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**ELECTRICAL ACTIVATION OF THE DIAPHRAGM
USING EPIMYSIAL ELECTRODES**

by

BRIAN DAVID SCHMITT

Submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosophy

Dissertation Advisor: J. Thomas Mortimer, Ph.D.

Department of Biomedical Engineering
CASE WESTERN RESERVE UNIVERSITY

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*We also certify that written approval has been obtained for any proprietary material contained therein.

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Brian V. Schmit

ELECTRICAL ACTIVATION OF THE DIAPHRAGM USING EPIMYSIAL ELECTRODES

Abstract

by

BRIAN D. SCHMITT

The goal of this research was to test epimysial electrodes for electrical activation of the diaphragm (diaphragm pacing) for ventilatory assist. Epimysial electrodes were applied to diaphragm pacing to alleviate risk of phrenic nerve damage associated with cuff electrodes and placement difficulties associated with intramuscular electrodes.

Epimysial electrodes were stapled onto the abdominal surface of the canine diaphragm within 1.4 cm of the phrenic nerve motor point using a laparoscopic surgery and test stimulation of many potential implant sites. Improvements in electrode placement to within 0.5 cm of the motor point were developed using recruitment curve measurements and retrospective laparoscopic image data to locate the motor point. An Endopath laparoscopic stapler and an electrode thickness between 0.75 mm and 1.0 mm enabled attachment of epimysial electrodes to the diaphragm with low risk of muscle perforation. An impedance pneumograph using the implanted electrodes was effective for detecting breathing events during diaphragm pacing and the feasibility for detection of airway obstruction and calibration of tidal volume was demonstrated.

Full activation of the diaphragm was achieved with electrodes placed within 1.0 cm of the phrenic nerve motor point. Muscle length dependent recruitment was

documented and correlated with electrode location relative to the motor point and the longitudinal muscle fiber direction. The long term recruitment improvements were documented in 21 of 32 implanted electrodes

Optimal stimulus parameters that minimize the risk of diaphragm fatigue while maintaining a minimum level of ventilation were found using the surrogate worth trade-off method. We found that similar risks of fatigue occur for a 14 Hz change in stimulation frequency and 0.1 change in duty cycle based on 30 minute recordings of tidal volume during diaphragm pacing.

Histological results from the long term implants showed an active chronic tissue reaction consistent with mechanical stresses placed on the tissue near the electrodes. Capsule thicknesses after 3 months averaged 1.24 mm and the risk of continued capsule growth prevented recommendation of clinical application of this electrode design.

DEDICATION

To my parents, George and Joanne Schmit
The most generous people I have ever known

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Chapter 1

Electrical Activation of the Diaphragm

HISTORY

Electrical activation of the phrenic nerve was recognized as a method to produce ventilation by Hufeland in 1783. Boulogne and others used this approach as a technique for resuscitation, particularly in the newborn. The field was relatively dormant until Sarnoff and co-workers at Harvard began investigating prolonged phrenic stimulation in 1948 (Sarnoff 1948). Long-term stimulation of the phrenic nerve became a clinical reality with the introduction of a radio frequency (RF) transmission system developed by Dr. William Glenn at Yale University. The majority of the clinical data available to date has come from this group (Ciesielski 1983, Glenn 1980, Glenn 1983, Glenn 1988). Approximately 700 phrenic stimulators have been implanted worldwide in the last 25 years in high quadriplegics and in people with miscellaneous hypoventilation syndromes. The concept of artificially stimulating the diaphragm to support or assist respiration in chronic respiratory disorders has been conceptually appealing but has been limited in application to a small patient population. The major problems with the current prosthetic devices have been associated with the technique or with clinical problems related to complex patient applications.

The management of respiratory failure now routinely includes the use of mechanical ventilation in a wide range of clinical settings to support or assist respiration. The goals of artificial ventilatory support have been primarily related to achieving adequate oxygenation and ventilation. In recent years however, ventilatory assist devices have been prescribed specifically in the management of acute and chronic respiratory muscle fatigue. There are a range of conventional positive and negative pressure devices which are familiar to most health

professionals in respiratory medicine. Phrenic nerve pacing enhances speech abilities and facilitates mobility for occupational and recreational activities. The psychological advantage of being free from a respirator is also an important aspect of this ventilator. Electrical activation of the diaphragm is a relatively new and infrequently utilized technology that opens new potential avenues for the management of respiratory failure.

PHYSIOLOGICAL BACKGROUND

The diaphragm is the major muscle of respiration and is innervated bilaterally by the phrenic nerves, which originate from the third, fourth, and fifth cervical spinal roots. Accessory motor fibers originating from other roots have been described and are cited as the rationale for implanting electrodes in the thorax rather than the neck. Under normal conditions, the anterior horn cells of the phrenic nerve in the spinal cord (C3,4,5) are under the control of nuclei of the respiratory center situated in the dorsal medulla at the base of the brain. The precise anatomy of these nuclei and the nature of their interconnections are not well understood. This respiratory controller governs the activity of other respiratory muscles responsible for opening the upper airway and stabilizing or expanding the rib cage. Damage to the brain stem nuclei and connecting tracts to the ventral root cells compromise ventilation while sparing the phrenic nerve, which makes the individual a candidate for diaphragm pacing.

Ventilation is controlled by the respiratory center to insure little change in normal values of arterial PCO_2 and PO_2 over years. It is well known that arterial blood gases can vary from normal limits for short periods because adjustments in ventilation are not instantaneous and the automatic control system in the medulla can be modified or even temporarily overridden by higher brain centers. The ability of

the automatic control system to correct disturbances in blood gas concentrations depends on the properties of the respiratory controller, which may be determined by hereditary factors and/or altered by disease (Arkinstall 1974, Hirschman 1975). Though chemoreceptors are still thought to play the major role in regulating breathing, recent work has emphasized the role of mechanoreceptors in the lung and chest wall that can modify ventilation by transmitting signals to the medullary neurons via the vagus nerves (Nochomovitz 1981). The response to a given set of inputs varies among individuals. This complex interaction between chemical and mechanical factors and the body's respiratory modulation systems are bypassed with the present fixed-rate open-loop system of phrenic nerve stimulation.

RESPIRATORY MUSCLE ACTIVITY

The forces produced by respiratory muscle contraction cause the pressure changes observed in the thoracic and abdominal cavities during breathing. In the diaphragm, the conversion of force into pressure is approximated by Laplace's Law, which relates the pressure developed across the diaphragm, transdiaphragmatic pressure (P_{di}), to the force developed by the diaphragm and its radius of curvature (Goldman 1973). Since the radius of diaphragmatic muscle curvature may vary systematically with lung volume, so the relationship between force and P_{di} may also vary. The transformation of force into pressure by the other inspiratory muscles is not well understood (Roussos 1982, Sharp 1977).

The chest wall can be divided into a ribcage and an abdominal compartment with their respective musculature. Forces developed during inspiration act to displace the abdomen and rib cage and to increase lung volume. The sum of the volumes displaced by the abdominal wall and the rib cage is for practical purposes

the total volume change of the thoracic cavity, which must equal the volume change of the lung (Goldman 1973, Sharp 1977, Derenne 1978, Grimby 1968).

The inspiratory muscles have been conventionally divided into the diaphragm, external intercostal and "accessory" muscles. More recent work has disputed the accessory nature of the scalenes and intercostals, which are now considered to be primary muscles of inspiration involved in normal breathing (Sarnoff 1948, DeTroyer 1988, Gibson 1976). This has significant implications for present day diaphragm pacing where the diaphragm is driven independently from the other inspiratory muscles.

The Diaphragm

The diaphragm is inserted laterally onto the ribs and medially onto the central tendon (Figure 1.5). The muscle fibers at the periphery are applied to the chest wall as a zone of apposition. In this zone of apposition the fibers are oriented parallel to the rib cage. Diaphragm contraction pushes down on the abdominal viscera, displaces the abdominal wall outward, and increases abdominal pressure (P_{ab}) (Grimby 1968, D'Angelo 1974, DeTroyer 1984, Konno 1967, Sharp 1974). At the same time, the diaphragm normally lifts the rib cage upward, causing an outward displacement because of its rib articulation, and generates a negative pleural pressure (P_{pl}) that inflates the lungs. The increased abdominal pressure, applied to the lower rib cage below the diaphragm, also contributes to rib cage expansion. Although the diaphragm is primarily an inspiratory muscle, there is no direct action of the diaphragm on the upper rib cage. Upon diaphragm stimulation, with no intercostal or accessory activation, the upper rib cage diameter decreases (DeTroyer 1988, D'Angelo 1974) (an expiratory action) as it moves inward in

response to a lowered pleural pressure. The diaphragm also has an expiratory action on the rib cage when its dome is flattened and its peripheral fibers are directed perpendicular to the chest wall rather than parallel. This happens normally at high lung volumes, but may also occur during tidal breathing in hyperinflated patients with severe obstructive lung disease in whom the functional residual capacity (FRC) is markedly increased. In this case, the negative P_{pl} generated by the diaphragm sucks in the lower part of the chest, and the rib cage actually may decrease in its lateral dimension (DeTroyer 1988, D'Angelo 1974, Ashutosh 1975, DeTroyer 1981, Glenn 1986). The force generated by the diaphragm during inspiration is reflected in the transdiaphragmatic pressure gradient, which is the difference between P_{ab} and P_{pl} . These values can be obtained by simultaneously recording pressures in the esophagus and stomach using balloon tipped catheters. In normal persons, P_{di} ranges from 10-20cm H₂O during quiet breathing (Roussos 1982, Sharp 1974).

Recent experimental work in animals has suggested that the costal and crural parts of the diaphragm (Figure 1.5) are functionally distinct (DeTroyer 1981). When the costal part of the diaphragm contracts, the dome displaces the abdominal viscera downward. To the extent that the viscera resist being displaced, the costal fibers develop a direct inspiratory force on the rib cage, which lifts it. Thus, the costal diaphragmatic contraction displaces both the rib cage and the abdomen while inflating the lung. Contraction of the crural diaphragm, which lacks attachments to the rib cage, only displaces the abdomen while it inflates the lungs. It has no direct action on the rib cage. Recent work has also demonstrated apparent differences in the neural control of the two muscles. Motor outflow to the crural portion of the muscle is initiated earlier in inspiration than to the costal portion. Costal stimulation

alone results in the posterior diaphragm being displaced downward while crural stimulation results in movement of the anterior portion. The crural diaphragm also has a greater response to changes in posture, hypercapnia and histamine inhalation with bronchoconstriction (Glenn 1980, Colin 1969, VanLunteren 1984). Since the two parts of the diaphragm have different segmental innervation (for dogs, C5 = costal, C6 = posterior costal and crural, C7 = crural (DeTroyer 1982)), different actions, and different embryologic and evolutionary origins, they can appropriately be regarded as two separate muscles. Clinical diaphragm pacing, which is applied to as many of the phrenic nerve fibers as possible, seems to result in activation of nerve fibers supplying both costal and crural areas.

Unilateral pacing of the diaphragm in humans has been performed quite extensively. Until recently this was a primary method for limiting fatigue and providing continuous ventilatory support (in adults). In infants paradoxical movement of the contralateral diaphragm upon stimulation is a significant clinical obstacle to this form of pacing. Bellemare, Bigland-Ritchie et al (Bellamare 1986) have suggested that the tidal volume evoked from the hemidiaphragm is related to the tension of the contralateral diaphragm manifested through a non-additive relation between hemidiaphragm stimulation and bilateral stimulation. That is, the transdiaphragmatic pressure evoked by bilateral stimulation is 3 times the value of the same pressure evoked by unilateral stimulation. In clinical situations as well as in our animal experiments this has not been the case. Bilateral stimulation yields approximately twice the transdiaphragmatic pressure of unilateral stimulation.

Intercostals, Scalenes and Other Muscles of Inspiration

The parasternal intercostal muscles are regularly active during quiet inspiration in normal subjects (DeTroyer 1983, Pengally 1971). The effect of the internal interosseous and external intercostals is thought to depend upon the action of other accessory muscles and lung volume (DeTroyer 1988). The nonlinear compliance properties of the rib cage at functional residual capacity tend to increase lung volume upon intercostal stimulation, but activation of the external intercostal and internal interosseous is generally associated with expiration (DeTroyer 1983a). There is also good evidence suggesting that the scalene muscles act as primary muscles of inspiration and that they have inspiratory electrical activity during resting breathing through their action on the upper rib cage (DeTroyer 1984, DeTroyer 1988). The scalenes, sternocleidomastoids, and trapezoids are more actively recruited at high levels of inspiratory activity, at which point other back muscles that support the chest also become involved (Davis 1976, Sharp 1974, Sharp 1986). Normal inspiration results from contraction of the parasternal intercostals, scalenes and diaphragm.

Electrical activation of the intercostal muscles has been demonstrated to provide some ventilatory support in laboratory animals. Extradural spinal stimulation at the T2-T3 level leads to primarily upper rib cage ventilation at levels near 35% inspiratory capacity in dogs (DiMarco 1987, DiMarco 1989). This device can provide ventilation for patients not eligible for phrenic pacers (DiMarco 1994). In addition, the intercostals could be used as fixators for diaphragm stimulation, improving tidal volumes by eliminating upper rib cage paradoxical movements. The effect of intercostal and diaphragm stimulation is additive, the total ventilation being the sum of the ventilation provided by each system. The intercostal system

may be useful in patients whose diaphragm stimulation is marginal and cannot supply the necessary ventilatory needs. Intercostal stimulation may, in this case be a useful adjunct. There is a concern of adding an additional degree of complexity to already complex patients while the risk of infection in adults or children is not clear.

The sternocleidomastoids are often used by quadriplegics to produce ventilation (DeTroyer 1986). Ventilation is provided by an increase in the cephalad motion of the sternum and upper rib cage (and consequent expansion of the upper rib cage). Additionally, the lower rib cage has an associated inward movement of its lateral walls most probably due to the decrease in abdominal pressure (see below). Other accessory muscles include the trapezia (which hold the head stable), platysma, and other muscles of the neck (DeTroyer 1986).

If inspiration is performed with the diaphragm remaining relaxed (as in phrenic nerve paralysis), the fall in pleural pressure required to inflate the lung is transmitted to the abdomen across the flaccid diaphragm. Under these circumstances, in contrast with diaphragmatic contraction, abdominal pressure falls, and the abdominal wall is displaced inward instead of outward (DeTroyer 1983a). The change in lung volume is the sum of the displacements of the rib cage and abdomen. As a result, the volume displaced by the rib cage will be greater than the change in the lung volume by an amount equal to the volume displaced by the abdomen.

Abdominal Muscles

The abdominal respiratory muscles include the rectus and transverse abdominis and the external and internal obliques. These are classically regarded as expiratory muscles that augment the passive recoil of the lungs, especially during deep and

forceful breathing. They also play a facilitative role in inspiration in that their contraction tends to lengthen the diaphragm and diminish its radius of curvature. This places the muscle on a more favorable portion of its length tension curve and allows for the generation of a greater transdiaphragmatic pressure with contraction of the diaphragm during the subsequent inspiration (Roussos 1982, Sharp 1974).

Abdominal muscles can affect inspiration by contraction during expiration. This contraction forces extra air out of the lungs and may result in passive inspiration following expiration (DeTroyer 1988). The action of each abdominal muscle is balanced by its expiratory insertional forces and the forces associated with an increase in abdominal pressure. The insertional forces tend to displace the rib cage caudal, decreasing the rib cage diameter, while the increased abdominal pressure tends to increase the lower rib cage diameter. The orientation and insertions of the rectus abdominus make it primarily an expiratory muscle (when stimulated by itself) while the effects of the external obliques are now thought to be inspiratory (due to increased abdominal pressure with small force pulling the lower rib cage caudal) (DeTroyer 1983b).

Interaction of the Respiratory Muscles

The actions and influences of the muscles of respiration are summarized in Table 1.1. Present application of diaphragm pacing involves an "open loop" system that must ignore the complex physiological interaction between the different respiratory muscles. Upright adults that are neurologically intact move both rib cage and abdomen outward during inspiration. Both compartments return to their resting positions during expiration. In the supine position the movement of the abdominal wall is relatively more prominent and that of the rib cage relatively less.

In experiments performed in normal subjects in the upright position using their diaphragms alone, Goldman and Mead reported that the diaphragm performs all the body's respiratory muscle work during quiet breathing (Goldman 1973). They further demonstrated that diaphragm contraction expands the rib cage along its relaxation curve. Contrary to this concept, Macklem and co-workers demonstrated that the intercostal and accessory muscles are never electrically silent and that their contribution is necessary to properly displace the chest wall (Roussos 1982, Sharp 1974). Support for this point of view was provided by Danon et al (Danon 1971) who studied quadriplegic patients with high cervical cord lesions (C₂). These patients breathed only with their accessory muscles, with electrically-paced diaphragms, or with a combination of the two. The investigators demonstrated that the diaphragm functioning alone did not drive the rib cage along its relaxation curve, but instead produced paradoxical inward movement of the upper rib cage. This was apparently due to the absence of accessory muscle activity which would normally support the rib cage. These findings suggest that the other respiratory muscles are important in stabilizing the chest wall and converting diaphragmatic contraction into intrathoracic pressure and volume changes. The effect on tidal volume of adding the other inspiratory muscle component was studied by triggering the stimulus to the diaphragm from an ala nasi EMG (Nochomovitz 1983). Triggered pacing resulted in an augmented tidal volume for a given stimulus to the diaphragm. Increased tidal volume was thought to be a result of diminished ribcage paradox secondary to ribcage and strap muscle activity (Bilgutay 1970).

Synchronization with Upper Airway Opening

There have been a number of experimental attempts to overcome the problem of incoordination of the contracting diaphragm and the opening of the upper airway.

Successfully coordinating the diaphragm and other muscles could obviate the necessity of a tracheostomy, make use of the ventilatory contribution of the other respiratory muscles, and facilitate phonation and swallowing. An early attempt to accomplish this at Harvard used the EMG signal from the sternocleidomastoid to trigger the stimulus to the diaphragm (Scharf 1978). This muscle also moves the head from side to side and is therefore not ideal for this function. End tidal carbon dioxide and the change in normal air temperature during breathing also have been used as triggers in experimental "demand" diaphragm pacers (Bilgutay 1970, Sato 1977). An EMG activated diaphragm pacing system using the ala nasi muscle (responsible for flaring the nostril) as a central trigger (Nochomovitz 1983) has also been described. The ala nasi has phasic respiratory activity and its firing slightly precedes the onset of phrenic activity (Strohl 1980). Other approaches using stimulation of the laryngeal musculature could be used to open the airway in synchrony with diaphragm pacing (Obert 1984).

PRINCIPLES OF ELECTRICAL STIMULATION

Electrical stimulation may be used to activate the phrenic nerve and thus mimic the action of the nervous system. Activation of the diaphragm normally occurs as nerve action potentials travel down the phrenic nerves to the diaphragm muscle. In instances where the drive to the phrenic nerves has been compromised, artificial activation of the nervous tissue can restore function to the otherwise paralyzed diaphragm.

Physiology

Neurons have a resting electrical potential difference across their cell membranes. This "membrane potential" is established by the separation of ions

between the extracellular and intracellular spaces. Each ion has a net electrical charge and the effect of charge separation is a potential on the outside of the cell which is higher than the intracellular potential. The magnitude of the membrane potential depends on the relative concentrations and membrane permeabilities of the ions in the system (see Figure 1.1).

Ions are affected by two forces: diffusion (chemical) and voltage (electric) (Osmotic forces are also involved, but we will not consider them here). Diffusion forces result from concentration differences that tend to move particles from an area of high concentration to an area of low concentration. Ions also experience electrical forces when placed in an electric field gradient. The ion concentration differences that produce diffusion forces also result in electric field gradients. As a result, the ion driving forces are themselves interrelated. The electric potential necessary to balance an ion concentration difference across a membrane is given by the Nernst equation: $E_A = (RT/zF)\ln[A]_o/[A]_i$, where E_A is the Nernst potential for ion A, R is the gas constant, T is the absolute temperature, z is the valence of the ion, F is the Faraday constant, and $[A]_o$ and $[A]_i$ are the concentrations of ion A outside and inside the neuron, respectively. Consider potassium (K^+) as an example. The concentration of K^+ is higher inside the cell than out and as a result, K^+ ions will diffuse out of the cell leaving negative ions inside. This action decreases the positive charge inside the cell and creates an electric field gradient that increases the tendency of K^+ to enter the cell. Such a process continues until an equilibrium is established between the force of the electric field gradient and the diffusion force created by the concentration gradient. The membrane potential at equilibrium is the Nernst potential (E_A) as described by the Nernst equation above. It should also be noted that the number of particles necessary to set up the potential

difference is small compared to the concentrations of the ions. As a result the concentration change due to the outward flux of K^+ during an action potential is negligible.

The relative membrane permeabilities to individual ions play an important role in determining the membrane potential. For a system that has multiple ion species with different Nernst potentials (as is the case for a neuron), each ion type will attempt to change the membrane potential to its own Nernst potential. The contribution of each ion in the system to the membrane potential is determined by the relative membrane permeabilities. Ions with a greater permeability will have more ion mobility through the membrane and have a greater effect on the membrane potential. For the nerve at rest, the membrane is most permeable to K^+ and the resting membrane potential is near the K^+ Nernst potential. The membrane is not as permeable to sodium (Na^+) and as a result the membrane potential differs greatly from the Na^+ Nernst potential. Because the resting potential is not exactly equal to the Nernst potential for K^+ or Na^+ , there is a net flow of K^+ out of the cell and a net flow of Na^+ into the cell. The ion concentration gradients are maintained by an active transport sodium potassium pump.

The membrane voltage can be altered by a change in the permeability of the membrane to any of the ions of the physiological system. The membrane permeabilities to potassium and sodium ions are determined largely by ion specific channels. Such channels have characteristic voltage and time courses and can be opened and closed by changes in the membrane potential. Sodium permeability is increased when the membrane potential decreases (depolarization) and sodium channels are opened. The response yields a temporary change in the membrane

state best represented in Figure 1.2. The membrane potential eventually reaches a maximum and then the change in membrane potential is quickly reversed as the sodium channels close and the potassium channels open. The response is enough to depolarize the adjacent portion of the membrane where this same process is repeated. The result is a signal, called an action potential, which travels along the membrane.

The initial depolarization of the axonal membranes of the phrenic nerve is done naturally by the electrical output of the medullary respiratory centers. This can also be accomplished artificially using an extracellular electrode placed near the phrenic nerve. Much in the same way that an action potential propagates, a section of a nerve can be depolarized through charge injection from an electrode. The resulting compound action potential is conducted to the diaphragm muscle, the muscle contracts, and a breath is generated.

Excitation Mechanism

The initial depolarization mechanism, which leads to phrenic nerve activation, is based on the electrical properties of an axon. The passive properties of an axon can be described electrically by three components: the axoplasmic resistance (R_i), the membrane resistance (R_m), and the membrane capacitance (C_m) (extracellular resistance can be assumed to be zero).

Extracellular stimulation using an electrode on the phrenic nerve depolarizes the membrane by changing the electric field at the outside of the membrane. Injection of charge into the extracellular space at the stimulation point alters the potential at the stimulation site. The membrane is effectively depolarized by a cathodic stimulus pulse as the difference between the intracellular and extracellular potential is

decreased. As current flows out of the axon in response to the change in extracellular field, the potential on the inside of the cell changes (Ranck 1981).

The electrical properties of the axon determine its excitability. A large membrane resistance (R_m) and small axoplasmic resistance (R_i) increase the likelihood of firing an action potential. Both of these resistances decrease with increasing diameter but axoplasmic resistance decreases to a greater degree than membrane resistance with the same diameter change. As a result, large diameter axons are stimulated with less extracellular charge injection than small diameter axons. Graded muscle contractions can be produced by gradually increasing charge injection during the contraction. This results in initial recruitment of the larger nerve fibers, and later recruitment of small nerve fibers. Conversely, physiologic recruitment begins firing smaller diameter neurons prior to larger diameter fibers (the Henneman size principle) (Henneman 1980).

Electrode nerve distance is important for nerve fiber recruitment. The electric field decreases quickly with increasing distance from the electrode. As a result, a small axon near the electrode may be stimulated with less charge injection than a large axon farther away. The distance relation also depends on electrode type. When using a monopolar electrode configuration in an infinite, homogeneous, isotropic medium, the electric field decreases in proportion to $1/\text{distance}$ and for a bipolar electrode configuration the field falls off with $1/(\text{distance})^2$. This means that a bipolar electrode configuration will have a greater degree of selectivity for the stimulation of axons closest to the electrode. Stimulation using low stimulus levels requires electrode placement very close to the nerve. Electrode placement is not a limitation with the use of phrenic cuff electrodes but is of concern for nerve

recruitment using electrodes placed in (intramuscular electrodes) or on (epimysial electrodes) the muscle. With electrodes placed on the muscle, placement near the phrenic nerve entry is critical for full diaphragm recruitment.

There are other differences between electrical stimulation and natural activation of the phrenic nerve. Electrical stimulation results in synchronous firing of the axons. The motor units do not usually fire synchronously and synchronous firing may increase the fatiguability of artificially stimulated muscle. Additionally, electrical stimulation results in action potentials that travel in both orthodromic (the usual direction of propagation) and antidromic (opposite) directions.

Electrochemistry

Injection of charge for electrical activation of the phrenic nerve may evoke electrochemical reactions at the interface between the electrode surface and the body tissue. While electron movement causes current in a metal electrode, charge transfer in tissue is conveyed by ions. In order for charge to be passed across an electrode–tissue interface there must be a charge transfer mechanism. That mechanism depends, to a large extent, on the density of charge which is injected. Low charge densities are delivered by capacitive mechanisms and reversible faradaic reactions that are generally considered safe. Conversely, high charge densities may cause undesirable irreversible reactions that can be harmful (Brummer 1977a, Brummer 1977b, Loeb 1982, Robblee 1990). For instance, an anodic stimulus of unacceptable charge density causes chemical reactions that can result in metal corrosion, oxygen evolution and increase in the local hydrogen ion concentration. Cathodic reactions may produce strong oxidizing agents and result in a local decrease in hydrogen ion concentration (Robblee 1990, Mortimer 1981,

Morton 1994). Undesirable consequences of these reactions are electrode corrosion and tissue damage, either of which cause failure of the neuroprosthetic system. The risk of harmful electrochemical reactions can be reduced by electrode materials and by controlling electrode shape and size. Parameters of the stimulus waveform also have a strong influence on the electrochemical reactions at the electrode.

Stimulus Waveform

The safety and efficacy of a neural stimulation device is largely dependent on the stimulus waveform. In addition to the effect of stimulus parameters on the electrochemical reactions, the stimulus waveform plays an important role in the recruitment properties of the nerve, the fatiguability of the diaphragm and the biocompatibility of the prosthesis. In Table 1.2, is shown how parameters can affect diaphragm pacing.

The stimulus for phrenic nerve activation consists of a stimulus pulse train for each breath that can be described by several parameters (see Figure 1.3):

Pulse Amplitude: for a current regulated stimulus, the pulse amplitude is the amplitude of the current level of the stimulating pulse measured in milliamperes (mA). For a voltage regulated stimulus, the pulse amplitude is the amplitude of the voltage level of the stimulating pulse measured in volts (V).

Pulsewidth: the pulsewidth is the duration of the stimulating pulse. This quantity is usually specified in microseconds (μ s).

Delay: the delay describes the time between the pulse phases of a stimulus waveform. This value is expressed in microseconds (μ s).

Frequency: the frequency is the number of stimulus pulses in one second. The interpulse interval is alternatively expressed and is defined as the time

between the initiation of one pulse and the initiation of the next pulse. The interpulse interval is $1/\text{frequency}$.

Inspiratory time: the inspiratory time is the effective length of the stimulus train. This is often expressed in terms of duty cycle.

The applied stimulus may be either voltage regulated or current regulated although some advantages of using a current regulated source have been elucidated (Mortimer 1981). When a regulated current waveform is used, the stimulator produces the designated current independent of the impedances in the system. The result of a regulated current pulse is a constant field at the extracellular stimulation site. The charge injected is independent of electrochemical reactions and is the same for every stimulus pulse. Voltage regulated sources provide a stimulus at the nerve that may fluctuate resulting in less assurance of elimination of irreversible electrochemical reactions (Robblee 1990, Mortimer 1980, VandenHonert 1979). Available phrenic nerve pacers use current regulated pulses.

The stimulus parameters described above are important for nerve recruitment. The influence of pulsewidth and amplitude on the ability to produce an action potential is commonly expressed on a strength–duration curve. As the pulsewidth is decreased, a greater amplitude is required to elicit nerve excitation. However, the total amount of charge (pulsewidth * current amplitude) decreases as the pulse duration is decreased (Crago 1980, Mortimer 1990). Therefore, to limit the electrochemical reactions, which depend on total charge, short duration pulses (100 μs or less) are generally recommended (Mortimer 1981, Lan 1989).

Harmful electrochemical reactions are also limited by biphasic stimulation. Biphasic stimulation has been demonstrated to produce less tissue damage than

monophasic stimulation (Mortimer 1980, Lilly 1955) by reducing the accumulation of charge at the stimulation site and limiting the buildup of harmful electrochemical reaction byproducts (Brummer 1977, VandenHonert 1979). Each pulse consists of a cathodic phase for stimulation (although an anodic pulse may elicit an action potential in some cases (Mortimer 1990) and an anodic phase intended to reverse the electrochemical reactions of the cathodic phase. Biphasic stimulation also affects the activation of the nerve. The stimulatory effect may be compromised when the sodium channels activated by the cathodic phase are inactivated by the following anodic phase. For this reason, thresholds for biphasic stimulation are greater than thresholds for monophasic stimulation. A delay is generally inserted between the stimulus phases and a delay of 100 μ s or more yields a stimulus waveform with activation thresholds similar to monophasic stimulation (VandenHonert 1979, Mortimer 1990).

The force of the diaphragm contraction is important for the ventilation of a patient using a diaphragm pacer. This force, as measured by the transdiaphragmatic pressure, is strongly associated with the stimulus frequency (1/interpulse interval). The strength of muscle contraction is frequency coded to the initial nerve firing. A difference in the interpulse interval between the first pulses of a pulse train may significantly alter muscle tension (Burke 1970). When compared to the maximal diaphragmatic pressure that can be evoked using trained voluntary inspiration, about 82% of the maximum can be achieved using 35 Hz, and pressure equal to voluntary contraction may be evoked using stimulus frequencies of 60-100 Hz (Bellamare 1986). Conversely, fatigue and possible muscle damage is associated with stimulation frequencies in the range of 27-33 Hz (Ciesielski 1983) and nerve degeneration has been correlated to stimulus frequencies of 50 Hz when continuous

stimulation is used for periods in excess of two hours (Agnew 1989, Agnew 1990).

Stimulus parameters are also crucial for avoiding fatigue (Glenn 1988). Fatigue is reported to be more likely with high respiration rate and high stimulus frequency (Oda 1981). In addition to the direct effect of stimulus frequency on fatigue, muscle conditioning and muscle fiber conversion depend on stimulus frequency (Ferguson 1989). Another way to reduce the risk of fatigue is to keep the inspiratory time as small as possible and maintain long intervals between pulse trains (Bellamare 1982).

Biocompatibility

Electrical activation of the diaphragm requires implantation of a device into the human body. There are difficulties associated with placing any type of foreign material in the body. A successful pacing system must not cause damage to the host and the reaction of the host to the implant must be mild enough not to affect the function of the stimulating device.

The passive tissue reaction to an implanted device is minimized by selection of non toxic implant materials that cause only mild fibrous encapsulation around the implant. A severe tissue reaction may limit the effectiveness of the stimulation. For example, encapsulation of an electrode may affect the activation of a nerve by increasing the impedance between the electrode and the nerve or by altering the current distribution around the electrode (Loeb 1982).

Mechanical irritation may also cause a tissue reaction to the diaphragm pacing electrode which compromises the function of a stimulation device. The nature of

mechanical irritation caused by an implant is largely dependent on the type of electrode used. Cuff electrodes placed directly on the phrenic nerves may move and cuff electrodes that completely surround the nerve may apply pressure to the nerves and swelling occurs. For the phrenic pacing system developed by Glenn at Yale, monopolar cuff electrodes which do not completely surround the nerve are used instead of bipolar cuff electrodes because of the lower risk of trauma for the monopolar electrodes (Glenn 1988). Electrodes placed on the diaphragm place lower risks on the peripheral nerve and minimizes nerve damage that may be caused by mechanical irritation. However, these electrodes also undergo mechanical motion which could result in an adverse tissue reaction.

Electrode Design

The concepts which have been described above are all very important for the development of a stimulation device to activate the respiratory muscles. Many of these ideas are manifested in the design of an appropriate electrode for phrenic nerve stimulation.

For proper nerve fiber recruitment, the electrode must be placed close to the nerve. Accomplishing this may be simple or difficult depending on the technique used for stimulation. For cuff electrodes placed directly on the phrenic nerve this problem is trivial, but when intramuscular or epimysial electrodes are used it is more difficult to place the electrode close to the phrenic nerve.

The materials used for implantation must be passively biocompatible, corrosion resistant, and predisposed to favorable electrochemical reactions. The most widely used electrode metals are platinum and platinum alloys (Robblee 1990). Platinum has been demonstrated suitable for phrenic nerve cuff electrodes (Glenn 1973,

Glenn 1978). Stainless steel is often used for intramuscular electrodes because of its corrosion resistance and mechanical strength.

Potentially detrimental electrochemical reactions at the electrode surface can be reduced by limiting the charge density. Charge density is often reduced by changing the electrode surface area. Increasing the electrode size or roughing the electrode surface are two techniques that have been used to decrease charge density (Loeb 1982). However, selectivity of recruitment can be compromised by increasing the electrode size. Another technique that has been suggested is reducing the differences in local charge densities across the electrode surface. A uniform density of charge delivery maximizes the amount of charge that can be safely delivered by an electrode (Ksienski 1992).

Mechanical considerations play an important role in the electrode design for both nerve cuff electrodes and for intramuscular electrodes. Cuff electrodes require respect for compression of the peripheral nerve which has lead to a variety of different electrode designs (Naples 1990). Conversely, intramuscular electrodes and electrode leads require a design that accommodates high stress caused by contraction of the muscle. Winding the electrode lead into a helical coil increases the flexibility of the lead wire leading to a stronger implant (Caldwell 1975). Often a multistranded wire is used as a safety factor so that if one strand should break due to movement, an electrical connection will remain.

PHRENIC NERVE PACING APPLICATION

Unlike the heart, which requires a single stimulus to induce contraction, the inspiratory action of the diaphragm and other respiratory muscles (intercostals, upper airway) is produced by repetitive pulse trains. Due to greater power

requirements of repetitive pulse train stimulation, a battery powered implantable system has not been developed as of yet. One commercially available system (Avery Laboratories, Farmingdale, New York) consists of an external radio frequency transmitter that transmits a coded signal via an antenna to an implanted, subcutaneous receiver (Figure 1.4). Each RF pulse is demodulated, and the subsequent output is conducted through stainless steel wires to monopolar or bipolar platinum electrodes placed adjacent to or around the nerve. This system is well described in earlier publications (Glenn 1970, Glenn 1980). The application of the electrode in the chest requires a thoracotomy but obviates the need to do a sometimes difficult exploration in the neck, particularly in infants. Glenn and co-workers at Yale prefer the thoracic approach based on the fact that a variable percentage of patients have an extra cervical phrenic nerve root that only joins the main phrenic trunk in the chest (Glenn 1980). It is thought that these additional phrenic motoneurons might be advantageous to achieving maximal diaphragm contraction, but no studies have addressed this yet.

Other phrenic nerve pacing systems include the Vienna system (MedImplant GmbH) and the Tampere system (Atrotech OY) (Talonen 1990). These systems claim to implement a migrating field theory. It is thought that fatigue may be reduced by moving the field throughout the phrenic nerve stimulating different axons of the nerve. This effect has not been proven, and the widespread clinical application of these devices remains to be demonstrated.

CANDIDATES FOR DIAPHRAGM PACING

Quadriplegia with Respiratory Paralysis

Damage to the spinal cord above the origin of the phrenic nerve roots (C3,4,5) results in complete paralysis of the diaphragm in addition to the intercostal muscles (Colin 1969). Depending on the location and extent of these lesions, the sternocleidomastoid muscles innervated by the spinal accessory nerve may be spared. All of these patients still maintain control of the muscles of the upper airway including the function of the vocal cords. These injuries are usually secondary to motor vehicle accidents, sports accidents, and penetrating injuries (e.g., gunshot wounds). Prior to the development of the phrenic pacer, these patients were destined to be permanently dependent on a mechanical ventilator.

According to statistics of the National Spinal Cord Injury Data Research Center, there are probably 100 new cases of spinal cord injury above the C5 root per year in the United States (Young 1980). With the increasing use of Emergency Medical Services and a more widespread knowledge of cardiopulmonary resuscitation, considerably larger numbers of these patients are surviving their acute injury. Quadriplegic patients require full-time ventilatory support, which until recently could only be achieved by alternately pacing each hemidiaphragm for 12 hours. Continuous pacing of a phrenic nerve had resulted in a fatigue-like phenomenon and, in some cases, irreversible damage to the lower motoneuron (Glenn 1978). The mechanism of this phenomenon is not understood. Glenn and co-workers have demonstrated the efficacy of a very low frequency electrical stimulus (11-13 Hz) to reduce the risk of fatigue (Ciesielski 1983, Glenn 1986, Ilbawi 1985). The same group at Yale has reported ultrastructural damage in the diaphragms of dogs

stimulated with higher frequency stimulus. The theoretical physiological basis for these findings are not clear and work done by Mortimer et. al. in animal models have not attributed any deleterious effect on muscle of stimulus frequency per se (Mortimer 1980, Mortimer 1981, Peckham 1973).

In general, efforts are made to achieve the ventilatory goals with the smallest stimulus possible. Disuse of the diaphragm in the first months following acute injury, when patients with high quadriplegia are on mechanical ventilation, results in muscle atrophy that must be reversed by a process of conditioning. Two weeks following implantation of the pacers, the optimal electrical parameters for achieving the required tidal volume are obtained and the pacing periods are lengthened gradually during a period of weeks. An increase in diaphragm contractility for a given electrical stimulus and a shift upward of the force frequency curve of each hemi-diaphragm has been demonstrated during phrenic nerve pacing. This effect appears to plateau after approximately sixteen weeks.

The diaphragm pacer is a life supporting device and requires that certain precautions be taken. A backup portable ventilator is required when the patient is discharged either home or to an institution. Alarms attached to ventilation monitors or alarms that can be easily activated by the patient's tongue or chin must be available if the patient is unattended. Two independent channels are implemented (one for each hemidiaphragm) for added safety, and many quadriplegics are taught to breathe for short time periods using so called "frog" or glossopharyngeal breathing. A sigh function may also be incorporated into the system to elicit a cough for clearing the airway (Baer 1990). Recently, a transtelephonic monitoring

feature has been added to the phrenic pacer but its effectiveness remains to be demonstrated.

Patients require tracheostomies as the paced diaphragm is not synchronized with the spontaneous opening of the upper airway, still under control from the medullary respiratory centers. In some patients, the tracheostomy opening can be closed during the day with a button, and many of these patients appear to learn to synchronize their upper airway opening to the fixed-rate diaphragm contraction. During sleep, however, the tracheostomy must be kept open to avoid upper airway obstruction. The pacing of the diaphragm in the presence of paralyzed intercostal muscles and out of phase with any spontaneous strap muscle activity results in paradoxical inward movement of the chest wall during inspiration, which may reduce the maximal tidal volume (Danon 1979).

If one examines the largest experience by Glenn at Yale, 40 percent of all quadriplegics who have received this device have been supported fulltime by their pacers (Glenn 1980, Glenn 1986, Glenn 1988). The rest of these patients use the pacers part time and make use of ventilators (positive or negative pressure) for the remainder of the day. The patients who are successfully paced are freed from the mechanical ventilator either fulltime or for those parts of the day when they wish to speak, be mobile and/or participate in occupational and recreational activities. There are a few quadriplegic patients reported who have gone through college and conducted business from their homes while being supported by diaphragm pacers for periods extending beyond 10 years.

In addition to the expensive pacing equipment, prolonged hospitalization (as long as six months) may be required to achieve full-time pacing, and careful

selection usually is made for highly motivated patients who would otherwise be confined to ventilators. Most of the patient's rehabilitation should be completed before the decision to implant pacers is made. This would include the use of electronic aids and a decision regarding the patient's ultimate disposition. The reluctance of many medical centers to undertake this lengthy and costly procedure has severely limited the application of the technique even in these patients. Intense case management of these cases in selected centers with the necessary expertise will open the avenues for application of phrenic nerve pacing in quadriplegics over the next 5-10 years. The conditioning process that follows the implant might be performed in part with appropriate home care services.

Central Hypoventilation Syndromes

Though respiratory failure is most frequently related to intrinsic lung disease, the adequacy of central respiratory drive has in recent years been the focus of considerable clinical interest (Cherniack 1976, Lopata 1977). Central hypoventilation syndromes are characterized by an abnormally low ventilatory drive to the respiratory muscles that may be 1) congenital (neonates); 2) idiopathic (adults); or 3) due to anatomic damage to the respiratory center - surgery, CNS infections, brain stem infarction, tumor, and also secondary to functional depression of the central controller (prolonged hypoxia). The symptoms of such disorders may be quite severe (Barlow 1980, Coleman 1980).

An increasing number of neonates are now recognized with congenital central hypoventilation though no specific etiologic anatomic abnormalities have been documented. Hunt and co-workers have paced children for more than 10 years, but these patients all require bilateral stimulation and cannot, at present, be paced for 24

hours, even if their condition requires continuous ventilatory support (Hunt 1988, Ilbawi 1980, Ilbawi 1985). Like other pacing patients, infants require tracheostomies, which are more difficult to manage than in adults. It is not yet known how the system will adapt to their growing structures and whether nerve function will be compromised later. In at least one case the phrenic nerve has been thought to have been damaged in a growing child by traction of the phrenic nerve electrode (Hunt 1988). Subsequent electrode replacement has had to be done leaving the original electrode in place because of the dense fibrotic tissue around the original implant.

Severinghaus and Mitchell described the clinical syndromes associated with selective damage to the brain stem pathways concerned with automatic control of breathing (Severinghaus 1982). These patients are able to maintain normal blood gases while awake but have significant hypoventilation and apnea, which is most prominent during sleep (called "Ondine's Curse"). Patients with brain stem infarction, medullary involvement with infection or tumor, and idiopathic cases also have been reported with a similar syndrome (Mellins 1970). These patients are candidates for phrenic pacing to maintain normal oxygenation and adequate ventilation only at night. Unilateral pacing is attempted first. Of all implants, 46% pace only during sleep (Glenn 1988). The decision to implant pacers in these patients who have ventilatory function (albeit inadequate) is much more difficult than in quadriplegics. Both respiratory physicians and patients have indicated reluctance to undertake the necessary surgery with the risk of surgical or other medical complications that could potentially compromise the function of the phrenic nerve and render the patients worse off than before (Glenn 1973, Glenn 1976).

As in quadriplegic patients, diaphragm pacing may induce episodes of upper airway closure, particularly during sleep that impair ventilation and oxygenation. Patients who have episodes of obstructive sleep apnea when not paced have an exaggeration of the problem during pacing (Glenn 1978). It is likely that the augmented inspiratory action of the diaphragm collapses parts of the upper airway. Airway obstruction also occurs because the inspiratory action of the diaphragm is not coordinated in time with that of the upper airway muscles (Gottfried 1982). Treatment of upper airway obstruction during pacing has required a permanent tracheostomy, which usually is closed during the day. Glenn has studied 24 patients with central hypoventilation, who have undergone pacing during sleep; he observed upper airway obstruction in 18 (Glenn 1978).

Glenn has reported the implantation of 36 phrenic pacers in non-quadruplegic patients with miscellaneous central hypoventilation syndromes. The etiologies of their disorders included cerebrovascular accidents, organic lesions of the cervical cord, and encephalitis. Six patients with idiopathic hypoventilation and no documented cause also were reported. The patients in general appeared to benefit from pacing in terms of increasing PO_2 and lowering PCO_2 . Long-term data from these patients regarding their hemodynamic status and the success at preventing the development of cor pulmonale have not been published.

EVALUATION OF DIAPHRAGM FUNCTION

Following high spinal cord injury with quadriplegia and almost total respiratory paralysis, there may be recovery of some phrenic nerve function as long as six to nine months later. The presence of diaphragm function can be recognized by observing outward abdominal motion during inspiration and observing diaphragm

motion under fluoroscopy. The movement of the diaphragm can be quantitated for study purposes by measuring the surface movements of the rib cage and abdomen with inductive plethysmography or magnetometry (Danon 1979). Diaphragm action potentials are not used because they are not very reproducible nor representative of respiratory muscle force.

Quantification of diaphragm contraction can be made by measuring transdiaphragmatic pressure during maximum inspiratory maneuvers using esophageal and gastric balloon catheters connected to pressure transducers. This is a more direct measurement of diaphragm contraction than tidal volume. Tidal volume is dependent on contraction of the diaphragm as well as the resistance and compliance of the airways and lungs and is not a measurement of the muscle contraction per se.

An intact lower motoneuron is a prerequisite for phrenic pacing under all circumstances. Damage anywhere along the nerve results in irreversible Wallerian degeneration and lack of neural input leads to atrophy and fibrosis of the muscle. Proof of the viability of the phrenic lower motoneuron is obtained by percutaneously stimulating the phrenic nerve in the neck. A brisk outward movement of the abdomen usually indicates qualitatively a relatively intact lower motoneuron. The absence of diaphragm movement during percutaneous stimulation in experienced hands suggest non-viability of the nerve. The conductance time (CT) of the phrenic nerve from the stimulation in the neck to the diaphragm muscle action potential is recorded on a storage oscilloscope. Prolongation of the CT to more than 12 milliseconds suggests local damage to the nerve or a systemic neuropathy. Damage of this type is related to demyelinating

neuropathies, but gives no indications for axoplasmic neuropathies. In children, the conduction time is significantly shorter (mean of 6.5 ms vs. 8.3 ms for adults)(Brouillette 1983), and is age dependent.

FUTURE DIAPHRAGM PACING CANDIDATES

The achievements of phrenic nerve pacing indicate possibilities for a more general application of this concept in the management of ventilatory failure. Patients with chronic obstructive lung disease (COPD) are one of the largest groups receiving disability payments in the United States. There is considerable evidence that substantial numbers of these patients with only moderate or mild lung disease develop respiratory failure. It is believed that an abnormal reflex or chemical regulation of breathing contribute to the development of CO₂ retention and hypoxemia (Altose 1977, Aubier 1980, Nochomovitz 1980 Sorli 1978). Substantial data indicate that sensitivity to CO₂ and hypoxia is, in part, hereditary; respiratory failure is most likely to occur in patients with low sensitivity to CO₂. Tests have been developed in recent years, such as measurements of occlusion pressure and respiratory muscle EMG, that allow the identification of patients with diminished respiratory drives (Glenn 1980, Cherniack 1976, Lopata 1977). These patients might benefit from pacing to assist respiration, particularly if adequate ventilation could be maintained during normal activity. Recent studies indicate that patients with COPD and chronic respiratory failure benefit from home oxygen administration. New data indicate that long-term oxygen may prolong life in many of these patients, and it is expected that the use of home oxygen will now increase dramatically (NOTT 1980). In some of these patients relief of hypoxia depresses ventilation sufficiently to cause dangerous levels of hypercapnia and acidosis (Dunn 1991, Fleetham 1980). Diaphragm pacing in such patients might be useful in

maintaining ventilation when central drives are reduced by hyperoxia. This potentially large patient population can ill afford to lose the function of a phrenic nerve, and the present procedure has been reported only once in this clinical situation (Glenn 1978). The present technique is probably contraindicated because of risk of phrenic nerve damage. Some studies on diaphragms of patients with chronic lung disease have shown atrophy of the muscle perhaps secondary to the placement of the diaphragm at a severe mechanical disadvantage by lung hyperinflation (Steele 1973).

Electrical stimulation of skeletal muscle through its nerve supply has been shown experimentally to enhance the ability of the muscle to sustain repeated contraction (Ferguson 1989, Mortimer 1981, Peckham 1973). The diaphragm is also known to exhibit the same characteristics (Armenti 1984). It is possible that temporary pacing might assist in conditioning of the diaphragm and improving its endurance or strength. Non-quadruplegic patients, with or without lung disease, who require prolonged mechanical ventilation develop disuse atrophy, e.g., postoperative complications (sepsis); electrical stimulation could condition the main respiratory muscle (the diaphragm) and thus decrease the time required to wean these patients from mechanical ventilation. This is a significant clinical problem that involves quite large numbers of patients worldwide. Ciesielski (Ciesielski 1983) reports a conversion of muscle fibers from slow twitch to fast twitch upon electrical stimulation of the diaphragm. Others report a conversion from fast twitch to slow twitch (Peterson 1990), which is more consistent with studies of other skeletal muscles. The stimulus paradigm for muscle conditioning is not set. Muscle conditioning at frequencies near 10 Hz is well accepted (Oda 1981) while it is claimed that stimuli of higher frequency does not help in increasing fatigue

resistance. Ferguson et al (Ferguson 1989) report that a stimulus paradigm using 30 Hz bursts (with an average frequency of 10 Hz) over time produces more improvement in a muscle to develop a sustained contraction at moderate to high force levels than that achieved by 10 Hz continuous stimulation. The same study indicates an almost complete conversion to slow twitch fibers, which is confirmed for diaphragm stimulation using more traditional stimulus paradigms (Peterson 1990, Peterson 1994b).

Designated diaphragm pacing centers with the ability to conduct long-term follow up programs, facilities for monitoring pacing, improved techniques for stimulation and pacing, autopsy examination and the availability of alternate non invasive techniques for pacing would greatly assist the efforts to exploit this technique more widely in the future.

DIAPHRAGM PACING: THE DILEMMAS

The factors that have led to poor results include implantation problems, inadequate follow up, lack of patient or family support, complications of the underlying disease process, equipment problems, use of inadequate stimulation paradigms and no provision to supplement ventilation by mechanical means where needed (Glenn 1988).

Despite the remarkable advances made by Glenn and co-workers with this technique, the application of diaphragm pacing continues to be limited. The majority of high quadriplegics in the United States are supported by mechanical ventilators, and in non-paralyzed patients, there is a reluctance to implement a technique requiring surgical procedures and a tracheostomy. Despite experimental data suggesting that prolonged electrical stimulation of the canine phrenic nerve is

not injurious, (Kim 1976) there is potential risk of permanent damage to the nerve from the operative procedure or local injurious effects of the electrode. This issue remains a limiting factor for development of phrenic pacers in spite of some outstanding benefits to individual patients during long periods of pacing. There is insufficient post-mortem pathological data in patients who have had long-term stimulation to be of any definitive value (Glenn 1978, Kim 1983, MeiLieu 1978). Complications, when they occur, are usually associated with surgical procedure, pacing protocol, and pacemaker component failure.

It is often difficult to pinpoint the cause of failure to achieve adequate pacing. Surgical related injury may result from nerve manipulation, nerve contact with the electrode, compression by the cuff, or as a result of scar tissue formation. The precise incidence of these surgical complications is extremely difficult to estimate because of the lack of a uniform criterion to determine this problem. Obvious infection is reported to have occurred in 4.5% of all implantation procedures in Glenn's multicenter report. Most of these cases required reimplantation although removal of the original pacemaker was often impossible (Glenn 1988). Glenn has also reported a decrease in complications with unipolar electrodes compared with the bipolar electrodes that encircle the nerve. The unipolar electrodes make contact with the nerve on one side and this approach has been attributed to lower incidence of phrenic nerve damage due the elimination of compression (Glenn 1988). Talonen et al also use an electrode that does not completely encircle the nerve (Baer 1987, Talonen 1990). The infrequent nature of the implant procedure results in sporadic experience for surgeons, which is liable to result in a higher incidence of surgical complications.

The complex interaction between chemical and mechanical factors and the body's respiratory modulation systems discussed previously are bypassed with the present fixed-rate, open-loop system of phrenic nerve stimulation. The lack of coordination among the paced diaphragm, the upper airway muscles, and the accessory muscles necessitates chronic tracheostomy and limits the maximal tidal volume that can be achieved. Studies of rib cage and abdominal movements in canines paced during apnea suggest that rib cage collapse accounts for up to a 20 % reduction in the tidal volume possible with the rib cage held fixed (Nochomovitz 1983).

Children can also benefit from phrenic nerve stimulation (Ilbawi 1980, Ilbawi 1984, Weese-Mayer 1989, Weese-Mayer 1992). However, children require bilateral stimulation and the technique has been limited to 12 - 15 hours each day. Difficulties in long term, full time stimulation have been associated with a larger rib cage compliance leading to an exaggerated collapse of the upper rib cage. In addition, the implant procedure must be modified slightly to account for growth (Weese-Mayer 1992).

Of all phrenic pacers implanted, 47% have been termed a success in which no additional ventilatory support was needed. Patients receiving significant support from the device include 36% of the cases and 16% result in minimal support or failure (Glenn 1988).

MODIFICATIONS OF DIAPHRAGM PACING USING PHRENIC NERVE CUFF ELECTRODES

Glenn and co-workers have been evaluating the possibility of continuous phrenic nerve stimulation by modifying the electrical parameters used. They have

had some encouraging success in this regard by utilizing very low frequency (10 Hz) stimulation in quadriplegics (Ilbawi 1985). If this approach proves successful with further clinical experience, it will be particularly beneficial in the provision of ventilatory support to quadriplegics. Experimental studies in animals conducted by the same group (Ciesielski 1983) have suggested that higher frequency stimulation (27-33 Hz) results in ultrastructural damage to the muscle not observed in animals stimulated with lower frequency trains (11-13 Hz). This damage is qualitatively similar to that observed in skeletal muscle stimulated at fixed lengths (Stone 1985). A definitive interpretation of the studies by Glenn and co-workers cannot be made at this point pending future studies of stimulus paradigms in the electrically activated diaphragm.

Talonen and co-workers have begun implementing a new phrenic nerve stimulator device that uses “carousel” stimulation. This stimulation is designed to reduce the risk of fatigue by stimulating the phrenic nerves with a quadripolar electrode. Theoretically, four bipolar electrode pairs are each calibrated to stimulate non-overlapping quarters of the nerve. Then each bipolar pair is stimulated at a low frequency (approximately 6 Hz), but they are also stimulated 40 ms out of phase (Talonen 1990). This type of stimulation is designed to provide tetanic stimulation and higher tidal volumes with lower fatigue (Baer 1990, Talonen 1990). This group has reported successful clinical implementation of this technique (Baer 1987, Baer 1990, Talonen 1985, Talonen 1990).

DIAPHRAGM PACING USING INTRAMUSCULAR ELECTRODES

At Case Western Reserve University an experimental system has been developed for activating the phrenic nerves with intramuscular electrodes implanted

in the diaphragm via the abdomen. The implant procedure does not require surgical manipulation of the phrenic nerve and lends itself to temporary use and removal if necessary (Nochomovitz 1983). In studies performed in animals, the optimal placement of these electrodes has been described in relation to the point of entry of the phrenic nerves into the diaphragm (Figure 1.5). Optimal activation of the diaphragm is achieved when the electrodes are 2-3 cm from the nerve entry point in the muscle. In the same series of experiments the maximal trans-diaphragmatic pressure and tidal volume generated with electrical stimulation was similar for single intramuscular (hemidiaphragm) electrodes and directly placed phrenic nerve cuff electrodes placed in the neck. This technique is still dependent on the integrity of the phrenic lower motoneuron and would not be effective in conditions where the peripheral nerve was irreversibly damaged (Nochomovitz 1983). A laparoscopic technique has also been developed by Stellato et al (Stellato 1985) whereby the stimulating electrodes may be implanted without a laparotomy. The technique would allow the implantation of intramuscular electrodes in patients with the benefits of minimally invasive surgery.

Activation of the diaphragm with this technique is by stimulation of the intramuscular phrenic nerve branches; the magnitude of contraction critically depends on the proximity of the electrode to the main phrenic trunk entering the diaphragm. Single hemidiaphragm electrodes have been demonstrated to be capable of generating the same transdiaphragmatic pressures and tidal volumes as conventional nerve electrodes with unilateral or bilateral stimulation. Intramuscular phrenic nerve pacing has been tested chronically in animals. Peterson (Peterson 1990, Peterson 1994a, Peterson 1994b) has demonstrated an intramuscular

diaphragm pacing system that provides 167% of ventilation necessary to support basal metabolism.

Ventilation of this type is repeatable and full-time bilateral stimulation has been used without fatigue of the respiratory muscles. Peterson (Peterson 1986, Peterson 1990, Peterson 1994a, Peterson 1994b), using a set of chronic animal experiments has demonstrated the safety, reliability, and efficacy of an intramuscular electrode diaphragm pacing system. The stimulation parameters, and resulting diaphragmatic pressure and tidal volume are shown in Table 1.3. The intramuscular electrodes used for this system (Peterson 1986, Peterson 1990) show no change in recruitment over time, no mechanical damage to the electrode, sufficient anchoring characteristics, and a favorable tissue reaction to all portions of the electrode and the lead (Peterson 1990, Peterson 1994a, Peterson 1994b). Following explant of the electrodes, muscle fiber typing was done for the diaphragm. Peterson has shown that there is nearly complete conversion of muscle fibers to slow-twitch oxidative fibers which corresponds to a lower frequency required to produce a tetanic diaphragm contraction (Peterson 1990, Peterson 1994b). No change in the length of the diaphragm has been found (Peterson 1990). Evidence suggests that low frequency bilateral stimulation produces adequate ventilation with a lower risk of fatigue.

Electrical activation of the main respiratory muscle - the diaphragm - is at present a technique with limited application. The utilization of this approach usefully on a much larger scale appears to be promising with continued study in this area.

ELECTRICAL ACTIVATION OF THE DIAPHRAGM USING EPIMYSIAL ELECTRODES

In the following pages, research is described that addresses many of the dilemmas of diaphragm pacing through the use of epimysial electrodes to electrically activate the diaphragm. Epimysial electrodes were selected as an alternative to cuff or intramuscular electrodes in order to preserve the advantages of abdominal electrode implant, avoid the risk of diaphragm perforation and assure identification of the implanted electrode location. We tested the hypotheses that epimysial electrodes can be designed with the necessary electrochemical and mechanical properties for diaphragm pacing, that these electrodes can be safely stapled to the diaphragm, that epimysial electrodes can be placed at the phrenic nerve motor point during a laparoscopy, that implanted epimysial electrodes are safe and effective for diaphragm pacing, that the risk of diaphragm fatigue can be minimized by adjusting the stimulus parameters and that implanted epimysial electrodes can be used as electrodes for an impedance pneumograph for monitoring diaphragm pacing.

In order to test these hypotheses, the basic abdominal implant concept pioneered by Peterson and co-workers (Peterson 1990) was preserved in order to maintain the reduced surgical and phrenic nerve risks. However, the laparoscopic implant procedure was modified to assure placement of electrodes at the phrenic nerve motor point (Chapter 4). Newly emerging endoscopic stapling instruments enabled simple attachment of an epimysial electrode to the diaphragm during a laparoscopy (Chapter 3). Epimysial electrodes were designed specifically to withstand the rigorous mechanical and electrochemical demands of an abdominally placed diaphragm pacer (Chapter 2). The long term function and the histological response of three electrode designs were tested in dogs (Chapter 5). The issue of diaphragm

fatigue was addressed using working epimysial electrode diaphragm pacers to study the effects of stimulus parameters on tidal volume decline (Chapter 6). A technique was developed for determining optimal stimulus parameters that minimize the risk of diaphragmatic fatigue while maintaining a minimum level of ventilation (Chapter 7). Finally, the epimysial electrodes implanted for electrical activation of the diaphragm were tested for use as an impedance pneumograph monitor of ventilation (Chapter 8).

Muscle	Action	Influence
Crural Diaphragm	Inspiratory	Abdomen
Costal Diaphragm	Inspiratory	Abdomen/Lower Ribcage
Parasternal Intercostals	Inspiratory	Ribcage
Internal Interosseus	Expiratory	Ribcage
External Intercostals	Expiratory	Ribcage
Scalenes	Inspiratory	Upper Ribcage
Sternomastoids	Inspiratory	Upper Ribcage
Rectus Abdominus	Expiratory	Abdomen/Lower Ribcage
Transverse Abdominus	Expiratory	Abdomen
External Obliques	Inspiratory	Abdomen
Internal Obliques	Expiratory	Abdomen

Table 1.1: Summary of the actions and influences of the major respiratory muscles.

Relative Ion Concentrations

Figure 1.1: A representation of the intracellular and extracellular ion concentrations which establish the resting membrane potential. Size of letter denotes relative concentration.

Resting Potential Ionic Driving Forces

Ion Fluxes

$$\begin{array}{lcl} \text{Potassium Flux: } \uparrow \times P_{K^+} = & \uparrow & \\ \text{Sodium Flux: } \downarrow \times P_{Na^+} = & \downarrow & \\ \text{Net Flux} = 0 & & \end{array}$$

Depolarized Membrane Ionic Driving Forces

Ion Fluxes

$$\begin{array}{lcl} \text{Potassium Flux: } \uparrow \times P_{K^+} = & \uparrow & \\ \text{Sodium Flux: } \downarrow \times P_{Na^+} = & \downarrow & \\ \text{Net Flux} = & \downarrow & \text{(inward)} \end{array}$$

Figure 1.2: Comparison of net flux and driving forces for a resting membrane and a depolarized membrane. The net flux of the depolarized membrane may be sufficient to elicit an action potential. Arrow size represents relative strength of driving force or size of ion flux. Letter size indicates relative ion concentration or permeability of the membrane to a specific ion.

Parameter	Effect
Narrow Pulsewidth	Reduces Risk of Electrode Corrosion
Low Amplitude	Reduces Risk of Electrode Corrosion
Biphasic	Reduces Risk of Electrode Corrosion
Delay	Lowers Threshold for Biphasic Stimulation
Low Frequency	Reduces Risk of Fatigue
Low Respiratory Rate	Reduces Risk of Fatigue
Short Inspiratory Time	Reduces Risk of Fatigue
Graded Charge Injection	Gives Smooth Contraction

Table 1.2: Summary of stimulus parameters that may be adjusted for diaphragm pacing applications.

Stimulus Waveform

Stimulus Pulsetrain

Figure 1.3: Stimulus pulsetrain with a close up of the stimulus waveform. The stimulus is a balanced biphasic current regulated waveform. The stimulus parameters are shown.

Figure 1.4: Diagram of transcutaneous phrenic nerve pacing system. External radio frequency pacer, antenna, subcutaneous receiver and nerve electrode demonstrated.

Figure 1.5: Abdominal view of inferior aspect of diaphragm showing anatomical landmarks for entry points of the phrenic nerves into the muscle.

				Left Side		Right Side			
Dog	Days Stimulated	Hours per Day Stimulated	Breaths / Min	Amp litude (mA)	Pulse Interval (ms)	Amp litude (mA)	Pulse Interval (ms)	Maximum Diaphragm Pressure (cm water)	Maximum Tidal Volume / Critical Tidal Volume (Bilateral Stimulation)
Control									
Control								63.0	1.89
Part-time	183	8.2	15	25	50	25	50	11.8	0.95
Part-time	158	10.4	12	25	50	15	66	41.3	1.64
Full-time	164	22.1	12	25	66	25	66	42.3	1.84
Full-time	61	23.0	15	25	66	25	66	38.3	1.24
Full-time	62	23.3	12	25	66	25	66	49.2	2.45

Table 1.3: Chronic intramuscular diaphragm stimulation. Data from Peterson chronic dog study. Stimulus parameters, transdiaphragmatic pressure and tidal volumes are shown for animals stimulated full-time and part-time. The tidal volume has been normalized to critical tidal volume. Critical tidal volume is the tidal volume required for full time basal ventilation without diaphragm fatigue.

Chapter 2

In Vitro Evaluation of Epimysial Electrodes for Diaphragm Pacing

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INTRODUCTION

In this chapter, we tested the hypothesis that epimysial electrodes have adequate mechanical and electrochemical durability for long term electrical activation of the diaphragm (diaphragm pacing). Mechanical tests were conducted to determine the fatigue strength of the electrodes and electrochemical tests of the corrosion resistance of two types of stimulating surfaces were performed. The results of these tests may be pertinent to the design of epimysial electrodes for other applications, such as the upper motor prosthesis developed by Peckham (Peckham 1980). The use of epimysial electrodes for diaphragm pacing offers the advantages of low risk of damage to the phrenic nerves, final placement that is within sight of the surgeon and no risk of diaphragm perforation and resulting pneumothorax.

Mechanical fatigue failure of epimysial electrodes is of particular concern for diaphragm pacing because the electrodes undergo significant mechanical stress during motion of the diaphragm. The diaphragm uses the abdominal contents as a fulcrum for lifting the lower rib cage while at the same time sliding over the same abdominal contents (DeTroyer 1982). This action exerts a shear stress on an electrode that is implanted on the muscle surface. The mechanical fatigue strength of the lead wires for intramuscular electrodes has already been established (Peterson 1994b). The most susceptible location for mechanical failure of an epimysial electrode is the point where the flexible electrode lead wire connects to the stiff electrode tip. This region is characterized by a mechanical transition from high flexibility to very low flexibility. Thus any bending action concentrates the stress at this boundary. In this study we designed a strain relief between a flexible lead wire (Caldwell 1975, Peterson 1988) and an electrode tip made from a 316L stainless

steel disk (6.4 mm in diameter, 1.5 mm thick). The strain relief was tested for mechanical fatigue using a cyclical motion protocol (Comte 1983, Scheiner 1991).

We also tested the corrosion resistance of two epimysial electrode types designed for uniform current density. Epimysial electrodes may be designed with a specific geometry, shape, and texture. The electrode shape and texture affect local current densities, a major contributing factor in electrode corrosion (Rubinstein 1987). Theoretically, an electrode with uniform current density will be able to deliver the greatest amount of charge with the lowest risk of corrosion (Ksienski 1992). Thus an electrode with uniform current density will provide the maximum safe current levels for an electrode with a specific surface area. In this study we tested two electrode designs. The first design was a well electrode with a flat stimulating surface placed in a well. Although this is not a uniform current density design, even small wells reduce the theoretically infinite local edge current densities found on electrodes with a flush stimulating surface (Ksienski 1992, Rubinstein 1987). The second electrode design was an epimysial electrode with a hemispherical stimulating surface for uniform current density.

METHODS

Mechanical Fatigue Test

Strain relief was designed for a diaphragm pacing epimysial electrode. The design is illustrated in Figure 2.1. The strain relief design centered on a strain relief coil that was fixed to the electrode tip and the use of silicone rubber to grade the flexibility from the lead wire to the electrode tip.

The lead wire was constructed from a 7 strand (0.00135 in diameter, 316LVM stainless steel), FEP Teflon® insulated (coated to 0.009 in +/- 0.001 in) wire (Fort Wayne Metals, Fort Wayne, IN). Two such wires were wound in tandem to form a helix with an outside diameter of 0.03 in. A 3 cm length of the coil was deinsulated at the end for attachment to the electrode tip. A 5/0 polypropylene monofilament (SP 135, Look Inc, Norwell, MA) was threaded through the center of the helix.

The epimysial electrode tip was manufactured from a 0.25 in round bar stock of 316L stainless steel (Rycor Metals, Cleveland, OH). Disks were cut at 0.07 in thickness with a 0.05 in diameter slot on the back side using wire electrode discharge machining (Erie Shore Machining, Cleveland, OH). A strain relief coil was constructed of 0.010 in, 316L wire wound into a coil 0.5 in long with a outside diameter of 0.050 in. The strain relief coil was placed in the slot of the disk and welded into place using a laser welder (KLS 111-671, LASAG Corp., Arlington Heights, IL) in an argon environment. Two 0.010 in 316L stainless steel wires were used for filler metal. A minimum of 2 coil lengths (0.020 in) of the strain relief coil was left unwelded at the edge of the disk. In addition, a minimum of 5 coil lengths extended beyond the edge of the disk.

The lead wire was inserted through the center of the strain relief coil and the deinsulated portion was spot welded (Model 125 Unitek Corp., Monrovia CA) to the back of the disk in an argon environment. Stress annealing of the electrode components was not done at any point during manufacture. A polypropylene plug was attached to the monofilament that ran through the center of the lead coil. The polypropylene plug was heat molded into the end of the strain relief coil opposite

lead wire entry (Figure 2.1). This isolated lead wire loading from the weld connecting the lead wire to the disk. The back of the disk was coated with medical grade epoxy (Master Bond EP30, Master Bond Inc., Hackensack, NJ). The disk/lead assembly was then fitted into a premolded silicone rubber (Silastic® MDX 4-4210, Dow Corning Corp, Midland, MI) housing and a 0.040 in ID x 0.085 in OD x 0.5 in length silicone rubber tubing (Silastic®, Dow Corning Corp., Midland, MI) was placed over the strain relief coil. The housing and tubing were fixed in place by back filling with silicone rubber (Silastic® MDX 4-4210).

A diagram of the mechanical fatigue testing apparatus is located in Figure 2.2. The electrode disk was placed at the end of a rotating shaft and the end of the lead wire was placed in a counter rotating shaft. One of the shafts was driven by a constant speed motor and the other was geared to counter rotate at the same speed. A small current (< 5 mA) was passed through the system to detect wire breakage. Breakage time was recorded by a microprocessor controlled current stimulator. The shaft rotation was measured by a tachometer. The lead wire was passed around an angle control post in order to set the radius of curvature for the lead wire/electrode tip connection. This angle was set to ninety degrees for all trials. A total of three electrodes were tested at 2000 rpm for a minimum length of time (22 days) to simulate 10 years of breathing at 12 breaths per minute.

Electrochemical Testing

An electrochemical test was run to test the corrosion resistance of two different types of stimulating surfaces. The tested surfaces are diagrammed in Figure 2.3. The first stimulating electrode type had a flat stimulating surface placed in a well. Well electrodes were made from the same type of electrode disks used for the

Mechanical Fatigue Test (Figure 2.1). The well electrode surface was prepared by polishing flat disks on a lapping wheel down to $1/4\text{ }\mu\text{m}$ diamond grit. Hemispheres were created using a lathe (Figure 2.1) and then the disk was formed by electric discharge machining (EDM) cutting of the back side slot. The hemispherical portion was then polished using a lathe and polishing cloth down to $1/4\text{ }\mu\text{m}$ diamond grit. All electrode surfaces were passivated using 30 volume % nitric acid at room temperature for 30 minutes (ASTM F86) prior to lead wire attachment. Lead wires were attached using the protocol described in the Mechanical Fatigue Test section. The disks for the well electrode were molded into a silicone rubber mold (MDX 4-4210) with well dimensions of diameter = 1.78 mm, and a well depth of 0.32 mm. This provided a real area of 10 mm^2 for stimulation. The disks with hemispheres were fit into preformed silicone rubber housings as described in the Mechanical Fatigue Test. The hemispherical electrodes were made with a radius of 1.27 mm giving a real surface area of 20 mm^2 .

The apparatus for electrochemical testing of the lead wires is illustrated in Figure 2.4. The electrodes were placed in 25 ml Erlenmeyer flasks with 20.0 ml of 0.15M phosphate buffered saline (pH = 7.4). Iridium oxide return electrodes were also inserted into the saline. These electrodes were formed by iridium oxide coating (ELTECH Research Corp., Fairport Harbor, OH) coils of 0.010 in titanium wire (Rycor Metals, Cleveland, OH). The return electrodes had a large area ($> 240\text{ mm}^2$) to provide a stable, non-corroding, low polarizing surface. The entire system was sealed to prevent contamination. The flasks were stoppered and connected in series by 0.125 in glass tubing. One end of the series tubing was connected to compressed air (UN1002 Medical Air USP, Gas Technics, North Royalton, OH) and the other end was submersed in distilled water.

All components of the system were cleaned using a six step process prior to assembly. Each step used a specified solvent and 5 minutes in a sonicator. The cleaning solvents included (in order) 1) Freon TMS (MS-167 Miller Stephenson Chemical Co. Inc., Morton Grove, IL) 2) Safezone (MS-197 Miller Stephenson Chemical Co., Inc., Morton Grove, IL) 3) Liqui-nox® (Alconox, Inc., New York, NY) in double distilled water 4) double distilled water 5) 95% alcohol and 6) ultrapure water. The system was assembled as shown in Figure 2.4.

The electrodes were connected to a current stimulator (Applied Neural Control Laboratory, Cleveland, OH). A total of eight electrodes were tested including four hemispherical and four well electrodes. The electrodes were stimulated at 50 Hz, for 96 days. This simulated ten years of diaphragm pacing. The protocol was based on a stimulation frequency of 20 Hz, 1.5 s inspiratory time and a breathing rate of 12 breaths per minute. The stimulus waveform was based on the output of an available implantable stimulator (Smith 1987) and is diagrammed in Figure 2.5. A cathodic first, square pulse was used followed by a nominal 0.5 mA charge balancing anodic phase. A cathodic stimulus amplitude of 25 mA was used with a pulsewidth of 100 μ s.

During the 96 day stimulation period, the sealed system was flushed with air every 1-4 days. The stimulus waveform was checked at days 2, 12, 16, 34 and 96. At day 96 the voltage across the epimysial electrode was measured during stimulation with respect to the iridium oxide return electrode. Stimulation was then terminated and the samples were removed from the phosphate buffered saline. The pH of each sample solution was measured using a pH meter (Fisher Accumet 640, Fisher Scientific, Pittsburgh, PA). Portions of the saline solutions were diluted by

5 times in HCl solution and analyzed for chromium and nickel using atomic absorption spectrophotometry (Perk and Elmer). Iron was not tested only because we did not have the equipment for iron analysis. The silicone rubber housings were removed and the electrode disks were dried and examined under scanning electron microscopy (JEOL 840A, JEOL Ltd., Tokyo, Japan) for signs of corrosion.

RESULTS

Mechanical Fatigue Testing

All three electrodes survived the 10 year simulated breathing period. Survival was based on maintaining a conducting pathway during the test period. Figure 2.6 is a photograph of an electrode sample after testing. Cracking of the silicone rubber strain relief occurred at the junction between the lead wire and the strain relief coil but the Teflon® wire insulation was intact. The stress was most concentrated at this location during this test based on the location of the smallest radius of curvature (Scheiner 1991). The location of stress concentration depends upon the angle which the lead wire takes with respect to the electrode disk and the tension on the lead wire. In Figure 2.7 is shown an example of a combination of lead wire-electrode tip angle and tension to produce a concentration of stress at the border of the lead wire and the silicone rubber tubing.

Electrochemical Testing

The scanning electron microscopy revealed evidence of pitting corrosion on the well electrodes, but no evidence of any corrosion of the hemispherical electrodes. A well electrode sample is shown in Figure 2.8. Evidence of this type of corrosion was found in all of the tested well electrodes. These pitting features were

distributed randomly across the stimulating surface of the well. In addition, one sample had many pits located under an "insulated" portion of the disk. The pits generally ranged in size from 5 μm to 20 μm . There were, however occasionally smaller pits. In addition, pores less than 1 μm in diameter were noted in all samples, including the hemispherical electrodes. An unstimulated, polished disk was examined under scanning electron microscopy to determine whether the pores resulted from stimulation. Pores were also found on this disk (Figure 2.9).

Atomic absorption spectrophotometry did not detect any chromium or nickel in the phosphate buffered saline test solutions of either the well electrodes or the hemispherical electrodes. This test indicated that concentrations of these elements were less than 5 parts per billion. A summary of the data is shown in Table 2.1. There was no significant difference from zero. There was also no detectable change in pH (pH = 7.4) of any of the test solutions.

The transient voltage measurements for each test electrode with respect to the iridium oxide return electrodes are displayed Appendix 2A.

DISCUSSION

Results from this study indicate that the tested epimysial electrodes have the electrochemical and mechanical properties for successful long term electrical activation of the diaphragm. The mechanical fatigue strength of the electrodes was great enough to withstand an accelerated in vitro simulation of ten years of breathing. The mechanical tests yielded cracking of the silicone rubber strain relief system, but the mechanical loading of the electrodes was more extreme than expected during diaphragm pacing. The mechanical loads placed on the electrode and lead wire may also change the site of maximum stress concentration. Electrical

stimulation tests demonstrated no evidence of corrosion in a ten year, in vitro simulation using a 316L stainless steel hemispherical electrodes. However, pitting corrosion was observed on 316L stainless steel well electrodes. The difference in corrosion resistance of the two electrode types was attributed to differences in current density and fabrication techniques. In addition, the corrosion evidenced on the well electrodes was not enough to produce detectable metal concentrations in the test solutions. We concluded that the hemispherical stimulating surface and lead wire strain relief designs sufficiently reduced risks of failure caused by mechanical fatigue or corrosion.

The fatigue stress loading of an epimysial electrode implanted on the abdominal surface of the diaphragm will depend on the geometric orientation of the electrode and lead wire. Since the primary factor for fatigue strength is the amplitude of the maximum strain cycle (Scheiner, 1991), the radius of curvature and the diameter of the electrode at the bend will determine the in vivo electrode durability. The varied flexibility and nonuniform radius of the electrode lead wire connection results in a minimum radius of curvature determined by the magnitude and direction of the load placed on the lead wire (compare Figures 2.6 and 2.7). The ninety degree angle used in this study results in a smaller radius of curvature at a location with a larger electrode diameter than expected for the diaphragm pacing application. The viability of the electrodes under these extreme conditions indicates that the lead wire connection is robust and will withstand the mechanical loads of diaphragm pacing.

The cracking of the silicone rubber at the stress concentration area (Figure 2.6) was concerning because of the potential for the formation of silicone rubber wear debris. Silicone rubber wear debris can lead to a foreign body giant cell reaction

and possible autoimmune disease (Dolwick 1985, Kossovsky 1987, Rosenthal 1983, Travis 1985). However, neither wear debris nor discoloration of the silicone rubber were observed upon gross examination of the electrodes. This could be attributed to a decreased the amplitude of the maximum strain cycle as the silicone rubber cracking effectively reduced the radius of the electrode at the bend. Although we do not expect wear debris under the reduced loading of diaphragm pacing, care is required in the analysis of electrodes from in vivo tests in order to detect mechanical fatigue of the silicone rubber strain relief.

The difference in the charge density delivered by the well and the hemispherical electrodes may account for the difference in pitting corrosion observed in the electrochemical tests. For this study, well electrodes were tested at an average current density of $12.5 \mu\text{A}/\text{mm}^2$ ($0.25 \mu\text{C}/\text{mm}^2/\text{phase}$) and hemisphere electrodes at $6.25 \mu\text{A}/\text{mm}^2$ ($0.125 \mu\text{C}/\text{mm}^2/\text{phase}$). The pitting corrosion observed on the well electrode surfaces was consistent with recommended average current densities of less than $10 \mu\text{A}/\text{mm}^2$ to prevent electrode corrosion and tissue damage for intramuscular electrodes (Mortimer 1980). However, the $0.25 \mu\text{C}/\text{mm}^2$ charge density used for the well electrodes is significantly smaller than the $1.5 \mu\text{C}/\text{mm}^2$ pitting corrosion limit found by Lan et al. for 316LVM stainless steel (Lan 1989). The pitting corrosion limit discrepancy may be due to the stimulus waveform or differences in real area. We used a controlled current recharge phase (Figure 2.5) instead of the direct capacitive recharge used in the physiologic experiments (Mortimer 1980) and the symmetrical biphasic waveform used in vitro (Lan 1989). The controlled current recharge brings the electrode potential back to steady state more slowly than the other waveforms and may allow more time for electrochemical reactions to occur by holding the electrode potential at a damaging level (Weinman

1964, Brummer 1983). In addition, the geometric surface area that was measured for the epimysial electrodes in this study was similar to the real surface area because all samples were polished to 0.25 μm grit. The real surface area of the intramuscular electrodes may be significantly greater than the geometric surface area due to a surface that is less smooth.

The distribution of pits on the well electrode stimulating surface indicated that there was another factor affecting the corrosion process. We expected corrosion, if detected, to be concentrated near the edges of the disk because of the local maximal current density (Ksienski, 1992, Rubinstein 1987). However, pore defects observed on unstimulated disks (Figure 2.10) could have contributed to pitting corrosion. These pores may have provided enough of a surface defect to create local chemical differences and initiation of the corrosion process. The source of the porosity is unknown but we suspected gas inclusions in the metal (316L) suggesting that a vacuum melt metal such as 316LVM may be a more appropriate electrode material.

The differences in manufacturing techniques between the well electrode and the hemispherical electrode may also have affected corrosion resistance. The well electrode stimulating surface was created by polishing a disk that was originally cut using traveling wire electrical discharge machining (EDM). EDM causes vaporization of metal on the surface of the workpiece and there is an outer recast layer consisting of metal that has resolidified onto the metal surface. Microcracks have been reported on the surfaces of dies that were cut using EDM (Thomson 1989). There was no evidence of microcracks or other surface defects under SEM analysis of polished electrode disks. In addition, copper contamination found on

the surface of unpolished samples could not be found on polished samples using elemental X-ray diffraction analysis. Although the polishing process removed the recast layer, there may still have been residual stresses in the underlying heat affected metal, creating sites for local stress corrosion. The hemispherical stimulating surfaces were cut using a lathe rather than an EDM process, eliminating the risk of stress corrosion.

In conclusion, we found that the tested epimysial electrodes have adequate mechanical and electrochemical durability for long term diaphragm pacing. Animal testing is required to assure that the differences in the in vitro and in vivo mechanical loading and the electrochemical environment do not significantly alter the reliability of the electrodes.

APPENDIX 2A: Transient Electrode Potentials

Figure 2A.1: Stimulus voltages of the stimulating electrodes measured against the iridium oxide return electrodes. The well electrodes and hemispherical electrodes are marked separately. Note the difference between the initial anodic phase of the stimulus pulse (time 0 to 5 ms). The eight traces are superimposed on the same graph. Pitting corrosion was observed on the stimulating surface of the well electrodes.

The measured voltage waveforms for each test electrode with respect to the iridium oxide return electrodes is displayed in Figure 2A.1. The voltage waveforms were characterized by a negative spike associated with the cathodic stimulus pulse followed by a gradual rise and eventually an overshoot of the baseline voltage. The peak of the overshoot correlated with the end of the anodic recharge phase. After the overshoot peak, the voltage slowly returned to baseline. Slight differences were observed between the well electrodes and the hemispherical electrodes. The hemispherical electrodes were slower to return to baseline voltage.

Differences in the electrochemical reactions on the well and the hemispherical stimulating surfaces were reflected in the voltage waveforms. The voltage waveform differences could have been caused by a difference in the double layer capacitance (Brummer 1983, Dymond 1976, Weinman 1964), differences in oxygen reduction reactions (Lamb 1984, Lamb 1986, Morton 1994) or the presence of pitting corrosion on the surface of the well electrodes (Lan 1989). The correlation of the pitting corrosion with a difference in the stimulus voltage waveform implies that measurement of voltage waveforms may be useful for predicting the safety of a stimulating electrode or for setting charge injection limits. A pulse clamp experiment (Bonner 1993) could help identify the reactions occurring at the stimulating surface.

Voltage waveform measurements of current stimuli may also be useful for defining a charge imbalance setting to increase the safe charge injection level. Since the voltage waveform overshoots the baseline, a net cathodic, charge imbalanced current waveform may reduce the risk of corrosion and eliminate damaging electrochemical reactions (McHardy 1977, Scheiner 1990). Theoretically, the time limit for the anodic recharge could be set when the voltage waveform crosses the baseline (Figure 2A.1).

Figure 2.1: Strain relief coil used for connecting the lead wire to the stimulation disk. The top drawing displays the strain relief coil in the stimulating disk. This coil is laser welded into place along the top midline of the disk. The lower figure is a drawing of the lead wire attached to the disk. The lead wire passes through the center of the strain relief coil and is welded along the back of the disk. Mechanical loading of the lead wire is isolated from the weld along the back of the disk by the polypropylene monofilament and plug. A well type electrode is shown.

Figure 2.2: Test setup for mechanical fatigue test of the electrode tip to lead wire connection. The stimulator was used to check for interruption of an electrical connection. The angle of the lead wire-electrode tip was set to 90 degrees. The two chucks were counter rotated to put a net 180 degree flexion on the electrode tip. The speed of revolution was measured using an optical sensor.

Well Electrode Design

Hemispherical Electrode Design

Figure 2.3: Electrode designs for uniform current density. The hemisphere electrode design has uniform current density in an infinite isotropic media. A well electrode reduces the local high current density found at the edge of a flush ($d=0$) disk electrode. The current density becomes more uniform as the depth of the well is increased (Ksienski 1992).

Figure 2.4: Apparatus for electrochemistry test. Medical grade air was flushed through the sealed system at 1-4 day intervals. The flask was filled with 20 ml of 0.15M phosphate buffered saline at a pH of 7.4. The test electrode and the return electrode were connected to a current stimulator. Electrical current stimulation was passed through the electrodes at a constant 50 Hz for 96 days.

Figure 2.5: Stimulus waveform used for testing the corrosion resistance of epimysial electrodes for diaphragm pacing. The stimulus is a controlled current, charge balanced biphasic waveform with a short cathodic stimulating pulse followed by a long, low amplitude recharge phase. This waveform is consistent with the stimulus waveforms used in some radio frequency implantable stimulators (Smith 1987).

Figure 2.6: Sample after simulated cyclical motion associated with an equivalent of ten years of breathing. Note the area of stress concentration demarcated by the arrow. Electrical continuity remained intact throughout the experiment. Some cracking of the silicone rubber was noted near the site of stress concentration.

Figure 2.7: Electrode sample placed at a larger angle. Stress concentration occurs at the border between the lead wire and the strain relief tubing.

Figure 2.8: Evidence of pitting corrosion of a well electrode examined under SEM. Corrosion pits ranged in size from approximately 5 μm to 30 μm . The pits appeared to be randomly distributed across the stimulating surface.

Figure 2.9: Pores found on unstimulated electrode surface indicating origin in electrode manufacturing or present in the stock material. Evidence of pores was found in all samples of well and hemisphere stimulating surfaces. Pores were approximately 1 μm in diameter.

Chromium				
Sample	Trial1 (ppb)	Trial2 (ppb)	Trial3 (ppb)	Average
1 Well	1.3	0.9	0.8	1.0
2 Well	0.5	0.5	0.5	0.5
3 Well	0.1	0.2	0.2	0.2
4 Hemi	-0.1	0.0	0.0	0.0
5 Hemi	-0.1	-0.2	-0.2	-0.2
6 Hemi	0.1	0.0	-0.2	-0.1
7 Hemi	-0.2	-0.2	-0.2	-0.2
8 Well	0.0	-0.2	0.0	-0.1

Nickel				
Sample	Trial1 (ppb)	Trial2 (ppb)	Trial3 (ppb)	Average
1 Well	0.2	-0.1	0.0	0.0
2 Well	-0.7	2.0	-1.2	0.0
3 Well	-0.5	0.1	-0.8	-0.4
4 Hemi	-0.6	0.4	1.8	0.5
5 Hemi	1.1	1.1	0.3	0.8
6 Hemi	2.1	0.7	0.0	0.9
7 Hemi	0.4	0.1	-0.6	0.0
8 Well	0.1	2.0	-0.3	0.6

Table 2.1: Data from atomic absorption spectrophotometry. Samples were tested for chromium and nickel. No detectable amount of these elements were found in any of the samples.

Chapter 3

Staple Penetration and Staple Histological Response for Attaching an Epimysial Electrode onto the Abdominal Surface of the Diaphragm using a Laparoscopic Approach

INTRODUCTION

The objective of this study was to determine whether a laparoscopic stapler could be used to attach an epimysial electrode onto the abdominal surface of the diaphragm. We studied the penetration depth of the staples, the short term and long term tissue response and the ability of the staples to hold an electrode onto the dog diaphragm. Laparoscopic hernia staplers, the Endopath, made by Ethicon, and the Endo Hernia, made by Autosuture, were tested in a one week study and The EndoPath was also tested in a long term (3-14 months) study. The effect of electrode tab thickness on staple penetration determined the electrode design criteria for minimizing the risk of diaphragm perforation.

Laparoscopic implant of electrodes that electrically activate the diaphragm offers advantages over procedures for implanting phrenic nerve cuff electrodes (Peterson 1986, Peterson 1990, Peterson 1994b, Stellato 1985). Electrical activation of the diaphragm (diaphragm pacing) using cuff electrodes requires electrode placement directly on the phrenic nerves using a cervical or thoracic approach (Glenn 1984, Glenn 1985, Wetstein 1987). Placement of electrodes directly on the nerve has associated risks of phrenic nerve damage (Glenn 1988). As a result, a laparoscopic procedure has been developed for implanting intramuscular electrodes in the diaphragm (Stellato 1985), alleviating the risks of phrenic nerve damage. The minimally invasive surgery also provides accelerated recovery, rapid convalescence, reduced wound infection and facilitated surgery in the obese (Cuschieri 1991).

Epimysial electrodes were considered for diaphragm pacing because the implanted electrodes do not perforate the muscle, risking a pneumothorax, and the

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electrode location is evident after implant. Intramuscular electrodes are effective for producing ventilation in dogs (Peterson 1990, Peterson 1994a), but Peterson et al. found that 12 of 30 implanted electrodes perforated the diaphragm and 3 extended more than 1 cm into the thorax (Peterson 1994a). The risks of transdiaphragmatic electrode placement include pneumothorax and placement of the stimulating tip in the heart or lungs. Although epimysial electrodes cannot perforate the diaphragm, they are traditionally sutured onto the muscle which would be a difficult laparoscopic technique.

Laparoscopic staplers were tested as an alternative to suturing epimysial electrodes onto the diaphragm. The staplers were originally designed for laparoscopic hernia repair (Klein 1992, Toy 1992, Peters 1993), but are candidates for other applications. We studied the risks of staple diaphragm perforation by laparoscopic implant of four simulated electrode tabs and three electrodes, each with a different tab thickness. The histological response to the staples was tested at one week and at three to fourteen months following implant.

METHODS

Two staplers were tested in this study, the Endopath (Ethicon Inc., Somerville, NJ) and the Endo Hernia (Autosuture Co., Norwalk, CT). Both devices are disposable, multifire staplers designed for use in laparoscopic hernia repair. The Endopath has a rotating handle and contains 20 staples. The Endo Hernia has a rotating handle, an articulating head and holds 10 staples. The staples discharged by each stapler are shown in Figure 3.1 and are displayed in 4 stages of closure.

The Endopath and Endo Hernia staples were implanted in three dogs for one week and Endopath staples were implanted in 11 dogs for three to fourteen months.

The one week study was conducted to assess the risk of diaphragm perforation and determine the effect of electrode tab thickness on staple penetration for each stapler. In addition, the histological response of the muscle to the staples was measured after the one week implant. The Endopath was also studied in a long term study using the stapler to attach epimysial electrodes onto the abdominal surface of the diaphragm. The ability of the staples to hold a long term implant in place was assessed and the histological response to the staples was determined. Staple penetration was measured for the long term study and the effects of electrode tab thickness on staple penetration were documented.

One week study

The stapler/staples were tested in a one week study by attaching a simulated electrode tab (SET) onto the diaphragm muscle under laparoscopy. The SET, shown in Figure 3.2, was made of Silastic® MDX 4-4210 (Dow Corning Corp., Medical Products, Midland, MI) with a Dacron® reinforcement. These implants were custom made with 4 different thicknesses, 0.50 mm, 0.75 mm, 1.00 mm and 1.25 mm. One polypropylene mesh (Surgipro SPM-35, U.S. Surgical Corporation, Norwalk, CT) was also tested in one of the three implants. The SET dimensions were 12.7 mm x 19.1 mm. Each SET was cleaned using a six step cleaning process consisting of 5 minutes in a sonicator with the solvents Freon TMS (MS-167, Miller Stephenson Chemical Co., Inc., Morton Grove, IL), Safezone (MS-197 Miller Stephenson Chemical Co., Inc., Morton Grove, IL), Liqui-nox® (Alconox, Inc., New York, NY) in distilled water, distilled water, 95% ethanol and ultra pure water. Each implant was placed in a clean vial in ultra pure water and sterilized using gamma radiation.

Eight SETs were implanted using aseptic technique in each of three dogs, weights 33, 27, and 38 kg. The dogs were pre-anesthetized with Surital (15mg/kg), intubated, and shaved for surgery. Halothane anesthetic (1-2%) was used for the remainder of the implant procedure. The dogs were treated with 500 mg oxacillin IV at the beginning and end of surgery and cephalexin (500 mg, b.i.d.) for 3 days following surgery. Temperature was maintained using a heating pad and the dog was administered 500 ml 0.9% sodium chloride intravenously over the course of the implant procedure.

A 10 mm incision was made 1-3 cm caudal to the umbilicus, and a Veress needle was inserted to establish a pneumo-peritoneum. A 10 mm trocar and cannula were inserted and a 10 mm 0° laparoscope (Karl Storz Endoscopy-America, Inc., Culver City, CA) was introduced. A 10/11 mm cannula (Ethicon Inc.) and a 12 mm cannula (Surgiport, U.S. Surgical Corporation) were inserted 6-8 cm lateral and 3-5 cm cephalad to the initial cannula on opposite sides.

Each SET was introduced through the 12mm cannula and a stapler through the 10/11mm cannula. The SETs introduced on the right side were implanted on the right hemidiaphragm and visa versa allowing a stapler approach from the contralateral cannula. The contralateral approach aided the stapling procedure by improving the stapler angle.

Following surgery, the dogs were X-Rayed for pneumothorax (in case of diaphragm perforation). The animals were housed for 6, 6, and 7 days. At the time of explant, two of the dogs were anesthetized with sodium pentobarbital (30 mg/kg) and an aortic (whole body) perfusion was done (2 liter 1% paraformaldehyde in 25 mM cacodylate buffer with 0.9 mM $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$

followed by 4 liters 3.5% glutaraldehyde in 25 mM cacodylate buffer with 0.9 mM $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$). Upon tissue explant, the diaphragm was placed in 10% formalin (Formalde-Fresh, FisherChemical, Fisher Scientific, Pittsburgh, PA). The third animal was killed with an overdose of sodium pentobarbital and the diaphragm muscle was excised and placed in 10 % formalin.

Tissue samples cut from the diaphragm and staples were removed. Each tissue sample was sectioned along the longitudinal tract of the staple. Samples were dehydrated and embedded in paraffin. Sections of 7-10 μm thickness were stained with Hematoxylin and Eosin. Staple penetration was measured from images of the tissue section with a staple placed over the hypothetical staple tract. Images were then digitized and analyzed using JAVA video analysis software (version 1.4, Jandel Scientific, Corte Madera, CA). Staple penetration, muscle thickness, reactive layer thickness and areas of obvious staple location were measured.

Long Term Study

A long term study was conducted to determine if the Endopath staples could be used to hold an electrode onto the diaphragm muscle for long periods of time. Three electrode designs (Figure 3.3) were tested in a total of 11 dogs. Each dog was implanted with 2-4 electrodes that remained implanted for a minimum of three months. Each electrode type had a lead wire terminating in a disk, 6.4 mm in diameter. Electrode Type 1 incorporated a stimulating surface located in a well formed by a Dacron® reinforced Silastic® (MDX 4-4210) housing. Electrode Types 2 and 3 incorporated a protruding hemispherical stimulating surface (Chapter 2). Stapling pads (12.7 cm diameter) were placed on opposite sides of the disk. Electrode Type 2 did not have Dacron® reinforcement while Dacron®

reinforcement was added to the abdominal side of Type 3 electrodes. The pad thicknesses were 0.88 mm (Type 1), 0.60 mm (Type 2) and 0.75 mm (Type 3). Each electrode was cleaned using a six step cleaning process consisting of 5 minutes in a sonicator with the solvents Freon TMS, Safezone, Liqui-nox® in distilled water, distilled water, 95% ethanol and ultra pure water. Each electrode was sterilized by autoclave (Type 1) or ethylene oxide gas (Type 2 and Type 3). A two week degassing period was allowed for ethylene oxide sterilized electrodes.

The electrodes were implanted under laparoscopy using a 10 mm laparoscope (Karl Storz Endoscopy-America Inc.) through a 10 mm port (U.S. Surgical Corporation) placed 1-3 cm caudal to the umbilicus. Two 11 mm ports (U.S. Surgical Corporation) were placed 3-5 cm lateral and 3-5 cm cephalad to the first port. A 5 mm port (U.S. Surgical Corporation) was placed 2-3 cm caudal to the xiphoid. One to two electrodes were implanted on each hemidiaphragm. Each electrode was held for stapling through the ipsilateral port and stapled from the contralateral port. Two to three staples were used to hold each electrode onto the muscle. Lead wires to the electrodes exited the peritoneum at the xiphoid and traversed subcutaneously to an exit point on the back of the animal, midway between the scapula. The anesthesia and antibiotic regimen were identical to the one week test.

Prior to explant, the electrodes were again viewed under laparoscopy. Type 1 and Type 3 electrodes were explanted 3 months after implant and Type 2 electrodes were explanted 7-14 months after implant. Each dog was anesthetized with sodium pentobarbital (30mg/kg) and placed in the supine position. The electrodes were viewed using the laparoscope to evaluate gross tissue reaction. The dog was then

euthanized with an overdose of sodium pentobarbital and the diaphragm was excised. The muscle was fixed in 10% formalin for a minimum of 7 days.

Tissue samples were sectioned along the staple tract and the staple was removed. Muscle sections were dehydrated, embedded in paraffin and sliced for light microscopy. One set was stained with Hematoxylin and Eosin and another with Masson's Trichrome. Slides were studied under light microscopy and images were digitized and analyzed with JAVA image analysis software. Again, staple penetration, muscle thickness, reactive layer thickness and areas of obvious staple location were measured.

RESULTS

One week study

SETs attached to the diaphragm using the Endo Hernia stapler resulted in perforation of the diaphragm and even for the 1.25 mm thickness sample. The post implant X-rays indicated that each dog of the one week study had a pneumothorax. A muscle section of a perforated diaphragm is shown in Figure 3.4. The tissue reaction was characterized by no viable muscle within the staple opening. Nine of the eleven test samples resulted in complete penetration of the diaphragm. These data are summarized in Table 3.1.

The staple penetration data for the Endopath staples are shown in Table 3.2. SET thickness is included in the table. When staple depth was plotted versus SET thickness, the plot in Figure 3.5 was found. A Wilcoxon rank sum test was performed to compare staple depths for each thickness. No significant staple depth difference was found even comparing the thinnest SET (0.50 mm) to the thickest

SET (1.00 mm). SETs of thickness 1.25 mm could not be stapled to the diaphragm using the Endopath stapler.

A typical one week tissue response to an Endopath staple is shown in Figure 3.6. The response was characterized by regenerating muscle cells and acute inflammatory cells such as polymorphonuclear leukocytes and macrophages. Additionally, fibroblasts were present and active. The most remarkable feature of the tissue response was viable muscle in the enclosed portion of the staple. There was no indication of damage to many of these fibers. Tissue damage was located primarily inferior to the location of the staple where the staple apparently passed through the muscle during the stapling process.

Long Term Study

The staple penetration data for the long term study are shown in Table 3.3. For calculation of the mean staple penetration, each value was weighted by the staple area found in the histological cross section. The mean staple penetration was 1.40 mm for electrode Type 1 (thickness = 0.88 mm), 2.62 mm for electrode Type 2 (thickness = 0.57) and 1.66 mm for electrode Type 3 (thickness = 0.75 mm). When comparing only the electrodes implanted for three months, electrode Type 3 was found to penetrate a significantly greater depth than electrode Type 1 ($p < 0.02$, Student's *t* test). A comparison of these data is illustrated in Figure 3.7. The mean muscle thickness was 4.02 mm with standard deviation of 1.13 mm.

The relation between staple penetration and tab thickness for the long term electrode test is displayed in Figure 3.8. A linear regression line with slope = -4.25 (mm penetration)/(mm tab thickness) was fit to the data. An effect test indicated that the tab thickness had a significant effect on staple penetration ($p < 0.0001$).

A typical long term tissue response is shown in Figure 3.9. The muscle surface reaction is primarily a reaction of the muscle to the silicone rubber electrode. There was little evidence of a cellular reaction along the staple tract away from the muscle surface.

DISCUSSION

Our results indicate that laparoscopic stapling is a viable option for attaching epimysial electrodes onto the abdominal surface of the diaphragm. Stapling was preferable to suturing due to its simplicity and speed. Of the two staplers tested in this study, the Ethicon Endopath was preferred because it did not penetrate the diaphragm when an appropriate electrode thickness was used. The thickness of the electrode was an important factor in determining staple penetration but large variation in penetration depth indicated that other factors may also play a role.

Laparoscopic staplers were successful for attaching epimysial electrodes onto the diaphragm. The usefulness of laparoscopic staplers has been demonstrated in many applications including closure of the bladder under laparoscopy (Kerbl 1993, Chandhoke 1993), laparoscopy assisted vaginal hysterectomy (Summitt 1992, Lee 1993), laparoscopic appendectomy (Marrero 1991), laparoscopic splenectomy, thorascopic excision of the lung (Allen 1993), and laparoscopic hernia repair (Klein 1992, Toy 1992, Peters 1993). Of these applications, only laparoscopic hernia repair requires the use of the Endopath or Endo Hernia staplers. However, the usefulness of the Endopath stapler for attachment of epimysial electrodes onto the abdominal surface of the diaphragm was demonstrated in this study. Staples held stimulating electrodes in place for periods of three to fourteen months. There was no evidence of staple migration or adverse tissue response despite chronic

mechanical loading during breathing. These results indicate a good long term stability of laparoscopic staples for epimysial electrode diaphragm pacers.

The use of laparoscopic staplers for attaching electrodes onto the surface of the diaphragm was preferable to suturing. New techniques for intracorporeal suturing are being developed (Szabo 1993). However, laparoscopic suturing still requires proper technique, training and practice, and instrumentation (Szabo 1993, Marrero 1991). Suturing may be the method of choice for many applications including tissue approximation or hemostasis (Marrero 1991) however, laparoscopic staples and clips, when used with care, can significantly reduce the time required for a procedure (Daniell 1991, Lee 1993). The approach to the diaphragm made suturing the electrodes in place extremely difficult with existing surgical instruments while stapling was fast, safe and provided a secure attachment of the electrode to the muscle.

The Endopath stapler was preferred over the Endo Hernia for stapling electrodes onto the diaphragm because of smaller staple penetration. Nine of eleven Endo Hernia staples penetrated the diaphragm while none of the eleven Endopath staples resulted in diaphragm perforation in the one week study. Staple penetration is a primary concern because perforation of the diaphragm with an insufflated abdomen has a significant risk of inducing a pneumothorax. In our tests of the Endopath stapler, the mean staple penetration was less than the mean thickness of the diaphragm for all electrode tab thicknesses. However, the variation in both penetration and muscle thickness indicated a risk of pneumothorax when a high staple penetration coincided with a thin muscle. There was evidence of diaphragm perforation in 5 of 16 staple implants with Type 2 electrodes.

The electrode tab thickness had a significant effect on staple penetration. Although the staple depth could not be significantly correlated with SET thickness for the one week study, the long term study yielded a strong correlation between the staple penetration and electrode tab thickness. The difference between the tests was attributed to the large variation in staple penetration and the small sample size for the one week study. The slope of the linear regression to the staple penetration/electrode thickness relation was $-4.25 \text{ (mm penetration)/(mm tab thickness)}$ (Figure 3.8). We had hypothesized that the change in penetration would be inversely related to the thickness with a slope of -1 . However, the larger magnitude of slope implied that the staple penetration was not limited by the back of the staple (opposite the tines) pressing against the electrode. Other potential factors determining staple penetration may have been the length of staple tine that enters the muscle prior to staple closure or the stiffness of the electrode material. The thickest possible electrode tab that still enables stapling should be used to minimize staple penetration. This dimension was between 1.0 mm and 1.25 mm for the Endopath stapler.

Because of the large variation in the data, the electrode tab thickness was not the only factor influencing staple penetration. In this study, we did not control for stapler angle, the pressure placed against the electrode during stapling or the speed of staple closing. However, all staples were implanted under similar surgical situations and by the same investigator. The variation adequately reflected the variation in surgical conditions.

The Endopath staples were nonstrangulating and non-necrosing as evidenced by the viable tissue observed in the enclosure of the staple in the one week test. The

tissue reaction to the staples themselves was only 1-2 cell layers in thickness, however there was a more significant tissue response to the electrode tabs (See Chapter 5). It was often difficult to distinguish the electrode tab tissue reaction from the histological response to the staple, especially for staples with small muscle penetration. The Silastic® material did not elicit a strong enough tissue reaction to adhere the electrode tab to the surrounding tissue and the staple was the important fixating device. This resulted in transfer of stresses from the electrode to the staple and the surrounding tissue. However, the absence of a cellular reaction in the staple tracts of the long term study testifies to the mechanical stability and biocompatibility of the staples.

From our results we concluded that epimysial electrodes can be stapled to the abdominal surface of the diaphragm using an Endopath stapler with an electrode tab thickness between 0.75 mm and 1.0 mm with minimal risk of muscle perforation. Electrode tab thickness was an important factor for determining the penetration depth of the staples.

Figure 3.1: The Endopath (left) and Endo Hernia (right) staples. The staples are shown in open stage through two closing stages and in the final implanted configuration.

Figure 3.2: The silicone rubber test SET used for the short term test of the staples. Thickness was 0.50, 0.75, or 1.0 mm.

Figure 3.3: The electrodes used for the long term staple test. Type 1 electrodes (top) had a tab thickness of 0.88 mm, Type 2 (middle) was 0.60 mm and Type 3 (bottom) was 0.75mm. The staples were placed on either side of the center disk. Two to three staples were implanted per electrode.

Dog	SET Thickness (mm)	Complete Penetration?
575	0.35	yes
575	0.50	yes
575	0.75	yes
575	1.00	yes
645	0.75	yes
645	1.00	yes
645	1.25	no
646	0.75	no
646	1.00	yes
646	1.25	yes
646	1.25	yes

Table 3.1: Staple penetration data for the Endo Hernia. Penetration distance was not measured, but the table indicates whether complete penetration of the diaphragm was detected on the histological sections. Complete penetration was defined as an active tissue response that extended from the peritoneum to the pleura. Nine of eleven samples completely penetrated the diaphragm. Interestingly, one of the non penetrating samples occurred with a 0.75 mm simulated electrode tab (SET), which was not the thickest sample size.

Figure 3.4: Tissue sample from one week study. A perforated diaphragm from an Endo Hernia stapler through a 1.25 mm SET.

Dog	Mesh Thickness (mm)	Staple Penetration (mm) / Muscle Thickness (mm)
575	0.50	2.25 / 2.48
575	0.50	1.40 / 2.25
575	0.75	1.28 / 4.58
575	1.00	1.06 / 2.90
645	0.50	1.38 / 3.53
645	0.50	0.86 / 2.70
645	0.75	1.82 / 2.44
646	0.50	1.75 / 2.56
646	0.75	1.33 / 3.02
646	0.75	1.33 / 2.90
646	1.00	1.45 / 2.29

Table 3.2: Staple penetration and SET thicknesses of the one week staple test for the Endopath.

Figure 3.5: Staple penetration versus SET thickness for the one week study. There was no apparent relation between staple penetration and SET thickness.

Abdomen

Muscle Tissue

Figure 3.6: Tissue reaction to the Endopath staple at 6 days post implant.

Electrode Type	Mean Penetration (mm)	std error	std dev	n	Tab Thickness (mm)
1	1.40	0.07	0.33	37	0.88
2	2.62	0.31	1.19	20	0.60
3	1.66	0.08	0.25	21	0.75

Table 3.3: Staple penetration for the long term staple test. The electrode types are described in the text. Electrode Types 1 and 3 were implanted for three months and electrode Type 2 was implanted for 7-14 months. The n value indicates the number of staples tested for each electrode type. Staple penetration was calculated from histological slides of the staple tracts. The penetration for each sample was measured as the maximum penetration measured using a hypothetical staple location. The mean penetration was found using an arithmetic mean with a weight factor. The weight factor was determined by the amount of staple tract present in the histological section.

Figure 3.7: Comparison of electrodes implanted for three months. The penetration is shown on the y axis, and the electrode type on the x axis. Electrode Type 1 has a recessed stimulating surface and a tab thickness of 0.88 mm. Electrode Type 3 has a protruding stimulating surface and a tab thickness of 0.75 mm. The staple penetration for all the samples is displayed. The circles represent the means with the corresponding standard error of the mean. Standard deviations are shown as dotted lines. The mean penetration for electrode Type 3 was significantly greater than the mean penetration for electrode Type 1 ($p < 0.02$, Student's t test).

Figure 3.8: Relation between staple penetration and tab thickness for all long term electrode tests. A line with slope = $-4.25 \text{ (mm penetration)/(mm tab thickness)}$ was fit to the data. The tab thickness had a significant effect on staple penetration (effect test, $p < 0.0001$). The mean diaphragm thickness was $4.02 \text{ mm} \pm 1.13 \text{ mm}$ (standard deviation).

Figure 3.9: Tissue reaction to long term staple test. There was a thin layer of mature collagen lining the staple tract. One tine of the staple is shown. Masson's Trichrome stained the collagen dark. The space for the electrode tab was located within the collagen.

Chapter 4

Laparoscopic Placement of Electrodes for Diaphragm Pacing using Stimulation to Locate the Phrenic Nerve Motor Points

INTRODUCTION

We tested the hypothesis that electrodes could be implanted at the phrenic nerve motor point on the abdominal surface of the diaphragm using test stimulation to aid placement. Stimulation of the diaphragm during laparoscopy allowed testing of potential electrode implant locations to assure optimum placement. Abdominally placed electrodes may make diaphragm pacing available to a larger patient population by reducing risk of phrenic nerve damage.

Traditional diaphragm pacing systems use cuff electrodes placed on the intracervical or intrathoracic portions of the phrenic nerves. This technique was pioneered by Sarnoff in the late 1940's (Sarnoff 1948). Glenn (Glenn 1973) made diaphragm pacing a clinical reality in the 1960's and his technique has since been modified by Thoma (Thoma 1987) and Talonen (Talonen 1990). One reason for the success of these systems is that stimulation using cuff electrodes assures activation of the entire diaphragm. Complete muscle activation maximizes the ventilatory function of the system and increases the likelihood of full time diaphragm pacing ventilation.

An alternative diaphragm pacing method using intramuscular electrodes was developed by Peterson et al. (Peterson 1994, Peterson 1994). A laparoscope was used during implant to view the insertion of intramuscular electrodes into the diaphragm. Abdominal placement eliminates the risk of damage to the phrenic nerve due to surgical manipulation or electrode tissue reaction. In addition, it obviates the risks associated with the thoracic implant procedure that have limited the applicability of diaphragm pacing for chronic ventilatory assist (Nochomovitz 1990, Peterson 1986).

Full activation of the diaphragm is critically dependent on placement of electrodes at the sites where the phrenic nerves enter the muscle (phrenic nerve motor points) (Nochomovitz 1983). Peterson used anatomical landmarks to determine the placement of intramuscular electrodes at the phrenic nerve motor point. With electrodes placed near the nerves, long term dog studies demonstrate that intramuscular diaphragm pacing (IDP) produces 167% ($\pm$ 48%) of the tidal volume required for full time ventilation without fatigue (Peterson 1994, Peterson 1994).

Electrode placement using anatomical landmarks may be difficult. The phrenic nerves originate primarily from the cervical cord and traverse the neck and thorax to enter the diaphragm from the thoracic side. The right phrenic nerve lies along the inferior vena cava and the left phrenic nerve lies on the pericardial sac as the nerves enter the muscle. The thoracic entry of the phrenic nerve makes the motor point invisible to the abdominal surface of the muscle.

The phrenic nerve entry points and branch pathways are illustrated in Figure 4.1. In the dog, the phrenic nerve splits into two branches about 1 cm superior to the diaphragm (Merendino 1956). The nerve enters a fat pad at the point where branching occurs and the branches diverge as they reach the pleural surface of the diaphragm (Hidayet 1979, Berkmen 1989, Botha 1957). The anterior branch then divides again to form a sternal branch and an anterolateral branch. The posterior branch divides into a posterolateral and a crural branch just above the muscle and these branches run on the superficial aspect of the muscle for a short distance before entering the muscle itself. The lateral branches always lie closer to the central tendon than the costal margin. Once the branches enter the muscle, they run

approximately midway between the pleura and the peritoneum (in the center of the muscle tissue). The right and left phrenic nerves segmentally innervate ipsilateral hemidiaphragms. Each nerve branch segmentally innervates a distinct portion of the diaphragm muscle area (Merendino 1956, Hammond 1989).

Peterson and co-workers determined that complete diaphragm activation is obtained using intramuscular electrodes placed within 20 mm of the phrenic nerve motor point (Nochomovitz 1983, Peterson 1986). The motor points that have been identified using anatomical landmarks on the abdominal surface of the dog diaphragm are shown in Figure 4.1 (Nochomovitz 1983, Peterson 1986). However, errors in placement could occur because of individual anatomical variation. In order to improve the likelihood of electrode placement at the motor point, we have developed a technique for testing many implant sites prior to final electrode placement. In addition, data obtained from test stimulation may be useful for predicting the location of the phrenic nerve motor points.

In this study, we tested placement of epimysial electrodes on the abdominal surface of the diaphragm using visual assessment of diaphragm contraction or using recruitment curve measurements in response to stimulation at multiple test sites. Each implant technique was assessed using post mortem measurements of the distance between each electrode and corresponding motor point. Finally, a technique for improving electrode placement using video feedback and recruitment curve measurements was developed.

METHODS

Preparation

Twelve adult mongrel dogs (28-45 kg) were laparoscopically implanted with epimysial electrodes for diaphragm pacing. The dogs were pre-anesthetized with Surital (15 mg/kg, 4 dogs) or sodium pentothal (15 mg/kg, 8 dogs). Following intubation (8.0-9.5 mm endotracheal tube) anesthesia was maintained with Halothane (1-2%) for the duration of the procedure. Fluid homeostasis was preserved using intravenous 0.9% sodium chloride or lactated Ringer's. Body temperature was maintained with a heating pad and the ECG was monitored throughout the procedure. The dog was placed in the supine position and a Veress needle was inserted into the abdomen to enable CO₂ insufflation (<10 mm Hg using an Electronic Laparoflator 26012, Karl Storz Endoscopy-America Inc., Culver City, CA). A total of four ports were inserted into the resultant pneumoperitoneum (Figure 4.2). First a 10 mm port (Surgiport, U.S. Surgical Corporation, Norwalk, CT) was placed 1-2 cm caudal to the umbilicus. A 10 mm, 0° laparoscope (Karl Storz) was inserted through this port for viewing the surgical procedure. Then two 12 mm ports (Surgiport) were placed on either side of the 10 mm port 4-6 cm lateral and 4-6 cm rostral to the 10 mm port. The 12 mm ports were used for passing the surgical instruments through the abdominal wall. Finally a 5 mm port (Surgiport) was placed 2-3 cm caudal to the xiphoid. Epimysial electrodes were implanted onto the abdominal surface of the diaphragm and the electrode lead wires were passed through the 5 mm port. The electrode lead wires were tunneled subcutaneously to an exit site midway between the scapula.

Equipment

A laparoscopic instrument set was designed and fabricated to stimulate multiple test sites on the abdominal surface of the diaphragm. Components of the instrument set included a tethered vacuum delivery device (VDD) and a manipulating tool (Figure 4.3). The VDD consisted of a housing to carry the electrode and a pair of vacuum ports that allowed the electrode to be held against the diaphragm surface. The manipulating tool had a ball head hexagonal wrench end that fit into a hexagonal slot on the VDD. A tether extended from the slot on the VDD, through the center of the manipulating tool, to the surgeon. The manipulating tool was used to place the VDD at stimulus test sites. The VDD was removed after the electrode was permanently fixed in place using a laparoscopic stapler (Endopath EMS, Ethicon Inc., Somerville, NJ).

The stimulus was delivered to the muscle by the electrode. The stimulating surface of the electrode was a protruding hemisphere with a surface area of 20 mm^2 . The current delivered to the muscle was a maximum of 24 mA with a 100 μs pulsewidth.

Stimulus Testing

Two types of stimulation protocols were tested for determining placement of epimysial electrodes in dogs. Implant sites were tested using visual feedback of muscle activation in four dogs. The remaining eight were implanted using measurements of the recruitment curve at each test site. In both protocols, test sites were chosen by the investigator, and the VDD was held onto the diaphragm using the manipulating tool. The vacuum was applied and the manipulating tool was released from the VDD. The manipulating tool release allowed diaphragm motion

during the ensuing test stimulation. After a test site was evaluated, the vacuum was released and the VDD was retrieved using the manipulating tool. The VDD was then moved to a new location and the process was repeated. All laparoscopies were recorded on VHS or S-VHS video for post surgical evaluation of the test sites.

The test stimulation protocols were programmed into a NeuRx IS/4 (Applied Neural Control Laboratory, Cleveland, OH) stimulator using a Macintosh IIfx computer. LabVIEW (Version 2.1, National Instruments Corporation, Austin, TX) was used to create custom software for programming the stimulator. A digital input/output board (NB-MIO-16, National Instruments) was used to communicate with the microprocessor on the stimulator through an optical isolation unit (Applied Neural Control Laboratory) (See Figure 4.4). We connected the electrode lead wire from the electrode to the stimulator.

VISUAL ASSESSMENT TEST

The stimulation protocol for the VISUAL ASSESSMENT TEST is shown in Figure 4.5. The protocol consisted of five controlled current stimulus pulses. Each stimulus pulse was 100 μ s long, charge balanced, biphasic with 100 μ s delay between phases. There was a 500 ms pause between pulses. The pulse amplitudes were 2, 5, 10, 15 and 20 mA in ascending order and each pulse was accompanied by an auditory signal produced by the computer. The investigator assessed the muscle twitch produced by each pulse to obtain a subjective evaluation of the stimulus test site. The stimulation protocol was repeated until a site was located that provided a strong diaphragm twitch at the 2 mA or 5 mA pulse. Four electrodes were implanted in each of four dogs using the VISUAL ASSESSMENT TEST. Two electrodes were implanted on each hemidiaphragm.

RECRUITMENT CURVE TEST

The RECRUITMENT CURVE TEST was used to implant one or two epimysial electrodes on each hemidiaphragm of 8 dogs. The purpose of this test was to use the recruitment data of each test location to provide a more detailed description of how close the test site was to the actual motor point. A recruitment curve obtained during implant of an epimysial electrode in a dog is shown in Figure 4.7. This recruitment curve had two characteristic rises: one at approximately 4 mA and the other at about 16 mA. Theoretically, the 4 mA rise was associated with recruitment of a branch passing near the test site. We then assumed that the 16 mA rise corresponded to the recruitment of branches at the motor point. When testing potential implant sites, our goal was to minimize the current required to produce full recruitment. This was the same as obtaining an implant site in which the current for recruitment of all of the branches was the same. In effect, this would place the electrode between the phrenic nerve branch entry points.

A recruitment curve is the relation between muscle force and stimulus current. In order to estimate muscle force we measured the abdominal pressure response to stimulus pulses. A 10 mm polyethylene tube was inserted into the pneumoperitoneum and the other end of the tube was connected to a pressure transducer (MP45-3, Validyne Engineering Corp., Northridge, CA). The abdominal pressure signal was sampled at 100 Hz using a LabVIEW data acquisition program and an analog to digital converter (NB-MIO-16, National Instruments). The test setup is described by Figure 4.4.

The stimulation protocol is shown in Figure 4.6. The protocol consisted of a series of 12 pulses. Each stimulus pulse was 100 μ s long, charge balanced,

biphasic with 100 μ s between phases. There was a 700 ms pause between pulses. This stimulation resulted in a series of unfused twitches of the diaphragm. The stimulus pulse amplitudes were 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24 mA in random order (randomized for each trial by the computer). All stimulation was delivered with the dog in an apneic condition.

The peak change in abdominal pressure was recorded for each stimulus pulse. A recruitment curve was constructed by plotting the peak abdominal pressure changes versus the amplitude of the associated pulse. Recruitment curve measurements were made three or more times and the median abdominal pressure value for each pulse amplitude was used for determining the final recruitment curve.

Placement Assessment

Electrode placement relative to the phrenic nerve motor point was assessed 3-14 months after implant. Each dog was euthanized with an overdose of sodium pentobarbital and the entire diaphragm was excised and placed in 10% formalin (Buffered FormaldeFresh, Fisher Scientific, Pittsburgh, PA). After 7-10 days in the fixative, the diaphragm was removed and the phrenic nerves were identified on the thoracic side of the muscle. Each phrenic nerve branch was labeled with a 4-0 stainless steel suture at the point where the nerve entered the muscle. The border of the central tendon and the margin of the muscle were also labeled using stainless steel suture. A radiograph of each explanted diaphragm was taken (Figure 4.8).

The distance between the implanted electrode and the phrenic nerve branches was measured for each hemidiaphragm. Radiographs were digitized using a frame grabber (Truevision TARGA-M8, AT&T Corp.). Distances were measured using a

video image analysis software (JAVA version 1.4, Jandel Scientific, Corte Madera, CA).

For the RECRUITMENT CURVE TEST, images of each test site were sampled from the laparoscopic video of the implant procedure. The test site images were scaled, rotated and overlaid on the radiograph image of the corresponding hemidiaphragm. The radiograph of the excised diaphragm was used as a map for locating all of the test sites relative to the phrenic nerve branches (Figure 4.9). The distance between each test site and the geometric center of the phrenic nerve branches ($d_{phrenic}$) was measured and recorded.

Each recruitment curve from the RECRUITMENT CURVE TESTs was analyzed to determine the current that produced 90% of maximum based on abdominal pressure twitch and that value was defined as I_{90} for that test location. Only recruitment curves that obtained full recruitment were considered for further analysis. Each value for I_{90} was plotted against the $d_{phrenic}$ and a polynomial model was fit to the data using standard least squares model fitting (Figure 4.10). Once this model was determined, a distance, d_i was assigned to each test site based on I_{90} . A circle of radius d_i , centered at the i th test site location, was added to the radiographic map of the diaphragm (Figure 4.11). The intersections of the circles associated with each pair of test sites were identified as a measured location of the motor point. In cases where there were two intersection points, the intersection point closest to the phrenic nerve entry points was defined as the measured motor point. In cases where there was no intersection point, the location of minimum distance between the circles was defined as the measured motor point. Each diaphragm map then contained the locations of the phrenic nerve entry, the locations

of the test sites, the location of the implanted electrode and the locations of the measured motor points (Figure 4.11). The number of measured motor points depended on the number of test sites where full recruitment was attained, for example, in Figure 4.11 the six test sites resulted in 15 measured motor points. The X and Y coordinates of all measured motor points were averaged to define the predicted motor point. The distance between the predicted motor point and the geometric center of the phrenic nerve branch entry points was measured and recorded. This distance was compared to the distance between the implanted electrode and the geometric center of the phrenic nerve branch entry points.

RESULTS

Comparison of Implant Techniques

The measured distances between the implanted electrodes and the phrenic nerve motor points for both the VISUAL ASSESSMENT TEST and the RECRUITMENT CURVE TEST are shown in Table 4.1. Each distance value in Table 1 is the mean distance between the electrode and the geometric center of the nerve branch entry points on each hemidiaphragm. The objective of both techniques was to place the electrodes at a minimum distance to the phrenic nerve entry points. The mean distance between the implanted electrodes and the phrenic nerve motor point was 13.7 mm for electrodes implanted with the VISUAL ASSESSMENT TEST and 13.8 mm for electrodes implanted with the RECRUITMENT CURVE TEST. These data points are also displayed in Figure 4.12 with a quantile plot. The ends of the box mark the 25th and 75th quantiles. The line through the box marks the median and the whiskers mark the data points that fall within a distance of 1.5 times the interquantile range. The bracket is the

shortest half, the most dense 50% of the observations. The mean is drawn through the entire graph. Note that the shortest half of the RECRUITMENT CURVE TEST falls at a lower value than the shortest half of the VISUAL ASSESSMENT TEST. A Shapiro-Wilk W test indicated that the distribution of implant distances for the RECRUITMENT CURVE TEST was not a normal distribution ($p < 0.05$).

Placement of electrodes on the right and left sides was compared to determine which side resulted in placement closer to the motor point. Figure 4.13 shows the distribution of the electrode to motor point distances for epimysial electrodes implanted using the combined data from the VISUAL ASSESSMENT TESTs and the RECRUITMENT CURVE TESTs. The mean placement of left side electrodes was 11.1 +/- 4.0 (std dev) mm and the mean placement for right side electrodes was 17.0 +/- 5.4 (std dev) mm. This represented a significantly closer placement for left side electrodes compared to right side electrodes ($p < 0.01$ using Wilcoxon Rank Sums test).

Quantitative Evaluation of Recruitment Curve Test

The relation between I_{90} and $d_{phrenic}$ is displayed in Figure 4.10. A second order polynomial of the form:

$$d = A I_{90}^2 + B I_{90}$$

was fit to the data. **A** and **B** were the parameters of the model. Model fits were also obtained for first order and third order polynomials but the first order model had a higher root mean square error than the second order model and the third order model resulted in parameters that were not well determined. For the second order model, the parameter values were:

$$A = -0.033 \pm 0.008 \text{ std error}$$

$$B = 1.57 \pm 0.14 \text{ std error}$$

Both parameters were significant compared to 0 ($p < 0.0001$). In addition, both I_{90} and I_{90}^2 had significant effect on distance ($p < 0.001$ and $p < 0.0001$ tested against 0 effect using F-statistic and tested using leverage plots with a 95% confidence interval). The second order model is overlaid on the measured data in Figure 4.10.

An analysis of the residuals was conducted to determine whether there was an error in assuming that the model could be generalized for all dogs. The residuals for each dog were compared to 0 using a Wilcoxon Signed Rank test. The residuals were significantly greater than 0 for dog 480 ($p < 0.01$) and dog 589 ($p < 0.05$) and the residuals were significantly less than 0 for dog 451 ($p < 0.05$). As a result, the model estimated the I_{90} - distance relation too low for dogs 480 and 589 and too high for dog 451.

A comparison of the implanted test locations and the predicted motor point is shown in Table 2. The predicted motor point was obtained from the I_{90} implant data and the distance prediction model (Figure 4.10) and was compared to the distance between the implanted electrode and the phrenic nerve motor point measured from the radiograph. The paired distances were compared using a Wilcoxon Rank Sum test. The mean value of the predicted motor point was significantly less ($p < 0.002$) than the distance between implanted electrodes and the phrenic nerve motor point.

DISCUSSION

The use of either the VISUAL ASSESSMENT TEST or the RECRUITMENT CURVE TEST resulted in implant of epimysial electrodes an average of 14 mm away from the phrenic nerve motor point. Electrode implant at locations without full phrenic nerve recruitment were associated with anatomical limitations, lack of full recruitment at any of the test sites and lack of coordination between recruitment curve measurements and video feedback of the test site location. A new technique to improve placement by predicting the motor point was developed in this study. The motor point prediction technique was based upon locating test sites on a diaphragm map and using measured recruitment curves and an I90-distance model to predict the distance to the motor point from each test site. Retroactive application of the motor point prediction technique to the dogs implanted in this study implied that significant improvement in electrode placement could be achieved.

Efficacy of Electrode Placement Using the Visual Assessment and Recruitment Curve Tests

Electrode placement using the VISUAL ASSESSMENT TEST and the RECRUITMENT CURVE TEST resulted in an average distance of 14 mm between the electrode and the phrenic nerve motor point. Full activation of the diaphragm using intramuscular electrodes requires placement within 20 mm of the phrenic nerve motor point (Peterson 1986) while epimysial electrodes must be placed approximately 12 mm from the phrenic nerve motor point (See Chapter 5). Modification of the stimulus test procedure is required to improve the reliability of placement of electrodes at a location where full activation of the diaphragm can be achieved.

The mean distance between an implanted electrode and the motor point was not significantly different for the VISUAL ASSESSMENT TEST and the RECRUITMENT CURVE TEST. This result was unexpected considering that the VISUAL ASSESSMENT TEST lacked quantitative recruitment information, which could lead to poor electrode placement. For example, one test site may elicit muscle contraction on the first test pulse (2 mA) but never fully activate the muscle while another site may not elicit muscle activation until the third pulse (10 mA), but may still achieve full recruitment by the last pulse (20 mA). An electrode may be erroneously placed at first test site because the lower threshold is known while the maximum level of activation cannot be distinguished visually.

Despite the similar mean distances between an implanted electrode and the motor point, the RECRUITMENT CURVE TEST resulted in placement of a greater percentage of electrodes within the required distance for complete muscle activation using epimysial electrodes. The VISUAL ASSESSMENT TEST yielded 38% of electrodes within 12 mm of the motor point compared to 54% for implant using the RECRUITMENT CURVE TEST. A comparison of the data distributions showed that the median and shortest half of the RECRUITMENT CURVE TEST were less than the median and shortest half of the VISUAL ASSESSMENT TEST. In addition, the RECRUITMENT CURVE TEST distribution was skewed to the left. This indicated that placement was slightly better using the RECRUITMENT CURVE TEST.

Poor placement of one electrode, dog 760 right hemidiaphragm, occurred when no site providing full activation was found using the RECRUITMENT CURVE TEST. Failure to locate a test site that elicited full activation was attributed to

difficulties defining the abdominal pressure associated with complete phrenic nerve recruitment. Since the amplitude of the abdominal pressure twitch varies by subject and changes with muscle length, full recruitment was defined by the maximum pressure obtained from all test sites. In order to assure that a full recruitment test site is chosen, a set of standard test site locations should be used for each implant. The locations of the test sites could be determined from anatomical landmarks. In general, testing along the central tendon with test sites spaced no more than 15 mm is recommended.

The location of the right phrenic nerve motor point with respect to the central tendon affected placement of right hemidiaphragm electrodes. Often one or more of the right phrenic nerve branches enter the diaphragm on the central tendon (Figure 4.14). The significantly greater distance between implanted right electrodes compared to implanted left electrodes (Figure 4.13) was probably caused by the central tendon location of right phrenic nerve motor points. The central tendon must be avoided for electrode implants because it is too thin to implant an intramuscular electrode or hold a staple for implanted epimysial electrodes. As a result there may be a limit to the proximity of placement of electrodes to the right phrenic nerve.

Sources of Error in Prediction of Post-Implant Recruitment

The effect of the laparoscopic procedure on the diaphragm muscle length may have produced some error in placement of electrodes with respect to the post implant motor point. Abdominal insufflation changes the length of the diaphragm and may change the physical structure enough to indicate a motor point that is different from the optimal implant site without insufflation. Length dependent

recruitment has been observed for epimysial electrodes implanted on the cat tibialis anterior (Grandjean 1986). The length dependence is associated with movement of the fascia relative to the muscle. The diaphragm is thin (approximately 3.5 mm) and the staples holding the electrodes in place penetrated well into the muscle (greater than 1 mm). As a result, the effect of diaphragm muscle length on post implant recruitment should be minimal. However, length dependent recruitment has been demonstrated for electrical activation of the diaphragm using epimysial electrodes (Chapter 5).

In these RECRUITMENT CURVE TESTs, the twitch response was used to quickly and accurately estimate the recruitment curve. A single scaling factor adequately matches the peak twitch response to the steady state step response with less spread in the estimated recruitment curves, increased speed and reduces risk of fatigue (Durfee 1989). We chose to measure the recruitment curves using single twitches because a detailed recruitment curve could be obtained quickly and accurately.

The abdominal twitch pressure measurement was effectively used to obtain the stimulus current levels at which nerve branches were recruited. Transdiaphragmatic pressure is often used to measure muscle force and the relation between transdiaphragmatic twitch pressure and maximum voluntary contraction pressure is linear (Bellamare 1984). However, thoracic pressure was not recorded in this study. In addition an accurate measurement of the transdiaphragmatic pressure measurements for an awake standing dog cannot be accurately predicted by a transdiaphragmatic pressure measurement during laparoscopic implant conditions because of differences in respiratory mechanics (Newman 1986). Our goal was to

obtain the stimulus current levels at which nerve branches were recruited rather than the absolute measure of the muscle force. The abdominal twitch pressure measurement worked well as an indicator of phrenic nerve recruitment in this study.

The recruitment curve measured after implant may be different from the recruitment curve measured during the RECRUITMENT CURVE TEST at implant due to the histological response to the electrode. After implant, the recruitment properties of the electrode may be changed by the electrical properties of the encapsulation tissue. In addition to a change in dc resistance, the frequency response of the impedance depends on the structure of the cellular reaction (Grill 1994). As a result the changes in the recruitment curve after implant are difficult to predict. However, the goal of the implant procedure was to place the electrode at the phrenic nerve motor point. This goal minimizes the current required for full muscle activation in both the implant procedure and post implant recruitment.

A Technique for Predicting the Phrenic Nerve Motor Point

The results of this study indicated that a new implant technique that predicts the motor point based on measured recruitment curves would improve the selection of an electrode implant site (Table 4.2). This technique would be a modification of the RECRUITMENT CURVE TEST to include a map of previous test sites with the corresponding recruitment curves and would predict the motor point for each hemidiaphragm based on the geometrical orientation of the test sites and the I90-distance relation. The new implant test would use the vacuum delivery device to measure recruitment curves at multiple test sites. The laparoscopic video images of the test sites would then be used to construct a diaphragm map. A circle with a radius determined by the I90-distance relation would be superimposed on the test

sites that produced full diaphragm recruitment at less than 24 mA, 100 μ s. The location of the intersections of the circles would indicate the predicted motor point and suggest an implant location on the diaphragm map. It would be possible to locate the phrenic motor point geometrically using as few as 3 test sites. However, the correctness of the predicted motor point is critically dependent on the accuracy of each test site to motor point distance obtained from the I₉₀-distance relation.

Sources of Variation in the I₉₀-Distance Relation

Sources of error in obtaining the I₉₀-distance relationship included error in the recruitment curve measurement and error in the image analysis procedure required to locate the test sites on the diaphragm map. The recruitment curve measurements were subject to variation caused by diaphragm or abdominal muscle contraction and changes in abdominal pressure associated with insufflation during the RECRUITMENT CURVE TEST. In taking the test sites from the laparoscopic video, there were potential sources of error in image scaling, X-Y offset and angular orientation with respect to diaphragm landmarks. When transferring the video test site locations to the radiographic map of the diaphragm, scaling, offset and angular orientation were again possible sources of inaccuracy. Finally, in using the radiograph of the explanted, fixed diaphragm, muscle shrinkage due to fixation and changing the three dimensional muscle to a two dimensional image were potential sources of error. Despite these errors the predicted motor points represented a significant improvement over placement of electrodes without using a prediction routine.

Anisotropies in the muscle impedance may have contributed some error to the I₉₀-distance relation. Notable differences in the transverse and longitudinal

impedance of muscle have been described (Burger 1961, Geddes 1967, Fatt 1964). The ratio of measured resistances in the transverse direction to the longitudinal direction range from 1.8 to 14.4 (Geddes 1967). It may be possible to take this inhomogeneity into account during prediction of the motor point by using elliptical prediction rings instead of circular ones. The long axis would coincide with the longitudinal direction of the muscle fibers. However, the predicted motor points calculated using circular prediction rings were within 5 mm of the actual motor point. It is unclear that elliptical prediction rings would provide a significant improvement in the predicted motor point.

Variation in muscle thickness may affect the accuracy of the test site to motor point distance predicted by the I_{90} -distance relation. The predicted distance to the motor point will be longer than the actual distance for a thin muscle and shorter than the actual distance for a thick muscle. Differences in muscle thickness between animals may account for the non-optimum fit of the I_{90} -distance model to the data from dogs 451, 480 and 589. However, the distances between the predicted motor point and the actual motor point for dogs 451, 480 and 589 were not significantly different from the results of other dogs tested in this study.

In conclusion, test stimulation can be used to place epimysial electrodes within 14 mm of the phrenic nerve motor point. Electrode placement closer to the motor point may be possible using video image data and recruitment curve measurements to predict the location of the phrenic nerve motor point.

Figure 4.1: The abdominal surface of the diaphragm of the dog. Highlighted areas show the motor points. The theoretical locations of the phrenic nerve branches are labeled. Note the right and left phrenic nerve motor points. Anatomical landmarks include characteristic indentations of central tendon and the vena cava (right side).

Figure 4.2: Port locations for testing possible implant sites and for implanting epimysial electrodes onto the abdominal surface of the diaphragm. The 10 mm port was used for the laparoscope and was placed 1-2 cm caudal to the umbilicus. Two 12 mm ports were placed 4-6 cm rostral and 4-6 cm lateral to the 10 mm port, on either side. A 5 mm port was placed 2-3 cm caudal to the xiphoid. The 5 mm port was used to pass the electrode lead wires out of the abdomen.

Figure 4.3: Instrument set for test stimulation of potential implant sites on the abdominal surface of the diaphragm. A manipulating wrench was used for placing the vacuum delivery device (VDD) at each test location. A tether extended from the VDD, through the wrench to the surgeon for easy retrieval. Suction was used in the end segments of the VDD to hold the electrode onto the muscle surface during stimulation testing. The electrode, housed in the middle segment of the VDD, was permanently attached using laparoscopic staples. The VDD was removed after electrode fixation, leaving only the electrode in place.

Figure 4.4: Hardware setup for testing electrode implant test sites. Stimulation was delivered by the NeuRx IS/4 stimulator. The stimulator communicated with a Macintosh IIfx computer through the NB-MIO board using a LabVIEW algorithm. The computer program also included sampling of an abdominal pressure signal. Abdominal pressure was measured using an abdominal port connecting the pneumoperitoneum to a Validyne pressure transducer.

Figure 4.5: Stimulation protocol for the VISUAL ASSESSMENT TEST. The stimulus consists of 5 current pulses spaced 500 ms apart. Each pulse is biphasic and has a 100 μ s pulsewidth with a 100 μ s delay between phases. The amplitude of the pulses were 2, 5, 10, 15 and 20 mA in ascending order.

Figure 4.6: Stimulation protocol for the RECRUITMENT CURVE TEST. The charge balanced, biphasic, 100 μ s pulsewidth pulses were spaced 700 ms apart. There was a 100 μ s delay between the phases and the current controlled pulses had amplitudes of 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24 mA in random order.

Figure 4.7: An example of a recruitment curve plotting abdominal pressure vs. current. The top graph is a sample of the abdominal pressure response to a single pressure twitch. The amplitude of all 12 abdominal pressure twitches were used to construct the recruitment curve shown in the bottom graph during the RECRUITMENT CURVE TEST. Recruitment of the closest nerve branch begins at 4 mA and initiation of recruitment of additional branches occurs at 16 mA.

Figure 4.8: Radiograph of an excised diaphragm. The electrodes were radio opaque. The phrenic nerve branch entry points have been identified and labeled using radio opaque suture. Sutures also marked the boundaries of the central tendon and the muscle.

Figure 4.9: The relative locations of the stimulus test sites and the phrenic nerve branch entry points for dog #589, left hemidiaphragm.

Figure 4.10: Distance between the motor point and the test site plotted against the current that produced 90% of recruitment for 8 dogs. The distance prediction model, $d = A I_{90}^2 + B I_{90}$ with $A = -0.0329$ and $B = 1.56$, is superimposed onto the data.

Figure 4.11: Map of the left hemidiaphragm of dog 589. The large circles around the test sites have radii of d_i , the distance between the test site and the motor point predicted by a model. The intersections of the circles were labeled measured motor points. These measured motor points were used to calculate a predicted motor point.

VISUAL ASSESSMENT TEST				RECRUITMENT CURVE TEST			
		Primary Electrode Site	Secondary Electrode Site			Primary Electrode Site	Secondary Electrode Site
Dog	Side	Electrode Nerve Distance (cm)	Electrode Nerve Distance (cm)	Dog	Side	Electrode Nerve Distance (cm)	Electrode Nerve Distance (cm)
856	L	0.98	1.66	887	L	+	2.49
	R	1.91	4.35		R	2.54*	5.50*
694	L	0.63	1.91	760	L	0.90	+
	R	1.82	2.00		R	2.90	3.15
391	L	1.54	2.51	279	L	+	+
	R	1.67	2.30		R	0.87	+
702	L	1.12	1.19	480	L	1.04#	-
	R	1.29	1.64		R	1.67	1.89#
				481	L	0.72	-
					R	1.21	-
				482	L	2.00	-
					R	0.99	-
				451	L	1.19#	1.30#
					R	2.03#	-
				589	L	0.94	-
					R	1.48	2.80
mean:		1.37		mean:		1.38	
std dev:		0.44		std dev:		0.62	

Table 4.1: Data for placement of epimysial electrodes on the abdominal surface of the diaphragm using the VISUAL ASSESSMENT TEST (left) and the RECRUITMENT CURVE TEST (right). Primary electrodes were the electrodes placed at the optimal location. Secondary electrodes were implanted as backups to the primary electrodes. * indicates electrodes were implanted without a stimulation technique. # indicates electrodes were reimplanted in a second surgery. + indicates an electrode that became detached from the diaphragm. - indicates that an electrode was not implanted.

Figure 4.12: Graphical representation of data for electrode - nerve distance for RECRUITMENT CURVE TEST and VISUAL ASSESSMENT TEST. Quantile boxes are displayed to the right of the data. The ends of the box mark the 25th and 75th quantiles. The line through the box marks the median and the whiskers mark the data points that fall within a distance of 1.5 times the interquantile range. The bracket is the shortest half, the most dense 50% of the observations.

Figure 4.13: Comparison of the electrode-nerve distance for left electrodes and right electrodes. The means are overlaid on the data points with standard error bars. Quantile boxes are shown to the right of each data set.

Dog	Side	Distance (mm) Implanted Electrode to Motor Point	Distance (mm) Predicted Motor Point to Motor Point	Test Locations with Full Recruitment	Total Test Locations
887	L	16.2	9.6	5	8
	R	-	-	0	0
760	L	8.7	-	1	4
	R	29.5	-	0	8
279	L	9.9	4.7	4	6
	R	7.6	3.3	8	10
451	L	2.1	1.7	6	8
	R	8.8	6.5	6	9
481	L	8.9	-	1	3
	R	11.5	7.9	6	12
480	L	4.6	4.5	6	6
	R	11.8	2.7	4	7
482	L	16.6	5.1	8	11
	R	13.5	4.2	6	11
589	L	11.2	2.8	7	7
	R	12.8	3.7	8	11
mean:		11.58	4.73		
std dev:		6.29	2.29		

Table 4.2: Comparison of the measured distance from an implanted electrode to the actual motor point (defined as the geometric center of the phrenic nerve entry points) and from the predicted motor point to the actual motor point. The predicted motor point was calculated by averaging the measured motor point coordinates (See Figure 4.11). Measured motor points were calculated from the intersections of circles centered at the test location and given a radius determined by the I90-distance model (Figure 4.10).

Figure 4.14: Right hemidiaphragm of dog 481. The phrenic nerve branches entered the diaphragm on the central tendon.

Chapter 5

Epimysial Electrodes for Diaphragm Pacing: Long Term Recruitment Properties and Tissue Response

INTRODUCTION

The goal of this study was to test the long term (> three months) recruitment properties and tissue response of epimysial electrodes for diaphragm pacing in dogs. Although epimysial electrodes have been used clinically for upper and lower motor prostheses, they have not yet been used for diaphragm pacing. The epimysial electrode application with the greatest clinical significance is the neuroprosthesis designed for hand grasp, which uses eight epimysial electrodes manufactured from platinum disks molded into silicone rubber insulation (Keith 1988, Keith 1989). In addition, a lower motor prosthesis using titanium epimysial electrodes was effectively implemented for hip stability in patients with head trauma, stroke or spinal cord injury and the overall tissue response was acceptable despite an infection reported in one of six cases (Walters 1988). Based on the successes of epimysial electrodes for these applications, we were interested in using epimysial electrodes as an alternative to cuff electrodes for diaphragm pacing.

Glenn and colleagues pioneered clinical application of diaphragm pacing using cuff electrodes. Using a cervical or thoracic approach, silicone rubber insulated, platinum electrode cuffs are implanted on the phrenic nerves. A radiofrequency powered stimulator is used to electrically activate the phrenic nerves, thus pacing the diaphragm (Glenn 1976, Judson 1968). The largest patient populations to date have been quadriplegics and patients with central hypoventilation syndromes (Glenn 1976, Glenn 1984, Glenn 1988). Early applications of Glenn's diaphragm pacer met with mixed results including complications associated with damage to the phrenic nerves (15 of 74 nerves) (Glenn 1976, Glenn 1988, Kim 1976). Histological evaluation of phrenic nerves implanted with cuff electrodes demonstrated that many of the nerves had undergone mechanical trauma associated

with either surgical manipulation, or with the cuff electrode itself (Ciesielski 1983, Kim 1976). However, no phrenic nerve damage was associated with the actual stimulation of the nerve. Risk of nerve damage was reduced, but not eliminated, in later implants by using a unipolar electrodes instead of a circumferential bipolar electrode (Glenn 1988). Modifications of diaphragm pacing systems to eliminate risks of phrenic nerve damage and risks associated with the cervical or thoracic electrode implant may make diaphragm pacing available to other patient populations (Nochomovitz 1983a).

The risk of damage to the phrenic nerves led Peterson and co-workers to the development of a system for diaphragm pacing using intramuscular electrodes (Nochomovitz 1983b, Peterson 1986, Peterson 1994a, Peterson 1994b). Intramuscular electrodes minimize the risk of damage to the phrenic nerves because the implanted devices do not come into direct contact with the phrenic nerves. A laparoscopic implant eliminates the need for a thoracotomy, cervical surgery or a celiotomy (Stellato 1985, Peterson 1989). As a result, a diaphragm pacing device with reduced surgical risks was developed. In addition, this device practically eliminated the risk of damaging the phrenic nerves.

Stimulation of the phrenic nerves using an abdominal implant site has been shown to be efficacious (Peterson 1994a). Electrical activation of the diaphragm with intramuscular electrodes provides a mean of 167% of the tidal volume required for full time activation of the diaphragm without fatigue. However, there are difficulties with intramuscular diaphragm pacing including electrode placement and verification of placement at the time of implant. Full activation requires electrode placement within 2 cm of the phrenic nerve entry into the muscle (Nochomovitz

1983b, Peterson 1986, Peterson 1989, Peterson 1994a). Once implanted, electrode placement cannot be verified visually. In addition, 12 of the 32 electrodes implanted in dogs perforated the diaphragm (Peterson 1994a). Perforation of the diaphragm suggests that there may be risks of inducing a pneumothorax or implanting an electrode into cardiac tissue.

In this study we tested the hypothesis that the histological response and recruitment properties of epimysial electrodes implanted on the abdominal surface of the diaphragm are suitable for long term diaphragm pacing. A laparoscopic implant approach was used to place epimysial electrodes onto the abdominal muscle surface. This system maintained the advantages of abdominal electrode placement including minimal risk of phrenic nerve damage and reduced surgical risk. In addition there was no risk of placing an electrode in the thoracic cavity and placement of the implanted electrodes were visually verified. Finally, an epimysial electrode was used as a stimulating probe prior to implant eliminating the need for an additional mapping electrode. In this paper we present the results of tests of epimysial electrodes for pacing the diaphragm of dogs. We examined the long term recruitment properties and the histological response of epimysial electrodes laparoscopically implanted on the abdominal surface of the diaphragm.

METHODS

Electrodes

Three epimysial electrode types were tested for diaphragm pacing (Figures 5.1-5.3). These electrodes were designed for mechanical stability and electrochemical safety. In vitro electrode tests assured corrosion resistance and adequate mechanical fatigue strength (Chapter 2). All three electrode types were constructed

using a central disk with a stimulating surface that faced the muscle. A tab was molded onto either side of the electrode central disk to provide an area for staple attachment to the muscle. The central disk was constructed of 316L stainless steel and connected to a FEP insulated, multistranded, 316LVM stainless steel lead wire. The lead wire was a helix with a polypropylene monofilament threaded through the center. (Peterson 1989). The tissue reaction to this type of lead wire has been well characterized (Corey 1990, Peterson 1994b). Silastic® MDX4-4210 (Dow Corning Corporation, Midland, Michigan) was used as an insulating housing and for molding the electrode stapling tabs

Electrode Type 1 contained a stimulating surface placed in a well and tabs that were constructed of Silastic® MDX 4-4210 with Dacron® reinforcement. The Dacron® reinforcement was cast into the silicone rubber during electrode manufacture. The nylon (Xytel®) mold was cleaned with distilled water and 95% ethanol and dried by forced air prior to each molding. The elastomer was added to the mold and cured for a minimum of 20 minutes at 100°C. Overall dimensions of the Type 1 electrodes are described by Figure 5.4. Electrode Type 2 consisted of a hemispherical stimulating surface extending from the silicone rubber housing described by Figure 5.5. No reinforcing Dacron® was used for this electrode type. Electrode Type 3 was created by modifying a Type 2 electrode by tacking a Dacron® mesh to the stimulating side of the housing. This mesh was added to provide mechanical reinforcement and promote tissue ingrowth. We intended to use the histological response to stabilize the electrode with respect to the surrounding tissue. Electrode Type 2 and Type 3 housings were constructed by compression molding (10 tons) Silastic® MDX 4-4210 in a stainless steel mold and

curing for 20 min at 100°C. The mold was cleaned with distilled water and 95% ethanol prior to each molding and dried by forced air.

All electrodes were cleaned using a four step cleaning process prior to final assembly and packaging for implant. Each cleaning step consisted of five minutes in a sonicator (Cole Parmer Instrument Co., Chicago, IL) with a different solvent. The cleaning solvents were 1) Liqui-nox® (Alconox, Inc., New York, NY) in double distilled water 2) double distilled water 3) 95% ethanol 4) ultrapure water. Surgical implant instruments were also cleaned in the sonicator, however two additional solvents were used prior to the four step process. The first solvent was Freon TMS (MS-167 Miller Stephenson Chemical Co., Inc., Morton Grove, IL) which was followed by Safezone® (MS-197 Miller Stephenson Chemical Co., Inc., Morton Grove, IL). Electrodes were secured into the implant instruments using a 6-O polypropylene suture and packaged for sterilization in a class 10,000 clean hood (Lab Products, Inc., Maywood, NJ). Type 1 electrodes were autoclaved and Types 2 and 3 were sterilized by ethylene oxide. Ethylene oxide sterilized implants were degassed in vacuum for 12 hours and in room air for a minimum of two weeks prior to implant. At implant, the electrode assembly was rinsed in a saline bath containing Kefzol® (Eli Lilly and Co., Indianapolis, IN) (1000 mg in 500ml, 0.9% sodium chloride) before introduction into the peritoneum.

Implant

A total of sixteen Type 1 electrodes were implanted in four dogs (32-42 kg). Two electrodes were implanted on each hemidiaphragm. The primary electrodes were implanted as close as possible to the location on the abdominal surface of the

diaphragm opposite phrenic nerve entry points. The accessory electrode was placed as close to the location on the abdominal surface of the diaphragm opposite phrenic nerve entry as was possible without overlapping the primary electrode. A total of twenty Type 2 electrodes were implanted in five dogs (28-34 kg). Again two electrodes were implanted onto each hemidiaphragm with the same designation as was used for the Type 1 electrodes. A total of ten Type 3 electrodes were implanted in four dogs (29-34 kg). For Type 3 electrodes, each dog was implanted with two to three electrodes. Thus, either one or two electrodes were implanted on each hemidiaphragm of these four animals. Hemidiaphragms with only one electrode were considered to have a primary, but no accessory electrode.

All electrode types were implanted using a laparoscope to visualize the abdominal surface of the diaphragm. The dogs were pre-anesthetized with Surital® (15mg/kg, 4 dogs) or sodium pentothal (Abbott Laboratories, North Chicago, IL)(15mg/kg, 9 dogs). Following intubation (8.0-9.5 mm endotracheal tube) anesthesia was maintained with Halothane (1-2%) for the duration of the procedure. Fluid homeostasis was preserved using intravenous 0.9% sodium chloride or lactated Ringer's. Body temperature was maintained with a heating pad and the ECG was monitored throughout the procedure. Aseptic technique was used for the entire implant surgery. A chest tube was prophylactically placed on the right side of the dog in the event of a pneumothorax. A trocar catheter (Size 16 Fr., 10 inch length, Sherwood Medical, St. Louis, MO) was inserted into the right lateral tenth intercostal space and a Heimlich chest drain valve (Becton Dickinson and Company, Lincoln Park, NJ) was placed on the end. The dog was placed in the supine position and a Veress needle was inserted into the abdomen to enable CO₂ insufflation (<10 mm Hg using an Electronic Laparoflator 26012, Karl Storz

Endoscopy-America Inc., Culver City, CA). A total of four ports were inserted into the resultant pneumoperitoneum. First a 10 mm port (Surgiport, U.S. Surgical Corporation, Norwalk, CT) was placed 1-2 cm caudal to the umbilicus. A 10 mm, 0° laparoscope (Karl Storz) was inserted through this port for viewing the surgical procedure. Then two 11 mm ports were placed on either side of the 10 mm port 4-6 cm lateral and 4-6 cm rostral to the 10 mm port. The 11 mm ports were used for passing the surgical instruments through the abdominal wall. Finally a 5 mm port was placed 2-3 cm caudal to the xiphoid. Epimysial electrodes were stapled (Endopath, Ethicon Inc., Somerville, NJ) onto the abdominal surface of the diaphragm using a minimum of one staple on each stapling pad. The two to four electrode lead wires were passed through the 5 mm port and tunneled subcutaneously to an exit site midway between the scapula. Individual lead wires were then looped subcutaneously and secured with a knot to isolate mechanical loading from the main exit site. A subcutaneous coiled lead wire anode (minimum 100 mm² surface area) was also placed on the back near the lead wire exit site. Port incisions were closed using 5-O chromic gut for the peritoneum, muscle and subcutaneous layers and 4-O stainless steel for the skin. A lateral radiograph was taken to assure the absence of a pneumothorax and the chest tube was removed. Cephalexin (Schein Pharmaceutical, Inc., Port Washington, NY) was administered for three days following implant (1000-1500 mg p.o. b.i.d.) Stainless steel sutures were removed 10-14 days after implant. Dogs were jacketed to protect the lead wires and a two week convalescence was allowed prior to electrode testing.

System Tests

Tests were conducted on the implanted epimysial electrodes at two week intervals for the duration of the study. The study lasted three months (4 dogs) for

Type 1 electrodes, three, seven, nine, twelve and fourteen months (1 dog each) for Type 2 electrodes and three months (4 dogs) for Type 3 electrodes. Two of the dogs with Type 3 electrodes had prior implants of Type 2 electrodes with at least one failed electrode. Tests of recruitment, recruitment overlap of the primary and accessory electrodes and a test of the effects of interpulse interval on tidal volume were routinely conducted. The anesthetic regimen was identical to the implant procedure. Again, fluid homeostasis was preserved using intravenous 0.9% sodium chloride, body temperature was maintained with a heating pad and the ECG was monitored throughout the procedure. Prior to system testing, the supine dog was hyperventilated to apnea. Stimulus pulses were delivered during the apneic period and airflow was measured.

A diagram of the hardware for the test setup is illustrated in Figure 5.6. The endotracheal tube was connected to a three way stopcock with options of either anesthesia or a Fleisch pneumotachometer (model 3813, Hans Rudolph, Inc., Kansas City, MO). The pressure difference across the pneumotachometer was measured using a pressure transducer (± 2 cm H₂O, model MP45-14-871, Validyne Engineering Corporation, Northridge, CA). The airflow signal was sampled using a data acquisition board (NB-MIO-16, National Instruments Corporation, Austin, TX) on a Macintosh IIfx computer. The airflow was sampled at 100 Hz, beginning 0.5 s prior to the onset of stimulation for a total of 3 s. The signal was software integrated to obtain lung volume. The tidal volume was defined as the difference between the minimum and maximum lung volume for a breath. Tidal volumes were recorded for all of the tested stimulus paradigms and were used to quantitate the results of recruitment (changes in injected charge) and changes in interpulse interval.

Stimulus amplitude and/or IPI were automatically changed during every test using the computer and the digital I/O ports of the NB-MIO-16 data acquisition board. The microprocessor of the NeuRx IS-4 stimulator (Applied Neural Control Laboratory, Cleveland, OH) used in the system tests was programmed breath by breath from the computer. The computer obtained a complete record of the stimulus parameters and associated sampled data.

The stimulus waveform is displayed in Figure 5.7. The stimulus consisted of a series of current controlled, charge balanced, biphasic pulses. The first phase was a rectangular cathodic pulse with an pulsewidth of 100 μ s. The second phase followed a 100 μ s delay and consisted of an anodic capacitive discharge. The duration of the stimuli defined the inspiratory time and was set to 1.5 s for all system tests. The stimulus amplitude and interpulse interval (IPI) depended upon the specific test. The tests were the RECRUITMENT TEST, the RECRUITMENT OVERLAP TEST and the IPI TEST.

RECRUITMENT TEST

A test of electrode recruitment was conducted to determine the relationship between stimulus charge and tidal volume. Charge was varied during stimulus testing using stimulus amplitudes in the range of 2 to 24 mA, in 2 mA increments, in random order. Each 1.5 s pulsetrain consisted of a single amplitude (2 through 24 mA) and a nominal 50 ms IPI. Three test runs were performed at each of the twelve stimulus amplitudes for each electrode. Each test run consisted of 12 breaths spaced 5 sec apart ($T_{\text{cycle}} = 5$ s) and was conducted in a single apneic period. Test runs were spaced 5 minutes apart.

Recruitment curves were obtained from each RECRUITMENT TEST by plotting tidal volume versus stimulus amplitude for each electrode; an example is shown in Figure 5.8. Specific current values including threshold current (I_{th}), rise currents (I_1 , I_2), and the saturation current (I_{sat}) were calculated from the recruitment curves and these values were monitored throughout the duration of the study. The threshold current was defined as the current producing 10% of the maximum tidal volume and the saturation current defined as the current producing 90% of the maximum tidal volume (Peterson 1986). The rise currents were the currents at which significant rises in recruitment occurred and were defined as the inflection points in the recruitment curves. Rise current values were obtained from locations of the maxima of the second derivative of the recruitment curve. Definitions of I_{th} , I_1 , I_2 , and I_{sat} are illustrated for an example recruitment curve in Figure 5.8. Trends in recruitment changes were monitored by plotting I_{th} , I_1 , I_2 , and I_{sat} versus implant time.

During the final test, recruitment was also tested with an insufflated abdomen in three animals by measuring the tidal volume response to stimulus pulsetrains and by measuring the abdominal pressure twitch response to single pulse stimuli. The peritoneum was insufflated with CO₂ to 10 mm Hg pressure. The RECRUITMENT TEST was repeated to obtain an insufflated abdomen recruitment curve. Finally, recruitment was measured with an insufflated abdomen using single pulses while recording the intraperitoneal pressure twitch response using a pressure transducer (+/- 50 cm H₂O, model MP45-28, Validyne Engineering Corp., Northridge, CA). Single 100 μ s pulses with amplitudes of 2 to 24 mA, in 2 mA increments, in random order, were delivered to the diaphragm after hyperventilation to apnea. The pulses were separated by 700 ms. Since the insufflated abdomen

increased the muscle length and the twitch response recorded recruitment without the effect of muscle shortening during contraction, the three recruitment curves: normal, insufflated and insufflated using impulses were used to compare length dependence of recruitment.

RECRUITMENT OVERLAP TEST

The RECRUITMENT OVERLAP TEST was conducted to determine whether multiple electrode stimulation could provide additional tidal volume over single electrode stimulation. Recruitment overlap of electrodes implanted on the same hemidiaphragm was tested by comparing individual stimulation of the primary and accessory electrodes with simultaneous stimulation of the primary and accessory electrodes. During simultaneous stimulation, individual pulses to the accessory electrode were delivered 750 μ s after the pulses to the primary electrode (Figure 5.9). This technique eliminated any additive electric field effects occurring during simultaneous stimulation. In addition, additive nerve depolarization was minimized because neural tissue that fired an action potential during the first pulse (primary electrode) was refractory during the second pulse (accessory electrode). The RECRUITMENT OVERLAP TEST was conducted using an amplitude of 25 mA, pulsewidth 100 μ s, interphase delay 100 μ s, interpulse interval 50 ms and inspiratory time 1.5 s. Stimulation was initiated with the primary electrode followed by both electrodes and finished with accessory electrode stimulation.

Recruitment overlap was quantitated by expressing the tidal volume associated with the primary and accessory electrodes as a percentage of the tidal volume obtained with simultaneous stimulation. Hemidiaphragms with a primary electrode

that produced less than 90% of the tidal volume obtained with both electrodes were considered cases that would benefit from multiple electrode stimulation.

IPI TEST

A test of the IPI relationship to tidal volume was conducted for each electrode. Nine IPI values were tested including 25, 33, 40, 50, 59, 67, 83, 100 and 125 ms in random order. A nominal 20 mA amplitude was used with a pulsewidth of 100 μ s, a 100 μ s delay and an inspiratory time of 1.5 s. The cycle time was 5 s and each test run consisted of the nine breaths. Three test runs were conducted at each IPI, one test run was conducted every apneic period with 5 minutes between test runs. Tidal volume was plotted versus interpulse interval for each electrode.

Explant

Type 1 and Type 3 electrodes were explanted 89-98 days after implant. Type 2 electrodes were explanted 7-14 months after implant. At explant, each dog was anesthetized with intravenous sodium pentobarbital (Nembutal®, Abbott Laboratories, North Chicago, IL), (up to 30mg/kg) and maintained on intravenous sodium pentobarbital for duration of the test. Fluid homeostasis was preserved using intravenous 0.9% sodium chloride, body temperature was maintained with a heating pad and the ECG was monitored throughout the procedure. RECRUITMENT, IPI and RECRUITMENT OVERLAP tests were conducted and then a laparoscopy was done. The laparoscopic procedure was similar to the implant procedure except that a single 10 mm trocar was inserted 2-3 cm caudal to the umbilicus. Three dogs were also used to conduct muscle length dependent recruitment tests described in the RECRUITMENT TEST methods. In all cases,

stimulation of each electrode was observed under laparoscopy prior to explanting the diaphragm.

Each dog was killed with an overdose of sodium pentobarbital (> 60 mg/kg) and the entire diaphragm muscle was excised intact with electrodes in place. The diaphragm was placed in 10% formalin (FormaldeFresh, Fisher Scientific, Pittsburgh, PA) for a minimum of 10 days. The liver and subcutaneous lead wire tracts were also excised and placed in 10% formalin.

After 10 days, the phrenic branch entry points, the central tendon and the lateral muscle margin were marked using radio opaque sutures. An X-ray of each diaphragm was taken revealing the electrodes on the abdominal surface of the diaphragm as well as the phrenic nerve entry points on the thoracic surface of the muscle. The radiographs were digitized using a frame grabber (Truevision Targa M8, AT&T Corporation) and the relative distance between the phrenic nerve motor point and the electrodes were measured using image analysis software (JAVA version 1.4, Jandel Scientific, Corte Madera, CA).

The diaphragm was then sectioned for histological evaluation. The electrode was removed, cutting the silicone rubber housing and Dacron® reinforcement when necessary. Dacron® from Type 3 electrodes was left in place at locations where it was tightly embedded in encapsulation tissue. Sections were cut along the lead wire and electrode including the stimulating surface, well (Type 1) or hemisphere (Types 2,3). Sections were dehydrated and embedded in paraffin. Ten µm slices were cut and stained with Hemotoxylin and Eosin. Slides were also stained for collagen analysis using Masson's Trichrome stain and for elastin using Verhoeff's elastica. Microscopic images of the electrode tissue response were digitized using a

framegrabber. Thicknesses of granular tissue, collagen and overall reactive tissue were measured from the digitized images using image analysis software.

RESULTS

Electrode Performance

All Type 1 and Type 3 electrodes functioned for the duration of the study (89-98 days). However, many Type 2 electrodes failed to elicit a muscle contraction. Figure 5.10 displays the time between electrode implant and electrode failure for Type 2 electrodes. A majority (10/11) of electrode failures occurred within the first 2 months. We examined the electrode status by X-ray and traced failure to electrode detachment from the diaphragm. Examination of the electrodes at explant confirmed that the staple had torn through the silicone rubber tab leaving the staple in the muscle for all cases.

A single dog with Type 1 electrodes demonstrated electrode failure characterized by complete loss of recruitment and an open circuit when impedance was tested. This failure was found to be at the subcutaneous connector, which was omitted in future implants.

System Tests

RECRUITMENT TEST

Recruitment measurements of all electrodes were compared using 20 Hz, 1.5 sec pulsetrains with 24 mA, 100 μ s pulses as displayed in Figure 5.11. These results were the average tidal volume over the entire implant period. Generally, tidal volumes greater than 0.3 L for a single hemidiaphragm indicated full diaphragm recruitment for dogs of this size.

One of the primary determining factors for phrenic nerve recruitment was the distance between the electrode and the phrenic nerve branches. The relationship between tidal volume and distance between the stimulating electrode and the phrenic nerve entry into the muscle is illustrated in Figure 5.12. These data indicate that epimysial electrodes must be placed within approximately 1.0 cm of the phrenic nerve motor point to provide full recruitment. The tidal volume drop-off from full recruitment is very steep as the distance from the motor point is increased. No difference in the nerve recruitment to electrode-nerve distance relationship was observed for different electrode types.

RECRUITMENT OVERLAP TEST

The RECRUITMENT OVERLAP TEST provided a measure of the degree of overlap between two electrodes but also indicated whether the accessory electrode could be used for additional recruitment of the phrenic nerve. Seven of the fifteen tested hemidiaphragms resulted in a significant improvement in tidal volume with two electrodes compared with single electrode stimulation (Table 1). The degree of recruitment overlap and usefulness of the accessory electrode for providing additional recruitment depended on the relative placement of the electrodes with respect to the motor point. When the primary electrode was placed close to the motor point, full recruitment was achieved with a single electrode and the accessory electrode provided no additional recruitment (e.g. dog 694 left side, Table 1). Similarly, electrodes both placed to the same side of the motor point resulted in complete recruitment redundancy of the accessory electrode. For example, dog 856 right hemidiaphragm had both electrodes placed anterior to the motor point. However, all seven cases of non-overlapping recruitment were characterized by placement of one electrode anterior to the motor point and the other electrode

posterior to the motor point. Presumably the anterior electrode stimulates the sternal or antero-lateral phrenic nerve branch and the posterior electrode stimulates the postero-lateral and/or crural branches. Accessory electrodes with non-overlapping recruitment could be used to augment tidal volume.

LONG TERM RECRUITMENT PATTERNS

Changes in recruitment during the electrode implant were documented either as changes in tidal volume or as changes in recruitment currents. Dog 391, implanted with Type 1 electrodes, demonstrated significant increases in tidal volume over the time of implant for three of the four implanted electrodes. This example is shown in Figure 5.13. Improvements in recruitment were exhibited as tidal volume changes in this case. However, changes in recruitment were also reflected by changes in the recruitment currents, I_{sat} , I_1 , I_2 and I_{th} . In Figure 5.14 we show changes in I_{sat} , I_1 , I_2 and I_{th} over the time course of an implanted Type 3 electrode (dog 589).

When electrode recruitment was classified as increasing, decreasing or not changing, we found that there were 21 increases, 7 decreases and 4 cases of no change. Increases in recruitment were defined as a tidal volume increase or an I_{sat} decrease. A linear regression of the tidal volume-time relation was calculated for each electrode. A magnitude of slope greater than 1 ml per day for the first three months of implant was considered a significant change in tidal volume. For electrodes without a significant tidal volume change, a linear regression was conducted on the I_{sat} -time relation. A magnitude of slope greater than 0.02 mA per day was considered as a significant change in recruitment current. The increases and decreases in recruitment are summarized by the mosaic plot of Figure 5.15.

More electrodes increased than decreased recruitment during the first three months of implant.

IPI TEST

Relative motion of the electrode during stimulation and diaphragm muscle length were two factors that affected recruitment using epimysial electrodes to electrically activate the diaphragm. The effects of these factors were documented by the IPI test results.

Unexpected recruitment patterns were observed during IPI testing in seven of the fifty-one electrodes studied. Typically, the tidal volume monotonically increased with decreasing IPI, as displayed in Figure 5.16. However, the IPI test results from seven electrodes were characterized by a tidal volume IPI relation that was not monotonic. In Figure 5.17 is shown this unexpected relation between tidal volume and IPI for a left electrode of dog 856. The mechanism of this phenomenon was examined in greater detail by studying the lung volume-time curves for stimuli at the different IPI's (Figure 5.18). In Figure 5.18, stimulation with IPIs of 25 and 40 ms resulted in recruitment fall off during the initial segment of the stimulus pulsetrain, stimulation with an IPI of 59 ms resulted in a recruitment pattern that modulated during the pulsetrain and stimulation at 83 and 125 ms resulted in consistent recruitment during the pulsetrain. For comparison, recruitment properties of this electrode were examined from the lung volume-time curves of the RECRUITMENT TEST. Similar trends in recruitment fall off were found as the stimulus amplitude was increased (See Figure 5.19).

A possible cause for the recruitment pattern shown in Figures 5.18 and 5.19 was mechanical motion of the electrode at high levels of muscle activation. At the

time of the terminal experiment, electrodes producing the unusual recruitment patterns were observed under laparoscopy to undergo a "buckling" during stimulation. This "buckling" correlated with the changes in recruitment seen in Figures 5.18 and 5.19. The mechanical motion, described by the schematic in Figure 5.20, apparently caused a significant change in the impedance between the stimulating surface and the phrenic nerves.

The tidal volume-IPI relation was used to test length dependent recruitment. The IPI test is useful for testing length dependent recruitment because the final muscle length is different for each IPI while the charge injected for each pulse is the same for all IPIs. Since recruitment is associated only with injected charge, differences in the tidal volume-IPI relation between electrodes reflect differences in length dependent recruitment. The data from week 12 IPI tests were compared for each electrode. First, each tidal volume-IPI curve was normalized by the tidal volume obtained at 25 ms. Most often this meant that the maximum value was now 1.0. Then the median normalized tidal volume for each tested IPI was used to build a "standard" tidal volume-IPI relation. In Figure 5.21 is shown plots of the "standard" and two normalized tidal volume-IPI relations. The normalized tidal volume for each individual electrode was plotted against the "standard" tidal volume at the same IPI values. Finally, a linear regression was calculated for each plot and the slope (m) and Pearson's correlation coefficient (R^2) values were recorded (See Figure 5.22 for description). The R^2 values denoted whether the curves had the same shape and the m values were defined as frequency gain. For instance, an R^2 of 1.0 and a frequency gain of 1.0 indicated that the individual IPI response was the same as the "standard" response. The linear regression data are displayed in Table 5.2. Although most of the data (74%) had a correlation coefficient (Pearson's, R^2)

of 0.97 or greater, the frequency gains had greater variability. Only 12 of the 35 electrodes had a calculated frequency gain within 5% of the standard. The standard deviation for the frequency gain was ± 0.14 (14%). The frequency gain parameter was used for analysis of length dependent recruitment.

The frequency gain was found to be correlated with tidal volume, but was not correlated with electrode type, dog, side (right or left), distance between the staples, angle of the electrode with respect to the longitudinal direction of the muscle fibers or back encapsulation (see HISTOLOGICAL EVALUATION). The frequency gain was negatively correlated (correlation coefficient = - 0.29 measured with a Spearman-Rho, $p < 0.09$) with the tidal volume produced by the electrode. In addition, the absolute value of the difference in the frequency gain from one was even more strongly correlated (correlation coefficient = 0.38 measured with a Spearman-Rho, $p < 0.03$) with the tidal volume. As a result, we hypothesized that variations in the frequency gain were caused by changes in recruitment associated with muscle shortening. For example, an electrode may move closer to the motor point as the muscle shortens.

In order to test the effect of muscle shortening on recruitment, we examined the effects of the geometric configuration of the electrode, the muscle fiber orientation and the motor point on the frequency gain. The geometric configuration was determined from the X-ray image of each muscle and is represented by Figure 5.23. A Cartesian coordinate system was defined using the motor point as the origin and the lateral longitudinal direction of the muscle fibers as the positive X axis. The electrode location vector was defined within the coordinate system as the vector from the motor point to the electrode location. The relative angle between the X

axis and the electrode location vector was used in further analysis. We plotted the frequency gain against the relative angle and found that the frequency gain was smaller for angles between 30° and 60° and between -30° and -60° (See Figure 5.24). We interpreted these data to mean that the recruitment with an epimysial electrode placed on the diaphragm depended upon the length of the muscle. The degree of length dependence varies with the relative position of the electrode with respect to the motor point and the longitudinal direction of the muscle fibers.

Muscle length dependent recruitment was verified by comparison of recruitment curves obtained with pulsetrains, with pulsetrains and an insufflated abdomen and with single pulses and an insufflated abdomen. These superimposed recruitment curves are shown in Figure 5.25. In this dog, insufflating the abdomen, which lengthened the muscle, resulted in an increased I_{th} and decreased I_{sat} . When single pulses were applied, which tested recruitment without muscle shortening, I_{th} was further increased and I_{sat} further decreased. Although these trends were not consistent across all electrodes, changes in I_{th} , I_1 , I_2 and I_{sat} with abdominal insufflation were observed in all tested electrodes.

HISTOLOGICAL EVALUATION

The tissue response to epimysial electrodes implanted on the abdominal surface of the diaphragm included granular tissue and collagen formation consistent with chronic motion of the electrode relative to the diaphragm. The thickness of the granular tissue was inversely correlated with encapsulation across the abdominal surface of the electrode. In addition collagen fiber orientation was not parallel with the implant surfaces. No difference in histological response were observed for the

three electrode types with the exception of giant cells located adjacent to the Dacron® fibers of Type 3 electrodes.

The gross tissue reaction to the electrodes was characterized by the collagen formation on the diaphragm surrounding the electrode and the presence or lack of encapsulation tissue across the electrode surface facing the abdomen. An example of the three month gross tissue reaction to epimysial electrodes implanted on the abdominal surface of the diaphragm is displayed in Figure 5.26. The scar tissue on the diaphragm surrounding the electrodes appeared to be organized into a network of collagen bundles. The tissue reaction on the backside of the electrode generally consisted of a capsule that was either very thin or could not be detected. Electrodes with a capsule across the center portion of the electrode surface facing the abdomen were classified as positive for back encapsulation. No detectable tissue reaction across the center portion was considered negative for back encapsulation. Back encapsulation data are presented in Table 5.3. Five of the eleven dogs contained at least one electrode with back encapsulation. Two of the five dogs with electrodes that had back encapsulation also had liver adhesions to the diaphragm and electrodes at the implant sites.

The histological response between the electrode and the muscle was a characteristic foreign body response with an active granular tissue layer and a collagen layer. This two layer response is illustrated in Figure 5.27. The granulation tissue was adjacent to the electrode and the layer of dense collagen was located between the granulation tissue and the muscle. A typical granulation tissue layer is displayed in Figure 5.28. This tissue was a well vascularized, loose matrix of mononuclear leukocytes, fibroblasts and collagen fibers. In addition, 23 of the

35 electrode samples included polymorphonuclear leukocytes (PMN's). Figure 5.29 displays the denser, less vascularized collagen layer located adjacent to the muscle. The fibroblast nuclei were decreased in size and the tissue was free of mononuclear leukocytes. The thicknesses of both of these layers were measured for each electrode and are shown in Table 5.3. The mean granulation layer thickness was 0.38 mm and the mean collagen layer thickness was 0.85 mm. The collagen layer thickness was not correlated to the granulation layer thickness and neither the total thickness, the granulation tissue layer thickness nor the collagen layer thickness were correlated to electrode type.

The thickness of the granular layer was found to be significantly reduced when a back capsule was present. These data are shown in Figure 5.30. A Student's t test was used to compare granulation layer thickness for positive and negative back encapsulation and the difference was found to be significant ($p < 0.0001$). Interestingly, the collagen layer thickness could not be correlated with the presence of a back capsule ($p > 0.8$ Student's t test).

The electrodes with exposed Dacron® fabric (Type 3) had tissue reactions and capsule thicknesses that could not be distinguished from the other electrode types except for a layer of foreign body giant cells adjacent to the polyester fibers. The giant cell layer is displayed in Figure 5.31. The tissue adjacent to the giant cell layer was similar to the granulation or collagen tissue observed in the histological response to electrode Types 1 and 2.

Collagen fiber orientation was not consistently parallel to the implant surface and collagen formations with circular fiber orientations were identified. An example of collagen fiber orientation that was nonparallel to the implant surface is

shown in Figure 5.32. This type of reaction was extraperitoneal, intraperitoneal or both. Extraperitoneal collagen formation was verified using an EVG stain for elastin fibers. Elastin fibers were found in the peritoneum, but not in the extraperitoneal collagenous material associated with the electrode implant. Regenerating muscle fibers near the extraperitoneal collagen formations suggested a small amount of muscle damage.

DISCUSSION

The histological response consistent with chronic motion of the electrode relative to the diaphragm probably precludes clinical application of the epimysial electrodes tested in this study. However, the results of these tests provided useful information for future epimysial electrode designs and other issues regarding electrical activation of the diaphragm. There were no failures associated with electrochemical or mechanical damage of the electrodes. Full activation of the diaphragm was achieved using epimysial electrodes placed within 1.0 cm of the phrenic nerve motor point. However, the recruitment of electrodes placed on the abdominal surface of the diaphragm was affected by the muscle length. The degree of muscle length dependence was affected by the geometry of the electrode position, the motor point and the longitudinal muscle fiber direction. Recruitment was also affected by electrode motion, but recruitment increases in time were observed and were associated with mechanical stabilization of the electrode by the maturing tissue response. Back encapsulation of the electrodes minimized the active tissue response and indicated that an electrode design eliminating the motion of the electrode relative to the muscle could produce a more desirable tissue response.

Histological Response

The results of this study suggest that the tissue response may be a result of chronic mechanical irritation of the tissue caused by motion of the electrode relative to the diaphragm during contraction of the muscle. A relatively thick, 1.24 mm capsule was comprised of layers of active granulation tissue and collagen and the capsule was located almost exclusively between the electrode and the muscle. The granular tissue layer thickness was negatively correlated with back encapsulation, and the collagen fiber orientation was not consistently parallel with the implant surface. The presence of PMN's indicated that acute inflammatory processes are present three months after implant. Overall, the histological results are consistent with a chronic inflammatory response that is never able to resolve because of repeated focal mechanical injury to the capsule.

The mechanics the diaphragm probably placed a significant amount of mechanical loading on the electrode diaphragm interface. The diaphragm uses the abdominal contents to lift the lower rib cage while simultaneously sliding over these contents. The mean capsule thickness for epimysial electrode placed on the diaphragm was 1.24 mm, compared to 0.105 mm for epimysial electrodes implanted on the forelimbs of dogs (Akers 1994) and 1-2 mm surrounding electrodes placed on the tibialis anterior of cats (Grandjean 1986). The capsule thickness of epimysial electrodes implanted on dog forelimbs has been correlated with suture anchoring. Electrodes with all sutures in place were observed to have significantly thinner capsule thicknesses compared with electrodes that had missing or displaced anchoring sutures (Akers 1994). The tissue encapsulation of epimysial electrodes placed between the tibialis anterior and the extensor digitorum longus was thinner than electrodes placed on the superficial surface of the tibialis anterior

in cats (Grandjean 1986). The difference in capsule thicknesses was attributed to mechanical isolation of electrodes placed between the muscles. Peterson et al. noted visible fibrous tissue on the abdominal surface of the diaphragm at locations associated with electrode lead wire motion for intramuscular electrodes implanted in the diaphragm (Peterson 1994b). Epimysial electrodes implanted on the diaphragm could also be expected to produce some mechanical based tissue response.

For the epimysial electrodes implanted on the diaphragm, the correlation of active granulation tissue thickness with minimal back encapsulation implied that mechanical loading played an important role in the chronic tissue reaction. Grandjean et al. also noted that capsule thickness was significantly greater on the side of epimysial electrodes experiencing the most relative motion (Grandjean 1986). The back encapsulation of diaphragm pacing electrodes may prevent motion by isolating the electrode from sliding stresses of the abdominal contents. Alternatively, the back encapsulation may simply maintain the electrode against the muscle and not allow buckling to occur. In either case, back encapsulation apparently reduced the motion of the electrode relative to the muscle.

The structure and direction of collagen fibers around the implanted epimysial electrodes also provided evidence of electrode motion. Collagenous capsules around implants generally have fibers that run parallel to the surface of the implant in an organized manner (Matlaga 1976, Taylor 1986). Parallel fiber orientation of collagen fibers was common in the tissue reaction to the epimysial electrodes implanted on the surface of the diaphragm. However, there were a number of instances of swirling or circular oriented collagen structures as well. Other implants have been documented with oblique fiber orientation that appears to be related to the

direction of load transmission (Pilliar 1981). In addition, parallel collagen fiber structures such as tendons and ligaments have the function of tension transmission (Fung 1993). The presence of non-parallel collagen fiber orientation within the encapsulation tissue of epimysial electrodes for diaphragm pacing provided evidence that the electrodes underwent significant mechanical loading.

The presence of polymorphonuclear leukocytes (PMN's) in some of the histological sections was consistent with mechanical trauma as the cause of the chronic foreign body response. PMN's are associated with acute inflammation and generally subside in less than one week. The presence of PMN's three months after implant suggests that there was a chronic mechanism for new injury. The motion of an epimysial electrode on the diaphragm could result in focal tissue injury and alternate focal areas of acute and chronic inflammatory reactions.

The lack of correlation between granulation layer thickness and collagen layer thickness suggested that collagen remodeling was occurring during the time the electrode was implanted. Additional evidence of collagen remodeling was that the collagen layer thickness for electrodes implanted longer than three months was similar to the thickness from three month implants. Collagen remodeling, defined as simultaneous collagen formation and degradation, has been documented in normal incisional healing in the gastrointestinal tract (Danielsen 1981). Macrophages are known to mediate collagen degradation through the release of collagenase and the stimulation of collagen production by fibroblasts (Lasser 1983). PMN's can also release collagenase during exudation (Gallin 1984). Suppression of collagen synthesis by granulation tissue extracts has been demonstrated (Kulonen 1980). The prevalence of macrophages in the granulation tissue provides

a built in mechanism for collagen degradation or reformation. As a result, mechanical trauma may reduce the collagen at the capsule through collagenase while at the same time initiating new collagen formation.

The granulation tissue thickness for Type 3 electrodes was not significantly smaller than the other electrode types despite using Dacron® to promote tissue ingrowth and stabilize the mechanical interface between the silicone rubber electrode and the diaphragm. This technique has proven useful for reducing the tissue response in other anchoring applications (Whalen 1988). Although the reason for the apparent lack of reduction was unknown, we speculated that the Dacron® did not effectively anchor the electrode. Granulation tissue was observed between the Dacron fibers and the silicone rubber which implied that the loose edges of the Dacron did not stabilize the electrode. An electrode surface with significantly greater porosity may be advantageous for tissue ingrowth and better mechanical stability.

Minimum Electrode-Motor Point Distance

Epimysial electrodes must be placed closer to the motor point than intramuscular electrodes to achieve the same level of recruitment. Peterson et al. found that full activation of the diaphragm required electrodes within approximately 2.0 cm of the phrenic nerve entry point (Peterson 1986, Peterson 1989, Peterson 1994b). Electrodes that produced incomplete activation were between 0.5 and 5.0 cm, while those that provided full activation were all within 3.0 cm (Peterson 1994b). We required electrode placement within approximately 1.0 cm of the phrenic nerve motor point. In addition, many epimysial electrodes near 1.0 cm from the motor

point required stimulus currents greater than the 15 mA, 100 μ s used for intramuscular electrode stimulation (Peterson 1989).

The difference in required distance to the motor point for full activation of the phrenic nerves can be attributed to the electrical properties of the peritoneum and differences in encapsulation thickness. The intramuscular electrode is implanted in the muscle itself, and is thus closer to the thoracic nerve entry point by approximately 1-3 mm. In addition, the peritoneum remains between the epimysial electrode and the nerve tissue, while the intramuscular electrodes penetrate this tissue. The peritoneum is made up of relatively nonconducting connective tissue (collagen and elastin) and would be expected to raise the threshold charge. Finally, the capsule thickness of the epimysial electrodes was thicker than the capsule thickness of the intramuscular electrodes. This places more collagen between the epimysial electrode and the phrenic nerves compared to intramuscular electrodes. The low conductance of collagen may make this difference in capsule thickness significant.

Long Term Recruitment Trends

Improvements in recruitment with implant time probably resulted from effects of mechanical stabilization that outweighed increases in encapsulation tissue impedance. Impedance of encapsulation tissue surrounding silicone rubber electrodes implanted subcutaneously (Grill 1994) or on the sciatic nerve (Stein 1978) of cats increases for periods up to 2 months. The ongoing tissue response to epimysial electrodes placed on the diaphragm should increase the tissue impedance between the electrode and the phrenic nerve over time and thus reduce recruitment. The improved recruitment with time observed in this study indicated that factors

other than the electrical properties of the encapsulation tissue had greater effects on recruitment. Improved recruitment may have been linked to tissue responses that helped mechanically stabilize the electrode. Theoretically, back encapsulation should hold the stimulating surface against the muscle and prevent the "buckling" observed for some of the electrodes. Alternately, collagen formation or continued crosslinking would increase the stiffness of the tissue beneath the electrode and thereby mechanically stabilize the electrode during stimulation. The mechanical stabilization would provide stable recruitment during stimulation.

Frequency Gain:

The variation of the frequency gain could be accounted for by one of three possible mechanisms: 1) a change in impedance between the electrode and the motor point resulting from a change in muscle fiber length 2) respiratory mechanics of the costal and crural diaphragms and/or 3) a difference in the composition of recruited muscle fibers. The results from this study suggested that the most likely mechanism was muscle length dependent recruitment.

A difference in the stimulated population of muscle fiber types could account for the variation in frequency gain. Slow twitch muscle fibers have a lower fusion frequency and smaller maximum muscle force than fast twitch muscle fibers resulting in larger tidal volumes at low stimulus frequencies and smaller tidal volumes at high stimulus frequencies. As a result, slow twitch oxidative fibers have a lower frequency gain than fast twitch muscle fibers. Although the percentage of muscle fiber types for costal, crural and sternal diaphragm regions is similar (Sieck 1983, Sieck 1987), the individual variation may be different. We tested whether the a difference in activated muscle fiber types could account for the

variation in frequency gain by comparing the variability of frequency gain for electrodes placed on the same hemidiaphragm to those placed on different hemidiaphragms. Recall that there was significant recruitment overlap for nearly all electrodes placed on the same hemidiaphragm (Table 5.2). Therefore, we expected that the variability of the frequency gains would be lower for electrodes that activated similar muscle fiber populations. However, the variation in frequency gain for electrodes placed on the same hemidiaphragm was not significantly different from the frequency gain across all electrodes. We concluded that any differences in the activated population of muscle fiber types did not account for a significant amount of the variability in frequency gain.

Another possible explanation for the variation in frequency gain is the difference in mechanics of the costal and crural diaphragms. The costal diaphragm of a supine dog is approximately 105% of the optimal muscle length (defined as the length that results in maximum tension) and the crural diaphragm is at approximately 92% of the optimal muscle length (Road 1986). This places each diaphragm muscle type at a different location on its length tension curve. In addition, the length tension relations of the crural and costal diaphragms are different (Road 1986). As a result, we would expect a different length tension slope for an electrode stimulating the crural diaphragm than we would for costal diaphragm stimulation. We tested the effects of diaphragm mechanics on frequency gain by comparing the variation in frequency gain for submaximally stimulated hemidiaphragms with supramaximally stimulated hemidiaphragms. The submaximal stimulation is likely to activate only the costal or only the crural diaphragm. However, supramaximal stimulation consistently activates all of the hemidiaphragm. We expected that the variation in frequency gain would be larger for submaximally stimulated hemidiaphragms if the

frequency gain were dependent on the mechanics of the separate diaphragm muscles. However, we found that the variation in frequency gain was significantly larger for supramaximally stimulated hemidiaphragms than submaximally stimulated muscles. We concluded that the difference in respiratory mechanics did not account for a significant portion of the frequency gain.

The most convincing data to account for the variation in frequency gain was correlation with electrode movement (Figure 5.20) and relative position of the electrode with respect to the motor point and the muscle fiber direction (Figure 5.23). Length dependence of recruitment has been reported for epimysial electrodes placed on the cat soleus and tibialis anterior muscles. The length dependence is positively correlated to the distance between the electrode and the nerve entry into the muscle (Grandjean 1986). Length dependent recruitment has also been examined for intramuscular electrodes placed in the soleus muscle of the cat and in the forearm and hand of the human and the direction, but not the magnitude of length dependence was consistent across all subjects (Crago 1980). Diaphragm shortening has also been proposed as a possible explanation for changes in I_{sat} at different stimulus frequencies (Peterson 1986).

Mechanical motion, observed as electrode buckling, accounts for anomalies in the tidal volume-IPI relation in at least five electrodes. Although the same mechanical motion was not observed in the other thirty cases, all electrodes may have been submitted to similar forces. Such forces could alter the impedance between the electrode and the tissue enough to change the recruitment. For example, the mechanical forces produced by the contracting diaphragm may act on the electrode and its associated capsule enough to move serum from one location to

another within the capsule. The relative conductivity of the serum and the surrounding tissue would be important to determining the recruitment under different geometrical configurations. However, the mechanics of the electrode and capsule are difficult to document during normal stimulation conditions. Even the electrode buckling was observed during stimulation with an insufflated abdomen, which is certain to affect the mechanics of the electrode motion. We attempted to verify mechanical motion as a cause of variation in the frequency gain by examining the correlation between the frequency gain and the electrode orientation with respect to the longitudinal direction of the muscle fibers. The electrodes implanted in the same direction as the muscle fibers should undergo greater mechanical stress because the distance between the fixed staples decreases as the muscle shortens. This analysis revealed no significant correlation between the tested factors.

In addition to the mechanical motion observed during stimulation, frequency gain was also dependent on the location of the electrode with respect to the motor point and the muscle fiber direction. The motor point on the abdominal surface of the diaphragm may change as the length of the muscle changes. The diaphragm descends during contraction acting mechanically to stretch the phrenic nerves. As a result, the location of the phrenic nerve tissue on the thoracic surface is likely to change during muscle activation. Since the descent of the diaphragm depends on the stimulus frequency, the change in location of the motor point would also depend on stimulus frequency. In addition, the shortening of the diaphragm muscle may bring the electrode and motor point closer together. This effect would be more pronounced if the electrode and motor point are in the longitudinal direction of the muscle fibers (Peterson 1986). If the electrode moves closer to the phrenic nerves, we would expect a larger frequency gain and similarly, if the electrode moves

farther away, we would expect a smaller frequency gain. We tested possible correlations of electrode position for diaphragm pacing with placement of the epimysial electrodes. The frequency gain was dependent on the relative angle between the electrode-motor point vector and the longitudinal muscle fiber direction. As expected the frequency gain was relatively large for relative angles between 0° and 20° and decreased as the angle became larger. However, the frequency gain recovered at angles larger than 60° . This recovery in gain at high angles was not expected. However, the analysis assumes that the stimulation site is the motor point and the stimulation site for many electrodes may be located along the nerve branch away from the motor point. Generally, the phrenic nerve branches that innervate the costal diaphragm course in anterolateral and posterolateral directions along the central tendon. Considering that electrodes with relative angles approaching 90° would lie near the central tendon, it is reasonable to assume that the threshold activation site is located on a nerve branch remote from the motor point. Thus as the muscle shortens, the electrode will not be brought closer to the motor point, but may still be drawn closer to the activation site. Therefore we attributed the variation in frequency gain to the relative position of the electrode, the activation site and the orientation to the muscle fibers.

The muscle length dependence of recruitment was verified by measurements of recruitment using a stimulus pulsetrain with a normal supine anesthetized dog and using both a stimulus pulsetrain and single twitches in a dog with an insufflated abdomen. The insufflation increases the muscle length and the single twitches measure recruitment at longer lengths than pulsetrains because the recruitment depends only on the resting length. In the example shown (Figure 5.25), the I_{th} increased with muscle length and the I_{sat} decreased with muscle length. This was

not consistent across the samples tested in this way. Additional studies are needed to determine a more precise relation between the recruitment and the muscle length for different electrode positions.

We concluded that the long term recruitment properties of the epimysial electrodes were adequate for diaphragm pacing, however the long term active histological response contraindicated clinical application of this electrode.

Figure 5.1: Electrode Type 1. This electrode is characterized by a stimulating surface placed within a well to reduce high current densities at the edge of the stimulating surface. A Dacron® mesh was molded into the tabs on the sides of the stimulating disk for reinforcement during staple attachment to the muscle. Sixteen Type 1 electrodes were implanted in four dogs.

Figure 5.2: Electrode Type 2. This electrode type has a hemispherical stimulating surface for uniform current density. The tabs are Dacron®-free to reduce electrode stiffness. Eighteen Type 2 electrodes were implanted in a total of five dogs. The absence of Dacron® reinforcement resulted in staple tearing of the tabs and displacement of the electrodes from the muscle surface.

Figure 5.3: Electrode Type 3. This electrode type has a hemispherical stimulating surface for uniform current density. An exposed Dacron® mesh was tacked to the electrode on the surface that opposes the muscle. The Dacron® was incorporated into the design to reinforce the tabs and to promote tissue ingrowth and mechanical anchoring of the electrode. Ten Type 3 electrodes were implanted in four dogs.

Figure 5.4: Electrode housing for well electrodes. Dacron® reinforced tabs were constructed on either side of the central stimulating disk for stapling the electrode onto the abdominal surface of the muscle. These housings were cast from Silastic® MDX 4-4210.

Figure 5.5: Electrode housings for hemispherical stimulating surface electrodes (Types 2 and 3). Tabs are constructed on either side of the central stimulation disk for staple attachment to the diaphragm. This housing is compression molded from Silastic® MDX 4-4210. A Dacron® backing was tacked onto the stimulating side of the housing to make Type 3 electrodes.

Figure 5.6: Test setup for RECRUITMENT TEST, RECRUITMENT OVERLAP TEST and IPI TEST. Airflow was measured using a Fleisch pneumotachometer and a Validyne pressure transducer. Airflow was sampled at 100 Hz by a National Instruments NB-MIO-16 data acquisition board and a Macintosh IIfx computer using custom LabVIEW® software. The airflow signal was integrated to obtain lung volume. Data acquisition was coordinated with stimulation using a communication link between the computer and a microprocessor aboard the stimulator.

Figure 5.7: Description of the current controlled stimulus used for the system tests. The RECRUITMENT TEST used an IPI of 50 ms and the IPI TEST used an amplitude of 20 mA. All other parameters are described by the figure. The y direction indicates current amplitude and the x direction indicates time in all three diagrams. T_{cycle} = cycle time, T_{insp} = inspiratory time.

Dog 589, Test #6

Left Electrode

Figure 5.8: Definitions of recruitment currents I_{th} , I_1 , I_2 and I_{sat} . The threshold current, I_{th} , was defined as the current producing 10% of maximal tidal volume. Saturation current, I_{sat} , was defined as the current producing 90% of maximal tidal volume. The rise currents, I_1 , I_2 , were obtained from the zero crossings of the second derivative of the tidal volume-current relation.

Figure 5.9: Simultaneous stimulation that occurs during a RECRUITMENT OVERLAP TEST. The pulses are spaced 750 μ s apart in order to assess simultaneous stimulation without including any additive field effects. In addition, the neural tissue activated by the first pulse is refractory during the delivery of the second pulse.

Figure 5.11: Average tidal volumes measured for each electrode over the entire implant duration. Stimulus parameters for these tidal volume measurements were: Current = 24 mA, Pulwidth = 100 μ s, Interpulse Interval = 50 ms, and Inspiration Time = 1.5 s. The tidal volumes were normalized by the critical tidal volume, $V_{t_{crit}}$, and displayed in the lower graph. $V_{t_{crit}}$ is the minimum tidal volume for full time ventilation without fatigue (Peterson 1988).

Figure 5.12: Relation between tidal volume and distance between the stimulating electrode and the phrenic nerve entry into the muscle. Open symbols in the graph represent electrodes that did not obtain full recruitment while the closed symbols represent electrodes providing full recruitment. The conditions defining full recruitment were evidence of both crural and costal activation evaluated using a physical exam of the abdominal motion during breathing, and absence of additional recruitment by the accessory electrode. The largest electrode-motor point distance that still obtained full recruitment was 1.04 cm and the smallest electrode-motor point distance providing submaximal recruitment was 0.99 cm. Thus, full diaphragm recruitment requires electrodes placed within approximately 1.0 cm of the phrenic nerve entry into the muscle. There was no apparent effect of electrode type on the tidal volume - distance relation.

	Dog #856	Dog #694	Dog #391	Dog #702	Dog #887	Dog #760	Dog #451	Dog #480	Dog #589
Left Side									
Primary Electrode: % Volume obtained with both electrodes	97.2%	97.0%	84.6 %	82.9 %	93.2%		86.0 %		
Accessory Electrode: % Volume obtained with both electrodes	79.6%	31.7%	35.5%	75.2%	39.7%		69.8%		
Right Side									
Primary Electrode: % Volume obtained with both electrodes	99.6%	95.8%	78.2 %	75.4 %	93.2%	92.9%	95.1%	81.6 %	81.0 %
Accessory Electrode: % Volume obtained with both electrodes	41.1%	72.5%	34.9%	63.8%	56.7%	80.3%	53.8%	50.4%	68.8%

Table 5.1: Table displaying results from the RECRUITMENT OVERLAP TEST. Hemidiaphragms with less than 90% of the tidal volume evoked by the primary electrode when compared to both electrodes are bolded. These hemidiaphragms would benefit from stimulation with multiple electrodes.

Figure 5.13: Changes in tidal volume over time. Dog 391 was implanted with Type 1 electrodes and represented the greatest changes in tidal volume of any implanted electrodes. All but the accessory right electrode demonstrated significant increases in tidal volume with time. A slope of ± 1.0 ml/day was defined as a significant increase or decrease in recruitment.

Dog 589
Left Electrode, Type 3

Figure 5.14: Changes in recruitment currents over time. This electrode was an example of an electrode with improving recruitment properties that were not reflected by increases in tidal volume. A linear regression was done on the I_{sat} and a slope of ± 0.02 mA/day or greater was defined as a significant change in recruitment. A decrease in I_{sat} , as shown above, characterized an increase in recruitment.

Figure 5.15: Mosaic plot of trends in recruitment. I_{sat} and tidal volume (V_t) were used as measures of the level of recruitment. An increase in V_t or a decrease in I_{sat} indicated an improvement in recruitment. For V_t , a linear regression was done on the V_t over time. A slope of 1 ml per day was deemed significant. For electrodes without a significant change in V_t , a linear regression was done on I_{sat} over time. A magnitude of slope greater than 0.02 mA per day was considered significant. There were a total of 21 cases of Increase, 7 of Decrease and 4 of No change. There was no significant difference with electrode type.

Dog 589
Left Side Electrode

Figure 5.16: Example of a tidal volume IPI relation from an IPI TEST. These data were obtained from a Type 3 electrode three months after implant. The three trials displayed at each IPI demonstrate the low variation in the measurements. The stimulus amplitude was 20 mA with a 100 μ s pulsewidth. This is a typical relation between tidal volume and IPI for epimysial electrode stimulation of the diaphragm.

Dog #856
Left Side Electrode

Figure 5.17: A tidal volume IPI relation that demonstrates a length dependence of recruitment. The decreased tidal volumes observed at small IPI values compared to large IPI was atypical. Five of the 35 electrodes exhibited a relation that was not monotonic.

Figure 5.18: Traces of lung volume during stimulation at 5 different IPI's. The stimulation was initiated at time = 0.5 s and lasted until time = 2.0 s. The stimulus current amplitude was 20 mA with a 100 μ s pulsewidth. Airflow data was sampled at 100 Hz from a Validyne pressure transducer across a Fleisch pneumotachometer. Airflow was integrated to obtain lung volume and tidal volume was defined as the maximum change in volume over the stimulation time. Tidal volume increased as the IPI was decreased from 125 to 59 ms. As IPI decreased further, tidal volume decreased. The lung volume waveforms at IPIs smaller than 83 ms were atypical and appeared to indicate inconsistent recruitment.

Dog #856
RECRUITMENT TEST
Left Electrode

Figure 5.19: Traces of lung volume during stimulation at 6 different current amplitudes (100 μ s pulsewidth). Stimulation IPI was 50 ms. Tidal volume increased with increasing amplitude, but the waveform changed. The lung volume waveforms indicated inconsistent recruitment during the stimulus pulse train.

Figure 5.20: Schematic illustrating mechanical motion of an epimysial electrode observed by laparoscopy. Stimulation resulted in a “buckling” of the electrode that coincided with changes in recruitment. Such motion changes the location of the stimulating surface with respect to the phrenic nerves.

Variation in Tidal Volume - IPI Relation

Figure 5.21: The variation of the tidal volume-IPI relation. Comparison of the tidal volume-IPI relation for all electrodes was done by normalization to the tidal volume obtained with an IPI of 25 ms. Individual points of the "standard" tidal volume-IPI relation were defined by the median normalized tidal volume at each IPI.

Frequency Gain of Three Electrodes

Figure 5.22: Description of the frequency gain. Individual normalized tidal volumes from the IPI test were plotted against the “standard” for each IPI. A linear regression was done for each electrode and the slope was defined as the frequency gain. R^2 is the Pearson’s correlation coefficient. The data from three electrodes are shown. Dog 391, electrode #1 had a high frequency gain (1.16), dog 760 electrode #4 had a low frequency gain (0.80) and dog 589 electrode #1 had a frequency gain that was the same as the “standard”.

Dog	Electrode Type	Correlation Coefficient (R-squared)	Frequency Gain (slope)
279	2	0.99	0.93
391	1	0.98	1.16
391	1	0.84	0.95
391	1	1.00	1.07
391	1	0.99	1.05
451	3	0.99	1.12
451	3	0.99	0.92
451	3	0.48	0.37
480	2	0.97	0.91
480	3	0.99	1.01
480	3	0.97	1.29
482	3	0.97	0.86
482	3	0.94	1.20
589	3	0.99	1.00
589	3	1.00	1.00
589	3	0.99	1.13
694	1	0.87	0.63
694	1	0.98	1.03
694	1	0.97	1.01
694	1	0.97	1.05
702	1	0.99	0.79
702	1	1.00	0.92
702	1	0.95	0.63
702	1	0.99	0.97
760	2	0.99	1.05
760	2	0.99	0.97
760	2	0.97	0.80
856	1	0.99	1.06
856	1	0.99	0.79
856	1	0.52	0.50
856	1	0.81	0.86
887	2	0.97	1.11
887	2	0.99	1.05
887	2	0.83	1.27
887	2	0.94	1.14

Table 5.2: Results of comparison of IPI tests to a "standard" IPI curve obtained from the median of all tests at each IPI. Each individual IPI test was plotted versus the "standard". A linear regression was done and the slope and correlation coefficients are shown. 26 of 35 electrodes (74%) had correlation coefficients (R^2) of 0.97 or greater. Only 12 of 35 had slopes within 5% of the standard. The slope was defined the frequency gain and was used for analysis of muscle length dependent recruitment.

Figure 5.23: Measurements of the relative angle between the electrode location vector and the muscle fiber direction. The motor point was defined as the origin and the X axis direction followed the direction of the muscle fibers. The anterior direction was the positive angle direction and the posterior the negative direction resulting in a total range of -180° to 180° . An electrode with a relative angle of 0° was directly lateral to the motor point while a $\pm 90^{\circ}$ was perpendicular to the muscle fibers.

Figure 5.24: The frequency gain as a function of the angle between the electrode placement vector and the phrenic nerve motor point. Angle measurements (Figure 5.23) were converted to a -90° to +90° range. Since the frequency gain was symmetric around 0°, the frequency gains were converted to a 0°-90° range. A notable decrease in frequency gain occurred between 30° and 60° compared to 0°-30° and 60°-90°.

Figure 5.25: Recruitment curves obtained using three different methods. First the tidal volume recruitment curve was obtained with the anesthetized apneic dog in the supine position. Next the abdomen was insufflated to 10 mm Hg pressure and the tidal volume recruitment curve was measured. Lastly, an abdominal pressure measurement was recorded during insufflation using single pulse twitches of the diaphragm. A 100 μ s charge balanced biphasic stimulus pulse was used. Tidal volume recruitment curves were obtained using 20 Hz pulsetrains of 1.5 s length. Note the changes in I_{th} , I_1 , I_2 and I_{sat} . Differences in recruitment were associated with differences in muscle length.

Electrode Type	Dog Number	Back Encapsulation	Hemi-diaphragm	Days Implanted	Granulation Tissue Thickness (mm)	Collagen Thickness (mm)	Total Thickness (mm)
2	279	-	Right	359	1.03	0.36	1.40
1	391	-	Right	89	0.38	0.50	0.88
1	391	-	Left	89	0.27	0.61	0.89
1	391	-	Right	89	0.48	0.43	0.91
1	391	-	Left	89	0.82	0.87	1.69
3	451	+	Right	91	0.01	1.25	1.26
3	451	-	Left	91	0.20	1.25	1.45
3	451	-	Left	91	0.00	0.79	0.79
2	480	-	Right	197	0.75	0.93	1.68
3	480	-	Right	92	0.82	0.66	1.48
3	480	-	Left	92	0.74	0.91	1.65
3	482	-	Left	91	0.58	0.54	1.12
3	482	-	Right	91	0.38	1.22	1.59
3	589	-	Right	95	0.24	2.25	2.49
3	589	-	Right	95	0.66	1.17	1.83
3	589	-	Left	95	0.94	0.91	1.85
1	694	-	Left	89	0.42	0.54	0.96
1	694	-	Right	89	0.34	1.11	1.45
1	694	-	Left	89	0.64	0.57	1.21
1	694	-	Right	89	0.46	0.87	1.33
1	702	-	Right	96	0.25	0.53	0.78
1	702	+	Left	96	0.11	0.16	0.28
1	702	+	Right	96	0.11	1.10	1.22
1	702	+	Left	96	0.31	0.23	0.54
2	760	+	Left	420	0.09	1.61	1.70
2	760	+	Right	420	0.03	2.40	2.43
2	760	+	Right	420	0.02	1.50	1.52
1	856	+	Right	98	0.22	0.88	1.10
1	856	+	Left	98	0.11	0.34	0.45
1	856	+	Left	98	0.15	0.52	0.67
1	856	+	Right	98	0.18	0.29	0.48
2	887	-	Left	266	0.33	1.32	1.65
2	887	+	Right	266	0.46	0.14	0.60
2	887	+	Right	266	0.45	0.29	0.74

Mean: **0.38 0.85 1.24**

Table 5.3: Table of tissue reaction measurements. Granulation tissue defined by the presence of a loose collagen matrix, fibroblasts, macrophages and in some cases, polymorphonuclear leukocytes. Collagen layer was defined by a denser collagen matrix. The electrode types were 1=well electrode, 2=hemisphere electrode with no Dacron, 3=hemisphere electrode with Dacron backing. Back encapsulation indicates either no tissue across the raised back of the electrode (-) or an intact capsule across the electrode back (+) at the time of explant.

Figure 5.26: Gross tissue response to a Type 3 electrode implanted for three months. Note the lack of capsule across the back of the electrode. The exposed Dacron® mesh of the electrode is adhered to the peritoneum by connective tissue.

Hematoxylin and Eosin

Masson's Trichrome

Figure 5.27: Hematoxylin and Eosin stain of the tissue reaction to a Type 1 electrode implanted on the abdominal surface of the diaphragm for three months. The response was characterized by a granulation tissue layer near the electrode and a collagen layer near the muscle.

Electrode

Figure 5.28: Closer view of the granulation tissue that lies adjacent to the electrode. Note the fibroblasts, macrophages, polymorphonuclear leukocytes, neovascularization and loose collagen matrix.

Figure 5.29: Closer view of the more mature, primarily collagen layer that lies adjacent to the muscle. Note the circular collagen fiber orientation.

Figure 5.30: Comparison of granular layer thickness for electrodes with significant back encapsulation. Back encapsulation was defined as coherent tissue encapsulation across the surface of the electrode opposing the abdominal contents. The circles mark the means of each data set. The lines indicate the standard error of the mean and the dotted lines $\pm$ one standard deviation. Positive back encapsulation was defined as the complete covering of the back of the electrode by either collagen, or by liver adhesion. The granular layer thickness was significantly smaller for samples with back encapsulation ($P < 0.0001$, Student's t test).

Masson's Trichrome

Figure 5.31: Tissue reaction to a Type 3 electrode. An additional active layer is interposed between the more mature collagen layers. This layer was associated with a reaction to the exposed Dacron® mesh. There was evidence of giant cells near the Dacron mesh.

Hematoxylin and Eosin

Masson's Trichrome

Figure 5.32: Extraperitoneal tissue response of electrode Type 1. The peritoneum is characterized by the presence of elastin fibers stained black in the Verhoeff's elastica stain. Note the regenerating muscle fibers and the collagen infiltration into the muscle.

Chapter 6

The Effects of Stimulation Frequency and Duty Cycle on Tidal Volume Decline During Diaphragm Pacing in Dogs

INTRODUCTION

The goal of this study was to determine the effect of a change in either stimulation frequency or duty cycle on the risk of diaphragm fatigue. Duty cycle was defined as the ratio of the inspiratory time to the cycle time. Risk of fatigue, defined as a decrease in muscle contraction over 12-24 hours, was assessed using tidal volume decreases resulting from short term diaphragm pacing with different combinations of stimulation frequency and duty cycle. The data on the risk of fatigue were combined with ventilation data in Chapter 7 to develop an optimization algorithm that identifies diaphragm pacing stimulus parameters based on the relative tradeoff between ventilation and fatigue.

Fatigue of the diaphragm has been one of the primary factors limiting full time diaphragm pacing. (Glenn 1984). The effect of diaphragm pacing stimulus parameters on fatigue was recognized as a limiting factor of diaphragm pacing in the initial applications of the device. Biphasic waveforms were instituted to eliminate nerve conduction failure at the stimulation site presumably caused by nerve damage resulting from electrochemical reaction products (Tanae 1973). Full time diaphragm pacing was first achieved using alternate maximal unilateral stimulation of each hemidiaphragm. Stimulation was alternated for 12 hours on one hemidiaphragm then 12 hours on the opposite side (Glenn 1984, Oda 1981). This type of regimen was necessary to avoid fatigue. Typically patients were stimulated at 25-33 Hz, 12-17 breaths per minute with a 1.3 second inspiratory time. However, fatigue still plagued many patients who required full time diaphragm pacing. Later, full time ventilatory support was achieved using bilateral stimulation with very low stimulation frequencies (< 10 Hz) and lower respiratory rates (5-9 breaths per minute) (Glenn 1984). Improved fatigue resistance has been associated

with both lower stimulation frequencies and with lower duty cycle activation. However, the relative importance of each stimulus parameter on fatigue has not been well described.

The importance of duty cycle on the reduction of fatigue has been demonstrated in both voluntarily contracted muscle and stimulated muscle. Bellamare and Grassino found that the time to fatigue the diaphragm depends on both the duty cycle and the fraction of maximum muscle force (Bellamare 1982a). However, for diaphragm pacing, Oda et al. claimed that changing the breathing rate from 20 breaths per minute to 10 breaths per minute did not result in a reduction in diaphragm fatigue in long term stimulation (Oda 1981). These results were contradicted by experiments of stimulation of the human quadriceps where stimulation using a duty cycle demonstrated significant increases in the time constant of force decay and the asymptotic force of the muscle when compared to constant stimulation (Boom 1993). Similarly, in diaphragm pacing experiments in dogs, tests at respiratory rates of 37, 25, and 12 breaths per min with a constant inspiratory time of 1.2 s resulted in significant differences in the time to descend to 60% of original transdiaphragmatic pressure (Kido 1988).

The effects of stimulation frequency on fatigue have also been studied. Isometrically stimulated quadriceps fatigue faster and to lower levels with stimulation at 83 Hz when compared to stimulation at 20 Hz (constant stimulation) (Carroll 1989). In similar experiments of quadriceps stimulation, higher stimulation frequencies resulted in lower asymptotic torques and a less pronounced increase in the rate of force decline (Franken 1993). Long term (26 weeks) diaphragm pacing experiments in dogs using stimulus frequencies of 11, 25 and 33

Hz resulted in 33 Hz stimulation causing a steady fall in tidal volume to 33%, 25 Hz producing a fall to 50% and 11 Hz no fall in tidal volume (Oda 1981). Post mortem analysis revealed permanent damage to the muscle stimulated at 33 Hz characterized by shorter muscle length and proportionately larger central tendon area (Ciesielski 1983, Oda 1981).

In this study, we hypothesized that both stimulation frequency and duty cycle influence muscle fatigue and that the relative effects can be identified. We examined the relative worth of changes in stimulation frequency and duty cycle using the risk of diaphragm fatigue to define the worth. Risk of diaphragm fatigue was quantitated using the asymptotic tidal volume and time constant of tidal volume decline estimated by the first thirty minutes of diaphragm pacing. We tested stimulation frequencies in the range of 20-40 Hz and duty cycles in the range of 0.3-0.6 by evaluating the tidal volume decline in dogs undergoing diaphragm pacing. From the results, we obtained the equivalent changes in stimulation frequency and duty cycle for the same risk of diaphragm fatigue. This information will be used to construct a worth function for optimizing the stimulus parameters for diaphragm pacing (Chapter 7). The worth function will be constructed by calculating the risk of fatigue associated with simultaneous changes in stimulus frequency and duty cycle.

METHODS

Preparation

Epimysial electrodes for diaphragm pacing were implanted onto the abdominal surface of the diaphragm of two dogs. The electrodes are shown in Figure 6.1. The electrodes were implanted using a laparoscopic procedure with aseptic

technique. Fluids and temperature homeostasis were maintained over the course of the implant procedure. In addition, ECG was monitored during implant and prophylactic antibiotics were administered following surgery. Additional details of the implant procedure are described in Chapter 5. Two electrodes were implanted on each hemidiaphragm using stimulation to map the location of the phrenic nerves (See Chapter 4). When the phrenic nerve motor point was located, the electrodes were stapled to the diaphragm using a laparoscopic stapler (EndoPath, Ethicon Inc., Somerville, NJ). The electrode lead wires exited the peritoneum near the xiphoid and were tunneled subcutaneously to a point midway between the scapula. The external portion of percutaneous lead wire was looped subcutaneously and tied. The dogs were jacketed to prevent them from disturbing the external wires during the course of the study. A minimum two week recovery period was allowed prior to testing.

Following the recovery period, testing was conducted at two week intervals for the duration of the study. Implanted electrodes were initially tested to establish long term recruitment stability (Phase I) and then tested for tidal volume decline (Phase II).

Test Setup

The setup for all Phase I and Phase II experiments was similar. The dogs were pre-anesthetized with sodium pentothal (15mg/kg). Following intubation (8.0-9.5 mm endotracheal tube) anesthesia was maintained with Halothane (1-2%) for the duration of the procedure. The balance of the inhaled gas was oxygen. Fluid homeostasis was preserved using intravenous 0.9% sodium chloride. Body temperature was maintained with a heating pad and the ECG was monitored

throughout the procedure. All tests were conducted with the dog placed in the supine position. Testing was conducted by hyperventilating the dog to apnea and making measurements in response to the test stimulation during the apneic period.

The instrumentation for the stimulation and coinciding measurements of airflow and transdiaphragmatic pressure is shown in Figure 6.2. The endotracheal tube of the dog was connected to a Fleisch pneumotachometer to obtain an airflow measurement. The pressure difference across the pneumotachometer was measured using a Validyne pressure transducer (MP45-14-871, Validyne Engineering Corporation, Northridge, CA). For the RECRUITMENT TEST and the TIDAL VOLUME-STIMULUS FREQUENCY TEST, the airflow signal was sampled for 0.5 s prior to and 1 s following stimulation. The sampling rate was 100 Hz using a data acquisition board (NB-MIO-16, National Instruments Corporation, Austin, TX) on a Macintosh IIfx computer. An airflow signal sampled at 50 Hz was used for the TIDAL VOLUME DECLINE TEST. The airflow was software integrated to obtain a lung volume signal. The tidal volume was defined as the difference between the minimum and maximum lung volume. Tidal volumes were measured for all of the tested stimulus paradigms.

Transdiaphragmatic pressure was also recorded for the TIDAL VOLUME DECLINE TEST using a pair of thin wall latex balloons (Alto Development, Farmingdale, NJ). One balloon was placed into the stomach to estimate abdominal pressure and the other placed in the esophagus, just above the diaphragm, to estimate thoracic pressure. The balloons were connected to Validyne pressure transducers (MP45-34 and MP45-28) for the pressure measurement. These

thoracic and abdominal pressure measurements were sampled at 50 Hz for the entire stimulation period.

Phase I: Experiments to Establish Long Term Recruitment Stability

The first phase experiments consisted of RECRUITMENT TESTs and TIDAL VOLUME-STIMULUS FREQUENCY TESTs. Phase I experiments were conducted on both electrodes in each hemidiaphragm for a minimum of five months. This allowed adequate time for evaluation of long term recruitment and tidal volume-frequency stability.

RECRUITMENT TEST

Recruitment tests were conducted for both Phase I and Phase II experiments by changing the injected current for different pulsetrains. The stimulus amplitude was varied from 2 to 24 mA, in 2 mA increments, in random order with a 100 μ s pulsewidth. Each 1.5s pulsetrain consisted of a single amplitude (2 through 24 mA) at a 20 Hz frequency. Three test runs were done on each electrode at each amplitude. Each test run consisted of 12 breaths spaced 5 sec apart ($T_{\text{cycle}} = 5$ s). One test run was conducted every apneic period, with test runs spaced 5 minutes apart. Recruitment curves were constructed by plotting tidal volume versus stimulus amplitude.

TIDAL VOLUME-STIMULUS FREQUENCY TEST

A test of the tidal volume-stimulus frequency relation was conducted for each electrode for each Phase I and Phase II experiment. Nine frequency values were tested including 40, 30, 25, 20, 17, 15, 12, 10, and 8 Hz in random order. Again, three test runs were conducted for each electrode, each test run consisting of the nine breaths at a nominal 20 mA amplitude, 1.5 s pulsetrain duration. One test run

was conducted every apneic period with 5 minutes between test runs. Tidal volume was plotted against stimulus frequency for each test.

Phase II: Experiments to Test Tidal Volume Decline

The criteria for inclusion into the Phase II experiments were stable recruitment pattern for a minimum of three months, stable tidal volume-stimulus frequency relation for a minimum of three months, full diaphragm recruitment at less than 15 mA, 100 μ s, charge balanced, biphasic stimulus pulses and maintenance of dogs in an apneic state using stimulation of a single hemidiaphragm. One of the two dogs had a qualified electrode on the left hemidiaphragm (dog #760) and the other had a qualified electrode on the right hemidiaphragm (dog #279). Phase II experiments were initiated at 5 1/2 months after electrode implant for dog #279 and 7 1/2 months after electrode implant for dog #760. Phase II experiments consisted of a RECRUITMENT TEST followed by a TIDAL VOLUME-STIMULUS FREQUENCY TEST and a TIDAL VOLUME DECLINE TEST. In two experiments with dog #279 and three experiments with dog #760, an additional RECRUITMENT TEST was conducted after completion of the TIDAL VOLUME DECLINE TEST to assure that the changes in tidal volume were not the result of changes in recruitment.

TIDAL VOLUME DECLINE TEST

A total of 27 TIDAL VOLUME DECLINE TESTs were conducted using nine different stimulation protocols that are summarized in Table 6.1. Three inspiratory times, 0.75, 1.0 and 1.5 s were tested. A cycle time of 2.5 s was used for all test runs, so that the tested duty cycles were 0.3, 0.4 and 0.6. The stimulus amplitude was 25 mA (> 150% of the current producing maximal response) with a pulsewidth

of 100 μ s. In addition, four stimulus frequencies were tested including 40, 30, 25 and 20 Hz. Each stimulation protocol was tested three times with at least one test from each dog.

Each test consisted of two to six hours of stimulation during an apneic period. Prior to initiation of stimulation, the dog was hyperventilated to apnea. Stimulation was initiated and maintained for the entire test period. The dog remained apneic for the entire test period because of ventilation provided by the stimulation. Apnea was assured by monitoring the transdiaphragmatic pressure waveform.

Data Processing

The data for the first thirty minutes of the TIDAL VOLUME DECLINE TEST (720 breaths) was processed after completion of the experiment. Each breath cycle was identified from the transdiaphragmatic pressure and subsequently used to define the breath cycles for the airflow curves. The airflow was integrated to obtain lung volume and the difference between the maximum and the minimum was defined as the tidal volume. A tidal volume versus breath number relation was obtained. Each tidal volume decline was characterized by fitting the data to the empirical model:

$$V_t = K_0 + K_1 e^{-(K_2 n)}$$

where V_t is tidal volume and n is breath number. K_0 is a parameter that represents the asymptotic tidal volume, K_1 is the difference between the initial and asymptotic tidal volume and K_2 is the time constant. The model was fit using a non-linear, chi-squared least squares approximation (Levenberg-Marquardt algorithm, Igor Pro, Wavemetrics, Inc., Lake Oswego, CA).

RESULTS

Recruitment Stability

Recruitment curves and tidal volume-stimulus frequency relations were similar for all Phase II tests and for Phase I tests after 1 month post implant. Typical recruitment curves for dog #279 and #760 are shown in Figures 6.3 and 6.4 respectively. Dog #279 reached full recruitment at approximately 14 mA while dog #760 reached full recruitment at approximately 12 mA.

There were slight changes in the recruitment curves after the TIDAL VOLUME DECLINE TESTs. A post stimulus recruitment curve for dog #760 is shown in Figure 6.5. There was the expected change in maximal tidal volume. However, there was also a slight shift in the current levels that produce threshold and full recruitment. Prior to stimulation, maximal response was achieved at approximately 12 mA and after four hours of stimulation the current providing full recruitment had increased to 14 mA. However, the currents necessary for full recruitment never exceeded 20 mA after 4 hours of stimulation. As a result, we assumed that stimulation at 25 mA provided full activation of the diaphragm for the duration of the TIDAL VOLUME DECLINE TEST.

Effects of Stimulation Frequency and Duty Cycle on $K_0/(K_0 + K_1)$ and K_2

A single exponential model was representative of the tidal volume decline. A scatter plot of tidal volume data of the first 720 breaths (30 min) obtained in one of the TIDAL VOLUME DECLINE TESTs is displayed in Figure 6.6. The exponential model fit is superimposed on the data. The tidal volume data in the figure were normalized by the model parameters ($K_0 + K_1$). The variation in tidal volume data in Figure 6.6 was typical of the other data sets.

The standard deviation of K_2 was greater than the standard deviation of $K_0/(K_0 + K_1)$, the normalized asymptotic tidal volume. A summary of the estimated model parameters for each tested stimulation frequency and duty cycle is shown in Table 6.2. Note that K_0 was normalized by the initial tidal volume ($K_0 + K_1$) in order to standardize the results from the two dogs and in order to compare different stimulation protocols. The mean parameter values of the normalized asymptotic tidal volume, $K_0/(K_0 + K_1)$ and the time constant K_2 were calculated for each of the nine different stimulation protocols. Note that the $K_0/(K_0 + K_1)$ standard deviation was approximately 5% of the mean, while the K_2 standard deviation was approximately 100% of the mean.

As duty cycle or stimulus frequency was increased, the tidal volume decline progressed more rapidly and to a lower asymptotic value. The effect of a change in duty cycle is represented in Figure 6.7. As the duty cycle increased, the rate of tidal volume decline increased and the asymptotic tidal volume decreased. Similarly, an increase in stimulation frequency resulted in an increase in the rate of tidal volume decline and a decrease in the asymptotic tidal volume (Figure 6.8).

A multiple regression analysis, done on $K_0/(K_0 + K_1)$ using stimulation frequency and duty cycle as linear dependent parameters, indicated that a change in duty cycle of approximately 0.1 was equivalent to a frequency change of approximately 14 Hz. The results of the regression analysis are displayed in Table 6.3. The slope for the duty cycle relation was well determined (t test, $p=0.0028$), but the frequency relation was not as confident ($p=0.12$). Both slopes were negative confirming the relations described in Figures 6.7 and 6.8. Namely, as duty cycle or frequency increase, the asymptotic value of the tidal volume

decreases. Using $K_0/(K_0 + K_1)$ as an indicator of the risk of diaphragm fatigue, it was possible to quantitate the effect of a change in either stimulation frequency or duty cycle. Then, the equivalent changes in duty cycle and stimulation frequency were found by comparing the slopes:

$$\text{Equivalent Fatigue} = \frac{\Delta dc / K_0 / (K_0 + K_1)}{\Delta f / K_0 / (K_0 + K_1)} = \frac{-0.27}{-2.10E-03} = \frac{0.1}{14\text{Hz}}$$

Therefore, if the duty cycle was increased by 0.1 (by changing either the inspiratory time or the breaths per minute), the frequency would have to be reduced by 14 Hz in order to maintain the same degree of fatigue resistance.

A multiple linear regression analysis of K_2 was also done and the results are displayed in Table 6.4. Again, stimulation frequency and duty cycle were used as linear components of K_2 . For K_2 , the frequency sensitivity was well determined ($p=0.023$), but the duty cycle parameter was not ($p=0.20$). Both slopes were positive indicating an increase in the time constant (more rapid fall in tidal volume) with increasing frequency or duty cycle (See Figures 6.7 and 6.8). If K_2 was used as an indicator of the risk of fatigue, the multiple regression parameters of Table 6.4 were used:

$$\text{Equivalent Fatigue} = \frac{\Delta dc / K_2}{\Delta f / K_2} = \frac{1.14E-02}{3.50E-04} = \frac{0.1}{3\text{Hz}}$$

An increase in duty cycle of 0.1 required a frequency decrease of approximately 3 Hz in order to maintain the same degree of fatigue resistance. Note that the relation holds only over the range of the tested duty cycle and stimulation frequency.

The sensitivity of $K_0/(K_0 + K_1)$ and K_2 to duty cycle and stimulation frequency was not independent of the duty cycle or frequency range. A piecewise multiple regression was done to calculate the effects of stimulation frequency or duty cycle changes on $K_0/(K_0 + K_1)$ and K_2 over subranges of duty cycle and frequency. We tested the duty cycle ranges of 0.3-0.4 and 0.4-0.6 and the frequency ranges of 20-30 Hz and 30-40 Hz. The results are tabulated in Tables 6.3 and 6.4 for $K_0/(K_0 + K_1)$ and K_2 respectively. The effects of stimulation frequency and duty cycle on $K_0/(K_0 + K_1)$ for both the multiple piecewise regression analysis and the multiple regression analysis is displayed graphically in Figure 6.9. The effect of stimulation frequency on $K_0/(K_0 + K_1)$ was more pronounced between 20 and 30 Hz than between 30 and 40 Hz. Similarly, the effect of duty cycle was more pronounced between 0.3 and 0.4 than between 0.4 and 0.6. If these data were used to quantitate the risk of fatigue, the relative worth of a change in duty cycle between 0.3 and 0.4 would be greater than the relative worth of a change in duty cycle between 0.4 and 0.6. However, the parameters of the piecewise regression were generally not determined well enough to establish statistical significance (See Tables 6.3 and 6.4 for p values).

The parameters of the single exponential model estimated from the first 30 minutes of the TIDAL VOLUME DECLINE TEST resulted in approximately 15% error in predicting the tidal volume after four hours (See Table 6.5). The first thirty minutes of data was used for the parameter estimation in order to minimize the effects of variations in halothane anesthesia and blood pH on diaphragm contractility. This restriction was also justified because the estimated time constants ($1/K_2$) were on the order of 15 minutes. The thirty minute data set then included 2 time constants and the tidal volume at the end of the data set was within 2% of the

asymptotic value (See Table 6.5). However, when K_0 was compared to the tidal volume at thirty minute increments of the entire experiment, the tidal volume declined below the estimated K_0 after one hour (See Figure 6.10). We concluded from this analysis that the single exponential model does not accurately describe the tidal volume of an anesthetized supine dog undergoing long term diaphragm pacing. The error was most likely associated with physiologic changes in the diaphragm associated with the long experiment. In any case, the model accurately described the first thirty minutes of data (Figure 6.6) and the parameters were still indicative of the risk of fatigue.

The model parameters $K_0/(K_0 + K_1)$ and K_2 were also examined as a function of the number of pulses in each cycle. A graph of $K_0/(K_0 + K_1)$ versus the number of pulses in each cycle is shown in Figure 6.11 and K_2 versus the number of pulses in each cycle is shown in Figure 6.12. A linear regression was applied to the data and an increase in the number of pulses resulted in a reduced $K_0/(K_0 + K_1)$ and an increased K_2 . However, the Pearson's regression coefficients, R^2 were 0.36 for $K_0/(K_0 + K_1)$ and 0.25 for K_2 , which indicated a poor linear fit.

DISCUSSION

Increases in stimulus frequency and duty cycle were both found to increase the rate (K_2) and decrease the asymptotic ($K_0/(K_0 + K_1)$) parameters of tidal volume decline during diaphragm pacing. An increase in stimulus frequency of 14 Hz resulted in the same change in $K_0/(K_0 + K_1)$ as an increase in duty cycle of 0.1. Similarly, a change in frequency of 3 Hz and a duty cycle change of 0.1 resulted in an equivalent change in K_2 . The exponential model used in this study adequately

described the tidal volume decline over the first 30 minutes, however, there was less variance in $K_0/(K_0 + K_1)$ than K_2 . As a result, $K_0/(K_0 + K_1)$ provided a better predictor of diaphragm fatigue.

Effects of Stimulus Frequency and Duty Cycle on Tidal Volume Decline

The TIDAL VOLUME DECLINE TEST considered the effects of both stimulus frequency duty cycle changes on fatigue. Both stimulation parameters affected fatigue. With a single exponential model of tidal volume decline, a statistically significant positive relationship was established between stimulus frequency and K_2 . A statistically significant negative relationship was established between duty cycle and $K_0/(K_0 + K_1)$. However, it was difficult to determine the exact equivalent changes in duty cycle and stimulus frequency with regards to fatigue because the relation between frequency and $K_0/(K_0 + K_1)$ and the relation between duty cycle and K_2 were not well determined. It is, however, reasonable to use a relative tradeoff of approximately 10 Hz frequency change for a 0.1 duty cycle change, in the range of the stimulus parameters tested in this study.

Changes within the subranges of the stimulus frequencies and duty cycles tested in this study may have greater effects on fatigue than other subranges. However, additional experiments are required to establish statistical significance of the piecewise multiple regression coefficients. It would also be valuable to extend the frequency range to include all clinically relevant frequencies (down to 8 Hz). However, low frequency stimulation requires activation of both hemidiaphragms in order to maintain an apnea throughout the entire four hour test period. The effect of diaphragm fatigue using both hemidiaphragms has not been compared with single hemidiaphragm during diaphragm pacing.

A Single Exponential Model of Tidal Volume Decline for Predicting Fatigue

A single exponential model was used to approximate the tidal volume decline during diaphragm pacing. We then used the parameters of the model as indicators of the risk of fatigue. Other indicators of muscle fatigue have been considered including the parameters of a double exponential model (Boom 1993), percent of initial muscle force after a specified time (Peckham 1976) and the time that it takes the force to decrease to a specific percentage of initial force (Peckham 1976). However, the single exponential model adequately describes the force decline during cyclical quadriceps stimulation (Franken 1993) and changes in the ratio of high to low frequency components of EMG during fatigue (Bellamare 1982b). These studies suggest that muscle force decline is well described by a single exponential model.

We found that the single exponential model did not accurately predict the asymptotic tidal volume during diaphragm pacing. However, the overpredicted asymptotic tidal volume may have been a result of changes in the physiologic system. The slow decrease in tidal volume could have resulted from an accumulation of halothane or a change in blood gases. Since the model parameters were only used to compare the relative effects of stimulation frequency and duty cycle on the risk of fatigue, the long term model accuracy was not important. We do not recommend using the single exponential model to predict the long term tidal volumes obtained with diaphragm pacing.

The Tidal Volume Decline of the Anesthetized Supine Dog as an Indicator for Diaphragm Pacing Fatigue

The model of fatigue used in the TIDAL VOLUME DECLINE TEST was an anesthetized, supine dog, breathing oxygen. Fatigue has often been modeled using

systems that accelerate the onset of fatigue including models involving inspiratory loading (Bellamare 1982a, Bellamare 1982b), isometric muscle contractions (Bigland-Ritchie 1979, Boom 1993, Cady 1989, Carroll 1989, Fang 1991, Garland 1988) and ischemia (Cady 1989, Garland 1988). However, the results of tests under isometric conditions or conditions of inspiratory loading have limitations because they alter the velocity and extent of muscle shortening. The angular velocity of a knee joint has been shown to have an inverse correlation with the time constant of force decline during fatigue (Franken 1993). We concluded that the animal model that we used more closely approximated conditions of clinically applied diaphragm pacing than many previous models and was suitable for predicting fatigue.

Fatigue and the Number of Stimulus Pulses

Although fatigue has been associated with the number of pulses delivered to the muscle, our results indicated that independent consideration of stimulus frequency and duty was better for predicting fatigue. Correlation between fatigue and the number of stimulus pulses was demonstrated using in vitro rat diaphragm, stimulating at different duty cycles with a single stimulus frequency (Kelsen 1982). However, Garland et al. found that stimulation induced fatigue occurred with significantly fewer pulses using 15 Hz stimulation than occurred with 30 Hz stimulation (Garland 1988). This implies that the number of pulses predicts fatigue only when a constant frequency of stimulation is used. This is consistent with the results obtained in this experiment. Figures 6.11 and 6.12 demonstrated that some trials contain points that all fall well above the linear regression line and other trials (different stimulation frequencies and/or duty cycles) have points that all fall well below the linear regression line. It is reasonable to assume that fatigue is more

strongly related to the stimulation frequency and the duty cycle rather than the total number of pulses.

Future Work:

The results of the TIDAL VOLUME DECLINE TEST suggest consideration of a number of experiments for future work including additional experiments using the stimulus parameters employed in this study, experiments with lower frequencies and a wider range of duty cycles, experiments on conditioned diaphragm muscles and experiments using doublets or modulated stimulus frequencies.

Additional experiments using stimulus frequencies and duty cycles tested in this study would improve the significance of the results. In addition, the parameter space of the current experiments should be expanded to include lower frequencies and a wider range of duty cycles in future experiments. One potential problem with expanding the frequency range to low frequency stimulation is that the apneic period could not be maintained using single hemidiaphragm stimulation. Testing would require either qualification of a subject with both hemidiaphragms that meet the inclusion criteria or including one hemidiaphragm with submaximal recruitment. The possibility of using electrodes without full recruitment for testing fatigue may be justified because differences in fatigue of maximal and sub-maximal recruitment are considered negligible (Boom 1993). Additional experiments using parameters already tested would improve the significance of the parameters relating fatigue and the stimulus parameters. The relation between $K_0/(K_0 + K_1)$ and stimulus frequency and between K_2 and duty cycle could be determined with greater certainty. Similarly, the piecewise regression could be improved to increase the

significance of the relations between the frequency or duty cycle and the model parameters.

Tidal volume declines must also be studied in muscles that have been conditioned and muscles that have atrophied to understand how stimulus frequency and duty cycle effects are changed by muscle conditioning. Muscle conditioning can have two effects: 1) muscle force increase of atrophied muscle and 2) increased fatigue resistance. Peckham and co-workers found that the strength of finger flexor muscles of quadriplegics often increased by more than four times using exercise protocols of 10 Hz stimulation, 0.5 duty cycle and 2-6 hours of stimulation each day (Peckham 1976). Similarly, they found that the fatigue resistance was increased with electrical stimulation muscle conditioning (Peckham 1976). Increases in the oxidative capacity of conditioned diaphragm have been observed in dog studies (Ciesielski 1983, Peterson 1994a). Extension of the current studies to dogs with conditioned diaphragms would identify any changes in the relative effects of stimulation frequency and duty cycle on diaphragm fatigue.

There may be other ways of increasing the tidal volume without increasing the risk of fatigue by modulating the stimulus frequency during the stimulus pulsetrain. Smooth rectified EMG and surface action potential patterns could be made to follow the fatigue patterns elicited by maximum voluntary contraction by modulating the stimulus frequency during the pulsetrain (Bigland-Ritchie 1979, Jones 1979). Modulation of frequency would deliver a greater muscle force with fewer stimulus pulses. This type of stimulation may be more efficient with regards to the fatiguability of the muscle.

In a similar way, fatigue may be reduced by stimulation sequences using doublets or triplets of 5 ms interpulse intervals. This type of stimulation has been shown to improve torque tracking times (time that force could be maintained) of quadriceps stimulation and knee torques (Karu 1995). This concept is intuitively appealing because the force produced using a doublet can be more than double the force produced with a single pulse. This indicates that the metabolic processes may be more efficient using doublet stimulation and thus result in less fatigue.

In conclusion, we verified the importance of both duty cycle and stimulation frequency on the risk of diaphragm fatigue. In addition, we identified the relative worth of changes in stimulation frequency and duty cycle with respect to the risk of fatigue based on the tidal volume decline during diaphragm pacing of the supine dog. An equivalent risk of fatigue was found for a 14 Hz stimulation frequency change and a 0.1 duty cycle change when asymptotic tidal volume was used as the criteria for risk of diaphragm fatigue. Similarly, an equivalent risk of fatigue was found for a 3 Hz stimulation frequency change and a 0.1 duty cycle change when rate of tidal volume decline was used as the criteria for risk of diaphragm fatigue

Figure 6.1: Epimysial electrode for diaphragm pacing. Charge was delivered to the phrenic nerves by a hemispherical stimulating surface in the center portion of the electrode. The tabs on the sides of the center stimulating portion were used for stapling the electrode to the abdominal surface of the diaphragm.

Figure 6.2: Test setup for the TIDAL VOLUME DECLINE TEST. Measurements of airflow and transdiaphragmatic pressure were made. Airflow was measured using a Fleisch pneumotachometer. Transdiaphragmatic pressure was measured using esophageal (for thoracic pressure) and gastric (for abdominal pressure) balloons. Stimulation was delivered by a stimulator that was controlled by the computer. Data was acquired at 50 Hz by the computer from three channels for the duration of the test.

		Stimulus		Frequency	
		20 Hz	25 Hz	30 Hz	40 Hz
Duty Cycle	0.3	Dog #760		Dog #760	Dog #760
		Dog #279		Dog #760	Dog #279
		Dog #279		Dog #279	Dog #279
	0.4	Dog #760		Dog #760	Dog #760
		Dog #279		Dog #279	Dog #760
		Dog #279		Dog #279	Dog #279
	0.6		Dog #760	Dog #760	Dog #760
			Dog #279	Dog #760	Dog #760
			Dog #279	Dog #279	Dog #279

Table 6.1: This table displays the parameters that were tested in the TIDAL VOLUME DECLINE TEST. Three different duty cycles and 4 different stimulus frequencies were tested. The dog number indicates that a test was run for that stimulation protocol. Three tests were run for each stimulation protocol.

Figure 6.3: Recruitment curve for dog #279. This test was conducted eight months after implant. Note that maximum tidal volume was reached at approximately 14 mA. The other stimulus parameters were: pulsewidth = 100 μ s, frequency = 20 Hz, inspiratory time = 1.5s. Three tidal volumes were measured at each stimulus amplitude.

Figure 6.4: Recruitment curve for dog #760. Note that maximum recruitment occurs at approximately 12 mA, well below the 15 mA requirement. This test was done eleven months after electrode implant. The other stimulus parameters were: pulsewidth = 100 μ s, frequency = 20 Hz, inspiratory time = 1.5s. Three tidal volumes were measured at each stimulus amplitude.

Figure 6.5: Recruitment curve obtained post stimulation. Note that the maximum tidal volume has decreased, but the recruitment curve waveform has not changed significantly. The maximal recruitment has increased slightly to about 14 mA. These electrodes were implanted eleven months prior to this test. The pre-stimulation recruitment curve is shown in Figure 6.4.

Figure 6.6: Data from one TIDAL VOLUME DECLINE TEST. The duty cycle for this test was 0.6 and the stimulus frequency was 40 Hz. The line shows the model fit: $V_t = K_0 + K_1 e^{-(K_2 n)}$. The tidal volume was normalized by $(K_0 + K_1)$. The X axis shows the breath number. A cycle time of 2.5 seconds was used, resulting in a breathing rate of 24 breaths per minute. The 720 breaths shown on the graph represents 30 minutes of breathing.

Ton (s)	duty cycle	Frequency (Hz)	mean $K_0/(K_0+K_1)$	std dev	mean K_2	std dev
0.7	0.3	20	0.91	0.048	2.39E-03	2.28E-03
0.7	0.3	30	0.83	0.084	2.55E-03	1.39E-03
0.7	0.3	40	0.89	0.034	8.46E-03	5.88E-03
1	0.4	20	0.86	0.023	2.79E-03	1.83E-03
1	0.4	30	0.86	0.027	6.90E-03	3.53E-03
1	0.4	40	0.78	0.027	4.16E-03	2.44E-03
1.5	0.6	25	0.79	0.100	3.09E-03	1.08E-03
1.5	0.6	30	0.81	0.042	5.79E-03	2.38E-03
1.5	0.6	40	0.78	0.009	1.61E-02	1.47E-02

Table 6.2: The parameters obtained from the model fit to the tidal volume decline. Note that the standard deviation for K_2 is on the same order of magnitude as K_2 . The standard deviation of $K_0/(K_0 + K_1)$ is an order of magnitude smaller than $K_0/(K_0 + K_1)$.

Figure 6.7: Effect of duty cycle on tidal volume decline. The model fits for the 40 Hz stimulation curves are displayed in this graph. The curves represent the single exponential model using the mean parameters for the three trials at each pair of duty cycle-frequency parameters. Generally the trend was a greater decline when a larger duty cycle was used.

Figure 6.8: Effect of stimulus frequency on tidal volume decline. Generally as the stimulus frequency was increased, the decline was greater. The curves are constructed from the model fit to the data at a duty cycle of 0.4. The models shown are derived from an average of the estimated parameters.

$$K_0/(K_0+K_1)$$

Multiple Regression Analysis:		Student's t Test vs 0
	Parameter	p value
frequency	-2.10E-03	0.12
duty cycle	-0.27	0.0028

Piecewise Regression:		Student's t Test vs 0
	Parameter	p value
frequency 20 - 30 Hz	-4.10E-03	0.22
frequency 30 - 40 Hz	-2.20E-03	0.42
duty cycle 0.3 - 0.4	-0.41	0.11
duty cycle 0.4 - 0.6	-0.17	0.19

Table 6.3: Summary of regression analyses of the effects of the input parameters of stimulus frequency and duty cycle on the model parameter $K_0/(K_0 + K_1)$. The parameter values of the sensitivity (slope) of each parameter are displayed for entire range (above) of segments of the input parameter ranges. The p values were obtained from t tests and represent the confidence in the estimate. The variance in the data prevented confidence in the parameter estimates with the exception of duty cycle over the entire parameter range. The piecewise regression parameters could not be considered well determined.

K₂

Multiple Regression Analysis:		Student's t Test vs 0
	Parameter	p value
frequency	3.50E-04	0.022
duty cycle	1.14E-02	0.2

Piecewise Regression:		Student's t Test vs 0
	Parameter	p value
frequency 20 - 30 Hz	2.70E-04	0.049
frequency 30 - 40 Hz	4.30E-04	0.19
duty cycle 0.3 - 0.4	3.80E-03	0.83
duty cycle 0.4 - 0.6	1.74E-02	0.29

Table 6.4: Summary of the regression analysis of the effects of the input parameters of frequency and duty cycle on the model parameter **K₂**. The sensitivity of stimulus frequency on **K₂** and stimulus frequency in the 20-30 Hz range on **K₂** were well determined. A high degree of confidence could not be placed in the other sensitivity parameters.

Figure 6.9: The effects of duty cycle and stimulation frequency on the asymptotic tidal volume, $K_0/(K_0 + K_1)$. The piecewise regression analysis is shown in gray and the multiple regression analysis in black. The dashed lines indicate the 95% confidence region for the linear regression line.

Time	Mean % Error	Standard Deviation	Standard Error Mean	n
30 min	2.5	7.1	1.4	27
1 hr	-2.6	7.1	1.4	27
1 hr 30 min	-5.1	7.7	1.5	26
2 hr	-8.0	8.8	1.8	25
2 hr 30 min	-12.3	7.1	1.5	23
3 hr	-13.7	8.5	1.8	22
3 hr 30 min	-13.7	12.7	2.9	19
4 hr	-15.9	9.9	2.7	13
4 hr 30 min	-15.3	9.3	4.2	5

Table 6.5: The mean % error of the model estimate of asymptotic tidal volume (K_0) compared to the tidal volume at thirty minute intervals from 30 minutes to 4 hours and 30 minutes. The tidal volume used for comparison was an average of 10 breaths. K_0 was estimated using the first 30 minutes of data.

Figure 6.10: Graphical representation of the error in the asymptotic tidal volume predicted by a single exponential model fit to the first 30 minutes of data. K_0 was compared to the tidal volumes at thirty minute increments. K_0 was overestimated by approximately 15% compared to the experimental long term tidal volume.

Figure 6.11: Plot of the parameter $K_0/(K_0 + K_1)$ versus the number of pulses in each cycle (stimulus frequency times inspiratory time). Each symbol represents a different parameter pair. A line was fit to the data with slope = -0.0028, $R^2=0.36$. The slope may be different for each frequency.

Figure 6.12: Plot of K_2 versus the number of pulse in each cycle. Each symbol represents a different parameter pair. A line with slope = 0.00023, $R^2=0.25$ was fit to the data.

Chapter 7

Optimization of Stimulation Parameters for a Diaphragm Pacing System Using the Surrogate Worth Trade-off Method

INTRODUCTION

The objective of this study was to optimize stimulation frequency and inspiratory time for electrical activation of the diaphragm (diaphragm pacing) using the surrogate worth trade-off method. The emphasis on stimulation frequency and inspiratory time was based on the effects of these parameters on the risk of fatigue (See Chapter 6). The algorithm will be incorporated into the functional test schemes used for setting the stimulation parameters for long term diaphragm pacing.

The two issues that were important for setting stimulation frequency and inspiratory time were ventilation and fatigue. The trade-off between the risk of fatigue and the level of ventilation for these two parameters is illustrated in Table 7.1. As stimulation frequency and inspiratory time are increased, the tidal volume increases, but stimulation may be limited by fatigue. Conversely, if stimulation frequency and inspiratory time are decreased to reduce the risk of fatigue, tidal volume is compromised.

In this study, we developed a procedure for setting diaphragm pacing stimulus parameters using the surrogate worth trade-off method (Haimes 1975) in order to minimize the risk of fatigue. The surrogate worth tradeoff method is useful for this procedure because 1) the inputs are minimized instead of the outputs and 2) there are two objective functions that must simultaneously be minimized (one for frequency and one for inspiration time). Using the surrogate worth tradeoff method, we formulated the relative tradeoff between stimulation frequency and inspiratory time, restricted by a necessary tidal volume. The results from Chapter 6 were then used to construct a worth function which related the risk of fatigue to

changes in the stimulation frequency and inspiratory time. The utility of the algorithm was demonstrated with an example using data from diaphragm pacing experiments in dogs.

METHODS AND RESULTS

This project is divided into two parts: modeling the system and minimization of the stimulation parameters. Empirical models of the nerve/muscle and lung/ribcage were developed to set up a multiple objective minimization problem. Solution of the multiple objective function was done using the surrogate worth tradeoff method. The procedure was used to recommend stimulus parameters for pacing a dog diaphragm based on data from an intramuscular diaphragm pacing system developed by Peterson (Peterson 1990).

Models

Empirical models of the nerve/muscle and lung/ribcage systems were used to develop a mathematical relation between the inputs: stimulation frequency and inspiratory time and the output: tidal volume. A block diagram of the systems that relate stimulus frequency and inspiration time to tidal volume is described in Figure 7.1. A nerve/muscle model was used to relate stimulation frequency to transdiaphragmatic pressure. The lung/ribcage model was then used to relate the transdiaphragmatic pressure to tidal volume.

An increase in transdiaphragmatic pressure with increasing stimulation frequency was described by a two parameter mathematical expression (Equation 1). This mathematical expression represented the nerve/muscle model in Figure 7.1 and related the stimulation frequency input to the transdiaphragmatic pressure (P_{di}) output. The relation between trans-diaphragmatic pressure and time is shown in

Figure 7.2 for nine different stimulation frequencies (Peterson 1990). The dynamics of the transdiaphragmatic pressure curve were approximated by a square wave that rises when stimulation begins and falls when stimulation ends (see Figure 7.3). The amplitude of the square wave (Figure 7.3) was determined by stimulation frequency. The relation between the amplitude of trans-diaphragmatic pressure and frequency was expressed by the mathematical equation:

$$(1) \quad A = \frac{\beta f}{\gamma + f}$$

where **A** is the amplitude of the transdiaphragmatic pressure (See Figure 7.3), **f** is the stimulation frequency, and β and γ are mathematical parameters. β and γ were used only to describe the relation between the stimulation frequency and the amplitude of the transdiaphragmatic pressure and do not represent functional parameters of the physiological system.

The parameters of Equation 1 were estimated for the data shown in Figure 7.2. P_{di} was plotted versus stimulation frequency in Figure 7.4. A non-linear least squares minimization algorithm (NL2SOL) was used to estimate $\beta = 11$ and $\gamma = 11$ and the model is superimposed on the data in Figure 7.4 with these parameters. By inspection of the graph in Figure 7.4, we determined that the model adequately described the nerve/muscle model.

A mathematical expression was found for the lung/ribcage system. The lung volume is determined by the transdiaphragmatic pressure and the dynamic properties of the lung/ribcage system. The dynamic properties of the lung/ribcage system are demonstrated by the plot of lung volume versus time shown in Figure 7.5. Using the transdiaphragmatic pressure amplitude determined by Equation 1,

we approximated the lung/ribcage model by a first order differential equation with the solution:

$$(2) \quad V = \frac{A}{\delta} [1 - e^{(-\alpha t)}]$$

where V is lung volume, t is time, α is a mathematical parameter describing the system dynamics and δ is a mathematical parameter describing a linear approximation of the relation between A , the amplitude of the transdiaphragmatic pressure, and the steady state lung volume.

An expression for the tidal volume output with stimulation frequency and inspiratory time inputs was derived. First, equations 1 and 2 were combined

$$V = \frac{\frac{\beta f}{\gamma + f}}{\delta} [1 - e^{(-\alpha t)}]$$

to obtain an expression for lung volume using the frequency input. By setting time equal to the inspiratory time, an expression for tidal volume was obtained:

$$(3) \quad V_t = \frac{\frac{\beta f}{\gamma + f}}{\delta} [1 - e^{(-\alpha T_i)}]$$

where V_t was the tidal volume.

Since α determines the dynamics of the lung/ribcage system, an approximate value for α was found by graphically examining the volume-time relation in Figure 7.5. Equation 3 is graphed for four different values of α in Figure 7.6. Comparison of Figure 7.6 with the lung volume data in Figure 7.5 showed that the

appropriate value of α was within the range of 2.0 and 5.0. These two values were used for further analyses.

Next, a relation was found between stimulation frequency and inspiratory time that incorporated the tidal volume trade-off. This was accomplished by solving equation 3 for stimulation frequency:

$$(4) \quad f = - \frac{V_t \delta \gamma e^{\alpha T_I}}{V_t \delta e^{\alpha T_I} + \beta (1 - e^{\alpha T_I})}$$

or similarly by solving equation 3 for inspiratory time:

$$(5) \quad T_I = \frac{-\ln \left[\frac{-V_t \delta (f + \gamma)}{\beta f} + 1 \right]}{\alpha}$$

The tradeoff was demonstrated by plotting the frequency against the inspiratory time for specific values of tidal volume. The stimulation frequency - inspiratory time graphs using tidal volume values of 0.15 and 0.25 L and α values of 2 and 5 are shown in Figure 7.7.

Objective functions were derived directly from equations 4 and 5 to minimize the stimulation frequency and inspiratory time for reducing the risk of fatigue. Since the frequency could be expressed as a function of inspiratory time and visa versa, there were two possible pairs of objective functions that could be minimized:

$$(6a) \quad h_1 = - \frac{V_t \delta \gamma e^{\alpha T_I}}{V_t \delta e^{\alpha T_I} + \beta (1 - e^{\alpha T_I})}$$

$$h_2 = T_I$$

subject to the constraints:

$$(6b) \quad T_{I \min} < T_I < T_{I \max}$$

or:

$$(7a) \quad h_1 = \frac{-\ln \left[\frac{-V_t \delta (f + \gamma)}{\beta f} + 1 \right]}{\alpha}$$

$$h_2 = f$$

subject to the constraints:

$$(7b) \quad f_{\min} < f < f_{\max}$$

The maximum values for f or T_I were set and the minimum values were calculated using the monotonic relation between f and T_I . For our analysis we used a maximum T_I of 2.0 s and a maximum f of 40 Hz. Each problem set involved two objectives and one decision variable (T_I for Equation 6 and f for Equation 7). Equation 6 was used for the minimization process.

Minimization

The surrogate worth trade-off method was used to minimize stimulation frequency and inspiratory time in order to minimize the risk of fatigue. This method was used because the relative worth of the objectives was easily determined. This gave the decision maker more confidence in the choice of values for the minimized objectives (for this problem, stimulation frequency and

inspiratory time). The general solution to the static two objective problem solved below is given in Appendix 7A.

The multiple objective problem described by equation 6 was solved by the surrogate worth trade-off method in three stages. First the trade-off function was constructed. Second, the surrogate worth function was obtained. Finally, the preferred solutions were identified. We optimized the stimulus parameters for the diaphragm pacing system that produced the data shown in Figures 7.2 and 7.5. We assumed that the breathing rate was set at 15 breaths per minute, giving a cycle time of 4 seconds and we constrained the tidal volume to 0.2 liters to set the ventilation from this electrode at 3.0 L/min.

Step 1: The problem was set up as an epsilon-constraint problem.

To do this, Equation 6 was expressed as:

$$(8) \quad h_1(T_I) = \frac{V_t \delta \gamma e^{\alpha T_I}}{V_t \delta e^{\alpha T_I} + \beta (1 - e^{\alpha T_I})}$$

$$h_2(T_I) \leq \varepsilon_2$$

Since $h_2 = T_I$ the decision space (which is simply T_I) constraints became equal to the objective (h_2) constraints. As a result, h_2 was a constraint on h_1 .

We used the parameters:

$$(9a) \quad \alpha = 5$$

$$(9b) \quad \beta = 11$$

$$(9c) \quad \gamma = 11$$

$$(9d) \quad \delta = 33$$

$$(9e) \quad V_t = 0.2$$

The parameters α , β and γ were found from the model fits and V_t was set to provide adequate ventilation. δ was estimated from a comparison of the transdiaphragmatic pressure (Figure 7.2) and the steady state tidal volume (Figure 7.5). Equation 9 was substituted into equation 8 to obtain:

$$(10) \quad h_1(T_I) = \frac{-73 e^{5 T_I}}{11 - 4.4 e^{5 T_I}}$$

$$h_2(T_I) \leq \varepsilon_2$$

Step 2: We found the minimum value for h_2 . Since h_1 was a monotonic function of h_2 , the evaluation of the limits was greatly simplified. The minimum value of h_2 was found by setting the maximum value for h_1 and solving for h_2 . We set

$$h_{1 \max} = f_{\max} = 40 \text{ Hz}$$

to obtain:

$$(11) \quad h_{2 \min} = \frac{-\ln\left[\frac{-V_t \alpha (f_{\max} + \gamma)}{\beta f_{\max}} + 1\right]}{\alpha}$$

Substituting equation 9 into equation 11 and using a maximum stimulation frequency of 40 Hz we found the solution:

$$h_{2 \min} = 0.29$$

In order to simplify the calculations, we used $h_{2 \min} = 0.3$.

Step 3: We then found the maximum value for h_2 . The maximum value was set by the decision maker. We set

$$h_2(T_I) = h_{2 \max} = 2.0 \text{ s}$$

At this point we checked the minimum frequency to assure that it was a reasonable value. Since the stimulation frequency-inspiratory time relation was monotonic (Figure 7.7), the minimum frequency was found by evaluating equation 10 at the maximum inspiratory time:

$$(10) \quad h_1(T_I) = \frac{-73 e^{5 T_I}}{11 - 4.4 e^{5 T_I}}$$

Solving, for $T_I = 2.0$ seconds:

$$h_{1 \min} = f_{\min} = 16.5 \text{ Hz}$$

This was a reasonable value for the minimum frequency.

Step 4: We set the initial ε_2 first by setting the number of points to evaluate, $m = 17$, and solving for the increment:

$$\Delta = \frac{h_{2 \max} - h_{2 \min}}{m} = 0.1$$

Then:

$$\varepsilon_2 = h_{2 \max} - \Delta = 1.9$$

Step 5a:

$$\text{MIN } h_1(T_1)$$

$$\text{such that } h_2(T_1) \leq \varepsilon_2$$

Since h_1 was a monotonically decreasing function of h_2 , the minimum value of h_1 given the constraint: $h_2(T_1) \leq \varepsilon_2$ occurred at: $h_2(T_1) = \varepsilon_2$ and the minimum was calculated by substitution into Equation 6:

$$\text{MIN } h_1(T_1) = h_1(\varepsilon_2) = \frac{-73 e^{5 \varepsilon_2}}{11 - 4.4 e^{5 \varepsilon_2}} = 16.5$$

Step 5b: Next we found the trade-off function. The trade-off function is also the LaGrange multiplier (Haimes 1975). Using the formula for the LaGrange multiplier evaluated at $h_2(T_1) = \varepsilon_2$, we found:

$$\lambda_{12} = \frac{\partial h_1}{\partial T_1} = \frac{-1597 e^{10 T_1}}{(11 - 4.4 e^{5 T_1})^2} - \frac{363 e^{5 T_1}}{(11 - 4.4 e^{5 T_1})}$$

$$@ \quad h_2(T_1) = T_1 = \varepsilon_2 = 1.9$$

$$\lambda_{12} = 0.00511$$

Step 6: We then set $\varepsilon_2 = \varepsilon_2 - \Delta$ and repeated steps 4-6 until $h_{2\min}$ was reached. Values were obtained for the minimum h_1 , the trade-off ratio, and for ε_2 . These values are shown in Table 7.3. The tradeoff function is graphed in Figure 7.8.

Step 7-8: The surrogate worth function was developed. This was done by comparing

$$\lambda_{12}(\hat{h}_2) \text{ units of } h_1 \longleftrightarrow 1 \text{ unit } h_2$$

and assigning a number on a relative scale from -10 to 10. A positive value was assigned to the worth function if the left side was greater than the right, a negative value was assigned if the opposite was true and zero was assigned if the trade-off was equal.

We used the results from Chapter 6 to aid in constructing the surrogate worth function. In Chapter 6 we found that a change in frequency of 10 Hz was approximately equal to a change in duty cycle of 0.1. In this study, a change in inspiratory time of 1 s was equivalent to a change in duty cycle of 0.25 (the breathing rate was 15 breaths per minute). A change in inspiratory time of 1 s was the same as a 25 Hz change in frequency. As a result, the worth function was set to zero at $h_2=0.5s$. The values of the worth function are shown in Table 7.3 and the worth function is plotted in Figure 7.9.

Step 9: Find the preferred solution. The preferred solution, taken directly from Table 7.3, was the region where the worth function was zero. This solution was:

$$T_i = 0.5 \text{ s}$$

$$f = 21 \text{ Hz}$$

Thus, the recommended stimulation parameters were found. These recommended stimulus parameters were within the range of stimulus parameters expected for diaphragm pacing.

DISCUSSION

The surrogate worth tradeoff method was a useful technique for minimizing the stimulation parameters used for this project. Its usefulness came mainly from the advantages it gave to the decision maker for comparing the relative worth of the two objectives. The use of the surrogate worth method has been demonstrated and the steps for solving the minimization of stimulation frequency and inspiratory time have been outlined. The application of this technique will be valuable for recommending stimulus parameters for clinical diaphragm pacing. However, the accuracy of the surrogate worth function was limited by the accuracy of the knowledge of the relative effects of stimulation frequency and inspiration time on the risk of fatigue. In addition, the current technique required the breathing rate to be set prior to analysis. Expansion of the technique to a three objective problem or incorporation of more sophisticated lung/ribcage models may make the algorithm more powerful, but may not be worth the additional complications.

Clinical Significance

Application of a parameter optimization algorithm to clinical diaphragm pacing would provide a valuable tool to the physician for selecting stimulation parameters. Each diaphragm pacer patient would be tested to determine the P_{di} - stimulation frequency relation by measuring the transdiaphragmatic pressure response during stimulation at several frequencies. An automated computer algorithm would then estimate the parameters β and γ . Then the δ and α parameters would be estimated from the lung volume - time relation. The physician would enter the patient data including the required tidal volume and the computer algorithm would then apply the surrogate worth trade-off method and suggest stimulus parameters as demonstrated in the example in this chapter. Each case must be considered

separately to compensate for individual variation in model parameters and tidal volume requirements.

The inspiratory time of 0.5 s that was calculated for the example in this study was smaller than the 1.2 s typically used for diaphragm pacing with phrenic nerve cuff electrodes (Oda 1981). The importance of minimizing the inspiratory time has not been emphasized in the past. Risk of diaphragm fatigue can be reduced by reducing inspiratory time as well as stimulation frequency (Bellamare 1982a, Boom 1993, Kido 1988). However, the example that was used in this study did not incorporate a mechanism for graded diaphragm contraction during inspiration which is often used in clinical diaphragm pacing. A graded diaphragm contraction will decrease α and increase the required inspiratory time.

Factors Limiting the Surrogate Worth Function

Additional information relative to construction of the worth function would be valuable for improving the efficacy of optimization of the stimulus parameters using the surrogate worth trade-off technique. Quantitative evaluation of the relative effects of changes in stimulation frequency and duty cycle on fatigue have already begun (See Chapter 6) We found that a 10 Hz change in frequency is roughly equivalent to a 0.1 change in duty cycle in the frequency range of 20-40 Hz and duty cycle range of 0.3-0.6. However, the relative effects of stimulation frequency and duty cycle on the risk of fatigue have not been verified outside the 20-40 Hz or 0.3-0.6 ranges, nor within subranges of 20-40 Hz or 0.3-0.6. Demonstration of the optimization technique in this paper required knowledge of the effect of changes in stimulation frequency and duty cycle at frequencies down to 16 Hz and duty cycles down to 0.15. Additional quantitative tests of the relative effects of

stimulation frequency and duty cycle on fatigue would improve the accuracy of the worth function.

The Breathing Rate

The empirical model could also be used to minimize the breathing rate as well as stimulation frequency and inspiratory time. The problem would have to be reformulated so that three objectives would be simultaneously minimized and the computations would become more complex. Ventilation would then be used instead of tidal volume and the relation between ventilation, tidal volume and fatigue would have to be derived. There are methods available for solving this three objective problem using the surrogate worth trade-off function (Haimes 1975). However, the added complexity of the algorithm may not outweigh the advantages of incorporating this parameter into the problem.

Lung/Ribcage Models

In the future a new model could be developed for the lung/ribcage system. A dynamic model incorporating physical parameters could be developed for analysis of the diaphragm pacing system. There may be some advantages in changing from the empirical model. A mechanistic model may aid in the diagnostic capability of the physician. Problems that were originally attributed to the stimulation parameters may actually be associated with the physiological system. Estimation of the mechanistic model parameters may indicate where the problems lie and may be compensated for with adjustment of the stimulation parameters. In addition a new model may necessitate changes in the steps described for the minimization of stimulation frequency and inspiratory time. Namely, many of the simplifications

used above may no longer be applicable. Naturally, the complications will depend to a large extent on the model used.

We concluded from this study that the surrogate worth tradeoff method is useful for optimizing stimulus parameters for diaphragm pacing. However, the accuracy of the suggested parameters is dependent on the accuracy of the relative worth of changes in stimulation frequency and inspiratory time determined using risk of fatigue as a measure of worth.

Appendix 7A: (From Haimes 1975)General algorithm for solution of the static two-objective problem

Step 1: Find the minimum value, $f_{2\text{MIN}}$, for f_2 by solving:

$$\begin{array}{ll} \text{MIN } f_2(\underline{x}) \\ \text{s.t. } \underline{x} \in T \end{array}$$

The solution to this problem is $f_{2\text{MIN}}$.

Step 2: Find the maximum value, $f_{2\text{MAX}}$, for f_2 by solving:

$$\begin{array}{ll} \text{MIN } f_1(\underline{x}) \\ \text{s.t. } \underline{x} \in T \end{array}$$

If the solution vector to this problem is $\underline{x}^*$ then $f_{2\text{MAX}}$ is $f_2(\underline{x}^*)$; if there is more than one solution vector $\underline{x}^*$, then the minimum value of $f_2(\underline{x}^*)$ is $f_{2\text{MAX}}$.

Step 3: Set the initial value for $\varepsilon_2 = f_{2\text{MAX}} - \Delta$ where $\Delta > 0$.

Step 4:

$$\begin{array}{ll} \text{MIN } f_1(\underline{x}) \\ \text{s.t. } f_2(\underline{x}) \leq \varepsilon_2 \\ \underline{x} \in T \end{array}$$

Generally the Kuhn-Tucker conditions can be used to solve this problem. Of course, any optimization technique which is appropriate can be utilized. Let $\underline{x}^*$ be the decision vector which solves this problem. The solution is $f_1^*(\varepsilon_2) = f_1(\underline{x}^*)$; each solution should also contain λ_{12} the LaGrange multiplier for the ε_2 constraint. Also a check to see if the constraint is binding must be made as part of this step. If the constraint is binding then $\varepsilon_2 = f_2$ so that the outputs of this step are $\lambda_{12}(f_2)$ and $f_1^*(f_2)$ at the value $f_2 = \varepsilon_2$. If the constraint is not binding then ignore these values.

Step 5: If the ε_2 constraint was binding in step 4, then set $\varepsilon_2 = \varepsilon_2 - \Delta$; otherwise set $\varepsilon_2 = f_2(\underline{x}^*)$. If ε_2 is greater than $f_{2\text{MIN}}$ then return to step 3; otherwise proceed to step 6.

Step 6: Develop the surrogate worth function $W_{12}(f_2)$ as follows: For each value f_2^* at which the worth is desired, ask the decision maker for his assessment of how much $\lambda_{12}(f_2)$ additional units of objective f_1 are worth in relation to one additional unit of objective f_2 , given f_2^* units of f_2 and $f_1^*(f_2^*)$ units of f_1 . His assessment can be made on a relative scale of say -10 to +10 with zero signifying equal worth; this assessment is the value of W_{12} at f_2^* .

Step 7. The preceding step is repeated until the entire indifference band is found.

Step 8. Find the preferred decision vector $\underline{x}^*$ by solving:

$$\begin{aligned} & \text{MIN } f_1(\underline{x}) \\ & \text{s.t. } f_2(\underline{x}) \leq f_2^* \\ & \quad \underline{x} \in T \end{aligned}$$

In many problems there will be more than one solution f_2^* to step 7. In that case, there will be more than one preferred solution, and step 8 must be repeated for each f_2^* in order to find all of the preferred decisions vectors; some other criteria must be introduced to decide among them.

Step 9: A sensitivity analysis could be performed to determine the possible effects of implementing the preferred solution.

Step 10: Stop - the solution is ready to be implemented.

Parameter	Change	Effects	
		Tidal Volume	Risk of Fatigue
Inspiration Time	Increase	Increase	Increase
	Decrease	Decrease	Decrease
Interpulse Interval	Increase	Decrease	Decrease
	Decrease	Increase	Increase

Table 7.1: Table showing the tradeoffs of tidal volume and risk of fatigue for the parameters of inspiration time and stimulation frequency.

Figure 7.1: This block diagram describes the entire system under consideration. Two models are used: the Nerve/Muscle model and the Lungs/Ribcage model. Simplifications to these models for development of the techniques used in this project are described in the text. f = stimulation frequency, TI = inspiratory time, Pdi = transdiaphragmatic pressure, V_t = tidal volume.

Figure 7.2: Transdiaphragmatic pressure versus time (Peterson 1988). The waveforms of 9 different stimulation frequencies are shown. As stimulus frequency decreases, the ripple decreases and the maximum pressure increases.

Figure 7.3: The model simplification for the relations between trans-diaphragmatic pressure (P_{di}) and time. The model is a square wave with the amplitude, A , determined by stimulation frequency, f .

Figure 7.4: The graph demonstrates the relation between trans-diaphragmatic pressure and stimulation frequency. Points are given for experimental data at times ranging from the beginning of stimulation to a time of one second. The model is superimposed on the experimental data. The parameters of the model were estimated using NL2SOL on the data shown. These data were taken from Peterson 1988.

Figure 7.5: Lung volume vs. time for nine different stimulus frequencies (Peterson 1988). Note that increasing the stimulus frequency increases the tidal volume.

Figure 7.6: Calculation of tidal volume for 4 different α values for the empirical model of the volume time relation. The α parameter determines how fast the volume rise occurs. A value between 2 and 5 would correlate best with volume-time relation (Figure 7.8). The black lines are the model fits using different values for α (Equation 3) and the gray lines are normalized data from the lung volume curves of Figure 7.5.

Figure 7.7: Stimulation frequency versus inspiratory time for constant tidal volumes. Calculations were computed using alpha values of 2 and 5 with tidal volumes of 0.15 and 0.25 L. The lines represent the combinations of stimulus parameters that may be used to produce a single tidal volume. Since α affects the rise in tidal volume of the lung/ribcage model, an increase in α shifts the stimulation frequency-inspiratory time lines to the left.

Frequency $h_1(T_I)$	Tradeoff $\lambda_{12}(T_I)$	T_I $h_2(T_I)$	Worth W_{12}
37	235	0.3	-10
25	63.7	0.4	-5
21	26.8	0.5	0
19	13.4	0.6	5
18	7.27	0.7	7
17	4.13	0.8	8
17	2.41	0.9	8
17	1.42	1.0	9
17	0.85	1.1	9
17	0.51	1.2	9
17	0.30	1.3	10
17	0.18	1.4	10
17	0.10	1.5	10
17	0.06	1.6	10
17	0.03	1.7	10
17	0.01	1.8	10
17	0.01	1.9	10

Table 7.3: Values of frequency ($h_1(T_I)$), trade-off $\lambda_{12}(T_I)$, inspiratory time $h_2(T_I)$ and relative worth W_{12} calculated for the example. The stimulus parameters should be set at values where the worth function is 0. In this case a stimulus frequency of 21 Hz should be used with an inspiratory time of 0.5 s.

Figure 7.8: The trade-off function for the example. The tradeoff function was used to construct a worth function. The tradeoff function provided the magnitude of change in frequency that was used to compare with a 1 s change in inspiratory time.

Figure 7.9: The worth function for the example. The worth function, used to set the stimulus parameters, was constructed by comparing a change in frequency, the magnitude of the change determined by the tradeoff function, with a change in inspiratory time of 1 s. A value between -10 and 10 was assigned to the worth function for each comparison. The location where the worth function crossed zero indicated the inspiratory time that should be used for diaphragm pacing. In this example, the worth function indicated an inspiratory time of 0.5 s. From Table 7.3, the required frequency at this inspiratory time was 21 Hz.

Chapter 8

Impedance Pneumography for Diaphragm Pacing

INTRODUCTION

We investigated impedance pneumography for monitoring diaphragm pacing using epimysial electrodes implanted on the abdominal surface of the diaphragm. The goals of implementing an impedance pneumograph monitor were to detect diaphragm contraction, predict tidal volume and detect an airway obstruction.

The need for a monitor for detection of airway obstruction during diaphragm pacing has been expressed (Baer 1992, Glenn 1984). At least two deaths of patients with diaphragm pacing systems have been associated with airway obstruction that went undetected because of a decreased patient arousal response (Baer 1992, Marzocchi 1990). Alarm systems for clinical diaphragm pacing devices have concentrated primarily on pulse oximetry because oxygen desaturation occurs regardless of the mechanism of respiratory failure. Application of impedance pneumography has been limited because thoracic impedance changes that could be misinterpreted as breaths have been reported during diaphragm pacing with an obstructed airway (Marzocchi 1990). However, pulse oximetry requires extra instrumentation and an additional transducer for monitoring blood oxygen levels.

A respiratory monitor that can be incorporated into the diaphragm pacing instrumentation is attractive because no external transducers or additional instrumentation would be needed. Electrical activation of the diaphragm using electrodes placed on or in the diaphragm muscle offers the possibility of incorporating an impedance pneumograph device into an implanted diaphragm pacing stimulator and electrode system. The implanted electrode system could be

used to bypass two of the main sources of impedance artifact: electrode movement and the impedance of the electrode-skin interface (Neuman 1984).

In this study we designed and tested an impedance pneumograph for diaphragm pacing using epimysial electrodes implanted in dogs. The device was designed to minimize the effects of stimulus artifacts and test the feasibility of impedance pneumography as a useful alarm system for diaphragm pacing. We tested detection of diaphragm contraction, calibration of tidal volumes produced by diaphragm pacing, and detection of airway obstruction.

METHODS

Animal Preparation:

Epimysial electrodes for diaphragm pacing were implanted in 7 dogs. Three or four electrodes were implanted in each dog. The epimysial electrodes were designed with a hemispherical stimulating surface that opposed the diaphragm (Figure 8.1). The charge density delivered by the electrode was $0.125 \mu\text{C}/\text{mm}^2/\text{phase}$ to ensure that corrosion would not occur during long term diaphragm pacing. The electrode was attached to the surface of the muscle by stapling.

Electrodes were implanted onto the diaphragm under laparoscopy using aseptic technique. Dogs were anesthetized with intravenous sodium pentothal (Abbott Laboratories, North Chicago, IL)(15mg/kg) and intubated (8.5-9.5 mm endotracheal tube). Anesthesia was maintained with inhaled halothane (1-2%). Body temperature was maintained with a heating pad and fluid homeostasis maintained with an I.V. drip (1.0-1.5L Lactated Ringer's). Electrodes were placed

near the point on the abdominal surface of the diaphragm opposite phrenic nerve entry (Figure 8.2). Electrodes were permanently attached to the diaphragm using an endoscopic stapler (Endopath, Ethicon Inc., Somerville, NJ). The electrode lead wires were tunneled subcutaneously to an exit point midway between the scapula.

Electrodes remained implanted a minimum of two weeks prior to testing the impedance pneumograph. This time allowed the acute inflammation around the electrodes to subside and the tissue reaction to stabilize. Testing was conducted at two to ten week intervals for 3 to 12 months following implant. Tests were conducted on anesthetized (I.V. sodium pentothal followed by 1-2% halothane in oxygen) dogs placed in the supine position. Body temperature was maintained with a heating pad and fluid homeostasis maintained with an I.V. drip. The electrocardiogram was monitored throughout the test. The dogs were hyperventilated to apnea prior to test stimulation using positive pressure ventilation. Test stimulation and impedance pneumography were conducted during the 2-3 minute apneic period.

Test Setup and Instrumentation:

A schematic of the experimental test setup is contained in Figure 8.3. Electrode lead wires were connected to a stimulator (NeuRx IS/4, Applied Neural Control Laboratory). The stimulator was under the control of a Macintosh IIfx computer through a NB-MIO-16 data acquisition board (National Instruments Corporation, Austin, TX). The computer was optically isolated from the stimulator using a custom made device. During stimulation, airflow and impedance were sampled at 100 Hz by the computer through two channels. Channel one was used to sample airflow from a pressure transducer (± 2 cm H₂O, model MP45-14-871, Validyne

Engineering Corporation, Northridge, CA) placed across a Fleisch pneumotachometer (model 3813, Hans Rudolph, Inc., Kansas City, MO). The airflow signal was software integrated to obtain a measurement of lung volume. Channel two was used to sample the impedance pneumograph signal.

A block diagram of the impedance pneumograph circuit is described by Figure 8.4. A two electrode approach to impedance measurement was used, measuring from the same electrodes that the current was passed. Only the magnitude of the impedance was considered. The device consisted of a current oscillator and a detection/demodulator circuit (See Appendix 8A for circuit diagrams). The current oscillator delivered a controlled current sinusoidal waveform. The current frequency was 20 KHz, with an amplitude that could be varied between 0.1 and 1 mA. A nominal value of 0.2 mA was used for these experiments. The impedance was measured across two electrodes using a third electrode as a reference. The signal was first input into a differential amplifier. The signal was then filtered to reduce the stimulus artifact and finally demodulated to obtain the impedance signal.

In order to test the epimysial electrodes for impedance pneumography, one of the epimysial electrodes was connected to one of the impedance pneumograph leads. The second pneumograph lead was attached to a subcutaneous needle electrode (25 gauge, 1 1/2 inch length) nominally placed in a midaxillary position at the ninth rib. Other subcutaneous electrode locations that were tested included midaxillary positions at the fifth and seventh ribs, and the back of the dog, midway between the scapulae. The reference electrode was a subcutaneous needle electrode (25 gauge, 1 1/2 inch length) placed on the sternum, 5 cm rostral to the xiphoid.

Impedance Pneumography Tests:

The impedance pneumograph was tested during diaphragm pacing using different stimulus paradigms. Impedance and lung volume were simultaneously measured during variations in the stimulus current, variation of stimulus interpulse interval (IPI) and stimulation against an occluded airway.

First, recruitment curves were measured using simultaneous measurement of both the impedance and the lung volume during test stimulation. The test stimulation consisted of a 1.5 s duration pulsetrains of biphasic, charge balanced, current pulses with a pulsewidth of 100 μ s and an IPI of 50 ms. The tested current amplitudes ranged from 2 to 24 mA in 2 mA increments. Three test runs were conducted at each of the 12 current amplitudes. Each test run consisted of 12 pulsetrains with the tested current amplitudes delivered in random order. Tidal volume was defined as the maximum change in lung volume resulting from stimulation. Recruitment curves were constructed using tidal volume and using the maximum change in measured impedance. The impedance measured for each test was classified as increasing, decreasing, or both. Impedance was plotted against tidal volume and a linear regression was done to determine the correlation between impedance and tidal volume for each stimulating electrode.

The second test conducted was a test of impedance change and tidal volume with changes in IPI. The test stimulation consisted of 1.5 s pulsetrains of biphasic, charge balanced current pulses of 100 μ s pulsewidth and 20 mA amplitude. Nine IPI's were tested including 25, 33, 40, 50, 57, 63, 87, 100 and 125 ms. Again, three test runs were done, with each test run consisting of nine pulsetrains with different IPI, in random order. Tidal volume and maximum impedance changes

were plotted against IPI for comparison. Impedance was plotted against tidal volume and a linear regression was done for each electrode.

The recruitment curve and IPI tests were repeated for tests of detection of an obstructed airway during diaphragm pacing. Airway obstruction was modeled by clamping the endotracheal tube closed during test stimulation. Impedance waveforms for open and occluded airways were compared using overlay plots.

Finally, the effect of the stimulus artifact on impedance pneumography monitoring was checked by applying stimulation to two subcutaneous needle electrodes. One electrode was placed at the sternum, 5 cm rostral to the xiphoid, and the other was placed in the right forelimb. Current delivery was verified using the ECG. The test stimulus consisted of 1.5 s pulsetrains of 50 ms interpulse interval (IPI), 24 mA, 100 μ s biphasic current pulses.

RESULTS

Impedance Waveforms:

An overlay of lung volume and impedance change is displayed in Figure 8.5. A positive change in impedance with an increase in lung volume is shown in this graph. However, this was not always the case. Many of the measurements resulted in negative changes in the impedance with increases in tidal volume (Figure 8.6). Other cases resulted in both positive and negative changes in impedance with increases in lung volume (Figure 8.7). Cases of both increases and decreases in impedance with increasing lung volume occurred only when the maximum tidal volume was greater than 0.15 L. The impedance changes (INCREASE, DECREASE or BOTH) are summarized by the mosaic plot in Figure 8.8. The

count of the impedance change types is presented in Table 8.1 for tidal volume categorized into three levels: 0.05 - 0.15 L, 0.15 - 0.25 L and > 0.25 L for the 57 trials of the study.

Stimulus Artifact:

Introducing the stimulus artifact during apnea resulted in no change in the impedance pneumograph.

Tidal Volume and Impedance:

Mixed results were obtained from recruitment curve measurements and measurements of the response to stimulation with different IPI's. A recruitment curve obtained from impedance changes overlaid on a recruitment curve obtained with tidal volume measurements is shown in Figure 8.9. A linear regression of the tidal volume versus the impedance changes resulted in a Pearson's correlation coefficient (R^2) of 0.98 (Figure 8.10). These type of data could also be produced for the IPI test. A linear regression of the tidal volume and impedance change for an IPI test is shown in Figure 8.11. The resulting R^2 was 0.97, indicating a good linear approximation.

Other trials resulted in impedance changes that did not correlate well with tidal volume during recruitment or during IPI tests. Results of a recruitment curve and an IPI test are displayed in Figures 8.12 and 8.14 respectively. These data indicated a poor correlation between tidal volume and impedance changes. The linear regression of the tidal volume and impedance for the recruitment curve is shown in Figure 8.13. The R^2 was calculated as 0.01. Similarly, the linear regression of tidal volume and impedance for an IPI test is shown in Figure 8.15. This R^2 was calculated as 0.49.

The reason for the poor correlation between tidal volume and impedance change for the recruitment test in Figure 8.13 was an impedance measurement that initially began with a positive change in impedance with tidal volume but then changed as tidal volume increased. After reaching a specific tidal volume the impedance measurement was affected by a negative change in impedance with increasing tidal volume. In many cases the second impedance effect dominated the total impedance and the impedance waveform reversed polarity (Figure 8.16). The currents producing the reversal of trend in impedance are shown on the recruitment curve in Figure 8.17. In this example, the impedance changed from decreasing impedance to increasing impedance as the first major rise in tidal volume occurred. Eventually, impedance changed from increasing back to decreasing again when a second major increase in recruitment occurred. This was an example of the case labeled BOTH in Figure 8.8.

The mean R^2 was 0.68 for all of the recruitment tests and 0.72 for all of the IPI tests. There was no significant difference in recruitment or IPI tests for predicting tidal volume. The responses to stimulation were classified as either SINGLE or BOTH. A BOTH classification consisted of tests with components of both increasing and decreasing impedance changes. A SINGLE classification required an impedance change that was either increasing or decreasing exclusively. The R^2 was significantly higher for responses classified as SINGLE ($p < 0.05$, Wilcoxon Rank Sum) than for BOTH responses.

Electrode configuration was also considered when estimating tidal volume by subdividing the tests into two classifications. Tests were classified as either SAME or CROSS based on the relative locations of the electrodes. SAME consisted of a

stimulating electrode on the same hemidiaphragm as the recording electrode. CROSS consisted of stimulating and recording electrodes on opposite hemidiaphragms (Figure 8.18). Impedance measured in a CROSS configuration resulted in a more accurate estimate of tidal volume than impedance measured in a SAME configuration. These data are summarized in Table 8.2.

A subset of the 57 recruitment experiments was used to compare differences between SAME and CROSS configurations with similar placement of the subcutaneous recording electrode. The data subset consisted of 14 recruitment test pairs with the subcutaneous recording electrode placed at the 9th rib. CROSS resulted in a significantly greater R^2 than SAME for the 9th rib test ($p < 0.001$, paired t test). These results are shown in Table 8.3. The corresponding IPI test did not yield significant results but only 7 experiments were conducted. The BOTH classification was also tested on this data set, indicating a significantly lower R^2 for BOTH compared to SINGLE type responses.

Occluded Airway Tests:

Occluded airway tests were evaluated by comparing the difference of the open airway and the occluded airway. The occluded ratio, OccRat, was defined as:

$$\text{OccRat} = \text{Maximum Change of (Open-Occluded)} / \text{Maximum Change of Open}$$

where Open was the impedance measurement with electrical activation of the diaphragm and an open airway and Occluded was the impedance measurement during stimulation against an occluded airway. A small OccRat indicated that there was no change in the impedance measurement when the airway was occluded. An OccRat greater than one indicated that Open and Occluded were opposite. That is,

one resulted in an increase in impedance and the other resulted in a decrease in impedance. A larger OccRat makes occluded airway detection easier and more reliable.

An occluded airway impedance measurement that is significantly different from the corresponding open airway measurement (OccRat = 2.52) is demonstrated in Figure 8.19. An occluded airway impedance measurement that is similar to the corresponding open airway measurement (OccRat = 0.18) is illustrated in Figure 8.20. These examples represented the extremes of differences between an open and an occluded airway. Electrode positions were also considered as a possible factor in determining OccRat. Subcutaneous electrodes placed at the fifth rib (n=6) were compared to placement at the ninth rib (n=12). Fifth rib placement had a greater OccRat than ninth rib placement ($p<0.01$, Student's t test). In addition, SAME had a greater mean OccRat than CROSS ($p<0.03$, Paired t test). The statistical data for the occluded test is displayed in Table 8.4.

DISCUSSION

Impedance pneumography using epimysial electrodes placed on the diaphragm was useful for detecting diaphragm contraction. However, it was difficult to calibrate the tidal volume from the impedance measurements using a linear calibration factor. Improvements in the linearity of the impedance change/tidal volume ($\Delta Z/\Delta V$) calibration factor were found using a contralateral electrode placement. Impedance pneumography was not reliable for detection of airway obstruction without further research into electrode positioning and impedance waveform analysis. Differences between open and occluded airway measurements

were greater for placement of the subcutaneous electrode on the upper rib cage at the 5th intercostal space than placement at the 9th intercostal space.

Detection of Diaphragm Contraction

Diaphragm contraction was detected in all diaphragm pacing tests in this study using an impedance pneumograph. However, there were measurements of impedance increases, decreases and cases of both increases and decreases depending on the level of muscle activation. Although the nature of the impedance change was not important to detection of muscle contraction, it affected both the tidal volume calibration and the detection of an occluded airway

Factors Affecting Tidal Volume Calibration and Obstructed Airway Detection

The linearity of $\Delta Z/\Delta V$ for tidal volume calibration and detection of airway obstruction depended on the component of lung tissue impedance change in the impedance pneumograph measurements. We were certain of other factors affecting the impedance pneumograph because decreases in impedance were often measured during inspiration while the impedance of lung tissue increases when air is added.

The measured impedance included changes in total lung tissue impedance, changes in the geometry of the electrodes and ribcage and localized measurements of changes in lung and muscle impedance. Impedance measurements using two electrode pneumographs measure predominantly local changes in impedance (Cooley 1970). The small electrode size also limited the volume of tissue that was measured (Albisser 1974, Cooley 1970). Sixty percent of changes in transthoracic impedance are associated with changes in geometry rather than changes in lung impedance (Albisser 1974). For our system, the epimysial electrodes were attached

to a muscle, which changes position during breathing, thereby enhancing the geometry change of the recording system.

Due to the local nature of the impedance change measurements, we were concerned primarily with impedance changes of the diaphragm muscle, the lung tissue near the epimysial electrode, and the chest wall and lung tissue near the subcutaneous electrode. Diaphragm muscle resistivity may be affected during stimulation by altered blood perfusion to the muscle. Diaphragm thickness is also changed by muscle shortening during contraction. The effects of chest wall thickness are confirmed by the differences in measured impedance changes for subjects with slender, medium and heavy build (Baker 1965, Baker 1966a).

In addition to changes in diaphragm resistivity and thickness, the interelectrode distance also changes during stimulation. The decrease in impedance in some recordings (Figure 8.8) is most likely associated with a movement of the electrodes closer together. Decreases in impedance have also been measured with midaxillary electrodes placed on the lower rib cage (10th intercostal space) of humans (Logic 1967). The decreasing impedance was associated with a geometrical change in the rib cage from an elliptical to a circular cross section (Logic 1967).

Calibration of the Impedance Pneumograph using a Linear $\Delta Z/\Delta V$ Calibration Factor

Impedance pneumography for measuring diaphragm pacing depends on electrode placement to maximize the linearity of the $\Delta Z/\Delta V$ calibration factor. Impedance pneumography measurements with a large component of lung tissue impedance change will have a greater correlation with tidal volume. If there is a

significant component due to geometric changes or non-lung tissue impedance changes, the linearity of the tidal volume calibration is compromised.

We found that CROSS electrode placement resulted in greater linearity of $\Delta Z/\Delta V$ than SAME placement (Table 8.3). The superiority of the CROSS placement could be explained either by diaphragm impedance changes or by differences in the interelectrode distance changes. With the SAME configuration, the recording electrode was placed on the contracting muscle and measurements included changes in muscle impedance with contraction. The SAME configuration uses electrodes placed on the upper and lower ribcage that undergo the greatest changes in pressure during breathing (D'Angelo 1974b). Thus, the electrodes undergo greater motion, increasing the component of the impedance measurement resulting from changes in geometry. In either case, the component of the impedance pneumograph associated with lung tissue impedance changes would be smaller for the SAME configuration.

Lower rib cage recordings with the subcutaneous electrode placed between the 7th and 11th intercostal spaces provided the greatest $\Delta Z/\Delta V$ gains in the dogs in this study. Similarly, Baker and co-workers found that the greatest ratio of impedance change to volume change ($\Delta Z/\Delta V$) occurred at the eighth intercostal space in dogs for both spontaneous breathing and for diaphragm pacing (Baker 1966b). In humans the xiphoid level has been found to provide the greatest $\Delta Z/\Delta V$ (Baker 1966a). Although this location provides the greatest gain, it does not guarantee the greatest linearity of the $\Delta Z/\Delta V$ calibration factor.

The results of this study indicated that there was no change in the linearity of the $\Delta Z/\Delta V$ calibration factor with a change in the position of the subcutaneous

electrode. Placement at the 5th rib was used for 6 trials with no significant difference in the linearity of the $\Delta Z/\Delta V$ calibration factor compared to the 9th intercostal space placement. Improvements in linearity have been associated with electrodes placed on the upper rib cage. In humans, the $\Delta Z/\Delta V$ relation is more linear with midaxillary electrodes placed at the 5th intercostal space than the 7th intercostal space (Logic 1967). The lack of significance of electrode placement on the $\Delta Z/\Delta V$ calibration factor for the diaphragm pacing system tested in this study may be attributed to the difference in location of the epimysial electrode or to the small number of trials for upper ribcage placement.

We found that changes were required in the system prior to use of impedance pneumography for monitoring tidal volume for diaphragm pacing. When a SINGLE response was obtained using a CROSS setup, the linearity of the $\Delta Z/\Delta V$ calibration factor was comparable to the linearity obtained with transthoracic electrodes (Baker 1965). However, the conditions resulting in a SINGLE response were not identified. Possible modifications of the system include testing of new electrode locations, use of a different monotonic function to describe the $\Delta Z/\Delta V$ relation or use of a pattern recognition algorithm to associate tidal volume to the entire impedance waveform instead of just the magnitude of the impedance change.

Detection of an Obstructed Airway

The results of impedance pneumography tests using the epimysial electrode diaphragm pacing system demonstrated that a major component of the impedance changes is caused by something other than a change in lung tissue resistance. Two possible sources of other impedance changes are changes in the local distribution of air within the lung or a difference in the geometrical configuration of the thorax and

electrodes. Both sources are related to the changes in the upper and lower ribcage that occur with an open airway and an obstructed airway during diaphragm pacing.

The mechanics of the upper and lower rib cages were important for placement of electrodes for detection of an obstructed airway. Diaphragm activation causes an expansion of the lower ribcage and a reduction of the upper ribcage diameter (Peterson 1986). During diaphragm pacing against an occluded airway, the geometrical changes of the diaphragm and rib cage differ from the open airway by a slightly greater collapse of the upper rib cage. The similarity of the open and occluded impedance recordings reflected similarities in the respiratory mechanics and the difference between the open and obstructed airway impedance reflected the changes in impedance due to tidal volume and due to the difference in the upper rib cage geometry. As a result, we expected that airway obstruction would depend on electrode location.

The best recording electrode configuration for detection of an airway obstruction was SAME using electrodes placed on the fifth intercostal space. The preference for the fifth intercostal space compared to the ninth intercostal space was attributed to respiratory mechanics. The difference in geometrical change of the thorax at the level of the ninth intercostal space was small compared to the fifth intercostal space when stimulation against an open airway was compared to an occluded airway. Electrode location is important for detection of chronic obstructive pulmonary disease (COPD) using an impedance pneumograph. In human experiments, measurements at the fifth intercostal space were better for detecting COPD than measurements at the second intercostal space (Khalafalla 1970). Other electrode locations should be tested to determine whether the

difference between the impedance changes of an open and obstructed airway could be increased.

We concluded from this study that the impedance pneumograph used for diaphragm pacing with epimysial electrode implanted on the muscle may also be useful for detecting an airway obstruction. However, the impedance pneumograph must be set to detect the changes in impedance waveform instead of the changes in the impedance magnitude that occur with obstruction. In addition, the long term stability of the impedance recordings must be demonstrated in order to eliminate false negative alarms and the effects of changes in position must be described.

Advantages of Implanted Electrodes:

The implanted electrodes used during diaphragm pacing may eliminate artifacts associated motion against the skin and changes in impedance associated with changes in electrode contact. In addition, a significant amount of offset resistance is bypassed by placing electrodes beneath the skin (Pasquali 1967). A final advantage is that if implanted electrodes are used for predicting tidal volume, another calibration is not required. However, body position must be tested to determine the effects on the $\Delta Z/\Delta V$ gain and long term monitoring of tidal volume must be conducted to determine the robustness of the calibration.

From the results of this study, we concluded that impedance pneumography with electrodes implanted on the diaphragm is useful for detecting breathing events associated with diaphragm pacing. However, calibration of tidal volume and detection of airway obstruction is dependent on electrode location and may require analysis of the impedance waveform.

Appendix 8A: Circuit Diagrams

Figure 8A.1: Circuit diagram of current generator circuit.

Figure 8.1: Stimulating epimysial electrodes placed on the abdominal surface of the diaphragm. The electrodes were designed with a protruding hemispherical stimulating surface to provide uniform current density stimulation and consistent contact with the muscle.

Figure 8.2: View of the abdominal surface of the diaphragm. Epimysial electrodes were implanted at the phrenic nerve motor points. These electrodes were also used as one of the impedance pneumograph electrodes.

Figure 8.3: Experimental test setup for testing impedance pneumography for diaphragm pacing. Data acquisition and stimulator control were executed using custom LabVIEW® software. Airflow was measured using a Fleisch pneumotachometer sampled at 100 Hz and software integrated to obtain lung volume. Tidal volume was defined as the difference between the minimum and maximum lung volumes during a single breath. Impedance was also sampled at 100 Hz for comparison. Data acquisition began 0.5 s prior to stimulation and extended 1.0 s after stimulation. The stimulator delivered 1.5 s pulsetrains with stimulus interpulse interval and pulse charge controlled by the computer.

Figure 8.4: A block diagram of the impedance pneumograph that was used for detection of electrical activation of the diaphragm.

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Dog #760 12/7/94
Electrode 1, 20Hz, 24mA

Figure 8.5: Overlay of impedance and lung volume during electrical activation of the diaphragm. Example of increase in impedance with increasing lung volume. The impedance curve amplitude and offset were adjusted to superimpose the plots.

Dog #673 1/10/95
Electrode #1, 20Hz, 24mA

Figure 8.6: Overlay of impedance and lung volume during electrical activation of the diaphragm. This example demonstrated a decrease in impedance with an increase in lung volume.

Dog #760 12/7/94
Electrode #2, 20Hz, 18mA

Figure 8.7: Overlay of impedance and lung volume during electrical activation of the diaphragm. This example demonstrates a combination of increasing impedance components and decreasing impedance components.

Figure 8.8: Mosaic plot of the proportion of tests that resulted in increases, decreases, or both increases and decreases in impedance during electrical activation of the diaphragm. The recruitment test was used to obtain these data and the maximum tidal volume was grouped into three categories.

Vt max				
DIRECTION	.05-.15	.15-.25	>0.25	Total
BOTH	0	6	6	12
DECREASE	4	5	2	11
INCREASE	13	4	17	34
Total	17	15	25	57

Table 8.1: Tabulation of the data categorized by direction of impedance change and by maximum tidal volume. A total of 57 trials were used for the analysis.

Dog #589 10/5/94
Electrode 3, Recruitment Curve

Figure 8.9: Overlay of recruitment curves obtained using tidal volume and impedance changes. Tidal volume was defined as the maximum change in lung volume as measured by software integration of a Fleisch pneumotachograph flow signal. Impedance change was defined as the maximum change in impedance over the stimulation cycle.

Dog #589 10/5/94
Electrode 3, Recruitment Test
Impedance vs. Tidal Volume

Figure 8.10: Plot of maximum change in impedance against tidal volume. A linear regression line was fit to the data. $R^2 = 0.98$.

Dog #672 12/16/94
Electrode 1, IPI Test
Impedance vs. Tidal Volume

Figure 8.11: Plot of maximum change in impedance against tidal volume for the IPI test. $R^2 = 0.97$.

Dog #451 8/4/94
Electrode 1, Recruitment Curve

Figure 8.12: Recruitment curve with a poor correlation between impedance change and tidal volume. The impedance change decreases at the second major rise in tidal volumes (at 20 mA).

Figure 8.13: Linear regression of recruitment data of Figure 8.12. A linear regression of the impedance change vs. the tidal volume resulted in an R^2 of 0.01.

Dog #672 1/19/95
Electrode 1, IPI Test

Figure 8.14: A poor relation between impedance change and tidal volume for the interpulse interval (IPI) test. Nine different interpulse intervals were tested at a stimulus amplitude of 20 mA in 1.5 s pulsetrains.

Dog #672 1/19/95
Electrode 1, IPI Test
Impedance vs Tidal Volume

Figure 8.15: A linear regression of the data from Figure 8.14. The correlation coefficient was $R^2 = 0.49$.

Dog #451 8/4/94
Electrode 2, 20Hz

Figure 8.16: Changes in impedance measurements with stimulus amplitude. A 4 mA pulse resulted in a small decrease in impedance. When the stimulus amplitude was increased to 10 mA, the impedance increased during diaphragm activation. When the amplitude was increased further, the impedance again decreased with increasing lung volume.

Recruitment Curve

Dog #451 8/4/94

Electrode 2, 20Hz

Figure 8.17: Curve of tidal volume vs. current level. Tidal volumes defined as the maximum change in volume during a 1.5 s, 20Hz stimulus burst of a single diaphragm. The waveforms from Figure 8.16 occurred at the locations on the recruitment curve shown above.

Figure 8.18: Definition of SAME and CROSS classifications. The SAME classification had a stimulating and recording electrode located on the same hemidiaphragm. The other recording electrode was placed in the subcutaneous space of the thorax on the opposite side. The CROSS classification included electrode configurations with a recording electrode on the opposite hemidiaphragm of the stimulating electrode. The other recording electrode was opposite the abdominal recording electrode in the subcutaneous space of the thorax. A subcutaneous reference electrode at the sternum was used for all tests.

Test Type	Classification	Mean R 2	std dev	n
Recruitment	BOTH	0.54	0.29	12
	SINGLE	0.72	0.22	45
SINGLE > BOTH; Significant $p < 0.05$ Wilcoxon Rank Sum				
IPI	BOTH	0.67	0.27	7
	SINGLE	0.73	0.18	30
No Significant Difference $p > 0.05$ Wilcoxon Rank Sum				
Recruitment	CROSS	0.76	0.22	28
	SAME	0.59	0.25	23
CROSS > SAME; Significant $p < 0.01$ Wilcoxon Rank Sum				
IPI	CROSS	0.77	0.19	19
	SAME	0.65	0.20	16
CROSS > SAME; Significant $p < 0.05$ Wilcoxon Rank Sum				
Recruitment	ALL	0.68	0.24	57
IPI	ALL	0.72	0.20	37

Table 8.2: Summary of comparisons. Classifications are: BOTH is an impedance change that has increasing and decreasing components (Figure 8.4), SINGLE is an impedance change that was either increasing or decreasing for the entire range of the test, and CROSS and SAME are defined in Figure 8.18. The BOTH results accounted for a significant amount of nonlinearity for the recruitment tests. The CROSS configuration provided a more linear relation of tidal volume to impedance change than the SAME configuration for both the recruitment and the IPI tests.

Data Subset - Subcutaneous Electrode at 9th Rib				
Test Type	Classification	Mean R ²	std dev	n
Recruitment	CROSS	0.83	0.14	14
	SAME	0.57	0.24	14
CROSS > SAME; Significant p<0.01 Wilcoxon Rank Sum				

Table 8.3: Data subset with the subcutaneous electrode placed at the ninth rib. There were 14 trials each of CROSS and SAME electrode configuration. CROSS again resulted in a greater R² value. Traces with the BOTH response resulted in significantly lower R² than SINGLE responses (P<0.05, Wilcoxon Rank Sum). The IPI test was also checked, but the 7 pairs of CROSS/SAME did not show a significant difference.

Dog #673 2/9/95
Electrode 1, 20Hz, 16mA
Open and Occluded Airway

Figure 8.19: Comparison of the waveforms of an occluded airway and an open airway. This example demonstrated a difference between an open and an occluded airway (OccRat = 2.52). Three tests are superimposed for the open and the occluded airway for these stimulus parameters.

Dog #673 11/22/94
Electrode 1, 20Hz, 24mA
Open and Occluded Airway

Figure 8.20: Comparison of waveforms of an open airway and an occluded airway. This example demonstrated that there may be only a small difference in the impedance measurements for open and occluded airways (OccRat = 0.18). There are three tests for each of the open and occluded airway tests.

Test Type	Configuration	OccRat	std dev	n
Recruitment	Rib 5	1.38	0.88	6
	Rib 9	0.54	0.3	12
	Rib 5 > Rib 9; $p < 0.01$ Student's t test			
Recruitment	SAME	1.13	0.82	8
	CROSS	0.57	0.42	10
	SAME > CROSS; $p < 0.03$ Paired t test			
Test Type	Configuration	Mean R2	std dev	n
Recruitment	Open Airway	0.69	0.27	25
	Difference	0.57	0.24	25
	Open > Difference; $p < 0.15$ Wilcoxon Rank Sum			

Table 8.4: Comparison of the data from the occluded airway test. The difference between an occluded airway impedance measurement and an open airway impedance measurement is described by OccRat. Data indicated that detection of an airway occlusion was dependent upon electrode location with a preference for the SAME configuration and preferred placement of the subcutaneous electrode at the 5th rib rather than the ninth rib. The R^2 values for the linear regression of recruitment changes and tidal volume were calculated for an open airway and the difference between the open and occluded airway. The difference did not improve prediction of tidal volume.

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