INTRODUCTION

Patients in intensive care units (ICU) who require mechanical ventilation (MV) for ≥1 week are at high risk of complications such as ventilator-acquired pneumonia (VAP) and nosocomial infections, are 7X more likely to die in the ICU and account for ½ the ICU budget and 1/6 of all hospital in-patient costs in US1.

For certain patients who require life-long assisted ventilation, an alternative to MV is to “pace” their diaphragm with electrical stimulation2. In the past 30 years, about 1,600 adult and pediatric patients have benefited from a permanently implanted phrenic nerve pacing system. However, these systems are costly, require risky surgery under general anesthesia, and are not feasible options for fragile ICU patients.

The diaphragm muscle is known to atrophy rapidly in MV patients3 and this atrophy contributes to failure to wean from ventilation4. In order to speed up the weaning process from MV, we are developing a novel, minimally invasive electrode, intended to be deployed intravenously in close proximity to the phrenic nerves and stimulated appropriately to maintain the strength of the diaphragm and support ventilation5.

Selective stimulation of phrenic nerves is highly dependent on electrode proximity and orientation. To help guide the design of the intravascular electrodes we have 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 low-impedance conductive medium, the threshold stimulation current is substantially reduced by the addition of an insulating electrode backing5. We describe here stimulation parameters and guidelines used in our model that helped us predict the recruitment selectivity encountered with intravascular phrenic nerve stimulation in animal tests.

MODELING APPROACH

The intravenous device under development (Fig. 1) includes an electrode structure deployed against the inner wall of the left subclavian vein (LSV) near the left phrenic nerve (LPN), and a second electrode structure deployed inside the superior vena cava (SVC) near the right phrenic nerve (RPN).

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The strength of the electric field will depend on many factors, such as electrode configuration, target proximity and permittivity of the surrounding tissues. In order to determine threshold stimulation current requirements these factors were modeled in this study. We modeled two nerve-vein configurations, parallel and transverse, shown in Fig.2A and Fig 2B.

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

Figure 2. A: nerve parallel to vein. B: nerve transverse to vein.

Clinical applicability will require recruiting the target phrenic nerves in the regions of interest with
lowest possible current and also with high stimulation selectivity, to avoid activating other structures such as the vagus nerves that course roughly parallel and about 2 cm medial with respect to the phrenic nerves.

The requirements for selective phrenic nerve activation with intravenous electrodes were modeled using 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 model changes in electrode locations, insulation thickness and inter-electrode distances. Table 1 summarizes the modeled dielectric properties.

<table>
<thead>
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<th>Component</th>
<th>Connective Tissue</th>
<th>Vessel Wall</th>
<th>Blood</th>
<th>Silicone</th>
<th>Nerve</th>
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<td>Conductivity</td>
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<td>0.027</td>
<td>0.066</td>
<td>10e-4</td>
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<td>Relative Permittivity</td>
<td>25</td>
<td>45</td>
<td>300</td>
<td>11</td>
<td>650</td>
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</table>

Table 1: Dielectric properties of human tissue (Ref. 7)

Our model compared the relative stimulation efficacy of two types of electrodes: an intravenous insulating cuff placed snugly against the vein wall with two electrodes facing outward, as described by Hoffer5 (Fig. 3A-B) and a 2-mm diameter vessel dilator with two electrodes on its outer surface (Fig. 3C-D). In both these cases, the cathode and anode were placed at 90° from each other in a plane transverse to the vein, parallel to the phrenic nerve, as in Fig 2B.

Fig. 3A-C reveals the powerful effect of adding an insulating cuff backing to intravenous electrodes. Cuff wall thickness must not occlude blood flow, so we limited wall cross-sectional area to <10% of vein lumen area. The insulating value provided by a 0.5mm thick silicone cuff wall is demonstrated by comparing the optimally placed cuff electrode (Fig. 3A) vs. the optimally placed lead dilator electrode (Fig. 3C). The cuff insulating barrier acts to steer the current away from the blood, resulting in a much larger fraction of the current radiating outwardly and towards the nerve.

![Figure 4. Stimulation potentials generated at phrenic nerve (Y-axis) as function of cathodic potentials generated with cuff (red) or dilator (blue) intravascular electrodes.](image)

Fig. 4 compares the efficacy of stimulation with cuff electrodes vs. dilator electrodes when each electrode type is placed at its optimal location with respect to the target nerve. The green dashed line indicates the threshold potential for phrenic nerve stimulation (1.26 V; Elefteriades, 2002). Intersections of graphed lines with threshold line (red, blue arrows) indicate the minimum stimulation voltages required to activate phrenic nerve axons. According to the model, the cuff electrode is >3x more efficient than a dilator electrode at its optimal location (i.e., the stimulus current required to activate the nerve using an insulating cuff is >3x lower than if a cuff is not used).

We determined stimulation sensitivity to device rotation and/or translation along the vein by modeling the displacement of each electrode in the longitudinal and transverse directions. Fig. 3B shows an example of a cuff electrode rotated 45° away from its optimal position. Fig. 5 plots the results of rotating the cuff cathode from -180° to +180° with respect to its optimal position. 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 a 50-fold reduction in nerve stimulation efficacy.

Fig. 3D shows an example of a 2-mm dilator electrode displaced inside a 10-mm diameter vein. Note that when the dilator electrode drifts away from
the vein wall, most of the electric field is dissipated within the blood. As a consequence, the nerve stimulation efficacy is greatly reduced. Fig. 6 plots the results of progressively displacing the 2-mm dilator electrode away from the vein wall adjacent to the nerve. A 7-mm displacement results in >10-fold reduction in nerve stimulation efficacy.

Finally, Fig. 7 shows the dependence of stimulation efficacy on the axial position of the intravenous device, modeled for a dilator-type lead electrode adjacent to the vein wall that is moved progressively toward and away from the target nerve. A steep parabolic function of distance is evident, indicating that a 10-fold reduction in stimulation efficacy can be expected if the cathode is displaced as little as 2 cm away from its optimal location for transvascular stimulation.

SUMMARY AND CONCLUSIONS

The present results of modeling intravascular electrode performance in COMSOL provide clear guidelines for electrode designs that maximize target nerve stimulation efficacy, while also minimizing unwanted stimulation of other structures. Our modeling confirms that stimulation efficacy is strongly dependent on cathode electrode position with respect to both the vessel wall and the target nerve. As well, modeling has confirmed that stimulation efficacy is greatly improved by inserting an electrically insulating barrier between the electrodes and blood in the vein. Given the steep dependence on the distance from the target nerves, effective transvascular diaphragm stimulation requires that the cuff electrodes be deployed within a few millimeters from the target phrenic nerves. Of clinical importance, it is unlikely that intravascular cuff electrodes that are correctly positioned for diaphragm pacing will also produce unwanted stimulation of the vagus nerves, since the vagus nerves course >2 cm away from the phrenic nerves in the region of interest. Our preliminary results using transvascular diaphragm pacing electrodes in anaesthetized pigs are consistent with predictions from the present modeling study.

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REFERENCES