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# Effects of selective hypoglossal nerve stimulation on canine upper airway mechanics

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**Yoo, Paul B., and Dominique M. Durand.** Effects of selective hypoglossal nerve stimulation on canine upper airway mechanics. *J Appl Physiol* 99: 937–943, 2005. First published April 14, 2005; doi:10.1152/jappphysiol.00652.2004.—Electrical stimulation of the hypoglossal (XII) nerve has been demonstrated as an effective approach to treating obstructive sleep apnea. The physiological effects of conventional modes of stimulation (i.e., genioglossus activation or whole XII nerve stimulation), however, have yielded inconsistent and only partial alleviations of hypopneic or apneic events. Although selective stimulation of the multifasciculated XII nerve offers many stimulus options, it is not clear how these will functionally affect the upper airway (UAW). To study these effects, animal experiments in eight beagles were performed to investigate changes in the UAW resistance and critical pressure during simulated expiration ( $n = 4$ ) and inspiration ( $n = 4$ ). During expiration, nonselective XII nerve stimulation yielded the greatest improvement in UAW resistance ( $-0.66 \pm 0.11 \text{ cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{min}^{-1}$ ), compared with that for selective activation of the genioglossus ( $-0.29 \pm 0.09 \text{ cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{min}^{-1}$ ), genioglossus ( $-0.31 \pm 0.12 \text{ cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{min}^{-1}$ ), and hyoglossus/styloglossus ( $0.37 \pm 0.06 \text{ cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{min}^{-1}$ ) muscles. For simulated inspiration, on the other hand, only whole XII nerve stimulation ( $-0.9 \pm 0.4 \text{ cmH}_2\text{O}$ ) and coactivation of the genioglossus + hyoglossus/styloglossus muscles ( $-1.18 \pm 0.6 \text{ cmH}_2\text{O}$ ) produced significant ( $P < 0.05$ ) improvements in UAW stability (i.e., lowered critical pressure), compared with baseline ( $-0.52 \pm 0.32 \text{ cmH}_2\text{O}$ ). The results of this study suggest that a multicontact nerve electrode can be used to achieve both UAW dilation and patency, comparable to that obtained with nonselective stimulation, by selectively activating the various branches of the XII nerve.

critical pressure; upper airway resistance; flat interface nerve electrode; obstructive sleep apnea; functional electrical stimulation

CERTAIN ANATOMICAL CHARACTERISTICS of the human upper airway (UAW) are thought to indicate a predisposition to obstructive sleep apnea (OSA). These include increased pharyngeal wall thickness, enlargement of the tongue, and retroposition of the mandible and/or hyoid bone (10, 26). For individuals with OSA, the repeated nocturnal episodes of UAW narrowing and occlusion result in microarousals that are linked to excessive daytime sleepiness. Aside from the increased risk for automobile accidents related to excessive daytime sleepiness, such individuals also exhibit a greater likelihood for developing more serious long-term pathological sequelae: hypertension, right-sided heart failure, arrhythmia, and stroke (13, 30, 40). The socioeconomic significance of OSA is further underscored by the number (estimated 4% of adults in the US) of individuals identified with this often undiagnosed medical condition (45).

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Although there are numerous options for treating OSA such as invasive surgery (e.g., uvulopalatopharyngoplasty) or oral appliances (9, 12), the most effective treatment involves the application of continuous positive airway pressure (CPAP) to the entire UAW, where the intraluminal pressure along this tube is maintained above the critical pressure (Pcrit) at which airway narrowing and flow limitation occurs (6). Although patency is achieved regardless of the position and number of airflow-limiting sites (4, 23, 31), noncompliance has significantly limited the long-term efficacy of CPAP.

Electrical stimulation of the hypoglossal (XII) nerve has been investigated as an alternative mode of therapy to compensate for the increased airway collapsibility observed in OSA patients: diminished or insufficient nocturnal activity of UAW dilators (41, 42). As a result, activation of either the genioglossus (GG) or genioglossus (GH) muscles has been targeted to increase UAW caliber (18, 20, 34). In both animal and human experiments, results have shown significant improvements in UAW resistance (Ruaw) and stability (Pcrit) in response to electrical stimulation (1, 2, 5, 7, 14–16, 21, 28). Although long-term studies in OSA patients have demonstrated improvements in the apnea + hypopnea index (number of events per hour), there is a significant subpopulation of individuals exhibiting limited or unpredictable outcomes, which may also involve stimulation induced arousal (22, 29).

As described by Mu and Sanders (18–20), the canine XII nerve trunk yields a rather complex branching pattern that is characteristic of the diverse movements of each respective muscle: hyoid bone displacement (GH), tongue stiffening and protrusion (intrinsic muscles and GG), and also retraction [hyoglossus (HG) and styloglossus (SG)]. Previous work, however, has shown a consistent fascicular nerve pattern just proximal to this region of divergence, which is suitable for a flat interface nerve electrode (FINE) to selectively activate each innervated muscle (43). As such, there is an impetus to further investigate the effects of selective XII nerve activation on the UAW. This may include, for example, coactivation of the tongue protruder and retractor muscles or simply isolated activation of the GH, either of which have been shown to improve airway characteristics (3, 37, 39, 41).

This study investigated the effects of selectively activating the muscles innervated by the beagle XII nerve as a means of improving UAW caliber and stability: Ruaw and Pcrit, respectively. To account for both phases of respiration, our experimental setup simulated airflow in the 1) inspiratory and 2) expiratory directions. The measured responses to different stimuli were subsequently compared with a baseline (no stim-

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ulation) and statistically evaluated for significance. Finally, the feasibility of achieving functionally selective activation with a multicontact nerve cuff electrode (i.e., FINE) was determined.

**METHODS**

The effect of selective XII nerve stimulation on the canine UAW was investigated in eight supine adult beagles (10–13 kg; Fig. 1) that were initially injected with an intravenous bolus of 2.5% sodium thiopental (1 ml/kg). Anesthesia was maintained with ventilation (12–15 breaths/min) of 1–3% halothane plus 100% oxygen during surgery and later switched to bolus administrations of  $\alpha$ -chloralose (initial 60 mg/kg; supplemental 15 mg/kg) for the remainder of the experiment. Normal body temperature (38–39°C) was maintained, and the blood pressure was continuously monitored via a catheterized femoral artery. Single bolus injections of dexamethasone (0.5 ml/kg) were given to minimize UAW secretions. All animal care and experimental protocols were approved by the Institutional Animal Care and Use Committee of Case Western Reserve University.

**Surgical preparation.** With the head tilted  $\sim 45^\circ$  from the horizontal position, an incision was made along the midline of the submandibular area to provide access to one of the XII nerves and its distal branches (i.e., unilateral stimulation). The layer of mylohyoid muscle was carefully removed and the overlying fascia was bluntly dissected to expose the nerve and the innervated muscles (Fig. 2A): GH, GG, HG, and SG. A multicontact FINE was implanted just proximal to the branching point of the nerve, and single-contact cuff electrodes were placed on the distal nerve branches. Pairs of insulated stainless steel wires were then inserted into the body of each muscle to record electromyographic (EMG) signals via an alternating-current-coupled amplifier (Grass P511, Astromed). By applying monophasic current

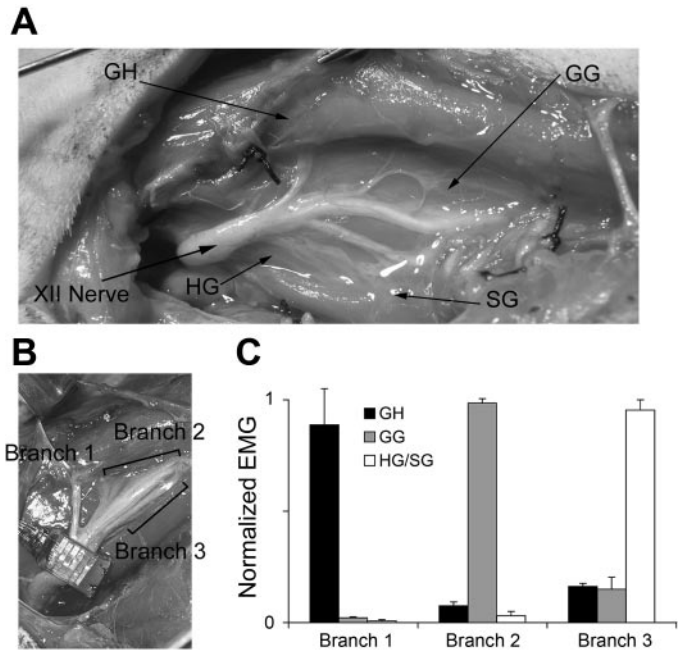


Fig. 2. A: canine XII nerve and innervated muscles are shown in geniohyoid (GH), genioglossus (GG), hyoglossus (HG), and the styloglossus (SG) muscles. In this image, the GH has been elevated to expose the neuromuscular anatomy. Note that the HG muscle is located underneath the nerve, whereas the GG is adjacent to the GH muscle. B: a flat interface nerve electrode (FINE) is implanted just proximal to the point divergence, where the functional branches are identified as branches 1, 2, and 3. C: normalized EMG response of the muscles as a result of electrically stimulating (monophasic cathodic pulses; PW = 50  $\mu$ s;  $f$  = 2 Hz;  $n$  = 16) each nerve branch. The averaged EMG signal was used for HG/SG.

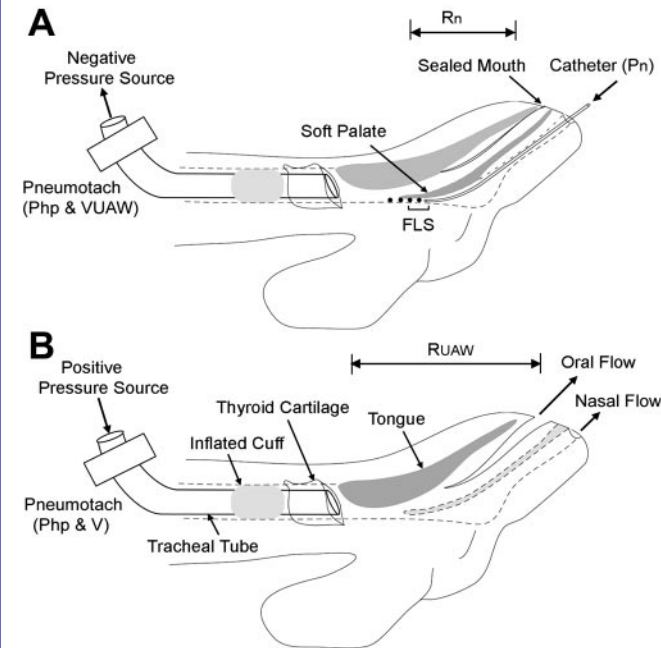


Fig. 1. Experimental setup of isolated beagle upper airway. A: a negative pressure source (rate of increase  $\approx -25$  cmH<sub>2</sub>O/s) was applied to generate a rostral-to-caudal flow (V) of air (inspiration). In this case, oral flow was occluded and a catheter was inserted through one nostril [at points along the upper airway (UAW) to measure the nasopharyngeal pressure (Pn) at the flow-limiting site (FLS)]. This recording point was generally  $\sim 2$ –3 cm upstream from the rim of the soft palate. B: a constant caudal-to-rostral flow (expiration; rate = 6 l/min) of air was applied to the isolated UAW. Measured changes in the hypopharyngeal pressure (Php) were used to characterize (Ruaw) the effects of selective hypoglossal (XII) nerve stimulation on the UAW. Rn, airflow resistance rostral to the FLS.

pulses to each branch (PW = 50  $\mu$ s;  $f$  = 2 Hz; and  $I$  = threshold–1 mA), the innervation pattern of the XII nerve was determined with the EMG recordings (gain = 1,000, BW = 10 Hz–10 kHz; sampling frequency = 40 kHz) of the muscles (Fig. 2C). However, to further confirm the functional innervation of these branches (43), tongue and mandibular movements were observed for pulse trains ( $I$  = 0.5–1 mA; PW = 50  $\mu$ s;  $f$  = 25 Hz) applied to each of the branches defined in Fig. 2B: superior-ventral movement of hyoid bone (GH), tongue stiffening and protrusion contralateral to the stimulating electrode (intrinsic muscles and GG), and tongue retraction with ipsilateral curling of the lateral aspect (HG/SG), respectively. Given the functional similarity and the small size of the nerve branches innervating the HG and SG, these were grouped as branch 3, and the average EMG activity of these muscles was defined as HG/SG (43). Finally, mineral oil was applied to the nerve and muscles to prevent desiccation.

A second incision was made along the ventral surface of the neck to expose and transect the cervical trachea,  $\sim 3$  cm caudal to the cricoid cartilage. Ventilation (e.g., surgical anesthesia) was maintained through the caudal stump of the trachea. A cuffed tracheal tube (Tracheofix, Rüschi) connected in series to a pneumotach (3700 series, Hans Rudolph) was inserted such that the tip was positioned at the level of the vocal folds (Fig. 1). By use of a pneumotach measurement system (RSS 100HR, Hans Rudolph), both the applied hypopharyngeal pressure (Php, positive or negative) and UAW flow rate (V) were measured and digitally archived (sampling = 50 Hz). The nasopharyngeal pressure (Pn) was also measured via a 56-cm-long polyethylene catheter (2.7-mm OD, two side holes at tip) inserted through one nostril. To ensure proper Pcrit measurement, the Pn was measured at 0.5-cm intervals beginning at the rim of the soft palate. The point at which Pn exhibited flow limitation was defined as the flow-limiting

site (FLS; Fig. 1A). This generally resulted in the catheter tip being positioned ~2–3 cm rostral to the point of original measurement.

**Negative pressure: inspiration.** The first set of experiments determined the effects of selective XII nerve stimulation on the stability of the UAW. This was characterized by a Pcrit: the nasopharyngeal pressure at which the UAW becomes unstable and flow limited, regardless of increased inspiratory drive. As a negative pressure source was applied to the caudal end of the isolated UAW, the Php, V, and Pn were simultaneously measured (Fig. 1A). The position of the inserted polyethylene tube was adjusted such that flow limitation was reflected in the measured Pn (3, 28). It is noted that these inspiratory measurements were obtained with only nasal flow, which was achieved by suturing the mouth and forming a tight seal with epoxy. Furthermore, the potentially detrimental effects of complete tongue relapse and epiglottal UAW occlusion were prevented by 1) loosely suturing the tongue to the upper lip and 2) tying a suture through the ventral side of the epiglottis and looping it around the incisors.

The effects of electrical stimulation on Pcrit were studied according to the following protocol: 1) acquire pressure and flow measurements using the pneumotach system; 2) apply continuous stimulation; 3) decrease the negative pressure source (rate ≈ 50 cmH<sub>2</sub>O in 2 s) at the caudal end of the isolated UAW. Each stimulation protocol was repeated three times for various modes of stimulation: individual branches (*branches 1–3*); paired branches (*branches 1 and 2, 1 and 3, and 2 and 3*); and whole XII nerve. The measured pressure (Pn), maximum airflow (V<sub>max</sub>), and resistance (Rn) at flow limitation were related as follows (27):

$$R_n = \frac{P_{atm} - P_{crit} \text{ (cmH}_2\text{O)}}{V_{max} \text{ (l/min)}}$$

where Rn denotes the airflow resistance rostral to the FLS (Fig. 1B) and Patm is atmospheric pressure.

**Positive pressure: expiration.** The next set of experiments investigated the effects of selective XII nerve stimulation on the Ruaw during expiration, which was achieved by applying a source of constant airflow (6 l/min; caudal-to-rostral direction) to the caudal end of the isolated upper airway (Fig. 1B). Using this constant hypopharyngeal pressure (Php) as baseline, changes in Php were measured as trains of stimuli (*I* = supramaximal; *f* = 25 Hz; *PW* = 50 μs) were applied through 1) each XII nerve branch and 2) each contact of the FINE. The resulting changes in Ruaw for each mode of stimulation were compared with that for the whole XII nerve (nonselective). This resistance was defined as the change in pressure along the UAW with respect to the rate of airflow:

$$R_{uaw} = \frac{P_{hp} - P_{atm} \text{ (cmH}_2\text{O)}}{V \text{ (l/min)}}$$

where Ruaw is the resistance to airflow (cmH<sub>2</sub>O · l<sup>-1</sup> · min<sup>-1</sup>).

It is noted that, in addition to mapping the innervation pattern of the XII nerve, EMG signals were recorded for current pulses delivered through each contact of the FINE. The objective of this was to identify the stimulating contacts of the FINE that were selective for each muscle innervated by this nerve.

**Statistical analysis.** The statistical significance of the effects of activating the various nerve branch combinations was initially by using a two-way ANOVA and subsequently followed with pairwise Tukey's tests (Minitab). Analysis was performed at a *P* < 0.05 significance level for each comparison.

## RESULTS

The effects of selective XII nerve stimulation were investigated for both modes of respiration by 1) measuring variations in UAW stability for rostral-to-caudal airflow (*n* = 4) and 2) calculating the changes in UAW caliber during caudal-to-

rostral airflow (*n* = 4). The functional significance of each mode of stimulation was statistically analyzed.

**Inspiratory airflow (UAW stability).** The first series of experiments investigated the influence of selective XII nerve activation on the mechanical stability of the canine UAW during simulated inspiration. In addition to Php and V, the Pn was measured to determine the Pcrit at which flow limitation occurs. The position of the nasal catheter tip used to measure this pressure was determined by comparing Php with the Pn at several positions along the UAW. The point at which Pn did not directly follow Php (i.e., flow limitation) indicated the target location and generally corresponded to ~2–3 cm rostral to the rim of the soft palate. It is important to note that the placement of the catheter tip, in addition to intra-animal variations of the UAW, significantly affected pressure measurements.

The baseline response to a negative pressure applied to the caudal stump of the trachea resulted in flow limitation, as indicated by the flow and pressure measurements below Php = -16 cmH<sub>2</sub>O (Fig. 3A). In this particular example, both the Pcrit and V<sub>max</sub> occurred at -1.2 cmH<sub>2</sub>O and 4.7 l/min, respectively. In comparison, coactivation of *branches 2 and 3* (GG + HG/SG) resulted in a marked improvement in UAW stability: flow limitation occurred at a lower Pcrit = -2.4

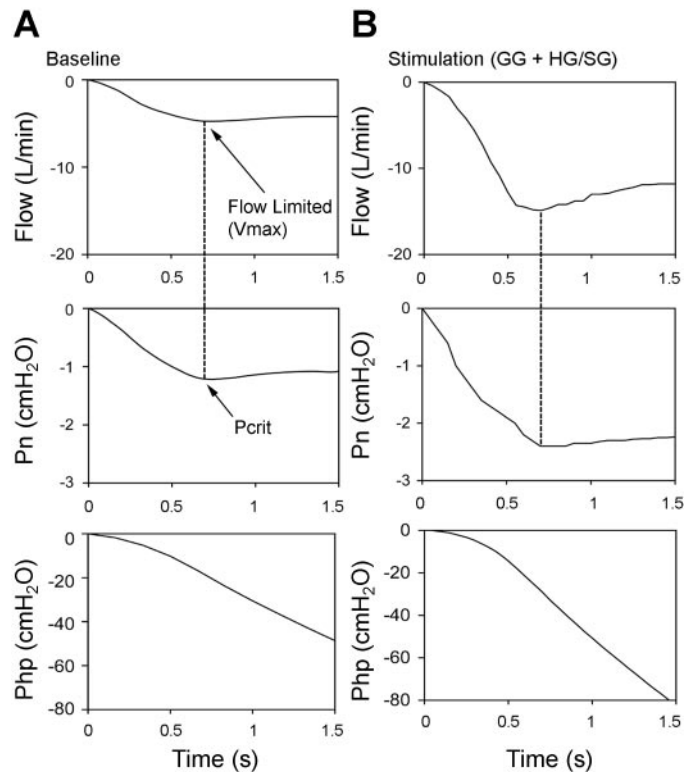


Fig. 3. Sample data set of the measured nasopharyngeal pressure (Pn) and flow (i.e., rostral-to-caudal) as a vacuum source was applied (rate ≈ -25 cmH<sub>2</sub>O/s) to an isolated canine UAW (refer to Fig. 1A). A: baseline (no stimulation) response of the UAW as the negative pressure source is applied: flow limitation occurs as Php falls below -16 cmH<sub>2</sub>O. The Pn and flow that correspond to this event are defined as critical pressure (Pcrit; -1.2 cmH<sub>2</sub>O) and maximal airflow (V<sub>max</sub>; 4.7 l/min), respectively. B: effect of selective XII nerve stimulation (i.e., coactivation of *branches 2 and 3*) on the UAW: observed changes in measured Pcrit (-2.4 cmH<sub>2</sub>O) and V<sub>max</sub> (13.4 l/min) as Php drops below -21 cmH<sub>2</sub>O.

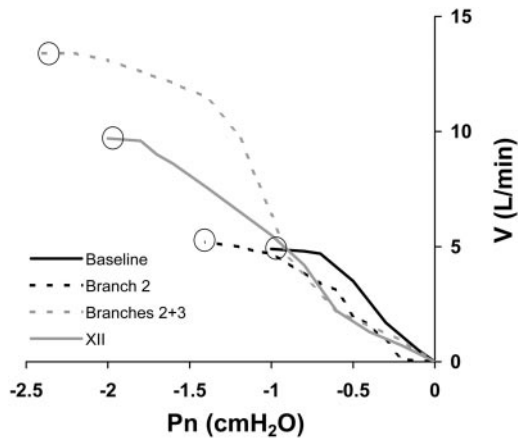


Fig. 4. Effect of selective XII nerve stimulation on measured Pn (abscissa) and inspiratory flow (V; ordinate). The point of flow limitation is indicated by the circles where the corresponding pressure and flow (Pcrit and V<sub>max</sub>) for baseline, *branch 2*, *branches 2 + 3*, and whole nerve (XII) stimulation are  $-1.2$  cmH<sub>2</sub>O, 4.7 l/min;  $-1.6$  cmH<sub>2</sub>O, 5.5 l/min;  $-2.0$  cmH<sub>2</sub>O, 9.7 l/min; and  $-2.4$  cmH<sub>2</sub>O, 13.4 l/min, respectively.

cmH<sub>2</sub>O (Fig. 3B). The effects of this particular mode of stimulation were reflected both in the lower P<sub>hp</sub> ( $-21$  cmH<sub>2</sub>O) and the observed increase in V<sub>max</sub> = 13.4 l/min. A closer look at the effects of selective stimulation on the UAW is shown in Fig. 4. In this example from a single experiment, the measured V was plotted as a function of Pn, which is shown up to maximum flow (Pcrit). Although there is a modest decrease in Pcrit (with respect to baseline) during activation of *branch 2* (GG), concomitant activation of the tongue retractor muscles (*branches 2 + 3*) and also the GH (whole XII nerve) yield significantly larger negative shifts in the Pcrit.

Overall, statistically significant ( $P < 0.05$ ) improvements in UAW stability were observed for only two cases: 1) coactivation of *branches 2 + 3* and 2) whole XII nerve activation. In both of these modes of stimulation, changes in both Pcrit and V<sub>max</sub> were measured (Fig. 5), whereas the UAW was not affected otherwise. The inspiratory Ruaw also exhibited significant changes ( $P < 0.05$ ) in response to selective stimu-

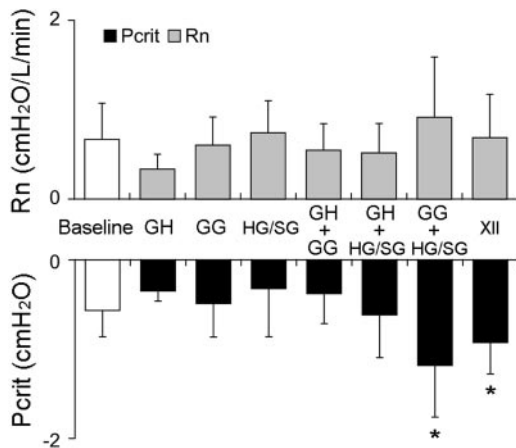


Fig. 5. Effects of selective stimulation on UAW stability were characterized by changes in Rn and Pcrit. Rn was not affected by stimulation, whereas statistically significant improvements in Pcrit ( $n = 4$ ) were observed for only coactivation of *branches 2 and 3* and whole XII nerve stimulation.  $*P < 0.05$  significance compared with baseline.

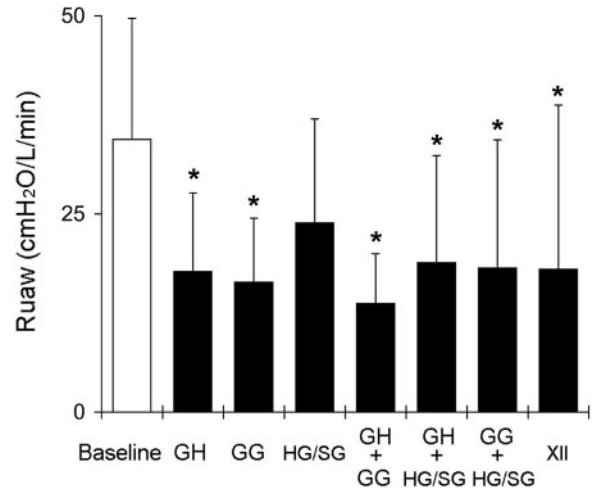


Fig. 6. Effects of selective stimulation on UAW caliber ( $n = 4$ ) were characterized by the change in Ruaw. The results show that all modes of stimulation produce a significant reduction in Ruaw, except for selective stimulation of *branch 3*.  $*P < 0.05$  significance compared with baseline.

lation (Fig. 6): all modes reduced Ruaw except for *branch 3*. In contrast, Fig. 6 shows that electrical stimulation did not have any effect on the nasopharyngeal resistance (Rn; defined in Fig. 1A).

**Expiratory airflow (UAW caliber).** The objective of this next series of experiments was to study the effects of stimulating each canine XII nerve branch during simulated expiration. On the basis of the innervation pattern of the XII nerve using EMG recordings, trains of stimulus pulses were delivered through each branch. Changes in the overall Ruaw were computed for each mode of stimulation: individual *branches 1–3* and whole nerve (XII). The mean (SD) responses to stimulation are shown in Fig. 7 and indicate that only *branch 3* increased Ruaw ( $0.37 \pm 0.06$  cmH<sub>2</sub>O·l<sup>-1</sup>·min<sup>-1</sup>), whereas activation of *branches 1 and 2* and XII reduced the Ruaw:  $-0.29 \pm 0.09$ ;  $-0.31 \pm 0.12$ ; and  $-0.66 \pm 0.11$  cmH<sub>2</sub>O·l<sup>-1</sup>·min<sup>-1</sup>, respectively. Interestingly, the results indicate that electrical stimulation of the whole XII nerve yielded a significantly greater increase in UAW caliber than either selective GH or GG stimulation.

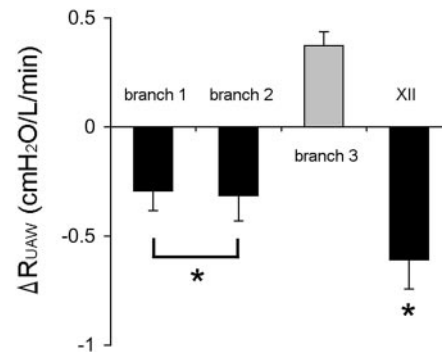


Fig. 7. Effects of XII nerve stimulation on the UAW resistance of the isolated canine UAW ( $n = 4$ ) during simulated expiration. Selective stimulation of *branches 1, 2, and 3* yielded changes ( $\Delta$ ) in Ruaw. This is compared with the response in Ruaw for whole nerve (XII) stimulation (in cmH<sub>2</sub>O·l<sup>-1</sup>·min<sup>-1</sup>).  $*P < 0.005$  level.

Finally, the feasibility of selectively stimulating the XII nerve with a multicontact FINE was investigated in this series of experiments, where sample recruitment curves depicting the functional selectivity of this electrode are shown in Fig. 8. In this figure, the normalized EMG and Ruaw recordings were plotted for *contacts 4* and *12*, which were selective for the functionally opposite GG and HG/SG muscles, respectively. As evident in both the normalized EMG and Ruaw of Fig. 8A, *contact 4* was only selective up to  $I = 0.7$  mA, beyond which spillover occurred and the functional dynamics of the UAW were effectively reversed. *Contact 12*, on the other hand, was selective for the HG/SG muscles up to 1 mA.

## DISCUSSION

The isolated beagle UAW was used to test the hypothesis that selective stimulation of the XII nerve can improve respiratory flow mechanics, compared with nonselective activation of the whole nerve. With cuff electrodes implanted on each functionally identified XII nerve branch, the Pcrit, V, and Ruaw were initially measured and compared for simulated inspiratory airflow. The results of this part of the study revealed two important observations concerning the effects of electrical stimulation on the inherent collapsibility of the canine UAW: 1) selective activation of the GG muscle impairs UAW stability, whereas 2) coactivation of the GG + HG/SG muscles and nonselective whole nerve stimulation both decrease Pcrit. This coactivation of the tongue protruder and retractor muscles is particularly significant because this has only been reported in the isolated rodent UAW (3). In fact, it

is the synergistic effect of activating these functionally opposite muscles that is shown to be as effective in improving UAW stability as activation of only the GG or even the whole XII nerve (21, 22, 28).

Although the relatively short and flaccid soft palate make the beagle a rather good approximation to the human pharynx (11), these same characteristics also contribute to the anesthesia-induced increase in UAW collapsibility commonly observed in human subjects. As a consequence, selective GG muscle activation of this particular mammalian UAW model did not yield significant changes in Pcrit, as predicted by similar experimental studies (1, 22, 32). In fact, the comparatively diminished range of airflow during both baseline and electrical activation (1, 27, 28, 35) required the tongue to be loosely sutured to the upper lip to prevent complete occlusion of the UAW. This was in addition to efforts made to further minimize this inherent collapsibility: administration of dexamethasone, switching anesthetic agent from halothane to  $\alpha$ -chloralose, and reduced intravenous fluids. Nevertheless, our canine model is validated by the UAW responses to the applied negative P<sub>hp</sub> that indicated flow limitation (Fig. 5). Furthermore, our results confirm that tongue protrusion (GG activation) is necessary to improve UAW mechanics and that UAW patency can be achieved by stiffening the base of the tongue through concomitant activation of the tongue protruder and retractor muscles. It is difficult, however, to predict the most effective mode of stimulation without more detailed information regarding stimulation-induced changes in the tongue (e.g., conformational)

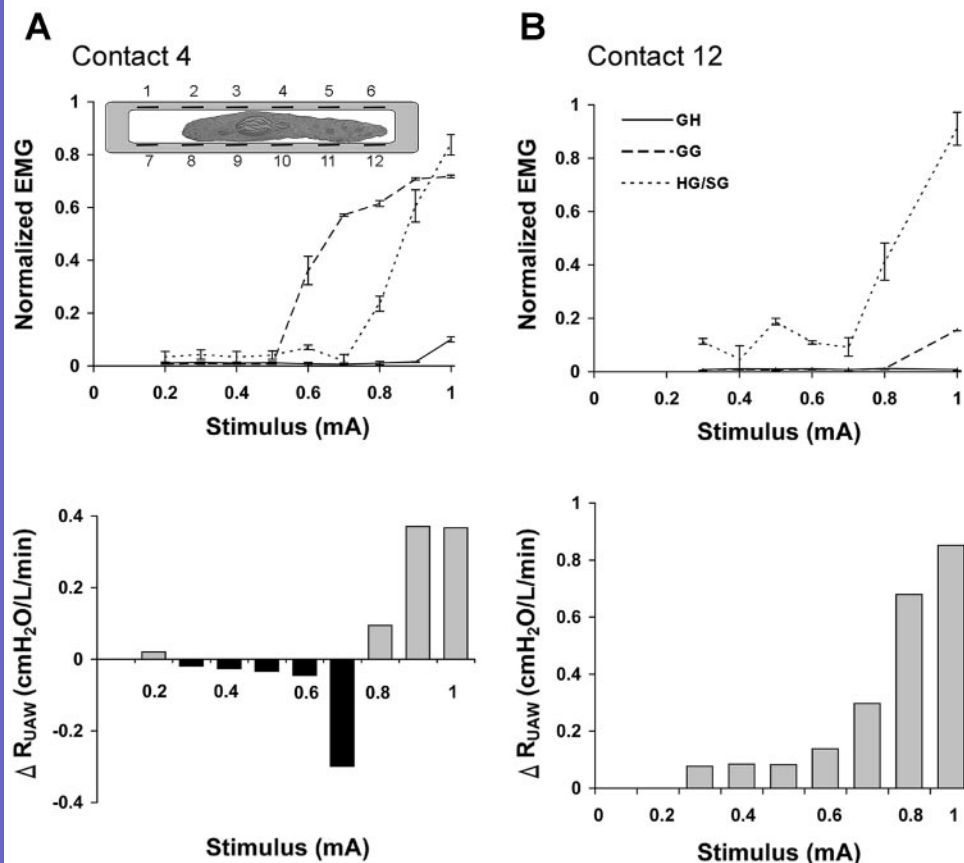


Fig. 8. Selective stimulation of the XII nerve with the FINE implanted on the canine XII nerve. *A*: electrical stimulation via *contact 4* shows selective recruitment of the medial XII nerve branch up to  $I = 0.7$  mA. This is indicated by both the normalized EMG response from the GG muscle and the corresponding decrease in Ruaw. At higher amplitudes, spillover into *branch 3* (HG/SG) resulted in an increase in resistance. *B*: selective activation of *branch 3*, via *contact 12*, is indicated by the normalized EMG response of HG/SG and the observed increase in Ruaw.



and the specific effects of this therapy on the flow-limiting sites within the UAW (8, 31).

It is clear that airway narrowing and collapse are inspiratory-related phenomena and that electrical stimulation during this phase of respiration is necessary and, to a certain extent, effective. However, there is compelling evidence suggesting that these obstructive mechanisms also occur during expiration. These include studies showing significant decreases in oropharyngeal caliber and flow limitation, particularly at end expiration (17, 25, 33). The therapeutic importance of expiratory UAW caliber is further underscored by the observed interaction between both modes of respiration on UAW patency (24).

As a result, the second part of this experiment involved Ruaw measurement during simulated expiratory airflow (caudal-to-rostral direction). As shown in Fig. 7, selective stimulation of the branches yielded changes in Ruaw that were related to the function of the innervated muscles, whereas whole nerve stimulation resulted in significantly larger increases in UAW caliber compared with that for either GH or GG activation. A closer examination of this nonselective mode of stimulation showed that the effects were quantitatively similar to the sum of the  $\Delta Ruaw$  for the GH and GG muscles, suggesting that the tongue retractor muscles became functionally negligible. It is clear from these results that nonselective XII nerve stimulation was most effective in increasing UAW caliber, regardless of mechanism (i.e., the result of a linear sum of the two UAW dilating muscles) or any other additional factors that may have affected the physiological outcome of stimulation: path of airflow, direction of tongue movement with respect to stimulation, and even species (1–3, 16, 21, 28).

In contrast, changes in the Ruaw during inspiratory flow did not indicate a dominant mode of stimulation. The results in Fig. 6 showed significant ( $P < 0.05$ ) decreases in the percent change in all cases, except for activation of the tongue retractor (HG/SG) muscles. The fact that different combinations of activation resulted in similar functional outcomes suggests that certain muscles are required to improve Ruaw: namely, the GG and GH muscles. Similar to that demonstrated for expiration, the effect of the tongue retractor (HG/SG) muscles was negligible when concomitantly activated with either the GH and GG muscles (compared to the selective activation of these UAW dilators). It is noted that Rn was not affected by any mode of stimulation, suggesting that activation of the XII nerve does not physically alter the nasopharynx nor does it elicit reflex contractions of the nasal passageway using this experimental setup (38).

As an extension to our main hypothesis, the ability of a single multicontact nerve cuff electrode to selectively alter the UAW mechanical properties was also investigated. In contrast to previous direct recordings of the neural and muscular responses (43), changes in the Ruaw were detected in this study to obtain a measure of functional selectivity. As presented in Fig. 8, electrical stimulation at each specified contact position of the FINE yielded gradual changes in Ruaw that were indicative of the functional aspect of the innervated muscle. The advantages of this particular implantable device for therapeutic use in OSA are 1) the shape of the XII nerve just proximal to the branching point is ideal for this flat-shaped electrode, 2) subfascicular selectivity can be achieved to activate different populations of fibers within the same fascicle,

and 3) it is feasible to record selectively from the same electrode to trigger electrical stimulation (44). The long-term safety of this electrode, particularly in humans, has not yet been demonstrated, and the potential for compression-induced neuropathy is a valid concern. However, evidence of safety based on functional and histological studies involving animals chronically implanted with the FINE has been provided (36). Although minimal anatomical and physiological changes were observed, further investigation of the long-term effects of the FINE and the potential benefits of optimal electrode design are warranted.

Electrical stimulation of the XII nerve has been shown to be effective as a therapeutic treatment for OSA patients (22). However, the observed physiological responses have been unpredictable as some patients exhibit little or no improvement (14, 29). The therapeutic realization of OSA is further confounded not only by the current lack of identification of the neuromuscular mechanisms responsible for the initiation of apneic or hypopneic events but also by factors such as 1) incomplete expiration (i.e., hypercapnia), 2) sleep stage, and 3) multiple flow-limiting sites that contribute to the persistence and even progressive worsening of such events throughout the night.

The results of this study show that electrical stimulation of the XII nerve can modulate the mechanical characteristics of an isolated canine UAW and that this can be achieved with a single implanted multicontact FINE. Both selective (i.e., individual branch) and nonselective modes of stimulation demonstrated significant increases in UAW caliber during simulated expiration, whereas UAW patency during inspiration was achieved via coactivation of *branches 2 + 3* and also through whole nerve stimulation. Although simplifying the clinical implementation of this technology (e.g., single-contact nerve electrode) may benefit the long-term reliability of the implanted device, the observed complex interactions among the muscles innervated by the XII nerve suggest that a higher degree of control may be required to 1) optimize specific activation levels and combinations of different muscle groups and 2) account for interpatient variations. As a result, further work into maximizing therapeutic efficacy of OSA could incorporate periodic stimulation trains that are synchronized with both the expiratory and inspiratory phases of respiration.

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