Diaphragm Pacing with Endovascular Electrodes

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Abstract

Patients in intensive care units (ICU) who require mechanical ventilation (MV) for ≥1 week have high risk of medical complications such as ventilator-acquired pneumonia (VAP) and nosocomial infections, are 7X more likely to die in the ICU, and account for 50% of the ICU budget and 1/6 of all hospital in-patient costs in the US. In patients on MV the diaphragm muscle has been shown to atrophy rapidly and profoundly contributing to complications and frequent failure to wean from ventilators. We are developing endovascular electrodes suitable for percutaneous insertion in critically ill patients with only local anaesthesia, intended to electrically pace the phrenic nerves in order to maintain diaphragm strength and resistance to fatigue, improve ventilation, facilitate rapid weaning from MV, shorten the duration of ICU stay, reduce mortality, and decrease overall hospitalization costs. We present proof-of-concept, safety and stability results obtained with prototype electrodes that were implanted in pigs acutely or chronically for up to 3 weeks.

Keywords: *endovascular electrode, transvascular nerve stimulation, diaphragm pacing, phrenic nerve pacing, diaphragm atrophy, intensive care, mechanical ventilation, ventilator-acquired pneumonia, failure to wean.*

Introduction

Patients in intensive care units (ICU) who become dependent on mechanical ventilation (MV) are at high risk of complications such as ventilator-acquired pneumonia (VAP) and nosocomial infections, are seven times more likely to die in the ICU, and account for half the ICU budget and one-sixth of all hospital in-patient costs in the US [1].

Patients who require life-long assisted ventilation can sometimes benefit from electrical "pacing" of the diaphragm, as a partial or full alternative to mechanical ventilation [2]. In the past 30 years about 1,600 adult and paediatric patients have received permanently implanted phrenic nerve pacing systems. However, these systems require complex surgery under general anaesthesia, so they are not a feasible option for fragile ICU patients.

In MV patients in the ICU the diaphragm muscle is known to atrophy rapidly and profoundly [3] which contributes to frequent failure to wean from MV [4]. In order to support the ability of ICU patients to breathe naturally again and successfully wean from MV, we are developing novel, minimally invasive electrodes that can be deployed endovascularly in close proximity to the phrenic nerves and activated to produce rhythmic diaphragm contractions [5].

Nerve stimulation with endovascular electrodes is highly dependent on electrode design, location and orientation. Clinical success will require recruiting the phrenic nerves with low current and with high selectivity, to avoid activating other structures such as the vagus nerves, since they course 2-3 cm medial with respect to the phrenic nerves.

To validate our intravascular electrode designs we modeled the dielectric properties of the vessel wall, fluid and surrounding tissues and determined how these parameters alter the dispersion of the electric field and influence stimulation efficacy for various electrode geometries and locations. Since blood is a highly conductive medium, the stimulation current is substantially reduced by addition of an insulating electrode backing [5]. We subsequently tested intravascular electrode performance in acute and 3-week chronic pig implants. We present here our model predictions and initial findings on electrode selectivity, stability and safety.

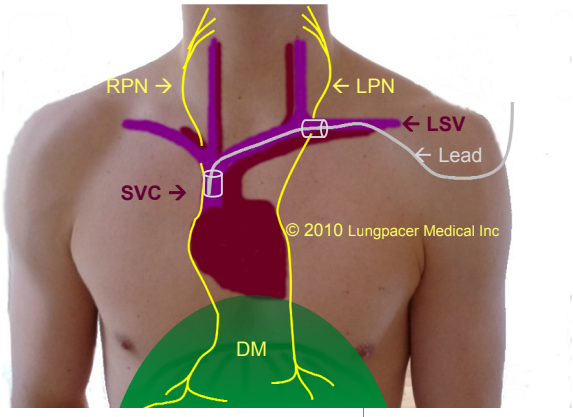

Figure 1: Diagram of target nerves and electrode locations inside central veins. **LPN**: left phrenic nerve **RPN**: right phrenic nerve **LSV**: left subclavian vein **SVC**: superior vena cava **DM**: diaphragm muscle

Material and Methods

We modeled the requirements for selective phrenic nerve activation with COMSOL Multiphysics 3.3a (COMSOL Inc., Stockholm Sweden), a graphical environment useful for changing parameter values that could not be conveniently evaluated in vivo. A 3D conductive media model was used to vary electrode locations, insulation thickness and inter-electrode distances. **Table 1** summarizes the dielectric properties used in our model.

Component	Connective Tissue	Vessel Wall	Blood	Silicone	Nerve
Conductivity [S/m]	0.020	0.027	0.066	10e-4	0.087
Relative Permittivity	25	45	300	11	650

Table 1: Dielectric properties of human tissue [7]

As shown in **Fig. 1**, endovascular electrodes were modeled as deployed inside the left subclavian vein in close proximity to the left phrenic nerve, and inside the superior vena cava, along which the right phrenic nerve courses.

Our model compared relative stimulation efficacy of 2 types of electrodes: an endovascular insulating cuff placed snugly against the vein wall with two electrodes facing outward as described by Hoffer [5] (**Fig. 2A-B**) and a 6F (~2 mm diameter) vessel dilator with two electrodes attached to its outer surface (**Fig. 2C-D**). In both cases, the cathode and anode were placed at 90° from each other in a plane transverse to vein, parallel to phrenic nerve.

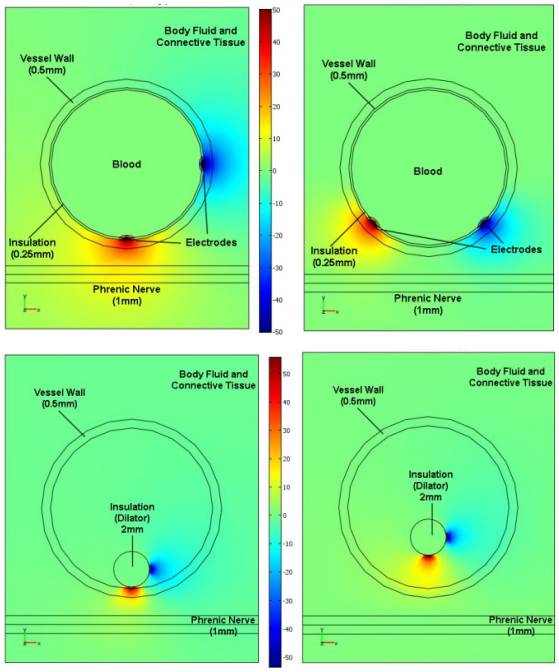

Figure 2: A. cuff with cathode electrode (**red**) optimally located inside vein wall to stimulate the phrenic nerve. **B.** cuff rotated 45° away from its optimal orientation. **C.** 6F dilator with its cathode contacting the vein wall at the optimal location and orientation. **D.** Dilator electrode shown displaced 1.5 mm away from vein wall and nerve.

Following the approvals from the SFU and UBC Animal Ethics Committees, prototype cuff and dilator electrodes (to be described in full detail elsewhere) were endovascularly implanted using the Seldinger technique. Stimulation selectivity, safety and stability properties were tested in nine acute and three 21-day chronic pigs (65 +/- 15 kg).

Model Results

Figs. **2A & C** reveal the powerful effect of placing an insulating wall behind endovascular electrodes. To minimize occlusion of blood flow, we specified cuff cross-section area <10 % of vein lumen area. A 0.5 mm thick silicone cuff (**Fig. 2A**) shields the interior of the vein, resulting in more current flowing out the vein wall and into the nerve than for a similarly placed dilator electrode (**Fig. 2C**). These findings are evident in plots shown in **Fig 3**.

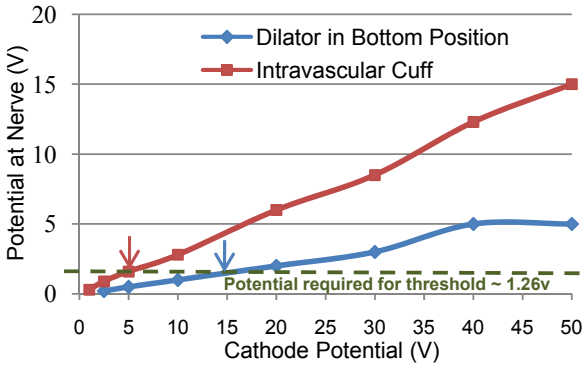

Figure 3. Stimulation potentials reaching the phrenic nerve as function of cathodic potentials generated with **cuff** (**red**) vs. **dilator** (**blue**) endovascular electrodes.

A green dashed line in **Fig. 3** shows the threshold potential (1.26 V; see [6]) required for phrenic nerve stimulation. Our model predicts the endovascular current required to activate a nerve with a shielded electrode (**red arrow**) is 3 times less than required from a lead-type dilator electrode (**blue arrow**).

We estimated the stimulation sensitivity to electrode rotation and/or translation along the vein, by modeling the displacement of each electrode in

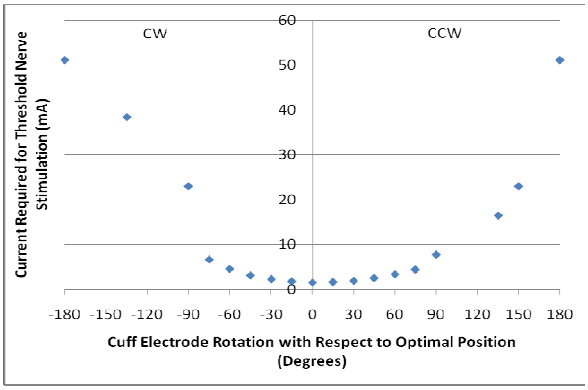

Figure 4: Stimulus efficacy vs. cuff rotation angle.

longitudinal and transverse directions. An example of a cuff electrode rotated 45° away from its optimal position is shown in **Fig. 2B**. Results of rotating the cuff cathode from -180° to +180° with respect to optimal position are plotted in **Fig. 4**. The model predicts that 90° rotation away from the optimal position results in a 5-fold reduction in nerve stimulation efficacy, and 180° rotation results in 50-fold reduction in stimulation efficacy.

The dependence of stimulation efficacy on distance between electrode and nerve is modeled in **Fig. 5.** Advancing the cathode toward and then past the target nerve results in a steep parabolic function. If the cathode is placed just 2 cm away from its optimal location, our model predicts nearly 10-fold reduction in efficacy of transvascular stimulation.

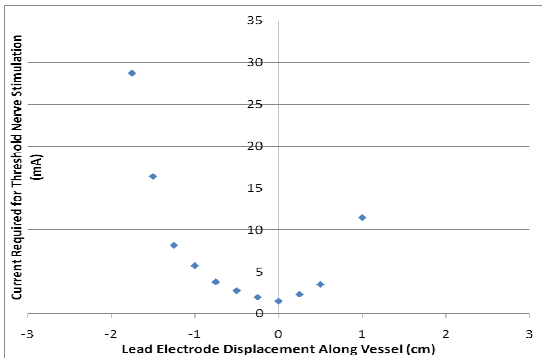

Figure 5: Model of efficacy vs. distance along vein.

Pig Implant Results

We mapped in acute and chronic pigs the threshold currents required for left phrenic nerve recruitment as function of electrode depth into the vein, and found fundamental agreement with model predictions. **Fig. 6** shows a representative result**.**

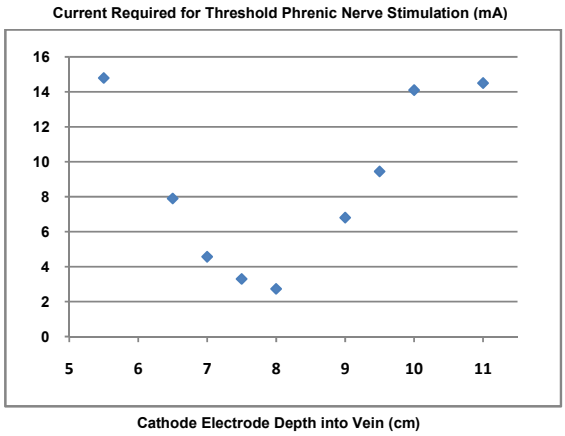

Figure 6: Left phrenic nerve stimulation efficacy as a function of electrode depth into vein (Chronic Pig #1).

Balanced biphasic pulses of 180 µs phase duration were used. Electrode placements within 1 cm from the nerve required stimulus currents ≤ 2 mA, but when the electrode was moved along the vein in either direction, away from the nerve, threshold currents increased rapidly in parabolic fashion.

In 3 pigs, endovascular electrodes were aseptically implanted and left in situ for 3 weeks. Electrode performance was assessed under anaesthesia on days 1, 11 and 21. Stimulation properties remained stable and the pigs remained healthy and gained weight normally throughout the testing period.

Discussion

Our model results provide guidelines for designing endovascular electrodes that maximize target nerve stimulation efficacy and also minimize unwanted stimulation of other structures. Stimulus efficacy is strongly dependent on electrode position with respect to both the vein wall and the target nerve, and is greatly improved by placing an electrically insulating barrier between the electrodes and blood inside the vein. Our results in anaesthetized pigs are consistent with these model predictions.

Conclusions

Effective transvascular diaphragm pacing in ICU patients will require deployment of endovascular electrodes within 1 cm from each phrenic nerve. Insulated endovascular electrodes that are stably positioned for diaphragm pacing are unlikely to produce unwanted stimulation of vagus nerves, since the latter course ≥2 cm away from the phrenic nerves in the regions of interest.

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