New sacral neurostimulation strategy to enhance micturition in paraplegics: Acute dog experiments.

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Abstract

Sacral neurostimulation is one of the most promising techniques for bladder rehabilitation in spinal cord-injured (SCI) patients. In order to avoid rhizotomy, which is irreversible and may abolish sexual and defecation reflexes as well as sacral sensations, if still present in case of incomplete SCI, we propose a new stimulation strategy based on nerve conduction blockade using high-frequency stimulation as an alternative to rhizotomy. Acute dog experiments were carried out to verify the potential benefit of this strategy. High-frequency blockade has been observed in 8 animals among 9 and shows efficient micturition technique for SCI patients.

1. Introduction

The efficiency of bladder emptying by means of sacral neurostimulation depends on the capability to contract the bladder muscle without generating a dyssynergic contraction of the urethral sphincter. In order to improve the neurostimulation selectivity, several techniques have been proposed, among which rhizotomy, anodal block and high-frequency blockade. Introduced at the end of the 19th century, dorsal sacral roots 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 incontinence reflex is reduced, and the upper urinary tract is protected from ureteral reflux and hydronephrosis. In addition, stimulation with rhizotomy reduces the external sphincter dyssynergia, improves urine flow, and prevents autonomic dysreflexia.

In case of a complete spinal cord injury (SCI), rhizotomy is combined with an implantable sacral ventral root stimulator such as the Finetech-Brindley (also known as the VOCARE in North America) Bladder System [1]. Actually, this neurostimulation system is the only commercialised FDA-approved solution aiming for micturition in SCI patients [2]. 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 presents in case of incomplete SCI.

In the following section, we propose a new sacral neurostimulation strategy based on nerve conduction blockade using high frequency stimulation as an alternative to rhizotomy. In section 3, we review and discuss the principle of high-frequency blockade. Then, we state our hypothesis in section 4 and present preliminary results from acute dog experiments in section 5.

2. Neurostimulation strategy

The proposed strategy, based on a dog model, is illustrated in Figure 1.

- **Low-frequency stimulation (Bladder contraction)**
  - Rectangular pulse waveform (e.g. 30Hz)
- **High-frequency stimulation (Sphincter blockade)**
  - Sinusoidal waveform (e.g. 1kHz)

**Figure 1 Proposed neurostimulation strategy**

A low-frequency (e.g. 30 Hz) monophasic current stimulation is applied, unilaterally or bilaterally, on S2 sacral nerve(s) 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, dyssynergia is present and the sphincter contracts as well. Sphincteric dyssynergia can be triggered by direct and/or reflex mechanisms due to efferent and/or afferent fibres activation respectively. Both types of dyssynergia can be avoided by blocking large diameter axons innervating the sphincter with high-frequency stimulation. In the example of Figure 1, a sinusoidal waveform at 1kHz is chosen. In order to eliminate direct dyssynergia, a selective blockade must be applied between the low frequency stimulation site and the sphincter, whereas for reflex dyssynergia, a complete blockade must be applied between the low frequency stimulation site and the spinal cord. However, reflex dyssynergia may involve
S1 sacral root(s), which should be blocked as well in this case. We should note that blocking at all sites as shown in Figure 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 dyssynergia is dominant or that only one blockade site is sufficient.

3. High-Frequency Blockade

As an alternative to rhizotomy, high-frequency stimulation can be used to achieve a complete or graded block of the compound action potential (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 600Hz was an optimum frequency in terms of required stimulation intensity [3]. In 1998, Shaker et al. studied the efficiency of this technique in acute dog experiments using a neurostimulator designed by our Polystim laboratory [4, 5]. The stimulator generated a rectangular waveform combining two frequencies (e.g. 600Hz and 30Hz) such that the higher frequency blocks the urethral sphincter activity and reduces dyssynergia 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 electrode. Here, the used term “blockade” refers more to the stimulation result which is the inhibition of the sphincter 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 target muscle [6-8].

According to [6], a reversible nerve blockade can be achieved with different waveforms with frequencies from 2 to 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 600Hz can also achieve a complete blockade but would require high stimulation currents (higher than 4mA). Thus, blockade with 600 Hz is probably due to a muscle fatigue mechanism rather than nerve conduction blockade. In the case of sinusoidal waveforms, low frequencies (500Hz-1kHz) generates CAPs at the same or sub-multiple rate [9]. The generated CAP amplitude vanishes for frequencies beyond 1 kHz. Blockade of each axon within the nerve is also influenced by the stimulation amplitude as well as the axon diameter [7]. 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 achieved by adjusting stimulation amplitudes [8]. In the urinary system case, Sievert et al. present several animal experimental results especially the bladder and sphincter pressure responses to a sinusoidal stimulation up to 10 kHz [10]. It is shown that sphincteric pressure is maximal around 100Hz, and decreases drastically as the frequency is increased. Beyond 1 kHz, the sphincteric pressure becomes very low. The blockade discussed so far concerned motor action potentials induced by neurostimulation. A complete blockade of sensory activity would probably require higher stimulation amplitudes [6].

4. Hypothesis

In view of these observations, we state the following hypothesis in the case of the lower urinary tract: The use of a high-frequency alternating stimulation waveform (e.g. sinusoidal) 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 stimulation strategy based on this technique would allow better micturition by increasing bladder contraction selectivity and decreasing sphincter dyssynergia without any rhizotomy. To our knowledge, such a strategy has not been tested yet in the particular case of the urinary system.

5. Experimental results

We present in this section preliminary results from 9 acute dog experiments carried out with the objective of verifying the potential benefit of the proposed strategy. After spinalization, the result of stimulation is observed with a real time recording of the internal bladder (Pves) and urethral (Pura) pressures as well as the sphincter muscle activity (EMG). Blockade has been observed in 8 animals among 9 with a frequency of 1 kHz. In the case of a sinusoidal waveform, if we keep the same amount of charge injection per phase (CIP), stimulation at 2 kHz would require twice the current amplitude at 1 kHz. However, if we extrapolate results from [9], the mean required CIP would be about 0.65 and 0.4 uC for 1 and 2 kHz respectively. So the required blockade amplitude at 2 kHz would be about (2^*0.4) / (1^*0.65) = 1.23 times that at 1 kHz. Thus using higher frequency for blockade is not necessarily advantageous with respect to stimulation intensity. Two animals showed low dyssynergia with conventional unilateral stimulation and even if blockade was observed, all tried strategies did not improve the response. Figures 2 to 4 represents stimulation sets from three different experiments: A, B and C respectively. They have been selected for being the most successful. 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 sphincter which can be observed as a decrease of Pura and/or a decrease of EMG.
beneficial and the best strategy in this case was to increasing the stimulation intensity to reach satisfying particularly high Pura peak that prevented us from not enough. In experiment C, we observed a dyssynergia in “Stimulation n°2” of experiment B was efficient strategy. Note that blocking direct dyssynergia on the same stimulated nerve was a very preventing bladder emptying. Blocking reflex cmH2O. However, Pura remained higher than Pves satisfactory with a maximum Pves increase of over 20

For all experiments, “Stimulation n°1” shows the response to conventional unilateral S2 low frequency stimulation. “Stimulation n°3” represents the best strategy that has been tested. In experiments A and B, the bladder response to unilateral stimulation was satisfactory with a maximum Pves increase of over 20 cmH2O. However, Pura remained higher than Pves preventing bladder emptying. Blocking reflex dyssynergia on the same stimulated nerve was a very efficient strategy. Note that blocking direct dyssynergia in “Stimulation n°2” of experiment B was not enough. In experiment C, we observed a particularly high Pura peak that prevented us from increasing the stimulation intensity to reach satisfying Pves amplitude. Bilateral S2 stimulation was beneficial and the best strategy in this case was to block reflex dyssynergia on both S1 roots. Following these experiments, the main observation is that high-frequency blockade can be very efficient in reducing the urethral sphincter pressure and that the optimal strategy is different from one animal to another.

8. CONCLUSION

We proposed a new sacral neurostimulation strategy based on nerve conduction blockade using high frequency stimulation as an alternative to rhizotomy. Acute dog experiments were carried out to test the proposed strategy and blockade has been observed in 8 animals among 9. These results show the potential benefit of the proposed strategy in decreasing sphincter dyssynergia without any rhizotomy.

References


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