IMPLANTABLE DIAPHRAGMATIC BREATHING PACEMAKER USING TRANCUTANEOUS ENERGY TRANSMISSION

Hoon Ki Lee*, Seong Wook Choi*, Choong Hyo Kim**, Hyun Jib Kim** and Hee Chan Kim***

* Interdisciplinary Program, Biomedical Engineering Major, Graduate School,
** Department of Neurosurgery, College of Medicine and
*** Department of Biological Engineering, College of Medicine and
Institute of Medical & Biological Engineering, Medical Research Center,
Seoul National University, Seoul, Korea

hckim@snu.ac.kr

Abstract: Breathing pacemaker that stimulates phrenic nerve motor point of diaphragm is an alternative for mechanical ventilator and phrenic nerve stimulator because it is less discomfortable and less invasive. We developed a new diaphragmatic breathing pacemaking system to obviate the disadvantages. The system uses transcutaneous energy transmission (TET) technology originally developed for the wireless transmission with the highest efficiency. Finally, we proposed a very thin coil which is printed on PCB, for the implantable unit. Animal experiment was conducted in Seoul National University Hospital and the respirations recruited by stimulation were successful in four cases.

Introduction

The patients with high cervical spinal cord injury (SCI) or central alveolar hypoventilation (CAH) typically require mechanical ventilator surrport. Mechanical ventilator, however, has many disadvantages associated with substantial morbidity, physical discomfort, difficulty with speech, mortality, inconvenience, fear of disconnection, impaired sense of smell, and encumbered mobility.[1] Phrenic nerve pacing (PNP) provides significant clinical advantages over the mechanical ventilator. Currently, two PNP systems are commercially available, the Avery Mark IV (Avery Laboratories, Commack, NY) and the Atrostim system (Atrotech Ltd, Tampere, Finland).[2] Unfortunately, this technique generally requires a thoracotomy and lengthen hospital stay with its attendant risks, inconvenience, and high cost. Moreover this technique involves phrenic nerve dissection and electrode placement that carries some risk of injury to the phrenic nerves.[3]

First of all, in order to reduce invasiveness of the PNP, we have developed a new diaphragmatic breathing pacing system that uses a minimally invasive laparoscopic procedure to position intramuscular electrodes near the opposite sides of the phrenic nerve motor point. Secondly, the system uses TET technology originally developed in the artificial organ research for the wireless transmission of electrical energy with the

highest efficiency to the implanted electronic device. Finally, the secondary coil was fabricated using spiral patterns on a printed circuit board (PCB), which could reduce the total thickness of the implanted component as one third of the Litz wire coil based system.

In this pilot study, we report the *in vitro* and *in vivo* performance of the developed system in respect of possible clinical application in the near future.

Materials and Methods

A. Stimulation Signal

Stimulation signal consists of a periodic electrical pulse train. This pulse train stimulates diaphragm causing its contraction and subsequent inhalation. When the pulse train stops, diaphragm relaxes and exhalation occurs. Then the cyclic repetition of this intermittent pulse train produces a normal breathing pattern.

The strength of muscle contraction can be controlled by manipulating stimulating pulse amplitude, pulse duration, and interpulse interval (IPI). Long IPI – low burst frequency - causes series of twitches. Short IPI - high burst frequency – produces muscle contraction, but increases the rate of muscle fatigue.[3] So, we maintained the IPI value as long as possible to produce a smooth contraction and strength of muscle contraction was controlled by adjusting the pulse amplitude. The
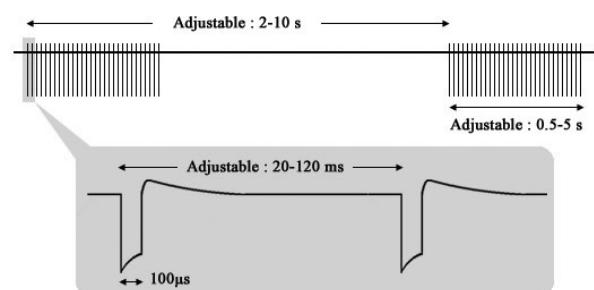

Figure 1: Stimulation signal parameters. Waveform of pulse train consists of a repeating biphasic pulse that has a cathodic phase followed by an anodic phase with same area under the curve for the charge balance. The pulse width is 100μs.
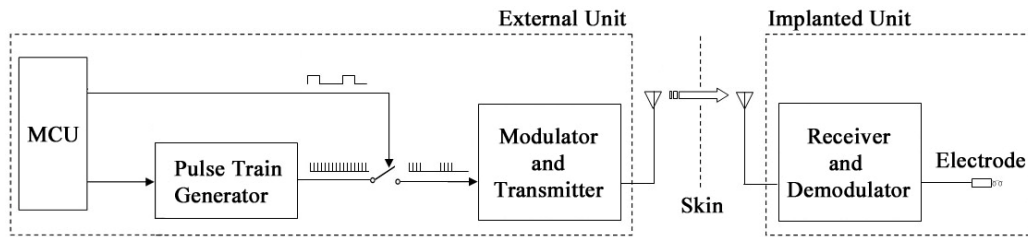
Figure 2: Functional block diagram of the total system

detail of stimulation signal parameter is shown in figure 1.

B. Systems

Developed system has dual units for stimulating both hemidiaphragm simultaneously. Each unit is composed of an external driver circuitry with a first coil and a secondary coil connected to a passive component circuitry with a stimulating electrode which is to be implanted in subcutaneous tissue around each hemidiaphragm's motor point.

In TET system, electrical energy is transmitted transcutaneously as a several hundred kHz AC signal between inductively coupled external coil to the implanted secondary coil. This high frequency AC current generates magnetic field around the external coil and thereby induces AC current on the coil of the implanted unit. DC electrical power can be achieved by rectifying this AC current. We applied same technology to stimulating pulse transmission where stimulation pulse was modulated with a 400 kHz AC signal in first external coil and then the stimulation pulse was reproduced by demodulating the received signal in the implanted unit. This wireless transmission makes it possible to obviate problems caused by percutaneous wires. Figure 2 is a block diagram of the system.

One of the important issues in designing the coils is its shape and size. Because two coils must align face-to-face with a minimum gap, a flat and thin type of coil is adventageous. After trying to examine many kinds of coils, we proposed a spiral disc-shaped coil. A disc type external coil with 42 mm in diameter was made of a multistrand Litz wire with 0.8 mm conductors.

This multistrand configuration minimizes the power losses otherwise encountered in a solid conductor due to the skin effect, or the tendency of radio frequency current to be concentrated at the surface of the conductor.[4]

Thickness of the coil is especially important for the internal unit in term of easiness of implantation and possible tissue damage due to disturbance of blood circulation. So, we proposed a very thin structure made of copper conductor patterned as a spiral coil on a PCB. Total thickness of the coil is 0.6 mm only and its diameter and number of turns are same as external coil. This PCB-based internal coil has enough hardness and flatness simultaneously as an internal coil and provides an adequate coupling coefficienct with the external coil.

A disc-shaped permanent magnet with 5 mm in diameter is placed at the center of both external and internal coils for easy location of the external coil on the very top of the implanted internal coil.

The external driving circuitary was made as a wearable transmitter. A microcontroller (PIC16F73, Microchips, USA) generates stimulation pulse as programmed. Pulse amplitude and IPI are made adjustable independently and separately for each hemidiaphragm unit. The transmitter is powered by a Li-ion battery which has enough capacity for 50 hours continuous operation. Photograph of the external unit is shown in Figure 3.

Internal device is composed of main body that contains a secondary coil and passive components on a PCB and one or two bipolar electrodes (CAPSUREFIX 4068, Medtroic, Inc., USA). The dual electrode type device (type II as shown in Figure 5) was devised for surgical variation problem. After implantation, the primary coil may turn out to be located not close enough to the motor point of the phrenic nerve so that the stimulation strength is not enough. Then the secondary electrode can provide an assistive stimulation which is expected to provide the practically same result with the primary electrode only stimulation on the exact motor point of the phrenic nerve. [5]

In order to maintain a high reliability level of the implanted unit, minimum number of electronic components was used for electronic circuitry of the internal unit. Functions of this circuitry include the demodulation of the received signal and the waveshaping of the demodulated signal as biphasic one.
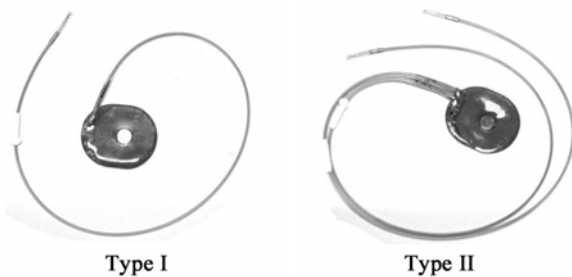

Figure 3: Photograph of External Unit

Figure 4: Photograph of Implantable Electrode Unit

Packaging of the implantable unit is also a very critical point. Medical grade epoxy was used for the primary coating of the electronic circuitry and then the total device was coated using biocompetible polyurethane. Figure 4 is a photograph of the internal units.

C. Animal Experiments

A total 10 type I internal units were implanted in 5 dogs (25-30 kg) with one unit for each hemidiaphragm. The dog was anesthetized using atropin, xylazine, and ketamine, and maintained using isoflurane. Fluid homeostasis was preserved using intravenous normal saline, and body temperature was maintained with a heating pad. Two internal units were implanted side by side in subcutanoues tissue of the left flank. Each electrode was located as close as possible to the opposite side of the phrenic motor point, or abdominal surface of each hemidiaphragm. The exact motor point was selected as a point that a contraction reponse was maximized with the minimum amplitude of stimulation pulse which was varied from 2 mA to 25 mA. During the finding of the phrenic nerve motor point, IPI was set nominally as 50 ms. After implantation of internal unit is over, IPI values were varied for the range of 20-120 ms, in random order. Then, the optimal IPI was set as the highest value that could provide a smooth contraction.

Stimulation tests for training the muscle started after one week from surgery, which were conducted at two days per week intervals for 3 and 4 weeks for each dog and still in process. Tests were conducted twice a day with a gradually increased stimulation period up to 25 minutes in maximum for the adaptation of the muscle to the electrical stimulation. Inspiratory time was 1 s and period of respiration was 3 s.

The supine dog was hyperventilated to apnea, and then individual stimulation test was conducted during the apneic period. Test was stopped when apnea was gone and self respiration appeared.

Throughout the procedure, airflow of breath, ECG, and SpO$_2$ were continuously monitored. Ariflow was acquired from a commercial spirometer (Webdoc Spiro^{TM}, ELBIO, Korea), and ECG, SpO$_2$ from a patient monitor. All data was sampled at 100 Hz using an analog to digital converter (EZAD-512, ELBIO, Korea). The resulting tidal volume calculated from airflow data was used to qualify the response to the stimulation.
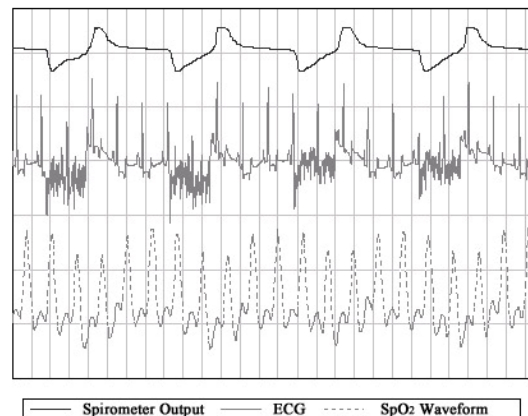

Figure 5: Waveforms of monitored physiological variables. Electrical stimulation signal can be confirmed as noise added on the ECG.

Electrical stimulation adds noises on ECG, so stimulation signal could be recognized by monitoring the noises on ECG. Typical waveforms of all monitored variables are in Figure 5. If some airflows started to shown up not synchronized with the noise on ECG, it represented the end of an apneic period.

Results

During the experiments, IPI value was maintained in range of 20-30 ms. From one week after the surgery, the response to the stimulation was getting greater. Dog #192 showed the maximal response from 2 weeks after the surgery, the others have shown the maximal response since 4 weeks after the surgery. From 4 out of 5 dogs, we could get the feasible data of tidal volume. Table1 summarizes the averages and the standard deviation of tidal volumes achieved from the stimulation for 25 minutes with the maximum currents on the 4th week after surgery.

Since tidal volume of a dog weighing more than 20 kg is generally 10 ml/kg in a normal state [6], dogs used for the experiment (25-30 kg) were expected to have tidal volume of 200-300 ml/breath. Comparing to this reference' value, the results indicate that the system operates properly in all cases except for dog #191.

If a dog recovered self-respiration, then the response to the stimulation appeared fluctuating. In a case that the phase was synchronized, tidal volumes were

Table 1: Mean and standard deviation (SD) value of tidal volume in ml/breath (SD in parentheses)

Subject	Tidal Volume per Breath
Dog #187	275.6 (17.07)
Dog #188	330.5 (9.27)
Dog #190	234.3 (16.85)
Dog #191	136.8 (3.27)
Dog #192	388.3 (22.09)

constructively added, otherwise a destructive addition was observed.

Discussion

An implantable breathing pacemaker based on a new and efficient idea was developed and verified in animal experiments with total 5 dogs. The purpose of this pilot study was to verify *in vivo* performance of the developed breathing pacemaker system be achieving complete activation of the diaphagm with a stimulating current level less than 25 mA. The respirations recruited by stimulation were successful in four cases, the results suggest that we have achieved almost complete activation of diaphragm.

In one case of dog #191, tidal volume did not reach to the reference value. In this case, the breathing muscle may not have reached to its maximum response to stimulation yet even after 4 weeks of training period. The best case showed a gradual increment of response level during the training period. There is a possibility that the location of electrode is too far from motor point of phrenic nerve. If the response of this dog does not increase any more, then we are going to perform laparotomy to inspect the actual location of electrodes and then implant the internal unit with two electrodes (type II). Additional stimulation of the secondary electrode may provide complete contraction of diaphragm. Other possible causes of the low response will be examined through autopsy after the animal is sacrificed.

At the end of apneic period, self respiration appeared and it made constructive respiratory addition with the response of stimulation. For patients who can maintain self breathing with incomplete level, if a adequate amplitude of stimulation is added to self breath in well-synchronized phase, it will produce a full breath. Detection of self respiration and synchronization of stimulation are the future works to do.

Conclusions

We developed a new implantable breathing pacemaker that stimulates the phrenic nerve motor point of diaphragm using the TET technology for higher efficiency of transmission. This system is a good alternative to direct stimulation of phrenic nerve, and can be implanted by a minimally invasive surgery. We also proposed a thin secondary coil which is printed on a PCB, for an implantable unit. Promising results were obtained from animal experiment with 5 dogs for longer than 4 weeks.

Acknowledgement

References

[1] DiMarco AF. (1999): 'Diaphragm pacing in patients with spinal cord injury', *Top. Spina Cord. Unj. Rehabil.*, **5**, pp. 6-2

[2] P. Hunter Peckham and Jayme S. Knutson (2005): 'Functional Electrical Stimulation for Neuromuscular Applications', *Annu. Rev. Biomed. Eng.*, **7**, pp. 337-60

[3] Anthony F. DiMarco, Ramond P. Onders, Krzysztof E. Kowalski, Michael E. Miller, Sandra Ferek, and J. Tomas Mortimer (2002):ifulco P., Cesarelli M., Allen R., Sansone M., and Bracale M. (2001): 'Phrenic Nerve Pacing in a Tetraplegic Patient via Intramuscular Diaphragm Electrodes', *American Journal of Respiratory and Critical Care Medicine*, **166**, pp. 1604-6

[4] MWS, internet site address: http://www.mwswire.com

[5] Brian D. Schimit and J. Thomas Mortimer (1999): 'The Effects of Epimysial Electrode Location on Phrenic Nerve Recruitment and the Relation between Tidal Volume and Interpulse Interval', *IEEE Transaction on Rehabilitation Engineering*, **7**, pp. 150-8

[6] Willam W. Muir III, John A. E. Hubbell, Roman T. Skarda, Richard M.Bednarski (2000): 'Handbook of Veterinary Anesthesia, third edition', in Mosby, p 237