CLOSED-LOOP STIMULATIONS OF HYPOGLOSSAL NERVE USING ITS SPONTANEOUS ACTIVITY AS THE FEEDBACK SIGNAL

Mesut Sahin, *Student Member, IEEE*, and Dominique M. Durand, *Member, IEEE*
The 20th Annual International Conference of the IEEE-EMBS, EMBS'98, Hong Kong
Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH, USA
E-mail: mxs44@po.cwru.edu

Abstract— **Electrical recruitment of the upper airway (UAW) muscles has been attempted as a treatment method for Obstructive Sleep Apnea (OSA) [1-6]. Hypoglossal nerve (HG) and genioglossus muscle (GG) stimulations have given successful results in OSA patients [3-6]. A reliable method for detection of obstructions is needed to trigger the stimulations in phase with respiration during obstructive breaths before this technique can be used clinically. In this paper, we investigate the possibility of closed-loop HG nerve stimulations using its spontaneous activity for detection of obstructions in a dog model. The activity of the HG nerve is recorded with chronically implanted nerve cuff electrodes in sleeping dogs while a force is being applied onto the submental region to collapse the airways. The increase in the phasic HG activity as a response to the submental force is used to trigger the stimulations. Closed-loop stimulations are shown to relieve the UAWs from the collapsing effect of the submental force.**

Index Terms— **Nerve recording, nerve cuff electrodes, hypoglossal, animal model, obstructive sleep apnea.**

I. INTRODUCTION

Hypoglossal nerve (HG) plays an important role in the patency of upper airways (UAWs) during sleep. The activity of the HG nerve has been studied to a great extent especially in relation to the sleep disorder Obstructive Sleep Apnea (OSA). Among the muscles innervated by the HG nerve, genioglossus (GG) muscle has been given the most attention since its main function is to protrude the tongue. A number of attempts have been made to electrically recruit either the GG muscle with transcutaneous stimulations [1-2] or directly with wire electrodes [3] or the HG nerve directly using either wire [3-5] or nerve cuff electrodes [6] for the purpose of removing or preventing obstructions in sleep in OSA patients. Direct stimulation of the main trunk of the HG nerve or its medial branch, which innervates the GG muscle, has given successful results in OSA patients with acute implantations under local anesthesia [6]. Regardless of the stimulation strategy, an implantable electrical stimulation device that can be used as a treatment method for OSA will require a reliable method for detection of obstructions to trigger the stimulations in phase with respiration during obstructive breaths. To our knowledge, such a method has not been reported yet.

Nerve cuff electrodes [7,8] have been shown to be safe in a number of animal and human implants. In this study, we investigate the feasibility of using the HG nerve recordings with nerve cuff electrodes for detection of obstructions in a dog model. We developed a method to simulate an obstruction by applying an external force directly onto the submental region thereby collapsing the UAWs in sleeping dogs. With this method, we study the temporal response of the HG nerve to internal loadings of the UAWs and investigate the possibility of using this response to trigger the stimulations to be delivered to the same nerve for removal of obstructions. If successful, this method can lead to a totally implantable closed-loop electrical stimulation device that will use the same electrode both for detection and removal of obstructions in OSA patients.

II. METHODS

A. Experimental Set-up

Two healthy Beagles (young adult, 10-12 kg.) with normal upper airway anatomy were chronically implanted with nerve cuff electrodes for recordings of HG activity and electroencephalogram (EEG) and electrooculogram (EOG) electrodes for sleep staging. All the wires from the implanted electrodes were tunneled subcutaneously to an exit site between the shoulders and attached to a connector. The dogs were trained to sleep lying on one side with their neck in a straight position in a recording cage that is covered with wire mesh (52x70x165cm, one side is open) in the presence of the experimenter. The leads from the implanted electrodes were connected to the recording amplifiers before each session via a flat cable. 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 an inch rostral to the hyoid bone, for collapsing, i.e. loading, the upper airways. A custom-made cylindrical balloon (Fig. 2) was swallowed by the animal before each sleep session with a bolus of soft food for measurements of the esophageal pressure (Pes) and thus for evaluation of the amount of narrowing in the UAWs caused by the submental force. Abdominal movements were measured with an inductive plethysmograph (Respitrace). All the raw signals were continuously digitized (Digital Data Recorder, Model: VR-10B, Instrutech Corp.) and stored on video tapes during sleep sessions. Experiments were held in the evening during normal sleeping hours of the dogs.

B. Cuff Electrode Design

The self-coiling spiral design was chosen for the cuff electrode whose ability to record the activity of the HG nerve

0-7803-5164-9/98/$10.00

was demonstrated in anesthetized preparations before [9]. A detailed description of the electrode fabrication can be found elsewhere [7,9]. The cuff electrodes used in this study were 20 mm in length and 2.5 mm in diameter (inner diameter of the first layer) and had 2.25 to 2.75 turns, snugly fitting the nerves in their resting position. Cuff electrodes had three contacts (each 9 mm apart) made from Platinum foil (25 μm thickness, Goodfellow Corp.) which were spot-welded to multi-strand stainless steel (316 LVM) Teflon coated wires (1x7x0.00135", Fort Wayne Metals) for connections.

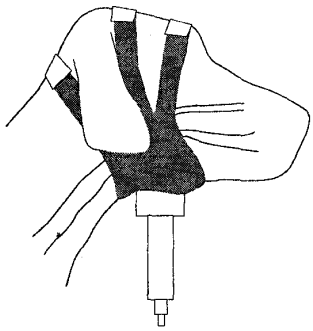

Fig. 1. The submental force applicator as worn by the dog.

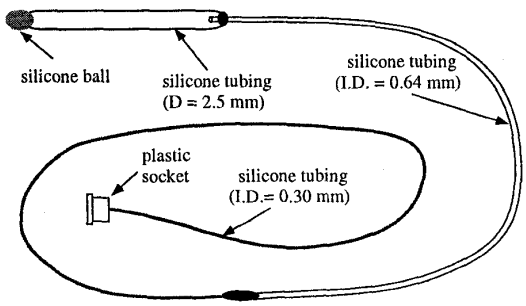

Fig. 2. Esophageal balloon design. A 5 cm long silicone tubing with very thin walls serves as a pressure sensor.

C. Submental Force Applicator

A 5 cc glass syringe (Micro-Mate®, popper & sons, Inc., New Hyde Park, NY) was mounted on a thermo-plastic mold that is shaped to fit around the dog's head comfortably (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. The Plexiglas piece was shaped to conform to the anatomical structures in the submental area in order to minimize the disturbing effect of the force to the animal during sleep. A piece of rubber sheath was wrapped around the mold and the ends were held together over the head with the help of Velcro attachments in order to further stabilize the apparatus around the animal's head. A 40 cm long flexible tubing (I.D.=2.4 mm, O.D.=4 mm, Tygon®, Fisher Scientific) was attached to the plunger and continued with a longer and stiffer polyethylene tubing (I.D.=3.05 mm, length=2 m, TFE 9 Standard Wall, Zeus Industrial Products, Inc.) that was run along the flat cable to transmit the pressure to a remote transducer (Deltran, Utah Medical Products, Inc.). 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 piston to find the force applied on the upper airway muscles.

D. Signal Conditioning

The circuitry shown in Figure 3 is used for recordings and stimulations of the HG nerve. Hypoglossal signal was first amplified with a step-up audio transformer (turn ratio = 1:5, Part# 24500, PICO Electronics) which also improved the signal-to-noise ratio of the recordings by matching the cuff electrode/nerve impedance to the noise characteristics of the head stage [10]. Hypoglossal signal was further amplified with a pre-amplifier (P5 Series, Grass Medical Instr.), digitized at a sampling rate of 47.2 kHz, and converted to an appropriate format for storing the data on video tapes (Digital Data Recorder, Model: VR-10B, Instrutech Corp.). Hypoglossal signal is filtered with a high-order band-pass filter (900-2400 Hz, Butterworth) to remove the EMG contamination from the surrounding muscles. All the signals (ENG, EEG, EOG, submental force, esophageal pressure, and the abdominal movements) stored on video tapes continuously during sleep sessions.

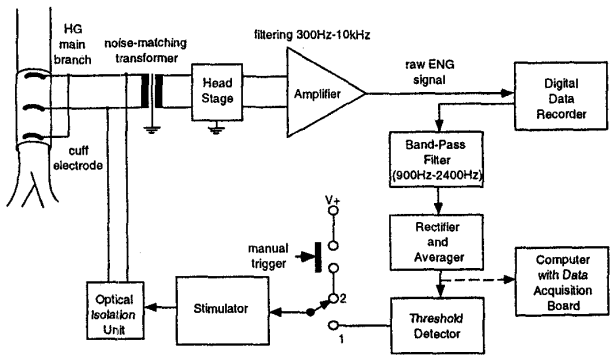

Fig. 3. Block diagram of the circuitry used for recordings and stimulations of the HG nerve. The stimulator (Grass S88) could be triggered either manually (the switch in position 2) or by the HG nerve's spontaneous activity (the switch in position 1) in a closed-loop manner.

III. RESULTS

A. Hypoglossal Response to Submental Force

A typical force transition maneuver during NREM sleep is shown in Figure 4. Phasic HG activity increases immediately in the next breath following the force transition from 2 N to 4 N and it persists as long as the submental force is applied. Contrary to the phasic component, the baseline activity does

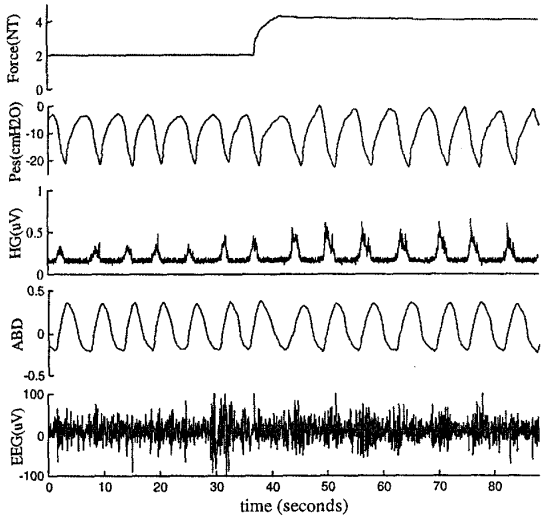

Fig. 4. A force transition maneuver in NREM sleep. The traces from top to bottom are the submental force, esophageal pressure (Pes), rectified-integrated HG activity, abdominal movements (ABD), and EEG signal.

not increase with increasing submental force. A simple threshold circuit is sufficient to determine whether the airways are loaded based on the phasic component of the HG activity. The phasic component increases with increasing submental force values (not shown).

B. The Effect of Stimulations on the Upper Airways

The effect of electrical stimulations of the HG nerve on the area of the phasic esophageal pressure (AreaPes) is studied during UAW loading in NREM sleep. AreaPes is used as an estimate of the size of the airway passage (i.e. amount of loading or relief). The submental force is first raised to 5 N. Then, a train of cathodic pulses (40 Hz, pulse width=100 μsec, train duration=3 sec) is delivered to the center contact in the cuff electrode by triggering the stimulator manually in the beginning of each breath for ten consecutive breaths. Another ten breaths were allowed without stimulation before raising the current to a higher value. A similar procedure is repeated for current values ranging from 0.2 mA to 0.6 mA in steps of 0.1 mA. The mean AreaPes measured from five to ten breaths immediately preceding the loading is taken as control. Figure 5 shows a typical stimulation scheme at the current value of 0.4 mA. The peak esophageal pressure decreases during stimulations indicating that the size of airway passage in the UAWs increases due to stimulations. Peak esophageal values return to pre-stimulus values immediately after the stimulations are stopped. Notice that the abdominal movement is relatively larger during the first breath of stimulations indicating a sigh due to relief from the effect of loading. The AreaPes measurements from three different stimulation maneuvers are plotted in Figure 6 without normalization. Stimulations at 0.2 mA do not result in very large changes in the pressure measurements probably owing to the fact that they are subthreshold for the recruitment of the HG nerve fibers. AreaPes falls rather sharply with increasing current amplitudes and it returns to near control values for larger current values indicating a complete removal of the internal loading caused by the submental force.

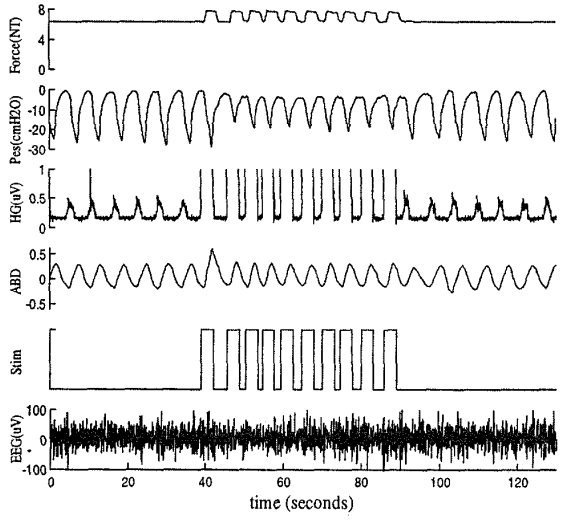

Fig. 5. Hypoglossal stimulation during UAW loading in NREM sleep. Stimulations are triggered manually (see Fig. 3) at the onset of each breath. The traces from top to bottom are the submental force, esophageal pressure (Pes), rectified-integrated HG activity, abdominal movements (ABD), the envelope of the stimulation pulse trains (Stim), and EEG signal.

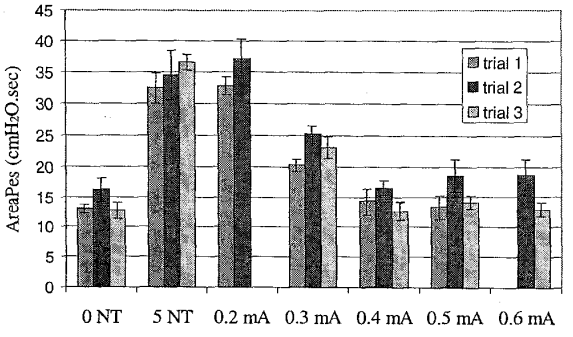

Fig. 6. Effect of HG nerve stimulation on the esophageal pressure during UAW loading in NREM sleep. Three different trials are indicated with three different shades of gray. The mean±SD value of AreaPes measurements without normalization are shown.

C. Closed-loop HG stimulation

Figure 7 demonstrates the closed-loop HG stimulation. The submental force is first raised to 5 N. The closed-loop operation is started by turning the switch in Figure 3 to position 1. At the start of each breath, the threshold circuit detects the onset of the phasic HG signal and triggers the stimulation pulses for a predetermined period of time. Upon detection of a phasic HG component, the output of the trigger circuitry is disabled for approximately one inter-breath interval (5 sec) to prevent false stimulations of the nerve between the inspiratory phases. Because the disable time is chosen too long in this example, the trigger circuitry misses the early occurring breath after the second train of pulses. Notice how the animal takes a deeper breath on the first stimulated breath indicating a relief from the loading effect of the submental force. The peak esophageal pressure stays at a lower level as long as the stimulations are applied and returns to its pre-stimulation level within the next breath after the output of the trigger circuitry is turned off manually. Forces generated due the electrical recruitment of the muscles innervated by HG nerve are superimposed on the submental force measurements.

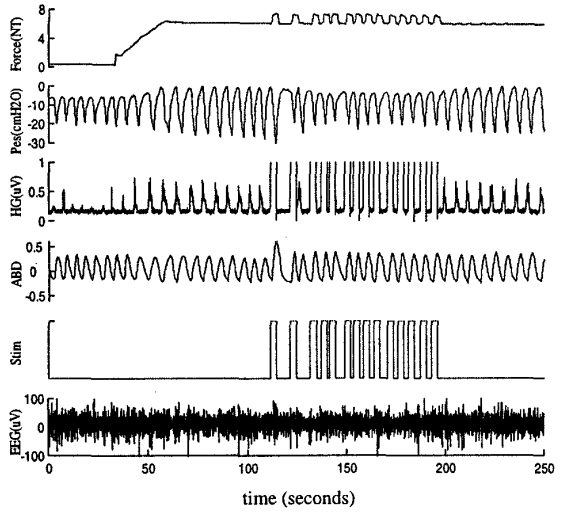

Fig. 7. Closed-loop HG stimulation in NREM sleep. Stimulations are triggered by the activity of the HG nerve. Peak esophageal pressure stays at a lower level as long the stimulations are applied. See the legend for figure 5 for explanation of the traces.

IV. DISCUSSION

Our findings indicate that the quality, i.e. the signal-to-noise ratio, of the HG recordings with the nerve cuff electrodes is sufficient to allow timely detection of the phasic HG activity in each breath during sleep when there is an internal loading of UAWs. The variation in the baseline HG signal was not very large neither from session to session nor as a response to the submental force to cause false detections of the phasic component. Simple filtering techniques or algorithms are adequate to prevent false detections that might result from the variations in the baseline.

Because HG had an immediate response to loading in these healthy Beagles and this response could reliably be detected with chronically implanted nerve cuff electrodes, we think that it may be feasible to use the activity of the HG nerve for detection of obstructions in OSA patients during NREM sleep. If successful, this method can lead to a totally implantable electrical stimulation device that uses the same electrode for both detection and removal of the obstructions. This possibility needs to be further investigated in OSA patients.

V. CONCLUSIONS

Phasic HG activity increases immediately with internal loadings of the upper airways during NREM sleep. This response can be used as a trigger signal for closed-loop stimulations of the same nerve to prevent the obstructions in the upper airways.

ACKNOWLEDGMENT

The work is supported by an NIH grant # ROI NS 32485

REFERENCES

[1] Miki, H., W. Hida, T. Chonan, Y. Kikuchi, and T. Takishima, "Effects of submental electrical stimulation during sleep on upper airway patency in patients with obstructive sleep apnea", *Am. Rev. Respir. Dis.*, 140:1285-1289, 1989.

[2] Edmonds, L.C., B.K. Daniels, A.W. Stanson, P.F. Sheedy II, and J.W. Shepard, Jr., "The Effects of transcutaneous electrical stimulation during wakefulness and sleep in patients with obstructive sleep apnea",*Am. Rev. Resp. Dis.*,146:1030-36, 1992.

[3] Smith, P.L., D.W. Eisele, T. Podszus, T. Penzel, L. Grote, J.H. Peter, and A.R. Schwartz, "Electrical stimulation of upper airway musculature", *Sleep*, 19(10):S284-S287, 1996.

[4] Schwartz, A.R., D.C. Thut, B. Russ, et al., "Effects of electrical stimulation of the hypoglossal nerve on airflow mechanics in the isolated upper airway", *Am. Rev. Resp. Dis.*, 147:1144-1150, 1993.

[5] Eisele, D.W., A.R. Schwartz, A. Hari, D.C. Thut, P.L. Smith, "The effects of selective nerve stimulation on upper airway airflow mechanics", *Arch. of Otolaryn.-Head&Neck Surg.*, 121:1361-1364, 1995.

[6] Eisele, D.W., P.L. Smith, D.S. Alam, A.R. Schwartz, "Direct hypoglossal nerve stimulation in obstructive sleep apnea", *Arch. Otolaryngol. Head Neck Surg.*, 123:57-61, 1997.

[7] Naples, G.G., J.T. Mortimer, A. Scheiner, and J.D. Sweeney, "A spiral nerve cuff electrode for peripheral nerve stimulation", *IEEE Tran. on Biomed. Eng.*, 35(11):905-915, 1988.

[8] Stein, R.B., D. Charles, L. Davis, L. Jhamandas, A. Mannard, and T.R. Nichols, "Principles underlying new methods for chronic neural recording", *The Can. J. Neur. Scien.*, Aug, 235-244, 1975.

[9] Sahin, M., M.A. Haxhiu, D.M. Durand, and I.A. Dreshaj, "Spiral nerve cuff electrode for recordings of respiratory output", *J. Appl. Physiol.*, 83(1):317-322, 1997.

[10] Sahin, M., and D.M. Durand, "An Interface for nerve recording and stimulation with cuff electrodes", *19th Annual International Conference of the IEEE Eng. in Med. and Biol. Soc.*, 1997.