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New Neurostimulation and Blockade Strategy to Enhance Bladder Voiding in Paraplegics

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Abstract

Sacral root stimulation is one of the most promising techniques for bladder rehabilitation in spinal cord-injured (SCI) patients. The only commercialized implantable neurostimulator aiming for improved micturition and having obtained satisfactory results requires rhizotomy to reduce detrusor-sphincter dyssynergia (DSD). However, rhizotomy is irreversible and may abolish sexual and defecation reflexes as well as sacral sensations, if still present in case of incomplete SCI. In order to avoid rhizotomy, we propose a new multisite stimulation strategy applied to extradural combined (dorsal plus ventral) sacral roots, and based on nerve conduction blockade using high-frequency stimulation as an alternative to rhizotomy. This approach would allow a better micturition by increasing bladder contraction selectively and decreasing DSD. Eight (8) acute dog experiments were carried out to verify the bladder and the external urethral sphincter (EUS) responses to the proposed stimulation strategy. High-frequency blockade (1 kHz) combined with low-frequency stimulation (30 Hz) increased the average intravesical-intraurethral pressure difference up to 53 cmH2O and reduced the average intraurethral pressure with respect to baseline by up to 86 %. A custom bi-cuff-electrode design has been developed to be applied around two nerves in distinct cuffs. This could provide a more efficient micturition technique for SCI patients.

Keywords: Sacral root stimulation, High-frequency nerve block, Micturition, Detrusor-sphincter dyssynergia, Rhizotomy, Cuff-electrodes

1. Introduction

The efficiency of micturition by means of sacral neurostimulation in spinal cord-injured (SCI) patients depends on the capability to contract the bladder muscle without generating detrusor-sphincter dyssynergia (DSD). In order to improve the neurostimulation selectivity that allows reducing DSD, several techniques have been proposed, among which are rhizotomy, anodal block and high-frequency blockade.

Introduced at the end of the 19th century, dorsal rhizotomy consists of severing afferent sacral nerve roots that are involved in pathological reflex arc in suprasacral spinal cord lesions. When combined with sacral ventral root stimulation, dorsal rhizotomy abolishes detrusor overactivity. As a beneficial result, the bladder capacity and compliance are increased, the uninhibited contractions are reduced, and the upper urinary tract is protected from ureteral reflux and hydronephrosis. In addition, rhizotomy reduces DSD, improves urine flow, and prevents autonomic dysreflexia. In case of a complete SCI, rhizotomy is combined with an implantable sacral ventral root stimulator such as the Finetech-Brindley Bladder System (also known as the VOCARE in North America) [9]. Actually, this neurostimulation system is the only commercialized and FDA-approved solution aiming for micturition in SCI patients [6]. Unfortunately, rhizotomy which is obviously irreversible, has a fundamental disadvantage which is the abolition of sexual and defecation reflexes, as well as sacral sensations if still present in case of incomplete SCI.

The propagation of a nerve action potential can be blocked by hyperpolarization of the nerve fibre membrane with an anodal electrode. If sufficiently hyperpolarized, a complete blockade of the compound action potential (CAP) propagating on different fibres within a nerve bundle can be achieved. Moreover, the anodal blockade threshold of large diameter fibres is lower than that of small diameter. Thus, a selective activation of small fibres can be obtained by combining a high-intensity stimulation to excite all fibres, with a distant low-intensity anodal electrode to block large axons only [6]. In 1994, Koldewijn et al. used this technique and reported the blockade of the external urethral sphincter (EUS) contraction in 7 dogs among 10 with current amplitudes of 0.4 to 0.9 mA and pulse widths of 600 to 800 μs [8]. In 1998, Rijkhoff et al. investigated the anodal blockade in spinal cord injured patients having the FineTech-Brindley implanted stimulator. In 8 patients among 12, EUS contractions have been blocked completely with a 6 mA current and 700 μs pulse width. However, such combination of high-current and long-duration anodal pulse means a large amount of injected charge that would lead to irreversible electrochemical reactions at the electrode-nerve interface, especially if those charges are not retrieved using a biphasic pulse. In addition, it may be difficult to find the optimal blockade parameters and chronic studies are necessary to investigate their variation over time [11].

High-frequency stimulation can be used to achieve a complete or graded block of the CAP propagating on different fibres within a nerve bundle. In 1984, Solomonow demonstrated that the blockade can be achieved with an alternating stimulation and found that 600 Hz was an optimum frequency in terms of required stimulation intensity [16]. The mechanism may be explained by a refractory status in which the nerve fibres and/or the motor end-plate are maintained. In 1998, Shaker et al. studied the efficiency of this technique in acute dog experiments using a neurostimulator designed by Polystim Neurotechnologies Laboratory [12, 14]. Similar results were reported by Zhang and Jiang that combined a low-amplitude frequency of 550 Hz with a high-amplitude frequency of 33 Hz [19]. The Polystim's stimulator generated a rectangular waveform combining two frequencies (e.g. 600 Hz and 30 Hz) such that the higher frequency blocks the EUS activity and reduces DSD during micturition. It is important to point out in this case, that stimulation and blockade are both applied simultaneously at the same nerve site, with the same bipolar electrode. It was observed that blockade depends greatly on the high-frequency amplitude. The optimal amplitude window giving a maximal blockade of the urethral contraction with minimal blockade of the bladder was 1.1 to 1.5 mA. The same neurostimulator was also implanted in paraplegic dogs for chronic experiments where it was demonstrated that urine evacuation improved up to 91% of the mean bladder capacity during the six months of chronic stimulation [1].

However, these neurostimulation approaches suffer from different drawbacks such as rhizotomy, non-physiological micturition, large amount of charge injection, and/or high volume of residual urine. The only clinically available implantable neurostimulator aiming for micturition and having obtained satisfactory results, requires rhizotomy to avoid DSD. So, how can we maximize the sacral neurostimulation selectivity in paraplegics in order to induce urine evacuation as close as possible to the physiological micturition, free from DSD, and without the use of rhizotomy?

2. Hypothesis

In the case of blockade using the high-frequency stimulation (600 Hz) described earlier, the term "blockade" refers more to the stimulation result which is the inhibition of the EUS muscle contraction. In fact, the mechanism by which this inhibition is obtained is not well understood and three explanations are possible: high-frequency stimulation may stop the propagation of nerve action potentials, may maintain the motor end-plate (neuromuscular junction) in a refractory status, or may fatigue the aimed muscle [7, 17, 18].

According to Kilgore et al. [7], an alternating stimulation at high-frequency produces a reversible nerve blockade. A complete blockade can be achieved with different waveforms at higher frequencies between 2 and 20 kHz. It is shown that this blockade is not indirectly induced by fatigue. In addition, some simulations corroborate the hypothesis that high-frequency stimulation maintains the nerve membrane in a depolarization status. It is also stated that a frequency of 600 Hz can achieve a complete blockade but would require high stimulation currents (higher than 4 mA). Thus, blockade with 600 Hz is probably due to a muscle fatigue mechanism rather than nerve conduction blockade. In fact, nerves can fire action potentials at frequencies as high as 700 Hz for short periods of time.

In the report by Schuettler et al. [13], we learn that in the case of sinusoidal waveforms, frequencies from 300 Hz to 10 kHz are suitable for blocking CAPs travelling along a peripheral amphibian nerve. Keeping the same amount of charge injected per phase, lower frequencies waveforms would require lower amplitudes. But increasing the frequency has the advantage of lowering the amount of injected charge per-phase needed for blockade. Below 1 kHz, the sinusoidal stimulation can generate CAPs at the same or a submultiple rate and cause "collision block". The generated CAP amplitude vanishes for frequencies beyond 1 kHz.

In fact, this may be more complex according to simulations proposed by Tai et al. [17]. Blockade of each axon within the nerve is also influenced by the stimulation amplitude as well as the axon diameter. Thus a graded blockade can be achieved. If applied in combination with low-frequency stimulation (at different nerve sites), selectivity with respect to axon diameter can be obtained by adjusting stimulation amplitudes [18]. The blockade discussed so far concerned motor action potentials induced by neurostimulation. A complete blockade of sensory activity would probably require higher stimulation amplitudes [7].

In the urinary system case, Sievert et al. present several animal experimental results especially the bladder and EUS pressure responses to a sinusoidal stimulation up to 10 kHz [15]. It is shown that the EUS pressure is maximal around 100 Hz, and decreases drastically as the frequency is increased. Beyond 1kHz, the EUS pressure becomes very low (less than 10 % of the maximum). Bhadra et al. [2] applied the high frequency block to the pudendal nerves of male cats and successfully blocked the EUS contractions. It is demonstrated that a complete reversible conduction block could be achieved over all tested frequencies (1 to 30 kHz) at varying stimulus amplitudes (1 to 10 V). Finally, Boger et al. [3] demonstrated effective micturition in male cats by combining sacral root stimulation with bilateral high frequency pudendal nerve block.

In view of these observations, we propose the following hypothesis in the case of the lower urinary tract: The use of a high-frequency alternating stimulation waveform (e.g. sinusoidal or rectangular) with optimum parameters, allows a blockade of the nerve activity (motor and/or sensory), that may be complete (all axons) or partial (large diameter axons only). If the blockade is complete, the effect would be equivalent to that of rhizotomy while being controlled and totally reversible. If the blockade is partial, a selective stimulation can be achieved by blocking large axons. Consequently, a neurostimulation strategy based on this technique would allow a better micturition by increasing bladder contraction selectively and decreasing DSD without any rhizotomy. To our knowledge, such a strategy has not been tested yet in the particular case of sacral roots stimulation. In fact, our team recently presented preliminary results obtained with this strategy

[10], which we elaborate in this proposed work.

3. Materials and Methods

3.1. Neurostimulation strategy

We propose a new neurostimulation strategy based on the hypothesis we stated previously. The strategy, based on a dog model, is illustrated in Fig. 1.

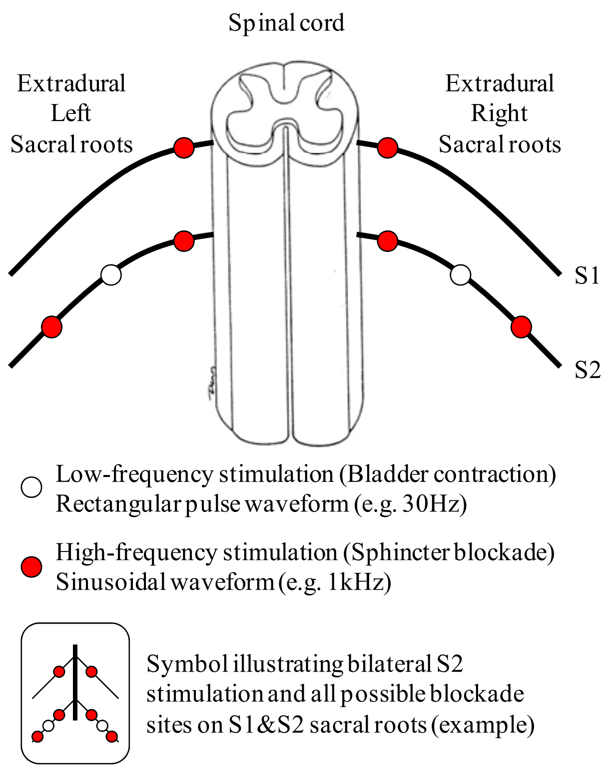


Fig. 1 Proposed neurostimulation strategy (dog model). Low-frequency stimulation is applied, unilaterally or bilaterally, to S2 or S1 sacral nerves in order to induce a satisfactory contraction of the bladder muscle. Distal selective and/or proximal complete high-frequency blockade is applied to S2 and/or S1 to eliminate direct and reflex stimulation-evoked EUS contractions.

A low-frequency (e.g. 30 Hz) monophasic current stimulation is applied, unilaterally or bilaterally, to S2 sacral nerve(s) (or S1 eventually) in order to induce a satisfactory contraction of the bladder muscle. The degree of contraction can be modulated by adjusting the amplitude and pulse width of stimulation. In most cases, detrusor contractions are present and the EUS contracts as well. The stimulation-evoked EUS contraction can be triggered by direct and/or reflex mechanisms due to efferent and/or afferent fibres activation respectively. According to our hypothesis, both types of EUS activation can be avoided by blocking axons innervating the EUS with high-frequency stimulation. In the example of Fig. 1, a sinusoidal waveform at 1 kHz is chosen. In order to eliminate direct EUS activation, a selective blockade can be applied distally (between the low-frequency stimulation site and the EUS), whereas for reflex EUS activation, a complete blockade can be applied proximally (between the low-frequency stimulation site and the spinal cord). However, reflex EUS activation may involve sacral root(s) other than the one(s) stimulated by the low-frequency, which should be blocked as well in this case. We should note that blocking at all sites as shown in Fig. 1 is just for illustration purposes. Anatomically, the lower urinary tract innervations are the same from one animal to another but there is a functional variability. It is possible that one type of the direct or reflex EUS activation mechanisms is dominant, or that only one blockade site is sufficient. Conventional sacral nerve stimulation in patients with incomplete SCI may lead to pain perception. Rhizotomy can be a way to avoid the stimulation-evoked pain but will probably not be considered if important reflexes and sensations are still present. With the proposed stimulation strategy, proximal high frequency stimulation can achieve a complete blockade of sensory activity and consequently prevent pain sensation as well.

3.2. Acute animal experiments

In order to evaluate the proposed stimulation strategy, acute animal experiments are mandatory before designing an implantable neurostimulator and moving on to chronic experiments. For the present project, a total of 8 acute studies have been approved by the McGill Animal Care Ethics Committee and conducted on male mongrel dogs at the Animal Resource Center of The Montreal General Hospital. The dog has been chosen as it is known to provide an acceptable model to study the effect of neurostimulation on the peripheral nervous system [5].

Under A-chloralose anaesthesia (100mg/kg), animals are subjected to laminectomy at the T10-11 level and spinal cord transection, followed by a limited sacral laminectomy in order to expose the sacral roots. Although the spinal shock affects the micturition reflex, the spinal micturition center is still intact and responds to stimulation. The S1-S3 combined (dorsal plus ventral) sacral roots supplying the bladder and the EUS are separated extradurally and clearly identified by their anatomical arrangement as well as by electrical stimulation with hook electrodes while recording the intravesical and urethral pressure changes with computerized urodynamic equipment (Laborie Medical Technologies Inc – AQUARIUS UDS-120). The urinary bladder is emptied and a 7-French triple lumen urethral catheter (C.R. Bard Inc. – Bard Urodynamic catheter) is inserted into the bladder. One channel of the catheter is used to monitor the intravesical pressure (PVES), the second channel to monitor the intraurethral pressure (PURA), and the third channel to fill the bladder when needed. The position of the catheter is confirmed by gently pressing on the bladder and the posterior urethra, which results in changes in PVES and PURA, respectively. The catheter is then secured to the foreskin to avoid displacement during the experiment. Electromyographic activity (EMG) of the EUS and pelvic floor muscles are continuously recorded using needle electrodes and an EMG amplifier (Laborie Medical Technologies Inc – UDS-110). Thus our aim is to assess the effect of the stimulation strategy on voiding parameters in terms of PVES, PURA and EMG. In general, S1 root is identified to be of a large diameter (1.5-2 mm) and gives rise to a marked increase in PURA with a minimal change in PVES. Stimulation of S2 nerve root gives mixed bladder and sphinteric responses, while stimulation of S3 nerve gives rise to almost no or a very weak change in both PVES and PURA. Then, according to the desired strategy, cuff-electrodes are wrapped around the targeted sacral roots. The bladder is slowly filled with saline to its full capacity then evacuated by neurostimulation. The bladder capacity was first determined by cystometry prior to the surgery. After the experiment, the animal under study is sacrificed by the animal care technician.

3.3. Cuff-Electrodes

In previous chronic studies, we used split-cylinder cuff electrodes with a shape memory alloy (SMA) armature embedded inside the cuff wall [4]. The electrode cuff is moulded in a biocompatible silicone, and the electrode contacts are platinum foil bands welded to leads made of multi-strands stainless steel wires coated with Teflon. The SMA electrode is easy to manipulate at low temperature, but it automatically recovers its original shape (cylindrical around the nerve) when heated at body temperature. However, despite the advantage of such an innovative design, the production of the electrodes remains laborious and costly, especially that our strategy requires multiple electrodes.

For our acute experiments, we proposed a simpler electrode design, yet very practical and efficient. Instead of silicone, we used a hydrophilic vinyl polysiloxane material used for dental impressions (DENTSPLY/CAULK, Reprosil®Light Orange), that is much easier and faster to prepare. The stainless steel wires are embedded inside the cuff wall but exposed at the inner surface of the cuff by removing the Teflon coat. Thus the exposed wires serve as electrode contacts and no platinum is used. Without any SMA armature, the resulting Reprosile cuff-electrode already offers interesting mechanical properties. It is easy to manipulate and it also recovers its original shape to a certain degree, at least for the time of the acute experiment. Keeping the cuff opened by pulling apart its two edges, the nerve can be easily inserted inside. As soon as the cuff is released, it self-closes around the nerve. In order to maintain the installed electrode closed and stable for the duration of the experiment, the cuff edges are attached together with a small staple or sutures.

In addition, instead of using a dedicated cuff for each stimulation or blockade site, we proposed to merge the cuffs that are placed on the same nerve. In other words, only one cuff is placed around each sacral nerve. If on a single nerve for example, one tripolar stimulation site and two bipolar (distal and proximal) blockade sites are required, then the cuff-electrode must offer 7 different contacts. With a contact width of less than 1 mm, and an inter-electrode distance of 1 mm, the maximum cuff length is 15 mm. The cuff inner diameter must be slightly larger than the nerve diameter (between 1 and 2 mm). Moreover, given that our strategy involves S1 and S2 sacral nerves, we also propose that both S1 and S2 cuffs (of the same side) be moulded together. Thus, the designed bi-cuff-electrode shown in Fig. 2 can host two nerves in distinct cuffs. Each cuff may have a different inner diameter and may contain up to 7 contacts.

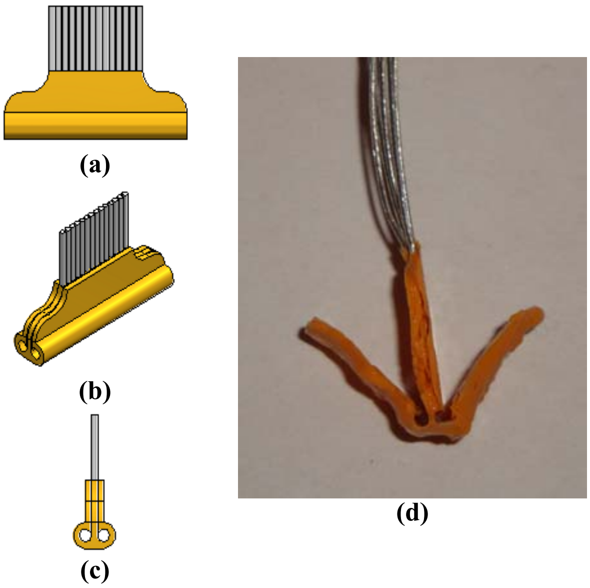


Fig. 2 Different views of the proposed and used bi-cuff electrode. The electrode is made of hydrophilic vinyl polysiloxane material. Stainless steel wires are embedded inside the cuff wall but exposed at the inner surface of the cuff. Exposed wires serve as electrode contacts. The cuff edges are attached together with a small staple. The resulting electrode can host two nerves in distinct cuffs.

3.4. Electrical stimulation setup

A square pulse stimulator (GRASS Technologies - SD9) with built-in output isolation circuit was used to apply a monophasic low-frequency voltage stimulation to sacral nerve S2 (or possibly S1), unilaterally or bilaterally (Fig. 3). The pulse frequency was fixed to 30 Hz, the pulse width was 300 µs in most experiments, while the pulse amplitude was adjusted to the minimum value that produced a satisfactory intravesical pressure (about 40 cmH2O). Tripolar electrode configuration was preferred in general.

A function generator (Wavetek - 19) was used to produce the high-frequency AC voltage waveform that is converted into current with a linear stimulus isolator (World Precision Instruments - SYS-A395D). The resulting current was delivered to one or multiple blockade sites on sacral nerves S1 and/or S2 using bipolar electrode configuration (Fig. 3). The stimulation amplitude was adjusted to the minimum value that produced a satisfactory blockade of the EUS. Frequency of 1 kHz has been chosen because with increasing frequency, the voltage required to achieve a complete block increases [2], and so does the stimulation current for a given electrode impedance. Consequently, such combination of high frequency and high stimulation current leads to high current consumption and high supply voltage requirements that are difficult to meet for a chronic implantable neurostimulation device. However, the charge per phase required for a complete block decreases with increasing frequency [13]. If we keep the same amount of charge injection per phase (CIP) using a sinusoidal waveform, stimulation at 2 kHz would require twice the current amplitude of that at 1 kHz. If we extrapolate results from [13], the mean required CIP would be about 0.65 and 0.4 µC for 1 and 2 kHz respectively. So the required blockade current amplitude at 2 kHz would be about (2 x 0.4) / (1 x 0.65) = 1.23 times that of 1 kHz. Thus using higher frequency for blockade is not necessarily advantageous with respect to stimulation intensity.

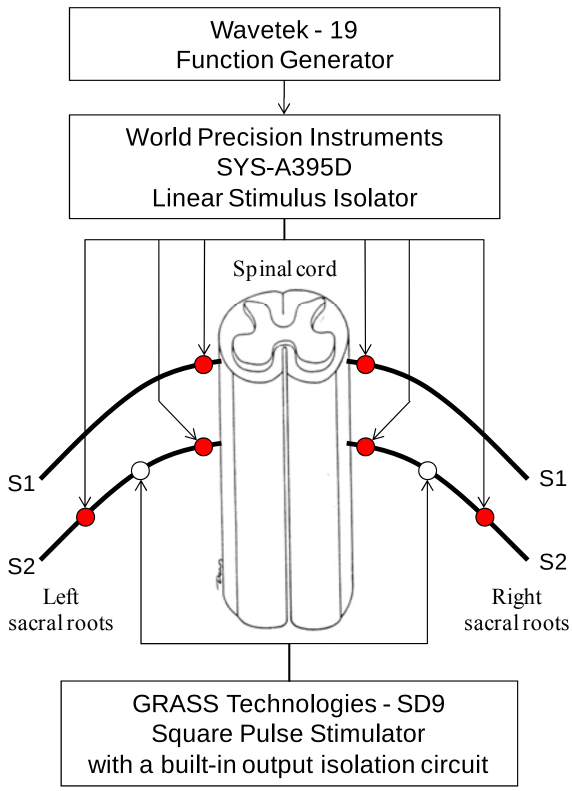


Fig. 3 Block diagram of the electrical stimulation setup

4. Results

We present in this section results from 8 acute dog experiments carried out with the objective of verifying the potential benefit of the proposed strategy. The result of stimulation is observed with a real time recording of the intravesical and urethral pressures (PVES and PURA respectively) as well as the EUS and pelvic floor muscles EMG activity. Fig. 4 shows the EUS EMG activity during 30 sec of low-frequency stimulation of S2 nerve and 1 kHz distal blockade that is applied for 10 sec only after a delay of 5 sec. The EMG activity clearly decays when blockade is activated. If the blockade intensity is increased, the EMG decay is faster and reaches lower values. Once the blockade is stopped, the EMG returns back to a higher value as the low-frequency stimulation continues. However, using high amplitude currents seems to induce some fatigue as the EMG is lower and decreases after the blockade has been stopped.

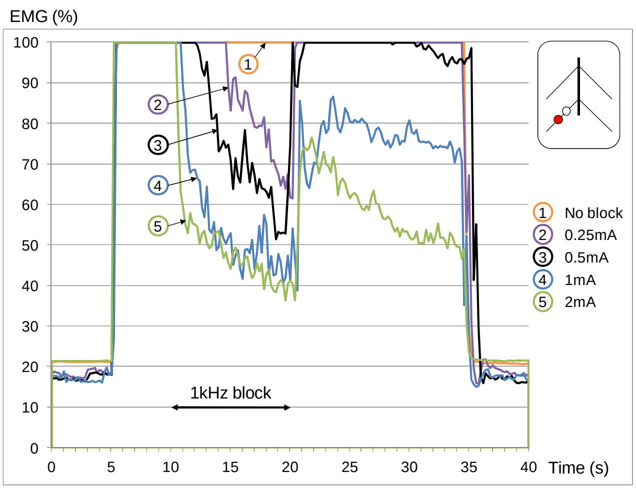
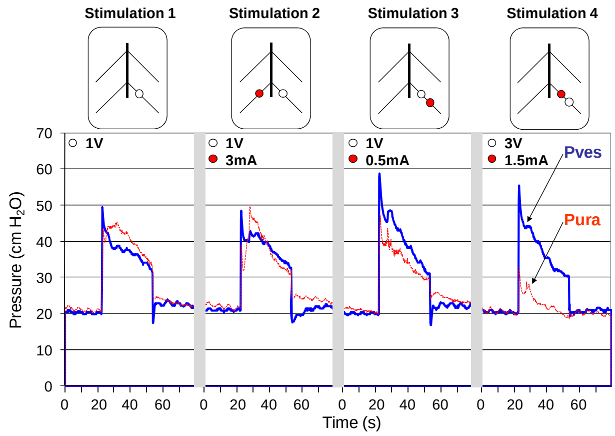
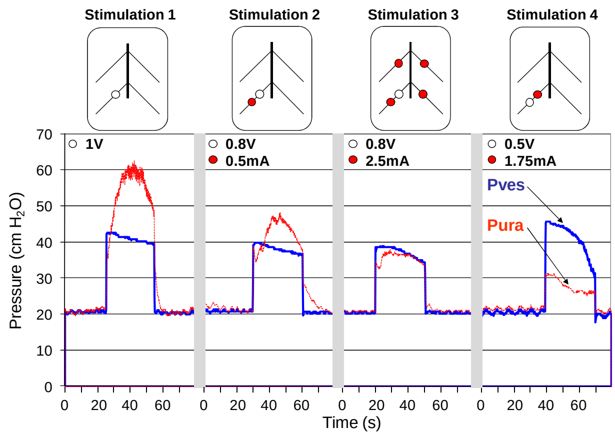


Fig. 4 The EUS EMG activity for different blockade intensities. Low-frequency (30 Hz) stimulation is applied unilaterally to S2 nerve for 30 sec. High-frequency (1 kHz) distal blockade is applied for 10 sec after a delay of 5 sec. The EMG activity decays when blockade is activated. For higher blockade intensities, the EMG decay is faster and more important.

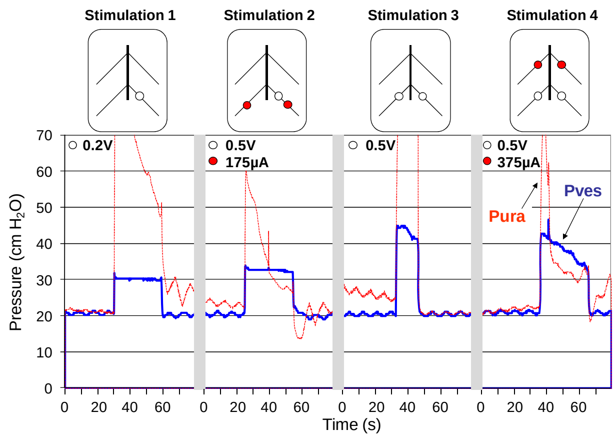
Figs. 5 and 6 represent stimulation sets from four different animals. They have been selected for being the most representative. In each experiment, we looked for the best stimulation strategy that would lead to an optimal micturition. That corresponds to a maximal rising of PVES associated with a maximal relaxation of the EUS which can be observed as a decrease of PURA. In Fig. 5, "Stimulation 1" shows the response to conventional unilateral S2 low-frequency stimulation, "Stimulations 2 and 3" represent various configurations of stimulation/blockade, whereas "Stimulation 4" gives the best strategy that has been tested.



(a)



(b)



(c)

Fig. 5 Stimulation sets from different animals: (a) animal 4, (b) animal 2, and (c) animal 1. "Stimulation 1" shows the response to conventional unilateral S2 low-frequency stimulation. "Stimulations 2 and 3" represent various configurations of stimulation/blockade. "Stimulation 4" is the best strategy that has been tested for that particular animal.

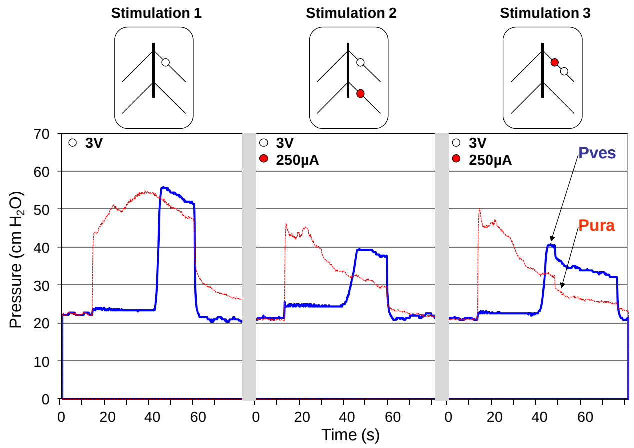


Fig. 6 Stimulation set from animal 5. "Stimulation 1" shows the response to Right S1 nerve low-frequency stimulation that is maintained for more than 45 sec. A large second PVES rising pressure occurs after a delay of about 30 sec, while no change has been made to the stimulation setup. Adding blockade as in "Stimulations 2 and 3" makes it an efficient strategy in this case.

In Fig. 5(a) (animal 4), the bladder response to unilateral stimulation (Right S2 nerve) was satisfactory with a maximum PVES increase of over 20 cmH2O (Stimulation 1). However, PURA remained higher than PVES preventing bladder emptying. Blockade of Left S2 nerve (Stimulation 2) led to a slight reduction of PURA. Distal blockade of Right S2 nerve (Stimulation 3) achieved a PVES higher than PURA, but both latter blockade types remained insufficient. It is a proximal blockade of the Right S2 nerve (Stimulations 4) that proved to be a very efficient strategy even without distal blockade. This means that, in this case, reflex EUS activation triggered by the low-frequency stimulation is dominant and should be blocked.

In Fig. 5(b) (animal 2), it is a unilateral stimulation of the Left S2 nerve that has been chosen to induce a satisfactory PVES response (Stimulation 1). In this case, PURA is much higher than PVES during stimulation. A distal blockade of Left S2 nerve (Stimulation 2) showed a significant decrease of PURA but still insufficient. Adding blockade on all other (S1 & S2) sacral nerves reduced even more PURA but it remained almost equal to PVES (Stimulation 3). Again, similarly to animal 4, it is a proximal blockade of the Left S2 nerve, without distal blockade, that proved to be efficient (Stimulations 4).

In Fig. 5(c) (animal 1), we observed a particularly high PURA peak that prevented us from increasing the Right S2 unilateral stimulation intensity to reach a satisfactory PVES amplitude (Stimulation 1). A simultaneous blockade of Left S2 nerve and a distal blockade of Right S2 nerve showed a significant decrease of PURA but PVES remained insufficient (Stimulation 2). Bilateral S2 stimulation was beneficial in increasing PVES (Stimulation 3) and the best strategy was to apply blockade on both S1 roots. This means that, in this case, reflex EUS activation involving S1 nerves (as opposite to the stimulated S2 nerves) is not only present but important to the point that it becomes necessary to block it.

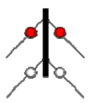
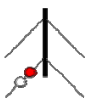
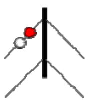
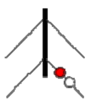
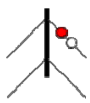
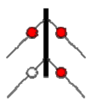
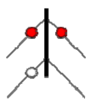
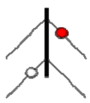
In Fig. 6 (animal 5), we had to stimulate the Right S1 nerve in order to obtain a response of the bladder (Stimulation 1). However, this response is quite different from that of common S2 stimulation. Interestingly, there is first, a small increase of PVES when low-frequency stimulation is switched on, then a second large PVES rising pressure occurs after a delay of about 30 sec, while no change has been made to the stimulation setup. This delayed rising pressure brings PVES to a value higher than PURA, and adding blockade as in Stimulations 2 and 3 makes it an efficient strategy in this case. Such a response was never reported in our previous Polystim experiments as the duration of stimulation was limited to less than 15 sec in general. We also observed this response, even though less important, in three other animals using S2 nerves in two of them. We can hypothesize that a longer stimulation of S1 or S2 nerves may trigger a spinal micturition reflex.

A summary of best stimulation strategies and achieved results from the 8 acute dog experiments is presented in Table 1. For each animal, the best stimulation strategy is the one that led to a maximum (PVES-PURA) pressure difference that is maintained as long as possible during the target stimulation period of about 30 sec. Mean(PVES-PURA) and Mean(ΔPURA) values are both given with and without blockade. ΔPURA is PURA during stimulation minus PURA baseline prior to stimulation. The increase of Mean(PVES-PURA) and the percentage reduction of Mean(ΔPURA) give a measure of the achieved selectivity and EUS blockade success respectively. The animals are ordered with respect to the former. The achieved increase of Mean(PVES-PURA) ranged from -4 to 53.2 cmH2O, while the percentage reduction of Mean(ΔPURA) ranged from 10.7 to 86.1 %. The blockade current intensity used in these cases ranged from 125 µA to 1.75 mA. When multiple blockade electrodes are used, blockade current is distributed depending on their impedances. Electrode impedances measured at 1 kHz ranged from 1.2 to 4.8 kΩ. In animal 8, even if blockade was observed, all utilized strategies did not improve the response. Among the best stimulation strategies, three of them involved bilateral blockade of S1 nerves (animals 1, 6, 7), and four others involved proximal blockade of the same stimulated nerve (animals 2-5).

5. Discussion

Following these experiments, the first observations are that the optimal configuration of stimulation/blockade is different from one animal to another and that the success of blockade is variable. In addition, for the same animal, the response to stimulation varies along the 6 hours experiment. Even if the blockade efficiency was variable, it was possible to block the EUS in all 8 experiments. A sinusoidal waveform of 1 kHz frequency is capable of blocking the nerve activity with different degrees depending on the current amplitude. Indeed, in the case of blockade of direct EUS activation, which assumes blocking only large fibres innervating the EUS, if the sinusoid amplitude is increased above a threshold even the bladder contraction is blocked, which assumes blocking all fibres including small ones innervating the detrusor muscle.

Table 1 Summary of best stimulation strategies for each animal and achieved results. The best stimulation strategy is the one that led to a maximum (PVES-PURA) pressure difference that is maintained as long as possible during the target stimulation period of about 30 sec. The animals are ordered with respect to the increase of Mean(PVES-PURA) which gives a measure of the achieved selectivity. The percentage reduction of Mean(ΔPURA) gives a measure of the EUS blockade success. Among the best stimulation strategies, three of them involved bilateral blockade of S1 nerves (animals 1, 6, 7), and four others involved proximal blockade of the same stimulated nerve (animals 2-5).

Animal nº	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Best stimulation strategy					[1] 			
Blockade intensity[2] (mA)	0.375	1.75	2.5	1.5	0.250	1	1.25	0.125
Mean(Pves-Pura) with blockade (cmH_2O)	4.7	13.5	-9.7	13.7	7.5	6.1	6.6	3.2
Mean(Pves-Pura) without blockade (cmH_2O)	-48.5	-12.8	-28.2	-2.7	3.9	3.1	3.7	7.2
Increase of Mean(Pves-Pura) (cmH_2O)	53.2	26.3	18.5	16.4	3.6	3	2.9	-4
Mean(ΔPura)[3] with blockade (cmH_2O)	12.6	7.9	20.4	2.8	7.2	2.1	10.8	10
Mean(ΔPura)[3] without blockade (cmH_2O)	71.1	33.8	47.1	20.2	28.7	12.4	12.1	13.4
Reduction of Mean(ΔPura)[3] (%)	82.3	76.6	56.7	86.1	74.9	83.1	10.7	25.4
Second Response[4]	with S2 root	with S2 root	with S1 root	N.A.	with S1 root	N.A.	N.A.	N.A.

[1]"Pves > Pura" period during second response[4].
[2]Current is shared by all blockade electrodes depending on their impedances.
[3]ΔPura = Pura during stimulation – Pura baseline prior to stimulation.
[4]Second large Pves pressure rising observed about 30 sec after start of stimulation (see Fig. 6).

Anatomically, the lower urinary tract innervations are the same from one animal to another but there is a functional variability. Thus it is necessary to look for an optimal stimulation/blockade configuration. In most cases, a satisfactory contraction of the bladder can be obtained with a unilateral or bilateral stimulation of S2 sacral nerves at low-frequency. If that is not enough, then S1 nerve stimulation may be considered even though it leads to higher sphincteric pressures. Afterwards, blockade can be tested on all S1 and S2 sacral nerves, individually first, then in combination. The optimal stimulation/blockade configuration is the one which gives a minimal EUS pressure in presence of maximal bladder contraction. It is important to note here that during the time of experiments, effective blockade was reversible as the EUS is activated whenever blockade action was removed.

Finally, we don't know how different can be the response to the proposed stimulation strategy in a chronic condition of DSD compared to that obtained in a state of acute spinal shock with A-chloralose anaesthesia. So acute experiments are not sufficient to validate our hypothesis especially that spinal shock generally lasts several weeks after the spinal cord transection. However, the presented results are promising and we consider chronic experiments in order to evaluate the long-term efficiency of the proposed strategy. This obviously requires a custom implantable neurostimulator that implements the proposed strategy and electrodes properly modified for chronic experiments with biocompatible materials. We are currently designing such neurostimulator that will be capable of generating conventional stimulation waveforms as well as high-frequency sinusoids simultaneously over multiple channels.

6. Conclusion

We proposed a new sacral multisite stimulation strategy based on nerve conduction blockade using high-frequency stimulation as an alternative to rhizotomy. This approach aims at increasing bladder contraction selectively and decreasing DSD. Thus, better micturition could be achieved while preserving sexual and defecation reflexes as well as sacral sensations, if still present in case of incomplete SCI. Acute dog experiments were carried out to test the proposed strategy and EUS blockade has been achieved in 8 animals. Given the eventually high number of electrodes required for this strategy, a custom multiple-contacts bi-cuff-electrode design has also been developed to be applied around two nerves in distinct cuffs. Following these experiments, the main observations are that high-frequency blockade can be very efficient in reducing the EUS resistance and that the optimal strategy is different from one animal to another. Results show an interesting potential benefit of the proposed strategy in decreasing DSD without any rhizotomy.

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