Interventional neurophysiology and an implantable system for neurostimulation of the sacral area

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Summary

Surgical or interventional neurophysiology is a term commonly used to refer to a large number of neurosurgical procedures involving the brain, cranial nerves, spinal cord and peripheral nervous system which, to be efficient and safe, demand specific neurophysiological know-how. As a result of the development of these procedures and their increasing use in the operating room, the role of clinical neurophysiology, traditionally diagnostic, has been extended.

With the advent of ‘neurostimulation’ and ‘neuromodulation’, some neurophysiological techniques have, in themselves, progressively become more therapeutic, the therapeutic alteration of nervous system activity being achieved not only by surgical ablation or medication but also through electrophysiological means via implanted or non-implanted devices, whose development was made possible by extensive studies in the field of neurophysiology. The first application of electrical stimulation in urology opened up the way for progress in the therapeutic direction.

Moreover, with regard to the mechanism of action underlying neuromodulation, the application of neurophysiology and neuroimaging procedures has contributed to understanding of the neural control mechanism of visceral (e.g. lower urinary tract) function.

In our experience, the advent of sacral neuromodulation, the application of neurophysiology and neuroimaging has made it possible to shed light on the pathophysiological mechanisms of neuro-urological disorders, allowing us to assess and validate new therapeutic approaches and finally to develop a new method and device for chronic pudendal nerve stimulation.

KEY WORDS: interventional surgical neurophysiology, sacral neuromodulation, pudendal nerve stimulation.

Historical background

The application of neurophysiological studies and electrical stimulation in the field of urology dates back to the discovery, in the 18th century, of the relationship between electricity and nerves, and the creation, in the early 20th century, of the first electric generators, oscillators, stimulators and amplifiers.

The first report, by Saxtorph, on the use of electrical stimulation in bladder treatment – a metal electrode placed transurethrally into the bladder – appeared in 1878 (1). However, it was not until the 1950s and 1960s that research into therapeutic applications of electricity, for stimulation of the pelvic floor, detrusor, spinal cord, and pelvic and sacral nerves, really began: in 1963 Caldwell et al. (2), using the first pelvic floor stimulator, applied electrical stimulation as a means of controlling sphincter incompetence and Bradley et al. (3) published their experience with an implantable stimulator.

The first descriptions of the effects, on voiding, of electrical stimulation of the sacral roots were published in 1963 and 1968 by Habib (4,5) who discovered the location of neural trigger points that, in the human, were found to be the third and fourth sacral nerves at their exit from the sacral foramina anteriorly: successful voiding was induced using an electric current about 80 to 100 times smaller than the one used for direct stimulation of the muscle.

In 1964 Boyce (6) used an implantable iron core induction coil stimulator in three patients with detrusor paralysis, with complete success in one patient for six months until the wire broke, partial success in the second and failure in the third.

In 1968 Holmquist (7) published results on electromicturition induced by stimulation of the pelvic nerves in dogs in which voiding was followed by urethrocystography and measurements of bladder pressure. These stages in the history of electrical stimulation in functional urology are illustrated in figure 1 (over).

But it was to be a further two decades before Tanagho and his group (8,9), in 1982 and 1988, developed experimental models to evaluate the feasibility of stimulation of various sacral root components in both normal and paraplegic animals: by obtaining bladder contraction separately from sphincter activity it proved possible to work on and develop a true bladder pacemaker.

With Brindley (10), electrical stimulation of the sacral nerves became a clinical reality, producing effective long-term micturition in spinal cord injured patients, reducing constipation and restoring erection in a high percentage of male patients. These advances marked the advent of new era in functional urology.

Neuromodulation of the sacral area and interventional neurophysiology

Sacral nerve stimulation (SNS) has become established in recent years as a treatment option for the treatment of urge incontinence, non-obstructive urinary retention and severe symptoms of urgency-frequency. Medtronic de-
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developed Interstim® therapy for urinary control. The implantable Interstim system (Medtronic Inc., Minneapolis USA) uses mild electrical stimulation of the sacral nerve that influences the behaviour of the bladder, sphincter, and pelvic floor muscles.

Since SNS therapy depends not so much on direct stimulation of the sacral nerve as on the indirect effects of this stimulation, neuromodulation is becoming a term increasingly widely accepted and used in the recent literature: neuromodulation is a physiological process in which the influence of activity in one neural pathway modulates the pre-existing activity in another through synaptic interaction (11).

Neuromodulation techniques are used to treat many conditions that involve the central nervous system (CNS) and they work by reprogramming CNS processes and enhancing communication between bodily systems, as well as by modifying and reorganising the cortical brain map: their effects are achieved through long-term learning processes, which are sub-served by new neurophysiological dynamics and the mechanisms of neuroplasticity that develop during neural regeneration (12,13). In contrast to non-invasive methods, SNS is based on continuous stimulation and close nerve contact. This requires surgical implantation of a pulse generator and electrode.

The aim of SNS is to relieve bladder symptoms by rebalancing micturition control: bladder contractions can be suppressed by external sphincter and pelvic floor contractions, therefore it is not surprising that electrical stimulation of the sacral nerves causes bladder inhibition in both animals and man (14).

However, when mixed S3 nerves are stimulated at the level of the sacral foramina it is not always clear whether the therapeutic neuromodulation obtained is the result of direct activation of the sensory nerves, or of indirect activation of the striated external sphincter and pelvic floor muscles leading to reflex detrusor relaxation.

Two main theories have been advanced to explain the effect of SNS on the lower urinary tract: the basis of the older one is re-education of the pelvic floor, in which stimulation of the pelvic efferent nerves plays a major role, while the more recent one is a sensory theory and suggests that the pudendal afferents have a mediating effect, leading to detrusor inhibition.

Important evidence in support the latter theory was provided by experimental work done by Lindström et al. in 1983 (15), who demonstrated that the pudendal afferent nerve effect could be obtained during suppression of pelvic efferent nerve activity, and by Vodusek in 1986 (16), who carried out a critical analysis of therapeutic velcro inhibitory electrical stimulation on the basis of a study of 10 patients with suprasacral spinal cord lesions and detrusor hyperreflexia in whom the detrusor contraction was either completely abolished, or the threshold of the contraction was significantly increased, with electrical stimulation delivered to the dorsal nerves of the penis (or clitoris) via surface electrodes.

Both mechanisms have been considered and researchers now conclude that it is the afferent pathways, causing inhibition at either spinal or supraspinal level, that play a crucial role (17). (Fig.s 2,3).
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A thorough evaluation of the pelvic floor is normally performed in patients with sacral area complaints, and the diagnostic protocol is completed with exploration of motor units via pelvic floor EMG, a conduction study of terminal branches of the pudendal nerve by means of terminal motor latency, somatosensory evoked potentials (SSEPs) of the pudendal nerve, which explore the afferent pathway, and motor evoked potentials of the external anal sphincter for the efferent pathway, sacral reflex-
es and sympathetic skin responses.
The picture resulting from the diagnostic evaluation defines the residual functional potential, which provides the basis on which to develop an appropriate therapeutic-rehabilitation programme.

**Anatomical-physiological background**

To better understand the basis of the studies we have conducted, it is worth recalling, briefly, the anatomy and physiology of the pelvic organs (Fig. 4).

The ventral and dorsal lumbar and sacral nerve roots exit laterally through the nerve root foramina to form the lumbar and sacral plexuses that provide motor and sensory innervations of the bladder, bowel and sexual organs. The efferent parasympathetic outflow (via the pelvic nerves S2-S4) synapses on postganglionic neurons in the pelvic plexus or in ganglia of the bladder wall, providing the major input to the bladder and an inhibitory input to the urethra. The parasympathetic afferents have their cell bodies in the S2-S4 dorsal root ganglia before entering the dorsal horn. Sympathetic supply to the pelvic organs (T10-L1) provides excitatory input to the bladder neck and urethra and inhibitory input to the bladder smooth muscle. The sympathetic afferents are in the T11 to L2 dorsal root ganglia. The pudendal nerve provides the efferent somatic pathway (Fig. 5).

The pudendal nerve derives its fibres from the ventral branches of the second, third, and fourth sacral nerves. It passes between the piriformis and coccygeus muscles and exits the pelvis through the lower part of the greater sciatic foramen. It then crosses the spine of the ischium before re-entering the pelvis through the lesser sciatic foramen. Thereafter, travelling in a space within the obturator fascia, termed Alcock’s canal, it accompanies the internal pudendal vessels upwards and forwards along the lateral wall of the ischiorectal fossa, before dividing into two terminal branches: the perineal nerve, and the dorsal nerve of the penis or clitoris. Before its division, it gives off the inferior rectal nerve.

The pudendal nerve which originates from the anterior horn cells, supplies the motor innervation to the urethral sphincter (rhabdosphincter) and pelvic floor muscles; the anterior horn cells lie in the ventral horn of sacral segments S2-S4 (Onuf’s nucleus). The pudendal nerve contains sensory fibres from the penis, urethra, anus, and pelvic floor muscles. Afferent activity arising in the bladder and urethra originates from small myelinated A-delta and unmyelinated C-fibres in the urothelium of the bladder and urethra. These fibres convey tension, volume and nociceptive information to the CNS through the spinal cord via the dorsal roots which run together with the somatic, parasympathetic and sympathetic nerves. Information from the pelvic and perineal area is carried in ascending tracts of the dorsal spinal cord (ascending pathways) to the brainstem, thalamus, and somatosensory cortex (for conscious control). The preoperative neurophysiological protocol consists of a battery of diagnostic tests:

- Concentric needle electromyography (CNEMG) of the perineal muscles. The striated muscles of the pelvic floor, external anal sphincter and external urethral sphincter, bulbocavernosus, and levator ani are supplied by Onuf’s motoneurons in the sacral spinal cord S2 to S4. By means of CNEMG it is possible to detect the presence of active or chronic denervation and re-innervation associated with sacral radicular impairment.

Figure 4 - Innervation of the lower urinary tract.

Figure 5 - Sacral roots and the pudendal nerve.
By means of voluntary contraction it is possible to define the characteristic features of motor units (morphology, amplitude, duration, frequency of discharge); motor unit recruitment is evaluated during maximum effort of contraction or particular tasks.

2. Sacral reflexes: bulbocavernosus (BCR) and pudendo-anal (PAR) reflexes. These reflexes can be used to test the integrity of the sacral arch (pudendal nerve-S2S4 spinal cord-pudendal nerve) including its afferent and efferent branches.

The BCR is evoked by electrical stimulation of the dorsal nerve of the penis or clitoris and the resulting contraction of the BC is recorded by means of needle EMG. In elicitation of the PAR the contraction of the external anal sphincter muscle is detected by means of needle EMG.

3. Pudendal nerve terminal motor latency (PNTML). Intraretal or intravaginal stimulation of the pudendal nerve at the ischial spine by means of a St Mark’s Hospital electrode mounted on the examiner’s gloved index finger, and recording of evoked contraction of the external anal sphincter muscle, makes it possible to identify any delayed conduction due to a distal impairment of the nerve.

4. Somatosensory evoked potentials of the pudendal nerve. These, obtained through electrical stimulation of the dorsal nerve of the penis or clitoris and recording of the N1 peripheral response at the spinal cord (T12-T10) and the P40-N50-P60 responses at cortical level (Cz-Fpz), can be used to explore the afferent conduction pathway. In this way, it is possible to establish the central conduction time, which can be delayed by a peripheral nerve or a spinal cord lesion or by a combination of the two.

5. Motor evoked potentials of pelvic floor muscles. Magnetic stimulation of the cortical area or sacral roots evokes a muscle contraction that can be detected by a needle EMG or a surface electrode placed in or on the perineal muscles; any delay in conduction indicates an alteration in the efferent pathway from the motor cortex to the spinal cord and pelvic floor.

6. Sympathetic skin response of the perineal area. This is a reflex mediated by myelinated sensory fibres, a central integration mechanism and efferent sympathetic cholinergic branches (myelinated C fibres) which supply the perineal glands. Electrical stimulation of a peripheral nerve evokes modification of skin conductance; this response is recorded via superficial electrodes on the perineal or genital area, and on planter foot and palmar hand skin: by comparing the responses recorded it is possible to identify the site of an alteration.

By taking into account all the data recorded for a single patient it is possible to define the pathophysiology of the dysfunction and what we call the “functional residual potential” (FRP), i.e. the potential of the neural system to react to the mechanisms of neuroplasticity that can be increased during neural regeneration enhanced by neuromodulation techniques.

The worst FRP is that of a patient whose neurophysiological tests show severe chronic denervation with loss of motor units on CNEMG, very delayed PNTML, BCR and PAR, and delayed SSEPs (as in cauda equina lesion).

In the context of voiding dysfunction due to incomplete urinary retention, the patient who emerges as the best candidate for SNS (i.e. the one with the best FRP) is the one who shows mildly altered SSEPs and BCR, but normal MEP and PNTML (as in the case of bio-mechanical lumbar problems with L5-S1 central posterior prolapse with mild “stretch” effect on the sacral roots), findings which indicate an alteration in the afferent pathway that can be translated into a down-regulation of the sensory information in the sacral area: chronic stimulation of the third sacral root (into which the afferent fibres of the pudendal and pelvic nerves travel) influences and modifies the activity of undamaged fibres, thereby promoting reorganisation and re-innervation of damaged fibres through the formation of new synaptic interactions.

Our experience in the use of neurophysiological tests to disclose predictive factors led us to make some important observations (19-21) and to develop a new device for use in patients not responding to SNS, and in neurogenic situations like spinal cord incomplete lesions. This device is able to chronically stimulate the pudendal nerve in order to control an overactive bladder, and improve bowel and sexual function (22).

The best candidate for pudendal nerve stimulation is a patient suffering from urinary incontinence due to incomplete spinal cord lesion, with delayed MEPs and SSEPs, early BCR and PAR, and normal PNTML: chronic stimulation of the pudendal nerve can inhibit the uninhibited contraction of pelvic floor and detrusor muscles whose control has been lost due to the neurogenic damage, through the formation of new synaptic interactions and reorganisation of the neural structures.

The implantation of a sacral neuromodulator is performed under anaesthesia by a minimally invasive percutaneous approach in two stages (16) (Fig.s 6 and 7, over).

Figure 6 - Sacral nerve stimulation is a two-stage procedure.
We have been working as a multidisciplinary team at Magenta Hospital in Milan, Italy, since 2001, routinely applying interventional neurophysiology techniques in patients undergoing SNS implantation and conducting many follow-up observations: neurophysiological responses are monitored intraoperatively (Figs 8, 9) during the first stage of the implantation, performed under radiological control, of a quadripolar electrode (i.e. consisting of four independent stimulation electrodes). For at least two weeks the quadripolar electrode is connected with an external stimulator in order to evaluate the efficacy of continuous stimulation. During this period a neurophysiological study of the afferent pathway to the cortical area is performed by means of SEPs in order to optimise the configuration of the stimulation parameters: frequency, amplitude and rate of stimulation (Fig. 2). If the clinical and neurophysiological results show an improvement of the dysfunction, then a definitive pulse generator is implanted for chronic stimulation, and any adjustment of stimulation parameters can thereafter be done by telemetry link.

**Neurophysiological assessment during follow-up of SNS**

To evaluate the effect of SNS on the primary sensory cortical area and to identify specific features of lower urinary tract dysfunction as different indications for SNS we routinely perform SSEPs of the pudendal nerve. Pa-
tients are tested with monolateral electrical modulation through a quadripolar electrode implanted in the third sacral root, the first stage of the sacral percutaneous implant technique. We also evaluate the possibility of modifying the SNS pulse rate in order to improve outcomes. Somatosensory evoked potentials provide electrical evidence of how the brain received and responded to an external stimulus, thus providing an objective measure of somatosensory system function (Fig. 9).

Since the pudendal nerve is mainly supplied by the third sacral root, its stimulation causes an efferent and afferent effect on the pelvic-perineal area. For pudendal SSEPs, the two dorsal clitoris (or penis) nerves are electrically stimulated via surface bipolar electrodes placed laterally on the clitoris or penis, the cathode being placed 3 cm proximal to the anode: the stimuli consist of rectangular pulses 0.2 msec in duration, frequency 3Hz, while recording needle electrodes, applied according to the International 10-20 EEG System, are placed subcutaneously over the scalp: the active electrode being 2 cm posterior to Cz (Cz') referred to Fpz.

Impedance is kept under 2000 ohms. The sampling window is set at 100 msec, 1 mV/Div. The intensity of stimulation is set at 2.5 times the threshold. The amplifier band-pass is 1 Hz-3 KHz; usually 500 responses are averaged twice to extract the evoked potentials from the cortical background noise and the latency of the first positive deflection (P40) is analysed. The P40 response observed at the scalp contralateral to the stimulated nerve over the corresponding somatosensory cortex displays a series of waves which, in sequence, reflect neural activity in the thalamus, thalamo-cortical radiations, primary and secondary somatosensory cortex and association parietal cortex (Fig. 10, over).

In our experience, integrated interventional and clinical neurophysiological evaluation has shown itself to be an important tool both as a diagnostic instrument for patient selection and as a predictive factor of SNS results (Fig. 11, over).

**Description of a new implantation procedure and interventional neurophysiology evaluation**

Since 2002, in a bid to increase the success rate of SNS and to find an alternative option for patients who failed SNS (all with neurogenic overactive bladder due to an incomplete upper motor neuron lesion), we developed a new, original method for chronic pudendal nerve stimulation (23) (Fig. 12, over).

Neurophysiological monitoring, using the lead and the introducer kit available for minimally invasive implants for sacral neuromodulation, is performed throughout pudendal nerve stimulation and electrode placement procedures.

Our technique consists of measuring several PNTML responses and compound muscle action potentials (CMAPs) from the external anal sphincter. The best evoked response (constituted by maximal amplitude, regular shape, shorter latency) is identified, recorded and memorised: this will serve as the reference potential response (RPR). The surgical procedure is performed under local anaesthesia. An insulated needle is

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**Figure 9 - Somatosensory evoked potentials during sacral nerve stimulation.**
Figure 10 - Somatosensory evoked potentials during follow up of sacral nerve stimulation.

Figure 11 - Patients submitted to sacral nerve stimulation and interventional neurophysiology from 2002 to 2008.
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inserted perpendicular to the skin for about 4 cm to reach the ischial tuberosity. The needle is tilted laterally and dorsally to reach the recto-ischial fossa until it is located below and behind the ischial spine in Alcock's channel. Once the needle is in this correct position, it is possible to place either a temporary stimulation lead (peripheral nerve evaluation, PNE) or a definitive quadripolar tined lead along the pudendal nerve in Alcock's channel. In each step the neurophysiological monitoring is repeated in order to confirm the consistency between the recorded trace and the RPR (Fig.s 13-18).

Figure 12 - Set up for interventional neurophysiology during pudendal nerve implantation.

TO STIMULATE PUDEAL NERVE

The examiner's index finger with St Mark's electrode is inserted into the rectum, to palpate the ischial spine.

Figure 13 - Pudendal nerve terminal motor latency.
**TO RECORD PUDENDAL NERVE CMAP**

- Insert the EMG concentric needle into the intermediate portion of left or right subcutaneous part of the EAS muscle.
- Record the EMG activity of the EAS at rest, during voluntary contraction and reflex contraction (e.g. cough).

![Figure 14 - EMG recording during pudendal nerve implantation.](image1)

**Pudendal nerve intraoperative monitoring** is performed at each step of the implant.

![Figure 15 - Pudendal nerve implantation procedure.](image2)
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Figure 16 - Algorithm of pudendal nerve implantation.

- Prepare pt St. Mark's electrode
- Intereaetral stimulation of Pudendal Nerve
- Is trace good? yes no
- Pudendal Nerve Terminal Motor Latency CMAP
- Insert needle
- Monitor CMAP
- Adjust needle
- Does trace reproduce CMAP? yes no
- Insert tined lead
- Monitor CMAP
- Adjust lead
- Does trace reproduce CMAP? yes no
- Deploy tines

Figure 17 - Interventional neurophysiology in pudendal nerve implantation (Ref. 24).

- 1 - bony landmarks
- 2 - needle insertion
- 3 - insertion of introducer kit on guidewire
- 4 - stimulation of introducer kit
- 5 - lead insertion
- 6 - recording of pudendal nerve CMAP

Check of reference potential responses during every step of the implant

Spinelli, Malaguti et al. original method proposed in 2002
Concluding remarks

Neurophysiological monitoring of peripheral nerves during surgery is an extremely valuable procedure that provides the surgical team with vital, real-time information. The preoperative neurophysiological tests provide the surgeon with valuable data to assist with decision making; however there is information that simply cannot be garnered from these studies and intraoperative studies help to bridge this gap.

It is important to realise that, as a rule, the neural structures that will be monitored are not actually damaged. This can usually be ascertained from preoperative examination and neurophysiological studies. Should, on the contrary, there exist an undisclosed lesion or damage to the nerve (or perineal muscles), there is, nevertheless, no risk of further damage to that nerve or muscles. The modalities monitored are the CMAPs of the pudendal nerve.

There are no specific contraindications to pudendal nerve monitoring given the very low stimulus intensities used for this direct nerve stimulation technique. The equipment includes an at least two-channel EMG machine with bipolar stimulating and recording electrodes; a round electrode is used separate from the electrocautery ground. A needle electrode is used for recording the CMAPs. A St Mark’s electrode is used to stimulate the pudendal nerve at the ischial spine: the CMAP generated is recorded via an EMG electrode placed on the external anal sphincter (EAS).

The usefulness of neurophysiological investigation can be summed up as its ability to clarify normal physiology, to diagnose individual patients, to carry out intraoperative “mapping” and “monitoring”, to assist in therapy with electrical stimulation, and to study the pathophysiology of sacral dysfunction (in research settings). Neuroromodulation of the sacral area is now an important therapeutic option for a variety of sacral area dysfunctions, especially in patients with nervous system lesions (25). Interventional neurophysiology of the sacral area is crucial for correct selection of patients, for guiding the implantation of new devices and for optimising neuroromodulation therapy.

References

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