Perspective

Neuromodulation and neurostimulation: overview and future potential

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Introduction

The history of neuromodulation and neurostimulation began after several important discoveries in the fields of neurophysiology and electricity. In 1811, Bell (1) was the first to conduct experiments on the spinal nerve roots. He reported that manipulation of the anterior sacral roots led to muscle contractions of the back, but not the posterior fibers of the spinal nerves. Magendie (1822) further recognized the anterior motor and the posterior sensory function of the roots (2). In 1833, Hall (3) uncovered the distinct function of the spinal cord and medulla oblongata and well as the reflex function. These were the pioneering discoveries that open the door for further examination of the somatic and autonomic nervous system. In the mid-19th century, Giannuzzi (4) (1863) stimulated the spinal cord in dogs and concluded that the hypo gastric and pelvic nerves are involved in regulating the bladder function. In 1872, Budge (5) postulated that there are two sets of nerves innervating the bladder: the motor fibers from the anterior roots of S1, 2, and 3, and the sensory fibers from the hypo gastric plexus. He postulated the presence of a micturition center in S2 to S4 in 1864 (6). The early 20th century saw the development of electric oscillators, stimulators, and amplifiers that greatly improved the understanding of nerve impulses, synaptic transmission, and function of the nervous system. Significant improvement was also achieved by radiofrequency induction that led Glen and his associates (7) to develop the totally implantable heart pacemaker, one of the first commercially available stimulators. In the ensuing years, stimulators for different organ systems were developed: a heart pacemaker, a diaphragmatic pacemaker, and a cochlear implant.

Modern interest in electrical control of bladder function began in the 1950s and 1960s. The most pressing question at that time was the best location for stimulation. Several groups attempted to initiate or prevent voiding by stimulating the pelvic floor, the detrusor muscle, the spinal cord or the pelvic sacral nerve roots. Even other parts of the body, such as the skin, were stimulated to influence bladder function.

McGuire (1955) (8) and Boyce (9) and his associates (1964), tried direct bladder stimulation using different forms of electrodes with limited success. In 1963, Bradley (10) and his associates published their experience with an implantable stimulator in a chronic dog model. However, when applied to humans, it induced bladder contractions, but no voiding. In the early 70's Nashold and Freedman (11,12) were the first to attempt to achieve micturition by direct spinal cord stimulation. They applied direct electrical activation of the micturition center in the sacral segment of the conus medullaris and reported that the region for optimum stimulation is S1 to S3. They compared the stimulation of the dorsal surface of the spinal cord at L5, S1, and S2 with depth stimulation (2-3 millimeters) at S1 and S2 in an acute and then in a chronic setting. They reported that only the depth electrode induced voiding. In 1975, Dr. Nashold (13,14) and his associates reported that eight patients with electrodes implanted in the sacral segment produced bladder contractions and bladder emptying when stimulated. Their success excited a great deal of interest in the neuroprothesis program at the NIH regarding the potential use of neurostimulation as a means of bladder control in paraplegic and quadriplegic patients. This prompted the leaders of this program, Drs. Terry Hambrecht and Karl Frank, to reach out and visit us at UCSF. After a long day of discussions about the potential of this new approach, we were contracted by NIH to pursue the neuroprosthetic work and explore its potential. We started testing a varieties of electrodes in 1975 (15), including surface electrode, dorsal column electrodes, wrap around electrodes, in depth electrodes, as well as bipolar, tripolar, horizontal, vertical, and transverse designs. Regardless of the type of electrodes, the detrusor response to neurostimulation was similar. The wrap around surface electrode with the most extensive current spread gave the same results as the coaxial electrode with the least current spread, prompting us to theorize that current did not cross the midline of the spinal cord. Unfortunately, no real voiding was achieved. Besides the expected detrusor contractions there was also a strong sphincteric contraction. Nevertheless, small amount of voiding happened at the end of the stimulation- the so-called post-stimulus voiding (16). This result contrasted with the earlier work of Nashold and Freedman, inspired us to map the neuronal cell bodies in the spinal cord that differentially controls the detrusor and the sphincter. Using retrograde tracers, horseradish peroxidase, injected in various locations of the lower urinary tract, the existence of two separate groups of nuclei was delineated: the parasympathetic and the pudendal nucleus. Interestingly, the pudendal nucleus extends beyond the parasympathetic nucleus both caudally and cranially (17) and we realized that it is very difficult to stimulate the bladder nuclei without stimulating the sphincter nuclei at the spinal cord level even with very fine microelectrodes.

For these reasons, sacral root stimulation was investigated based on the hypothesis that different roots would carry different neuronal axons to different locations. We performed numerous experiments on a canine mode (18,19) as the anatomy of the bladder innervation is similar to the human's. After a dorsal lumber laminectomy, the sacral spinal roots were exposed and were stimulated either intradurally or extradurally, within the spinal canal. We developed several models: I. Unilateral stimulation of the intact sacral root at various levels; II. Simultaneous bilateral stimulation of the intact sacral root at various levels; III. Stimulation of the intact ventral and dorsal roots separately; IV. Stimulation of the proximal and distal cut ends of the divided dorsal and ventral roots. From these studies, it was evident that stimulating an intact root is the least effective and stimulating the ventral component is the most effective; while no difference was noted between right and left roots stimulation. We also noted that besides the detrusor contractions, stimulation caused some sphincter contraction, owing to the presence of both autonomic and somatic fibers in the ventral root. The study then continued with the addition of neurotomy to eliminate the afferent fibers. The dorsal fibers were separated and cut and only the ventral component was stimulated. These experiments showed that to achieve maximum specific detrusor contraction, the dorsal component must be separated from the ventral component and the somatic fibers of the root must be isolated and selectively cut. These studies also showed that stimulation with low frequency and low voltage can maintain adequate sphincteric activity (20,21). However, stimulation with high frequency and low voltage will fatigue the external sphincter and block its activity. When high frequency and low voltage stimulation is followed by high voltage stimulation, bladder contraction could be induced and voiding achieved (22,23). These findings, when combined together, showed that detrusor contractions could be activated separately from sphincteric activity.

Sacral roots were also evaluated by histologic and electronmicroscopic examination of chronic stimulated sacral roots, as compared to the contralateral non-stimulated roots. The studies revealed no damage to the neurons. We noted also that the responses to neurostimulation remained stable over several months, and the integrity and viability of the sacral root were maintained.

In 1974, Brindley (24) working on the baboons, isolated the sacral roots intradurally and placed them into slots of his implant. When he applied weak electrical stimulation, it resulted in activation only of the striated sphincter muscles. When he used continuous stimulation with high voltage, he obtained activation of both the detrusor muscles as well as the sphincter muscles. Knowing that the detrusor smooth muscles relax much slower than the prompt relaxation of the striated muscles, he achieved micturition by delivering bursts of stimulation for one second with stimulation/rest ratio of 2 to 1. The bladder contracted smoothly while the striated sphincteric relaxed in the off interval, and the female baboons consistently emptied the bladder. In 1977 (25), Brindley and his associates began implanting sacral anterior root stimulator in paraplegic patients with incontinence. In 1986 (26), they presented their experience with the first fifty cases of whom about thirty were completely continent and five were continent at night. Forty-three patients regularly used their implants for micturition. Twenty-six of thirty-eight male patients were able to produce penile erection under stimulation. In 1986, Sauerwein combined sacral anterior root stimulation with sacral de-afferentiation in patients with spinal cord lesions to overcome reflex urinary incontinence (27,28). Rhizotomy of the posterior roots of S2 to S5 in forty-five patients resulted in diminished spasticity in 93% and secured continence in 91% of patients.

In 1982 and 1983, we developed a colony of paraplegic dogs in which we implanted newly designed spiral electrodes to minimize nerve damage on selected sacral roots (29). After dorsal root rhizotomy, usually S2 was selected for the electrode implant, which was secured in place to the sacral lamina to prevent any tension. Complete bladder evacuation was achieved with high frequency (200 Hz) low voltage stimulation followed by high voltage stimulation. This colony of dogs was maintained on this stimulation regiment for over eight months. After that, they were euthanized, and we performed histological evaluation of the stimulated sacral roots, which would reveal complete preservation of normal integrity. Based on these results, we embarked on human clinical trials through the 1980s. After several variations, we performed electrode implantation on the ventral root of S3 most of the time, rarely combining with S4. After doing extensive posterior rhizotomy and occasional selective peripheral neurotomy, we concluded that this model was the most successful combination to achieve continence and to promote bladder evacuation. In 1990 (30,31), we reported on the first thirty-five patients suffering from neuropathic voiding dysfunction caused by suprasegmental spinal cord lesions. Of the twenty-five patients that were available for follow up, 60% experienced restored reservoir function and restored continence with complete bladder evacuation.

In our continuing neuroanatomic studies, it was determined that the dorsal sacral neurotomies could be done more extensively and easier if performed intradurally rather than extradurally (32). Our previous studies have also shown the existence of a separate parasympathetic nucleus and a pudendal nucleus in the sacral segment. We noted that the ventral sacral roots emerged as numerous separate rootlets (33). The spatial orientation of these rootlets imply that each carries the axons of the closest neuronal cell group in the spinal cord and gathered in a few rootlets-the rootlets formed by axons emerging from the parasympathetic nuclei maintained their identity throughout the entire intra spinal course. The same arrangement was noted in those emerging from the pudendal nuclei. These rootlets grouped into bundles that later constitute the ventral root, which then exit the dura. The dissection of these rootlets throughout their entire intradural course showed that they maintained their identity until they exit from the dura. This suggests that the stimulation of the specific rootlet might be equivalent in its specificity and selectivity to micro stimulation of specific neuron groupings in the spinal cord itself. In addition, the fiber that might carry somatic fibers to the sphincter could be identified by stimulating these rootlets intradurally. They could be cut, and then electrode is placed extradurally on the entire ventral root, avoiding the activation of the striated sphincter. This could make the stimulation more selective, eliminating detrusor sphincter dyssynergia. As an outcome from this work, we can consider intradural dorsal rhitzomy, plus cutting selective anterior somatic rootlets that are mostly carrying somatic fibers, then extradural electrode placement on the intact selected sacral root.

In additional work (22), taking advantage of the knowledge that high frequency current can block large somatic fibers, electrical blockade of undesirable responses was tested to replace selective somatic neuroautomies. High frequency sinusoidal stimulation was effective in blocking external sphincteric activity. However, the sinusoidal wave form is not efficient. An alternate phase rectangular wave was more efficient and induced the same blockade. Alternating pulses of high frequency and low aptitude, followed by low frequency and high amplitude, were effective in inducing low pressure voiding without the need for somatic neurotimies. This approach has not yet been tried clinically, but it might prove to be the answer to the problem of the detrusor sphincter dyssynergia in electrically stimulated voiding.

Neuromodulation

The widely applied neuromodulation (34) in the management of voiding dysfunctions and pelvic pain is a small byproduct of this extensive work on the development of what we look at as a bladder pacemaker to restore bladder function in high spinal cord lesions. During our testing of the spinalized animal in which we had implanted electrodes in various segment of the sacral roots and while doing our urodynamic monitoring, we noted that when the bladder went into activity with any degree of filling, if we stimulated the sacral roots, we could immediately inhibit this activity. The bladder stayed quiet as long as the stimulation was maintained. The moment stimulation stopped, the bladder became overactive again. That took us by surprise initially, but after considering it, we realized that this is a normal natural reflex. If the bladder tends to overact, we can suppress it by overactivating a sacral root, which would have tightened the perineal muscles and that inhibits detrusor activity. That was the first insight into the fact that driving the sacral roots can inhibit detrusor overactivity. We felt that if this could be accomplished in the full-blown overactive spastic neurogenic bladder, it would definitely be easier to accomplish the same under less severe conditions. There is a reflex inhibitory mechanism that exists between pelvic floor and detrusor activity. As it was noted, sphincteric contraction suppressed detrusor activity and also pudendal nerve blockade improved bladder capacity. Excluding mechanical obstruction, most voiding dysfunctions are related to the urinary bladder or the pelvic floor. To the latter group, they ascribed the severe urge and frequency to sphincteric instability and pelvic pain because of the constant pelvic floor hyperactivity. It became clear that whenever we diminished the uretheral sphincter and pelvic floor instability, it stabilized the entire micturition reflex mechanism. This is what initiated the concept of neuromodulation. Activation of the external sphincter by sacral root stimulation inhibited detrusor activity as a normal reflex, and this diminished detrusor instability. This however requires an intact sensory pathway. The stimulating parameters are too low to activate the autonomic component of the sacral root; however, it stimulates mainly the somatic component in both the afferent sensory fibers and efferent motor fibers. Intraspinal connections between the pudendal and the parasympathetic nuclei in the sacral segment are likely responsible for the modulation of the voiding reflex and detrusor activity. Having this knowledge and understanding, we started testing our patients. The first sacral root implant was actually done per cutaneously in 1981. We tested numerous patients with a variety of voiding and pelvic floor dysfunction with very encouraging results. With proper selection, this modality of neuromodulation became highly successful. This approach is now being used worldwide and becoming highly popular and successful and is being called interstim neuromodulation. The basic principle of it is the interaction between the pelvic floor and detrusor activity.

Neuromodulation, however, had a broader application as it is currently being tested and applied on a variety of other dysfunctions as fecal incontinence, spastic colon, dyssynergia interstitial cystitis, and other varieties of pelvis floor dysfunctions with varying degrees of success.

Future potential of neurostimulation and neuromodulation

Neurostimulation and neuromodulation are here to stay (35). They have already proven their effectiveness and their potential benefits. Considerable progress has been made during the last two decades in understanding the basic issues that are related to neurostimulation and its potential application, not only in the urinary tract and the pelvic organs, but also in other organs. Whenever there is an intact motor neuron system that can be isolated, it can be stimulated to drive the function it was intended for. Electrophrenic respirators are clear examples of the successful application of neurostimulation to drive the diaphragm in high quadriplegic patients. The auditory prosthesis is another successful application of neurostimulation to restore hearing loss.

Application of neurostimulation to lower and upper extremities for rehabilitation has been investigated widely and is highly promising of achieving mobility as well as restoring and maintaining function of either extremity. The optimum goal is to restore full function to make the individual capable of utilizing both upper and lower extremities. With the progress being made, this potential is likely achievable.

The nervous system is fortunately quite specific for its function, whether it is sensory or motor, whether it is somatic or autonomic. A knowledge of the precise anatomic connections and distributions open the door for reproducing specific function by tapping into the segments of the nervous system to do the job desired. A clear example of that is seen in the sacral roots, which we tapped into to control pelvic floor function. The complete root is considered in its two basic components, the sensory dorsal and the motor ventral components. Both roots are made out of several rootlets. These rootlets are derived from the spinal cord and from the adjacent neural cells with a certain degree of specificity for their function. This knowledge is raising the potential that we can identify precisely the neural unit that is responsible for a certain function to be stimulated and driven.

As discussed earlier, these are the basic knowledge and know how to develop a complete bladder pacemaker that can achieve restoration of the basic function of the urinary bladder, making it gain capacity as a reservoir and be able to empty completely and at the same time maintain continence. In spite of this knowledge, this has not yet been clinically applied. There are several reasons for this. Primarily, there is no prothesis available at the moment that can deliver the specific stimulation parameters required for the successful bladder pacemaker. It has not been developed because of its complexity, and the limited population in need of this kind of approach. In addition, the surgical approach proposed is highly demanding.

The patient population for this approach, the complete bladder pacemaker, is primarily high paraplegic and quadriplegic patients as the result of spinal cord injury. The approach, as it stands today, does require certain neurotmesis, whether it is dorsal rhizotomy or selective somatic neurotomy of one kind or another. Those patients are usually adamant against any more nerve cutting or nerve damage. They already sustained extensive injury to their spinal cord, and they refuse any approach that will further interfere with the integrity of what is left of their nervous system. The most important is the approach itself, which is a quite demanding surgery. It needs the interested neurourologist, who should have the surgical capability close to that of a neurosurgeon or a neurosurgeon, who is deeply interested in neurourology to be encouraged to embark on such a highly demanding delicate surgical intervention. Either way, it will require extensive training before wide application and wide use of that knowledge and technology become available.

If we combine all of these factors together, we start to appreciate why this technology is not much widely used and properly applied for this needy population. Industries are less than enthusiastic to embark on the development of such a complex prostheses. There is a limited population. Compound that with the limited number of neurourologist, who care for them and who have learned this neurosurgical expertise to consider such an approach, coupled by a vast segment of discriminative population, who would not consent to any surgical intervention that would include further neurotmesis.

Technology and knowledge on how to develop the true perfect bladder pacemaker that can also be a bowel pacemaker as well as an erectile function pacemaker for the quadriplegic or the high paraplegic is with us. Further development in our understanding of electrical blockade of neural transmission might help in eliminating most if not all neurotmesis. That in itself would be a major step forward because a simplified surgical technique, and no neurotomy would be more acceptable to patients.

Neurostimulation for the control of the visceral organs has a long and arduous history. However, great progress has been made and knowledge has been expanded. What has been a dream is getting closer to becoming a reality.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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