

Closed-Loop Stimulation of Hypoglossal Nerve in a Dog Model of Upper Airway Obstruction

Mesut Sahin*, *Member, IEEE*, Dominique M. Durand, *Member, IEEE*, and Musa A. Haxhiu

Abstract—Electrical stimulation of upper airway (UAW) muscles has been under investigation as a treatment method for obstructive sleep apnea (OSA). Particular attention has been given to the electrical activation of the genioglossal muscle, either directly or via the stimulation of the hypoglossal nerve (HG), since the genioglossus is the main tongue protruder muscle. Regardless of the stimulation site or method, an implantable electrical stimulation device for OSA patients will require a reliable method for detection of obstructive breaths to apply the stimulation when needed. In this paper, we test the hypothesis that the activity of the HG nerve can be used as a feedback signal for closed-loop stimulation of the HG nerve in an animal model of UAW obstruction where a force is applied on the submental region to physically narrow the airways. As an advantage, the method uses a single electrode for both recording and stimulation of the HG nerve. Simple linear filtering techniques were found to be adequate for producing the trigger signal for the electrical stimulation from the HG recordings. Esophageal pressure, which was used to estimate the size of the UAW passage, returned to the preloading values during closed-loop stimulation of the HG nerve. The data demonstrate the feasibility of the closed-loop stimulation of the HG nerve using its activity as the feedback signal.

Index Terms—Chronic nerve recording, closed-loop functional electrical stimulation, obstructive sleep apnea, upper airway loading.

I. INTRODUCTION

OBSTRUCTIVE sleep apnea (OSA) is characterized by occlusions of upper airways (UAW's) during sleep. The genioglossus muscle (GG), which is innervated by the hypoglossal (HG) nerve, plays an important role in the patency of UAW's since its main function is to protrude the tongue. A number of attempts have been made to demonstrate that direct electrical stimulation of either the GG muscle [1]–[3] or the HG nerve [3]–[7] can improve the UAW patency in humans during sleep. Electrical stimulation of GG muscle using submental electrodes has also been investigated [4], [8]–[11]. Stimulation of other UAW dilator muscles, geniohyoid, sternohyoid, and sternothyroid, did not result in significant changes in the pharyngeal re-

sistance that was raised with an application of external pressure to the submental hyoid region in awake humans [1].

Regardless of the stimulation site or strategy, it is evident that an implantable electrical stimulation device for OSA patients will require a reliable method for detection of obstructions that lends itself to chronic applications. To our knowledge, such a method has not been reported yet. Various physiological variables have been used to synchronize the electrical stimulation with respiration in the acute trials. Among those are the hypopharyngeal or esophageal pressure measurements [2], [5] and airflow measurements with thermistors placed near the nose and mouth [9] in humans, and tracheal inter-ring distance measurements with a strain gauge [6] in dogs.

In this paper, we investigated the possibility of using the HG nerve activity for detection of UAW obstructions and controlling the electrical stimulation applied to the same nerve for removal of the obstructions. A dog model of UAW obstruction was developed to test the main hypothesis. If successful, this technique can lead to a totally implantable electrical stimulation device that will use only one electrode implanted around the HG nerve for both detection and removal of the obstructions. The results of this study were partially published in the abstract form [12].

II. METHODS

Two healthy Beagles (young adult, 10–12 kg.) with normal UAW anatomy were chronically implanted with spiral nerve cuff electrodes [13] on the main trunk of the HG nerve, and electroencephalogram (EEG) and electrooculogram (EOG) electrodes (stainless steel cortical screws, 2 mm in diameter, Synthes) on the skull for sleep staging in the same surgical procedure. Hypoglossal nerve recordings with spiral nerve cuff electrodes were demonstrated previously in acute animals [14], [15]. The cuff electrodes of this study were 20 mm in length and 2.5 mm in diameter and were implanted bilaterally in one animal (Beagle #1) and unilaterally in the other (Beagle #2). The electrode leads were attached to a connector which was kept inside a pocket on the dog's jacket that was worn by the animal following surgery. All surgical and experimental procedures were designed according to The Guide for Care and Use of Laboratory Animals and approved by the Institutional Animal Care and Use Committee of Case Western Reserve University, Cleveland, OH.

A. Experimental Setup

The dogs were trained to sleep lying on one side with their neck in a straight position in a recording cage (52×70×165 cm, one longitudinal side is open) in the presence of the experimenter. The recording cage was covered with wire mesh

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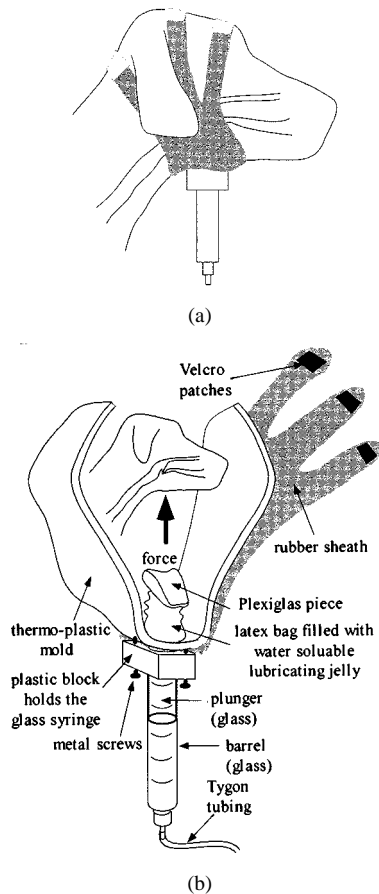


Fig. 1. The force applicator is shown (a) from the profile as worn by the animal and (b) separately in detail (see Methods for explanation). The small dog-head figure shows the point at which the force is applied to the pharynx.

forming a Faraday cage that helped reduce the interference from the outside electromagnetic sources. The leads from the implanted electrodes were connected to the recording electronics before each sleep session via a flat cable long enough to allow the animal to move freely inside the cage. A custom-design apparatus with a pneumatic piston that could be advanced remotely (Fig. 1) was used to apply a perpendicular force on the submental region, approximately a few cm rostral to the hyoid bone, for collapsing and, therefore, loading the UAW's. The force applicator was held in place with the help of a thermo-plastic mold which was worn around the animal's head. A custom-made cylindrical balloon (see [12, Fig. 2]) was placed inside the animal's esophagus before each sleep session for measurements of the esophageal pressure (P_{es}). Respiratory abdominal movements were measured with a plethysmograph (Respirace, Ambulatory Monitoring, Inc., New York) that had an inductive band transducer worn around the belly. All the raw signals were continuously digitized (Digital Data Recorder, Model: VR-10B, Instrutech Corp., New York) and stored on video tapes during sleep sessions.

B. Experimental Procedure

Sleep experiments were held at night. The animals were exercised 30–45 min before each session by walking them on leash. With the two dogs studied, a total of 53 sessions were held spread over a period of 17 months. Each session lasted between

2–4 h and included multiple sleep cycles. NREM sleep stage was characterized with larger amplitudes and slower frequency components in the EEG signal relative to either wakefulness or REM sleep stage. Once a NREM sleep pattern was observed, the submental force was increased in steps of 1 or 2 N, waiting at least ten breaths at each level, until the animal was aroused. The maximum submental force in each maneuver was defined as the largest force value at which the animal was not yet aroused from sleep. Arousal was judged visually when the EEG pattern changed from that of NREM to wakefulness.

The hypoglossal nerve was stimulated (Grass S88 Stimulator) at near maximum and maximum force levels in some of the sessions using either manual triggering (switch in Fig. 2 in position 2) in the beginning of each breath or in a closed-loop manner using the HG nerve's own activity as the trigger (the switch is in position 1). False triggers due to stimulation artifacts in the recorded HG signal were prevented by disabling the output of the trigger enable circuitry (Fig. 2) for about an inter-breath interval. Electrical stimulation was applied to the HG nerve between the middle and the end contacts of the tripolar cuff electrodes through an optically isolated voltage to current converter unit (Model PSIU6, Grass Instruments). A train of cathodic pulses (train duration = 1–3 s, frequency = 40 Hz, pulse width = 100 μ s) at amplitudes between 0.2 and 0.6 mA were used. Ten breaths during and ten breaths between the stimulated breaths were allowed before raising the current amplitude to a higher value.

C. Force Applicator

The force applicator consisted of a 5-cc glass syringe mounted on a thermo-plastic mold that was shaped to fit around the dog's head (Fig. 1). The outside end of the piston was cut off and a Plexiglas piece with a relatively larger surface area (2.75 cm^2) was glued on the top using fast drying epoxy. A piece of rubber sheath with Velcro attachments was wrapped around the mold in order to further stabilize the apparatus around the dog's head. A 40-cm-long flexible Tygon tubing (I.D. = 2.4 mm) was attached to the plunger and continued with a longer and stiffer polyethylene tubing (I.D. = 3.05 mm) to transmit the pressure to a remote transducer (Deltran, Utah Medical Products, Inc., Midvale, UT). Another syringe was included into the system for controlling the force applied on the plunger remotely by adding or removing air. The pressure measurements inside the system were scaled with the cross-sectional area of the plunger shown in Fig. 1 to determine the force applied on the UAW muscles.

D. Signal Conditioning

The electronic noise of the Grass head-stage was found to be at least twice larger than the thermal noise that was due to the nerve/cuff impedances. Thus, the noise contribution from the preamplifier was minimized using a transformer (turn ratio = 1 : 5, Part# 24500, PICO Electronics) that matched the nerve/cuff resistance to the input noise characteristics of the head-stage [16] as shown in Fig. 2. The hypoglossal signal was amplified and filtered between 300 Hz and 10 kHz (P5 Series, Grass Medical Instruments). The electroencephalogram and EOG signals were bandpass filtered between 1 and 30 Hz (P5 Series, Grass Medical Instr.). The pressure measurements from

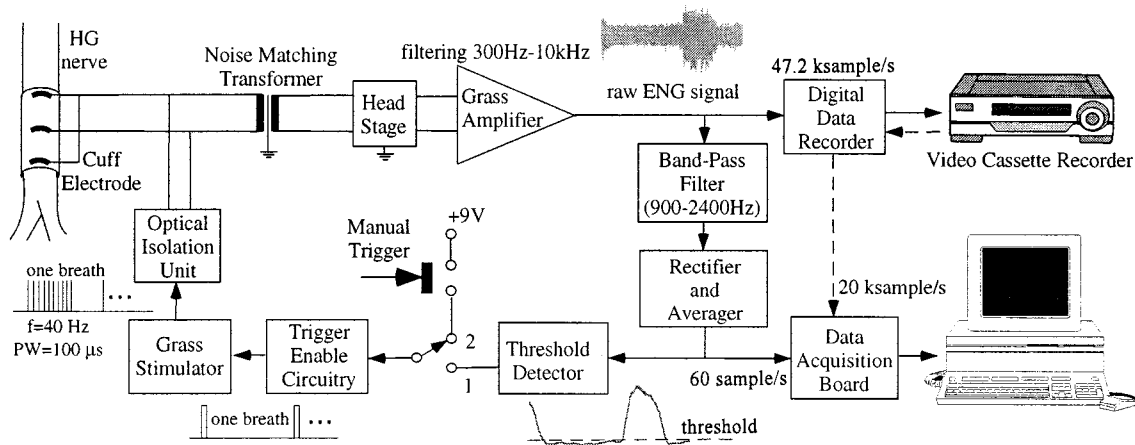


Fig. 2. Block diagram of the circuitry used for recordings and closed-loop stimulation of the HG nerve. Phasic HG activity is detected by a simple threshold detector at the output of the rectifier/averager (see Methods for more details). For manual triggering, the button is pressed while the switch is in position 2. For closed-loop stimulation, the switch is simply turned to position 1.

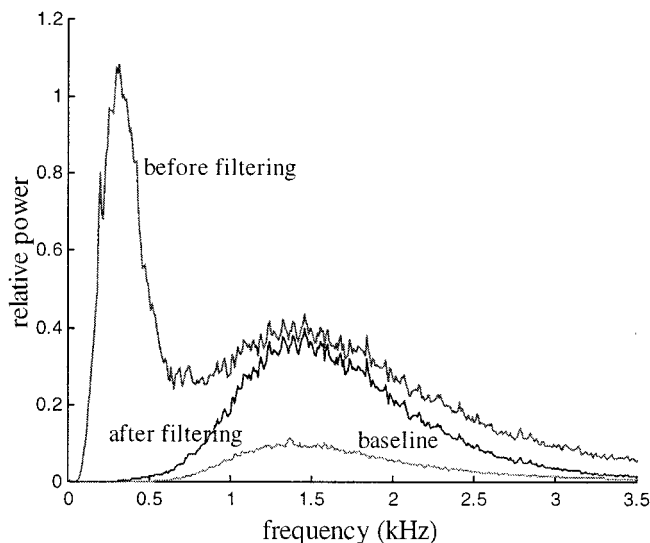


Fig. 3. Power spectra of the phasic HG nerve activity recorded during a force maneuver in NREM sleep and plotted before and after the 900–2400-Hz bandpass filter (see Fig. 2). The large peak below 500 Hz in the unfiltered spectrum is the EMG activity picked up from the surrounding muscles. Power spectrum of the baseline noise after filtering is also shown.

the force applicator and the esophageal balloon were amplified with custom-made amplifiers (INA102, Burr-Brown). The HG signal was digitized and converted to an appropriate format for storing on video tapes at a rate of 47.2 k sample/s (Digital Data Recorder, Model: VR-10B, Instrutech Corp., New York). Other raw signals were digitized at a rate of 60 sample/s.

Hypoglossal recordings were further filtered with a custom design bandpass filter (a third-order high-pass Butterworth filter at 900 Hz and a second-order low-pass Butterworth filter at 2400 Hz) to eliminate the EMG contamination from the nearby muscles and passed through a rectifier, a 100-ms time averager, and a threshold detector to produce the trigger signal for electrical stimulation (Fig. 2). The power spectra of the HG recordings before and after the 900–2400-Hz bandpass filter are shown in Fig. 3. The activity from the nearby muscles appeared as a large peak below 500 Hz and the nerve activity mainly occupied the high portion of the spectrum with a peak

around 1.5 kHz. The high-pass filter at 900 Hz removed the lower frequency components to ensure that the nerve recordings were not contaminated with the muscle activity from the surrounding muscles. The low-pass filter at 2400 Hz removed the high portion of the spectrum, which was primarily thermal noise. For frequency spectrum analysis, the raw HG signals were replayed from the video tapes retrospectively, resampled at a rate of 20 000 samples/s using a data acquisition board (NB-MIO-16P-5, National Instr.) and LabVIEW software tool, and stored on a personal computer. For breath-by-breath analysis and the temporal plots of the data, the rectified and averaged version of the HG signal and other measured variables were sampled at a rate of 60 sample/s into the computer. The area under the esophageal pressure during the inspiratory time (AreaPes) was calculated in each breath to evaluate the effect of loading and electrical stimulation on the size of the UAW passage.

III. RESULTS

A. Hypoglossal Nerve Signal

Hypoglossal nerve recordings had a phasic component above a baseline when the UAW's were loaded with the submental force in NREM sleep. The phasic HG activity increased immediately in the following breath as a response to an increase in the submental force and stayed at an elevated activity level as long as the force was applied (Fig. 4). There was never a noticeable increase in the baseline level as a response to the submental force in Beagle #1 with neither of the cuffs implanted. The baseline increased slightly with the submental force in Beagle #2 (not shown). However, the increase in the baseline signal was negligible compared to that in the phasic activity and, therefore, it did not interfere with the detection of the phasic component.

The mean signal-to-noise ratio (SNR), defined as the peak phasic activity divided by the baseline in the rectified-averaged version of the signal, had a mean \pm SD of 2.37 ± 0.74 ($n = 25$ force maneuvers) at the maximum force level. The hypoglossal nerve was active in every breath cycle at the maximum force level. Flow-limited inspiration was often observed at the maximum force as confirmed by the presence of snoring. The

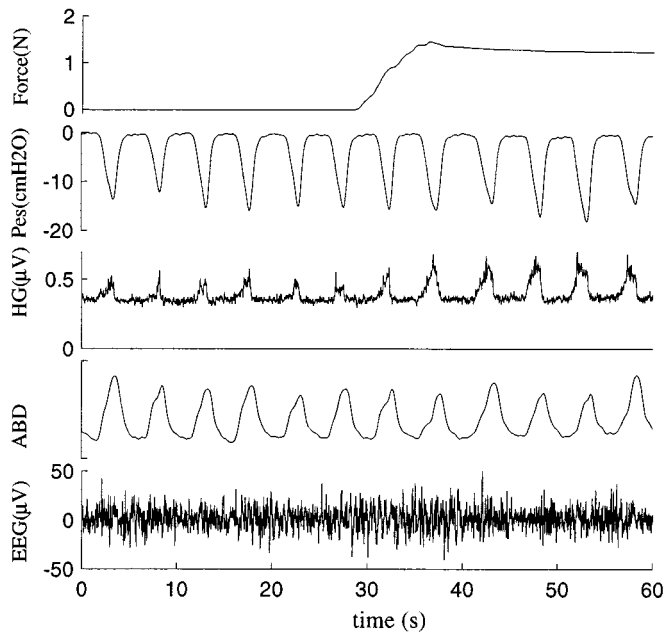


Fig. 4. Hypoglossal response during a force transition maneuver in NREM sleep where the force was quickly increased from 0–1.5 N. The traces from top to bottom are the submental force, esophageal pressure, rectified-integrated HG activity, abdominal movements, and EEG signal.

esophageal pressure also increased with the application of the submental force (as can be seen in the first 100 s of Fig. 7). The area under the esophageal pressure (AreaPes) was twice more sensitive to loading in Beagle #1 and about 50% more sensitive in Beagle #2 than the peak values (PeakPes) of the pressure during maximum loading in NREM sleep. AreaPes parameter also had a stronger correlation with the submental force (0.83 and 0.85 for Beagle #1 and Beagle #2, respectively) than the PeakPes (0.76 and 0.77). Thus, AreaPes was used as an estimate of UAW loading. The correlation between the area of phasic HG activity and AreaPes, was $R = 0.82$ and $R = 0.88$ for Beagle #1 and Beagle #2, respectively. The onset time of the phasic HG activity with respect to the beginning of the phasic esophageal pressure was measured at the maximum force level on breath-by-breath basis in multiple trials. The phasic HG signal began to rise earlier than the esophageal pressure with a mean \pm SD onset time of 17 ± 196 ms (220 breaths in 20 force maneuvers).

B. The Effect of HG Stimulation

The effect of HG nerve stimulation on the size of the UAW's was investigated at the maximum submental force level in NREM sleep. Fig. 5 shows the results of a typical stimulation experiment at the current amplitude of 0.4 mA in Beagle #1. A train of electric pulses (40 Hz for 3 s, each pulse is $100 \mu\text{s}$) was applied at the beginning of each breath manually by observing the esophageal pressure for 10 consecutive breaths between $t \cong 40$ s and $t \cong 90$ s. The electrical stimulation caused large artifacts in the HG recordings, however, the output of the amplifier stabilized quickly after each pulse train. Both the peak esophageal pressure and the area underneath the pressure decreased during stimulation and returned to prestimulus values following the stimulus. Note that the abdominal movement was

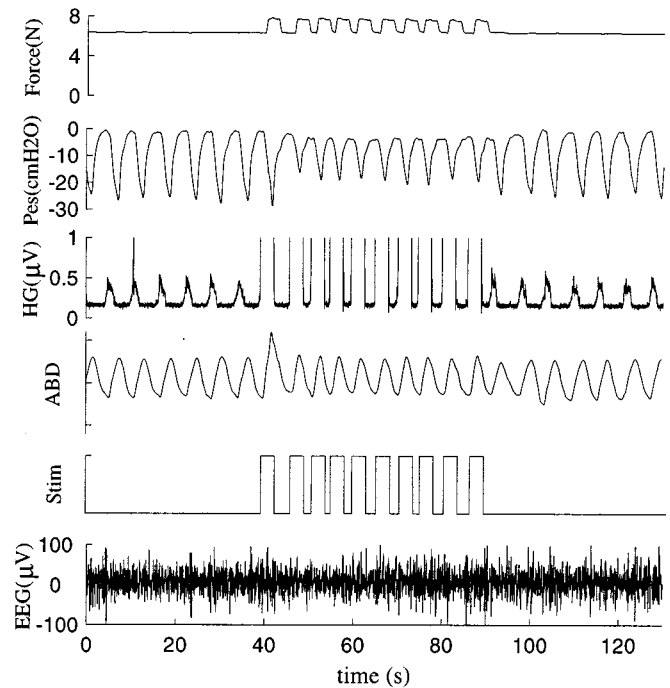


Fig. 5. Hypoglossal stimulation during maximum loading in NREM sleep. Electrical stimulation is triggered manually (see Fig. 2) at the onset of each breath. Notice the decrease in the peak esophageal pressure during the stimulated breaths. The large amplitudes in the HG signal during stimulation are artifacts. The traces from top to bottom are the submental force, esophageal pressure, rectified-integrated HG activity, respiratory abdominal movements, the envelope of the stimulation pulse trains that consist of $100 \mu\text{s}$ long pulses at 40 Hz, and the EEG signal.

relatively larger during the first breath of stimulation indicating a sigh due to relief from the effect of loading. For the remaining stimulated breaths, the abdominal signal amplitude indicated a change in the tidal volume that was far less than that of the esophageal pressure from the prestimulus level. This suggested that the decrease in the esophageal pressure amplitude was mainly due to the decrease in the mechanical resistance of the UAW passage that resulted from electrical activation of the UAW muscles. The phasic forces created by the electrical activation of the muscles innervated by the HG nerve were superimposed on the applied submental force. The electrical stimulation did not arouse the animal from sleep, as indicated by the EEG signal.

The effect of the electrical stimulation on the area of the phasic esophageal pressure (AreaPes) in NREM sleep is shown in Fig. 6 from a few trials ($n = 3$) in Beagle #1. The submental force value of 0 N was applied as control. A force value of 5 N caused a twofold to threefold increase in AreaPes. Stimulation at 0.2 mA did not result in very large changes in the pressure measurements probably owing to the fact that it was subthreshold for the recruitment of the fibers in the HG nerve. AreaPes fell rather sharply with increasing current amplitudes and it returned to near control values indicating a complete removal of the UAW loading effect caused by the submental force. In these trials, the animal was not aroused from sleep even at a current amplitudes 50% larger than what was sufficient to completely reverse the loading effect of the submental force (0.6 mA versus 0.4 mA). In Beagle #2, the current values similar to those used in Beagle

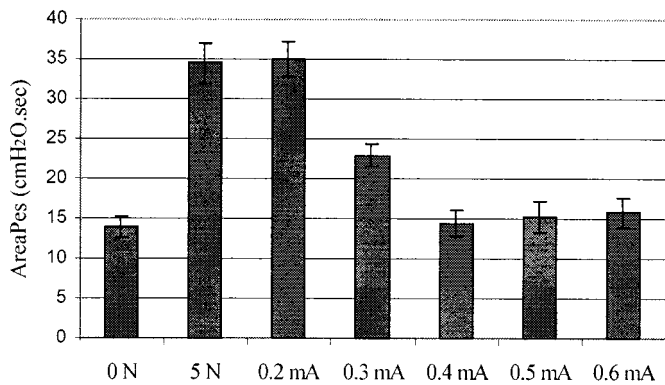


Fig. 6. The Effect of HG nerve stimulation on the area under the phasic esophageal pressure (AreaPes) during maximum loading in NREM sleep. In three different trials ($N = 3$) with Beagle #1, AreaPes was first measured at 0 N for 5–10 breaths as the control value, then 5 N was applied for loading the UAW's. Stimulation current amplitude was increased from 0.2 to 0.6 mA in steps of 0.1 mA waiting at least ten breaths at each level. The mean \pm SD value of the AreaPes measurements from all three trials is shown for each current value.

#1 did not result in significant changes in the esophageal pressure measurements with or without the submental force applied. The threshold current was determined by observing the mechanical movement of the muscles in the region and the current level was increased at least twice the threshold value before deciding that the stimulation did not relieve the airways in these trials.

C. Closed-Loop Stimulation of the HG Nerve

Fig. 7 demonstrates the closed-loop HG stimulation using the activity of the HG nerve as the feedback signal. The submental force was first raised to 6 N to load the UAW's. As a result, the phasic components of the submental force and the HG signal increased. The closed-loop operation was started by turning the switch in Fig. 2 to position 1 at $t \cong 110$ s. In this (and all other) stimulation trial(s), the threshold for detection of the phasic component was set just above the baseline. At the start of each breath, the electronic circuitry detected the onset of the phasic HG signal and triggered the stimulator that generated a train of pulses (pulse width = $100\mu\text{s}$ at 40 Hz) for a predetermined period of time (3 s). Upon detection of each phasic HG component, the output of the trigger enable circuitry was disabled for approximately one inter-breath interval (5 s) to prevent false stimulation of the nerve due to the stimulation artifacts in the HG signal. Notice that the stimulator was not activated after the second train of pulses when the animal took a breath that was too early. The phasic HG bursts were completely obscured by the stimulation artifacts in the recordings since the detection occurred very early in each breath cycle. The animal took a deeper breath on the first stimulated breath indicating a relief from the effect of the submental force. The amplitude of the phasic esophageal pressure stayed at a low level as long as the electrical stimulation was applied and returned to its prestimulation level within the next breath at the end of the stimulation. As in Fig. 5, the tidal volume did not decrease during stimulation, as indicated by the respiratory abdominal movements, which suggested that the decrease in the pressure was mainly due to the mechanical effect of the UAW muscle activation. The EEG channel indicated no arousal from sleep during stimulation.

IV. DISCUSSION

This study shows the feasibility of the closed-loop stimulation of the HG nerve using its activity as the feedback signal. The HG recordings obtained with cuff electrodes have sufficiently large SNR's for detection of the phasic component without missing a breath when the airways are loaded with the maximum force. Simple filtering techniques and algorithms are adequate to prevent false detections due to baseline shifts and EMG contamination from the surrounding muscles. The HG nerve signal recorded in this study should primarily be of efferent origin since the afferent fibers in the HG nerve are only a few in number [18].

The variation in the onset time of the phasic HG signal in each breath (SD = 196 ms) is probably due to the variation in the actual timing of the phasic HG activity rather than problems associated with the detection of the signal in a noisy background. However, there might be a constant delay introduced into the detection time of the phasic HG component by the presence of a constant background noise. The noise matching transformer used in this study reduces the electronic noise by converting the resistive component of the source impedance to a value that is equal to the ratio of the input voltage noise (e_N) over the input current noise (i_N) of the head-stage [17]. Using this technique, the electronic noise contribution from the preamplifier is reduced to a level that is negligible compared to the nerve signals [16]. However, the thermal noise that constitutes most of the HG baseline signal is a function of the resistive component of the nerve/cuff impedance. Thus, the thermal noise in the recordings cannot be eliminated but it can be further reduced by increasing the size of the electrode contacts.

The stimulation artifacts that occur in the HG recordings do not interfere with detection scheme of the phasic component since the stimulator is turned on after the detection occurs in each breath and the output of the trigger enable circuitry is disabled until the artifact is over. The time interval during which the output of the trigger enable circuitry is disabled should be short enough in order not to miss early occurring breaths (see the breath after the second stimulated breath in Fig. 7) and it should be long enough to avoid false triggers due to the stimulation artifacts. The expiratory period is usually long enough to allow sufficient flexibility for the set value of this parameter. However, if it is desired to suppress the stimulation artifacts in the recordings instead of dealing with them by trigger disabling mechanism, a special electrode interface circuitry can be used [16].

Hypoglossal nerve stimulation in Beagle #2 failed to elicit a significant change in the size of the esophageal pressure swings or in the AreaPes parameter. This may be due to several reasons: 1) the placement of the cuff electrode around the HG nerve may not be optimum to activate the protrusor muscles before the retractors; 2) the site of obstruction may not be optimum to see the effect of the activation of the muscles innervated by the HG nerve; 3) there may be anatomical differences between the two dogs. The first possibility is currently being investigated by stimulating the HG nerve using multi-contact electrodes to activate sub-portions of this nerve through separate channels.

Several animal models of UAW obstruction have been developed and published in the literature. One such model involves

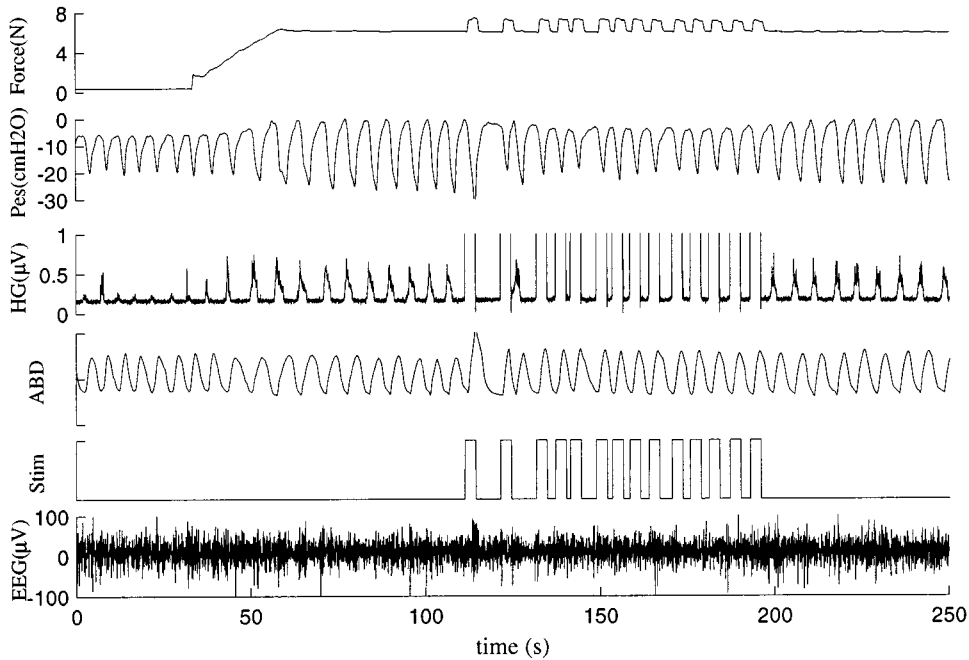


Fig. 7. Closed-loop HG stimulation in NREM sleep. Electrical stimulation is triggered by the HG nerve's own activity (see Fig. 2). Peak esophageal pressure is decreased during stimulation indicating a relief of the UAW's from the loading effect of the submental force. The traces from top to bottom are the submental force, esophageal pressure, rectified-integrated HG activity, respiratory abdominal movements, the envelope of the stimulation pulse trains that consist of $100\mu\text{s}$ -long pulses at 40 Hz, and the EEG signal.

a snout mask terminated with a mechanical load to simulate the effect of obstructions in unsedated animals [19]–[22]. In other animal models, the UAW is closed remotely with a computer controlled valve [23] or an inflatable balloon placed in the trachea [24] to study the physiological consequences of occlusions. In this study, however, these models are not appropriate for demonstrating the effect of electrical stimulation of the HG nerve on the size of the UAW passage since these methods do not necessarily result in physical narrowing of the airways. The UAW functions as a Starling resistor [25] with a collapsible segment in the oropharynx [26]. Partial obstructions were obtained in awake humans by placing an inflatable rubber bag externally over the hyoid and submental areas [1] and a flow-limiting pattern was observed when lard bags were placed externally over the airways in anesthetized rabbits [27]. Negative pressures applied to the UAW's were also able to close the oral passage and the nasopharynx in the anesthetized dogs [28]. These reports show that, using external means, the UAW's can be closed to the extent that flow-limitation or partial obstructions can be achieved. The animal model developed in this study applies an external force directly on the submental region to mechanically close the UAW's. This animal model is useful for demonstrating the effect of both UAW loading on the HG activity and HG nerve stimulation on the passage. The increase in the phasic esophageal pressure amplitude without an increase in the tidal volume demonstrates that the UAW mechanical resistance is indeed elevated by the submental force (see first 100 s in Fig. 7). Although, total occlusion of the pharynx is not feasible due to arousal from sleep at large submental forces, one can obtain near obstructive states with this animal model. It should be noted that the mechanical changes introduced to the UAW's during the partial occlusions produced with this animal model may not

necessarily represent the natural obstructions that occur in OSA patients.

In future electrical stimulation devices for OSA patients, a straight forward algorithm may be adopted where the HG nerve is stimulated in those breaths when its activity is above a certain threshold. However, obstructions follow a different temporal pattern in each patient. Moreover, in some patients, the obstructive apneas might be mixed with central apneas. Therefore, a unique algorithm for each type of OSA patient might be necessary. For instance, in some patients with periodic airway occlusion, the obstructions started when the genioglossal activity level was minimum and the phasic genioglossal continually increased until arousals from sleep occurred [29]–[31]. In these patients, it might be possible to develop an algorithm that anticipates an occlusion when the HG activity decreases below a certain threshold. Then, the electrical stimulation can be turned on before the obstructions begin to keep the airways open through the vulnerable period where the HG activity is the lowest.

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