

## PHYSIOLOGICAL TARGETING OF SACRAL NEUROMODULATION

### Hypothesis / aims of study

InterStim® Therapy for overactive bladder (OAB) and fecal incontinence is most often delivered in a continuous mode. Recent clinical evidence [1] and the emergence of intermittent percutaneous tibial neuromodulation for treatment of OAB suggest equal therapeutic efficacy can be achieved with non-continuous sacral neuromodulation (SNM). If true, it would give insight into therapeutic mechanism of SNM and could potentially translate to an increase in battery savings. Previous rodent studies demonstrated that SNM during latter parts of the bladder fill cycle increase bladder capacity equal to that of continuous SNM [2]. The goal of this study was to use cystometry in fully conscious sheep and determine if SNM “targeted” to early or latter stages of the bladder fill cycle could elicit the same increase in capacity as continuous SNM.

### Study design, materials and methods

Adult, female, Polypay sheep (n=8) were used in two separate sets of studies using an implanted research stimulator connected to bilateral leads (Model 3889) placed at S3 or S4 foramen to deliver SNM [3]. Acute cystometry, infused at 15 or 30 ml/minute, was performed in the fully conscious sheep comparing bladder capacity in baseline trials to those with SNM. The timing of SNM (parameters: bilateral, 10 Hz, 0.21 ms pulses, at maximum tolerable amplitude) was based on the total duration of three baseline SNM trials and was then targeted at different times of the bladder filling cycle (e.g. first 50%, second 50%, last 25% or last 10%). In some cases, multiple SNM trials occurred with two baseline trials given between SNM trials. Groups were compared with t-test or ANOVA with  $p < 0.05$  considered significant.

### Results

Initial data from 12 cystometry sessions in four sheep showed that SNM during the second 50%, but not first 50%, of bladder filling cycle significantly increased bladder capacity ( $p < 0.05$ ). The increase in bladder capacity with SNM applied during last 50% of filling (2<sup>nd</sup> half stim) and the lack of effect with SNM during first 50% of filling (1<sup>st</sup> half stim) was independent of order of presentation (Figure 1). Moreover, the increase in bladder capacity was not different from SNM applied continuously, consistent with previous rodent data [2]. Follow-up experiments in four sheep examined the effect of timing in more detail, comparing SNM during second 50%, last 25% and last 10% compared to first 50% and continuous delivery.

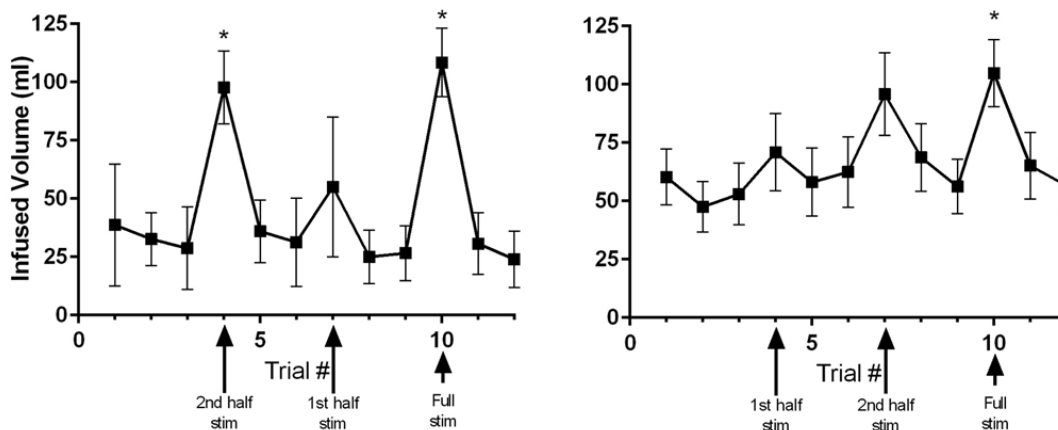


Figure 1. Bladder capacity is increased with SNM delivered to the latter phase of, but not early phase of bladder filling. Cystometric trial number is on the x-axis and bladder capacity is on the y-axis. The graph at left shows all trials where last 50% was presented before 1<sup>st</sup> 50% SNM, while the graph at right shows all trials where the 1<sup>st</sup> 50% was applied before 2<sup>nd</sup> 50%. Interestingly, 2<sup>nd</sup> 50% SNM showed an equivalent increase in bladder capacity to continuous SNM (Full stim).

### Interpretation of results

These cystometry data in the fully conscious sheep show that intermittent SNM applied at certain phases of the bladder filling cycle can significantly increase bladder capacity in a similar manner to continuously applied SNM. SNM applied early in the filling cycle did not have an effect, while SNM applied later in the filling cycle increased bladder capacity. This is consistent with the idea that the therapeutic mechanism of SNM is a sensory, neural modulation and that there must be a robust bladder afferent signal present for SNM to modulate. These data support clinical data showing effectiveness of cycling SNM and also may help to optimize temporal delivery.

### Concluding message

Non-continuous sacral neuromodulation can significantly increase bladder capacity, but only when applied to the latter phases of the bladder filling cycle. These data are consistent with a therapeutic effect of SNM being sensory afferent modulation.

### References

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2. Potts BA, Degoski DJ, Brooks JM, Peterson AC, Nelson DE, Brink TS & Fraser MO (2016). Late intermittent sacral neurostimulation significantly increases bladder capacity. SUFU Annual Meeting, New Orleans, LA.
3. Brink TS, Zimmerman PL, Mattson MA, Su X, Nelson DE (2015). A Chronic, Conscious Large Animal Platform to Quantify Therapeutic Effects of Sacral Neuromodulation on Bladder Function. Journal of Urology, 194:252-258.

Disclosures

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