The Effects of Selective Hypoglossal Nerve Stimulation on Canine Upper Airway Mechanics

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Abstract

Electrical stimulation of the hypoglossal (XII) nerve has been demonstrated as an effective approach to treating obstructive sleep apnea (OSA). 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. While selective stimulation of the multi-fasciculated 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 ($R_{UAW}$) and critical pressure ($P_{crit}$), during simulated expiration ($n = 4$) and inspiration ($n = 4$).

During expiration, non-selective XII nerve stimulation yielded the greatest improvement in $R_{UAW}$ ($-0.66 \pm 0.11$ cmH$_2$O/L/min), compared to that for selective activation of the geniohyoid (GH; $-0.29 \pm 0.09$ cmH$_2$O/L/min), genioglossus (GG; $-0.31 \pm 0.12$ cmH$_2$O/L/min) and hyoglossus/styloglossus (HG/SG: $0.37 \pm 0.06$ cmH$_2$O/L/min) muscles. For simulated inspiration, on the other hand, only whole XII nerve stimulation ($-0.9 \pm 0.4$ cmH$_2$O) and co-activation of the GG + HG/SG muscles ($-1.18 \pm 0.6$ cmH$_2$O) produced significant ($p < 0.05$) improvements in UAW stability (i.e., lowered $P_{crit}$), compared to baseline ($-0.52 \pm 0.32$ cmH$_2$O). The results of this study suggest that a multi-contact nerve electrode can be used to achieve both UAW dilation and patency, comparable to that obtained with non-selective stimulation, by selectively activating the various branches of the XII nerve.

Keywords — critical pressure, upper airway resistance, flat interface nerve electrode, obstructive sleep apnea, functional electrical stimulation
Introduction

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 micro-arousals that are linked to excessive daytime sleepiness (EDS). Aside from the increased risk for automobile accidents related to EDS, such individuals also exhibit a greater likelihood for developing more serious long-term pathologic sequelae: hypertension, right-sided heart failure, arrhythmia and stroke [13, 30, 40]. The socioeconomic significance of OSA is further underscored by the number (est. 4% of adults in the US) of individuals identified with this often undiagnosed medical condition [45].

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 continuous application of positive pressure (CPAP) to the entire UAW, where the intraluminal pressure along this tube is maintained above the critical pressure \( P_{\text{crit}} \) at which airway narrowing and flow limitation occurs [6]. While patency is achieved regardless of the position and number of airflow limiting sites [4, 23, 31], non-compliance 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 geniohyoid (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 ($R_{UAW}$) and stability ($P_{crit}$) 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 (AHI; number of events per hour), there is a significant sub-population of individuals exhibiting limited or unpredictable outcomes, which may also involve stimulation induced arousal [22, 29].

As described by Mu et al. [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, co-activation of the tongue protrudor 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: $R_{UAW}$ and $P_{crit}$, respectively. In order 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 to a baseline (no stimulation) and statistically evaluated for significance. Finally, the feasibility of achieving functionally selective activation with a multi-contact 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; Figure 1) that were initially injected with an I.V. bolus of 2.5% sodium thiopental (1 ml/kg). Anesthesia was maintained with ventilation (12–15 bpm) of 1-3% halothane plus 100% oxygen during surgery and later switched to bolus administrations of α-chlorolose (initial 60 mg/kg; supplemental 15 mg/kg) for the remainder or the experiment. Normal body temperature (38–39 ºC) 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 approximately 45º 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 blunt dissected to expose the nerve and the innervated muscles (Figure 2(a)): geniohyoid (GH), genioglossus (GG), hyoglossus (HG) and styloglossus (SG). A multi-contact FINE was implanted just proximal to the branching point of the nerve, while 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 AC-coupled amplifier (Grass P511, Astromed Inc). By applying monophasic current pulses to each branch ($PW = 50 \mu s; f = 2 \text{ Hz};$ and $I = \text{threshold} – 1 \text{ mA}$), the innervation pattern of the XII nerve was determined with the EMG recordings (gain = 1000, $BW$
= 10 Hz – 10 kHz; sampling frequency = 40 kHz) of the muscles (Figure 2(c)). However, to
further confirm the functional innervation of these branches [43], tongue or mandibular
movements were observed for pulse trains ($I = 0.5 – 1$ mA; $PW = 50$ µs; $f = 25$ Hz) applied to
each of the branches defined in Figure 2(b): 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, approximately 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, Rüsch Inc.) connected in series to a pneumotach (3700 series, Hans Rudolph Inc.)
was inserted such that the tip was positioned at the level of the vocal folds (Figure 1). Using a
pneumotach measurement system (RSS 100HR, Hans Rudolph Inc.), both the applied
hypopharyngeal pressure ($P_{hp}$, positive or negative) and UAW flow rate ($V$) were measured and
digitally archived (sampling = 50 Hz). The nasopharyngeal pressure ($P_n$) was also measured via a
56 cm-long PE catheter (2.7 mm OD, two side holes at tip) inserted through one nostril. To
ensure proper $P_{crit}$ measurement, the $P_n$ was measured at 0.5 cm intervals beginning at the rim of
the soft palate. The point at which $P_n$ exhibited flow-limitation was defined as the flow limiting
site (FLS; figure 1(a)). 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 critical pressure ($P_{\text{crit}}$): 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 $P_{\text{hp}}$, $V$ and $P_n$ were simultaneously measured (figure 1(a)). The position of the inserted PE tube was adjusted such that flow-limitation was reflected in the measured $P_n$ [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 (a) loosely suturing the tongue to the upper lip and (b) tying a suture through the ventral side of the epiglottis and looping it around the incisors.

The effects of electrical stimulation on $P_{\text{crit}}$ were studied according to the following protocol: (a) acquire pressure and flow measurements using the pneumotach system; (b) apply continuous stimulation; (c) decrease the negative pressure source (rate $\approx 50$ cmH$_2$O in 2 seconds) 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&2, 1&3 and 2&3); and whole XII nerve. The measured pressure ($P_n$), maximum airflow ($V_{\text{max}}$) and resistance ($R_n$) at flow limitation was related as follows [27]:

$$R_n = \frac{P_{\text{atm}} - P_{\text{crit}} \ [\text{cmH}_2\text{O}] }{V_{\text{max}} \ [\text{L/min}]}$$

(2)

where, $R_n$ denotes the airflow resistance rostral to the FLS (figure 1(b)).
Positive Pressure – Expiration

The next set of experiments investigated the effects of selective XII nerve stimulation on the UAW resistance 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 (Figure 1(b)). Using this constant hypopharyngeal pressure (P_{hp}) as baseline, changes in P_{hp} were measured as trains of stimuli (I = supra-maximal; \( f = 25 \) Hz; \( PW = 50 \) µs) were applied through (a) each XII nerve branch and (b) each contact of the FINE. The resulting changes in UAW resistance for each mode of stimulation were compared to that for the whole XII nerve (non-selective). This resistance was defined as the change in pressure along the UAW with respect to the rate of airflow:

\[
R_{UAW} = \frac{P_{hp} - P_{atm}}{V} \quad \text{[cmH}_2\text{O/L/min]} 
\]

where, \( R_{UAW} \) is the resistance to airflow [cmH\(_2\)O/L/min] and \( P_{atm} \) is atmospheric pressure.

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 determined using a two-way ANOVA and subsequently followed with pair-wise tukey tests (Minitab, Minitab Inc.). 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 statistical 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 \( P_{hp} \) and \( V \), the nasopharyngeal pressure \( (P_n) \) was measured to determine the critical pressure \( (P_{crit}) \) at which flow-limitation occurs. The position of the nasal catheter tip used to measure this pressure was determined by comparing \( P_{hp} \) with the \( P_n \) at several positions along the UAW. The point at which \( P_n \) did not directly follow \( P_{hp} \) (i.e., flow limitation) indicated the target location and generally corresponded to approximately 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. As a result, the effects of electrical stimulation were quantified as a percent change with respect to baseline.

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 \( P_{hp} = -16 \) cmH\(_2\)O (figure 3(a)). In this particular example, both the critical pressure and maximal flow occurred at -1.2 cmH\(_2\)O and \( V_{max} = 4.7 \) L/min, respectively. In comparison, co-activation of branches 2 and 3 \((GG + HG/SG)\) resulted in a marked improvement in UAW stability: flow-limitation occurred at a lower \( P_{crit} = -2.4 \) cmH\(_2\)O (figure 3(b)). The effects of this particular mode of stimulation were reflected both in the lower \( P_{hp} \) (-21 cmH\(_2\)O) and the observed increase in
$V_{\text{max}} = 13.4$ L/min. A closer look at the effects of selective stimulation on the UAW is shown in figure 4. In this example from a single experiment, the measured flow ($V$) was plotted as a function of $P_n$, which is shown up to maximum flow ($P_{\text{crit}}$). While there is a modest decrease in $P_{\text{crit}}$ (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 critical pressure.

Overall, statistically significant ($p < 0.05$) improvements in UAW stability were observed for only two cases: (a) co-activation of branches 2+3 and (b) whole XII nerve activation. In both of these modes of stimulation, changes in both $P_{\text{crit}}$ and $V_{\text{max}}$ were measured (figure 5), while the UAW was not affected otherwise. The inspiratory UAW resistance ($R_{\text{UAW}}$) also exhibited significant changes ($p < 0.05$) in response to selective stimulation (figure 6): all modes reduced $R_{\text{UAW}}$ except for branch 3. In contrast, Figure 6 shows that electrical stimulation did not have any effect on the nasopharyngeal resistance ($R_n$; defined in Figure 1(a)).

**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. Based on the innervation pattern of the XII nerve using EMG recordings, trains of stimulus pulses were delivered through each branch. Changes in the overall resistance of the UAW ($R_{\text{UAW}}$) were computed for each mode of stimulation: individual branches 1~3 and whole nerve (XII). The mean ($\pm$ SD) responses to stimulation are shown in figure 7 and indicate that only branch 3 increased UAW resistance ($0.37 \pm 0.06$ cmH$_2$O/L/min), while activation of branches 1, 2 and XII reduced the $R_{\text{UAW}}$: $-0.29 \pm 0.09$; $-0.31 \pm 0.12$; and $-0.66 \pm 0.11$ cmH$_2$O/L/min, 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.

Finally, the feasibility of selectively stimulating the XII nerve with a multi-contact FINE was investigated in this series of experiments, where sample recruitment curves depicting the functional selectivity of this electrode is shown in figure 8. In this figure, the normalized EMG and $R_{UAW}$ 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 $R_{UAW}$ of figure 8(a), contact 4 was only selective up to $I = 0.7 \text{ mA}$, 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.
The isolated beagle UAW was used to test the hypothesis that selective stimulation of the XII nerve can improve respiratory flow mechanics, compared to non-selective activation of the whole nerve. With cuff electrodes implanted on each functionally identified XII nerve branch, the critical pressure ($P_{\text{crit}}$), flow rate ($V$) and airway resistance ($R_{\text{UAW}}$) 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: (a) selective activation of the GH muscle impairs UAW stability, while (b) co-activation of the GG + HG/SG muscles and non-selective whole nerve stimulation both decrease $P_{\text{crit}}$. This co-activation of the tongue protrudor and retractor muscles is particularly significant, as 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 $P_{\text{crit}}$, 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 I.V. fluids. Nevertheless, our canine model is validated by the UAW responses to the applied negative hypopharyngeal pressures ($P_{hp}$) that indicated flow limitation (figure 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) 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 electrical stimulation during this phase of respiration is necessary and, to a certain extent, effective. However, there is compelling evidence that suggest 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 UAW resistance measurement during simulated expiratory airflow (caudal-to-rostral direction). As shown in Figure 7, selective stimulation of the branches yielded changes in UAW resistance that were related to the function of the innervated muscles, while whole nerve stimulation resulted in significantly larger increases in UAW caliber compared to that for either GH or GG activation. A closer examination of this non-selective mode of stimulation showed that the effects were quantitatively similar to the sum of the $\Delta R_{UAW}$ for the GH and GG muscles, suggesting that the tongue retractor muscles became functionally negligible. It is clear from these results, that non-selective 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 UAW resistance ($R_{UAW}$) during inspiratory flow did not indicate a dominant mode of stimulation. The results in Figure 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 UAW resistance: 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 $R_n$ 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 multi-contact 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 UAW resistance were detected in this study to obtain a measure of functional selectivity. As presented in figure 8, electrical stimulation at each specified contact position of the FINE yielded gradual changes in $R_{UAW}$ that were indicative of the functional aspect of the innervated muscle. The advantages of this particular implantable device for therapeutic use in OSA are (a) the shape of the XII nerve just proximal to the branching point is ideal for this flat-shaped electrode, (b) sub-
fascicular selectivity can be achieved to activate different populations of fibers within the same fascicle and (c) 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 identifying the neuromuscular mechanisms responsible for the initiation of apneic or hypopneic events, but also by factors such as (a) incomplete expiration (i.e., hypercapnia) (b) sleep stage and (c) 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 multi-contact FINE. Both selective (i.e., individual branch) and non-selective modes of stimulation demonstrated significant increases in UAW caliber during simulated expiration, while UAW patency during inspiration was achieved via co-activation of branches 2+3 and also through whole nerve stimulation. While 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 a higher degree of control may be required to (a) optimize specific activation levels and combinations of different muscle groups and (b) account for inter-patient 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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References


Figure 1 Experimental setup of isolated beagle upper airway. (a) A negative pressure source (rate of increase $\approx -25$ cmH$_2$O/s) was applied to generate a rostral-to-caudal flow of air (inspiration). In this case, oral flow was occluded and a catheter was inserted through one nostril (at points along the UAW) to measure the nasopharyngeal pressure ($P_n$), at the flow limiting site (FLS). This recording point was generally 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 ($P_{hp}$) were used to characterize ($R_{UAW}$) the effects of selective XII nerve stimulation on the UAW.
Figure 2 The canine XII nerve and the innervated muscles are shown in (a): 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, while the GG is adjacent to the GH muscle. (b) A 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 μs; f = 2 Hz; n = 16) each nerve branch. The averaged EMG signal was used for HG/SG.
Figure 3 Sample data set of the measured nasal pressure ($P_n$) and flow (i.e., rostral-to-caudal) as a vacuum source was applied (rate $\approx -25$ cmH$_2$O/s) to an isolated canine UAW (refer to figure 1(a)). (a) The baseline (no stimulation) response of the UAW as the negative pressure source is applied: flow limitation occurs as $P_{hp}$ falls below -16 cmH$_2$O. The $P_n$ and flow that correspond to this event are defined as $P_{crit}$ (-1.2 cmH$_2$O) and $V_{max}$ (4.7 L/min), respectively. (b) The effect of selective XII nerve stimulation (i.e., co-activation of branches 2 and 3) on the UAW: observed changes in measured $P_{crit}$ (-2.4 cmH$_2$O) and $V_{max}$ (13.4 L/min) as $P_{hp}$ drops below -21 cmH$_2$O.
Figure 4: Effect of selective XII nerve stimulation on measured nasopharyngeal pressure ($P_n$; abscissa) and inspiratory flow ($V$; ordinate). The point of flow-limitation is indicated by the circles where the corresponding pressure and flow ($P_{\text{crit}}$ and $V_{\text{max}}$) for baseline, branch 2, branches 2+3 and whole nerve (XII) stimulation are (a) -1.2 cmH$_2$O; 4.7 L/min, (b) -1.6 cmH$_2$O; 5.5 L/min, (c) -2.0 cmH$_2$O; 9.7 L/min and (d) -2.4 cmH$_2$O; 13.4 L/min, respectively.
Figure 5. The effects of selective stimulation on UAW stability were characterized by changes in $R_n$ and $P_{crit}$. Nasal resistance was not affected by stimulation, while statistically significant improvements in critical pressures ($n = 4$) were observed for only co-activation of branches 2&3 and whole XII nerve stimulation. Asterisk indicates $p < 0.05$ significance compared to baseline.
Figure 6. The effects of selective stimulation on UAW caliber ($n = 4$) were characterized by the change in $R_{UAW}$. The results show that all modes of stimulation produce a significant reduction in $R_{UAW}$, except for selective stimulation of branch 3. Asterisk indicates $p < 0.05$ significance compared to baseline.
Figure 7 The 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 in $\Delta R_{UAW}$ (mean ± SD). This is compared to the response in $R_{UAW}$ for whole nerve (XII) stimulation: cmH$_2$O/L/min. Asterisk indicates $p < 0.005$ level.
Figure 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 $R_{UAW}$. 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 $R_{UAW}$. 