous positive airway pressure to the upper airway. Previously, we have shown that a change in P_{CRIT} of ~5cm H_2O due to neuromuscular activity is clinically relevant, [9] because this represents the magnitude of the response required to convert either obstructive apneic events to the less severe hypopneic events or hypopneic events to stable breathing. In the current study, the component of upper airway collapsibility attributed to increased neuromuscular activity in response to obstruction in men ranged from almost no response (0.1 cm H_2O) to a maximum of 5.7 cm H_2O, with only 2 of the 14 men having a $\Delta P_{CRIT\ A\text{-}P}$ more than or equal to 5 cm H_2O. Therefore, less than 15% of men have compensatory neuromuscular responses that provide sufficient airway support during upper airway collapse with midazolam anesthesia. In contrast, the compensatory neuromuscular response in women ranged from 1.6 cm H_2O to 11.0 cm H_2O, and more than one-third of the women had a $\Delta P_{CRIT\ A\text{-}P}$ of more than 5 cm H_2O. More than twice as many women maintained adequate neuromuscular activity, suggesting that women preserve upper airway compensatory neuromuscular responses to a greater extent than men during midazolam anesthesia.

The gender effect on compensatory neuromuscular responses is not due to differences in the tonic activity of upper airway dilator muscles, although we cannot exclude the possibility of a small increase in the phasic EMG_{GG} in response to obstruction. Furthermore, the ΔP_{CRIT} is not simply a measure of upper airway dilator muscle activity, but is the composite of the alterations in muscle activity and any structural changes that result from increased activity. Gender-related differences in the hypoxic and hypercapnic ventilation response may partly determine the threshold for recruiting upper airway dilator muscles. It has also been suggested that the arousal response and compensatory neuromuscular response (arousal-independent airway opening) are the 2 most important factors that promote upper airway reopening in the face of sustained obstruction.[30] Previous studies have reported that the arousal response is triggered when a critical level of chemo-mechanoreceptor input is reached[31] and that the arousal-independent recruitment of upper airway dilators is sensitive to the same inputs.[32] Younes[30] indicated that many older subjects are protected from further hypoxia by a relatively high arousal threshold from sleep. Therefore, if men have a relatively high threshold for chemo-mechanoreceptor inputs (hypoxia and hypercapnia) compared to women, men may require the arousal response to compensate for upper airway collapse. Women, on the other hand, are able to activate their compensatory neuromuscular response to upper airway obstruction via an arousal-independent mechanism. We speculate that male subjects are unable to elicit a compensatory neuromuscular response (arousal-dependent system) because midazolam significantly alters the threshold for chemo-mechanoreceptor input and arousal response.

Resistance Upstream from the Site of Collapse (R_{US})

R_{US} reflects the degree of upper airway narrowing upstream from the site of collapse. The lack of change in R_{US} reported in our subjects may reflect a relatively constant airway size between the passive and active states at a given $V_I$max despite changes in upper airway P_{CRIT} in response to increased EMG_{GG}.[14,33] The most likely explanation for this finding is that the upper airway segment upstream from the site of collapse was not involved in the compensatory neuromuscular response at the depressed level of dilator muscle activity associated with midazolam anesthesia. The velopharyngeal segment of the upper airway is particularly prone to collapse and has been found to be the predominant flow-limiting site during sleep,[34] sedation, [35–37] and anesthesia.[38] In the current study, we did not find any difference in the upstream resistance between men and women in either the passive or active states, which suggests that the site of upper airway collapse is most likely the same.

Possible Limitations of the Current Study

Several anatomic, demographic and anthropometric factors related to the study population may have influenced our findings. Older individuals,[39] those with increased BMI,[10] and postmenopausal women[23,40] have more collapsible upper airways. Older individuals also seem to be more susceptible to midazolam anesthesia.[41] The current study, however, was performed in a homogenous population of normal, young healthy Japanese men and women. Although it is difficult to generalize our findings to all patients undergoing midazolam anesthesia, the current study is well suited to examine the effect of gender on upper airway neuromuscular responses to upper airway obstruction. Moreover, it has previously been shown that progesterone decreases tonic neuromuscular activity of dilator muscles during the luteal phase of the menstrual cycle.[23] The phase of menstruation was not recorded in the present study, thus we cannot exclude the potential for menopause or variations in sex hormones to influence either upper airway dilator muscle activity or upper airway collapsibility. Additionally, there are a variety of anatomical features of the maxilla and mandible in Japanese subjects that contribute to the patency of the upper airway[42] but which do not necessarily apply to other ethnic populations.

A number of methodological factors were also considered as potential confounders of this study. First, there is not always a direct correlation between the Ramsay Score and BIS values. In the current study, however, steady-state anesthesia was established using the behavioral indicators of the Ramsay Score both before and after measurement in the passive and active states. BIS values were recorded as a secondary quantitative measure, as commonly adopted in clinical practice. Second, we applied a number of constraints to ensure the safety of the healthy participants in our study. The SpO_2 was maintained above 90% during the application of negative collapsing pressure to the airway. In the current study, we have not determined whether more severe oxyhemoglobin desaturation and concomitant hypercapnia alter the neuromuscular responses to obstruction. Third, the absence of supraglottic pressure measurements limits our ability to determine changes in airway resistance during non-flow-limited breathing from wakefulness to anesthesia. Since spontaneous breathing during general anesthesia in the absence of secure airway management procedures is likely to be associated with airflow limitation, the relevant comparison for the assessment of compensatory neuromuscular responses to airway obstruction is between the baseline passive state and the heightened EMG neuromuscular activity in the active state. Additional investigations are required to assess the maintenance of neuromuscular responses as patients transition from wakefulness to general anesthesia. Lastly, in the current study only a single pair of bipolar intramuscular electrodes was used to directly record the genioglossus, one of many dilator muscles involved in patency of the upper airway. Thus, we acknowledge that we are only able to determine the contribution of the small increase in EMG_{GG} that is associated with the total increased neuromuscular activity of the numerous upper airway muscles and may not have fully represented the overall neuromuscular responses to airflow obstruction. Also in the current study, EMG_{GG} activity was monitored in approximately 75% of our subjects. Thus we acknowledge the possibility of incorrectly reporting no gender difference in the magnitude of the phasic EMG_{GG} during the active state, as this study does not have adequate power to discern a group difference. If women truly have greater phasic EMG_{GG} responses to upper airway collapse, group sample sizes of 26 would be required to achieve 95% power to detect a difference of 5% of maximum EMG_{GG} with group standard deviations of less than 5% of maximum at a significance level of 0.05 using a two-sided two-sample t-test. Furthermore, in the current study the compensatory neuromuscular responses were not examined during wakefulness, therefore future studies should investigate the magnitude of these responses preserved with general anesthesia in both men and women.

Clinical Implications

The major clinical finding of this study is that men have depressed compensatory neuromuscular responses to upper airway obstruction ($\Delta P_{CRIT\ A\text{-}P}$) during midazolam anesthesia compared to women. It appears that healthy women are able to preserve their capacity to respond to upper airway obstruction in the absence of an intact means of arousal, to a greater extent than men. In addition to a mechanical disadvantage, healthy men have a reduced ability to respond to upper airway obstruction without an intact arousal response, further predisposing them to upper airway obstruction during sleep or deepened anesthesia.

There are still many clinical advantages and considerable demand for the use of midazolam sedation and anesthesia during surgical procedures in intensive care units,[43] emergency departments,[44] and out-patient surgical units. We would recommend that the use of midazolam general anesthesia or deep sedation with spontaneous breathing be accompanied by additional secure airway management, i.e., continuous positive airway pressure treatment,[45] and progressive mandible advancement,[46] especially in men, since they are particularly vulnerable to reduced compensatory neuromuscular responses to sustained periods of upper airway obstruction. Furthermore, the implementation of quantitative measurement of airflow allows spontaneous assessment of ventilatory variables, such as tidal volume and maximum inspiratory airflow, on a continuous breath-by-breath basis. Moreover, the consciousness of anesthetized patients should be assessed if they display any signs of reduced airflow, snoring, reduced tidal volume, or paradoxic breathing. Inadequate neuromuscular responses may be exaggerated in other populations susceptible to upper collapse, such as the elderly or people with craniofacial abnormalities such as retrognathia.

Sleeping infants have stronger negative pressure reflex and responses to chemical stimuli than adults, which does not require full wakening for the reversal of pharyngeal airway obstruction.[47,48] It is possible that some airway-protective mechanisms that are present in infants are preserved to a greater extent in women than men. We further speculate that the reduced compensatory neuromuscular response to upper airway obstruction is a major contributor to upper airway obstruction in both anesthesia and sleep, and thus may explain the increased severity of sleep apnea disease in men.

In conclusion, our findings demonstrate that women have greater compensatory neuromuscular responses to upper airway obstruction during midazolam general anesthesia than men. Furthermore, we speculate that gender-related differences in the strength of compensatory responses to sustained upper airway obstruction may explain the increased prevalence of upper airway collapse during sleep in sleep apnea.

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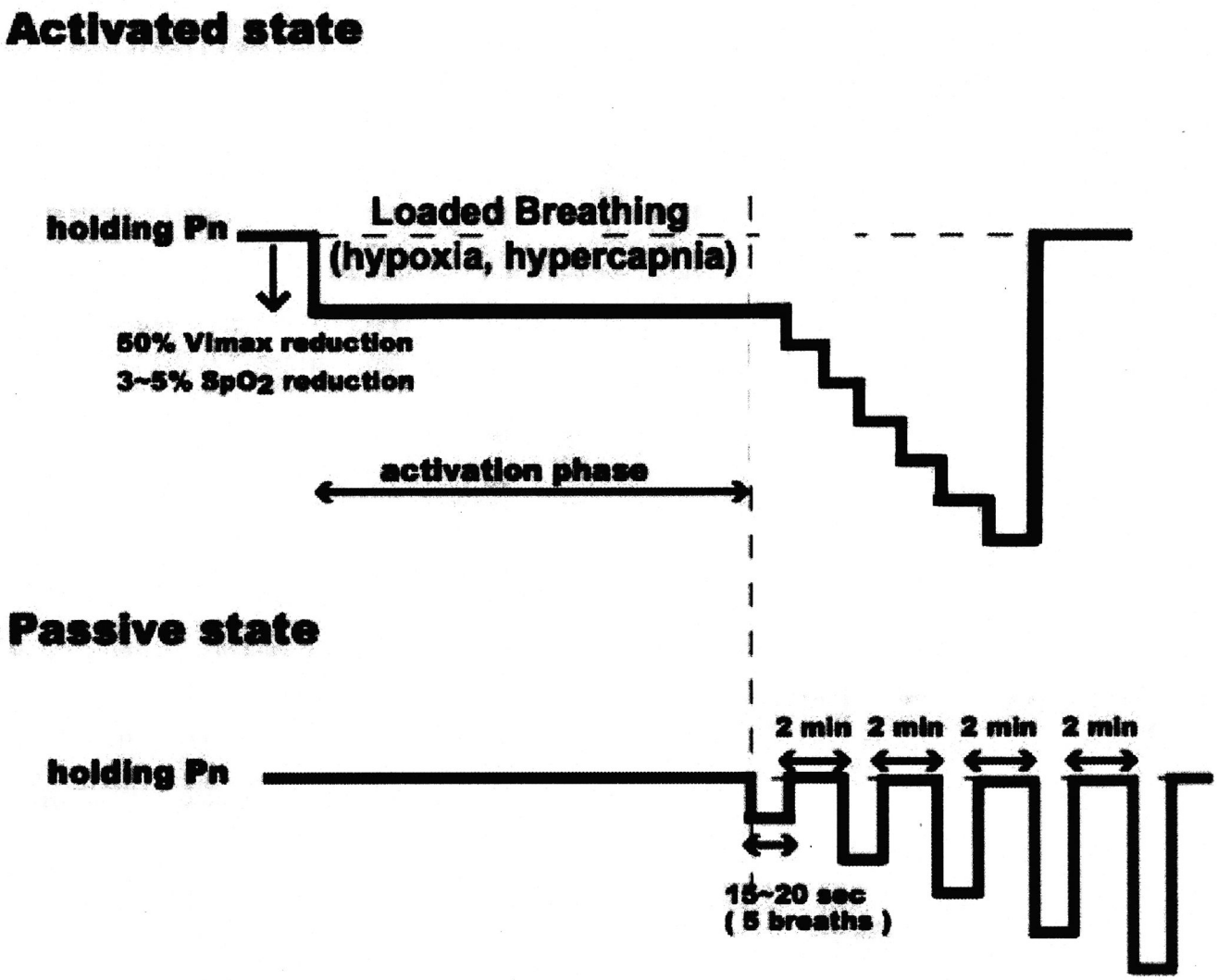

Figure 1.

Schematic diagram of the experimental protocol. The nasal pressure (P_N) is modulated in a stepwise fashion to produce either the "passive state" for evaluating the mechanical properties of the upper airway during reduced genioglossal electromyograph (EMG_{GG}) or the "active state" for evaluating the upper airway in the presence of increased tonic and phasic EMG_{GG} activity.

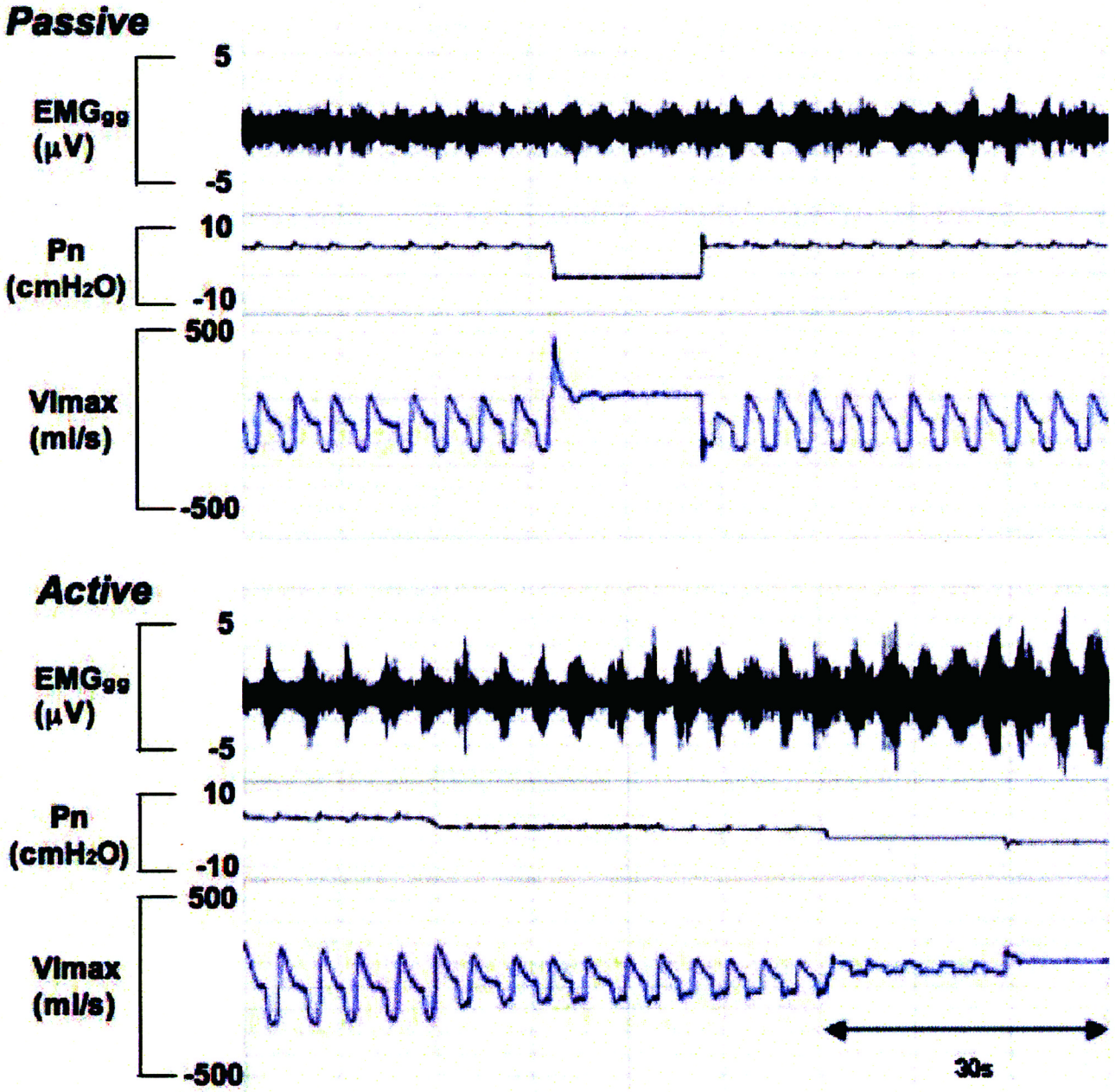

Figure 2.

Raw data obtained from the protocol in passive and active states. In the passive state, nasal pressure (P_N) was reduced in a stepwise fashion from holding pressure (non-flow-limited breathing) to zero flow. In the activated state, after obtaining a stable unobstructed breathing pattern at a positive holding pressure, nasal pressure was then decreased by 2 cmH_2O (associated with 40 ~50% reduction in maximum inspiratory airflow) from holding pressure to cause hypercapnia and resistive loads with partial flow limitation ("*activation state*"). Once the activity of the genioglossal electromyogram (EMG_{GG}) started to increase, associated with a reduction in oxygen saturation of between 3% and 5% as well as an increase in transcutaneous PCO_2 of between 5 and 10 mmHg above baseline value, then P_N was held constant for 1 minute. Thereafter, P_N was decreased again by 2 cmH_2O in a stepwise fashion and maintained for 5

breaths until either obtaining zero flow or a lower limit of oxygen saturation of 88%. nasal pressure (Pn), maximum inspiratory airflow ($V_I$max), genioglossal EMG activity (EMG_{GG})

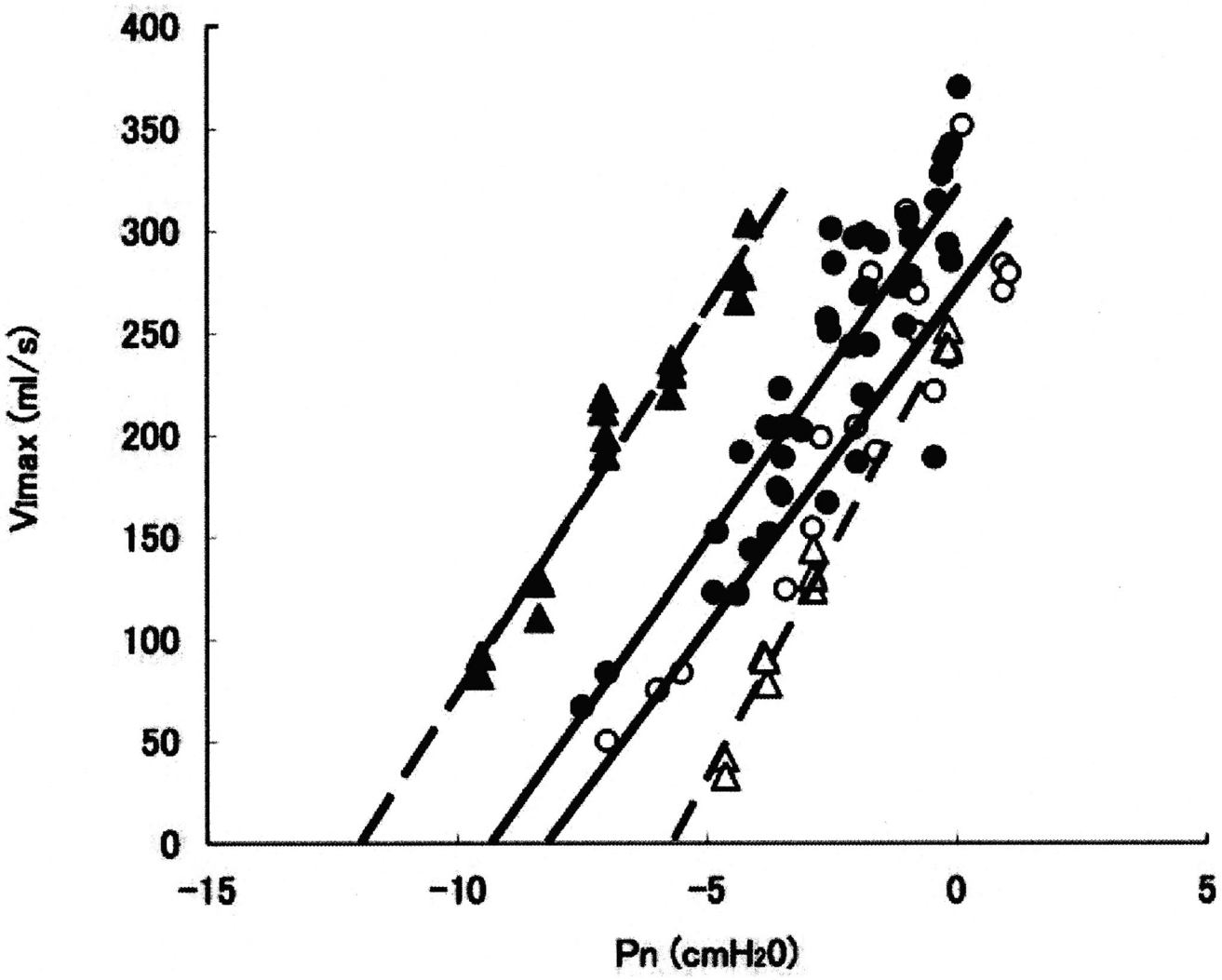

Figure 3.

An example of the nasal pressure (Pn) vs. maximum inspiratory airflow ($V_I$max) relationships in one female subject (ID = *p*) and one male subject (ID = *M*) during passive and active conditions. Upstream resistance (R_{US}) was defined as the reciprocal of slope of the relationship between $V_I$max and P_N, and critical closing pressure (P_{CRIT}) as the *x* intercept of the regression line. In the passive state for subject - *p*, P_{CRIT} = −5.7 cmH_2O (open triangle) and R_{US} = 22.2 cmH_2O/L/sec. In the active state, P_{CRIT} = −12.0 cmH_2O (solid triangle) and R_{US} = 24.9 cmH_2O/L/sec. Similarly for subject *M*, In the passive state, P_{CRIT} = −7.9 cmH_2O (open circle) and R_{US} = 31.4 cmH_2O/L/sec, whereas in the active state, P_{CRIT} = −9.7 cmH_2O and R_{US} = 34.3 cmH_2O/L/sec (solid circle). There was a larger increase in difference between the passive and active P_{CRIT} values in subject *p*, representing a greater improvement in collapsibility in the activated state, compared to subject *M*.

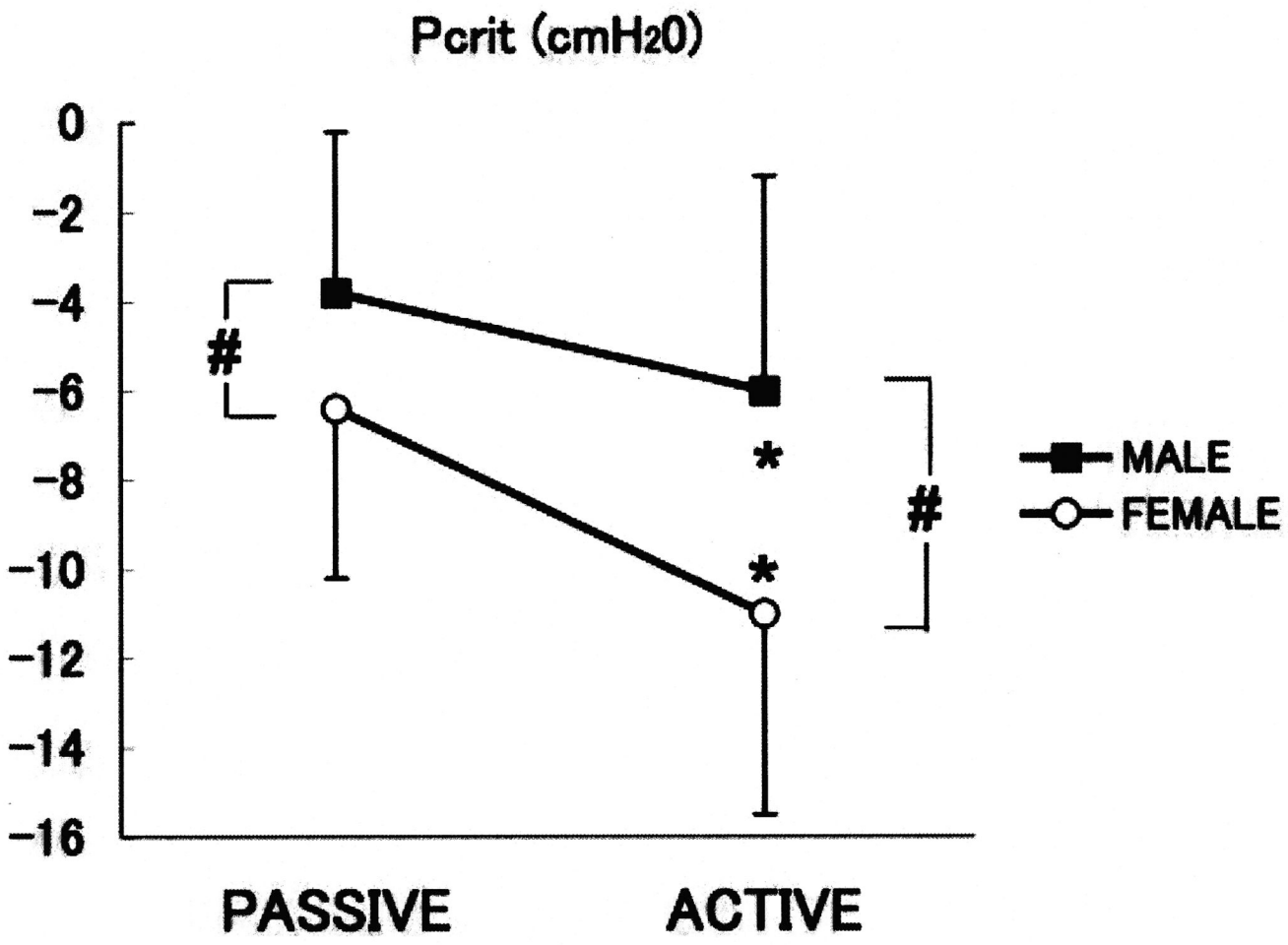

Figure 4.

Box plots showing the tonic and phasic genioglossus electromyograph (EMG) (EMG_{GG}) activity as a percent of max in male and female subgroups. Line = median, box = 25^{th}–50^{th} percentiles, whiskers and cap = 95^{th} percentile, diamond-shaped = 95% confidence interval; *=$p<0.05$. Note that there is an increase in the tonic and phasic EMG_{GG} in the activated state; however, there were no significant differences between men and women.

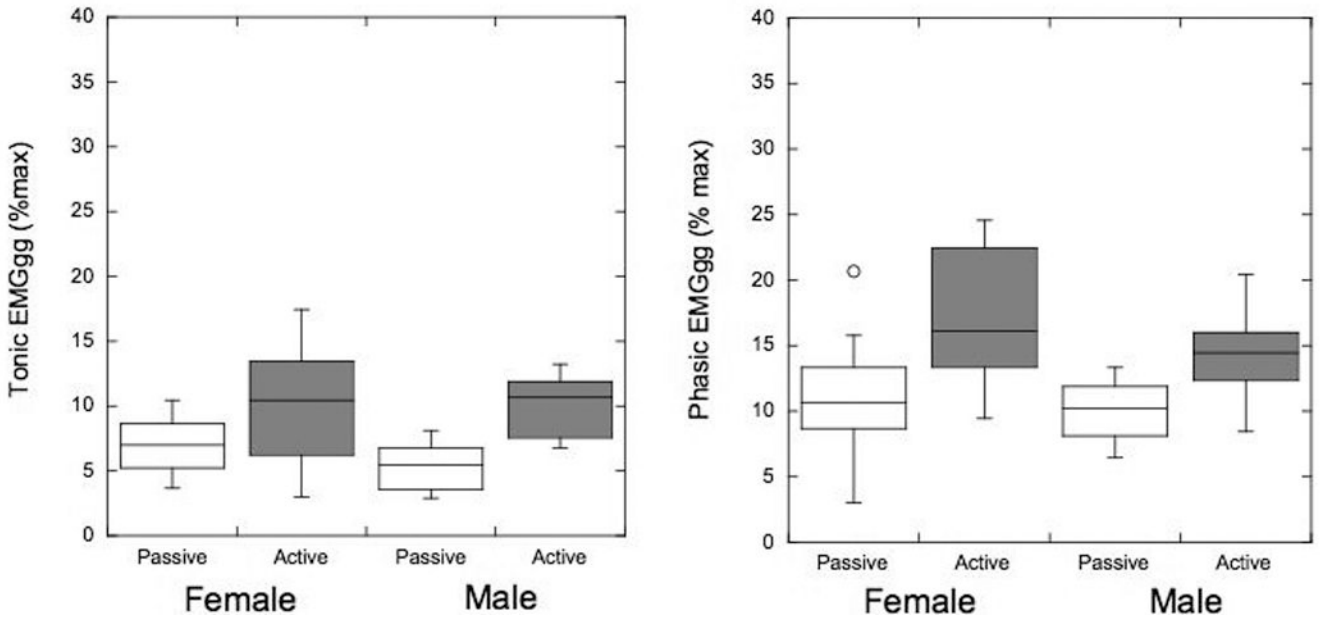

Figure 5.

The mean data in passive and active critical closing pressure (P_{CRIT}) in men (squares) and women (circles) subjects are shown in Figure 5. There is a significant difference between active P_{CRIT} and passive P_{CRIT} values ($p<0.05$).

Table 1

Subject Demographics

	Men	Women	P value
Age (years)	24.2±3.7	23.5±2.1	n.s.
Height (m)	64.4±6.4	49.9±5.5	<0.001
Weight (kg)	1.7±0.1	1.6±0.1	<0.001
BMI (kg/m^2)	21.6±2.1	20.3±1.3	n.s.
Completed Time (minutes)	53.4±7.4	55.2±5.9	n.s.
Initial midazolam dose (mg)	4.8±0.5	3.9±0.4	<0.001
Total midazolam dose (mg)	6.2±0.7	5.0±0.5	<0.001
Mean midazolam dose (μg/kg/min)	1.83±0.23	1.82±0.17	n.s.
Passive BIS	53.4±4.3	51.5±4.6	n.s.
Active BIS	55.9±2.9	54.2±4.6	n.s.

BMI = Body Mass Index, BIS = Bispectral Index, n.s. = not significant

Table 2

Table 2 A. Individual Upper Airway Collapsibility Values in Men (n=14)

	Passive			Active	
Subject ID	**P_{CRIT} (cm H_2O)**	**R_{US} (cm H_2O/L/s)**	**$\Delta P_{CRIT\ A\text{-}P}$ (cm H_2O)**	**P_{CRIT} (cm H_2O)**	**R_{US} (cm H_2O/L/s)**
A	−7.2	38.5	2.6	−9.8	54.3
B	−5.7	24.2	1.8	−7.5	32.9
C	1.2	21.7	4.1	−2.9	19.5
D	1.0	25.0	0.1	0.9	22.0
E	−6.3	21.4	2.3	−8.6	36.9
F	−0.6	68.5	1.5	−2.1	54.6
G	−2.7	15.9	0.3	−3.0	10.8
H	−10.6	21.2	5.0	−15.6	47.6
I	1.9	76.1	0.2	1.7	74.4
J	−7.9	31.4	1.8	−9.7	34.3
K	−6.0	25.7	0.8	−6.8	36.1
L	−3.8	12.3	1.9	−5.7	2.3
M	−2.0	34.9	5.7	−7.7	12.3
O	−4.7	13.4	2.6	−7.3	18.9
Mean (95%CI)	−3.8 (−5.9, −1.8)	30.7 (20.5, 41.0)	2.2 (1.2, 3.2)	−6.0 (−8.5, −3.5)	32.6 (21.2, 44.1)
SD	3.8	19.2	1.7	4.6	20.1

Table 2 B. Individual Upper Airway Collapsibility Values in Women (n=18)

	Passive			Active	
Subject ID	**P_{CRIT} (cm H_2O)**	**R_{US} (cm H_2O/L/s)**	**$\Delta P_{CRIT\ A-P}$ (cm H_2O)**	**P_{CRIT} (cm H_2O)**	**R_{US} (cm H_2O/L/s)**
a	−3.8	21.5	4.1	−7.8	17.8
b	−4.6	25.6	2.3	−6.9	19.5
c	−4.0	15.0	2.1	−6.11	16.0
d	−8.0	40.2	3.1	−11.1	38.5
e	−2.8	46.5	11.0	−13.8	80.6
f	−14.5	81.0	4.5	−19.0	90.0
g	−4.7	32.7	5.2	−9.9	64.8
h	−13.5	67.2	2.0	−15.5	58.2
i	−8.0	30.5	2.0	−10.0	28.0
j	−5.5	33.3	8.6	−14.1	28.7
k	−4.3	21.4	1.6	−5.9	19.8
l	−1.4	26.9	1.6	−3.0	40.7
m	−8.8	33.4	3.6	−12.4	36.9
n	−2.2	44.3	3.1	−5.3	36.4
o	−3.9	16.1	8.5	−12.4	28.0
p	−5.7	22.2	6.3	−12.0	24.9
q	−11.2	25.9	7.0	−18.3	22.3
r	−8.3	64.4	6.6	−14.9	41.1
Mean (95% CI)	−6.4 (−8.2 −4.6)	36.0 (27.0 45.0)	4.6 (3.2 6.0)	−11.0 (−13.2 −8.8)	38.5 (28.4 48.5)
SD	3.8	18.5	2.8	4.5	21.6

P_{CRIT} = critical closing pressure; R_{US} = upstream resistance; $\Delta P_{CRIT\ A-P}$ = difference between the active and passive P_{CRIT}; 95% CI= confidence interval, SD = standard deviation