

## DEVELOPMENT AND USE OF A LARGE ANIMAL MODEL FOR CHRONIC TESTING OF SACRAL NEUROMODULATION THERAPIES USING CONSCIOUS CYSTOMETRY TO QUANTIFY UROLOGICAL EFFECTS

### Hypothesis / aims of study

Sacral neuromodulation (SNM) is used clinically for treating urinary incontinence. While preclinical testing models have been used to address parameter optimization, compare nerve targets and gain insight to therapeutic mechanism [1-3], this work is performed in anesthetized rats and cats using acute periods of stimulation. To more accurately reflect clinical use of neuromodulation therapies, we aimed to establish a large animal model to chronically test SNM in the conscious animal. Specifically, this work tests the hypothesis that the effects of sacral neuromodulation therapy can be quantified using cystometry in conscious sheep.

### Study design, materials and methods

Adult, female, Polypay sheep (n=6) were screened for the ability to accept urinary bladder catheterization and demonstrate stable capacities with repeated filling cystometry (10 trials / day). Filling cystometry was performed using a 12 Fr urinary catheter and bladder pressure was recorded using a Millar pressure sensor line fed through the inside of the urinary catheter. Warmed saline (34 degrees C) was infused (30mL/min) until bladder pressure sharply rose past 30 cm H<sub>2</sub>O and the sheep assumed a voiding stance. The sheep was allowed to void and also manually emptied to ensure minimal residual volume. Animals that passed screening were anesthetized and implanted with two InterStim® II devices and leads (Models 3058 and 3889; Medtronic, Inc., Minneapolis, MN) targeting the left and right S3 or S4 nerve, confirming targeting with visualization of the anal bellows response. Animals were allowed 2 weeks recovery before resumption of cystometry. To test the effects of acute SNM, a similar 10 trial cystometry design was applied for three successive weeks using four baseline fills followed by six fills with bilateral neuromodulation (10 Hz, 0.21 ms pulse width, maximum tolerable amplitude). In addition to cystometry, motor threshold testing of each implant (voltage of neuromodulation to evoke the first motor reflex) was performed throughout the course of the study.

A mixed-effects regression model was used to analyze bladder capacity (mL) using all non-stimulation (n=192) and stimulation (n=108) trials. The fixed-effects factors entered into the model were animal, condition (baseline vs. neuromodulation), and their interaction. A random intercept, varying at the animal-by-week level, accounted for the grouped structure of the data. F-tests based on the fitted model were used to compare the difference between mean capacity in the two conditions. This difference was tested for each of the 6 individual animals and for the average across all animals, using a Bonferroni adjustment for multiple comparisons. A p-value of <0.01 was considered statistically significant. Calculations were performed using the R statistical computing environment (R Foundation, Vienna, Austria) and the nlme package.

### Results

The estimated mean bladder capacity in the baseline condition was 85 ml (75–96 mL, 95% CI). In the neuromodulation condition, this increased to 112 mL (100–124 mL 95% CI). The difference between these two estimates was statistically significant (F=35.0, df=(1, 264), p<0.01; Figure 1). The differences between neuromodulation and baseline mean capacities for specific animals varied substantially. The average max tolerable amplitude was 3.7x motor threshold (range 2.0–5.2). Three out of six animals had significantly larger mean capacities in the neuromodulation condition than in the baseline condition.

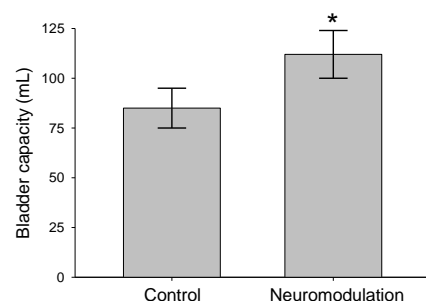


Figure 1: Sacral neuromodulation acutely increases bladder capacity in normal, conscious sheep. Data come from six sheep, 192 trials for control and 108 trials for neuromodulation; error bars represent 95% confidence intervals, \* = p<0.01.

Motor threshold testing showed a relatively stable response over time (Figure 2). As a group (n=12), motor thresholds were 1.0±0.2 V at the time of surgical implant and 0.8±0.3 V at 12 weeks. Similar to urological effects, there was some variability over time with individual motor thresholds. Analysis revealed no difference in motor threshold between the anesthetized data collected at implant versus the first conscious data collected at 1 month (Mann-Whitney rank sum test, p=0.75).

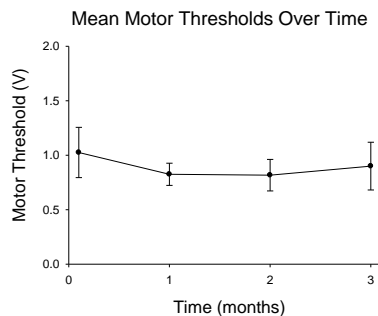


Figure 2: Motor thresholds over time. Motor thresholds were determined independently for each implant, evoking perianal or leg contractions. The first time point represents data collected at the surgical implant; n=12 at each time point.

#### Interpretation of results

These data describe the initial steps in the creation of a conscious, large animal sheep model for testing SNM effects on bladder capacity. Using filling cystometry, these data show that SNM significantly increased bladder capacity as compared to control, non SNM trials. Several advantages exist in this testing platform. Animals are implanted with clinically used devices, so no external component connections or tethering are needed to perform SNM. The sheep are conscious with neither anesthesia nor sedation needed during quantitative cystometry. This allows for repeated testing and the potential to examine time course of effects and to stimulate for long periods of time. The procedure itself (filling cystometry) is similar to clinical testing and is relatively easy to perform in the sheep.

#### Concluding message

This developing sheep model is a useful platform for testing the effects of sacral neuromodulation on urological physiology. We demonstrate that SNM significantly increases bladder capacity in normal animals. This platform can be used to test other therapy concepts such as different stimulation field parameters, optimal therapy delivery in normal and dysfunction models, and long-term therapy efficacy.

#### References

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#### Disclosures

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