Microstimulators and Intramuscular Hook Electrodes for the Stimulation of Respiratory Muscles

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Abstract

Background/Objectives: We determined the feasibility of stimulating the major muscles of respiration with different types of electrodes. Intramuscular hook electrodes, model microstimulators (M-Micro) developed in our laboratory, and commercial radiofrequency microstimulators (RFM) (Alfred Mann Foundation, Valencia, CA), were employed in this investigation.

Methods: In 8 anesthetized dogs, M-Micro were placed bilaterally on the diaphragm and in the abdominal muscles, and hook electrodes were placed in the 3rd and 5th intercostal regions adjacent to the intercostal nerves known to support inspiration. In 3 of the 8 animals, RFMs (Alfred Mann Foundation) in addition to the M-Micros were sutured to each hemidiaphragm at the same optimal site for phrenic nerve stimulation. During a hyperventilation-induced apnea, 2-second stimulations were applied to the diaphragm and with various combinations of diaphragm plus supporting muscles, both thoracic and abdominal.

Results: Diaphragm stimulation alone provided tidal volumes adequate for basal alveolar ventilation. However, implantation of the RFM required greater contact with the muscle. Stimulating other respiratory muscles along with the diaphragm further increased tidal volumes. The hook electrodes, M-Micro, and RFM performed equally well.

Conclusions: In the acute dog model, M-Micro and hook electrodes can provide an implant system for the maintenance of ventilation. Support of the intercostal and abdominal muscles has the potential to reduce the contraction requirements of the diaphragm with decreased likelihood of diaphragm fatigue and hypoventilation. Whether the electrodes under investigation could provide an implant system for long-term ventilation needs to be determined.

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INTRODUCTION

Electrical stimulation or pacing of respiratory muscles has been used to successfully maintain resting levels of alveolar ventilation in spinal cord injury patients who require permanent mechanical ventilation (1–4). Typically, cuff electrodes are placed in the neck or thorax adjacent to the phrenic nerves. However, cuff electrodes used in these locations may cause nerve injury (4). An alternative approach to stimulating the phrenic nerve is based on the use of electrodes inserted directly in the diaphragm (5,6). Both hook- and suture-type electrodes

placed close to the main phrenic trunk entering the diaphragm result in complete muscle recruitment (5). Advantages of this diaphragm approach include an electrode that is not in direct contact with the phrenic nerve and ease of placement via laparoscopy.

Although diaphragm pacing can provide sufficient alveolar ventilation to maintain satisfactory basal gas exchange, little reserve is available during times of increased ventilation demand (eg, fever, infections, pulmonary congestion). This limited ventilatory reserve is, at least in part, due to the absent intercostal inspiratory and abdominal expiratory muscle support during the ventilatory cycle. In particular, the lack of motor input to the intercostal muscles results in an inspiratory collapse of the chest wall and a decrease in the efficiency of breathing (7). This raises the possibility that concurrent

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intercostal and diaphragm stimulation could result in a decreased chest wall distortion during inspiration and increased tidal volumes.

Various methods of stimulating intercostal and abdominal muscles have been tried experimentally. In a previous investigation, we demonstrated that intramuscular electrodes are capable of stimulating intercostal muscles that support inspiration (5). Thoracic electrodes placed in the 3rd to 5th interspaces produced chest expansion and enhanced a diaphragm-induced tidal volume. Electrodes placed close to the ventral roots in thoracic segments can also activate thoracic muscles that support inspiration, but the concurrent stimulation of other muscle groups creates problems for clinical applications (8). Several investigators have also produced an electrical stimulation of abdominal wall muscles that support expiration (9–11). Surface electrodes applied to the abdominal wall create sufficiently high expiratory flow rates to assist the expulsion of airway secretions.

New implantable electrodes and microstimulators are in development that could greatly enhance the application of neuroprosthetics for respiratory support. Microstimulators require no connecting wires, are small (3×17 mm), and can be implanted through an introducer or laparoscope. One such device is the radiofrequency microstimulator (RFM) (Alfred Mann Foundation, Santa Clarita, CA). This is a very small device that uses radiofrequencies from an external coil for both the energy of electrical stimulation and stimulation protocols.

For these studies, we constructed model-microstimulators (M-Micro). These devices are similar to commercial devices under development but have connecting wires to external stimulators. The primary aim of this study was to determine the feasibility of using microstimulators placed on the diaphragm to support ventilation; both the M-Micro and the RFM were tested. We expected these 2 devices to perform similarly. However, because of slight differences in their electrode surfaces, it is important to compare the 2 devices. The secondary aims were to assess the effect on tidal volume of concurrent intercostal and diaphragm stimulation and of the sequential stimulation of abdominals, intercostals, and diaphragm.

METHODS

Animal Preparation

Eight fasted mongrel dogs weighing 13 to 18 kg were anesthetized with 22 mg/kg intravenous pentobarbital. Supplemental doses were given as required, and body temperature was kept at 38°C by the use of a heating pad. The tracheas were intubated and the animals artificially ventilated (Drager Anesthesia Ventilator, Louisville, KY). Tracheal air flow was monitored with a pneumotachometer (A. Fleish, OEM Medical, Richmond, VA) connected to the endotracheal tube. The signal was integrated (Gould, Gould Inc, Cleveland, OH) to give tidal volume. A low-pressure respiratory belt surrounded

Figure 1. Construction of model microstimulator (M-Micro) with connecting wires. Dimensions are 18 mm long (tubing 15 mm, wire electrodes 3 mm) and 3 mm in diameter. The electrodes of the M-Micro were formed as balls of stainless steel wire and glued with silicone to the ends of the tube.

the chest and was connected to a pressure transducer to provide thoracic dimensions. Esophageal pressure was monitored from a balloon-tipped catheter placed in the midthoracic region. All pressures were recorded by means of Statham pressure transducers (P23AC, Statham Inc, Hato Rey, Puerto Rico) and amplified by Gould preamplifiers. Recordings were displayed on an 8-channel recorder (Astro-med Inc, West Warwick, RI). Treatment of animals and protocols followed the guidelines set forth in the Helsinki Declaration.

Electrode Construction and Implantation

The M-Micros were assembled from multistranded stainless steel cable, Silastic tubing, and silicone adhesive (Figure 1). The cable consisted of 20 strands of 0.001-inch diameter stainless steel wire (Part# A5635, 316LVM Cooner Wire Inc, Chatworth, CA) coated with Teflon. The M-Micro used 1.5 cm of Silastic tubing (North American, Belle Mead, NJ) that had an inner and outer diameter of 0.062 and 0.092 inches, respectively. A 2-mm hole was cut in the middle of the tubing, and 2 cables were threaded through the hole to the opposite ends of the tubing. After passing through the tube, 5 cm of the cable was stripped of insulation to make the electrode. This

exposed wire was wrapped, shaped into a ball, and secured to the end of the tubing with silicone adhesive (Adhesive Silicone 1137, NuSil Inc, Carpinteria, CA). To connect to an external stimulator, the last 2 cm at the distal end of each cable was stripped and soldered (silver solder). The overall dimensions of the M-Micro were 18 × 3 mm.

After an abdominal incision, 1 M-Micro electrode was sutured to each hemidiaphragm (Figure 2). A 3-mm diameter monopolar test probe was used to identify the best location. On the left side, this was about 2 cm in length and close to the junction between the muscle and central tendon. On the right side, this placement was just lateral to the penetration of the vena cava. Wires from the M-Micros were pulled through the abdominal incision and connected to external Grass stimulators. In 3 animals, RFMs (Alfred Mann Foundation) in addition to the M-Micros were sutured to each hemidiaphragm (Figure 2) at the same optimal site for phrenic nerve stimulation.

Cooner wire hook electrodes for the intercostal muscles were constructed from the same Teflon-coated multistranded stainless cable used for the M-Micro. The last centimeter of wire was stripped and bent back as a hook. An 18-gauge needle containing the electrode was pushed through the skin along the inferior rib margin, and the electrode was placed in the superficial muscle layer. Hook electrodes were inserted bilaterally in the ventrolateral, lateral, and dorsal locations of the 3rd and 5th interspace. The most effective location was used in subsequent testing. For the intercostal muscles, we chose not to use M-Micro electrodes because such placement was more difficult than inserting the needle electrode along the rib margins.

The abdominal rectus and abdominal lateral muscles were implanted with 4 M-Micros, 2 on each side. An effective location was found with an exploring electrode run along the inner abdominal wall (same as for diaphragm). After making a 2-cm incision, the M-Micros were implanted within the abdominal rectus and abdominal lateral muscular tissue. The incision was closed with sutures after implantation. Like those on the diaphragm, the leads were pulled through the abdominal incision and connected to external stimulators.

Electrical Stimulation

Activation of the M-Micro and Cooner wire hook electrodes were conducted using 7 Grass stimulators (Astro-med Inc, West Warwick, RI) with capacitor coupling for charge balance (5). Activation of RFMs requires an external Helmholtz-type coil. This consisted of 1 coil placed on the dorsal and 1 coil on the ventral surface of the animal. The radiofrequency-generating system (Alfred Mann Foundation) consisted of a power unit, control unit, and computer that worked together to deliver the stimulations. Both the M-Micros and RFMs have a cathode and an anode for bipolar stimulation.

Figure 2. Right hemidiaphragm instrumented on the ventral side with radiofrequency microstimulators and model microstimulators. At arrows, diaphragm muscle is pulled up around the cathode end of the stimulators with silk sutures to provide good electrode contact with the diaphragm.

Monopolar stimulation was carried out for the intercostal hook electrodes. For this stimulation, a grounding positive electrode was placed under the skin in the upper leg. All stimulation was conducted in current-response protocols (4–6 increasing stimulation currents) with the following parameters that induced tetanus: 150 μ s pulse duration, 25 pulses per second, and a period of 2 seconds.

Protocol

We investigated the stimulation of all of the major muscles of inspiration and expiration. The tidal volume was the primary measure used to evaluate effective stimulation, but respiratory flow rates, thoracic and abdominal expansion, and esophageal and abdominal pressures were important secondary measures. Stimulation was always conducted during the period of respiratory apnea after hyperventilation. This period usually lasted 2 to 3 minutes. Stimulation records within 15 seconds of a spontaneous inspiration were excluded from the analysis.

For the diaphragm stimulation using both the M-Micro and the RFM, current-response studies were conducted with unilateral stimulation (on 1 side of the animal) and then with bilateral stimulation. The RFM was only evaluated in the last 3 animals. Next, intercostal and then combined intercostal and diaphragm stimulation were studied. For this protocol, only bilateral stimulation was used in both locations, and the diaphragm was only stimulated with the M-Micro at a current to produce a tidal volume of 150 to 275 cc, depending on the size of

Figure 3. Comparison of the tidal volumes (mL) obtained with unilateral and bilateral diaphragm stimulation with model microstimulators. Bilateral stimulation induced larger tidal volumes (*indicates significant differences). Data were collected from a total of 8 dogs; mean $\pm$ SEM. Numbers indicate the total observations made at each stimulation current.

the animal. Finally, abdominal muscle stimulation was added to the protocol. In some cases the abdominal muscles were stimulated first in order to begin inspiration closer to residual volume. Then coincident with abdominal relaxation, combined intercostal and bilateral diaphragm stimulation was performed. As with the preceding second protocol, only bilateral stimulation was used in these protocols.

Statistical Analysis

Values at any given current were compared with a *t* test. Differences were considered significant at the 0.05 level. Data are presented as the mean $\pm$ SEM.

RESULTS

Observing the test probe's response as it was moved over the ventral surface of the diaphragm ensured that the microstimulator's cathode was sutured to a location that was near the entry point of the phrenic nerve (5). The failure to obtain an initial diaphragm response from the microstimulator implant was always a contact problem solved by further suturing (Figure 2). Stimulus response curves for unilateral and bilateral diaphragm stimulation with the M-Micro are shown in Figure 3. As current strength increased, there was a progressive increase in tidal volume. As expected, bilateral stimulation produced a greater tidal volume than unilateral stimulation. A collapse of the chest wall was observed during both unilateral and bilateral diaphragm stimulation (Figure 3).

In our previous study (5), mapping of the chest wall indicated that the best electrode locations for chest expansion were in the ventrolateral region of the 3rd to 5th intercostal spaces. In the present study, a lateral

Figure 4. Tidal volumes produced with bilateral intercostal, diaphragm, and combined stimulation. Results represent 10 observations in 8 dogs. Intercostal stimulation 5–6 mA; diaphragm stimulation 2–5 mA; mean $\pm$ SEM. Combined stimulation was significantly different from diaphragm stimulation alone ($P < 0.05$).

location was found to be more effective. Carefully placed hook electrodes along the rib margins, when activated, consistently produced chest expansion but not always an inspired volume. Results of stimulation of the chest and diaphragm alone and then combined are shown in Figure 4. Chest wall stimulation alone produced chest wall expansion and a modest tidal volume. Stimulation of the combined diaphragm plus chest wall produced a 56% increase in tidal volume over the submaximal bilateral stimulation alone ($P < 0.05$).

The 2-second stimulation period produced a sudden movement of the chest, usually during the first half of the stimulation period. To reduce this sudden nonphysiological contraction, we investigated manually ramping the current with the M-Micro. This did produce a more even chest expansion (Figure 5). In comparison to spontaneous breathing, stimulation with ramping produced lower peak flow rates than without ramping.

Although abdominal muscles have expiratory functions, they can be incorporated into a sequence of stimulations that contributes to tidal volume. Their initial contraction at functional residual capacity decreases lung volume toward residual volume. The rebound in lung volume with their relaxation can be utilized as part of an overall inspiratory effort as demonstrated in Figure 6.

In the final 3 animals, RFMs were sutured to the diaphragm bilaterally adjacent to the M-Micro (Figure 2). Contact problems did arise with the RFM unless sutured into a muscle fold. When good contact was achieved and when the same stimulating currents were used, equivalent tidal volumes were obtained with unilateral and bilateral M-Micro and RFM stimulation (Figure 7).

DISCUSSION

It is now well established that diaphragm stimulation via the phrenic nerve can maintain adequate resting alveolar

Figure 5. Effects of ramping of the stimulating current applied to the diaphragm from a single animal. (A) Spontaneous breathing. (B) Bilateral diaphragm stimulation with model microstimulators using a 2-second stimulation period at 25 pulses per second and a current of 10 mA. (C) Bilateral diaphragm stimulation with model microstimulators using a 2-second ramp at 25 pulses per second and a maximal current of 7 mA.

ventilation and that intramuscular electrodes placed directly in the diaphragm have potential clinical applications in this regard (1–8). Microstimulators (with their small size, ease of placement, and potential lack of direct external connections) may be ideal for this application. Through use of a test probe on the ventral side of the diaphragm, it is possible to determine accurately the exact location for electrode placement, and our M-Micro

consistently produced adequate tidal volumes in the acute animal. As expected, the RFM produced similar results, but the small electrode tips at each end of the device created contact problems on the diaphragm unless sutured into a small muscle fold. It is important, therefore, to address general problems of electrical stimulation of the phrenic nerve innervating the diaphragm, which would include the effects of electrode

Figure 6. Effects from a single animal of individual and combined bilateral stimulation of the respiratory muscles lasting 2 seconds at 25 pulses per second. All stimulations were bilateral. Diaphragm stimulation with model microstimulators was at a current of 3 mA, abdominal muscle stimulation included rectus and oblique at 15 mA, and intercostal stimulation was at a current of 5 mA. “All together” included 3 stages: (a) abdominal stimulation (expiration); (b) coincident with abdominal relaxation, intercostal, and diaphragm stimulation; (3) intercostal and diaphragm relaxation.

movement during stimulation and electrode migration. An approach to these problems is to use an intramuscular hook electrode. Actually, Synapse Biomedical Inc has used a Peterson hook electrode in the diaphragm of tetraplegic patients with good results (6). Another alternative would be the RFM connected to the Peterson electrode.

Collapse of the chest wall with diaphragm stimulation reduces inspiratory efficiency (4). It is estimated that collapse of the chest wall reduces by 14 to 33% of the volume displaced by the diaphragm (4). Notably, thoracic paralysis in tetraplegia reduces tidal volumes and shifts respiration toward a less efficient, rapid shallow breathing pattern (4,11). Other investigators have investigated this issue by electrodes placed close to the ventral nerve roots in thoracic spinal segments (5–8). Our approach has been different with stimulation of the rib margins. With this technique we have observed stabilization or expansion of the chest wall during diaphragm

stimulation. In addition, in some of the animals (Figure 4), stimulation of the chest alone could induce an inspiratory volume. There was a synergistic effect between thoracic and diaphragm stimulation. A combined stimulation produced a larger tidal volume than the sum of the tidal volumes of their individual contractions (Figure 4).

We previously demonstrated in this animal model that upper thoracic intercostals are agonist muscles that support inspiration, whereas the lower thoracic intercostals support expiration (14). Electrodes placed between the 3rd and 5th interspaces were observed to be most effective at causing chest expansion. In addition, the ventral-lateral location was thought to be optimal. However, in the current studies a more lateral location was observed to be most effective. In both studies, the location in the stimulating electrode was next to the lower edge of the rib.

Figure 7. Tidal volume elicited by diaphragm stimulation with model microstimulators (M-Micro) and radio-frequency microstimulators (RFM) during unilateral (A) and bilateral (B) stimulation. The responses obtained with the RFM are equivalent to the M-Micro. Unilateral and bilateral stimulation with the M-Micro represents 3 to 21 observations at each current in 8 dogs. For the RFM, there are 2 to 10 observations at each current level from 3 dogs.

Prestimulation of the abdominal muscles reduced lung volume below functional residual capacity, and relaxation coincident with inspiratory muscle stimulation generated a larger tidal volume than stimulating inspiratory muscles alone (Figure 6). This suggests that incorporating abdominal muscle stimulation in a functional electrical stimulation regimen could reduce demands on the diaphragm and the prospect of diaphragm fatigue during longer-term pacing.

Other investigators have tested different methods to induce expiration for cough. Surface electrodes on the abdominal wall of tetraplegic patients were used for an electrically induced “cough” with sufficiently high expiratory flow rates to assist the expulsion of airway secretions (9–11). Others have used multiple RFM placed

in the lower thoracic interspaces to produce significant contractions that support expiration (15). The magnitude of the maximum expiratory flow rate during cough is dependent on the preinspiratory effort. Any enhancement of this inspiratory effort by a functional electrical stimulation of the inspiratory muscles could further increase expiratory flow rates. Thus, although cough was not studied here, our approach of combining the 3 respiratory muscles should be considered for promoting cough.

CONCLUSIONS

In this feasibility study, we demonstrated the potential of microstimulators implanted on the diaphragm to effectively stimulate the phrenic trunks and provide an adequate basal level of alveolar ventilation. Microstimulators and hook electrodes can also be used to stimulate thoracic and abdominal muscles. Support from these respiratory muscles may reduce the ventilatory load carried by the diaphragm, which would protect against fatigue of the system during long-term pacing. This needs to be demonstrated in a long-term study.

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