Transvascular Nerve Stimulation Electrodes

by

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Abstract

Patients in intensive care units (ICU) who require mechanical ventilation (MV) for more than a week have an increased risk of medical complications, such as ventilator-acquired pneumonia and nosocomial infections, and are seven-times more likely to die in the ICU. The disused diaphragm muscle atrophies rapidly in ventilated patients, contributing to complications and frequent failure to wean from MV. Current phrenic nerve and diaphragm pacing systems require long, complicated, and risky surgery, unsuitable for those in the ICU. This study documents the prototype development of a simple, minimally invasive, transvascular device for electrically pacing the diaphragm intended to maintain diaphragm viability, reduce mortality, facilitate weaning from MV, shorten duration of ICU stay, and decrease hospitalization costs. Proof-of-concept, safety and stability data from acute and 3-week chronic pig experiments were analyzed. This thesis provides insight into endovascular electrode designs, fabrication, material selection, and configuration and orientation effects on phrenic nerve stimulation.

Keywords: phrenic nerve pacing; diaphragm pacing; transvascular nerve stimulation; endovascular electrodes; mechanical ventilation; diaphragm atrophy
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## Glossary

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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACC</td>
<td>Animal Care Committee</td>
</tr>
<tr>
<td>ALS</td>
<td>Amyotrophic Lateral Sclerosis</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>CO₂</td>
<td>Carbon dioxide</td>
</tr>
<tr>
<td>DP</td>
<td>Diaphragm Pacing</td>
</tr>
<tr>
<td>ECU</td>
<td>External Control Unit</td>
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<tr>
<td>EMG</td>
<td>Electromyography</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FES</td>
<td>Functional Electrical Stimulation</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>LIVE</td>
<td>Lungpacer Intravascular Electrodes</td>
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<tr>
<td>MV</td>
<td>Mechanical Ventilation</td>
</tr>
<tr>
<td>O₂</td>
<td>Oxygen</td>
</tr>
<tr>
<td>PET</td>
<td>Polyethylene Terephthalate</td>
</tr>
<tr>
<td>PNP</td>
<td>Phrenic Nerve Pacing</td>
</tr>
<tr>
<td>Pt-Ir</td>
<td>Platinum-Iridium</td>
</tr>
<tr>
<td>PTFE</td>
<td>Polytetrafluoroethylene</td>
</tr>
<tr>
<td>RF</td>
<td>Radio-Frequency</td>
</tr>
<tr>
<td>SCI</td>
<td>Spinal Cord Injury</td>
</tr>
<tr>
<td>SFU</td>
<td>Simon Fraser University</td>
</tr>
<tr>
<td>SVC</td>
<td>Superior vena cava</td>
</tr>
<tr>
<td>UBC</td>
<td>University of British Columbia</td>
</tr>
<tr>
<td>VAP</td>
<td>Ventilator-Acquired Pneumonia</td>
</tr>
<tr>
<td>VIDD</td>
<td>Ventilator-Induced Diaphragmatic Dysfunction</td>
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1. Introduction

Breathing is mediated by a change in volume of the thoracic cavity, which ultimately changes pressure gradients within the lungs. This natural phenomenon ensures proper oxygen and carbon dioxide levels within the body. However, critically ill patients in hospital Intensive Care Units (ICU) may experience impairment in their ability to breathe volitionally due to their underlying condition, which often requires the patient to be placed onto a Mechanical Ventilator (MV). When combined with sedation, mechanical ventilation interferes with the active contraction of the diaphragm. Although lifesaving, prolonged mechanical ventilation results in the complete absence of neural activation and mechanical activity of the diaphragm, the primary muscle involved in respiration, which is innervated by the left and right phrenic nerves. This prolonged neural and mechanical inactivity has been shown to induce diaphragm atrophy, proteolysis, and reactive oxygen species liberation, which can lead to Ventilator-Induced Diaphragmatic Dysfunction (VIDD) (Jung et al., 2010). In addition, mechanical ventilation is associated with substantial morbidity, mortality, inconvenience, and social stigma. Some handicaps experienced by these patients include (Horch & Dhillon, 2004):

A. Insufficient venting of the lungs, which can lead to accumulation of fluid in the lungs and susceptibility to infection
B. Anxiety and fear associated with machine dependence and tube disconnection
C. Interference with eating, drinking, and speaking due to the insertion of a tube into the trachea
D. Reduced mobility, which can lead to disuse atrophy of muscles and an overall decline in well-being
E. Reduced venous return because the lungs are pressurized
F. Embarrassment associated with the ventilator and attached tubing
Eighteen to sixty-nine hours of mechanical ventilation can cause the diaphragm muscle fibre cross-sectional area to decrease by 53 to 57% (Levine et al., 2008), which leads to slower patient recovery, higher incidences of Ventilator-Acquired Pneumonia (VAP), nosocomial infections, longer hospital stays, poor prognosis for recovery, and high cost of care. In the United States, it was estimated that more than 33% of patients required MV in the ICU (Dasta, McLaughlin, Mody, & Piech, 2005). Of these patients, over 20% were on MV for more than a week, with 40-60% of their ventilator time spent on weaning after their initial critical illness was resolved (Onders, 2011). If the time spent in the ICU is reduced by medical interventions, such as reducing the exposure to mechanical ventilation, the health of the patient will drastically improve and hospitalization savings will be substantial (Dasta, McLaughlin, Mody, & Piech, 2005).

To protect the diaphragm of ventilated patients from disuse atrophy and reduce associated problems, a viable alternative to mechanical ventilation is phrenic nerve or diaphragm pacing via electrical stimulation, resulting in a more natural form of artificial ventilation that closely mimics natural breathing. Short periods of electrical stimulation can prevent diaphragm atrophy in ventilator-dependent patients (Ayas, McCool, Gore, Lieberman, & Brown, 1999). Conventional pacing systems have been used for patients requiring long-term ventilatory assistance, such as those with Spinal Cord Injury (SCI). However, these methods are potentially damaging to the nerves and can cause infections due to the amount of surgery required and are too risky for those in the ICU. In addition, these pacers are expensive and difficult to retrieve (Hirschfeld, Exner, Luukkaala, & Baer, 2008), making them unsuitable for short-term MV patients. The need for a minimally invasive option that prevents respiratory failure while maintaining diaphragmatic function is apparent, and could save the healthcare system a substantial portion of their annual budgets while improving the overall health of the patient.

The Neurokinesiology Lab at Simon Fraser University (SFU), in conjunction with Lungpacer Medical Inc., aim to address this need by developing a phrenic nerve pacing system (Hoffer, 2008), utilizing an alternative, lower risk, minimally invasive surgical approach. Disposable transvascular stimulation electrodes that are percutaneously inserted, under local anaesthesia, into a main vein in the neck or thorax and are deployed in close proximity to both the left and right phrenic nerves, thus removing the need for surgical exposure of nerves or the diaphragm (Hoffer et al., 2010). This simpler
surgical approach will make it possible to pace electrically the phrenic nerves in synchrony or intermittently with each administered breath delivered by the mechanical ventilator, or as a stand-alone system. Such a pacing system is expected to prevent, reduce, or even reverse diaphragm atrophy that typically occurs in patients on mechanical ventilation, allowing the patient to wean off the ventilator faster and breathe volitionally once again.

This thesis will document the various experiments performed as well as the evolution of the electrode device into its final stages of prototype development in a pig model.

1.1. Anatomy and Physiology

Respiration, both involuntary and voluntary, is the end result of coordinated action of a number of muscles including the diaphragm, internal, parasternal and external intercostals, scalenes, sternocleidomastoids, abdominal muscles, and the muscles of the upper airway (Figure 1.1-1). The coordinated contraction of these muscles creates pressure changes in the thoracic and abdominal cavities that result in the movement of air into and out of the lungs. These pressure changes must be sufficient to overcome the intrinsic elastic recoil of the chest and the airflow resistance. The elastic recoil of the chest arises from the elastic properties of the lungs and the surface tension at the alveolar gas-liquid interface. The airflow resistance accounts for the pressure needed to overcome the frictional and viscous forces in the airways (Kreit & Eschenbacher, 1988).
The diaphragm is the primary inspiratory muscle, accounting for 70% to 80% of the air that inflates the lungs during quiet breathing (Reid & Dechman, 1995). It is unique in that it is a skeletal muscle required to function rhythmically from birth until death. During normal inhalation, the thoracic volume increases due to the contraction of the diaphragm and other muscles. As the thoracic cavity expands, the pressure within the lungs decreases and air is drawn into the lungs. During exhalation, the diaphragm relaxes allowing the thoracic cage to lower to its original position, which reduces the thoracic volume, increasing the pressure within the lungs and allowing air to be expired passively (Figure 1.1-2) (Tortora, 2008).
The diaphragm is innervated by the left and right phrenic nerves that originate from the superior branches from the ventral rami of cervical processes C3-C5, as shown in Figure 1.1-3. The phrenic nerves (green) descend from the spinal cord. In humans, the left phrenic nerve crosses adjacent to the left subclavian vein and the left brachiocephalic vein, while the right phrenic nerve crosses near the right subclavian vein and descends along the superior vena cava and the pericardium. However, various conditions can prevent brain stem control signals from being delivered via the phrenic nerves. These include injury to the spinal cord or brain stem, Amyotrophic Lateral Sclerosis (ALS), and decreased day or night ventilatory drive, such as central sleep apnea and Ondine’s curse. These conditions affect a substantial number of people, many turning to mechanical ventilation to breathe.
Figure 1.1-3. Anatomical View of the Location of the Phrenic Nerves

Note: The phrenic nerves (green) descending from the spinal cord towards the diaphragm (Icon Learning Systems, 1998)

Mechanical Ventilation is an artificial process by which air is pushed into the lungs to provide adequate levels of oxygen (O₂) and carbon dioxide (CO₂). This method of ventilation is typically used in the ICU to ventilate patients who cannot breathe volitionally. These patients are usually heavily sedated, which can suppress the central control of the diaphragm. Since the diaphragm does not receive proper input signals from the brain, but the body maintains proper gas levels, the diaphragm becomes inactivated and fails to contract as normal. Like any muscle that does not contract, the diaphragm becomes weak and begins to atrophy. As the diaphragm weakens, the chance of weaning the patient off the ventilator decreases, meaning the patient will require a longer period of recovery. This translates into higher incidences of infection, ventilator acquired pneumonia, decreased patient well-being, and higher hospitalization costs.
1.2. Functional Electrical Stimulation

Functional Electrical Stimulation (FES) is the application of electrical stimulation to excitable tissue to supplement or replace function that is lost in neurologically impaired individuals (Peckham & Knutson, 2005). FES has the ability to restore voluntary control of paralyzed muscle, partially restore sensory-motor integration, provide sensory cues, alleviate spasticity, and alleviate chronic pain. This is accomplished through the electrical activation of intact lower motor neurons using electrodes placed on or near the innervating nerve fibres. Appropriate electrical stimuli can elicit action potentials in the innervating axons, and modulating the stimulus parameters can regulate the strength of the resultant muscle contraction (Peckham & Knutson, 2005).

This section will review the physiological and technological principles of functional electrical stimulation applied to the neuromuscular system.

1.2.1. Physiological Principles of FES

The central nervous system (CNS) controls all skeletal muscles through nerves, which are made up of nerve fibres, called axons. Motor axons relay signals from the spinal cord to the individual muscles and have an intracellular resting membrane potential of roughly -70 mV. If the membrane potential is depolarized to or beyond a predetermined threshold value, approximately -50 mV, voltage-gated sodium ion channels in the membrane open and the inward flow of current initiates an action potential (Figure 1.2-1). An axon will only fire if its threshold is reached. This means that the electrical impulses must be of a certain magnitude to elicit a muscle contraction.
Figure 1.2-1. Normal Action Potential Propagation

Note: A potential above threshold reaches the trigger zone. Voltage-gated Na+ channels open and Na+ enters the axon. Positive charges flow into adjacent sections of the axon by local current flow. Local current flow from the active region causes new sections of the membrane to depolarize. The refractory period prevents backward conduction. Loss of K+ from the cytoplasm repolarizes the membrane (Martini & Bartholomew, 2008).

Extracellular stimulation via appropriately placed electrodes can produce localized electric fields and cause the cell membrane of nearby neurons to depolarize. If the depolarization reaches threshold, an influx of sodium ions from the extracellular space into the intracellular space initiates an action potential that usually propagates in both directions away from the source of stimulation (Figure 1.2-2). The action potential that propagates towards the brain will stop at the cell body. The action potential that propagates towards the muscle will cause a normal synaptic event across the neuromuscular junction and cause the muscle fibres to contract (Peckham & Knutson, 2005).
Figure 1.2-2. *Action Potential Propagation from Electrical Stimulation*

Note: The local presence of negative ions extracellularly causes positive ions to accumulate inside the membrane and change the net voltage, causing depolarization.

Skeletal muscles consist of motor units. Each motor unit is comprised of a motoneuron and the muscle fibres that it innervates. Individual motor units have been classified into four major types, which are based on mechanical and fatigue characteristics. These include Type I (slow twitch, fatigue-resistant, highly oxidative), Type IIa (fast twitch, fatigue-resistant, highly oxidative), Type IIx (fast twitch, fatigue intermediate) and Type IIb (fast twitch, fatigable, glycolytic) (A. F. DiMarco, 2009). Normally, small-diameter axons, which innervate slow twitch motor units, are activated first and are followed by larger motor units. This orderly recruitment of motor units is known as the size principle. Smaller motoneurons are more excitable because they have a smaller membrane surface area and higher input resistance. This results in smaller motoneurons having a lower recruitment threshold than larger ones and thus recruited first (A. F. DiMarco, 2009). However, with electrical stimulation, larger axons are activated first. This is due to the fact that the membrane electrical depolarization is greatest on the largest diameter axons, which results in the preferred activation of fast (Type II) motor units. Thus, with electrical stimulation, motor unit recruitment order is reversed and more fatigable units are activated first.

In healthy diaphragms, the muscle is converted from one with near equal proportions of Type I and Type II fibres to one consisting of uniform population of fatigue-resistant Type I fibres. However, in atrophied diaphragms, both Type I and Type II fibres become smaller, and the fatigue-resistant Type I fibres are transformed into fast-
fatigable Type II fibres (Levine et al., 2008). However, the application of continuous low-frequency electrical stimulation conditions the diaphragm and converts Type II into Type I fibres, which can help avoid muscle fatigue and improve muscle endurance (Garcia-Morato & De Vito, 2004).

1.2.2. **Technological Principles of FES**

FES operates under the fundamental principle that electrical stimulation generally activates the nerve rather than the muscle. This is due to the fact that the threshold charge needed to elicit muscle fibre action potential is much greater than the threshold for producing an action potential in neurons (J. Mortimer, 1981). Therefore, lower motor neurons and neuromuscular junctions must be excitable and their target muscles must be healthy. This is usually the case for patients in the ICU.

1.2.2.1. **Electrode Configuration**

At least two electrodes are required for electrical activation of neuromuscular tissue. The electrodes are usually arranged in a monopolar or bipolar configuration, with one active electrode that is placed near the target nerve. In monopolar stimulation, the second electrode, known as the return or reference electrode, is placed in a remote area close to less excitable tissue, such as tendon or bone. In bipolar stimulation, the return or reference electrode is placed near the active electrode. In multi-channel monopolar systems, fewer numbers of electrodes and electrode leads are required because only one reference electrode is used with several active electrodes. In contrast, multi-channel bipolar systems require more leads because each active electrode has its own return/reference electrode. This allows for greater selectivity and a more focused electrical field (Figure 1.2-2) (Grandjean & Mortimer, 1986).
Figure 1.2-2. Bipolar and Monopolar Electrode Configurations

Note: Comparison of bipolar and monopolar electrode configurations (Modified from Zygote Human Anatomy, 2012).

1.2.2.2. Stimulation Parameters

Stimulation is delivered as a train of electrical current pulses and is characterized by the pulse frequency, amplitude, and duration. Varying one or more of these parameters will ultimately vary the strength of the muscle contraction. The degree of muscle contraction is determined by the pulse frequency. A pulse frequency set at a low rate will create a series of muscle twitches. If the frequency is set at the fusion frequency, a smooth muscle contraction is created, due to temporal summation. Higher frequencies will produce stronger contractions, up to a maximum, but will also increase the rate of muscle fatigue. Therefore, high frequency stimulation is typically avoided. In general, the stimulation rate needed for the summation of muscle twitches is approximate 12 to 15 Hz (Peckham & Knutson, 2005).

Increasing the number of motor units being activated can also increase the strength of a muscle contraction, an effect known as spatial summation. To achieve this, the pulse amplitude and/or pulse duration must be increased. By increasing these...
parameters, the electrical charge injected also increases, which allows for a larger electrical field and broader region of activation, since electrical charge ultimately changes the electrical potential of the nerve. These changes allow for more axons and motor units to become activated, allowing for a stronger contraction (Crago, Peckham, & Thrope, 1980).

Typically, the pulse amplitude or duration is modulated while the pulse frequency is set at a low constant rate, which is needed to avoid muscle fatigue. It is important to use stimulus parameters that are appropriate for the dimensions and material composition of the electrodes, such that the injected charge density per phase remains within safe limits, thus preventing electrode corrosion and tissue damage, which is described in the section below (J. Mortimer, 1981).

1.2.2.3. Stimulus Waveform

Stimulus waveforms are either monophasic or biphasic in shape. Monophasic waveforms consist of a repeating unidirectional (cathodic) pulse, whereas biphasic waveforms consist of a repeating pulse that has a primary cathodic (negative) phase, followed by secondary anodic (positive) phase (Peckham & Knutson, 2005). The primary cathodic phase elicits an action potential in nearby axons, and the secondary anodic phase balances and neutralizes the charge injection of the primary phase. This is necessary to reverse the electrochemical processes, such as electrode corrosion, that can occur at the electrode-tissue interface during the primary phase, which could potentially be damaging to the surrounding tissue (Figure 1.2-3) (J. Mortimer, 1981).

Typically, biphasic pulses are used for stimulating electrodes. Each pulse has a cathodal and anodal phase, with amplitudes and durations resulting in an overall zero net charge for the pulse (charge-balance). By doing so, damage to the electrodes and surrounding tissue is avoided. Theoretically, the balancing of charge is important, but in practice this can be difficult to achieve. This is due to the fact that an electrode may be polarized during delivery of the pulse to a point that tissue or electrode-damaging irreversibility occurs, such as electrolysis of water, which leads to pH changes and gas formation, electrode dissolution due to the oxidative formation of soluble metals, or corrosion. Oxidation of organics, such as glucose and tyrosine, or the reduction of oxygen is also possible. Although there is concern regarding tissue damage, tissue
degradation induced by the different irreversible processes is not well established. Therefore, stimulus waveforms must be limited to current and charge densities that allow for reversible processes that inject cathodic and anodic charges at a finite rate (Cogan, 2008).

Figure 1.2-3. Monophasic and Biphasic Stimulation

Note: Depiction of the various charge-balanced waveforms. $I_c$: cathodic current; $I_a$: anodic current; $t_c$: cathodic half-phase period; $t_{ip}$: interphase dwell; and $t_a$: anodic half-phase period (Cogan, 2008).

One study examined and quantified safe charge injection limits for stimulation electrodes (Cogan, 2008). Platinum electrodes, which are commonly used for stimulation electrodes because of their biocompatibility, inertness, and high corrosion resistance, have a charge-injection limit of 300 to 350 µC cm$^{-2}$. For Tantalum/Ta$_2$O$_5$ electrodes, the maximum charge injection limit is approximately 500 µC cm$^{-2}$. Finally, for Titanium nitride electrodes, the maximum charge injection limit is approximately 1000 µC cm$^{-2}$. Therefore, for the design of the stimulation electrodes, these limits must be respected.

1.2.2.4. Stimulator Type

Stimulators are designed to regulate either current or voltage. Voltage-regulated stimulators output a voltage, which means the delivered current is dependent on the tissue impedance at the electrode interface (Ohm’s Law; $V=IR$). As the tissue impedance increases, the delivered current decreases, which minimizes the possibility of tissue burns from high current densities. However, with voltage-regulated stimulators, the motor response is more variable than current-regulated stimulators. This is due to the impedance-dependent currents. With current-regulated stimulators, the current is directly
controlled and does not depend on the impedance of the tissue. Therefore, the charge
delivered per stimulus pulse can be guaranteed, which means that the motor response is
consistent and repeatable. Typically, voltage-dependent stimulators are used for surface
stimulation applications, whereas current-regulated stimulators are used for implanted
electrodes (Peckham & Knutson, 2005).

1.2.2.5. Stimulation Electrodes

Stimulation may be delivered through surface, percutaneous, or implanted
systems (Figure 1.2-4). Surface systems, also known as transcutaneous systems, utilize
electrodes that are placed directly on the skin. These electrodes are connected to a
imulator via flexible electrode leads. The electrodes are usually placed over the nerve
or over the motor points, an area where the strongest and most isolated contraction is
achieved at the lowest stimulation level, of the muscles to be activated. The advantage
of using this type of system are that the electrodes are non-invasive and the stimulator
uses relatively simple technology. However, after repetitive donning and doffing of the
system, skill and patience is required to accurately place the electrodes in the
appropriate locations. Furthermore, it can be difficult to achieve isolated contractions or
activate deep muscles, which would require higher levels of stimulation. This may
generate painful sensations because pain receptors are activated. Finally, the external
components of the system, such as the electrodes, leads, and stimulator, may attract
unwanted attention from others (Peckham & Knutson, 2005).

**Figure 1.2-4. Types of Stimulation Electrodes**

![Stimulation Electrodes Diagram]

Note: Stimulation electrodes can either be mounted on the skin, on the muscle, or directly
implanted within the body (Peckham & Knutson, 2005).

Percutaneous systems utilize intramuscular electrodes that pass through the skin
and are implanted directly into the muscles to be activated. This type of system has the
ability to activate deep muscles while providing isolated and repeatable muscle
contractions. Furthermore, there is a lower chance of producing pain during stimulation since sensory afferents in the skin are bypassed. The electrode is inserted through the skin and implanted into the muscle using a hypodermic needle, with the electrode leads exiting the skin and connected to an external stimulator. A large surface electrode is usually used as the return/reference electrode. The skin at the electrode site must be cleaned, dressed, inspected, and maintained to reduce the risk of complications (Knutson, Naples, Peckham, & Keith, 2002). Instead of performing the necessary surgery to implant a system, percutaneous electrodes are usually used to assess the patient and determine whether a fully implanted system can be used (Peckham, Mortimer, & Marsolais, 1980). This saves the patient from highly invasive surgery and the associated risks involved.

Implanted systems are designed for long-term use. This system embeds the electrodes, the electrode leads, and stimulator system within the body. The electrodes may be implanted on the muscle surface (epimysial) (Keith et al., 1989), within the muscle (intramuscular) (Mayr et al., 1993), adjacent to a nerve (epineural) (Naples, Mortimer, Scheiner, & Sweeney, 1988), or around a nerve (cuff) (Loeb & Peck, 1996). Epimysial electrodes are typically used for upper (Kilgore et al., 2003) and lower (Uhlir, Triolo, Davis, & Bieri, 2004) extremity applications. Furthermore, they are especially useful for activating broad, superficial, or thin muscles. Intramuscular electrodes allow deeper and smaller muscles to be activated. Nerve-based electrodes are used when it is difficult to access the target muscle directly or when complete muscle recruitment can be obtained by stimulating the nerve. Unlike percutaneous electrodes leads, the electrode leads are usually larger and more durable, since they do not need to pass through the skin. Implanted stimulators are usually encased within a titanium enclosure, which can also act as a return/reference electrode, and is usually powered and programmed through a radio-frequency (RF) telemetry link to an external control unit (ECU). A circular antenna coil connected to the ECU is taped to the skin over the implanted stimulator, where it receives and transmits information to the implanted stimulator (Figure 1.2-5). This eliminates the need for replacing the implanted stimulator when the battery drains or fails (Peckham & Knutson, 2005).
1.3. Phrenic Nerve and Diaphragm Pacing Systems

Electrical stimulation can be used to activate the diaphragm through the phrenic nerve or motor points in the diaphragm. This technique of stimulating the phrenic nerves, known as phrenic nerve pacing (PNP), was introduced in the 1960s by Dr. William Glenn and his colleagues at Yale University (Glenn et al., 1964). Since then, advances in research have allowed the diaphragm to be activated via nerve or intramuscular electrodes, each having their own advantages and disadvantages. Regardless of the stimulation type, phrenic pacing requires the availability of intact phrenic nerves, lungs, and diaphragm muscle, such as those in the ICU.

Those in the ICU are initially supported with mechanical ventilation since this is the most expeditious way of restoring ventilation. While effective, there is significant discomfort, limitation of mobility, and complications such as pneumonia and barotrauma. Furthermore, the diaphragm muscle is known to atrophy rapidly and profoundly (Levine et al., 2008), which contributes to frequent failure to wean from MV (Vassilakopoulos & Petrof, 2004), leading to longer stays in the hospital. Therefore, if PNP and diaphragm pacing (DP) can be utilized early in patient recovery, it can reduce or prevent many of the problems associated with MV, especially in preventing diaphragm atrophy. There are many potential benefits of PNP and DP, which include (A. DiMarco, 2010):
A. Improved Quality of Life
   1. Subjective sense of more normal breathing
      a. Utilization of breathing muscles
      b. Negative pressure respiratory muscles
   2. Reduced anxiety and embarrassment
      a. Elimination of ventilator noise
      b. Elimination of fear of ventilator disconnection
      c. Elimination of ventilator tubing
      d. Daytime closure of tracheostomy
   3. Improved comfort level
      a. Elimination of pull of ventilator tubing
      b. Negative pressure breathing
   4. Improved speech
   5. Restoration of olfactory sensation
   6. Increased mobility
      a. Easier transport outside the home
      b. Easier transfer to and from bed

B. Reduced Overall Costs
   1. Reduction or elimination of ventilator supplies
   2. Reduced level of nursing and respiratory therapy services

However, there are many potential disadvantages of using PNP and DP systems as well, which include (A. F. DiMarco, 2009):

A. Technical Malfunction
   1. Battery failure
   2. Breakage of antenna wires
   3. Receiver failure
   4. Electrode malfunction
   5. Breakage of implanted connecting wires

B. Surgical Complications
   1. Mechanical Injury to the phrenic nerve
   2. Iatrogenic injury
   3. Fibrosis and/or tension on the nerve
4. Upper airway obstruction following tracheostomy closure
5. Infection

Currently, there are four commercially available PNP and DP systems, which are open-looped systems that have predetermined inspired volumes and respiratory rates. The pattern of ventilation achieved during stimulation does not account for changes in metabolic needs or other adjustments that are normally made during speech and swallowing. Although important, this is not a major limitation, due to the relatively constant metabolic needs in spinal cord patients and those in intensive care.

All the current PNP systems consist of internal and external components, with each system employing RF transmission. The electrodes, RF receivers, and connecting wires are surgically implanted within the body, whereas the power supply, RF transmitter, and antenna wires are positioned outside the body. The transmitter generates an RF signal, which is inductively coupled to the implanted RF receiver using antenna wires. The signal is then demodulated by the receiver, converting it into an electrical signal that is transmitted to the electrodes via the electrode leads. Typically, PNP uses electrodes that are surgically placed on the phrenic nerves via a thoracotomy (Glenn et al., 1964; Glenn et al., 1973). On the other hand, DP systems have electrodes surgically placed into the diaphragm via intramuscular electrodes, with the electrical leads exiting the skin and connected to an external power supply (A. F. DiMarco et al., 2002; A. F. DiMarco, Onders, Ignagni, Kowalski, & Mortimer, 2005).

Commercially available manufacturers include Avery Biomedical Devices Inc. (Commack, NY, USA), Atrotech OY (Tempere, Finland), MedImplant Biotechnisches Labor (Vienna, Austria), and Synapse BioMedical Inc. (Oberlin, OH, USA). Currently, the Avery and Synapse systems are Food and Drug Administration (FDA) approved and available in the United States. The Atrotech OY system is available in Europe and is currently being used under an Investigational Device Exemption from the FDA in the USA. The MedImplant system is mainly used in Austria and Germany. The cost of the systems can range between $50,000 to $60,000 U.S. Dollars (Horch & Dhillon, 2004). Up to an additional $20,000 may be needed for the surgical procedure, hospitalization, and medical follow-up.
This section will describe the available diaphragm and phrenic nerve pacing systems.

1.3.1. **Avery Biomedical Devices, Inc. (USA)**

In the 1960s, Dr. William Glenn and his colleagues at Yale University developed and marketed the first available phrenic nerve pacing system at Avery Laboratories. The basic science and clinical studies performed by Dr. Glenn et al. has allowed this system to be the most widely employed and commercially available phrenic nerve stimulation device worldwide. The electrodes consist of a semicircular platinum-iridium (Pt-Ir) ribbon embedded in molded silicone rubber (Figure 1.3-1), with the nerve placed in a trough in the electrode. The Mark IV transmitter, which is powered by 9 V batteries, is portable and controls the respiratory rate, inspiratory time, stimulus amplitude, and pulse interval (Figure 1.3-2). In addition, the system allows biofeedback control from pulse oximetry and CO₂ monitoring. Transtelephonic monitoring is also available allowing the pacers electronic output and phrenic nerve/diaphragm neurophysiologic response to be monitored by telephone (Figure 1.3-3) (Horch & Dhillon, 2004).

**Figure 1.3-1. Avery Biomedical – Monopolar Electrode and RF Receiver**

Note: Monopolar electrode mounted on a silicone rubber sheet and connected to a RF receiver (Ginsburg, 2010).
Figure 1.3-2. Avery Biomedical – Battery-Powered RF Transmitter and Antennas

Note: External RF transmitter and antenna used in the Avery Biomedical System (Ginsburg, 2010).

Figure 1.3-3. Avery Biomedical – Transtelephonic Monitor

Note: Transtelephonic monitoring system used to monitor electronic output and phrenic nerve/diaphragm neurophysiologic response (Ginsburg, 2010).
This system typically uses half-cuff (180°, monopolar) electrodes as the interface with the nerve. A half-cuff electrode design has been found to exhibit lower risk of phrenic nerve damage; however, increased stimulation currents are typically needed to achieve full activation of the phrenic nerve. A full-cuff (360°, bipolar) design is also available for patients with implanted cardiac pacemakers. However, these electrodes increase the risk of phrenic nerve injury due to abnormal pressures on the nerve and from circumferential scarring (Dobelle et al., 1994). For bilateral stimulation, a cuff must be placed on each phrenic nerve. These electrodes are surgically placed adjacent to the phrenic nerves in the thorax through an incision in the second or third intercostal space on the anterior chest wall (J. A. Elefteriades & Quin, 1998). Next, a test probe is used to verify the phrenic nerve by watching for twitches in the diaphragm. Once confirmed, the nerve is placed within the half-cuff electrode such that the Pt-Ir electrode is in contact with the nerve (Figure 1.3-4). The electrode is then sutured to the pleura to prevent migration and drift. Finally, the electrode lead wires are tunnelled subcutaneously to a flat region in the lower rib cage, where the implantable receiver and return/reference electrode are placed (Figure 1.3-5) (J. A. Elefteriades & Quin, 1998).

Figure 1.3-4. Avery Biomedical – Placement of a Monopolar Electrode

Note: Surgically implanting a monopolar half-cuff electrode around the phrenic nerve (Ginsburg, 2010).
1.3.2. **Atrotech OY (Finland)**

The Atrotech System, developed at Tampere University of Technology in Finland, has been in use since 1980 and utilizes quadripolar electrodes with four evenly spaced contacts around the phrenic nerve (Aiyar & Mortimer, 2006). The electrode consists of two connected strips of Teflon, each containing two platinum electrode contacts. One strip is placed above the nerve and the second below the nerve, with a 5 mm separation between the two strips. These strips are positioned symmetrically around the nerve along its long axis via a thoracotomy (Figure 1.3-6). For bilateral stimulation, electrodes must be placed on each phrenic nerve. Each of the four contacts serves as a cathode, and a contact on the opposite side of the nerve acts as the anode. This means that there is no need for a remote return/reference electrode (Aiyar & Mortimer, 2006).
Each quadrant of the nerve, which supplies a specific set of motor units, is stimulated sequentially during the inspiratory phase at a stimulus frequency of 5-6 Hz. Combining all of the quadrants of the nerve results in a smooth contraction of the diaphragm, usually at the fusion frequency of 20-25 Hz. Multi-pole sequential stimulation is intended to reduce fatigue by activating motor units only one-fourth of the activation time that occurs with conventional monopolar stimulation. This allows for a greater time for recovery and reduced risk of fatigue (Oda, Glenn, Fukuda, Hogan, & Gorfien, 1981).

The stimulator, which is placed in a subcutaneous pocket on the lower rib cage, allows for the adjustment of the respiratory rate and tidal volume to accommodate for the changing needs of the patient (e.g. coughing, changes in posture). The stimulator, which is powered by a 12 V battery with a backup 9 V Ni-Cd, which are both rechargeable, has a fixed pulse width of 0.2 ms, but adjustments can be made to the stimulus amplitude, frequency, inspiratory time, and ramp size. To do so, however, an external programming unit is needed (Figure 1.3-7) (Horch & Dhillon, 2004).

**Figure 1.3-7. Atrotech – Electrodes, Antenna, and Transmitter**

Note: Various components in the Atrotech system, including electrodes, antennas, and transmitters (P. P. Talonen, Baer, Hakkinen, & Ojala, 1990).
1.3.3. **MedImplant Biotechnisches Labor (Austria)**

The MedImplant system uses a group of electrodes to activate different regions of the nerve. Unlike the Avery or Atrotech systems, the MedImplant system only requires one RF receiver for bilateral stimulation. For this system, electrodes are sutured to the epineurium of the phrenic nerves, which has four loops (0.8 mm in diameter) that surround the nerve (Figure 1.3-8). The nerve tissue between each electrode lead provides different stimulation compartments that activate different regions of the nerve. To stimulate the nerve, the four contacts are activated sequentially by a technique called “carousel stimulation.” This technique changes the electrode combination and sequence of contacts that are used as the active and return/reference electrodes with each breath. Up to sixteen different electrode combinations can be individually adjusted for each nerve. By doing so, there is a reduced incidence of fatigue since there is a greater amount of time for the phrenic nerve and diaphragm to recover. As with the other devices, stimulus amplitude, pulse interval, respiratory rate, and inspiratory time can be independently adjusted (Mayr et al., 1993; Thoma et al., 1987).

![Figure 1.3-8. MedImplant – Electrodes and Pacing System](image)

Note: MedImplant electrodes (left) with the pacing system (right) (Creasey et al., 1996).

1.3.4. **Synapse Biomedical Inc. (USA)**

The Synapse Biomedical system uses electrodes anchored near phrenic nerve branches in the diaphragm muscle (A. F. DiMarco et al., 2002; A. F. DiMarco, Onders, Ignagni, Kowalski, & Mortimer, 2005; M. L. Nochomovitz, Dimarco, Mortimer, & Cherniack, 1983; Peterson, Nochomovitz, DiMarco, & Mortimer, 1986). This can be more advantageous as the electrodes can be placed less invasively, via laparoscopic
surgery, than the conventional phrenic nerve pacing systems, via thoracotomy. Furthermore, the surgical procedure can be performed on an outpatient basis, reducing the cost significantly. Finally, the potential of damaging the phrenic nerves is virtually eliminated since there is no manipulation of the nerves.

Four laparoscopic ports are made through the abdominal wall to access the abdominal cavity. These ports are used for visualization, diaphragm mapping, and the insertion of surgical tools (Figure 1.3-9). First, a mapping tool is used to determine the appropriate placement of the electrodes. Stimulus currents are provided to the mapping tool and the inspired volume is measured. Several locations are tested and recorded to determine the location of the phrenic nerve branches. Next, with these surgical tools, a pair of specially designed stainless steel electrodes (Figure 1.3-10) is placed in each hemi-diaphragm near the phrenic motor points (Figure 1.3-11). Finally, a fifth electrode is placed under the skin and acts as a return/reference electrode. Typically, higher stimulus currents in the range of 24 to 25 mA are necessary to adequately stimulate the phrenic nerves. This is much higher than the electrodes that are placed directly on the nerves, which range between 1 and 2 mA. The electrodes leads then exit the skin where they are connected to the control unit (Figure 1.3-12). Since the leads exit the skin, there is a risk of infection and damage to the leads (A. DiMarco, 2010).

**Figure 1.3-9. Synapse Biomedical – Laparoscopic Ports**

![Laparoscopic Ports Diagram](image)

Note: Four laparoscopic ports are made through the abdominal wall to access the abdominal cavity. These ports are used to visualize, map the diaphragm, and insert surgical tools (A. DiMarco, 2010).
**Figure 1.3-10. Synapse Biomedical – Intramuscular Electrodes**

Note: Specially designed electrodes using 316 stainless steel and other biocompatible materials. Anchoring technology specifically for long-term implantation into the diaphragm muscle (Synapse Biomedical Inc., 2012).

**Figure 1.3-11. Synapse Biomedical – Phrenic Motor Points in the Diaphragm**

Note: Phrenic nerve motor point regions in the diaphragm (A. DiMarco, 2010).

**Figure 1.3-12. Synapse Biomedical – Control Unit**

Note: Synapse Biomedical control unit provides the timing and control of the stimulus (Synapse Biomedical Inc., 2012).
1.4. Transvascular Nerve Stimulation

1.4.1. Theory

Transvascular nerve stimulation activates nerves through blood vessels. There are advantages of using this method over the conventional methods, as there is no direct contact or manipulation of the phrenic nerves, meaning there is no risk of damaging the nerves. Furthermore, blood vessels are easily accessible, meaning electrodes can be inserted into the vessels with great ease, with less surgical time, and with less invasive surgery. However, to stimulate nerves at a safe level, the nerves must be in close proximity to the blood vessel. This prevents unwanted stimulation of surrounding muscles and nerves.

Stimulating nerves transvascularly is not a novel concept. Many have successfully experimented with transvascular nerve stimulation for the vagus nerve (Thompson et al., 1998) and other cardiac nerves (P. Schauerte, Scherlag, Scherlag, Jackman, & Lazzara, 2000; P. N. Schauerte et al., 1999). In 1966, Daggett et al. proposed and demonstrated the concept of transvascular phrenic nerve stimulation for artificial respiration (Daggett, Piccinini, & Austen, 1966). In these experiments, a special electrode catheter was inserted through the lumen of the superior vena cava and placed in the right phrenic nerve projection. The fact that the right phrenic nerve is directly adjacent to the superior vena cava wall was a clear advantage of this method.

In 1968, Escher et al. also successfully stimulated the left and right phrenic nerve transvenously (Escher et al., 1968). A standard cut down operation was used to expose the external jugular vein and left pulmonary artery in two dogs and in two human patients. Next, to stimulate the right phrenic nerve, a 6 Fr (2 mm OD) transvenous electrode catheter was inserted through the external jugular vein and positioned in the superior vena cava. For the left phrenic nerve, the electrode catheter was placed in the left pulmonary artery. They successfully activated the diaphragm. However, they did not further pursue this because of the “wealth of alternative respiratory supportive equipment available.”

However, in the 1980s, studies were performed to determine whether transvascular phrenic nerve stimulation was as effective as direct nerve stimulation
(Planas, McBrayer, & Koen, 1985). In these experiments, the right phrenic nerve was isolated in the neck region and bipolar platinum electrodes were placed directly on the phrenic nerve of dogs. For transvenous phrenic nerve stimulation, an electrode catheter, under fluoroscopic guidance, was inserted through the femoral vein and positioned in the inferior vena cava, 2 to 3 cm above the right hemi-diaphragm. The electrode catheter consisted of two 3 mm wide platinum electrodes at the distal tip separated by a distance of 14 mm. They concluded that transvascular stimulation could be used in lieu of direct nerve stimulation.

1.4.2. Technology

One of the reasons the original transvascular nerve stimulation concepts did not develop into a commercial product was mainly due to their design of the electrodes. Previous electrode designs placed an electrode catheter within the blood vessels, usually a vein since they are thinner walled, meaning the electrode would be closer to the nerves. This electrode would be able to float freely and randomly within the vein, which typically meant that higher and more variable currents were needed. In addition, the electrical currents would easily shunt through the blood, since blood is a low-resistance conductive medium, as it consists of various electrolytes. This has the potential to damage surrounding vessel walls and organs, via tissue burns, as well as stimulate surrounding structures and nerves, such as the vagus nerve, which can lead to bradycardia.

The Neurokinesiology Lab at Simon Fraser University (SFU), in partnership with Lungpacer Medical Inc., is evaluating an alternative, lower risk, minimally invasive surgical approach for diaphragm pacing (Hoffer, 2008) where specially designed disposable transvascular electrodes (Hoffer et al., 2010) are inserted under local anaesthesia, into main blood vessels in the neck or thorax, such as the superior vena cava, brachiocephalic veins, subclavian veins, and external jugular veins. For bilateral stimulation, electrodes are deployed in close proximity to both the left and right phrenic nerves, thus removing the need for surgical exposure of the nerves or the diaphragm (Figure 1.4-1). This system is designed to work either in synchrony or intermittently with a MV or as a stand-alone system. By contracting the diaphragm in synchrony/intermittently with MV, it is expected that such a system will prevent, reduce,
or even reverse diaphragm atrophy that typically occurs in patients on MV, such as those with spinal cord injury or those in the ICU. This will ultimately help patients wean off MV at a quicker rate, reduce the adverse effects associated with MV, and reduce hospitalization costs.

*Figure 1.4-1. Lungpacer Medical Inc. Concept*

Note: Lungpacer Medical Inc. concept where intravascular electrodes are percutaneously inserted through the left subclavian vein (LSV) and superior vena cava (SVC) and placed near the left (LPN) and right (RPN) phrenic nerves (yellow) that innervate the diaphragm (green) (Hoffer et al., 2010).

This technique deviates from previous transvascular stimulation designs as it uses a proprietary technique whereby a flexible insulating backing, which contains multiple electrode contacts, is used to minimize current shunt loss through the blood (Hoffer, 2008). Essentially, this design is an “inside-out” nerve cuff, in which the stimulation is directed outwards rather than inwards (Figure 1.4-2). In addition, this insulating backing ensures that the electrode contact is in close intimacy with the vessel wall. This feature reduces the variability in location and orientation of the electrodes. Once current is supplied to these electrode contacts, electric fields are generated and directed outwards, towards the surrounding structures. If the phrenic nerve is present within the electric field lines, and if the supplied current from the control unit is high enough to invoke an action potential, the phrenic nerves are activated which eventually causes the diaphragm to contract.
**Figure 1.4-2. Inside-Out Nerve Cuff**

Note: An inside-out nerve cuff directing electric field lines towards surrounding nerves and structures (Hoffer, 2008).

### 1.4.3. Computer Simulation and Modeling

Before electrode prototypes were developed, computer simulation and modeling was completed by Jessica Tang of the Neurokinesiology Lab to determine if an insulating backing reduces the activation current needed to stimulate the phrenic nerves transvascularly (Hoffer et al., 2010). Using COMSOL Multiphysics 3.3a (COMSOL Inc., Stockholm Sweden), a graphical environment useful for changing parameter values, a 3D model was used to vary the electrode locations, insulation thickness, and inter-electrode distances.

For this computer simulation, two electrode types were tested and their stimulation efficiencies compared. One electrode type utilized a flexible endovascular insulating electrode cuff (0.5 mm thick silicone) that was placed intimately against the vein wall, with two electrode contacts facing outwards. Another electrode type utilized a 2 mm outer diameter (OD) vessel dilator with two electrode contacts on the outer surface. In both cases, the cathode and anode were placed 90° apart in a plane transverse to the vein and parallel to the phrenic nerve (Figure 1.4-3).
Note: A) Electrode cuff with cathode electrode (red) optimally located inside the vein wall and towards the phrenic nerve. B) Electrode cuff rotated 45° away from its best position. C) A 2 mm OD (6 Fr) dilator electrode contacting the vein wall at its best location and orientation with respect to phrenic nerve. D) Dilator electrode displaced from the vein wall and phrenic nerve (Hoffer et al., 2010).

Another model evaluated how electrode rotation and translation along the vein affected stimulation efficacy. First, varying degrees (-180° to +180°) of electrode rotation, with respect to the optimal (ventral; 180°) position, were evaluated. By varying the electrode rotation, the electrode distance to the nerve and the electrical field that is generated is also affected, which ultimately affects how much current is needed to activate the nerve. Secondly, varying the translational distance of the electrode with respect to the nerve also affects the amount of current needed to activate the nerve. If the electrode is close to the nerve, less current is needed, but if the electrode is far from the nerve, more current is necessary. However, increasing the current has the potential
of damaging vessel walls as well as stimulating other structures, such as other nerves or muscles.

After running these simulations, it was found that, with the electrodes in the ventral position (180°) of the vessel, the electrode with the insulating sheet required three times less current than the lead-type dilator electrode (Figure 1.4-4). In addition, the model predicts that 90° rotation away from the optimal position results in a 5-fold reduction in nerve stimulation efficacy, and a 180° rotation results in 50-fold reduction in stimulation efficacy (Figure 1.4-5). Finally, the model predicts that advancing the cathode towards and then past the nerve will result in a steep parabolic function. It was found that a displacement of 2 cm from the optimal location could result in a 10-fold reduction in stimulation efficacy (Figure 1.4-6).

Figure 1.4-4. *Stimulation Potentials Reaching the Phrenic Nerve*

Note: Stimulation potentials at the phrenic nerve as a function of cathodic potentials generated with the intravascular electrode cuff (red) and dilator (blue). Approximately three-times less current was needed to activate the phrenic nerve using an insulating layer (Hoffer et al., 2010).
Figure 1.4-5. Rotational Dependence of Electrodes

Note: Stimulus efficacy plotted against cuff rotation angle. A $90^\circ$ rotation away from the optimal position results in a 5-fold reduction in nerve stimulation efficacy. A $180^\circ$ rotation results in 50-fold reduction in stimulation efficacy (Hoffer et al., 2010).

Figure 1.4-6. Distance Dependence of Electrodes

Note: Model of efficacy plotted against the distance along the vein. Displacement of 2 cm from the optimal location could result in a 10-fold reduction in stimulation efficacy (Hoffer et al., 2010).
With these findings, it is suggested that transvascular stimulation is highly dependent on electrode design, location, and orientation. The clinical and commercial success of these endovascular electrodes will require recruiting the phrenic nerves with low currents and with high selectivity, to avoid activating surrounding structures and nerves.

1.5. Purpose of Thesis

The main hypothesis that drives this research project is electrodes with an insulating backing can be used to safely and efficiently activate the phrenic nerves transvascularly. Furthermore, it is hypothesized that electrode design, location, and orientation are important for safe and efficient transvascular nerve stimulation.

To test these hypotheses, the Neurokinesiology Lab is developing intravascular electrodes that can be safely and rapidly inserted intravenously, deployed next to the phrenic nerves, and safely removed when the patient can breathe spontaneously again. Other projects in the Neurokinesiology Lab are related to the computer simulation of nerve cuffs, development of a stimulation system and various pacing modes, development of experimental software and tools to expedite electrode placement, development of non-invasive tools to capture diaphragm activity, quantify diaphragm muscle length changes and atrophy, as well as the development a human clinical trial to test many aspects of this system. These projects are detailed elsewhere. Specifically, this thesis will document quantitative and qualitative findings relating to electrode configurations, insulative properties, construction details, stimulation efficacy and the rationale behind the evolving design changes of the prototype intravascular electrodes tested in animal experiments in 2009-2011.

1.5.1. Basic Requirements and Research Questions

Stimulating transvascularly is not a novel concept; however, stimulating transvascularly with an insulating layer is a new frontier of research. Information regarding device size and shape, electrode design, the number of electrodes, and
insulation length and thickness is very limited or non-existent. Some basic requirements/goals of the intravascular electrode design is that they should be:

1. Introduced minimally invasively into a target vessel
2. Accurately deployed near the left and right phrenic nerves
3. Properly shaped and dimensioned such that blood flow is not fully occluded
4. Adequate enough for stimulating the phrenic nerves without fatiguing the diaphragm
5. Properly anchored to prevent the device from drifting within the vessel
6. retrievable without damaging vessel walls or the device itself
7. Safe and biocompatible

In order to achieve these requirements/goals, the following research questions were asked:

1. What are typical vessel dimensions?
2. What biocompatible materials can be used as the insulation backing?
3. How much insulation is needed to prevent current from being shunted through the blood?
4. What electrode configurations will best stimulate the right and left phrenic nerves?
5. How can blood flow occlusion be prevented?
6. How will the device be anchored in placed such that the electrodes do not drift or rotate within the body?
7. How will the device be safely introduced and retrieved from the blood vessels?
To answer these questions, experiments were conducted in a pig model and are described in the Section 2 below.

1.5.2. Clinical Significance

The use of intravascular electrodes to activate the phrenic nerves transvascularly could have a significant impact in a clinical setting, especially for those on mechanical ventilation, such as individuals with high cervical spine injuries and those in intensive care units. Stimulating transvascularly is much safer than having electrodes that are placed directly onto the nerve, since there is no mechanical manipulation of the phrenic nerves. In addition, only local anaesthesia is required, which makes this method more available than current pacing systems, as they require lengthy invasive surgery under general anaesthesia. By pacing the diaphragm, it is expected that diaphragm atrophy will be prevented, reduced, or even reversed. Keeping the diaphragm strong and active will allow the patient to wean faster off mechanical ventilation, ultimately reducing their chances of becoming dependant on a mechanical ventilator while lowering hospitalization costs in the process.
2. Method

To answer various research questions and test intravascular electrodes, experiments were conducted in pigs. All of the experiments that were conducted had the approval of the Animal Care Committee (ACC) at the University of British Columbia (UBC). Each trainee that partook in the experiments successfully passed an animal ethics exam. All of the experiments were conducted at Jack Bell Research Centre (Vancouver, BC) or at UBC Animal Care Facility, as these specialized facilities had appropriate equipment and trained animal care technicians.

2.1. Cadaver Pig Study

This first phase of animal studies used six fresh pig cadavers (size range: 40 to 60 kg) that had been used in other unrelated studies. Full anatomical dissection of the thoracic region was performed to expose the neck and thoracic region, vessels of interest, and the phrenic nerves. Once exposed, photographs and measurements were taken of surrounding vessels, such as the brachiocephalic vein and superior vena cava, and the distances between the two phrenic nerves (Figure 2.1-1; Table 2.1-1). In addition, potential access routes for device insertion were explored and determined. Finally, this set of experiments helped test and develop crucial equipment and devices, which would later help establish proof-of-concept in later experiments.

A substantial amount of work was already completed by Sheena Frisch of the Neurokinesiology Lab prior to the start of this thesis and is described elsewhere (Frisch, 2009). Given the similarities between human and pig anatomy and the vast cardiovascular research done on pigs, it was concluded that the pig is an excellent animal model for this project.
Figure 2.1-1. Human and Pig Anatomy Comparison

Note: Human vascular anatomy (left) compared to the pig vascular anatomy (right) (Frisch, 2009).

Table 2.1-1. Pig Vein Dimensions

<table>
<thead>
<tr>
<th>Distance from entry point (mm)</th>
<th>Vein Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 ± 5 (left axillary)</td>
<td>6.97</td>
</tr>
<tr>
<td>40 ± 10 (left axillary)</td>
<td>5.89</td>
</tr>
<tr>
<td>60 ± 15 (left subclavian)</td>
<td>7.74</td>
</tr>
<tr>
<td>80 ± 20 (left brachiocephalic)</td>
<td>&gt; 8.00</td>
</tr>
<tr>
<td>100 ± 25 (vena cava)</td>
<td>15*</td>
</tr>
</tbody>
</table>

Note: Measurements of vein diameter taken by a balloon measurement catheter system as it was advanced along the vein. The superior vena cava was manually measured with a ruler (Frisch, 2009).

2.2. Acute Pig Study

In total, eleven one-day acute (terminal) pig experiments (size range: 30 to 60 kg) under general anesthesia were conducted. In these animals, various electrode insertion routes were explored and tested. Furthermore, prototype devices were tested and evaluated in vivo based on their ease of use and other mechanical aspects. This phase established proof-of-concept for transvascular phrenic nerve stimulation, whereby electrode stimulation properties and diaphragm contraction were assessed.
A nerve mapping protocol using a carefully calibrated (Appendix A) modified voltage-regulated stimulator (Figure 2.2-1) (Body Shapers International, Toronto, ON; Part No. Tamexx 3004) or current-regulated stimulator was established to locate the phrenic nerves through EMG response of the diaphragm. For these experiments, either intramuscular or epimysial EMG electrodes were implanted into/onto the anterior costal region of the left and right hemi-diaphragm. Two amplifiers (BAK Electronics, Inc., Mount Airy, MD; Part No. MDA-4) were responsible for amplifying and filtering the left and right hemi-diaphragm EMG signals before they were acquired. Each of these amplifiers had a lower cutoff frequency of 100 Hz, an upper cutoff frequency of 2 kHz, and a gain of 1000. Offline analysis of stimulation amplitudes and EMG threshold values was completed by lab members using LabVIEW 2009 (National Instruments, Austin, TX) and Matlab software 2009b (MathWorks, Natick, MA).

This mapping protocol intermittently activated electrodes on the device at various insertion depths along the vein. As the intravascular stimulating electrodes approached the phrenic nerves, progressively less stimulation was required to reach threshold. However, as the electrodes advance pass the nerves the required stimulation raises once again, yielding a steep stimulus response curve. The best location was determined from the minimum stimulation value on the response curve (Figure 2.2-2). Once the electrodes were placed at the phrenic nerves, various electrode combinations were tested. By performing these protocols, useful information was gathered regarding the number of electrodes, electrode configuration and spacing, insulation length, and other mechanical aspects of the device.

Electrode impedances were measured at intermittent times throughout the experiment (BK Precision, Yorba Linda, CA; Part No. 886). At the end of each experiment, the pig was euthanized and the device was left inside the pig for post-mortem analysis. A full anatomical dissection of the thoracic region was performed to locate the stimulating electrodes, confirm vessel locations and dimensions, and verify phrenic nerve locations. Once this information was gathered, the device was retrieved from the animal for visual and mechanical inspection.
Figure 2.2-1. Modified Voltage-Regulated Stimulator

Note: A modified voltage-regulated stimulator that was used for most of the acute and chronic pig experiments.

Figure 2.2-2. Mapping Protocol – Concept

Note: Mapping response curve to locate the phrenic nerves. As the intravascular electrodes approach the phrenic nerves, less stimulation is required to activate the phrenic nerves.

In Acute Pig Experiments 1 through 6, Sheena Frisch and Colin Francis performed the necessary surgery to access various venous insertion points and insert intramuscular EMG electrodes into the diaphragm, which were designed and fabricated
by Dr. Andy Hoffer, David Lee and Helen Wang. Epimysial EMG electrodes attached to sonomicrometer crystals were designed and fabricated by Dr. Andy Hoffer and Rodrigo Sandoval. In later acute pig experiments, Dr. James Saunders, with the aid of ultrasound consultant Sabrina Lee, performed the necessary surgery to access the left external jugular vein. Mischa Snopkowski, Jessica Tang and Surhbi Seru modified the voltage-regulated stimulator and Lungpacer Medical Inc. provided the current-regulated stimulator. Members of the Neurokinesiology Lab and Dr. James Saunders performed a full anatomical dissection of the thoracic region. Experimental notes and data were recorded and analyzed by Almira Tanner, Caroline Chen, Helen Wang, Lauren Tinsdale, Ramasamy Meyyappan, and Surhbi Seru of the Neurokinesiology Lab. Automated analysis of EMG data using Matlab was later performed by Jessica Tang.

2.3. Chronic Pig Study

This set of experiments aimed to demonstrate the safety and stability of chronically implanted intravascular stimulation electrodes. In total, three 21-day chronic pig experiments (size range: 45 to 60 kg) were conducted under general anesthesia. On Day 0, intravascular electrodes, designed by Dr. Andy Hoffer and myself, were aseptically introduced into the left external jugular vein by Dr. James Saunders. A modified esophageal probe with recording electrodes (Figure 2.3-1), designed and fabricated by Dr. Andy Hoffer and Rodrigo Sandoval, was inserted into the esophagus. This probe was used to capture diaphragm EMG activity, since the esophagus is in close proximity to the diaphragm. This was necessary because the placement of the intramuscular EMG electrodes was too invasive for these sets of experiments. Similar to the acute experiments, two BAK amplifiers were responsible for amplifying and filtering the EMG signals before they were acquired. Each of these amplifiers had a lower cut-off frequency of 100 Hz, an upper cut-off frequency of 2 kHz, and a gain of 1000. Once acquired, offline analysis by Almira Tanner, Helen Wang, Jessica Tang, Ramasamy Meyyappan, and Surhbi Seru determined stimulation amplitudes and EMG threshold values using LabVIEW and Matlab software.
Figure 2.3-1. Modified Esophageal Probe with EMG Electrodes

Note: Modified esophageal probe with EMG electrodes used in Day 0 and Day 10 experiments.

Also on Day 0, the mapping and electrode cycling protocol was performed to determine the location of the phrenic nerves and the most efficient electrode combination(s). This was completed using the same voltage-regulated stimulator used in the acute pig experiments and palpation of the abdomen by Colin Francis. Once this information was gathered, the device was anchored in place and the electrode leads placed within a subcutaneous pocket. Afterwards, electrode impedances were measured and recorded by myself, and the pig was closed up and allowed to recover from surgery. Once recovered, the pig was returned to the animal care staff at Jack Bell Research Centre.

An intermediate follow-up, approximately 10 days later, examined the safety and performance of the implanted electrodes. The pig was prepped for surgery and the esophageal EMG probe was re-introduced into the esophagus. Dr. James Saunders recovered the electrode leads from the subcutaneous pocket and various electrode combinations were re-tested using the voltage-modulated stimulator. Afterwards, electrode impedances were measured, and the electrode leads were returned to the subcutaneous pocket and the pig was allowed to recover from the surgery. Once recovered, the pig was returned to the animal care staff at Jack Bell Research Centre.
On Day 21, the pig was re-anesthetized and the safety and performance of the implanted electrodes were re-tested for a final comparison. Intramuscular/epimysial EMG electrodes were implanted into/onto the diaphragm. After testing the safety and stability of the implanted electrodes, the pig was euthanized and a full anatomical dissection was performed by Dr. James Saunders. Once completed, the device was retrieved from the animal and visually/mechanically inspected.

2.4. Device Fabrication

Dr. Andy Hoffer and myself created various device designs. Equipment from the lab, such as a micro-welder, light microscopes, digital multi-meter, soldering equipment, oscilloscopes, autoclave, and miscellaneous hand and surgical tools, helped with the fabrication of the devices and accompanying equipment. In general, each device consists of several components, such as contact electrodes that are used for stimulation, insulative material that directs the stimulation towards the phrenic nerves rather than through the blood, and electrode leads that carries the stimulation from the control unit to the electrode contacts. Later prototypes also utilized stainless steel hypodermic tubes that helped advance and retract the electrodes within the animal, a percutaneous introducer that assisted with the insertion of the device, and catheter ports that administer drugs and fluids into the body. To ensure that the devices did not damage or puncture the blood vessels, stiffness of these devices was measured using a digital force gauge (Mark-10, Copiague, NY; Part No. Series 3).
3. Device Evolution

Early device prototypes utilized inside-out electrode cuff technology, which then evolved into electrodes attached onto springing arms that project outwards towards the vessel wall. With this concept, the device further evolved into electrodes mounted onto a single silicone petal. This section will detail the design evolution of the transvascular phrenic nerve stimulating device and the findings from bench testing and/or pig experiments.

3.1. Design 1 – Single Sheet Silicone Cuff

The first design utilized a single non-reinforced silicone sheet as the flexible insulation base. Four evenly spaced flexible PTFE (polytetrafluoroethylene; also known as Teflon®) coated electrode leads were attached to the top of the silicone sheet with silicone adhesive. A small section of the PTFE coating was stripped away, approximately 3 mm in length, to expose the flexible multi-stranded stainless steel wires within the coating (Figure 3.1-1). In cylindrical form, the silicone cuff fits within a 10 mm diameter vessel, typical of those found in pigs and humans. Both silicone and PTFE were used because they are excellent insulators. Silicone adhesive bonds well with other silicone parts, essentially forming one continuous piece with the silicone sheet. Furthermore, the thin and flexible silicone sheet conforms to the walls of the blood vessels, allowing the electrodes to be placed snugly against the vein walls. All the materials used in this design (silicone, PTFE, and stainless steel) are all safe and biocompatible materials, but were not of medical grade. However, during bench testing, it was found that the electrode leads would easily peel away and detach from the silicone sheet. This was likely due to the fact that the PTFE was not etched before being adhered to the silicone sheet. Furthermore, the silicone sheet was too flimsy. This prevented the device from holding a cylindrical shape and therefore, unsuitable for implantation.
Figure 3.1-1. Design 1 – Electrode Cuff Design

Note: Flat view perspective of the first electrode design (top). Cylindrical view of the cuff design (bottom).

3.2. Design 2 – Acute Pig Experiment 1 – Balloon Catheter Electrode

This design utilized a commercial balloon catheter (Neovasc, Richmond, BC, Canada) with four evenly spaced (6 mm separation) PTFE coated electrode leads. A small section of the PTFE coating was stripped away, approximately 2 mm in length, to expose the multi-stranded stainless steel wires within the PTFE insulation. When fully
inflated with either saline or air, the balloon catheter expands to a maximum diameter of 8 mm. The PTFE electrode leads were attached by silicone adhesive to the PET (Polyethylene Terephthalate) balloon (Figure 3.2-1).

*Figure 3.2-1. Mapping Tool – Balloon Catheter Electrode Design*  

Note: Partial construction of the balloon catheter electrode design (top). Final construction of the balloon catheter electrode with depth markers (bottom).

This design was tested in Acute Pig Experiment 1 and helped establish proof-of-concept of transvascular phrenic nerve stimulation. During the experiment, various venous access routes were tested. Initially, the device was inserted into the right axillary vein. However, this entry point was too difficult for the balloon electrode design. This could be due to the small vein diameter of the right axillary vein or the curvature of the vessels in this region. Eventual access was through the right external jugular vein (Figure 3.2-2). The balloon catheter was manually advanced and retracted, and manually inflated and deflated with air via a syringe. Transvascular phrenic nerve stimulation was achieved. However, only the right hemi-diaphragm was stimulated, as the left phrenic nerve was out of reach for the electrodes. Due to time restrictions, electrode impedances were not measured.
After the pig was euthanized and dissected, it was confirmed that stimulation had taken place in the superior vena cava (SVC). The balloon catheter inflated to maximum of 8 mm in diameter; however, the SVC was measured to be approximate 20 mm in diameter. This accounts for the high levels of stimulation, approximately 40 V, needed to activate the right phrenic nerve, as there was substantial shunting of current throughout the blood. It should be noted that the pig was able to breathe spontaneously when the level of anaesthesia was briefly reduced after phrenic nerve pacing, which according to Animal Care staff, is atypical in pigs mechanically ventilated for over six hours.
3.3. Design 3 – Silicone Sandwich Cuff with Tungsten Clip

This design utilized a non-reinforced and a silicone sheet that was reinforced with a Dacron® mesh. Four evenly spaced PTFE coated electrode leads were used. A small section of the PTFE coating was stripped away, approximately 3 mm in length, to expose the multi-stranded stainless steel wires within the insulation. Four evenly spaced windows (3 x 4 mm) were cut into the non-reinforced silicone sheet. To prevent the two ends of the silicone cuff from detaching from each other, a tungsten rod, 30 mm in length that was bent in half, was used to clip the two ends together. With silicone adhesive, the PTFE coated leads and one half of the tungsten rod were sandwiched between the two silicone sheets. The exposed stainless steel wires were placed within the windows of the silicone sheet with the electrode leads running longitudinally along the cuff (Figure 3.3-1).

Figure 3.3-1. Design 3 – Silicone Sandwich Cuff with Tungsten Clip

Note: Flattened electrode cuff with longitudinal electrodes sandwiched between two silicone sheets.

To introduce and deploy the device within the blood vessels, the silicone cuff was tightly wrapped around a deflated balloon catheter. With the cuff tightly coiled, the
electrical leads were fed through two tubes. One large diameter tube was used to house the cuff/balloon assembly, whereas the second smaller tube was used to push and free the cuff from the housing tube (Figure 3.3-2). A syringe was used to inflate the balloon catheter and expand the cuff to the size of the balloon catheter (8 mm diameter) (Figure 3.3-3). Once the device had expanded, the balloon catheter was deflated and removed from the body, closely resembling a cardiovascular stent made of silicone sheeting (Figure 3.3-4). The electrodes were then connected to the voltage-regulated stimulator via a connector cable. The expanded cuff was then advanced in 1 cm increments by pushing the two tubes inwards from the vein insertion point.

*Figure 3.3-2. Design 3 – Electrode Cuff and Balloon Catheter within a Housing Tube*

Note: Tightly coiled electrode cuff wrapped around a balloon catheter and inside a housing tube.
Figure 3.3-3. Design 3 – Fully Deployed Electrode Cuff with Balloon Catheter

Note: Fully deployed electrode cuff with balloon catheter.
Through bench testing, it was determined that the exposed ends of the tungsten clip had the potential to puncture the blood vessel. In addition, the electrode leads would easily tangle. This was due to the fact that the electrode leads were running parallel with each other, rather than transversely across the silicone sheet and gathering at one location. These factors increased the stresses applied to the electrode leads, eventually causing the electrode leads to break. Finally, it was found that the silicone end would unclip underneath the tungsten rod, causing the cuff to unravel (Figure 3.3-5). For these reasons, this design was not tested inside an animal.
Note: The electrode cuff unraveling underneath the tungsten clip due to over expansion of the balloon catheter.

3.4. Design 4 – Acute Pig Experiment 2 – Transverse Sandwched Electrodes

This design was similar to Design 3 in that electrode leads were sandwiched between two sheets of silicone that prevent electrode lead detachment. In addition, small windows in the non-reinforced silicone sheet were used to expose the contact electrodes. The exposed electrodes were evenly spaced, within the same plane, and parallel with each other. The design differs from previous concepts by having the electrode leads running transversely along the silicone surface and gathering at a single location. At this location, the leads were fed inside a silicone tube. This prevented the leads from tangling, which was seen in previous designs. Furthermore, the tungsten clip had a square bend rather than a sharp point, which decreased the likelihood of puncturing the vein wall. Inserting the free ends of the tungsten clip into the silicone tubing had also eliminated the sharp points of the tungsten clip found in Design 3. Once assembled, the free space within the silicone tube was filled with silicone adhesive,
which prevented blood from entering this space. Finally, the housing tube had a slight taper that facilitated with device insertion (Figure 3.4-1; Figure 3.4-2).

**Figure 3.4-1. Design 4 – Electrode Cuff Design within Housing Tube**

Note: Various views of the electrode cuff within its housing tube.
Figure 3.4-2. Design 4 – Deployed Electrode Cuff

Note: Different perspectives of the deployed electrode cuff (top). Flattened electrode cuff to show the electrode leads and exposed windows (bottom).

Before inserting this design into Acute Pig Experiment 2, a new mapping tool was used to determine the locations of the phrenic nerves. A modified thin blue dilator with electrodes was used to stimulate different locations inside the pig (Figure 3.4-3). This tool replaced the balloon catheter, which had the tendency to buckle and kink. Furthermore, the electrodes would easily detach from the balloon surface. This modified dilator was more rigid and could be advanced/retracted easier than the balloon catheter. This tool carried three electrodes that were attached to the dilator by tight fitting silicone tubes and cyanoacrylate adhesive. Finally, distance markings were provided on the surface of the dilator.
These devices were used in Acute Pig Experiment 2. During the experiment, various venous access routes were tested. Initially, the left axillary vein was tested. The thin blue dilator was able to enter this point; however, the dilator could not be advanced beyond the left brachial plexus. Trying to advance the dilator past this region caused the electrodes to detach from the dilator, rendering the mapping tool useless. The next entry point tested was the left external jugular vein. This location was easier to access and allowed the balloon catheter electrode to be inserted. Average electrode impedance was approximately 1.10 kΩ.

Stimulating at approximately 25 V (22.7 mA or 4544 nC) near the insertion point activated the brachial plexus, which caused the left arm of the pig to twitch and flex. Higher stimulation levels, approximately 90 V (81.8 mA or 16360 nC), caused full body contraction and vagus nerve activation, inferred from fluctuations in the heart rate. At
depths between 8 cm and 11 cm from the insertion point, both unilateral and bilateral diaphragm contractions occurred. The stimulation levels to activate the phrenic nerves were much lower than those needed to activate the vagus nerve, approximately 5 – 30 V (4.5 – 27.3 mA or 909 – 5455 nC), to selectively stimulate the phrenic nerves.

With the balloon catheter removed from the vein, the electrode cuff was inserted into the external jugular vein and placed at a depth of 10 cm from the insertion point. Activation of both the left and right phrenic nerves occurred at this location. Full diaphragm recruitment was achieved through this electrode design and the diaphragm paced with the mechanical ventilator disconnected. After the pig was euthanized, a full dissection of the thoracic area was carried out to determine the precise location of the electrodes. It was found that the cuff was in the region where the two brachiocephalic veins form the SVC (Figure 3.4-4). Upon further inspection, it was found that the cuff was unable to deploy from the pusher tube. In addition, it was found that the cuff did not fully open (Figure 3.4-5).

**Figure 3.4-4. Design 4 – Device Location Inside Acute Pig 2 Vasculature**

![Design 4 - Device Location Inside Acute Pig 2 Vasculature](image)

Note: Electrode cuff was found to be in superior vena cava (SVC).
Figure 3.4-5. Design 4 – Electrode Cuff within Acute Pig 2 SVC

Note: Electrode cuff failed to fully exit and deploy from the pusher tube.

3.5. Design 5 – Acute Pig Experiment 3 – SVC Electrode Cuff

This concept was similar to Design 4 in that electrode leads were sandwiched between two silicone sheets. In addition, the electrode leads gathered at a single location and were fed through a silicone tube to prevent the leads from tangling. However, the exposed electrodes run transversely across the silicone surface rather than longitudinally. In theory, this electrode orientation should allow for more efficient stimulation, since the phrenic nerve runs parallel to the SVC (Figure 3.5-1). A stainless steel rod was found within the silicone tube and terminates within the two silicone sheet layers. The tungsten clip was replaced with a stainless steel clip. This change allowed for a better micro-weld between the stainless rod within the silicone tube and the
stainless steel clip. The stainless steel rod also facilitated with the advancement/retraction and rotation of the silicone cuff.

Figure 3.5-1. Design 5 – Transverse Versus Longitudinal Stimulation

Note: Transverse and longitudinal electrode configuration relative to the phrenic nerve (yellow).

When maximally deployed, the cuff could fit within a 15 mm diameter vessel, typical dimension for the pig SVC. The silicone sandwich had two tabs at the end of the cuff that were designed to grab onto the stainless steel clip and prevent the silicone ends from detaching. Two stacked balloon catheters were used to inflate the cuff to its maximum diameter. The pusher tube had a thicker lip to prevent the cuff from being stuck within the tube. This was achieved by adhering a short silicone tube to the inside of the pusher tube (Figure 3.5-2).
Figure 3.5-2. Design 5 – Deploy and Flattened Electrode Cuff

Note: Two inflated balloon catheters expanding the electrode cuff.

Note: Deployed electrode cuff with balloon catheters removed.

Note: Flattened cuff showing transverse electrodes.
This design was tested in Acute Pig Experiment 3. Before inserting the cuff into the SVC, the thin blue dilator was used to locate the phrenic nerves. Four venous access points, the left and right axillary and left and right external jugular veins, were tested. However, only the left external jugular vein could be used to gain sufficient entry into the venous system. Through the left external jugular vein, unilateral and bilateral stimulation of the diaphragm was achieved. At depths between 5 cm and 8 cm from the insertion point, both unilateral and bilateral diaphragm activation occurred. The stimulation levels to activate the phrenic nerves were much lower than those needed to activate the surrounding structures, approximately 15 – 30 V. Due to time restrictions, electrode impedances were not measured.

The SVC cuff was deployed late into the experiment and was able to activate the right phrenic nerve at stimulation levels approximately 20 – 30 V. The cuff assembly was left in place and the pig was euthanized and dissected. It was found that the balloon catheters had moved past the cuff and were no longer aligned with it when inflated, meaning the cuff did not fully open (Figure 3.5-3). Unlike the previous experiment, the electrode cuff was pushed freely from the tubes and into the vein, which means that the thicker pusher tube lip was beneficial to the design.

Figure 3.5-3. Design 5 – Un-deployed Electrode Cuff in Acute Pig 3

Note: Two balloon catheters failed to open the electrode cuff to its maximum size.
3.6. Design 6 – Acute Pig Experiment 4 – Bullnose Electrodes

This design utilized a 6 mm diameter polypropylene tapered “bullnose” tip to facilitate entry into the left external jugular vein. This tapered tip was silicone adhered to a stainless steel hypodermic tube. A guidewire, typical of those used in the Seldinger technique (Appendix B), could be inserted through the hollow centre of the stainless steel tube, which would further facilitate a smooth entry into the vein. On the bullnose tip were four longitudinal electrodes used for mapping of the phrenic nerves. An electrode cuff, similar to Design 5, was used to stimulate the right phrenic nerve inside the SVC. However, this cuff no longer used a silicone tube to gather the electrode leads. Instead, to save space within the housing and pushing tubes, the electrode leads were wrapped around the stainless steel rod. Similar to the previous design, two balloon catheters were used to expand the cuff to its maximum 15 mm diameter (Figure 3.6-1 and 3.6-2).
Figure 3.6-1. Design 6 – Various Components in the Bullnose Cuff Design

Note: Assembly includes a bullnose tip, a housing tube, a pusher tube, silicone cuff, and two balloon catheters.
Figure 3.6-2. Design 6 – Bullnose Tip and Flattened Electrode Cuff

To deploy the cuff, the electrode cuff was wrapped tightly around the hypodermic tube and the two balloon catheters. Once the location of the right phrenic nerve had been determined, the stainless steel tubing that was attached to the bullnose was pushed into the vein. Next, the pusher tube freed the electrode cuff and the balloons into the SVC. Using two syringes, the balloons were inflated and the cuff expanded to its maximum size. Afterwards, the balloon catheters were deflated and individually removed from the body. Holding onto the stainless steel rod that was attached to the electrode cuff, the bullnose tip and tubes were removed from the body, leaving the cuff in place (Figure 3.6-3).
Figure 3.6-3. Design 6 – Electrode Cuff Deployment

Note: A) Expansion of the electrode cuff using two balloon catheters. B) Removal of bullnose tip through the expanded electrode cuff.

This design was tested in Acute Pig Experiment 4. Before the cuff was inserted, a cut-down operation was used to expose the left external jugular vein. Systematic mapping of the phrenic nerves occurred using the thin blue dilator. This systematic mapping generated a steep response curve in which phrenic nerve threshold stimulation amplitudes were plotted against insertion depth along the vein (Figure 3.6-4). To activate the left phrenic nerve, it required approximately 66 V at a depth of 5 cm within the vein. As the dilator was advanced, lower stimulation amplitudes were needed to activate the left phrenic nerve until reaching a minimum. The location with the lowest stimulation amplitude was taken to be where the left phrenic nerve was located. As the dilator was advanced pass the left phrenic nerve, higher stimulation amplitudes were needed. For the right phrenic nerve, as the mapping tool was advanced, lower stimulation amplitudes were needed until it reached a constant level. This is due to the fact that the right phrenic nerve runs parallel to the SVC whereas the left phrenic nerve runs transversely to the left external jugular vein. Due to time restrictions, electrode impedances were not measured.
Figure 3.6-4. Acute Pig Experiment 4 – Phrenic Nerve Mapping Curve

Note: The left phrenic nerve was approximately 8.5 cm (1.83 V) from the insertion point, whereas the right phrenic nerve was 9.5 to 13.5 cm (5.8 to 8 V) from the insertion point.

From the figure above, it was determined that the left phrenic nerve was approximately 8.5 cm from the insertion point and the right phrenic nerve was approximately 9.5 cm to 13.5 cm from the insertion point. Going beyond 13.5 cm created changes in the heart rate. This is likely due to the dilator tip entering the heart. The SVC cuff was deployed 12.5 cm into vein and was able to activate the right phrenic nerve at approximately 16 V. At higher levels, approximately 36 V, bilateral activation of both phrenic nerves occurred, resulting in full diaphragm contraction. Pacing of the diaphragm resulted in sufficient blood oxygen levels in the pig for at least one minute, without concurrent stimulation of other nerves or structures. The cuff assembly was left in place and the pig was euthanized and dissected. Again, it was found that the cuff did not fully open (Figure 3.6-5). It was thought that this was due to high rubbing and friction between the silicone layers and the tight coiling of the silicone cuff within the housing tube.
Figure 3.6-5. Design 6 – Unopened Electrode Cuff In Vivo

Note: The electrode cuff failed to fully open in vivo.

3.7. Design 7 – Acute Pig Experiment 5 – Teflon Cuffs

Phrenic nerve activation through transvascular electrode cuffs has been proven by previous concepts. However, previous concepts only introduced one cuff to activate one phrenic nerve or activate both nerves at higher stimulation levels. This design differs by introducing two independent electrode cuffs to stimulate each of the phrenic nerves. This design utilized the bullnose tip similar to the previous concept. However, this tip consisted of only two transverse ring electrodes, rather than four longitudinal electrodes. This reduced the dependency on electrode orientation and configuration during mapping, thereby expediting the mapping process.

The electrode cuffs were made of two biocompatible sheets (Figure 3.7-1; Figure 3.7-2). The outer layer that is in contact with the vessel walls was composed of a thin silicone sheet with small windows to expose the electrodes that was adhered to a PTFE sheet. To ensure proper adhesion of the two materials, the PTFE sheet was etched on one side using a PTFE etching solution. The smooth inner PTFE layer allows for
streamline blood flow and reduced friction during deployment, whereas the outer silicone layer allows the cuff to grip onto the vessel wall, preventing the device from drifting within the vein.

The right electrode cuff was housed within the main housing tube. The left electrode cuff was housed within a second smaller housing tube. A third thicker lipped tube was used to push the electrode cuffs from their housings and into the veins. Balloon catheters were used to expand the electrode cuffs to 15 mm (right) and 8 mm (left). To keep the electrode cuffs open, interlocking teeth were cut into the PTFE layer. A banner-type retrieval method was also implemented in this design. Two stainless steel rods were cut to the width of the cuff and adhered at the ends of the cuff and in between the two sheet layers. This allowed for more structure when retrieving the device. To retrieve the cuffs, two stainless steel rods traveled along the silicone tubes that house the electrode leads. Once in contact with the electrode cuff, the stainless steel retrieval tubes were turned to disengage the interlocking teeth and re-coil the electrode cuffs. Once tightly coiled, the cuffs could be pulled out from the body.
Figure 3.7-1. Design 7 – PTFE Electrode Cuff

Note: PTFE electrode cuff with interlocking teeth to hold the cuff open.

Figure 3.7-2. Design 7 – Final Assembly of PTFE Electrode Cuff

Note: Final assembly of PTFE electrode cuff showing the various components to the design.

This design was tested in Acute Pig Experiment 5. A cut-down operation was used to expose the left external jugular vein. Once exposed, the Seldinger technique was used to insert the thin blue dilator into the vein. Again, systematic mapping of the phrenic nerves occurred (Figure 3.7-3). In this experiment, the left phrenic nerve was 9
cm from the insertion point, whereas the right phrenic nerve was 13 to 16 cm from the insertion point. This averages out to be approximately 5.5 cm separating the two nerves. At higher a level of stimulation, approximately 76 V, the vagus nerve was stimulated, which created fluctuations in the heart rate. Due to time restrictions, electrode impedances were not measured.

*Figure 3.7-3. Acute Pig Experiment 5 – Phrenic Nerve Mapping Curve*

![Graph showing phrenic nerve mapping with threshold stimulation in V vs. depth in cm for left and right phrenic nerves and vagus nerve.]

Note: The left phrenic nerve was approximately 9 cm (3.5 V) from the insertion point, whereas the right phrenic nerve was 13 to 16 cm (12 to 14 V) from the insertion point. Vagus nerve activation at higher stimulation levels (76 V).

The right electrode cuff was deployed 15 cm into the vein, whereas the left electrode cuff was deployed 9 cm into the vein. Once inside the vein, various electrode combinations were attempted to find the most efficient stimulating electrodes. The right phrenic nerve was activated at approximately 8 V, whereas the left phrenic nerve required approximately 30 V. After a short break in the experiment, bilateral stimulation was attempted, but it was found that only the right electrode cuff was able to contract the
diaphragm. A high level of stimulation, approximately 100 V, was injected into the left electrode cuff, but no contraction was seen. The electrode cuffs were left in place and the pig was euthanized and dissected. It was found that the cuff did not fully open.

3.8. Design 8 – Acute Pig Experiment 6 – Springy “Flower” Arms

All of the previous electrode cuff concepts that were tested in live animals failed to fully deploy and expand. This resulted in higher simulation levels. It was clear that a new method was needed to ensure proper deployment and transvascular simulation. A new concept emerged that utilized springy arms with small insulation pads with sewn electrodes, known as “petals,” to stimulate the phrenic nerves (Figure 3.8-1). As the arms spring open, the petals were pushed towards the vein walls. This concept used stainless steel rods as the springy arms. This material was biocompatible and had a tendency to naturally spring open. The stainless steel arms were adhered with cyanoacrylate to a stainless steel hypodermic tube. A small stainless steel collar was used to cover the sharp ends of the arms and prevent petal detachment from the hypodermic tube.
Figure 3.8-1. Design 8 – Electrodes with Springy Arms Prototype

Note: Springy armed prototype in its retracted and expanded states.

This prototype concept was adapted to form a new design (Figure 3.8-2). This design utilized the same ring electrode bullnose dilator tip found in previous electrode cuff design. The bullnose tip was attached to a stainless steel hypodermic tube where the stainless steel arms were adhered. For the right phrenic nerve, two staggered pairs of three electrode petals with varying arm lengths are used. The arms were 18 mm, 14 mm, and 10 mm in length. By staggering the arm lengths, different electrode combinations and orientations could be tested to ensure that the most efficient electrode pairs were used to pace the diaphragm. For the left phrenic nerve, only one set of three electrode petals were used. These petals, 16 mm, 12 mm, and 8 mm in length, were attached to a separate tube that could be independently advanced/retracted as well as rotated about the stainless steel hypodermic tube. This was to accommodate for the varying separation distances and orientations between the left and right phrenic nerves.
To prevent the left petals from being inserted too far, a small plastic stopped was adhered to the hypodermic tube.

The Seldinger technique was used to introduce a 21 Ga guidewire into the vein. Once the guidewire was in place, the stainless steel hypodermic tube attached to the bullnose dilator could be inserted into the vein. A housing tube ensured that the petal arms could enter the vein without any issues. Retracting the housing tube released the petals into the vein. When fully deployed, the right petals could fit within a vessel that was 16 mm in diameter, whereas the left petals could fit within an 8 mm vessel. To remove the device, the housing tube was advanced to cover the petals. Once the petals were within the housing tube, the device could be removed from the body.

Figure 3.8-2. Design 8 – Final Assembly of Springy Armed Electrode Design

Note: Device in its retracted state (Top). Device in its expanded state (Bottom).

This design was tested in Acute Pig Experiment 6. A cut-down operation was used to expose the left external jugular vein. Once exposed, a springy armed mapping tool was inserted into the vein (Figure 3.8-3). Again, systematic mapping of the phrenic nerves occurred (Figure 3.8-4). In this experiment, the left phrenic nerve was 7 cm from the insertion point, whereas the right phrenic nerve was 12 to 16 cm from the insertion.
No vagus nerve activation was seen. Due to time restrictions, electrode impedances were not measured.

**Figure 3.8-3. Mapping Tool – Springy Armed Design**

Note: Retracted and deployed positions of the springy armed mapping tool.

**Figure 3.8-4. Acute Pig Experiment 6 – Phrenic Nerve Mapping Curve**

Note: The left phrenic nerve was approximately 7 cm (7 V) from the insertion point, whereas the right phrenic nerve was 12 to 16 cm (7.5 to 19 V) from the insertion point.
The tip of the bullnose dilator was 17 cm inside the vessel, which meant that the right electrode petals were deployed 14 cm into the vein, whereas the left electrode petals were deployed 7 cm into the vein. Once inside the vein, various electrode combinations were attempted to find the most efficient stimulating electrodes. The right phrenic nerve was activated at approximately 11 V, whereas the left phrenic nerve required approximately 26 V. The device was left in place and the pig was euthanized and dissected (Figure 3.8-5). It was found that the tip of the bullnose dilator entered the heart, but the right electrode petals were inside the SVC. Furthermore, all of the petals fully expanded within the veins. Upon closer examination, it was found that some of the cyanoacrylate adhesive failed, allowing the stainless steel arms to freely rotate underneath the stainless steel collars.

**Figure 3.8-5. Acute 6 – Device Location in Dissected Acute Pig 6**

Note: Right electrode petals were inside the SVC and were fully expanded within the veins.
3.9. Design 9 – Chronic Pig Experiment 1 – Long Petals

The previous design proved to be favourable because it allowed the device to open to the full size of the vessel, it was much easier to deploy and retrieve the electrodes, and it was more reliable than the electrode cuff design. However, the independently controlled left and right petals were difficult and time consuming to handle. Also, the failure of the cyanoacrylate adhesive was an issue. Furthermore, the number of mechanical parts was a bit worrisome when inside the vessel, which could increase the chances of mechanical failure or disruption of physiological processes, such as blood flow. Finally, since the petal arms were adhered to the bullnose stainless steel hypodermic tube, it was impossible to remove the bullnose tip while keeping the petals in place. Looking at the data from Acute Pig Experiments 4, 5, and 6, it was determined that the left and right phrenic nerves were separated, on average, by 5 cm (Table 3.9-1). This information is useful in the development of the next design where a fixed distance separates the left and right electrode petals.

**Table 3.9-1. Phrenic Nerve Separation Distances**

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Weight (kg)</th>
<th>Nerve Distance (cm)</th>
<th>Inter-Nerve Distance (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>Acute 4</td>
<td>55.0</td>
<td>8.5</td>
<td>10 – 14</td>
</tr>
<tr>
<td>Acute 5</td>
<td>55.5</td>
<td>9.5</td>
<td>13 – 16</td>
</tr>
<tr>
<td>Acute 6</td>
<td>55.0</td>
<td>7.5</td>
<td>12 – 16</td>
</tr>
<tr>
<td></td>
<td><strong>Average</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This design used springy arms similar to the previous concept. However, the bullnose dilator tip was no longer used. Instead, when the stainless steel arms were collapsed inside the PTFE housing tube, the insulating petals came together to form a tapered nose (Figure 3.9-1). The stainless steel arms were adhered to a stainless steel hypodermic tube. This hypodermic tube extended 40 mm distal to the right petal collar and was meant to accommodate a guidewire during insertion. For the right phrenic nerve, two stainless steel electrodes were sewn into each of the four 18 mm long silicone pads. Unlike the staggered arms in the previous concept, each arm was 20 mm in length with 5 mm separating the two electrodes. For the left phrenic nerve, four evenly spaced petals were used (90°). Each petal arm was 15 mm in length and each silicone
pad contained one electrode. Again, a stainless collar covered the sharp ends of the stainless steel arms and electrode leads. The electrode leads beyond the left electrode petals were enclosed within two silicone tubes, one for each set of electrode petals. The distal electrodes on the right petals and the electrodes on the left petal were 6 cm apart. This was due to the fact that the right phrenic nerve runs parallel to the SVC, meaning the right electrodes would be further separated than the minimum distance of 5 cm while maintaining sufficient stimulation.

**Figure 3.9-1. Design 9 – Final Assembly of Bullnose Arms**

The Seldinger technique was used to introduce a guidewire. Next, the end of the guidewire was inserted through the hypodermic tube. With the petals fully collapsed, the conical tip was inserted into the vein. Systematic mapping using the left and right electrode petals could be used to determine the location of the phrenic nerves. It should be noted that mapping of the left phrenic nerve is more important than the right phrenic nerve since the left phrenic nerve intersects the vein rather than runs adjacent to the
vein. Once the nerves are located, the petals are positioned and the housing tube is removed from the body.

This concept was tested in Chronic Pig Experiment 1. On Day 0, an aseptic cut-down operation was used to expose the left external jugular vein (Figure 3.9-2). Once exposed, the Seldinger technique was used to introduce the sterile device into the vein. Since this experiment was conducted in a sterile environment, a modified esophageal probe was used to capture EMG data; however, signals were too small or non-existent. Therefore, to perform the systematic mapping, palpation of the abdomen was used to determine perceived threshold stimulation levels (Figure 3.9-3). In this experiment, the left phrenic nerve was mapped using electrode pair 11-10, whereas the right phrenic nerve was mapped using electrode pair 2-4 (Figure 3.9-4). It was found that the left phrenic nerve was 8 cm from the insertion point, whereas the right phrenic nerve was 12 to 15 cm from the insertion point. This averages out to be approximately 5.5 cm separating the two nerves. No vagus nerve activation was seen.
Figure 3.9-2. Design 9 – Device Inserted into Left External Jugular Vein in Chronic Pig 1

Note: Device exiting the left external jugular vein.
Figure 3.9-3. Chronic Pig Experiment 1 – Phrenic Nerve Mapping Curve

![Chronic Pig Experiment 1 Graph]

Note: The left phrenic nerve was approximately 8 cm (12.4 V; 5.2 mA; 1042 nC) from the insertion point, whereas the right phrenic nerve was 12 to 15 cm (13.8 V; 5.8 mA; 1160 nC) from the insertion point. Values estimated based on abdominal palpation.

Figure 3.9-4. Design 9 – Best Electrodes on Day 0

![Design 9 Diagram]

Note: Electrodes 2-4 were the best electrodes for the right phrenic nerve on Day 0 (left). Electrodes 11-10 were the best electrodes for the left phrenic nerve on Day 0 (right).
With the left and right petals 8 cm and 14 cm from the insertion point, respectively, the pig was paced for 5 minutes via the intravascular electrodes. Afterwards, the distal and proximal portions of the external jugular vein were sutured off to prevent bleeding. Once sutured, the stainless steel hypodermic tube was bent to prevent drifting of the petals and the excess stainless steel tubing was cut away. The electrode leads were placed in two sterile bags and tucked away in a subcutaneous pocket. Once completed, the incision was closed up using suture ties and staples. After the pig recovered from surgery, it was returned to the animal care staff for proper care and attention.

On Day 10, the pig was prepared for follow-up analysis and to determine how the device was withstanding the biological environment. Again, this experiment was conducted in a sterile environment. The staples and sutures were removed to re-expose the left jugular vein and the electrode lead wires (Figure 3.9-5). The electrode leads were connected to the simulator and various electrode combinations were re-tested to determine if the device was still working properly, and to determine if there was any drifting or rotation of electrodes. It was found that there were no adverse affects of having the device implanted for 10 days, as the animal grew normally. Furthermore, there were no noticeable damages to the device. Cycling through the various electrode combinations provided sufficient stimulation to activate the phrenic nerves. From post-experiment analysis, it was found that electrodes 11-12 were the most efficient pair for the left phrenic nerve, whereas electrodes 4-5 were the most efficient pair for the right phrenic nerve (Figure 3.9-6). After data was collected, the electrode leads were again placed in two sterile bags and tucked away in a subcutaneous pocket. Once completed, the incision was closed up and the pig was returned to the animal care staff.
**Figure 3.9-5. Design 9 – Day 10 Follow-Up Experiment in Chronic Pig 1**

A) Closed incision. B) Electrode leads and sterile bag recovered from subcutaneous pocket. C) Electrode leads removed from sterile bag.

**Figure 3.9-6. Design 9 – Best Electrodes on Day 10**

Note: Electrodes 4-5 were the best electrodes for the right phrenic nerve on Day 10 (left). Electrodes 12-11 were the best electrodes for the left phrenic nerve on Day 10 (right).
Day 21 was similar to an acute experiment. The animal was prepared for surgery and both esophageal and intramuscular EMG electrodes were placed into the esophagus and the diaphragm, respectively. The incision was reopened to expose the left jugular vein and the device. The electrode leads were once again connected to the stimulator. Again, there were no adverse affects of having the device implanted for 21 days, as the animal grew normally. Also, there were no noticeable defects to the device. Cycling through the various electrode combinations provided sufficient stimulation to activate the phrenic nerves. During stimulation, the left electrode petals stimulated the left brachial plexus, which suggests that the electrodes may have drifted within the body. This could also be due to the expansion of the thoracic region as the pig grew over the 21 days.

After data was collected, the pig was paced bilaterally for 10 minutes using electrodes 2-4 and 11-10. Afterwards, the device was left in place and the pig was euthanized and dissected (Figure 3.9-7). It was found that the right electrode petals were within the SVC. Furthermore, it was found that there was substantial tissue growth around both the left and right electrode petals, which prevented the petals from fully opening to the size of the vessel. Furthermore, clotting and tissue growth was seen within the sewn stainless steel electrodes, which ultimately changed the electrode efficiency. However, from post-experiment analysis, it was found that electrodes 13-11 were the most efficient pair for the left phrenic nerve, whereas electrodes 8-6 were the most efficient pair for the right phrenic nerve (Figure 3.9-8). This is different from Day 0 and Day 10, meaning there may have been rotation of the petals within the veins. However, it should be noted that, for the left electrode petals, most threshold stimulation amplitudes worsened between Day 10 and Day 21 (Figure 3.9-9), whereas most threshold stimulation amplitudes improved for the right electrode petals. In addition, electrode impedances also changed over the duration of the experiment (Figure 3.9-10).
Figure 3.9-7. Design 9 – Recovered Device in Chronic Pig 1


Figure 3.9-8. Design 9 – Best Electrodes on Day 21

Note: Electrodes 8-6 were the best electrodes for the right phrenic nerve on Day 21 (left). Electrodes 13-11 were the best electrodes for the left phrenic nerve on Day 21 (right).
**Figure 3.9-9. Design 9 – Electrode Efficiency Comparison**

**LEFT Nerve Electrode Comparison**

![LEFT Nerve Electrode Comparison Chart - Log V vs Electrode Combination]

**RIGHT Nerve Electrode Comparison**

![RIGHT Nerve Electrode Comparison Chart - Log V vs Electrode Combination]

Note: Electrode efficiency for select electrode combinations on Day 10 and Day 21.
Figure 3.9-10. Chronic Pig Experiment 1 – Electrode Impedances

<table>
<thead>
<tr>
<th>Electrode Combination (Cathode/Anode)</th>
<th>Impedance (log₂ kΩhm)</th>
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<tbody>
<tr>
<td>2/3</td>
<td>0.5</td>
</tr>
<tr>
<td>2/4</td>
<td>1.0</td>
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<td>2.0</td>
</tr>
<tr>
<td>2/8</td>
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</tr>
<tr>
<td>4/5</td>
<td>4.0</td>
</tr>
<tr>
<td>4/6</td>
<td>5.0</td>
</tr>
<tr>
<td>4/8</td>
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</tr>
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<td>6/8</td>
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</tr>
<tr>
<td>8/9</td>
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</tr>
<tr>
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</tr>
<tr>
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<td>12.0</td>
</tr>
<tr>
<td>12/13</td>
<td>13.0</td>
</tr>
</tbody>
</table>

Note: Electrode impedances of each electrode combination over the course of the experiment.

Post experiment analysis of the device showed that there was no major damage to the device. However, some cyanoacrylate adhesive failed which allowed some of the stainless steel arms to freely rotate underneath the stainless steel collars. In addition, clotting was seen around the electrode leads. Furthermore, the stainless steel hypodermic tube that extends pass the right electrode petals had the potential to enter the heart or even puncture the vein. Finally, from Figure 3.9-9, there were no preferred stimulation directions between longitudinal and transverse electrodes.

3.10. Design 10 – Acute Pig Experiment 7 – Springy Arms with PTFE Covers

This design improved on some aspects from the previous concept (Figure 3.10-1). Unlike the previous concept where the stainless steel hypodermic tube extended beyond the right set of electrode petals, the hypodermic tube in this design aligned with the right stainless steel collar. This reduced the potential of puncturing any vein walls or entering the heart. The silicone pads were 12 mm in length, shorter than the 18 mm
length found in the previous design. The stainless steel arms were also shorter, from 20 mm to 14 mm. By reducing these lengths, it ensured that the silicone pads opened more forcefully, allowing for a better contact with the vein wall. These silicone pads and stainless steel arms were enclosed within a PTFE tube, with the right set of electrode petals coming together to form a conical tip, useful during insertion and mapping. Again, the left and right electrode petals were 6 cm apart.

**Figure 3.10-1. Design 10 – Final Assembly of Bullnose Device**

The exposed electrodes were made of Platinum–10% Iridium (Pt-Ir). Pt-Ir electrodes are commonly used in other medical applications, due to their inertness and biocompatibility. This reduced the chance of clotting within the electrode surface and ensured a uniform stimulation surface. The Pt-Ir electrodes were sandwiched between two reinforced silicone sheet layers with one surface exposed. On the underside, the Pt-
Ir electrode was micro-welded to the stainless steel strains of the electrode leads. For the right set of electrode petals, two Pt-Ir electrodes were used per petal, with 6 mm separating the two electrodes. Only one Pt-Ir electrode per petal was used for the left set of electrode petals. A ground reference electrode was also micro-welded to the stainless steel hypodermic tube.

To reduce clotting around the device, PTFE tubes enclosed the stainless steel arms and electrode leads. A larger PTFE tube was used to cover the stainless steel hypodermic tube and electrode leads. Once the device was enclosed within the PTFE tubing, silicone adhesive was injected into the empty space. In addition, a silicone tube was used to gather the electrode leads proximal to the left electrode petals. By covering the surfaces with silicone and PTFE tubing, blood could easily flow around the device, which reduced the likelihood of clotting.

This design was tested in Acute Pig Experiment 7. On Day 0, an aseptic cut-down operation was used to expose the left external jugular vein. Once exposed, the Seldinger technique was used to introduce the sterile device into the vein. Since this experiment was conducted in a sterile environment, a modified esophageal probe was used to capture EMG data; however, it was difficult to determine stimulation laterality using this probe. Therefore, palpation of the abdomen was used to determine perceived threshold stimulation levels (Figure 3.10-2). Once the phrenic nerve locations were determined, the left and right electrode petals were deployed at 6 cm and 12 cm from the insertion point, respectively. At these locations, various electrode configurations were used to activate the phrenic nerves and electrode impedances were measured (Figure 3.10-3). During electrode cycling, it was concluded that electrodes 5-7 and 10-12 were the most efficient for the right and left phrenic nerves, respectively (Figure 3.10-4). Again, no vagus nerve activation was seen.
Note: The left phrenic nerve was approximately 6 cm (4.41 mA) from the insertion point, whereas the right phrenic nerve was between 12 cm (4.93 mA) from the insertion point.

Note: Electrode impedances of each electrode combination over the course of the experiment.
Figure 3.10. Design 10 – Best Electrodes on Day 0

Note: Electrodes 5-7 were the best electrodes for the right phrenic nerve on Day 0 (left). Electrodes 10-12 were the best electrodes for the left phrenic nerve on Day 0 (right).

Afterwards, the distal and proximal portions of the external jugular vein were sutured off to prevent bleeding. Once sutured, the stainless steel hypodermic tube was bent to prevent drifting of the petals and the excess stainless steel tubing was cut away (Figure 3.10-5). The electrode leads were placed in two sterile bags and tucked away in a subcutaneous pocket. Once completed, the incision was closed up using suture ties and staples. After the pig recovered from surgery, it was returned to the animal care staff for proper care and attention. However, after a few hours of care, it was found that the animal was in distress and, due to complications, needed to be put down. It was later concluded that the animal suffered a pulmonary embolism that lead to its eventual death.
Figure 3.10-5. Design 10 – Anchored Device Inside Left External Jugular Vein in Acute Pig 7

Note: Hypodermic tube bent to anchor device within left external jugular vein.

After recovering the device, it was found that it was in a rather healthy state, with no damages or problems. Post-experimental analysis revealed that electrode 5-G was the most efficient for the right phrenic nerve (Figure 3.10-6), whereas 10-12 was the most efficient for the left phrenic nerve (Figure 3.10-7). Again, there were no preferred stimulation directions for either transverse or longitudinal pathways. One major concern for this design was the overall size of the device and housing tube, and the number of mechanical parts introduced into the body. Furthermore, the stainless steel hypodermic tube may be too stiff to adapt to the vessel curvature.
**Figure 3.10-6. Design 10 – Right Electrode Petal Efficiency Comparison**

Note: Electrode efficiency for select electrode combinations for Right electrode petal.

**Figure 3.10-7. Design 10 – Left Electrode Petal Efficiency Comparison**

Note: Electrode efficiency for select electrode combinations for Left electrode petal.
3.11. Design 11 – Acute Pig Experiment 8 – Staggered Springy Arms

For this design, both the left and right flowers contained six petals (Figure 3.11-1). These petals were grouped into two three-petal staggered sets, with each petal containing a single Pt-Ir electrode (1 x 2 mm). The two petal sets were 10 mm apart with the three petals 120° apart. The left and right flowers were fixed and set 60 mm apart. These modifications increased the electrode spacing and allowed for different electrode configurations and combinations, which could reduce the stimulation needed to activate the phrenic nerves. The stainless steel arms were 14 mm in length, with the sharp ends micro-welded to the stainless steel hypodermic tube, essentially removing the need for the stainless steel collar. The exposed stainless steel arms, electrode leads, and micro-welds were encased within an inside-etched PTFE tubing and filled with epoxy. The PTFE tubing ensured smoother blood flow and the epoxy prevented blood from clotting within the tubing.
To reduce stiffness of the device, a small section of stainless steel hypodermic tube was removed between the two flower sets. Instead, this section was replaced by a PTFE tube and was enclosed within a larger PTFE tube. When the front set of electrodes collapsed onto each other, a tapered tip was formed which facilitated with the insertion of the device into the blood vessel. Again, systematic mapping using the left and right petals was used to determine the location of the phrenic nerves.

This design was tested in Acute Pig Experiment 8. On Day 0, an aseptic cut-down operation was used to expose the left external jugular vein. Once exposed, the vein was ligated to prevent bleeding during the insertion of the device (Figure 3.11-2). Again, since this experiment was conducted in a sterile environment, a modified esophageal probe was used to capture EMG data. To perform the systematic mapping,
palpation of the abdomen was also used to determine perceived threshold stimulation levels. In this experiment, mapping of the left and right phrenic nerve was completed using electrode pair 4-6, as they proved to be able to stimulate the phrenic nerves. Post-experimental analysis of EMG data established a proper map of the phrenic nerves (Figure 3.11-3). It was found that the left phrenic nerve was 11.5 cm from the insertion point, whereas the right phrenic nerve was 13.5 to 18.5 cm from the insertion point. This averages out to be approximately 4.5 cm separation between the two phrenic nerves. Again, there was no vagus nerve activation.

Figure 3.11-2. Design 11 – Device Introduced into Left External Jugular Vein in Acute Pig 8

Note: Device inserted into the left external jugular vein and tied off using ligands.
Figure 3.11-3. Acute Pig Experiment 8 – Phrenic Nerve Mapping Curve

Note: The left phrenic nerve was approximately 11.5 cm (2.5 mA) from the insertion point, whereas the right phrenic nerve was 13.5 to 18.5 cm (2 to 7 mA) from the insertion point.

After a few hours into the experiment, complications to the animal occurred. The heart rate was unusually high and oxygen saturation was abnormally low, which lead to its eventual death. Since the death occurred mid-experiment, the full experimental protocol could not be completed. Namely, electrode cycling to determine the most efficient electrodes, electrode impedances and pacing of the diaphragm using only the intravascular electrodes could not be performed. After recovering the device, no major issues arose during the short experiment time. Again, the overall size of the device was worrisome. Also, the mechanical arms and moving parts were potential issues that needed to be addressed. Finally, the petals would often lose its springiness and angle once they were deployed from the housing tube.
3.12. Design 12 – Chronic Pig Experiment 2c(i) – Compressible Petal

This design addressed all of the issues found in the previous concept. This design reduced the overall size of the device, from 7 mm to 5 mm. Instead of having multiple staggered petals, two independently controlled petals were used. Each petal consisted of a silicone film and two 3 mm long Pt-Ir electrodes (Figure 3.12-1). The silicone film was adhered and sandwiched between two stainless steel rod loops that were micro-welded together. The stainless steel loops were then micro-welded onto a stainless steel hypodermic tube. To ensure the single petal was forced against the vein wall, a nitinol rod was utilized. Nitinol was used because of its shape memory properties and biocompatibility. This nitinol wire was bent into a loop, acting like a foot, with both ends inserted into the hypodermic tube and filled with epoxy. To ensure a smooth profile, the electrode leads and hypodermic tube were inserted through a PTFE tube.

*Figure 3.12-1. Design 12 – Final Assembly of Compressible Petal Design*

Note: Compressible petal design in sterile packaging.
The Seldinger technique was used to insert a valved-introducer into the left external jugular vein. With the introducer in place, the device could be inserted through the valve and hollow centre. The stainless steel rods had the ability to collapse within the introducer and spring open when inside the vein. To map, one petal was advanced and rotated into four different orientations (Right, Ventral, Left, Dorsal). To determine the orientation of the petal, a marker flag was bent at the proximal end of the stainless steel hypodermic tube. Once the nerve locations had been determined, the left petal could be inserted through the introducer and placed at the location of the left phrenic nerve.

This device was tested in Chronic Pig Experiment 2c(i). On Day 0, an aseptic cut-down operation was used to expose the left external jugular vein. The introducer was inserted into the jugular vein using the Seldinger technique (Figure 3.12-2). Prior to inserting the device for mapping, a bolus of heparin was injected into the animal to prevent clotting. Next, the device was inserted into the animal and connected to the stimulator. However, there was significant bleeding from the insertion point. This bleeding increased the heart rate from 85 bpm to 175 bpm. Stabilizing the pig vital signs was top priority, meaning no stimulation occurred. Instead, the device was removed and the incision closed. The pig was allowed to stabilize and recover for one week.

*Figure 3.12-2. Design 12 – Compressible Petal Inserted Through Introducer in Chronic Pig 2(i)*

Note: Compressible petal inserted through hollow introducer.
Upon the removal of the device from the pig, it was found that part of the silicone film detached from the stainless steel rod loop. This could have been caused by the repetitive insertion and removal of the device from the animal. In addition, it was found that one of the Pt-Ir electrodes detached from its electrode lead (Figure 3.12-3). With this information, this concept was abandoned.

*Figure 3.12-3. Design 12 – Damaged Compressible Petal*

![Figure 3.12-3](image)

Note: Silicone pad detaching from stainless steel rod loop.

### 3.13. Design 13 – Chronic Pig Experiment 2c(ii) – Reinforced Petal

The repetitive stress applied to the stainless steel loops in the previous design was one of the reasons why the electrode petal detached from the stainless steel rod loops. Another reason for detachment was the adhesive bond between the silicone sheet and stainless steel loops. To combat this issue, a more robust petal attachment method was used in this design (Figure 3.13-1). For the right electrode petal, a reinforced silicone sheet with two Pt-Ir electrodes (1 x 3 mm) was mounted onto a stainless steel loop. The flexible silicone sheet had the ability to collapse within a PTFE housing tube, which was inserted through a larger PTFE introducer, but spring open and adapt to the vessel curvature once freed from the introducer. The loop inserted through a silicone tube. Next, the stainless steel loop was folded back and micro-welded onto itself. This ensured a more secure bond between the silicone sheet and the silicone
Similar to the previous design, the stainless steel loop was micro-welded onto the stainless steel hypodermic tube. Again, a nitinol rod was inserted into the hypodermic tube and secured using epoxy. This rod ensured that the petal was pushed against the vein wall.

**Figure 3.13-1. Design 13 – Final Assembly of Single Petal Design**

Note: Final assembly view of single petal design after implanted for 21-days.

Similar to Design 11, a small section of stainless steel hypodermic tube was removed between the two petals to reduce overall stiffness. This section was replaced by four stainless steel rods that were micro-welded to both petals and was enclosed, along with the electrode leads, within a silicone tube. The left electrode petal was similar in construction as the right electrode petal. However, the nitinol rod was replaced with a shorter 0.010” stainless steel rod that was micro-welded to the hypodermic tube. The stainless steel loop of the left petal was micro-welded onto a stainless steel hypodermic tube. The left petal was unique in that the distance from the right electrode petal was
separated by 55 mm, but the left petal could freely rotate around a long silicone tube that was fixed onto the steel hypodermic tube. Various electrode combinations on the right electrode petal were used to map the vessel by advancing and rotating the petal in four different orientations (Right, Ventral, Left, Dorsal). Once the left and right phrenic nerve locations and orientations were determined, the device was removed from the body and the left petal orientated and fixed into its proper position.

This design was tested in Chronic Pig Experiment 2c(ii), later known as Chronic Pig Experiment 2. On Day 0, an aseptic cut-down operation was used to expose the left external jugular vein. Using the Seldinger technique, the introducer was inserted into the left external jugular vein. Again, since this experiment was conducted in a sterile environment, a modified esophageal probe was used to capture EMG data. However, diaphragm laterality could not be determined from this probe. In addition, one of the EMG leads was not working properly. Therefore, to perform the systematic mapping, palpation of the abdomen was used to determine perceived threshold stimulation levels. Systematic mapping using four different electrode combinations and four different electrode orientations were used at every 1 cm increment inside the vein (Figure 3.13-2; Figure 3.13-3). Using electrode combination 12-G, it was found that the left phrenic nerve was 6.3 cm in the left orientation from the insertion point, whereas using electrode 2-G, the right phrenic nerve was 7.8 to 11.8 cm in the ventral orientation from the insertion point (Figure 3.13-4). This averages out to be approximately 3.5 cm separating the two nerves. There was no vagus nerve activation.
Figure 3.13-2. Design 13 – Left Phrenic Nerve Threshold Stimulation Comparison

Note: Threshold stimulation of each electrode combination and orientation at each depth for the left phrenic nerve.
**Figure 3.13-3. Design 13 – Right Phrenic Nerve Threshold Stimulation Comparison**

Note: Threshold stimulation of each electrode combination and orientation at each depth for the right phrenic nerve.
With the left and right petals 6.3 cm and 11.8 cm from the insertion point, respectively, and in their proper electrode orientations, the pig was paced via the intravascular electrodes. Afterwards, the distal and proximal portions of the external jugular vein were sutured off to prevent bleeding. Once sutured, the stainless steel hypodermic tube was bent to prevent drifting of the petals and the excess stainless steel tubing was cut away. Again, the electrode leads were placed in two sterile bags and placed inside a subcutaneous pocket. Once completed, the incision was closed up using suture ties and staples. After the pig recovered from surgery, it was returned to the animal care staff for proper care and attention.

On Day 11, the pig was prepared for follow-up analysis and to determine how the device was withstanding the biological environment. Again, this experiment was conducted in a sterile environment. The staples and sutures were removed to re-expose the left jugular vein and the electrode leads. The electrode leads were connected to the simulator and various electrode combinations were re-tested to determine if the device
was still working properly, and to determine if there was any drifting or rotation of electrodes. It was found that there were no adverse affects of having the device implanted for 11 days, as the pig grew from 57.5 kg to 65.5 kg. Furthermore, there were no noticeable damages to the device.

Cycling through the various electrode combinations provided sufficient stimulation to activate the phrenic nerves. From post-experiment analysis, it was found that electrodes 12-13 were the most efficient pair for the left phrenic nerve, whereas electrodes 2-3 were the most efficient pair for the right phrenic nerve. Higher stimulation amplitudes were needed to activate the left phrenic nerve, which also activated the left brachial plexus. After data was collected, the electrode leads were again placed in two sterile bags and tucked away in a subcutaneous pocket. Once completed, the incision was closed up and the pig was returned to the animal care staff.

The pig was prepared for final analysis on Day 21. Both esophageal and epimysial EMG electrodes were placed into the esophagus and on the diaphragm, respectively. The incision was reopened to expose the left jugular vein and the device. It was found that there was an infection near the entry point, as there was substantial pus formation. Also, it was found that the electrode impedances were much higher than Day 0 and Day 11 (Figure 3.13-5), which meant that there was substantial connective tissue growth around the electrodes or the electrode leads were damaged. Cycling through the various electrode combinations provided sufficient stimulation to activate the phrenic nerves. However, much higher stimulation amplitudes were needed. Electrodes 13-12 and 2-G were the most efficient electrodes on Day 21, which was different than Day 0 and Day 11 electrode pairs. This suggests that electrodes either drifted or rotated within the body.
Figure 3.13. Chronic Pig Experiment 2 – Electrode Impedances

**Chronic Pig Experiment 2 - Impedances**

<table>
<thead>
<tr>
<th>Electrode Combination (Cathode/Anode)</th>
<th>Day 0</th>
<th>Day 11</th>
<th>Day 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-G</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-2</td>
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<td></td>
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<td>2-G</td>
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</tr>
<tr>
<td>12-G</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Electrode impedances of each electrode combination over the course of the experiment. Electrode leads of the right electrode petal broke, which accounts for the high impedances.

After data was collected, the pig was paced bilaterally. However, before the pig was euthanized, percutaneous insertion of a introducer into the right external jugular vein using the Seldinger technique and ultrasound was achieved. This quick 15-minute procedure would be beneficial for future experiments. Afterwards, the device was left in place and the pig was euthanized and dissected (Figure 3.13-6). It was found that the right electrode petal was within the SVC and in the ventral position. Furthermore, it was found that there was substantial connective tissue growth around both the left and right electrode petals. However, the tissue could be easily removed from the device. The stainless steel hypodermic tube was broken proximal to the left electrode petal. The sharp edge of the broken hypodermic tube caused the electrode leads to become damaged, which accounts for the high impedances found in Day 21. In addition, the stainless steel rods that were micro-welded in the gap between the two petals were broken. Luckily, the silicone tube that held the rods in place was not damaged (Figure 3.13-7).
Figure 3.13-6. Design 13 – Recovered Device in Chronic Pig 2

Note: A) Device excised from the SVC and left external jugular vein. B) Right electrode petal with removed connective tissue growth. C) Right electrode petal incased in connective tissue growth. D) SVC vessel after device removed.

Figure 3.13-7. Design 13 – Broken Stainless Steel Hypodermic Tube

Note: Hypodermic tube broke proximal to the left electrode petal.
Post-experiment analysis revealed that 2-G and 13-12 were the most efficient electrodes over the course of the experiment. Furthermore, there was no monopolar or bipolar simulation preferences, as the best electrode configurations changed over time (Figure 3.13-8). This experiment, in conjunction with previous experiments, revealed that the phrenic nerves were typically found in a certain orientation relative to the veins (Figure 3.13-9). Specifically, the left phrenic nerve was usually orientated to the left or dorsal positions, whereas the right phrenic nerve was usually orientated to the right or ventral positions. This information was crucial for the following designs.

Figure 3.13-8. Design 13 – Electrode Petal Efficiency Comparison

![Threshold Stimulation Chart]

**Chronic Pig Experiment 2c Electrode Cycling**

<table>
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<tr>
<th>Electrode Combination (Cathode/Anode)</th>
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<th>0.3</th>
<th>1.0</th>
<th>3.0</th>
<th>9.0</th>
</tr>
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<tr>
<td>3-G</td>
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<td></td>
</tr>
<tr>
<td>3-2</td>
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<td></td>
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<tr>
<td>12-G</td>
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<tr>
<td>12-13</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Day 0  Day 11  Day 21

Note: Electrode efficiency for each electrode combinations for both electrode petals.
Figure 3.13-9. Design 13 – Phrenic Nerve Locations Relative To Electrode Petals

Note: Best left electrode orientation relative to the left phrenic nerve (Head on view).

Note: Best right electrode orientation relative to the right phrenic nerve (Head on view).

3.14. Design 14 – Chronic Pig Experiment 3 – Peanut Petal

This design was similar to the previous concept (Figure 3.14-1). However, four 1 x 1.5 mm Pt-Ir electrodes were used. These electrodes were sandwiched between a reinforced silicone and non-reinforced silicone sheet. Reinforced silicone was primarily used because it was resistant to tearing and it could easily deform inside an introducer and spring open when inside the vein (Figure 3.14-2). A stainless steel “hairpin” rod loop was again used (Figure 3.14-3). However, this loop had one side exposed on the top surface of the reinforced silicone sheet and one side sandwiched between the two silicone layers, essentially stapling the silicone sheets to the hypodermic tube. This
hairpin loop was micro-welded onto a stainless steel hypodermic tube, and ensured that there was a smooth surface to facilitate entry into the introducer during retrieval of the device. In addition, this hairpin loop acted as an electrode ground (C) contact.

**Figure 3.14-1. Design 14 – Final Assembly of Fixed Petal Design (Stainless Steel)**

Note: Electrode petals at a fixed distance and orientation from each other on a stainless steel hypodermic tube.
**Figure 3.14-2. Design 14 – Petal Deployment from Housing Tube**

Note: A) Petal fully enclosed by housing tube. B-D) Partially deployed petal. E) Petal fully deployed from housing tube.

**Figure 3.14-3. Design 14 – Hairpin Loop**

Note: Hairpin loop used to staple petal to hypodermic tube.
Again, two electrode petals were used in this concept. Each petal consisted of four electrodes, two medial electrodes (10 mm separation) that were between the hairpin arms, and two lateral electrodes (6 mm off centre) that accounted for any rotational changes over time. The 25 mm long silicone pad closely resembled a peanut shape (Figure 3.14-4). This shape was used because it maximized the spacing between the lateral electrodes while minimizing the introducer size. The two petals were fixed 65 mm apart and 180° rotated. This was based on the previous findings of nerve separation and orientation. Each petal also consisted of a loop/foot that was used to help push the petal towards the vessel wall. The right distal petal used a nitinol rod loop, whereas the left proximal petal used a short stainless steel rod loop. The electrode leads, stainless steel arms, and hypodermic tube were all encapsulated within a thin-walled silicone tube. This ensured a smooth profile when inside the vein.

**Figure 3.14-4. Design 14 – Peanut-shaped Electrode Petals**

Note: A) Right electrode petal. B) Left electrode petal. C) Underside of left electrode petal.
A similar concept was also developed using a nitinol hypodermic tube (Figure 3.14-5). Comparable nitinol tubing is less stiff than stainless steel tubing, which helps the device adapt to the vessel curvature. However, during prototype assembly, it was difficult to micro-weld the stainless steel hairpin loops onto the surface of the nitinol tube. This is due to the fact that laser welding is needed to ensure a proper mate. In addition, the nitinol tube would easily buckle, which ultimately affected the insertion depth during mapping. With these issues known, the nitinol tubing concept was abandoned until proper technical issues were addressed.

**Figure 3.14-5. Design 14 – Final Assembly of Fixed Petal Design (Nitinol)**

Note: Electrode petals at a fixed distance and orientation from each other on a nitinol hypodermic tube.

The stainless steel hypodermic tubing concept was tested in Chronic Pig Experiment 3. On Day 0, using the Seldinger technique and ultrasound for visualization, a PTFE introducer was percutaneously inserted into the left external jugular vein. The device was then inserted through the introducer. Again, since this experiment was conducted in a sterile environment, a modified esophageal probe was used to capture
EMG data. Systematic mapping using different electrode combinations and four different electrode orientations were used at every 1 cm increment inside the vein. However, post-experimental analysis revealed that no mapping was conducted between 10 and 12.5 cm from the insertion point. Using electrode 1-2, it was found that the left phrenic nerve was 10 cm in the dorsal orientation from the insertion point, whereas using electrode 1-2, the right phrenic nerve was 14.5 to 16.5 cm in the ventral orientation from the insertion point (Figure 3.14-6). There was no vagus nerve activation.

**Figure 3.14-6. Chronic Pig Experiment 3 – Phrenic Nerve Mapping Curve**

![Graph showing phrenic nerve mapping depth vs. stimulation amplitude](image)

Note: The left phrenic nerve was approximately 10 cm (7.21 mA), in the Dorsal orientation, from the insertion point, whereas the right phrenic nerve was 15.5 cm (1.78 mA), in the Ventral orientation, from the insertion point.

With the left and right petals 10 cm and 16.5 cm from the insertion point, respectively, and in their proper electrode orientations, the pig was paced via the intravascular electrodes. Afterwards, the stainless steel hypodermic tube was bent to prevent drifting of the petals and the excess stainless steel tubing was cut away. Next, a subcutaneous pocket was created for the sterile bags that contained the electrode leads. Once completed, the incision was closed up using suture ties and staples. After the pig
recovered from surgery, it was returned to the animal care staff for proper care and attention.

On Day 7, the pig was prepared for follow-up analysis and to determine how the device was withstanding the biological environment. An aseptic procedure was used to access the electrode leads by removing the staples and sutures. The electrode leads were connected to the voltage-regulated simulator and various electrode combinations were re-tested to determine if the device was properly working, and to determine if there was any drifting or rotation of electrodes. Furthermore, the stainless steel hypodermic tube was jiggled to see if this effect would remove any connective tissue growth on the electrodes and device. It was suggested by the experimental team that the device should be advanced; however, due to the anchoring of the device to the vein, and high resistance to pushing, this could not be achieved. It was found that there were no adverse affects of having the device implanted for 7 days. Furthermore, there were no noticeable damages to the device.

Cycling through the various electrode combinations provided sufficient stimulation to activate the phrenic nerves, as well as left brachial plexus (Figure 3.14-7; Figure 3.14-8). However, these amplitudes were much higher than Day 0. From post-experiment analysis, it was found that electrodes 1-2 were the most efficient pair for the left phrenic nerve, whereas electrodes 3-C were the most efficient pair for the right phrenic nerve (Figure 3.14-10). After data was collected, the electrode leads were again placed in two sterile bags and tucked away in a subcutaneous pocket. Once completed, the incision was closed up and the pig was returned to the animal care staff.
Note: Threshold stimulation of each electrode combination at best depth for the left phrenic nerve on Day 7. Values in red were estimated from transcribed notes.
Note: Threshold stimulation of each electrode combination at best depth for the right phrenic nerve on Day 7. Values in red were estimated from transcribed notes.

The pig was prepared for final analysis on Day 21. Both esophageal and epimysial EMG electrodes were placed into the esophagus and on the diaphragm, respectively. The incision was reopened to expose the left jugular vein and the device. It was found that the electrode impedances changed over the course of the experiment (Figure 3.14-9). Cycling through the various electrode combinations provided sufficient stimulation to activate the phrenic nerves (Figure 3.14-10). However, in general, lower stimulation amplitudes were needed compared to Day 7. This could be due to the jiggling of the device encountered in Day 7. Electrodes 2-1 for the left phrenic nerve and 3-4 for the right phrenic nerve were the most efficient electrodes on Day 21 (Figure 3.14-11; Figure 3.14-12), which was different than Day 0 and Day 11 electrode pairs (Figure
Electrodes 3-4 were the lateral electrodes, which suggest that having the lateral electrodes is beneficial to the design.

Figure 3.14-9. Chronic Pig Experiment 3 – Electrode Impedances

Note: Electrode impedances of each electrode combination over the course of the experiment.
Figure 3.14-10. Design 14 – Electrode Petal Efficiency Comparison

Chronic Pig Experiment 3
Electrode Cycling
Left Phrenic Nerve

Chronic Pig Experiment 3
Electrode Cycling
Right Phrenic Nerve

Note: Electrode efficiency for each electrode combinations for left (top) and right (bottom) electrode petal.
Figure 3.14-11.  Design 14 – Left Phrenic Nerve Threshold Stimulation Comparison (Day 21)

Note: Threshold stimulation of each electrode combination at best depth for the left phrenic nerve on Day 21. Values in red are estimated from transcribed notes.
**Figure 3.14-12. Design 14 – Right Phrenic Nerve Threshold Stimulation Comparison (Day 21)**

Note: Threshold stimulation of each electrode combination at best depth for the left phrenic nerve on Day 21. Values in red are estimated from transcribed notes.

**Figure 3.14-13. Design 14 – Best Electrodes**

Note: Left petal best electrode combinations over the course of the experiment.
After data was collected, the pig was paced bilaterally. Afterwards, the device was left in place and the pig was euthanized and dissected (Figure 3.14-14). Upon inspection, it was found that the left stainless steel foot completely detached from the device. Luckily, there were no adverse affects from this event. Furthermore, there was tissue adhesion on both of the silicone petals and on the nitinol foot. However, the tissue was easily removable from the device. The silicone corners near the hairpin loop would sometimes catch onto the introducer when being pulled back into an introducer tube. In addition, small traces of blood were found between the two silicone sheet layers. Otherwise, there were no damage to the stainless steel hypodermic tube or electrode leads.

**Figure 3.14-14. Design 14 – Recovered Device In Vivo**

Note: A) Device excised from the SVC and left external jugular vein. B) Right electrode petal with connective tissue growth. C) Detached stainless steel foot.
3.15. Design 15 – Acute Pig Experiment 9 – Independent Petals

The Chronic Pig Experiments revealed very useful information regarding various design concepts, nerve orientations, material behaviour, and insertion methods. The material choices were safe and compatible with live tissue, as there were no adverse affects of having the devices inside a biological system for 21 days. With the information gathered from previous experiments, this design reduced the complexity and overall size of the device. In this design, an introducer was percutaneously inserted into the left external jugular vein. The Lungpacer Intravascular Electrodes (LIVE) could then be inserted through the introducer lumen and into the vein. Two LIVE devices could be inserted through the introducer tube, one for each of the phrenic nerves. Each LIVE consisted of an asymmetric silicone peanut shaped petal with four 1 x 1.5 mm Pt-Ir electrodes (Figure 3.15-1). The medial electrodes (Electrodes 2 and 3) were 7 mm apart and were electrically coupled to the 5 mm separated lateral electrodes. By electrically coupling the medial electrodes to the lateral electrodes, the lateral distance increased, the necessary charge injection was altered, and the overall size of the device was slimmer, since there were fewer electrodes leads.
Two stainless steel hypodermic tubes were micro-welded together along its entire length. Each hypodermic tube could accommodate one electrode lead within its hollow core, thereby reducing the outer diameter of the device. In addition, the device became less stiff and had a preferred bending direction than previous concepts. This concept no longer used springy arms or a foot loop to push the petal towards the vein wall. Instead, by using the vasculature anatomy, the inherent property of the hypodermic tubes naturally pushed the electrode petals towards the vein walls, allowing the petals to hug the walls of the vein (Figure 3.15-2). A hairpin loop, similar to the previous design, stapled the silicone petal to the two stainless steel hypodermic tubes. A short silicone pre-curling tube prevented the corners of the silicone pad from catching onto the introducer tube during retrieval. This tube provided a smooth transition between the silicone petal pad and silicone tube that encapsulated the hypodermic tubes and electrode leads. On the exterior of the silicone tube was an ECG electrode, which could detect electrical activity from the heart.
This design was tested in Acute Pig Experiment 9. The Seldinger technique was used to percutaneously insert an introducer into the left external jugular vein (Figure 3.15-3). Epimysial and esophageal EMG electrodes were placed on the surface of the diaphragm and in the esophagus, respectively. Afterwards, systematic mapping was completed using 2-G in four different electrode orientations at every 1 cm increment inside the vein (Figure 3.15-4; Figure 3.15-5). Prior to insertion of the device and mapping, it was realized that the electrode lead coupling the distal medial electrode (Electrode 2) to the lateral electrode needed to be cut. This was necessary for mapping, as well as electrode efficiency could be compared, as surface areas were different between electrode 2 and 3. Therefore, a small cut was made through the 0.002” (0.0508 mm) silicone under sheet to disconnect the lateral leads. Afterwards, a small bead of silicone adhesive was placed over the incision to act as insulation.
**Figure 3.15-3. Design 15 – Electrode Petal Insertion**

Note: Single electrode petal inserted through percutaneously introducer.

**Figure 3.15-4. Design 15 – Left Phrenic Nerve Electrode Petal Efficiency Comparison**

Note: Threshold stimulation of 2-G combination at each orientation and depth for the left phrenic nerve.
During mapping, it was found that the best orientation for the left phrenic nerve was with the electrode petal facing leftwards, whereas the electrode petal facing rightwards was the best orientation for the right phrenic nerve (Figure 3.15-6). The left phrenic nerve was 8 cm from the insertion point and the right phrenic nerve was between 11 and 13 cm from the insertion point. This averages out to be approximately 4 cm separating the two nerves. As the electrode petal was further advanced into the vein, it was found that device would self orientate itself, as the flag marker at the end of the hypodermic tubes would change angle. This suggests that there is a preferred orientation of the petal within the vessel. It was also found that the esophageal probe was unable to provide distinct EMG of different regions of the diaphragm. Impedances were typical of those found in previous experiments (Figure 3.15-7), and there was no vagus nerve activation.
Figure 3.15-6. Acute Pig Experiment 9 – Phrenic Nerve Mapping Curve

Note: The left phrenic nerve was approximately 8 cm (4 mA), in the Left orientation, from the insertion point, whereas the right phrenic nerve was between 11 and 13 cm (2.8 to 3.25 mA), in the Right orientation, from the insertion point.
Figure 3.15-7. Acute Pig Experiment 9 – Electrode Impedances

<table>
<thead>
<tr>
<th>Electrode Combination</th>
<th>Impedance (kOhm)</th>
</tr>
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<tbody>
<tr>
<td>2-G</td>
<td>2</td>
</tr>
<tr>
<td>3-G</td>
<td>1.5</td>
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<td>1</td>
</tr>
<tr>
<td>12-13</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Note: Electrode impedances of each electrode combination.

Once the mapping phase was completed, the right electrode was placed at 13 cm from the insertion point and the left electrode petal was inserted through the introducer tube. However, there was no room in the introducer tube for both petals. Therefore, the electrode petal was removed from the vein and introducer and replaced by a previous design that utilized springy armed electrodes. This device would be used to pace the pig and gather addition data for other aspects of the project, such as spirometer and sonomicrometer data. It should be noted that the pig was spontaneously breathing after pacing was completed, which, according to animal care staff, was atypical of pigs ventilated for long periods of time.

During mapping, it was quite easy to advance and retract the device within the vessel. There was no need for any sheath to assist with moving the petal. In addition, removing the device from the introducer was accomplished with great ease. The petal that was removed from the vessel showed clotting on both sides of the petal, silicone tubes, and ECG electrode (Figure 3.15-8). However, this clotting could be easily removed from the device. Otherwise, there were no real issues with this device other
than its overall diameter size. Post-experiment analysis revealed that stimulating between electrodes 3-2 required two times more voltage than stimulating between 2-G. This is due to the fact that electrode three had two electrode contacts compared to electrode 2, meaning it had a larger stimulation surface area.

**Figure 3.15-8. Design 15 – Recovered Device In Vivo**

![Image of recovered device](image)

Note: Device removed from the animal. A) Blood clotting on the underside of the electrode petal. B) Blood clotting on the topside of the electrode petal.

**3.16. Design 16 – Acute Pig Experiment 10a and 10b – Stabilizer**

One of the issues of using two independently controlled petals was the fact that the hypodermic tubes of the two devices would tend to rattle within the percutaneously inserted introducer, as well as interact and cross, affecting mapping of the nerves. This issue was resolved by utilizing an inside-etched PTFE stabilizer unit that separated the two devices (Figure 3.16-1). This stabilizer unit was small enough to fit within an introducer and had two separate lumens, one for each set of hypodermic tubes. A thin-walled silicone tube was adhered to the inside of the stabilizer tube. The hypodermic tubes and electrode leads of the left proximal device were then inserted through this tight-fitting lumen, essentially fixing the left device to the stabilizing tube. The second lumen accommodated the hypodermic tubes and electrode leads of the right distal device. This second lumen was wide enough to allow for the right distal device to be easily advanced and retracted, as well was rotated.
Figure 3.16-1. Design 16 – Final Assembly of Stabilizer Design

The electrode petals were essentially the same shape as the previous concept, but utilized four Pt-Ir electrodes (Figure 3.16-1). This design removed the silicone tube that encapsulated the hypodermic tubes and electrode leads. By removing this tube, there was more space for both devices within the introducer. Instead, two electrode leads were inserted through the hollow cores of the hypodermic tubes and the remaining two electrode leads were adhered to the exterior surface of the two stainless steel hypodermic tubes.

This design was tested in Acute Pig Experiment 10A and 10B. To insert and deploy the petals into the vein, an introducer was percutaneously inserted into the left external jugular vein. Prior to inserting the petals into the introducer, both petals were retracted into a plastic tube. This tube mated to the valve of the introducer and facilitated the smooth entry of the petals into the introducer (Figure 3.16-2). For this experiment, two simultaneous pigs were prepared. Both pigs were implanted with epimysial EMG
electrodes to measure diaphragm activity. With the device introduced into the vein of Pig B and using the new current-modulated stimulator, quick mapping at every 1 cm increment was completed using electrodes 1-Ground (C) in the left orientation for the left phrenic nerve and in the right orientation from the right phrenic nerve (Figure 3.16-3). Due to complications in the health of Pig B, the mapping protocol was suspended and attention was focused on Pig A.

**Figure 3.16-2. Design 16 – Three Devices with Stabilizer Tube and Introducer Accessory Tube**

Note: A) Top view of device. B) Side view of device.
For Pig A, quick mapping was completed with electrodes 1-2. The left phrenic nerve was mapped with the petal facing leftwards and the right phrenic nerve was mapped with the petal facing rightwards (Figure 3.16-4). Since the new current-modulated stimulator was used, there was no palpation of the abdomen to identify the current level at which the phrenic nerves were activated. It was later found that the right amplifier that was connected to the right hemi-diaphragm EMG electrode was in the incorrect settings and therefore displayed incorrect EMG activity during the mapping phase, which explains why no right phrenic nerve plot was shown. However, through visual inspection of the abdomen, the right phrenic nerve was determined to be 10 cm from the insertion point. The left petal was placed 4 cm from the insertion point. With the petals at these locations and in their proper orientations, various electrode combinations were tested to determine the most efficient electrode pairs (Figure 3.16-5; Figure 3.16-6; Figure 3.16-7). Electrodes 1-2 were used to pace the left phrenic nerve, and electrodes 3-4 pacing the right phrenic nerve. Post-experiment analysis revealed that electrodes 1-3 and 3-4 were in fact the most efficient electrodes for the left and right phrenic nerves,
respectively. There was no preferred stimulation between transverse and longitudinal electrodes. The impedances were found to be within normal range (Figure 3.16-8).

*Figure 3.16-4. Acute Pig Experiment 10A – Phrenic Nerve Mapping Curve*

![Graph showing threshold stimulation amplitude vs depth for the left and right phrenic nerves.](image)

Note: The left phrenic nerve was approximately 5 cm (111 nC), in the Left orientation, from the insertion point. Due to technical difficulties in acquiring data, there was no trace for the right phrenic nerve.
Note: Threshold stimulation of each electrode combination at best location and orientation.
Figure 3.16-6. Design 16 – Left Phrenic Nerve Threshold Stimulation Comparison

Note: Threshold stimulation of each electrode combination at best location for the left phrenic nerve. Values in red were estimated from transcribed notes.
Figure 3.16-7. Design 16 – Right Phrenic Nerve Threshold Stimulation Comparison

Note: Threshold stimulation of each electrode combination at best location for the right phrenic nerve. Values in red were estimated from transcribed notes.
Figure 3.16-8. Acute Pig Experiment 10A – Electrode Impedances

Left LIVE Petal Impedance

Right LIVE Petal Impedance

Note: Electrode impedances of each electrode combination over the course of the experiment.
For pig B, the electrode petals were successfully removed from the vessel without being retracted back into the introducer (Figure 3.16-9; Figure 3.16-10). Careful analysis of the device showed clotting on the petal, inside the stabilizer unit, and at the introducer exit. Some blood was also found between the sandwiched silicone sheets and inside the pre-curling silicone tube. However, it was relatively easy to remove this blood after washing the device. The blood that was inside the stabilizer tube was more difficult to remove. After washing the device, it was found that the PTFE coated electrode leads were detaching from the surface of the stainless steel hypodermic tubes.

*Figure 3.16-9. Design 16 – Retrieval of Fully Deployed Petal in Acute Pig 10B*

Note: Retrieval of fully deployed electrode petal from the left external jugular vein. A) Prior to being removed from body. B) Immediately after removed from the body.
The device was left in place during the dissection of Pig A. This was to see where the petals were in relation to the nerves (Figure 3.16-11). After the petals were located, with great ease, the device was retracted back into the introducer tube and the device removed from the body. It was found that there was blood clotting around the introducer when inside the vein (Figure 3.16-12; Figure 3.16-13). Also, when the device was removed and prepared for cleaned, it was found that blood was clotting around the petal, stabilizer unit, and introducer. Again, there was blood found between the two silicone sheets. However, the blood clots were easy to remove from the device. Otherwise, there were no drastic findings when the device was examined by microscope.
Figure 3.16-11.  Design 16 – Location of Electrode Petals

Note: A) Location of left electrode petal. B) Location of right electrode petal.
Figure 3.16-12. Design 16 – Retrieval of Fully Deployed Petal in Acute Pig

Note: A) Retracting electrode petals into introducer. B) Removing device and introducer from the body.
3.17 Design 17 – Acute Pig Experiment 11 – Three Lumen Catheter

After consultation with clinicians and doctors in the medical field, they were worried about introducing another device into a patient. Therefore, this design integrated electrode petals with a three-lumen catheter (Figure 3.17-1; Figure 3.17-2; Figure 3.17-3; Figure 3.17-4), which is a typical device that is inserted into patients in the ICU. This concept again used two independently controlled petals, a stabilizer unit, and many concepts from the previous design. Specifically, four Pt-Ir electrodes were embedded onto a silicone sheet, with the electrode leads sandwiched between two silicone sheets. The electrode petal was held in place by a long stainless steel hairpin rod, with one end inserted inside the hypodermic tube and the remaining length micro-welded along the entire length of a single stainless steel hypodermic tube. Using only one hypodermic tube reduced the overall dimensions of the device, while the micro-welded hairpin rod allowed for a preferred bending direction and orientation. In addition, by micro-welding the hairpin rod along the entire length of the hypodermic tube, there was added security in event that the petal detached.
For each of the two petals, an outside-etched PTFE tube encapsulated the hypodermic tube, hairpin rod, and electrode leads. These hollow tubes act as catheter lumens. At the proximal ends of each PTFE tube were catheter ports in which a luer lock syringe could attach to and administer fluids into the body. The third catheter lumen was the introducer, which had a catheter port directly embedded into the handle of the percutaneously inserted introducer. One PTFE tube was adhered to the inside-etched PTFE stabilizer tube. Again, this stabilizer prevented the hypodermic tubes from interacting with each other and rattling within the introducer. Two small PTFE balls were also adhered to the outer surface of the PTFE tubes. These balls were necessary for a new method of placing the electrode petals (P-Mode), which was being studied by Mark Nolette of the Neurokinesiology Lab.

*Figure 3.17-1. Design 17 – Computer Representation of Three-Lumen Catheter Design*

Note: Three-lumen catheter designed created using SolidWorks 2010.
**Figure 3.17-2. Design 17 – Electrode Petal Design with Catheter Lumens**

Note: A) Electrode petals with stabilizer tube. B) Electrode petals with catheter lumen exit. C) Electrode petals with introducer tube.
Figure 3.17-3. Design 17 – Proximal End of the Device

Note: Proximal end of the device showing catheter ports, flags, connector pins, and P-Mode.
This design was tested in Acute Pig Experiment 11. A cut down procedure was used to expose the left external jugular vein. Next, an introducer was inserted into the vein using the Seldinger technique. With the electrode petals retracted into a plastic tube, which mated to the end of the introducer, the petals were advanced into the external jugular vein (Figure 3.17-5). Epimysial EMG electrodes were used to capture diaphragm activity. With the device introduced into the vein, quick mapping at every 1 cm increment was completed using electrodes 1-2 in the left orientation (270°) for the left phrenic nerve and in the right orientation (90°) from the right phrenic nerve (Figure 3.17-6). It was determined that the left phrenic nerve was 6.5 cm from the exit of the introducer, whereas the right phrenic nerve was 10.7 cm from the exit of the introducer.
Figure 3.17-5. Design 17 – Insertion of Device Into Left External Jugular Vein

Note: Introducer inside the left external jugular vein with LIVE device inside the body.
Supramaximal EMG was also collected in this experiment. Previous experiments attempted to capture this data; however, stimulation amplitudes were usually below supramaximal levels or there were issues with completing the mapping protocol. Regardless, this experiment showed a response curve for supramaximal EMG (Figure 3.17-7). In general, as the electrode petal was further away from the phrenic nerve, higher stimulation amplitudes were needed to achieve maximal diaphragm contraction. However, as the electrode petal advanced closer to the phrenic nerve, lower stimulation levels were needed to fully contract the diaphragm. This information was useful for other aspects of the project, such as programming of the control unit and pacing regimes.
Figure 3.17-7. Design 17 – Left and Right Phrenic Nerve Threshold and Supramaximal Curves

Note: Comparison of phrenic nerve threshold and supramaximal mapping curves in Acute Pig Experiment 11. Left phrenic nerve (top). Right phrenic nerve (bottom).

The left electrode petal was moved to 6.5 cm and the right electrode petal was moved to 11.7 cm. With the petals at these locations and in their proper orientations,
various electrode combinations were tested (Figure 3.17-8; Figure 3.17-9). It was found that electrodes 3-2 and electrodes 4-2 were both equally efficient. Electrodes 3-2 were a longitudinal pair, whereas electrodes 4-2 were a transverse pair. This suggests that there was no preferred stimulation direction. For the right phrenic nerve, electrodes 4-3 were the most efficient pair. This pair is the furthest separated electrodes with a distance of 10 mm. Also, this pair was neither a transverse or longitudinal direction, which further suggests that there was no preferred stimulation direction. Finally, it was also found that flushing saline solution through the catheter lumens slightly lowered the impedances (Figure 3.17-10). This could be due to the saline solution washing away any blood clot formation on the electrode petals.

*Figure 3.17-8. Design 17 – Left Phrenic Nerve Threshold Stimulation Comparison*

<table>
<thead>
<tr>
<th>Electrode 1</th>
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**Note:** Threshold stimulation of each electrode combination at best location for the left phrenic nerve. Values in red were estimated from transcribed notes.
Figure 3.17-9. Design 17 – Right Phrenic Nerve Threshold Stimulation Comparison

Note: Threshold stimulation of each electrode combination at best location for the left phrenic nerve. Values in red were estimated from transcribed notes.
Figure 3.17-10.  Acute Pig Experiment 11 – Electrode Impedances

Left LIVE Impedances

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<th>Impedance (log₂ kOhm)</th>
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<td>1-3</td>
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<td>1-4</td>
<td>8:50PM</td>
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<td>3-C</td>
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Right LIVE Impedances

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<th>Impedance (log₂ kOhm)</th>
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</table>

Note: Electrode impedances of each electrode combination over the course of the experiment.

After the rest of the experiment protocol was completed, the device was removed from the body without retracting the petals into the introducer tube (Figure 3.17-11;
Figure 3.17-12). It was found that there was blood clotting within the introducer, around the electrode petals, inside the stabilizer unit, and inside the PTFE catheter lumens. Furthermore, there was blood found between the two silicone sheets. However, the blood clots were easy to remove from the device. After testing each of the three catheter ports, it was found that fluid would leak from the valve of the introducer (Figure 3.17-13). This is due to the PTFE catheter lumens exiting the introducer, as there was not a tight seal. Otherwise, the two manufactured PTFE lumens were still in proper working condition.

Figure 3.17-11. **Design 17 – Removed Device in Acute Pig 11**

Note: Blood clotting formed on the device. A) Immediately after being removed from the body. B) Electrode petals immediately after being removed.
Figure 3.17-12.  Design 17 – Removed Device in Acute Pig 11


Figure 3.17-13.  Design 17 – Catheter Lumen Testing

Note: Functionality testing of the three catheter lumens.
3.18. Design 18 – Catheter Prototypes

The previous concept revealed that a three-lumen catheter with electrodes is capable of activating the phrenic nerves. Although there were some issues with the catheter lumens for P-Mode, the device performed well in the animal experiment. The materials were safe and compatible within the animal. Furthermore, it was relatively easy to insert, deploy, and retrieve the electrode petals. Also, there were no issues with advancing or retracting the petals within the veins. However, one concern was the overall diameter of the device. The previous design used an introducer to insert the device into the left external jugular vein. However, this prototype design further reduced the overall size of the device, improved upon the catheter ports and P-Mode interaction, while utilizing many concepts from the previous designs (Figure 3.18-1; Figure 3.18-2; Figure 3.18-4).

Figure 3.18-1. Design 18 – Computer Representation of Three-Lumen Catheter Design

Note: Three-lumen catheter designed created using SolidWorks 2010.
Figure 3.18-2. Design 18 – Final Assembly of the Three-Lumen Catheter Design

Note: A) Overview of various components of the design. B) Electrode petals within stabilizer tube and introducer. C) Electrode petals and stabilizer tube.

Two independently controlled LIVE devices, one for each of the phrenic nerves, could be advanced through a percutaneously inserted introducer. Each LIVE device utilized an asymmetric peanut-shaped insulating petal with four Pt-Ir electrodes, with a minimum of 3 mm insulation around each electrode (Figure 3.18-3). The electrode leads were sandwiched between a reinforced silicone and a non-reinforced silicone sheet. Again, the asymmetric shape of the petal maximized the separation of the lateral electrodes, while minimizing the size of the introducer tube that was needed.
The silicone petal was attached to a stainless steel hypodermic tube by a stainless steel hairpin rod that was micro-welded along the entire length of the hypodermic tube. This essentially stapled the petal in place and prevented the silicone petal from detaching from the stainless steel tube. Micro-welding the hairpin rod to the hypodermic tube increased the robustness of the design, and also allowed the hairpin rod to act as an electrical ground electrode. A short silicone tube covered the junction of the silicone petal and the hypodermic tube. This ensured a smoother profile and transition from the hypodermic tube to the silicone electrode petal. This silicone tube also developed a pre-curving effect, which aided in retracting and retrieving the electrode petals into the introducer.

The remaining electrode leads and stainless steel hypodermic tube were inserted through an outside-etched PTFE tube. The hollow lumen of the PTFE tube allowed fluid
to easily pass through the open space. This PTFE tube was adhered to the inside of a short inside-etched PTFE tube. This short PTFE tube stabilized the device when inside the introducer and prevented the device from rattling within the introducer. This stabilizer tube also allowed for a second LIVE to be inserted through the remaining lumen space. This second device had the same construction as previous described LIVE. However, this LIVE was free-floating within the stabilizer, which allowed this LIVE to be easily advanced and rotated. At the proximal ends of each LIVE were flag markers that match the orientation of the electrode face. In addition, catheter ports and electrical connectors were located at the proximal end of each LIVE.

**Figure 3.18-4. Design 18 – Deployment of Electrode Petals from Introducer**

![Figure 3.18-4](image_url)

Note: A) Right distal electrode petal exiting the introducer lumen. B-C) Left proximal electrode petal partially exiting the introducer tube.

After careful thought and consideration, the stabilizer design closely resembled a common three-lumen catheter system, where two lumens were associated with each
LIVE and the third lumen was associated with the introducer. Instead of using the various PTFE tubes, the LIVE devices could be integrated into a commercially available 8.5 Fr (2.8 mm OD) polyurethane catheter, which are commonly used in intensive care units (Figure 3.18-5). This concept used a five-lumen catheter system. Three lumens could be used to administer fluids and drugs into the body, whereas the two larger lumens were used to house the electrode leads and stainless steel hypodermic tubes. The largest lumen had its exit at the distal tip of the catheter, whereas the smaller lumen had its exit at the side of the catheter.

*Figure 3.18-5. Design 18 – LIVE Devices Embedded into 8.5 French Catheter*

To ensure that these components fit within each lumen, a smaller stainless steel hypodermic tube was utilized. This further reduced the overall stiffness of the device and could be used to advance, retract, and rotate the petals. The hairpin rod that stapled the electrode petal in place was micro-welded to this hypodermic tube and acted as an electrical ground electrode. To further reduce the size of the device, three Pt-Ir
electrodes were used. This eliminated one of the electrode leads and reduced the outer diameter of the electrode leads and hypodermic tube, which was encapsulated within a PTFE heat shrink tube. The heat shrink tubing ensured a smooth profile within the catheter lumen.

The three Pt-Ir electrodes were orientated in an equilateral triangle configuration (Figure 3.18-6; Figure 3.18-7; Figure 3.18-8). By doing so, different stimulation directions could be tested and used to activate the phrenic nerves. Two electrodes were assigned to stimulate the phrenic nerves, and the unused electrode was assigned as the ECG electrode. These electrodes were mounted on top of a non-reinforced silicone sheet, with the electrode leads sandwiched between another non-reinforced silicone sheet. The thinner petal ensured a softer interaction with the blood vessel.

**Figure 3.18-6. Design 18 – Thinner Electrode Petal with Three Electrodes**

Note: Electrode petals exiting catheter lumens. A) Top view. B) Side view.
**Figure 3.18-7.** Design 18 – Asymmetric Proximal Peanut-Shaped Petal with Three Electrodes

Note: Three electrodes in a triangular formation exiting the catheter lumen.
Figure 3.18-8. Design 18 – Asymmetric Distal Peanut-Shaped Petal with Three Electrodes

Note: Distal electrode petal with three further separated electrodes in a triangle formation.

A percutaneously inserted introducer could be used to insert the modified catheter system into the body. Once inside the body, the independently controlled LIVE systems could be used to find the phrenic nerves. Once the phrenic nerves were located, the catheter could be positioned such that the electrode petals were in proper locations and orientations (Figure 3.18-9). To retrieve the device, the modified catheter and petals could be pulled through introducer and the entire system removed from the body.
Note: Electrode petals embedded within a catheter system inside the human body.

These prototypes have not been tested in animals. However, since these prototypes have evolved from previous working designs, and through bench testing and analysis, there was little concern or doubt that these concepts would not function properly within the animal model.
4. Design Recommendations

From the various design evolutions, there are certain aspects that should be included in the final design of the intravascular electrodes. The first is the amount of insulation around each electrode. By varying the amount of insulation, ultimately the electrode efficiency is disrupted. The number of electrodes, the electrode shape and size, spacing, and configuration also dictates stimulation efficiency. Furthermore, material selection also plays a vital role in stimulation efficiency. Finally, device stiffness is an importation consideration as it ensures the device conforms to the vessel curvature without damaging vein walls or harming the user.

4.1 Electrode Insulation and Configuration

From previous computer simulations, it was determined that 2 mm of insulation surrounding an electrode is sufficient in reducing the current leakage throughout the blood. Ideally, an infinite length of insulation surrounding each electrode would eliminate any current leakage throughout the blood. However, this is impractical and unfeasible. In animal experiments, the amount of electrode insulation was unintentionally varied and the results are shown in Table 4.1-1. Figure 4.1-1 and Figure 4.1-2 shows the threshold charge needed for each electrode combination. As shown, 3 mm of insulation around each electrode reduced the amount of charged needed to activate the phrenic nerves. However, it should be noted that different simulators were used for Chronic Pig Experiment 3 and Acute Pig Experiments 10 and 11. For Chronic 3, a voltage-modulated stimulator was used and the charge injection calculated based on impedances at the each electrode, where as Acute Pig Experiments 10 and 11 used a current-modulated stimulator.
Table 4.1-1. Electrode Insulation Around Each Electrode

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Dimension: 1.5x1 1.5x1 1.5x1 1.5x1 1.5x1 1.5x1 1.5x1 1.5x1

Figure 4.1-1. Electrode Threshold Charge per Electrode Combination for the Left Phrenic Nerve

Insulation Length

Left Phrenic Nerve

Note: Electrode charge for each electrode combination.
The number of electrodes varied throughout the evolution of the device. At one point, 16 electrodes with a ground reference electrode, was inserted into an animal. As the device evolved, fewer electrodes were needed. This was due to the location of the phrenic nerves in relation to the veins. By taking advantage of the anatomy of the animals, the number of electrodes reduced to four. This number can be further reduced to three. Two electrodes can be used for stimulation and one electrode can be assigned as an ECG electrode. A common ground electrode can also be incorporated into the final design.

Platinum-Iridium (Pt-Ir) electrodes were used in the latter part of the evolution of the device. Pt-Ir electrodes are commonly used for neural stimulation applications due to their biocompatibility, inertness, and high corrosion resistance. The charge-injection limit for Pt-Ir electrodes has been found to be 300 to 350 μC cm⁻² (Cogan, 2008). Charge densities above this limit cause the electrodes to corrode over time. Therefore, it is recommended that electrode shape and size is designed for this limit.
Table 4.1-2 shows the best electrode pairs that were used for Chronic Pig Experiment 3 and Acute Pig Experiments 10A and 11. Also shown is the electrode separation of each electrode and the stimulation direction. The Atrotech OY system uses quadripolar electrodes and, through various experiments, concluded that 5 mm-separated electrodes were sufficient in activating the phrenic nerves (P. P. Talonen, Baer, Hakkinen, & Ojala, 1990). Using this information and information from the animal experiments, it is recommended that the electrodes be 5 to 9 mm separated.

Table 4.1-2 also reveals the various stimulation directions of the most efficient pairs of electrodes. As shown, there were no conclusive or preferred stimulation directions between longitudinal and transverse electrode pairs. In fact, electrodes that combined both stimulation directions performed equally well. This is due to the fact that phrenic nerves, as they course down towards the diaphragm, may not be perfectly parallel or perpendicular to the electrode petal and the direction of stimulation. Therefore, it is recommended that the electrodes be configured in such a way that accounts for anatomical differences and the chance of angled nerves within the stimulation pathways. One possible configuration could have the three electrodes in a triangular formation (Figure 4.1-2). This formation allows for various stimulation pathways and accounts for anatomical differences.
Table 4.1-2. Best Electrode Pairs and their Electrode Separation

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<td>Chronic 3 – Day 7</td>
<td>1-2</td>
<td>Longitudinal</td>
</tr>
<tr>
<td>Chronic 3 – Day 21</td>
<td>2-1</td>
<td>Longitudinal</td>
</tr>
<tr>
<td>Acute 10A</td>
<td>1-3</td>
<td>Transverse</td>
</tr>
<tr>
<td>Acute 11</td>
<td>3-2</td>
<td>Mix</td>
</tr>
<tr>
<td></td>
<td>4-2</td>
<td>Transverse</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 4.1-2. Phrenic Nerve Locations Relative to Stimulation Pathways for a Three-Electrode Design

Note: Left proximal petal with three electrodes relative to various phrenic nerve (yellow) locations (left). Right distal petal with three electrodes relative to various phrenic nerve locations (right).
4.2 Material Selection

All the materials used in the animal experiments were safe and biocompatible. The 21-Day chronic pig experiments showed that the material choices were appropriate, as there were no adverse effects of having the device implanted. The latest LIVE devices consists of two non-reinforced silicone sheets, silicone tubing, a stainless steel rod, a stainless steel hypodermic tube, PTFE coated electrode leads, and various PTFE tubing. The catheter system is made from extruded polyurethane. All these materials are safe and biocompatible. If future designs utilize different materials, such as polyurethane, polyethylene, or nitinol, it is recommended that they have similar mechanical properties as the aforementioned materials.

4.3 Device Stiffness

Device stiffness is an important property in prototype development. A stiff device is easier to insert and advance within the body. However, a device too stiff would prevent the electrodes from properly conforming to the vessel curvature. Also, a stiff device has the potential of damaging or even puncturing the vein walls, which could have drastic consequences. Furthermore, studies have shown that a stiff catheter has a higher risk of thrombus or fibrin sleeve formation, which is an important risk factor in the development of central venous catheter infections. This could be due to the higher incidence of trauma during insertion and to the local pressure of the catheter and its tip on the walls of the vein (Polderman & Girbes, 2002).

The stiffness, the amount of bending when a force is applied at a given point, for each design utilizing a single asymmetric petal was determined. The force needed to deflect the tip of the device 2 to 14 cm from a fixed point (10, 15, and 20 cm Lengths) was measured (Figure 4.3-1).
Note: Experimental setup to measure device stiffness.

With these values known, the stiffness of each device can be calculated using the following equation:

\[ k = \frac{F}{d} \quad (1) \]

where, 
\( k \) = Stiffness (N/m) \\
\( F \) = Force (N) \\
\( d \) = deflection (m)

The results are summarized in Table 4.3-1 and Figure 4.3-2. The values in Table represent the force required to displace the device by 1 cm. For example, the device used in Chronic Pig Experiment 3, with 10 cm of the device free to bend, a stiffness of 0.10 N/cm was generated, meaning it requires 0.10 N to deflect the device 1 cm. It was found that, as the prototypes evolved, the stiffness of the device decreased. The stiffness of the 8.5 Fr 5-lumen catheter was also measured. By inserting one LIVE within its distal lumen, such as in Prototype 2, the stiffness doubled at a length of 10 cm. At a length of 15 cm, the stiffness of the device increased by one-third. Finally, at a length of 20 cm, the stiffness increased by a factor of ten.
Table 4.3-1. Device Stiffness

<table>
<thead>
<tr>
<th>Device</th>
<th>Stiffness (N/cm ± 0.3%)</th>
</tr>
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<tr>
<td></td>
<td>Bending Length (L)</td>
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<tr>
<td></td>
<td>10 cm</td>
</tr>
<tr>
<td>Chronic 3</td>
<td>0.100</td>
</tr>
<tr>
<td>Acute 9</td>
<td>0.059</td>
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<tr>
<td>Acute 10</td>
<td>0.065</td>
</tr>
<tr>
<td>Acute 11</td>
<td>0.018</td>
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<tr>
<td>Prototype 1</td>
<td>0.016</td>
</tr>
<tr>
<td>Prototype 2</td>
<td>0.010</td>
</tr>
<tr>
<td>5-Lumen Catheter (8.5 Fr)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Note: P-mode system prevented clamping of the device for Acute 11 at 20 cm.

Figure 4.3-2. Device Stiffness

One study evaluated the bending stiffness, the resistance of an applied bending moment to the resulting deflection, of 29 central venous catheters, approximately 7 Fr in diameter, made of various materials, including silicone elastomer, polyethylene, polyurethane, polyvinylchloride, and PTFE (Stenqvist, Curelaru, Linder, & Gustavsson, 1983). From this study, the range of catheter bending stiffness ranged from $1.1 \times 10^{-6}$ to $203.3 \times 10^{-6}$ Nm$^2$. Replicating their experimental setup and with force, length, and
deflection values known, the bending stiffness can be calculated from the following equation, with results summarized in Table 4.3-2:

\[
EI = \frac{FL^3}{3d}
\]  

(2)

where, \( EI \) = Bending stiffness (Nm\(^2\))

\( F \) = Force (N)

\( L \) = Bending length (m)

\( d \) = Deflection (m)

The value of \( EI \) is independent of experimental setup and is an inherent property of each material, meaning that the \( EI \) value remains constant if other values for L and d are chosen. \( E \) and \( I \) are two factors that contribute to the total catheter stiffness (bending stiffness). \( E \) represents the elastic properties of the material, called Young’s Modulus, whereas \( I \) is the moment of inertia, a geometric property, of the device (Stenqvist, Curelaru, Linder, & Gustavsson, 1983).

**Table 4.3-2. Device Total Stiffness (Bending Stiffness)**

<table>
<thead>
<tr>
<th>Device</th>
<th>Bending Stiffness (10(^{-6}) Nm(^2) ± 0.3%)</th>
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</thead>
<tbody>
<tr>
<td>Chronic 3</td>
<td>4315</td>
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<td>Acute 9</td>
<td>2481</td>
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<tr>
<td>Acute 10</td>
<td>2462</td>
</tr>
<tr>
<td>Acute 11</td>
<td>1017</td>
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<td>Prototype 1</td>
<td>614</td>
</tr>
<tr>
<td>Prototype 2</td>
<td>422</td>
</tr>
<tr>
<td>5-Lumen Catheter (8.5 Fr)</td>
<td>178</td>
</tr>
<tr>
<td>2-Lumen Catheter (8.5 Fr)</td>
<td>123</td>
</tr>
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<td>3-Lumen Catheter (7 Fr)</td>
<td>94</td>
</tr>
<tr>
<td>Guidewire</td>
<td>112</td>
</tr>
<tr>
<td>Hairpin Loop</td>
<td>135</td>
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</table>
It was found that earlier prototypes utilizing the largest hypodermic tubes had the highest stiffness (Figure 4.3-3). As the device evolved and smaller gauges of hypodermic tubes were used, the stiffness decreased. The bending stiffness of the 5-lumen catheter and 3-lumen catheters were also determined. It was found that the most evolved prototype utilizing the 5-lumen catheter with the right LIVE petal inserted through the distal lumen, the bending stiffness was 2.4-times greater than the catheter by itself. Also, the bending stiffness was over a 2-fold increase than the commercially available catheters presented in the study. However, it should be noted that smaller French catheter sizes were tested.

During the pig experiments, there were no issues with punctured veins. This could be due to the fact that the external jugular vein joins with the SVC in a fairly linear fashion, meaning that the stiffer devices did not have a problem with conforming to the vessel curvature. Regardless, for human applications, it is recommended that requirements be generated based on FDA and international central venous catheter guidelines and standards (ISO 10555-1 [1995] and ISO 10555-3 [1996]). These standards provide insight on sterilization methods, biocompatibility, surface profile, effective length, force at break, hub leakage, lumen flow rate, radio-detectability, tip
configuration, distance markings, lumen markings, catheter stiffness, catheter elongation, burst pressure, labeling, and flexural fatigue tolerance, to name a few.

4.4 Mapping Protocol

Future concepts of the device should have the LIVE catheter system integrated with the P-Mode. Integrating the two systems will reduce clinician confusion and reduce placement times of the LIVE device. Various manufacturing processes can be used to integrate these systems, such as insert molding. Once a human version of the device is ready to be tested in vivo, it is recommended that a smaller step size be used during mapping protocol. In the animal experiments, a step size of 1 cm was used during mapping; however, in some cases, this length was too long, often missing the best location of the phrenic nerves.

In addition, the general locations of the phrenic nerves are usually known. This can be determined from external measurements and landmarks from the insertion point to the approximate location of the nerves. With this information known, placement of the electrodes can be expedited by directly moving the electrodes to this location. Next, using a smaller step size during mapping, a more accurate map can be generated. Furthermore, for the animal experiments, up to 10 mA was injected into the animal. This was necessary to obtain the steep response curve. However, in some instances, 0.25 mA was sufficient to activate the phrenic nerves. Therefore, it is recommended that, for human subjects, the safe current limits be lowered to reduce risks to the patient.

The computer simulation that was preformed prior to the development of prototype electrodes gave account to how angular rotation of the electrodes from the optimal location changed the amount of charge reaching the nerve. It was difficult to test this concept in vivo. However, it is recommended that P-Mode play a larger role in locating the optimal depth and angle of the phrenic nerve instead of solely relying on the electrode configuration. One possible solution is performing a quick map to determine the approximate locations of the nerves. Once the nerves have been located, the angular displacement of the electrodes can be altered to determine the optimal electrode angle.
5. **Conclusions and Future Directions**

Mechanical ventilation (MV) is routinely used in intensive care units (ICU) to provide artificial ventilation to those who cannot breathe volitionally. Although life saving, when combined with sedation, MV has the ability to rapidly decrease diaphragmatic function, a syndrome known as Ventilator-Induced Diaphragmatic Dysfunction (VIDD). Prolonged mechanical ventilation can lead to rapid diaphragm atrophy (Levine et al., 2008), leading to slower patient recovery, which often results in ventilator dependence. In turn, there are higher incidences of Ventilator-Acquired Pneumonia (VAP) and nosocomial infections, longer stays in the ICU, higher hospitalization costs and diminished quality of life.

To protect the diaphragm of ventilated patients, a viable alternative to mechanical ventilation is phrenic nerve or diaphragmatic pacing via functional electrical stimulation, which results in a more natural form of artificial ventilation that closely mimics natural breathing. Currently, there are four commercially available pacing systems for those requiring long-term ventilator assistance. However, these systems are highly invasive and require lengthy and costly surgery, unsuitable for those in the ICU. The need for a minimally invasive option that prevents respiratory failure while maintaining diaphragmatic function is apparent, and has the potential to reduce patient hospital stays in the ICU and the health care budget.

The Neurokinesiology Lab at Simon Fraser University (SFU), in conjunction with Lungpacer Medical Inc., addresses this issue by developing a minimally invasive transvascular phrenic nerve pacing system. Disposable Lungpacer Intravascular Electrodes (LIVE) are percutaneously inserted into a main blood vessel in the neck or thorax, such as the jugular veins or the subclavian vein. Once inserted, the intravascular electrodes can be placed near the left and right phrenic nerves, which innervate the diaphragm, and pace the diaphragm in synchrony with a mechanical ventilator. By doing so, it is expected that diaphragm atrophy can be prevented, reduced, or even reversed.
In patients on mechanical ventilation, allowing the patient to wean off the ventilator sooner.

In this thesis, the evolution of the LIVE devices was thoroughly documented. Various prototypes were designed, developed and tested in the Neurokinesiology Lab as well as in pigs. Early prototypes were first inserted into cadaver experiments where pig anatomy, vasculature and phrenic nerve locations were also documented. As knowledge of the pig anatomy grew, prototypes were next inserted into acute one-day pigs. Various insertion points were tested, and it was eventually concluded that the left external jugular vein was the best entry point to gain access to the left and right phrenic nerves. These prototypes utilized an inside-out electrode cuff to stimulate the phrenic nerves. However, due to its difficulty in deploying and retrieving the cuffs, this concept was abandoned.

Another phase of acute pigs tested electrodes that were attached to springy arms. This concept had many advantages, as the springy arms would push the electrodes towards vein wall and closer to the phrenic nerves. Also, this concept was relatively easy to introduce, deploy, and retrieve. With these advantages, this concept was adapted for 21-Day chronic pigs. In these aseptic experiments, the device was inserted into the left external jugular vein and the electrodes placed near the phrenic nerves. The pig was returned to the care of animal care staff and a follow-up experiment was conducted midway through the 21 days. It was found that the chosen materials were safe, as there were no adverse effects of having the device implanted for 21 days. Furthermore, information regarding device shape, size, electrode configuration, insertion methods and nerve orientation with respect to major veins was gathered.

With increased knowledge from the chronic experiments, another set of acute experiments was used to test prototypes. These prototypes utilize a single insulation pad with multiple electrodes, called a petal, to stimulate the phrenic nerves. A percutaneously inserted introducer using the Seldinger technique was used to insert the LIVE device into the left external jugular vein. With the introducer in place, the LIVE devices were inserted through its hollow core. Instead of using the springy arms to push the petals towards the vessel walls, these concepts took advantage of the anatomy of the vessels and their position relative to the phrenic nerve. Various iterations were developed, which eventually lead to the decision of embedding the LIVE devices into a
five-lumen 8.5 Fr (2.8 mm OD) catheter. These central venous catheters are commercial available and are commonly used in many ICUs. Although untested in a pig experiment, many concepts were taken from previous acute experiments. This leads to the assumption that there should not be any problems in an animal experiment.

This thesis described the design evolution of intravascular electrodes for a pig model. To transfer this knowledge for human application, it is recommended that, first, human cadaver experiments be performed to determine vessel sizes, nerve locations and orientations, and general anatomy of the thoracic region. With this information, a new set of design requirements, following proper FDA and international standards, should be generated for the human version of the device, with the results and findings from this thesis acting as a guideline. These requirements should include, but not limited to, biocompatible material choices, number of electrodes, electrode array configuration, catheter length, catheter profile, depth markings, product labelling, device stiffness and flexibility, catheter trackability, pushability, torqueability, retraction force, lumen fluid flow properties, and sterilization methods.

Future experiments are needed to test the three-electrode petal concept and the catheter prototype. Both electrode configuration and spacing, as well as insulation length should be varied until an optimal configuration is determined. This can be achieved by testing more than one concept in a given experiment. This will provide conclusive information regarding electrode petal configuration. Once this is known, the findings and recommendations from this thesis can then be used in the design and development of intravascular electrodes for human application.
References


Appendices
Appendix A. Voltage-Modulated Stimulator – Calibration Table

Table A1. Voltage-Modulated Calibration (1.48 kΩ Load)

<table>
<thead>
<tr>
<th>Stim Level</th>
<th>0 kΩ</th>
<th>1.2 kΩ</th>
<th>3.2 kΩ</th>
<th>10 kΩ</th>
<th>32.4 kΩ</th>
<th>50 kΩ</th>
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**BOLD** denotes extrapolated data

Figure A-2. Voltage-Modulated Calibration Curve (1.48 kΩ Load)
Table A2. Voltage-Modulated Calibration (0.508 kΩ Load)

<table>
<thead>
<tr>
<th>Stim Level (K)</th>
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<th>10 kΩ</th>
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</table>

**BOLD** denotes extrapolated data

Figure A-2. Voltage-Modulated Calibration Curve (0.509 kΩ Load)
Appendix B. Seldinger Technique

(Taken directly from Catheterization Replacement Of The Needle In Percutaneous Arteriography by Sven Ivar Seldinger)

Equipment

1) A puncture needle with stilette.
2) A flexible rounded-end metal leader with increased flexibility of its distal 3 cm.
3) A polyethylene tube, of the same diameter as the needle, with an adapter for the attachment of a syringe.

Technique (see below Figure B-1)

a) After local anaesthesia, the artery is punctured percutaneously at a relatively small angle.
   After puncture it is best to rotate the needle 180° and push it a little into the artery using the bleeding as a guide to ensure that the needle remains in the artery. Puncture of arteries smaller than the femoral artery is facilitated by using an inner needle as a guide over which the outer needle is directed into the artery.

b) The supple tip of the leader is inserted a very short distance into the lumen of the artery through the needle.

c) The leader is held in place and the needle removed.
   At this moment bleeding should be controlled by pressure on the artery proximal to the puncture site, because the diameter of the leader is smaller than the hole in the artery.

d) The catheter is threaded on to the leader; when the tip reaches the skin the free end of the leader must protrude from the catheter.

e) The catheter and leader are gripped near the skin through which they are inserted. The catheter enters the artery easily as an opening has already been made by the needle. The catheter and leader are pushed just far enough to ensure that the tip of the former is in the lumen of the vessel.

f) The leader is removed and the catheter directed to the level required, after good arterial bleeding through the catheter has been obtained. The unsupported catheter is usually pushed up the vessel without difficulty, but occasionally the leader must be re-introduced into the catheter in order to support it. The leader should not be passed beyond the tip of the catheter.
Figure B-1. Seldinger Technique