Electrical Stimulation for Pelvic Floor Disorders

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Foreword I

The Greek philosopher Aristotle describes the brain as an banal-looking, insensitive organ without blood. He believed that the brain only served as a cooling system for the overheated body. This was probably the biggest mistake Aristotle made in his career. Nowadays the human brain and nervous system are considered to be the most complex part of the human body, controlling all its sensory and motor functions.

In the 1970s, at the University of California, San Francisco, Prof. Dr. E.Tanagho and his co-workers developed several experimental models to evaluate the feasibility of stimulating various sacral roots or components in order to gain control of the bladder function, restoring its storage and evacuation capabilities in both normal and paraplegic animals. On the basis of these experiments, clinical application was started in order to explore the possibilities of sacral nerve stimulation to control bladder function in human beings.

On 4 October 1994, I was invited by Prof. Dr. Catanzaro and Dr. Capellano to perform the first implantation of a neuromodulation system in Como, Italy. This was a turning point in the treatment of micturition disorders in Italy. Many urologists, who were interested in functional urology, started to treat patients with intractable voiding dysfunctions – patients that did not react to conservative and medical treatment – with this new electrical stimulation technique. Several years later I was so fortunate as to be involved in the first implantation for faecal incontinence in Rome, Italy, which proves that both urologists and colorectal surgeons in Italy collaborated in this new treatment modality.

Even though at first a great deal of criticism on the working mechanism came from colleagues, the urologists in Italy that had positive results with their patients started a central organisation to collect data from all the implantations that were performed. Many international presentations and publications resulted from this collaboration. Enthusiastic urologists in Italy also worked on simplifying the operation technique through percutaneous puncture, dilatation of the puncture channel, implantation and new stimulation sites like pudendal nerve stimulation.

This book distinguishes itself by being concerned not only with reporting successful clinical application of electrical stimulation but also with discussing the history of it: research, neurophysiology, mechanisms of neural control, effectiveness in an overactive bladder, urinary retention and other voiding dysfunctions. Both urologists and colorectal surgeons have contributed to and edited articles on

emerging indications such as pelvic pain, interstitial cystitis, faecal incontinence, chronic constipation, other colorectal disorders, sexual dysfunction and neurological disorders, and they present the results of successful treatments with electrical stimulation.

Although having worked with electrical stimulation for more than 30 years, I believe that we are at the beginning of discovering new possibilities for treating our patients. Professor Gert Holstege, et al., Groningen, The Netherlands, describes Pontine and Sacral Pelvic Organ Stimulation Centres as control centres for sensory and motor functions between the brain and pelvic organs. The European Community donated one billion euros to the Human Brain Project of Henry Markram, Lausanne, Switzerland, to investigate the brain function by building a brain model. This year a three-billion dollar Brain Initiative Project was supported by Barak Obama in the USA, to investigate the activity of all nerve networks in the complete brain. Eighty-six research institutes in 22 countries will participate. These initiatives will expand our knowledge of the neurological system of the human body.

This book is an important contribution to enhancing the knowledge of all physicians interested in applying electrical stimulation to patients with pelvic floor disorders.

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Foreword II

The therapeutic use of electrostimulation has undergone a remarkable evolution in the last decades. It has found and established its role in many areas of medicine. Our understanding of its mode of action and its clinical use increased continously. One of the more recently appreciated applications—and the focus of the current book—is the use of neurostimulation in pelvic organ dysfunction. Although not entirely new, it has gained great momentum only in recent years.

This new book encompasses multiple goals. It presents an overview of the current knowledge of the therapeutic use of neuromodulation, not shying away from its limitations and existing controversies. It addresses not just one pelvic organ system, but also the overlap and analogies with neighboring organ systems, with the relevant anatomy detailed. Likewise, not only one technique is described: most current techniques of clinical relevance are discussed. Today's knowledge is put into context of the history of electrostimulation as a therapy, with the basic principles of electricity and stimulation explained. The book's conclusion gives perspectives of this very fascinating therapy. However simple the concept—to evoke residual organ function through neuromodulation—the result is both rewarding for patients and exciting for investigators.

This Italian group, under the very active direction and participation of Jacobo Martelucci, must be congratulated. The book is comprehensive, interesting, and fruitful to read. It provides an excellent overview on the current state of neurostimulation for mainly pelvic organ dysfunction. Its presentation of various clinical conditions, of a variety of clinically relevant techniques, and its inclusion of history and future possibilities make it not only informative but also provocative of new ideas and a recommended resource for an audience from different clinical specialities. Not only will readers experienced in electrostimulation find it valuable; those new to the field will gain ready access to a vast pool of essential information.

It is hoped that this estimable contribution to the literature of electrostimulation will promote increasing interest in this exciting field of medicine and further broaden its acceptance.

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Preface

The remarkably complex pelvic floor and its disorders comprise one of the most interesting and challenging areas of physical therapy. In the last 5 years, about 2,500 papers have been published on this field, involving urologist, general or colorectal surgeons, gynecologist, anesthesiologists but also physiotherapists and alternative medicine pratictioners.

About half of the population suffers of at least one of the functional pelvic floor disorders, including urinary incontinence or retention, fecal incontinence, constipation, pelvic pain, sexual dysfunction or neurological diseases involving pelvic floor.

In the last 10 years, about 700 papers have been published about sacral nerve stimulation, and over 500 papers about other techniques as tibial nerve stimulation, pudendal nerve stimulation, transcutaneous electrical stimulation, electrical rehabilitation up to acupuncture or electroacupuncture.

Considering these information, the interest about minimally invasive and high-tech solutions for pelvic floor disorders appears evident.

The aim of the present book is to collect the experiences of some of the most important experts on electrical stimulation techniques of the pelvic floor, offering an unique and valuable volume.

In the published books about pelvic floor, little space is intended for the deepening of these techniques, their results, and their indications. On the contrary, in every urological or colorectal meeting, many presentations and a lot of time are spent in the discussion about these treatment options.

It is certain that the treatments of the future will not go to demolitive surgery but to technology and minimally invasive procedures.

Organized by therapeutic goals, the book provides a fundamental understanding of contemporary, evidence-based intervention and assessment procedures. The text takes a problem-oriented approach and recommends interventions consistent with both theory and the clinical efficacy of the intervention for specific, clearly identified clinical disorders.

Starting from the relevant experience of the authors, the book explores all the surgical or rehabilitative techniques requiring electrical stimulation for the treatment of pelvic floor disorders.

This book is in memory of a master and a friend, Dr. Alfonso Carriero, died January 3, 2014, who largely contributed to the development of this field, and it is dedicated to our families, from which we stole the time required to write it.

Florence, Italy Jacopo Martellucci

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Electrotherapy for Pelvic Floor Disorders: Historical Background

1

Jacopo Martellucci

1.1 Introduction

The remarkably complex pelvic floor and its disorders comprise one of the most interesting and challenging areas of physical therapy.

In the last 5 years, about 2,500 papers have been published on this field, involving urologists, general or colorectal surgeons, gynecologists, anesthesiologists, but also physiotherapists and alternative medicine practitioners.

About half of the population suffers of at least one of the functional pelvic floor disorders, including urinary incontinence or retention, fecal incontinence, constipation, pelvic pain, sexual dysfunction, or neurological diseases involving the pelvic floor.

In the last 10 years, more than 700 papers have been published about sacral nerve stimulation and over 500 papers about other techniques as tibial nerve stimulation, pudendal nerve stimulation, transcutaneous electrical stimulation, and electrical rehabilitation up to acupuncture or electroacupuncture.

In every urological or colorectal meeting, many presentations and a lot of time are spent on the discussion about these treatment options, confirming what history teaches us.

In fact, electrotherapy has always been a source of great interest, great discussions, and great suggestions.

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1.2 Early Historical Reports

Electrotherapy has been used for medical purposes since ancient times.

Aristotle noted the numbing effect of the torpedo ray: thus, the Greeks called this fish *Narke*, which is the root of the term narcosis. Indeed, torpedo is derived from the latin *torpere* (torpere – to be stiff or numb, torpid). The Arabs before the fifteenth century used the same word for lightning (*barq*) and the electric ray. Both Pline and Plutarch refer to the numbing effects of this fish, and it is widely reported that in ancient Greece, Egypt, and Rome, electric eels were used to treat arthralgias, migraines, melancholy, and epilepsy. Ancient Egyptians were aware of shocks when interacting with electric fish.

Electric fishes may generate currents of up to 200 V, but the average current is of the order of 10–50 V.

In 46–47 AD, Scribonus Largus, Roman emperor Claudius' court physician, in his *De Compositiones Medicae,* reported the treatment of headache (*Compositionem 11*) and gout (*Compositionem 162*) with electric eels (*Torpedo ocellata*). By either the direct application of electrical torpedo fish to the human body or by placing painful extremities into a pool of water containing torpedo fish, the resulting electrical shocks stunned the nervous system, allowing an immediate and residual numbness in the extremity, as described:

> Ad utramlibet podagram torpedinem nigram uiuam, cum accesserit dolor, subicere pedibus oportet tantibus in litore non sicco, sed quod alluit mare, donec sentiat torpere pedem totum et tibiam usque ad genua. hoc et in presenti tollit dolorem et in futurum remediat.
>
> (For any sort of podagra (foot gout), when the pain comes on, it is good to put a living black *torpedo-fish* under his feet standing on a beach, not dry but one on which the sea washes, until he feels that his whole foot and shank are numb up to the knees. This will both relieve the current pain and alleviate future recurrences.)

Claudius Galen (AD 129–216) in his *De Simplicium Medicamentorum facultatibus* (*Simpl. med*; lib XI) wrote of his cautious approach to these kinds of remedies. He tried to relieve headache and prolapsus ani with dead torpedo fish, but failed to achieve an effect. But when the fish was applied live, he found it as effective as any other remedy that numbs the senses. Indeed he wrote: "Headache, even if it is chronic and unbearable, is taken away and remedied forever by a live black torpedo placed on the spot which is in pain, until the pain ceases. As soon as the numbness has been felt, the remedy should be removed lest the ability to feel be taken from the part. Moreover several torpedoes of the same kind should be prepared because the cure, that is, the torpor which is a sign of betterment, is sometimes effective only after two or three."

The idea that prolapsus ani can be treated by electric shock must be one of the first recorded observations that electrical stimuli may cause muscle contractions [1].

Still unclear is the role of some examples of "batteries" found in the Middle East. The Baghdad Battery (Fig. 1.1), sometimes referred to as the Parthian Battery, is the common name for a number of artifacts created in Mesopotamia in

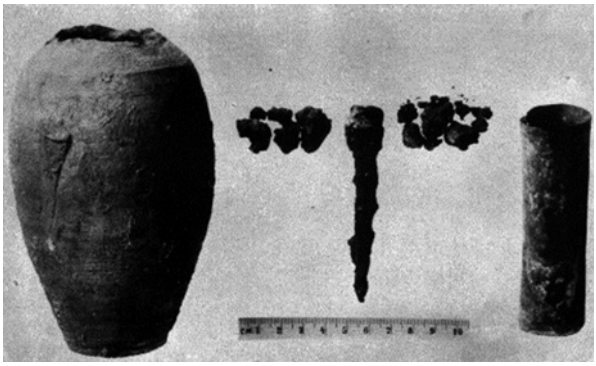

Fig. 1.1 The Baghdad Battery (Parthian battery) from the village of Khuyut Rabbou'a, near Baghdad, Iraq (Reproduced with permission from W. Koenig, Im verlorenen Paradies, R. Rohrer, Baden b. Wien, 1940)

the early centuries AD and discovered near Baghdad. These are the earliest proofs of the use of electricity, although they represent the result of an activity at a time when there seems little or no purpose for it. At present, there seems to be only one candidate for such a science, which is the electroplating of objects with fine layers of gold or silver. However, the earliest potential example of this art is from Sumeria, at about 2,000 BC, over a thousand years earlier than the discoveries of any batteries, offering more questions than answers over the presence of the electroplated objects.

However, Paul T. Keyser [2] suggested an alternative use of these electric batteries. He points out that considering the use of electric eels to numb an area of pain, or to anesthetize it for medical treatment, these batteries were used as an analgesic treatment in areas (like the Persian Gulf or the rivers of Mesopotamia) where electric fishes were not present, perhaps with conductive acupuncture needles in bronze or iron.

Acupuncture was already a standard practice in Chinese medicine since at least the Zhou Dynasty (1046–256 BC) and is described in the *Huangdi Neijing* (*The Yellow Emperor's Inner Canon* or *The Inner Canon of Huangdi*), variously dated, but no later than the first century AD, and this may explain the fact that bronze and iron needles are found with the Seleucian batteries.

There is evidence that electroichthiotherapy persisted elsewhere throughout the Middle Ages. Indeed as late as the 16th century, the hapless torpedo was found to be efficacious in the relief of chronic headache, unilateral headache, and vertigo. A seventeenth-century traveler to Ethiopia reported how patients suffering the ague were "Bound hard to a table, after which the fish being applied to his joints, causeth the most cruel pain all over his members, which being done the fit never returns again"[3, 4].

In the seventeenth century, however, the discovery of how to produce electrostatic electricity replaced the need for the living organism.

1.3 Franklinism, Galvanism, and Faradism: The Golden Age (1750–1900)

In 1650, Otto von Guericke built an electrostatic machine containing a sulfur ball rubbed by hand, and it was considered the first primitive form of frictional electric machine.

Since the middle of the eighteenth century, electrostatic machines were used in medicine to generate numbness.

The first recorded observation of the use of electricity specifically for medical purposes in Europe was attributed to Christian Kratzenstein, professor of medicine at Halle. The patient was a woman who suffered from a contraction of the little finger; after a quarter of an hour of electrification, the condition was reported as cured. Whatever the permanent effect on the finger may have been, Kratzenstein also noted the acceleration of the pulse rate as a sequel to electrification (*Abhandlung von die kraft der Electricitat der Arzeneiwissenschaft–1744*).

Jean Jallabert, professor of physics at Geneva, could be regarded as the first scientific electrotherapist, because in 1747 he effected some improvement in a locksmith's arm that had been paralyzed for 15 years. Jallabert noted that when sparks were drawn from the arm, muscle contractions were noted (*Expériences sur l'électricité avec quelques conjectures sur la cause de ses effets*, Genève, 1748). Even if the cause being recorded as a blow from a hammer, the man was also lame in the leg of the same side, so it seems probable that the case was one of genuine hemiplegia.

Jallabert continued his experiments on local muscular stimulation, and it could be considered the precursor of Duchenne, who published his results a century later and who used the induced current for effecting muscular stimulation.

A few years later (1752), the American scientist and politician Benjamin Franklin (1706–1790) (Fig. 1.2), while he was the US Ambassador to France, used a glass cylinder that generated sparks of static electricity when rubbed for the treatment of a good number of patients and invented the "Magic Square," a simple form of a condenser capable of giving strong shocks for the treatment of various illnesses.

The application of static electrical current, characterized by high voltage and low milliampere and produced by a friction generator, was called *Franklinism*, celebrating the experiment that proved clouds are charged with electricity performed by Benjamin Franklin.

In 1759, Rev. John Wesley published a little work, entitled *The Desideratum*, in which he sets forth descriptions of some electrical phenomena and recommends the use of electricity as a therapeutic agent.

The earliest work on medical electricity was *De hemiplegia per electricitatem curanda*, written by Deshais, and published at Montpellier, in 1749, and in 1751 appeared *De utditate electrisationis in Arte Medica*, which was written by Bohadsch and published at Prague.

In 1791, Luigi Galvani (Fig. 1.3), professor of anatomy at Bologna, announced the results of some experiments started in 1786. The limbs of a freshly killed frog, when placed close to the prime conductor of an electrical machine, were thrown into violent convulsions. Further investigations showed that the leg of the frog, with its

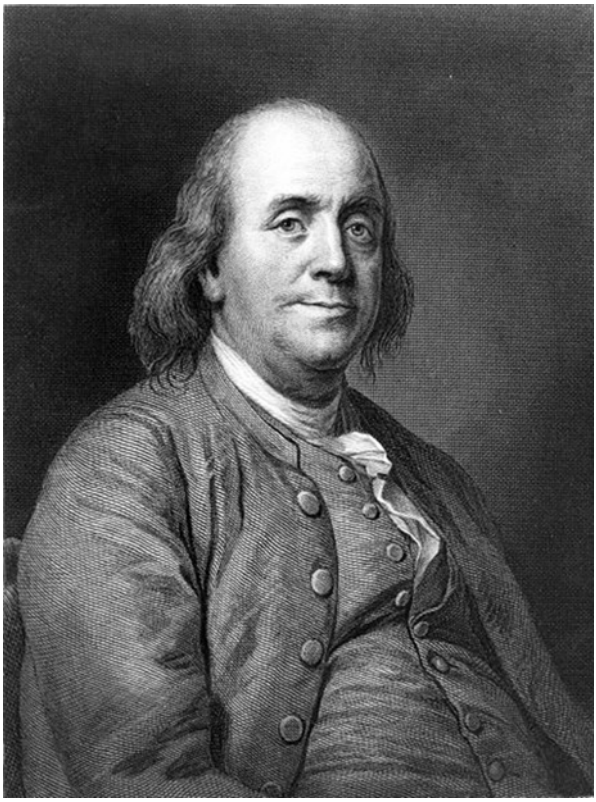

Fig. 1.2 Benjamin Franklin (1706–1790) (Engraving by H. B. Hall based on the original portrait painted from life by J. A. Duplessis, from Wikimedia Creative Commons, reproduction considered in the public domain)

Fig. 1.3 Luigi Galvani (1737–1798) (From Wikimedia Creative Commons, reproduction considered in the public domain)

Fig. 1.4 Alessandro Volta (1745–1827) (From Wikimedia Creative Commons, portrait of physicist Alessandro Volta, in *Practical Physics*, Millikan and Gale, 1920, considered in the public domain)

attached nerve, formed a delicate indicator for the presence of electricity, more delicate, indeed, than Bennet's gold-leaf electroscope, which was at that time the most sensitive piece of apparatus known for the purpose.

Galvani himself was led to an erroneous interpretation as to the result of his experiments, since he regarded the animal body as the source of the electricity and conceived that the metals only served to discharge it. As this type of electricity seemed quite distinct from electrostatic currents derived from frictional machines, it was called Galvanic current.

Galvani's assumption of "animal electricity" was criticized by Alessandro Volta (1745–1827) (Fig. 1.4), professor of experimental physics at Pavia. He demonstrated that the electricity leading to contraction of the frog muscle was not of animal source but of electrochemical origin. Subsequently in 1800, Volta showed that when two dissimilar metals and brine-soaked cloth are placed in a circuit, an electric current could be produced. This discovery resulted in the invention of the voltaic pile – the first form of a battery.

In modern times, it has been proven that both were partly right and partly wrong. In fact, when brief electrical stimulation by wires from some external source is applied to a nerve supplying a muscle, it may cause a current to be generated by the nerve itself that can pass a considerable distance from the site of the electrodes to initiate muscle contraction.

In honor of Luigi Galvani, whose work during his Iifetime on animal electricity was eclipsed by the aristocratic Volta, who had honors heaped upon him by Napoleon for his work on electricity from nonliving substances, the use of direct current in medicine is called *Galvanism*.

As is usual with new remedies, grossly exaggerated accounts of its beneficial effects were circulated, and from about 1803, until after the discovery of electromagnetic induction by Faraday in 1831, the use of electricity as a therapeutic agent largely fell into disrepute. It had been vaunted almost as a specific treatment for different nervous disorders, paralytic affections, deafness, some kinds of blindness, the recovery of the suffocated and drowned, and even for hydrophobia and insanity [5].

Benjamin Franklin, who had at least two accidents that resulted in electricity passing through his brain, witnessed a patient's similar accident and performed an experiment that showed how humans could endure shocks to the head without serious ill effects, other than amnesia. Jan Ingenhousz, Franklin's

Dutch-born medical correspondent better known for his discovery of photosynthesis, also had a serious accident that sent electricity though his head and, in a letter to Franklin, he described how he felt unusually elated the next day. During the 1780s, Franklin and Ingenhousz encouraged leading French and English electrical "operators" to try shocking the heads of melancholic and other deranged patients in their wards. Although they did not state that they were responding to Ingenhousz's and Franklin's suggestions, Birch, Aldini, and Gale soon did precisely what Ingenhousz and Franklin had suggested [6].

ln 1802, for example, Aldini (Galvani's nephew), professor of natural philosophy at Bologna, reported one of the earliest uses of electricity in treating severe depression and found that although the pain of the Galvanic shocks was hard to bear, the best site for producing relief of depression was on the head itself, particularly over the parietal region [7, 8].

This could be considered as the first form of electroconvulsive therapy (formerly known as electroshock), then reintroduced in 1938 by Italian neuropsychiatrists Ugo Cerletti and Lucio Bini as a therapeutic option for severe depression, schizophrenia, and other psychiatric disorders [9], and that, despite the controversial and violent idea transmitted in the years by cinema or literature, gained widespread popularity among psychiatrists as a form of treatment in the 1940s and 1950s and still find some accepted indications.

In 1803, Aldini published a treatise on "Galvanism"; among other experiments recorded, there was one in which he applied the terminals of a powerful battery to the body of a criminal hanged at Newgate and recorded extraordinary convulsions and facial contortions as a consequence of the stimulation [10].

In 1811, the composer and physician Hector Berlioz suggested the combination of classic Chinese method of acupuncture (introduced into France by Jesuit missionaries returning from China in 1774) with electrotherapy. He mentioned that "apparently the application of Galvanic shock produced by the voltaic pile heightens the medical effect of acupuncture."

In 1823, the French physician Jean-Baptiste Sarlandière argued that "All lesions of motion should be treated by Fraklinism and all those of sensation should be treated by Galvanism" and in 1825 demonstrated that the effect of Galvanism could be enhanced

by the use of acupuncture needles leading to the first development of electroacupuncture. He resumed: "in my opinion electro-acupuncture is the most proper method of treating rheumatism, nervous afflictions and attacks of gout" and about his method: "introduces shock into the very place I wish and this able to modify pain, motion or capillary circulation…As I have said, even the lightest discharges upon the needle introduced into our tissue will cause a feeling of vibration all through the suffering part. If this part is a muscle, one can feel, and even see, the contraction through the skin. Heavy discharges result in a sort of convulsion and, by its being suddenly shaken in this way, the nervous functions of a suffering part are modified and pain is relieved" [11].

Also Magendie performed electroacupuncture in the early nineteenth century, mentioning remarkable cures (but never failures and accidents) from the use of platinum and steel needles plunged into muscles, nerves, and even through the eyeball into the optic nerve and connecting them to a battery [12].

In 1835 also Guillaume Duchenne began experimenting with therapeutic "electropuncture."

However, the application of Galvanic current was not without side effects. Its prolonged use led to necrotic changes in the tissues. This damaging action was later employed (in Victorian times) for the destruction of superficial tumors.

The British scientist Michael Faraday (1791–1867) (Fig. 1.5) in 1832 employed the voltaic pile and discovered that the flow of electricity could be induced intermittently and in alternate directions. The use of this current was called *Faradism*. He

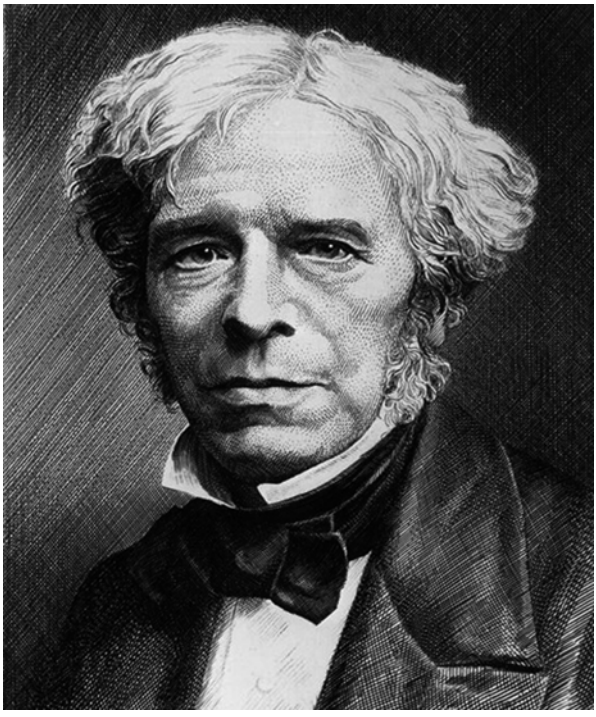

Fig. 1.5 Michael Faraday (1791–1867) (From Wikimedia Creative Commons, portrait of Michael Faraday, in *Practical Physics*, Millikan and Gale, 1920, reproduction considered in the public domain)

connected an inner or primary coil of wire to his voltaic pile, and as soon as the circuit was switched on, electricity flowed in one direction through an outer or secondary coil of wire (not connected to the first). When the primary current was switched off, the current in the secondary coil flowed in the opposite direction. By this means, Faraday established the possibility of introducing powerful currents of alternating polarity using a relatively weak direct current source. The advantage of this method is that a stimulation performed with a short pulse duration (<1 ms) should prevent any risk of tissue damage, because there is insufficient time for the electrolytic effect to develop.

The most important promoter of Faradism in the mid-nineteenth century was the French physician Guillaume Duchenne, who used this technique in particular for muscle stimulation.

In 1849 he stated: "Faradism is the best form of muscular electricity and can be practiced frequently and for a long time… The results are of highest importance" [13, 14].

Influenced by the fashionable beliefs of physiognomy of the nineteenth century, Duchenne wanted to determine how the muscles in the human face produce facial expressions which he believed to be directly linked to the soul of man (Fig. 1.6). He is known, in particular, for the way he triggered muscular contractions with electrical probes, recording the resulting distorted and often grotesque expressions with the recently invented camera. He published his findings in 1862, together with extraordinary photographs of the induced expressions, in the book *The Mechanism of Human Physiognomy* (*Mecanisme de la physionomie Humaine*).

Fig. 1.6 Guillaume Duchenne de Boulogne performing facial electrostimulus experiments (From Wikimedia Creative Commons, photographic portrait of Duchenne by A. Tournachon, reproduction considered in the public domain)

Throughout the nineteenth century, the analgesic effects of electricity were widely popular and enjoyed their "golden age." Electrotherapy was used for countless dental, neurological, psychiatric, and gynecological disturbances.

However, it was even used by quacks and charlatans.

Judah Moses, of Hartford, CT, received the first US patent for "galvanic spectacles" in 1868. Most of these spectacles relied on a small zinc and copper plate to generate the tiny current desired. This current was delivered to the wearer at the bridge or nosepieces, where it was thought to reach the optic nerves. The medical benefit of applying an electric current to the optic nerve was usually not specified in these patents; however, strengthening eyesight and allowing the user to read for a longer time were claimed in Smith and Martin's patent in 1889.

With regard to these unserious applications and to the advance of effective analgesic drugs, besides the difficulties and cost in producing reliable machines, the lack of knowledge of the working method, the ideal stimulus parameters, and the ideal location and size of electrodes, electricity has progressively fallen out of favor.

1.4 Revival of Electrotherapy for Pain and Pelvic Floor Disorders

In the second half of the twentieth century, the scientific bases of electrotherapy were increasingly elucidated, offering the chance for a rational treatment of various conditions. Studies of electrotherapy have been developed mainly for the purpose of treating pain. With the publication of their "gate control theory" of pain modulation in 1965, Wall and Melzack provided a conceptual mechanistic foundation for considering direct electrical stimulation of the spinal cord and peripheral nerves as a potential treatment for chronic pain [15].

The prophetic nature of this work was redeemed in 1967 when Shealy described positive responses in patients implanted with spinal cord stimulators (spinal cord stimulation (SCS)) [16] and Long implanted the first commercially available peripheral nerve stimulators [17].

Peripheral nerve stimulation (PNS) therapies for chronic pain developed in parallel to SCS, albeit somewhat more slowly. Over the 1970s and 1980s, Long, Nashold, and others documented favorable responses to open surgical PNS implants in patients with various neuropathic pain syndromes, most commonly of the limbs [18–22].

In 1982 Tanagho and Schmidt described the neurostimulation of the sacral roots (sacral nerve modulation (SNM)) [23], applied for the first time in human patients in 1988 [24].

Then the possible indications are progressively increased, involving overactive bladder, urinary functional retention, pelvic pain, but also coloproctological disorders as fecal incontinence and constipation [25], sexual dysfunction, and many other experimental fields.

Spinelli described in 2003 the tined lead for a minimally invasive procedure for SNM [26] that fundamentally changed the approach and the diffusion of sacral root stimulation, and few years later the procedure for the pudendal nerve stimulation [27].

In 1967 transcutaneous electrical nerve stimulation (TENS), based on the observation by Wall and Sweat [28] that an electrical stimulation with 100 Hz applied on the skin surface resulted in a dramatic relief of pain, was also applied and is currently the most frequent form of non-pharmacological pain management.

Percutaneous electrical nerve stimulation (PENS), which combines the effect of both TENS and acupuncture-like needle probes, leading to a transcutaneous hyperstimulation, was subsequently described [29]. Administration could be performed over muscles, acupuncture and trigger points.

In 1983, Mcguire introduced tibial nerve stimulation (TNS) to treat lower urinary tract symptoms (LUTS) using transcutaneous adhesive electrodes [30].

In 1973, Hosobuchi et al. [31] described the first deep brain stimulator system (deep brain stimulation (DBS)) to stimulate the ventral posteromedial nucleus of the thalamus in a patient with a severe intractable facial pain.

The treatment of many movement disorders (Parkinson disease), psychiatric disorders (severe intractable depression and obsessive compulsive disorder), epilepsy, and other neurological diseases have therefore been explored with DBS, sometimes with successful results [32, 33].

Motor cortex stimulation by means of brain surface electrodes was introduced in 1991 [34], and since then, its use has been extended for the treatment of several neuropathic conditions, including trigeminal deafferentation pain, postherpetic neuralgia, brachial plexus and phantom limb pain, and the pain suffered by some stroke victims.

Considering the increasing number of cerebral areas involved in the pelvic floor normal and pathologic physiology, DBS and cerebral surface stimulation could represent intriguing possibilities for future explorations.

In 2004 Shafik et al. [35] explored the possibility of an endoscopic functional electrical stimulation of the colon, and in 2013 Martellucci described the first placement of a colonic pacemaker for chronic constipation [36].

The implantable devices used for neuromodulation have steadily improved over the last four decades and recently have taken a leap forward with the introduction of rechargeable systems, smaller devices, and systems with greater but usable complexity. As the hardware becomes smaller and more user friendly for both the doctor and the patient, it seems likely that the use of neuromodulation will grow. Tens of thousands of units are already implanted annually, but this represents only a small proportion of those people who could benefit.

The increase of clinical indication and the evolution of technology glimpse only in part the clinical future of electrotherapies. Just research and imagination can show the rest.

1.5 Electricity: Between Therapy and Magic

In Sumeria, Akkad, and Babylon, there were two types of physicians: the “asipu” and the “asu.” The asipu practices divination and diagnosis from the patient’s symptoms, but not therapy; the asu was responsible for prescriptions and incantations, and he was considered a craftsman or technician and was associated with magicians; they may have been the ones to apply electric currents.

The torpedo fish, or electric ray, appears continuously in premodern natural histories as a magical creature, and its ability to numb fishermen without seeming to touch them was a significant source of evidence for the belief in occult qualities in nature during the ages before the discovery of electricity as an explanatory mode.

From the time predating the written word, there are descriptions of death and injury caused by lightning strikes. To this day, lightning is a source of awe, curiosity, inspiration, and fear. The brilliance, power, and destructive capacity of lighting have made it the subject for religion, superstition, politics, and, most recently, scientific investigation.

Polytheistic peoples of many cultures have postulated a Thunder God, the personification or source of the forces of thunder and lightning (and so electricity), frequently known as the chief or king of the gods.

Pliny in his *Naturalis Historia* (Book 2, Chapter 53) writes: "The Tuscan books inform us that there are nine Gods who discharge thunder-storms, that there are eleven different kinds of them, and that three of them are darted out by Jupiter. Of these the Romans retained only two, ascribing the diurnal kind to Jupiter, and the nocturnal to Summanus." This was in general the early pagan idea of lightning.

Because lightning was a manifestation of the gods, any spot that was struck was regarded as sacred. Greek and Roman temples were often erected at these sites, where the gods were worshipped in an attempt to appease them.

Benjamin Franklin invented the lighting rod and announced its use in 1753 in Poor Richard's Almanac. This idea was initially poorly understood. For instance, religious advocates maintained that it would be blasphemy to install such devices on church steeples as they were divinely protected. This same notion led to significant destruction and loss of life because churches were considered to be safe storage for munitions but were proven by incidence not to be divinely protected from lightning.

The observation of St. Elmo's fire, an aura appearing around the tip of lightning rods and ships' masts during thunderstorms, contributed to confusion about lightning rods. St. Elmo, derived from the Italian Sant Ermo or St. Erasmus (circa 300 BC), was the patron saint of the early Mediterranean sailors. The presence of St. Elmo's fire at the end of a dissipating storm was thought to be evidence that the prayers of the sailors had been answered and that St. Elmo was present to afford protection. Its presence before or at the beginning of a storm was interpreted as a sign of safety in the coming storm. It was thought that lightning rods and ship masts were diffusers of electric charges that could neutralize a storm cloud passing overhead.

In the eighteenth to nineteenth century, the magical power of electricity was still so attractive, emphasized by the various experiments of Franklin, Galvani, Volta, Faraday, and many others, that people were profoundly influenced.

The novel and myth of Frankenstein was born during a rainy summer of 1816, when Mary Shelley, her lover (and later husband) Percy Bysshe Shelley, and John William Polidori (Lord Byron's personal physician) visited Lord Byron at the Villa Diodati by Lake Geneva in Switzerland. The weather was consistently too cold and dreary that summer to enjoy the outdoor holiday activities they had planned, so the group retired indoors until dawn.

Among other subjects, the conversation turned to galvanism and the feasibility of returning a corpse or assembled body parts to life and to the experiments of the eighteenth-century natural philosopher and poet Erasmus Darwin, who was said to have animated dead matter.

Sitting around a log fire at Byron's villa, the company also amused themselves by reading ghost stories and then, as suggested by Byron, they each write their own supernatural tale. Surrounded by this atmosphere, Mary Shelley conceived the idea for *Frankenstein*.

Rev. John Wesley believed electricity was in some sense the spirit of God made manifest out of inanimate materials as glass, and he described that "A Mr Greenfield was reported to be dying…of the gout in the stomach, but on observing the symptoms I was convinced it was not the gout, but the angina pectoris. I advised him to take no more medicines but to be electrified through the breast. He was so. The violent symptoms immediately ceased and he fell into a sweet sleep."

The experiments of Aldini and others directed to the resuscitation of persons apparently drowned found their way into the public press, with the inevitable result of producing a cataract of nonsense about the use of electricity for medical purposes.

A first report is from the Morning Post of February 16, 1803, and is as follows: "Some curious Galvanic experiments were made on Friday last, by Professor Aldini, in Doctor Pearson's Lecture Room. They were instituted in the presence of his Excellency the Ambassador of France, General Andreossi, Lord Pelham, the Duke of Roxburgh, Lord Castlereagh, Lord Hervey, the Hon. Mr. Upton, etc. The head of an ox, recently decapitated, exhibited astonishing effects; for the tongue, being drawn out by a hook fixed into it, on applying the exciters, in spite of the strength of the assistant, was retracted, so as to detach itself by tearing itself from the hook; at the same time a loud noise issued from the mouth, attended by violent contortions of the whole head and eyes."

The second extract given is from an earlier number of the same paper, dated January 22, 1803: "*The body of Forster, who was executed on Monday last, for murder, was conveyed to a house not far distant, where it was subjected to the Galvanic Process, by Professor Aldini, under the inspection of Mr. Keate, Mr. Carpue, and several other Professional Gentlemen. M. Aldini, who is the nephew of the discoverer of this most interesting science, shewed the eminent and superior powers of Galvanism to be far beyond any other stimulant in nature. On the first application of the process to the face, the jaw of the deceased criminal began to quiver, and the adjoining muscles were horribly contorted, and one eye was actually opened. In the subsequent parts of the process the right hand was raised and clenched, and the legs and thighs were set in motion. It appeared to the uninformed part of the bystanders as if the wretched man was on the eve of being restored to life. This however was impossible, as several of his friends, who were near the scaffold, had violently pulled his legs in order to put a more speedy termination to his sufferings*."

Aldini also recommends the use of Galvanism in order to prevent premature burial.

The link between electricity, magnetism, and ghosts, born in that period, is one of the most durable beliefs; in the ghost hunter's kit, the electromagnetic field meter

is still essential, and many examples of the presumed communications with the spirits during the séances were electric performances.

The 1887 Seybert Commission report marred the credibility of spiritualism at the height of its popularity by publishing exposures of fraud and showmanship among secular séance leaders (*Preliminary Report of the Commission Appointed by the University of Pennsylvania*, The Seybert Commission, 1887).

Moreover, the reason why household furniture can appear to be possessed was exposed more than 160 years ago by Michael Faraday. In 1852 Faraday was fascinated by the new craze of table tipping – and whether people or spirits were responsible. So he took bundles of cardboard roughly the size of a table top and glued them weakly together. Each sheet got progressively smaller from top to bottom, allowing Faraday to mark their original positions on the card above with a pencil. He then placed the cards on a table and asked volunteers to put their hands on the cards and let the spirits move the table to the left. This experiment allowed Faraday to see what was moving the table. If it was spirits, the table top would slide out the cards from the bottom up. But if the participants were doing it, the top cards would be the first to move. By examining the position of the pencil marks, Faraday showed that people, not spirits, moved the table.

This, as many other stories, suggests the close relationship in the eighteenth to nineteenth century between the new scientific discoveries and explorations and the world of magic and unknown, and the main scientists of the period were also the most involved and curious about the explanation of the new phenomena they evoke with their electrical machines.

Another example could be considered Franz Anton Mesmer (1734–1815), who, following the studies of Volta, Galvani, Faraday, and others about electricity and magnetism, developed a new theory about animal magnetism.

He argued that the proper functioning of the human organism is guaranteed by a harmonious flow of a fluid, identified as the magnetic force. Diseases and disorders would therefore be due to the sliding blocks or difficulties of this flow that, according to his theories, had to be in harmony with the universal flow.

In 1784, a French Royal Commission appointed by Louis XVI studied Mesmer's magnetic fluid to try to establish it by scientific evidence. Benjamin Franklin was a member of the commission.

The commission concluded there was no evidence of the existence of his magnetic fluid and that its effects derived from either the imaginations of its subjects or through charlatanry.

Despite the failure on the scientific basis, the doctrine of Mesmer's experiments facilitated the development of studies to phenomena such as hypnosis.

Besides hypnotism, another of the important distinct branches that derived from mesmerism was spiritualism. As the spread of mesmerism increased, the idea of magnetism reached a popular audience, and some Mesmerist disciples fell into believing that what had been discovered amounted to a new revelation. Individuals in magnetic trance had shown peculiar abilities, and some had even claimed to be in touch with other personalities and worlds while in this state.

Fig. 1.7 Nude female voodoo doll in kneeling position, bound and pierced with thirteen pins. Found in a terracotta vase with a lead tablet bearing a binding spell in Egypt (© Marie-Lan Nguyen/Wikimedia Commons/CC-BY 2.5)

Mesmerist practices became so widespread that it reached also the Black slaves that incorporated them into the Voodoo cult.

Another strange association between voodoo and electrical stimulation and, above all, acupuncture could be considered the voodoo doll.

Voodoo dolls are an often misunderstood tradition associated with the Voodoo religion and forms of Hoodoo magic. Instead of stemming from the traditional Voodoo rituals as found in Haiti and nearby areas, the dolls originated in part from the New Orleans, Louisiana, area in the early twentieth century. They are popularly portrayed as revenge items and, contrary to the therapeutic aim of acupuncture and electrical stimulation, wherever someone pokes the doll with a pin or needle, the focus object will feel pain or have an illness.

Many cultures use dolls as a focusing point for spells and blessings (Fig. 1.7), but the use of revenge dolls did not come from Voodoo. Medieval European folk magic involved the use of poppets, effigies of specific people, that were used to place curses. Some Western African religious practices also used similar devices called *nkisi*. It is possible that the misconceptions about the origin of the dolls come from the Haitian Voodoo practice of nailing puppets to trees in graveyards. Rather than being used as a curse, however, these dolls were meant to be messengers to the spirit world, to contact dead loved ones.

Modern dolls are still sold as focal points for spells, but usually with the intention of creating positive effects, treating pain, but also for wealth in general, love, or financial success.

In the clinical practice, the response to treatment of people with pain is extremely variable. Some continue to experience pain in spite of trying a large variety of medications and non-pharmacologic measures. Others respond to treatments of all types, not only medications that have scientific rationale but also to modalities that seem to make no scientific sense. A well-recognized reason for pain amelioration is the natural remission of the underlying condition.

Voodoo and any other modality labeled as "therapy" may be effective in modifying pain perception by several mechanisms. The natural remission of the pain mechanism may be falsely attributed to therapy. Improvement of pain is often due to the placebo effect. Paradoxically, both stimulating and inhibiting the nervous system may ameliorate pain. Expectation and other psychological stimuli or cognitive factors may aggravate pain or may activate central antinociceptive mechanisms. Peripheral somatosensory stimuli not only may cause pain but may evoke antinociception at the peripheral nerve, spinal cord, or supraspinal levels [37].

One of the most recent ethical and metaphysical problems raised from electrotherapies concern deep brain stimulation. Ethical evaluation of deep brain stimulation is complicated by results that can be described as involving changes in the patient's identity. The risk of becoming another person following surgery is alarming for patients, caregivers, and clinicians alike [38].

However, the physiological and cerebral significance of personal identity is still unclear, and what really is "the identity of persons" or "personal identity" is still a topic of debate for philosophers, as well as the boundary between science and magic.

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Functional Anatomy of the Pelvic Floor

2

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2.1 Introduction

"An anatomist hesitates to write on the pelvic floor because the pelvic fascia has been discussed interminably. The subject is worn enough without further words. However, the treatment of it, even in the anatomies of the present day, is inadequate and the clinical literature is very confusing" [1].

Although human anatomy is unchanging, our understanding of the functional anatomy of the pelvic viscera and the biomechanics of pelvic organ support continues to evolve. Familiarity with the contemporary views of pelvic organ support is essential as we refine established methods for surgically correcting pelvic organ disorders and consider adopting new and innovative technologies.

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The pelvic floor is a complex interrelated structure of muscles, ligaments, and fascia with multiple functions. These functions concern support of visceral organs, maintaining continence, facilitating micturition and evacuation, as well as forming part of the birth canal. This multifunctional unit has connections to the bony pelvis, to organs, and to the extensive fibroelastic network in the fat-containing anatomical spaces.

2.2 Bones

The bony pelvis is the rigid foundation to which all of the pelvic structures are ultimately anchored. The bony pelvis is composed of the sacrum, ileum, ischium, and pubis. It is divided into the false (greater) and true (lesser) pelvis by the pelvic brim, bounded by the sacral promontory; the anterior ala of the sacrum; the arcuate line of the ilium; the pectineal line of the pubis; and the pubic crest that culminates in the symphysis pubis. The female pelvis has a wider diameter and a more circular shape than that of the male. The wider inlet facilitates head engagement and parturition, but the wider outlet predisposes to subsequent pelvic floor weakness.

Although pelvic surgeons often visualize the orientation of the pelvis in the supine or lithotomic position, it is important to understand and discuss the bony pelvis from the perspective of a standing woman. In the standing woman, the pelvis is oriented such that the anterior superior iliac spine and the front edge of the pubic symphysis are in the same vertical plane, perpendicular to the floor. As a consequence, the pelvic inlet is tilted anteriorly and the ischiopubic rami and genital hiatus are parallel to the ground. In the upright position the bony arches of the pelvic inlet are oriented in an almost vertical plane. This directs the pressure of the intra-abdominal and pelvic contents toward the bones of the pelvis instead of the muscles and endopelvic fascia attachments of the pelvic floor [2].

Thus, in the standing position, the bony pelvis is oriented such that forces are dispersed to minimize the pressures on the pelvic viscera and musculature and will transmit the forces to the bones that are better suited to the long-term, cumulative stress of daily life.

For these reasons, variations in the orientation and shape of the bony pelvis, such as a loss of lumbar lordosis and a less vertically oriented pelvic inlet, have been associated with the development of pelvic organ prolapse [3,4].

2.3 Muscles, Fascia, and Connective Tissue Support

Ligaments, muscles, and fascia constitute a musculoelastic system which gives form and function to the organs of the pelvic floor. Fascia is defined as that fibromuscular tissue which suspends or strengthens the organs or connects them to muscles. Fascia is composed of smooth muscle, collagen, elastin, nerves, and blood vessels. Discrete thickenings may be termed ligaments.

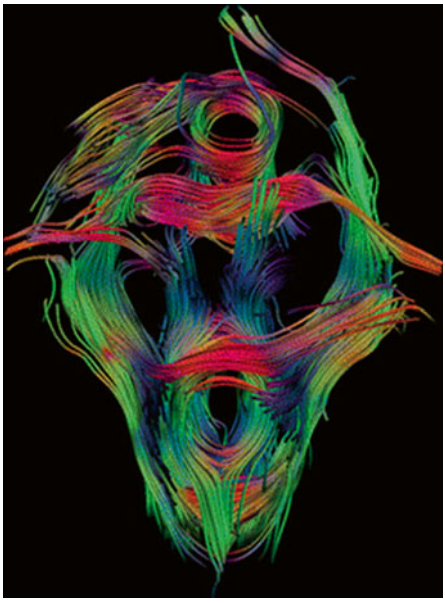

Fig. 2.1 Comprehensive overview of the complex pelvic floor anatomy (caudal view) of a female (Reproduced with permission from Zijta et al. [5])

The organs of the pelvis are the bladder, vagina, and rectum. None of these has any inherent shape or strength. While the role of fascia is to strengthen and support the organs, the role of the ligaments is to suspend the organs and act as anchoring points for the muscles. Muscle forces stretch the organs to contribute to their shape, form, and strength.

The pelvic floor is formed by the pelvic diaphragm consisting of the levator ani and the coccygeus muscles with their fasciae and the perineal membrane with the superficial and deep perineal muscles along with the perineal body (Fig. 2.1).

The piriformis and obturator internus muscles that form the lateral walls of the pelvis are functionally considered as muscles of the lower limb.

Pelvic floor muscles have two major functions: they provide support or act as a "floor" for the abdominal viscera and constrictor or continence mechanism to the urethral, anal, and vaginal orifices (in females).

The skeletal muscles of the pelvic floor include the levator ani muscles complex (that consists of the pubococcygeus, the iliococcygeus, and the puborectalis), the coccygeus (or ischiococcygeus), the external anal sphincter, the striated urethral sphincter, and the deep and superficial perineal muscles. The muscles of the pelvic floor, particularly the levator ani muscles, have a critical role in supporting the pelvic visceral organs and play an integral role in urinary, defecatory, and sexual function.

Pelvic floor muscles have a constant resting tone except during voiding, defecation, and the Valsalva maneuver. This activity serves to close the urethral and anal sphincters, narrow the urogenital hiatus, and provide a constant support for the pelvic viscera. The constant muscle tone of the levator ani and coccygeus muscles prevents the ligaments becoming overstretched and damaged by constant tension [6]. The levator muscles and the skeletal components of the urethral

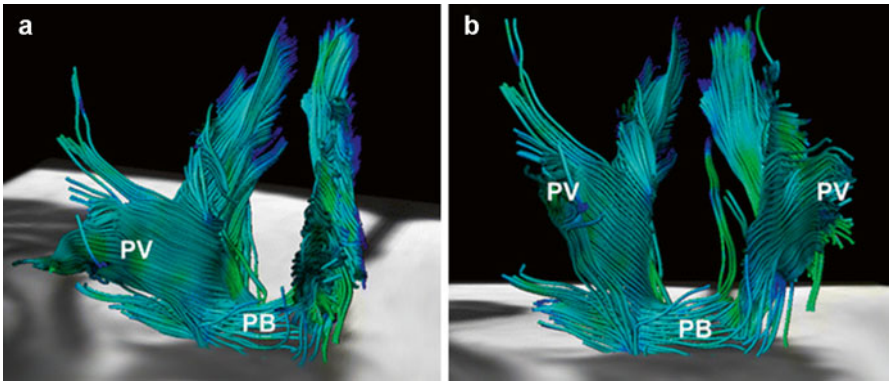

Fig. 2.2 Fiber tractography demonstrates the complex, multidirectional organization of the different pubovisceral (*PV*) muscle components in a 28-year old female subject in both oblique-anterior (**a**) and anterior-posterior view (**b**). At the bottom of the pelvic floor, transverse orientation of the fiber tracts are displayed matching the perineal body (*PB*) (Reproduced with permission from Zijta et al. [5])

and anal sphincters all have the ability to contract quickly at the time of an acute stress, such as a cough or sneeze, in order to maintain continence and to relax during evacuation.

2.3.1 Pelvic Diaphragm: Levator Ani and Coccygeus Muscles

The levator ani muscle is formed by the iliococcygeus, pubococcygeus, and puborectalis. These muscles can be identified as separate parts by their origin and direction [7,8]. The iliococcygeus originates from the posterior half of the arcus tendinous levator ani (ATLA), a linear thickening of the fascial covering of the obturator internus that runs from the ischial spine to the posterior surface of the ipsilateral superior pubic ramus. It inserts into the last two segments of the coccyx and in the midline of the anococcygeal raphe. The iliococcygeus forms a sheet-like layer and is often largely aponeurotic. The anococcygeal raphe is the interdigitation of the iliococcygeal fibers from both sides and extends from the coccyx to the anorectal junction.

The pubococcygeus originates from the anterior half of the tendinous arc and the periosteum of the posterior surface of the pubic bone at the lower border of the pubic symphysis and inserts on the midline visceral organs (vagina, urethra, anal sphincter complex), the perineal body, the anococcygeal raphe, and the inferior part of the coccyx. The pubococcygeus muscle (also called pubovisceral with the puborectalis) could be further subdivided into the puboperinealis, pubovaginalis, and puboanalis depending on its connections (Fig. 2.2).

The puborectalis also originates on the pubic bone, but its fibers pass posteriorly and go around the upper part of the anus, where it is attached posteriorly to the anococcygeal ligament, forming a sling around the vagina, the perineal body, and

the anorectum and resulting in the anorectal angle. The puborectalis muscle promotes the closure of the urogenital hiatus in cooperation with the pubococcygeus muscle.

Although the puborectalis and external anal sphincter muscle form a functional unit in maintaining continence and has suggested a possible anatomical correlation [9], developmental studies provide evidence that the puborectalis is anatomically a part of the levator ani muscle [10]. The pubococcygeus and puborectalis muscle have intervening and inseparable muscle fibers at their pubic origin, whereas the puborectalis muscle and external anal sphincter muscle have no muscle fiber connection and are separated by connective tissue. Additionally, the puborectalis and external anal sphincter muscle appear at different time points during development [11] and have a different innervation.

The space between the levator ani musculature through which the urethra, vagina, and rectum pass is called the urogenital hiatus. The fusion of levator ani where they meet in the midline is called levator plate.

The fascia covering the levator muscles is continuous with the endopelvic fascia above, perineal fascia below, and obturator fascia laterally.

The arcus tendinous fascia pelvis is a thickening in the obturator fascia and extends from the pubis anteriorly to the ischial spine, providing attachment to the paravaginal connective tissue. Arising from a similar location on the pubis but extending superior to the arcus tendinous fascia pelvis is a thickening of levator ani fascia called arcus tendinous levator ani, which is the origin of the levator ani muscle.

Although most anatomy and surgical texts depict the levator ani muscles as a bowl or funnel-shaped, this reflects the uncontracted state of the muscles as might be seen in a cadaver dissection and not that of a normally functioning levator. In a woman with normal pelvic floor function, the levator ani muscle complex in its tonically contracted state has an intricate three-dimensional structure in which its anterior portion (pubococcygeus and puborectalis) is oriented vertically as a sling around the mid-urethra, vagina, and anorectum and its posterior portion (the iliococcygeus) has a horizontal upwardly biconvex shape resembling a butterfly wing.

Thus, the anterior portion of the levator ani complex serves to close the urogenital hiatus and pull the urethra, vagina, perineum, and anorectum toward the pubic bone, whereas the horizontally oriented posterior portion (levator plate) serves as a supportive diaphragm or “backstop” behind the pelvic viscera.

Loss of normal levator ani tone, through denervation or direct muscle trauma, results in laxity of the urogenital hiatus, loss of the horizontal orientation of the levator plate, and a more bowl-like configuration.

These changes can be bilateral or asymmetric [12].

The coccygeus muscle (also called ischiococcygeus) extends from the ischial spine, courses along the posterior margin of the internal obturator muscle laying on the anterior surface of the sacrospinous ligament, inserts to the lateral part of the coccyx and the lower sacrum, and forms the posterior part of the pelvic diaphragm.

The sacrospinous ligament is at the posterior edge of the coccygeus muscle and is fused with this muscle. The proportions of the muscular and ligamentous parts

may vary. The coccygeus is not part of the levator ani, having a different function and origin.

Although the muscles of the pelvic floor were initially thought to have innervation both from direct branches of the sacral nerves on the pelvic surface and via the pudendal nerve on the perineal surface, recent evidences indicate that these standard descriptions are inaccurate and that the levator ani muscles are innervated solely by a nerve traveling on the superior (intrapelvic) surface of the muscles without contribution of the pudendal nerve [13–15]. The nerve supplying the coccygeus muscle and the levator ani muscles (all three) originates from S3, S4, and/or S5. Occasionally, a separate nerve comes directly from S5 to innervate the puborectalis muscle independently.

2.3.2 Perineum, Perineal Membrane, and Perineal Body

Although the area between the vagina and anus is described clinically as the "perineum," anatomically the perineum is the entirety of the pelvic outlet inferior to the pelvic floor.

The borders of the female perineum are the ischiopubic rami, ischial tuberosities, sacrotuberous ligaments, and coccyx. A line connecting the ischial tuberosities divides the perineum into the urogenital triangle anteriorly, which includes the female external genitalia and is characterized by the perineal membrane, and the anal triangle posteriorly, which contains the anal orifice and the posterior part of the perineum.

In the standing position, the urogenital triangle is oriented horizontally, whereas the anal triangle is tilted upward so that it faces more posteriorly.

Directly below the pelvic diaphragm is the perineal membrane, a triangular-shaped dense fibromuscular tissue that spans the urogenital triangle and attaches laterally to the ischiopubic rami, posteriorly to the perineal body, medially to lateral walls of the vagina and urethra, and apically to the arcuate pubic ligament.

In women, the perineal membrane is traversed by the urethra and vagina through a hiatus (the urogenital hiatus), and the membrane is attached to the lateral vaginal walls. In men, it is a continuous sheet.

Formerly the perineal membrane was named "urogenital diaphragm" and considered to constitute a tri-layered structure of the deep transverse perinei with a superior and inferior fascia. Although historically anatomists and clinicians have used the term urogenital diaphragm to describe this structure, this term has been abandoned because it erroneously implies a muscular diaphragm rather than a thick sheet of connective tissue [16,17].

Moreover, present insights indicate the presence of a musculofascial uni-layer structure. The presence of the superior fascia and deep transverse perinei is questionable [18], and muscle fibers previously considered to constitute the urogenital diaphragm most likely are part of the urethra support mechanism (compressor urethrae and urethrovaginalis part of the external urethral sphincter muscle).

The perineal membrane consists of a ventral and a dorsal component [19].

The ventral component is continuous with the paraurethral and paravaginal connective tissues and arcus tendinous fascia pelvis. It provides attachment to the female striated urogenital sphincter muscles and the vestibular bulbs and clitoris fuse to its inferior surface. The dorsal component attaches laterally to the ischiopubic rami on each side and medially to the vagina and the perineal body.

The urogenital triangle is divided into a superficial and deep perineal space by the perineal membrane.

The superficial perineal space lies between the perineal membrane and the subcutaneous tissues and contains the superficial perineal muscles (ischiocavernosus, bulbospongiosus or bulbocavernosus, superficial transverse perineal muscles), the erectile tissue of the clitoris, the vestibular bulbs, and Bartholin's glands.

The superficial transverse perinei, the bulbospongiosus, and the ischiocavernosus are the external genital muscles and form the most superficial component of the pelvic floor. The superficial transverse perinei that originate from the ischial tuberosity on each side and insert on the perineal body has a supportive function; the bulbospongiosus and the ischiocavernosus play a role in sexual function. The ischiocavernosus muscle arises from the ischial tuberosity and the clitoral crura along the inferior portion of the ischiopubic ramus and inserts on to the body of the clitoris. The bulbocavernosus muscle runs on either side of the vagina and attaches to the perineal body posteriorly and the body of the clitoris anteriorly.

The superficial transverse perinei spans the posterior edge of the perineal membrane and inserts at the external sphincter and perineal body or point.

In women, the superficial transverse perineal muscle is directly superior to the external sphincter, often with some overlap. In men, the superficial perineal muscle is directly anterior to the external sphincter.

The superficial Colles fascia of the urogenital triangle forms a clear, surgically recognizable plane beneath the skin of the anterior perineum. It is firmly attached posteriorly to the fascia over the superficial transverse perinei and the posterior limit of the perineal membrane. Laterally, it is attached to the margins of the ischiopubic rami as far back as the ischial tuberosities. From here it runs more superficially to the skin of the urogenital triangle, lining the external genitalia before running anteriorly into the skin of the lower abdominal wall where it is continuous with the membranous fascia of Scarpa.

The deep perineal space lies just deep to the perineal membrane and inferior to the levator ani muscles. Within this thin space lie the external urethral and the urethrovaginalis sphincter, compressor urethrae, and deep transverse perineal muscles [20].

These muscles lie superior to the perineal membrane in the deep perineal space that is continuous with the pelvic cavity. The superior fascia of these muscles is continuous with the endopelvic fascia.

The urethrovaginalis and compressor urethrae muscles provide accessory sphincter function to the urethra. The urethrovaginalis muscle surrounds the distal urethra and vagina without passing between them and therefore acts as a sphincter to the vagina as well as to the distal urethra. The deep transverse perineal muscle, along with its superficial counterpart, serves to stabilize the position of the perineal body and inferior border of the perineal membrane.

The pudendal nerve is the main sensory and motor nerve of the perineum. It arises from the ventral rami of S2–S4 (with S3 providing the largest contribution), runs underneath the piriformis, and exits the pelvis through the greater sciatic foramen. It passes just behind the ischial spine and reenters the pelvis through the lesser sciatic foramen. The pudendal nerve then runs in the Alcock's canal (pudendal canal) in the obturator fascia and ventral to the sacrotuberous ligament before separating into several terminal branches that terminate within the muscles and skin of the perineum [21,22]. As it enters the perineum, the pudendal nerve lies on the lateral wall of the ischiorectal fossa and divides into three branches: the inferior rectal, perineal, and dorsal nerve of the clitoris [23]. The dorsal nerve of the clitoris lies on the perineal membrane along the ischiopubic ramus and on the anterolateral surface of the clitoris, one on each side, and supplies the clitoris. The perineal nerve divides into several branches and supplies the bulbocavernosus, ischiocavernosus, superficial transverse perineal muscles, and the skin of the medial portion of labia majora, labia minora, and vestibule.

The perineal body (also named the central perineal tendon) is a pyramidal fibromuscular structure in the midline between the anus and vagina with the rectovaginal septum at its cephalad apex. It marks the point of convergence of the bulbospongiosus muscle, superficial and deep transverse perinei, perineal membrane, external anal sphincter, posterior vaginal muscularis, and fibers from the puborectalis and pubococcygeus. It represents a connection point between superficial and deep muscles of the pelvic floor [24] and plays an important role in support of the distal vagina and in normal anorectal function.

It has been suggested that the perineal body is not the site of insertion of perineal muscles but the site along which muscle fibers of these muscles and the external anal sphincter pass uninterrupted from one side to the other [25].

Acquired weakness or damages of the perineal body may predispose the pelvic organs to defects such as rectocele, prolapse, and enterocele [17,25,26].

Sex-related differences in perineal structures included a more superiorly located superficial transverse perineal muscle in women than in men. The central perineal tendon in men is a central muscular insertion point, with a cleavage plane with external anal sphincter; in women, it represents an area where muscle fibers converge, decussate, and imbricate [27], and there is no clear boundary between the perineal body and external sphincter.

Moreover, the perineal body could be considered as the center of female perineum and pelvic floor, while in male it is slightly more anterior and the anus is in a central position.

2.3.3 Urethral Sphincter Complex and Urethral Continence Mechanism

The urethra is a small complex tube with a mucous membrane that connects the urinary bladder to the genitals for the removal of fluids to the exterior of the body [28].

After leaving the bladder, the male urethra travels through the center of the prostate gland, enters the base of the penis, and ends as a urinary meatus at the tip of the penis. The average length of the male urethra is about 22 cm [29].

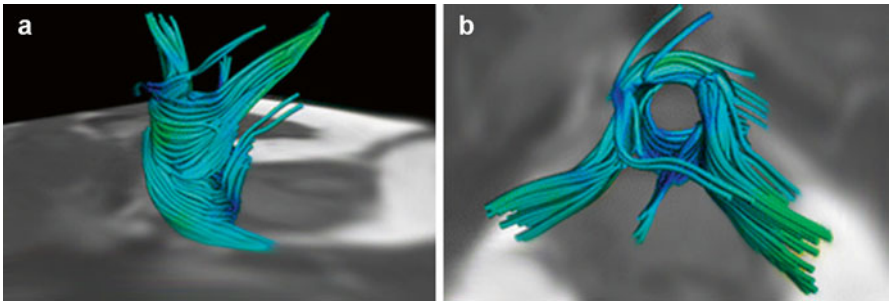

Fig. 2.3 Fiber trajectories reflecting the urethral sphincter complex with an anterolateral (**a**) and cranial view (**b**) (Reproduced with permission from Zijta et al. [5])

In females, the urethra is shorter (is about 3.5–4 cm long and averages 6 mm in diameter), slightly curved, and lies directly behind the symphysis pubis. After leaving the bladder it passes from the retropubic space, perforates the perineal membrane, and ends with its external orifice in the vestibule directly above the vaginal opening [30]. Throughout most of its length, the urethra is fused to the anterior vaginal wall. Although in females the urethra is used only for urinating, the relationship of the urethra with the vagina is functionally important to the muscular pelvic floor [31].

Histologically, the urethra has four distinct layers: mucosa, submucosa, smooth muscle internal urethral sphincter (IUS), and striated external urethral sphincter (EUS) (Fig. 2.3).

The urethral mucosa extends from the bladder transitional epithelium to the external meatus and is primarily nonkeratinizing squamous epithelium. It is derived from the urogenital sinus along with the lower vagina and vestibule. It is hormonally sensitive and undergoes changes with stimulation [32]. The hormonally sensitive submucosal tissue contains a rich and prominent vascular plexus. These vascular cushions, along with the urethral mucosa, provide a watertight closure of the mucosal surface with an increase in blood flow that may occur with an increase in pressure on abdominal vessels [33] and account for approximately one-third of the urethral resting tone, while the internal and external urethral sphincters account for the remainder [34].

The IUS is located at the inferior end of the bladder and the proximal end of the urethra, and it is contiguous with that of the detrusor, forming a horseshoe-like arrangement with oblique and longitudinal smooth muscle fibers, with a few circularly oriented outer fibers [35].

The function of the longitudinal smooth muscle fibers is probably related to a filler volume control, and their presence may improve the efficiency of the sphincter mechanism by allowing closure of the urethral lumen with only a small amount of circular muscle shortening [36].

Because the IUS is composed of smooth muscle, it is not under voluntary control and is controlled through the autonomic nervous system [37].

The skeletal muscle component of the urethral sphincter consists of the external urethral sphincter (also called sphincter urethrae) along with the previously

described compressor urethrae and urethrovaginalis muscles. These three muscles, which function as a single unit, have been called *striated urogenital sphincter* [20]. Together, they are approximately 2.5 cm long and encircle the urethra in its midportion from just below the bladder neck to the perineal membrane within the deep perineal space. They are located at the distal inferior end of the bladder in females [38] and at the level of the membranous urethra and the distal prostate in males [39].

The striated urogenital sphincter provides approximately one-third of the urethral resting tone and is responsible for the voluntary and reflex increases in intraurethral pressure needed to maintain continence. Unlike the IUS, the EUS is mainly composed of skeletal muscle and it is voluntarily controlled through the somatic nervous system [40]. The EUS plays a role in squeezing the urethra and closing where the urethra exits the body.

In female, where the EUS is more elaborate and the urogenital sphincter system more evident, the urethral sphincter surrounds the urethra in the middle third of its length, starting from the base of the bladder and as a continuation of the peripheral component of the compressor urethral muscle.

The compressor urethral muscle fibers begin as a small tendon attaching to the ischiopubic ramus in the lateral side. This muscle expands to the anterior surface of the urethra and is a continuation of the corresponding fibers of the opposite side of the body. It then forms a broad arcing muscle. The role of the compressor urethral muscles is to squeeze the urethra from its ventral part. This muscle can affect pulling caudally and inferiorly the urethral meatus and assist the urethral elongation as a way of providing continence. The urethrovaginal sphincter is a thin, flat, and broad muscle that intermingles ventrally with the compressor urethral muscle. These muscle fibers begin on the ventral side of the urethra and extend dorsally along the lateral wall of the urethra and the vagina to the beginning of the vestibular bulb. These fibers are continuous with the posterior vagina and correspond to the muscle of the opposite side. The contraction of these fibers leads to constriction of both the vagina and the urethra [41,42].

In male, the muscle fibers inferior to the caudal prostate are circular and form the external sphincter of the membranous urethra. The external fibers arise from the junction of the inferior rami of the pubis and ischium. The external sphincter lies in the urogenital hiatus of the pelvic diaphragm, and the EUS fills the area between the pudendal canals below the pelvic diaphragm [41]. The external sphincter muscle is surrounded by fibrous integument. This fibrous integument is a continuation of the prostatic sheath, which is derived from extraperitoneal connective tissue.

In addition to the muscular and vascular tissue of the urethra, there is a considerable quantity of connective tissue interspersed within the muscle and submucosa. This tissue contains collagen and elastin fibers and is thought to add to urethral closure passively. Lastly, a series of glands are found in the submucosa, mainly along the vaginal surface of the urethra [43]. They are most predominant in the middle and lower third of the urethra.

Normal urethral function depends upon normal support of the urethra as well as its intrinsic sphincter mechanism. As with vaginal support, dynamic interaction between the levator ani muscle complex and the connective tissue supports of the urethra is essential.

The requirements for continence, according to a hammock-like supportive system, include a quiescent bladder, functioning musculofascial supports (composed of periurethral endopelvic fascia and anterior vaginal wall), and a functional urethral sphincter mechanism [44], where urethral support is provided by a coordinated action of fascia and muscles acting as an integrated unit under neural control. The fascial attachments connect the periurethral tissue and anterior vaginal wall to the arcus tendinous at the pelvic sidewall, whereas the muscular attachments connect the periurethral tissue to the medial border of the levator ani. This musculofascial support provides a hammock onto which the urethra is compressed during increases in intra-abdominal pressure. Increased intra-abdominal pressure, as with a cough or sneeze, causes compression of the urethra against this hammock-like layer, thereby compressing the urethral lumen closed. The stability of the suburethral layer depends on the intact connection of the anterior vaginal wall and its connective tissue attachments to the arcus tendinous fasciae pelvis and levator ani muscles. These attachments allow the pelvic floor muscle's normal resting tone to maintain the position of the urethra and bladder neck. They are also responsible for the posterior movement of the vesical neck seen at the onset of micturition (when the pelvic floor relaxes) and for the elevation noted when a patient is instructed to arrest her urinary stream. Defects in these attachments can result in proximal urethral support defects (urethral hypermobility) or anterior vaginal wall prolapse (cystocele) and can contribute to stress urinary incontinence [2].

Furthermore, failure of one of the support components will not invariably produce stress incontinence because of the compensatory effect of the other components. This may explain why some women with hypermobility have no incontinence.

The innervation of the urethral sphincter is from both the somatic and the autonomic nervous systems.

The striated sphincter is innervated by the pudendal nerve from the S2 to S4 nerve roots.

The sympathetic innervation of the bladder begins at the lower thoracic and upper lumbar spinal cord segments (T10 to L2) and results in the closing of the IUS. Parasympathetic activity causes the bladder to contract and allows the internal sphincter to open [45]. The combination of functional innervations via the somatic pudendal nerve and autonomic innervation manages urination.

2.3.4 Anal Sphincter Complex and Anal Continence Mechanism

The anal sphincter complex can be considered as a multilayered cylindrical structure, with a smooth internal sphincter, the intersphincteric space with the longitudinal layer, and the outer striated external muscle layer (Fig. 2.4). The normal anal canal length is between 3 and 6 cm, depending on gender and age, but the functional anal canal (high-pressure zone) is slightly shorter. Relevant sex-related differences included a significantly shorter external sphincter in women than in men both laterally and anteriorly [27].

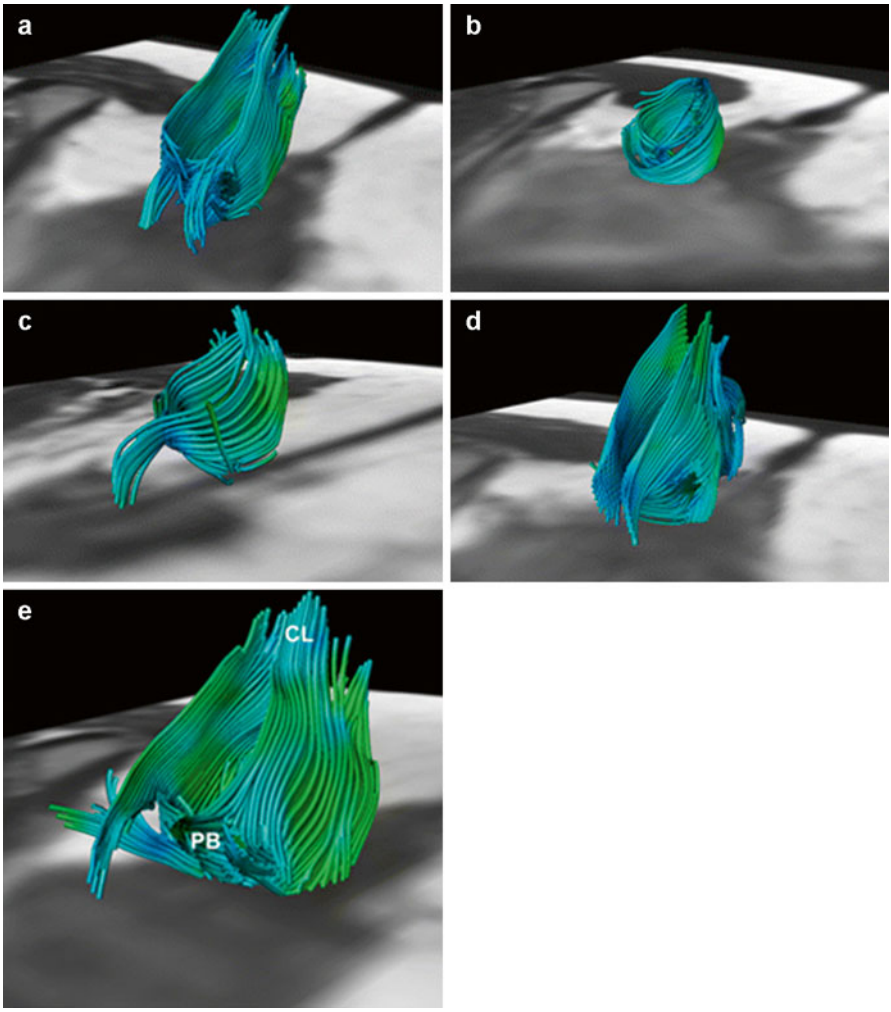

Fig. 2.4 Fiber trajectories representing the anal sphincter complex in five female subjects: 28, 32, 24, 27, and 31 years of age, respectively (**a**–**e**). Not all extrapolated fiber trajectories, matching the appearance of the anal sphincter complex, were perfectly circularly orientated. This might be attributed to both the predefined fiber angle cutoff point and the potential inaccurate fiber tractography based on signal originating from various muscles and ligamentous structures converging and interweaving in this area (e.g., perineal body (*PB*) and coccygeal ligament (*CL*)) (**e**) (Reproduced with permission from Zijta et al. [5])

Circular muscle layer of the rectum expands caudally into the anal canal and becomes the internal anal sphincter (IAS). The circular muscles in the sphincteric region are thicker than those of the rectal circular smooth muscle, about 2–5 mm, crossed by septa in between the muscle bundles.

The internal sphincter, about 3 mm in length and shorter than the external anal sphincter, does not extend to the lower edge of the anal canal but ends approximately 1 cm above this level. The lower muscular part of the anal sphincter therefore is only constituted by the external sphincter.

The internal sphincter has an intrinsic, sinusoidal "slow wave" activity with a frequency of 20–40 cycles per minute and is primarily responsible for the resting tone of the anus [46]. It contributes about 85 % of the resting anal sphincter pressure, which is measured at between 40 and 90 mmHg in health [47]. Weakness or disruption of the internal anal sphincter results in the passive leakage of fecal contents and incontinence of flatus [48].

Similarly to the IAS, the longitudinal muscles (LM) of the rectum extend into the anal canal in the space between the IAS and the external anal sphincter EAS. The longitudinal layer receives contributions from the levator ani, particularly the puboanalis [49,50], so it is also referred to as the conjoined tendon (muscle).

The structural function of LM consists in connecting the visceral and somatic parts of the anal sphincter complex. The LM may give rise to medial extensions that cross the internal anal sphincter to contribute to the smooth muscle of the submucosa (musculus canalis ani, sustentator tunicae mucosae, Treitz muscle, musculus submucosae ani) [51]. Fine and Lawes also described a longitudinal layer of muscle lying on the inner aspect of the internal sphincter arising from the conjoined longitudinal muscle and named it muscularis submucosae ani [52]. Moreover, some fibers of the longitudinal muscle that traverse the internal sphincter and become inserted just below the anal valves anchoring the submucosa were called by Parks mucosal suspensory ligament [53]. Other fibers cross the subcutaneous part of the EAS to become the muscle corrugator ani. Some authors consider that the meshwork formed by the conjoined longitudinal muscle may minimize functional deterioration of the sphincters after surgical division and act as a support to prevent hemorrhoidal and rectal prolapse [54,55].

Histologically, ganglionic cells and Vater-Pacinian-like corpuscles can be identified inside the LM. Morphology, topography, and histology of the LM suggest that this muscle also participates in maintaining anorectal continence, probably with a sensitive function of control related to anal canal distension.

The external sphincter is a cylindrical striated muscle under voluntary control that constitutes the outer layer of the anal sphincter complex and comprises fast and slow twitch types, which allow it to maintain sustained tonic contraction at rest and also allow it to contract rapidly with voluntary squeeze.

However, the EAS contributes a small part to the resting anal tone [47]. Rather, in its primary function of voluntary contraction, pressures of between 50 and 200 mmHg can be generated (approximately double than the resting pressure), significantly reduced in case of denervation or damages, as in obstetric injuries [56].

The external sphincter is approximately 2.7 cm high but is anteriorly shorter in women (approximately 1.5 cm). The external sphincter has a thickness of 4 mm on endoluminal imaging. A decrease in the thickness of the external sphincter in men with age has been demonstrated.

EAS is not a true circular muscle in its entirety; in fact, anteriorly the EAS is attached to the perineal body and transverse perinei muscle and posteriorly to the anococcygeal raphe [57].

Anatomists have characterized the external anal sphincter as a structure with 1, 2, 3, or 4 parts. There is general agreement that the subcutaneous EAS is a separate subdivision from the rest of the external sphincter. For the remainder of the EAS, various authors [58,59] still described a "superficial" and "deep" part, as reported in the original description of Santorini [60,61].

This finding is also confirmed by magnetic resonance imaging (MRI) studies [62]. However, other authors are quite convinced that the EAS muscle is composed of only the subcutaneous and superficial portion [50,63]. It must be stated that at MRI or other imaging techniques, a clear distinction between parts of the external sphincter can be identified in some individuals while none in others, and often several bundles (also more than three) can be identified without clear clefts.

Even if this discussion seems to lack a precise clinical meaning, subdividing the external anal sphincter could become necessary when the goal is to study the effect of specific anatomic disruptions on function.

The deep part of the external sphincter is intimately related to the puborectalis and probably wrongly confused by some authors.

In the continence mechanism the puborectalis, due to its sling-like anatomy, and unlike the EAS, has the additional function of increasing the anorectal angle (ARA). It displays some resting tone but contracts rapidly in response to any sudden increase in intra-abdominal pressure to prevent incontinence. With contraction, the anorectum is displaced anteriorly and the anorectal angle changes. Like the EAS, contraction of the puborectalis is voluntary and acts to close the anal canal. It appears that an acute ARA is the consequence of a normally functioning puborectalis muscle, contraction of which increases anal canal pressure in compliment with the EAS. The puborectalis can maintain some form of continence even in the absence of both IAS and EAS function [64,65].

The majority of the resting pressure (70–80 %) in the anal canal is related to the IAS and the remainder due to the EAS [66]. With voluntary anal squeeze, the increase in the anal canal pressure is mostly due to the external anal sphincter.

In the proximal part of the anal canal, the closure pressures are related to the contraction of IAS and puborectalis muscle, in the middle to the contraction of the EAS and IAS, and in the distal part to the contraction of the EAS only.

Hemorrhoidal tissue also could play a small role in the resting pressure of the anal canal [67].

Other factors that, although not important in the maintenance of continence, can significantly affect continence include rectum compliance and its sensitive function, colonic motility, stool volume, and stool consistency.

The autonomic nerves, sympathetic (spinal nerves) and parasympathetic (pelvic nerves), supply the internal anal sphincter. Sympathetic fibers originate from the lower thoracic ganglia (T10–L2) to form the superior hypogastric plexus. Parasympathetic fibers that originate from the 2nd, 3rd, and 4th sacral nerves meet the hypogastric nerves to form the inferior hypogastric plexus, which in turn gives

rise to superior, middle, and inferior rectal nerves that ultimately supply the rectum and anal canal. These nerves synapse with the myenteric plexus of the rectum and anal canal. Sympathetic nerves mediate IAS contraction while stimulation of parasympathetic or pelvic nerves causes internal anal sphincter relaxation.

However, the majority of tone of the internal anal sphincter is myogenic due to the unique properties of the smooth muscle itself.

The external sphincter has a nerve supply by the inferior rectal branch of the pudendal nerve (S2, S3) and the perineal branch of the fourth sacral nerve (S4).

2.3.5 Endopelvic Fascia and Connective Tissue Supports to the Pelvic Organs

Normal pelvic organ support and function depends on dynamic interaction between the pelvic floor musculature and the endopelvic fascia. The endopelvic fascia is an adventitial layer covered by parietal peritoneum on top of the pelvic diaphragm and visceral structures and connects these organs loosely to the supportive musculature and bones of the pelvis.

This fascia is important for passive support of visceral organs and pelvic floor and has expansible properties. The endopelvic fascia suspends the upper vagina, the bladder, and the rectum over the levator plate while the pelvic floor muscles close the urogenital hiatus and provide a stable platform on which the pelvic viscera rests. It has attachments to the tendinous arcs (arcus tendinous levator ani and the arcus tendinous fascia pelvis) at the pelvic side wall. The paravaginal connective tissue that attaches the anterior vaginal wall to the arcus tendinous fascia pelvis and the posterior vaginal wall to the levator ani is considered an extension of the endopelvic fascia. Moreover, the endopelvic fascia has ligamentous condensations with more fibrous elements, such as the rectal pillars [68].

With proper tone of the pelvic floor muscles, stress on the connective tissue attachments is minimized. Furthermore, in times of acute stress, such as a cough or a sneeze, there is a reflex contraction of the pelvic floor musculature, countering and further stabilizing the viscera. With pelvic floor weakness, such as neuropathic injury or mechanical muscular damage, there is loss of the horizontal orientation of the levator plate, the urogenital hiatus opens, and the pelvic floor assumes a more bowl-like configuration. The endopelvic fascia then becomes the primary mechanism of support. Over time, this stress can overcome the endopelvic fascial attachments and result in loss of the normal anatomic position through breaks, stretching, or attenuation of these connective tissue supports. This can result in changes in the vector forces applied to the viscera and may lead to pelvic organ prolapse and/or dysfunction.

The normal axis of the pelvic organs in a standing woman places the upper two-thirds of the vagina directly over the levator plate. The endopelvic fascia tethers the vagina and uterus in their normal anatomic location while allowing for the mobility of the viscera to permit the main physiological functions. Several areas of the endopelvic fascia have been named by anatomists and identified as ligaments.

Some of these have supportive functions (uterosacral ligament, cardinal ligament), while others do not play a role in the support of the pelvic organs (broad ligament, mesovarium, mesosalpinx, and round ligament).

The cardinal ligaments (also called the transverse cervical ligaments of Mackenrodt) extend from the lateral margins of the cervix and upper vagina to the lateral pelvic walls. They originate over a large area from the region of the greater sciatic foramen over the piriformis muscles, from the pelvic bones in the region of the sacroiliac joint, and from the lateral sacrum. They are condensations of the lowermost parts of the broad ligaments. Laterally, the cardinal ligaments are continuous with the connective tissue surrounding the hypogastric vessels. Medially, they are continuous with the paracolpium and parametrium as well as the connective tissue in the anterior vaginal wall, the so-called pubocervical fascia.

The uterosacral ligaments are attached to the cervix and upper vaginal fornices posterolaterally.

Posteriorly, they insert in the area of the coccygeus and sacrospinous ligament in most women [69]. The connective tissue of the uterosacral ligaments is continuous with that of the cardinals around the cervix. The cardinal and uterosacral ligaments hold the uterus and upper vagina in their proper place over the levator plate in its normal orientation [70,71].

2.3.5.1 Three Levels of Vaginal Support

DeLancey described the connective tissue supports of the vagina in three levels [72].

The level I support comprises the uterosacral/cardinal ligament complex. It is an intricate three-dimensional connective tissue structure that originates at the cervix and upper vagina and inserts at the pelvic sidewall and sacrum. It serves to maintain vaginal length and keep the vaginal axis nearly horizontal in a standing woman so that it can be supported by the levator plate. Loss of level I support contributes to prolapse of the uterus and/or vaginal apex.

Contiguous with the uterosacral/cardinal ligament complex, there are the paravaginal attachments, at the location of the ischial spine (level II support), that suspended the vagina laterally to the arcus tendinous fasciae pelvis (ATFP).

The anterior level II supports suspend the midportion of the anterior vaginal wall, creating the anterior lateral vaginal sulci. Detachment of these lateral supports can lead to paravaginal defects and prolapse of the anterior vaginal wall. In addition to the anterior paravaginal supports, there are posterior lateral supports at level II as well. The posterior vaginal wall is attached laterally to the pelvic sidewall in a slightly more complex arrangement than the anterior vaginal wall. The distal half of the posterior vaginal wall fuses with the aponeurosis of the levator ani muscle from the perineal body along a line referred to as the arcus tendinous rectovaginalis. It converges with the ATFP at a point approximately midway between the pubic symphysis and the ischial spine [73].

Level III support is provided by the perineal membrane, the muscles of the deep perineal space, and the perineal body. These structures support and maintain the normal anatomical position of the urethra and the distal third of the vagina, which is perpendicular to the floor in a standing woman. At level III, the vagina fuses with

the urethra anteriorly and with the perineal body posteriorly. Disruption of level III support anteriorly can result in urethral hypermobility and stress incontinence, and disruption posteriorly may result in rectocele, enterocele, and perineal descent.

2.3.5.2 Rectovaginal Fascia

Some authors still use the terms pubocervical fascia and rectovaginal fascia to describe the layer separating the vagina from the bladder and from the rectum, respectively. Although these terms are widely used, "fascia" is probably a misnomer in this context, as it does not accurately reflect the histology of the vagina. Numerous authors have performed histologic analysis of the vaginal wall and have failed to identify a distinct "fascial" layer [74,75].

The fascia often noted by pelvic surgeons during vaginal dissection may refer, in fact, to the muscular layer developed as a result of separating the vaginal epithelium from the muscularis or by splitting the vaginal muscularis layer. Moreover, although a posterior rectovaginal septum, consisting of fibromuscular elastic tissue, extending from the peritoneal reflection to the perineal body has been described [76], and during fetal life, the peritoneal cavity extends to the cranial part of the perineal body, it becomes obliterated in early life and this layer was not found to extend through the full length of the posterior vaginal wall [17].

However, it is possible that at the perineal body level, a fibromuscular connective tissue could be identified, although it is not still clear if it refers to a true rectovaginal fascia layer or rather to some fibromuscular connection directed to the perineal body itself.

2.4 Controversial Issues in Pelvic Floor Anatomy

Pelvic floor reconstructive surgery requires a comprehensive knowledge and a multidisciplinary interpretation of pelvic anatomy. Gynecologists, urologists, proctologists, and general surgeons approach pelvic floor surgery with different edges, and significant controversies exist on how the anatomy and function of the pelvis relate to pelvic floor defects or on how they should be recreated during surgery.

2.4.1 Conversation with a Urogynecologist

About variation in orientation and shape of the bony pelvis and predisposition to the development of pelvic organ prolapse: Compared to males, female pelvic anatomy has gone through more visible changes during evolution. The need to deliver fetuses with larger head diameters has driven a gender-specific pelvic modification that has added to the adaptive changes allowing upright standing and walking. Due to this overall reshaping and functional modification, the fascial and muscle supports of the pelvic floor have become more vulnerable, predisposing women to pelvic organ prolapse and incontinence, which are not found in other mammalians. However, the bony pelvis is still oriented in a way that minimizes the pressure on

the pelvic viscera and muscles, directing intra-abdominal forces toward the bones. Modifications in the normal orientation of the bony pelvis may predispose to prolapse: in particular, conditions such a decrease in lumbar lordosis, a wider transverse pelvic inlet, or a less vertically oriented pelvic inlet seem to be more common in women with prolapse. These anatomical variants may possibly alter the balance between abdominal forces and pelvic supports. In addition, they could also favor maternal nerves injury and compression and stretching or tearing of muscles and connective tissues during delivery.

About anterior and middle pelvic organs mechanisms of support and their role in surgical reconstruction: Once pelvic organ prolapse is established, it is of paramount importance to consider its full extension and complexity. Using the anatomical scheme described by DeLancey, identifying three main support levels, it is clinically possible to evaluate the pelvic floor as a fully integrated structure, but at the same time, to recognize the prevalent defect. This helps to fix realistic goals and discuss the risk of persistent or recurrent prolapse at the apex, anterior, or posterior vaginal walls. Moreover, it is important to remember that up to 60 % of continent women develop symptoms of stress incontinence after surgery for prolapse ("occult or potential stress incontinence") and that the correction of one defect can be followed by the development of another defect, which was latent before (e.g., the risk of an anterior vaginal wall prolapse after apical defect surgery). Thus, there is an open debate on whether pelvic floor defects should all be repaired at the time of surgery, in the effort to recreate a fully functional anatomic unit, or if reconstructive efforts should remain focused on those defects that are clinically relevant in the patient.

A very hot topic in pelvic floor reconstructive surgical anatomy is what the best support for the vaginal apex is. Since the uterosacral ligaments represent one of the physiological apical supports for the cervix and upper vagina, uterosacral ligament suspension has increased in popularity. Uterosacral ligaments plication and suture to the vaginal cuff or to the isthmus results in a normal vaginal axis and provides a good apical suspension. This technique is more easily performed at the time of hysterectomy, and it is linked to less risk of later cystocele compared to vaginal sacrospinous ligament suspension. For women with pelvic ligaments and connective tissue supports that are severely damaged or absent, sacrospinous ligament suspension is a good alternative providing a strong apical fixation. Moreover, this procedure is more easily performed to suspend a vaginal vault prolapse when uterosacral ligaments are difficult to be identified. An anatomical structure that is becoming increasingly popular to achieve apical fixation is the presacral ligament, used in abdominal sacral colpo- or hysteropexy. Use of this structure in reconstructive surgery seems to be associated with significantly lower rates of recurrent apical prolapse and is currently considered the gold standard for apical support.

About clinical role of rectovaginal fascia and perineal body: An important anatomical structure that can be damaged during delivery is the perineal body. This anatomical landmark sets the point of convergence of the bulbospongiosus muscles, of the superficial and deep transverse perineal muscles, of the perineal membrane, of the external anal sphincter, of the posterior vaginal muscularis, and of fibers from

the puborectalis and pubococcygeus muscles. The perineal body is key for the support of the distal vagina and for normal anorectal function. Lesions of the perineal body happen frequently during delivery. Suboptimal reconstruction predisposes to perineal descent syndrome and to anterior rectocele and couples with functional derangements such as incomplete or obstructed defecation and painful posterior vaginal bulge. Clinically significant perineal body lesions frequently come along with uni- or bilateral pudendal nerve lesions, thus playing a key role in many manifestations of pelvic floor dysfunction, such as urinary and fecal incontinence or sexual dysfunction.

The male perineal body is the distal anchorage of the Denonvillier's lamina. The anatomical existence of this structure in women is debated, since it cannot be clearly identified. Nonetheless, gynecologists have ever since treated posterior colpocele with surgical procedures allegedly aimed at reconstructing this septum. The many variants of these procedures generally end up with an external plication of the prerectal fascia or of the rectal muscularis, thereby in part reducing the internal width of the rectal lumen. This may explain why these procedures are somewhat effective in ameliorating obstructed defecation. While a distinct fascial structure between the posterior vaginal wall and the rectum cannot be found, a continuity exists between the outer muscular layer of the vagina and the perineal body on one side and with the uterosacral ligaments and the cervical ring on the other. Failure to recreate this continuity during pelvic floor reconstructive surgery is considered a major factor in posterior compartment prolapse relapse and in the development of enterocele.

(*TS*)

2.4.2 Conversation With a Coloproctologist

About anatomical and functional distinction of posterior pelvic muscles: Even if Iliococcygeus and pubococcygeus muscles seem to be in continuity between them, they have their own structural identity, they are located between pelvis bones, and they have a static function. Often bad posture of the pelvis may produce painful contractures of these muscles causing chronic pelvic pain.

Puborectalis muscle and external sphincter are not completely separated, and they play a dynamic and synergistic function that manages defecation and continence. Puborectalis muscle shrinks swiveling upon the insertion at the level of the pubis. Instead, external sphincter is an orbicularis muscle that shrinks with centripetal force vectors. However, the impression, confirmed by the experience of transanal ultrasound, is that orbicular fibers of the external sphincter are in direct continuity with the low fibers of the puborectalis that close anteriorly in the middle and lower part of the anal canal.

I do not think that the debate about a division into different parts of the external sphincter could find a significant value in clinical practice, and I have never tried to identify the various portions during surgical dissection. Especially in female patients, the anterior portion of the external sphincter is often extremely reduced in dimensions, and any additional attempted division seems to be contrived and useless.

About posterior pelvic organs mechanisms of support and their role in surgical reconstruction: What we can say for sure is that the muscles of the pelvic floor are not a rectal suspension mechanism but a structure on which the rectum lies. With the upward movements during straining and downward during contraction, these muscles allow the straightening and the stretching of the rectum, assisting the expulsion of stool, increasing the rectoanal angle, and closing the rectum to ensure continence. More than a suspension mechanism, the endopelvic fascia and especially the peritoneum have the function to maintain normal anatomical relationships and to allow the physiological movements of the organs and the "slippage" between the various organs at the time of functional needs. I believe that the rectum would not fall without the pelvic floor muscles, and rectal prolapse is not primarily due to pelvic floor muscle failure.

The lateral ligaments or stalks of the rectum are distal condensations of the pelvic fascia that form a roughly triangular structure with a base on the lateral pelvic wall and an apex attached to the lateral aspect of the rectum. During abdominal rectopexy, the rectum is mobilized down to the levator floor preserving the lateral ligaments that are then sutured to the presacral fascia just below the sacral promontory.

About clinical role of rectovaginal fascia and perineal body: Even if rectovaginal fascia could be identified in normal condition, its confirmation in pathological condition is uncommon. In fact, performing surgery almost exclusively in pelvic floor pathological conditions, it is almost impossible to identify it as a well-defined structure, and it cannot be used for reconstructive purposes.

The perineal body is the fulcrum on which the musculotendinous structures of the pelvic floor fit. Its integrity is essential for the maintenance of dynamic synergies of contraction. Also this structure is surgically difficult to identify in pathological conditions. (*GN*)

2.4.3 Conversation with a General Abdominal Surgeon

About abdominal approach to the posterior compartment of the pelvis: The abdominal view of the pelvis, in which the general surgeon has confidence, offers particular challenges, mainly related to the preservation of the anatomical structures of support and the observance of the nervous and vascular structures contained within them. Unfortunately, the role of the abdominal surgeon regarding the pelvis mainly involves the surgical treatment of malignancies and endometriosis. Although over the past decades the approach in radical pelvic surgery for rectal, ovarian, uterine, and bladder cancer, as well as deeply infiltrating endometriosis and perirectal connective tumors, has undergone great changes, becoming more accurate and minimally invasive, the pathological nature of the diseases treated often means extensive and deep dissections. To reduce local recurrences minimizing functional urinary, rectal, and sexual dysfunction, anatomical and surgical knowledge is essential.

The rectum is enveloped by mesorectal fat and the mesorectal fascia and is fixed to the sacrum by the presacral fascia (of Waldeyer). Lateral condensations of the

endopelvic fascia give lateral support to form the lateral rectal ligaments. The lateral ligaments course from the posterolateral pelvic wall at the level of the third sacral vertebra to the rectum. Within these ligaments run nerves and the middle rectal vessels.

Even if the lateral ligaments had an important role in the reconstruction step of some rectopexy techniques for rectal prolapse, when Heald, in 1982, described the total mesorectal excision for rectal cancer, emphasizing the anatomic isolation of spaces and septa, they were not mentioned.

However, the opening of Waldeyer's rectosacral space up to the rectosacral fascia, the dissection of the "holy plane" described by Heald, the dissection of the rectovaginal septum, and the development of the pararectal spaces (Latzko and Okabayashi) are mandatory and important key steps for an anatomic identification of the nerves joining the pelvic plexus essential for pelvic functions. Proper surgical skills as well as knowledge of the pelvic neuroanatomy and the relationship between the autonomic nerves, the blood vessels (middle rectal artery), the rectovaginal and the lateral rectal ligaments, and parietal and visceral pelvic fasciae facilitate nerve-sparing mesorectal excision.

During the rectal resection, after a nerve-sparing mesorectal excision, only the rectal nerve fibers of the resected bowel segment should be cut, thus minimizing the rectoanal denervation and leaving intact the visceral efferent bundles of the pelvic plexus for the bladder, uterus, and vagina.

Magnification provided by laparoscopic or robotic surgery allows a better dissection and improvement in executing the surgical steps, especially if the procedures require an associated nerve-sparing rectal resection or other radical surgical procedures for deeply infiltrating benign or advanced oncologic diseases extended to the pelvic walls. (*AV*)

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Neurophysiology and Neurophysiological Evaluation of the Pelvic Floor

3

Giuseppe Pelliccioni and Paolo Pelliccioni

Urinary and fecal continence, micturition and defecation, and sexual arousal and orgasm are dependent on the integrity of the central and peripheral nervous pathways to the sacral region. The coordination between bladder, urethra, anorectum, and sphincters is mediated by a complex neural control system in the brain, spinal cord, peripheral ganglia, and peripheral nerves.

3.1 Neural Control of Urinary Tract

Bladder and urethra have two primary functions: the storage and the periodic elimination of urine; these activities need the neural coordination in the central, somatic, and autonomic peripheral nervous systems. The voluntary control of micturition requires complex connections between sympathetic and parasympathetic autonomic nerves, pudendal somatic nerves, and many areas in the brain. Parasympathetic preganglionic cholinergic outflow, giving excitatory input to the bladder, arises in the sacral parasympathetic nucleus (SPN), localized in the intermediolateral column from the S2–S4 spinal segments. The parasympathetic fibers then travel through pelvic nerves to intramural bladder ganglia and pelvic plexus, where the postganglionic fibers induce detrusor contraction and urinary flow. The parasympathetic

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activation of M_3 muscarinic and P2X purinergic receptors is involved in voiding reflex, while nitric oxide transmission mediates inhibition of urethral smooth muscle. The sympathetic system, which plays a primary role in the continence mechanism inhibiting the parasympathetic action, originates from the intermediolateral columns in the T11–L2 spinal cord segments. Preganglionic may synapse on postganglionics in the paravertebral sympathetic chain or pelvic plexus; hypogastric nerve, conveying sympathetic afferents and efferents, releases noradrenaline (NA) on bladder and urethra. The sympathetic efferents therefore activate β_3-adrenergic inhibitory receptors in the detrusor muscle relaxing the bladder and α_1-adrenergic excitatory receptors in the bladder neck and urethra allowing the continence and urine storage and preventing retrograde ejaculation. The somatic cholinergic pathway originating from S2–S4 motor neurons in Onuf's nucleus (ON) innervates, through pudendal nerves, the external urethral sphincter (EUS) and pelvic floor muscles (Fig. 3.1). The somatic afferents from the bladder neck and the urethra are conveyed from pudendal nerves, the dorsal horn of the spinal cord, while the sensation of bladder fullness travels by pelvic and hypogastric nerves to the spinal cord.

The afferent Aδ fibers, lightly myelinated, and the unmyelinated C fibers travel through pelvic and hypogastric nerves. While Aδ fibers respond to active contraction and passive distension, conveying information about bladder filling, C fibers are insensitive to bladder filling under physiological conditions and activated only in pathological conditions.

These fibers convey nociceptive, volume, and tension information in the somatosensory pathways from the sacral dermatomes through the spinal cord to the CNS. The activity of volume and tension mechanoreceptors during bladder filling is conveyed to the dorsal horns by the pelvic nerves. A rostral intersegmental pathway projects to the thoracolumbar cord, stimulating sympathetic preganglionics, thus promoting continence via the hypogastric nerves. The persistence of low detrusor pressure, the absence of involuntary contractions, and the increased pressures at urethral level are the result of storage reflexes. Pelvic organ afferents can inhibit the sacral preganglionics to the bladder and induce increased urethral pressure. This guarding reflex is known as visceral-visceral reflex. This fact explains the possible therapeutic utility of intravaginal electrostimulation in the treatment of urgency-frequency syndrome. Another guarding reflex exists, in which afferents from pelvic organs and bladder filling stimulate ON to increase the outlet urethral resistance.

Urinary bladder and the other functional unit consisting of bladder neck, urethra, and EUS are controlled and regulated by various central neural circuits, involving midbrain periaqueductal gray (PAG), cell groups in the preoptic and caudal hypothalamus, pontine micturition center (PMC), also known as Barrington nucleus, and medial frontal cortex. PMC is activated during voiding (M-region) and bladder filling (L-region or pontine storage center) and appears to initiate and coordinate lower urinary tract function. This notion is supported by neurophysiological data; moreover, PET scanning of the human brain during micturition documents increased metabolic activity in the pons as well as in cortical and subcortical areas, giving further evidence for pontine involvement in urinary storage and release (Fig. 3.2).

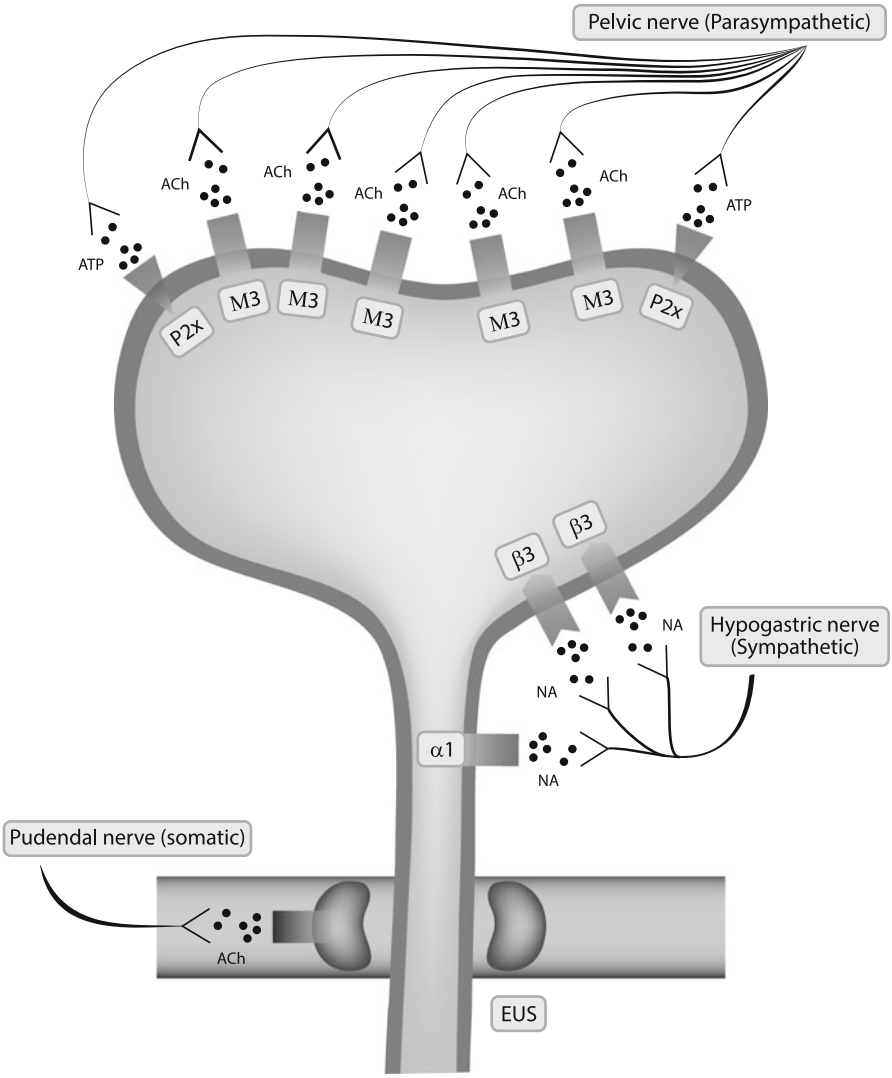

Fig. 3.1 Neurotransmitter mechanisms regulating urinary bladder and EUS function. Distribution of different autonomic and somatic axons

The cortical (prefrontal cortex, insula, anterior cingulate cortex, cerebellum), subcortical (basal ganglia, thalamus, hypothalamus), and pontine circuitry accomplishes three major functions: amplification of bladder contraction to allow complete micturition, control of micturition frequency, and coordination of the activity of lower urinary tract muscles (Fig. 3.3). Overlapping between voluntary control and a reflex mechanism is allowed by sympathetic, parasympathetic, and somatic peripheral innervation of bladder and urethra. Higher centers in the CNS induce a modulatory

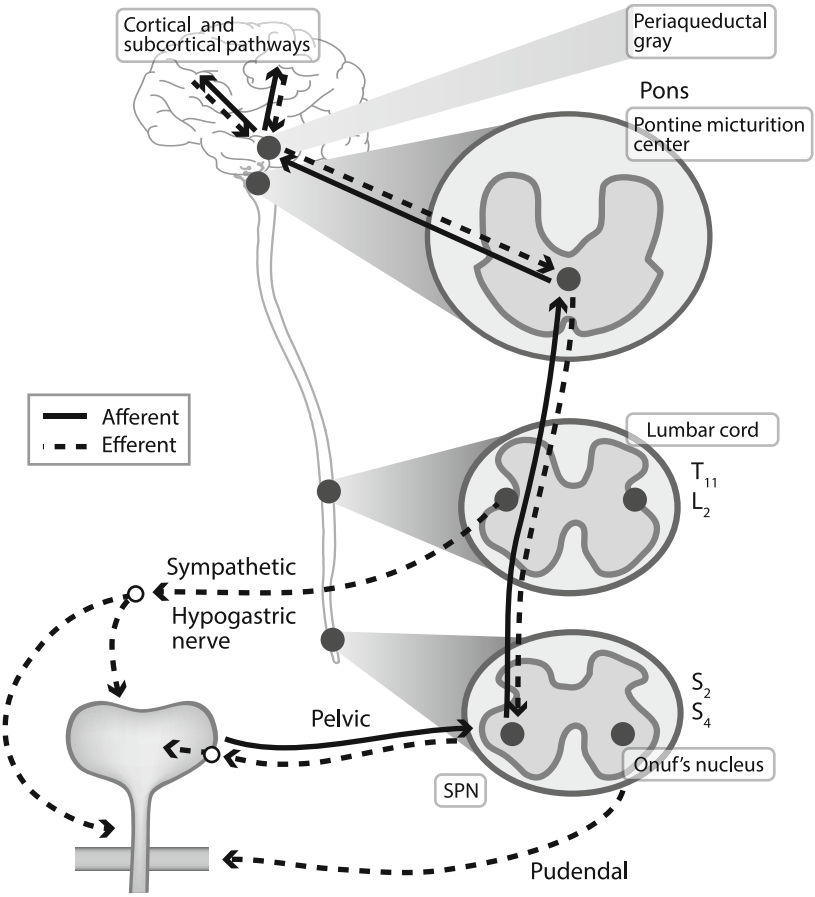

Fig. 3.2 Central and peripheral pathways involved in functional neural control of the urinary tract

effect over PMC, primarily mediated by an inhibitory input. The PMC appears to initiate and coordinate lower urinary tract function, pairing detrusor contraction with inhibition of urethral outlet, while sacral micturition center triggers an involuntary reflex detrusor contraction in response to bladder filling. In fact, two distinct voiding reflex pathways exist: a suprasacral reflex physiologically active in normal subjects and a sacral reflex which allows voiding in pathological conditions.

Such an anatomo-functional complexity allows to define urinary continence, as suggested by C.J. Fowler, "a severe test of neurological integrity" [1].

In fact, neurogenic lower urinary tract (LUT) disorders are neuroanatomically divided into suprapontine, spinal (infrapontine-suprasacral), sacral, and peripheral, showing different patterns of voiding dysfunctions. Based on knowledge of voiding centers, these different clinical features can be explained. The suprapontine, supraspinal neurological lesion induces a detrusor hyperreflexia with normal sphincter synergy (DHSS), caused by the loss of inhibition of sacral micturition center. The

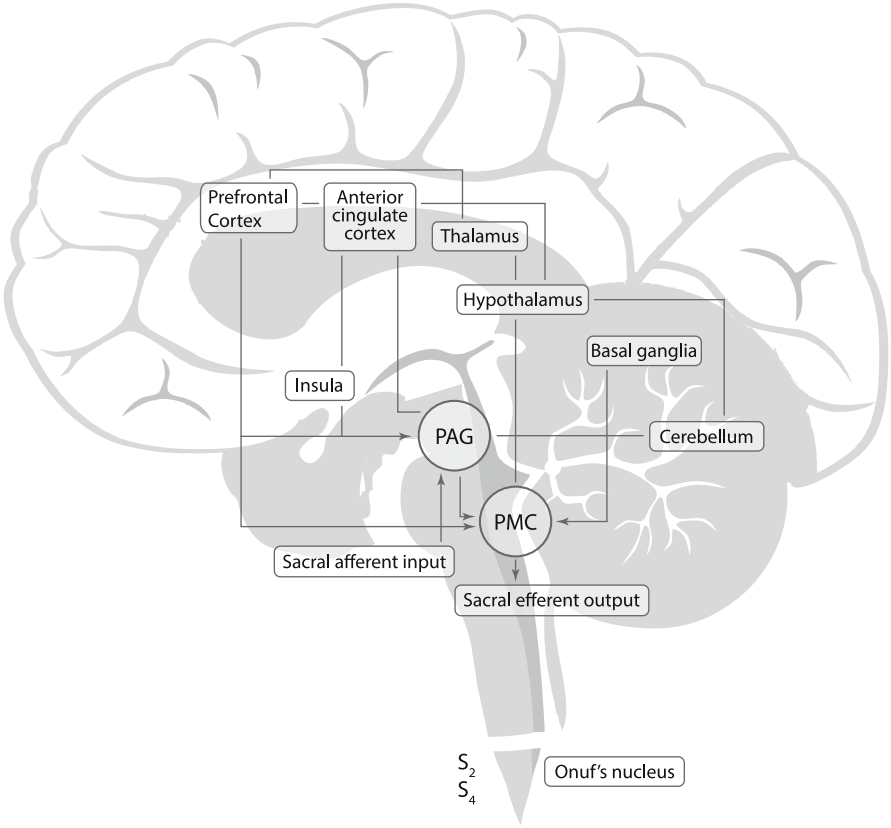

Fig. 3.3 Scheme of the neural interconnections between different cortical and subcortical areas involved in urinary storage and release

patient with DHSS has a volume trigger point, at which the bladder contracts, which is considerably lower than the normal bladder capacity, complaining urinary frequency, urgency, and incontinence. Spinal (infrapontine-suprasacral) lesions induce a disruption of connections between the PMC and the sacral center, causing loss of PMC activity and subsequent loss of coordinated relaxation of the EUS during bladder contraction. This loss results in detrusor sphincter dyssynergia (DSD), paired with detrusor hyperreflexia (as with suprapontine, supraspinal lesions) due to uninhibited bladder contractions. DHSS and DSD are dangerous pathological conditions, commonly leading to upper urinary tract damages, reflecting high intravesical pressures needed to obtain urinary flow, progressively impairing kidney function to the point of kidney failure.

Those with suprasacral injuries and intact bladder sensation usually complain of urgency-frequency syndrome; incontinence without awareness may be shown.

Patients with sacral lesions usually complain of suprapubic fullness, inability to void, and incontinence. Traumas are the most common cause responsible for conus

and cauda equina lesions. Clinical findings reflect urinary retention with overflow incontinence and elevated post-void residual (PVR).

Peripheral nerve lesions may involve parasympathetic, sympathetic, and/or somatic nerves.

Usually, parasympathetic involvement results in detrusor areflexia; large bladder capacities and chronic bladder overdistension with increased PVR may be seen in case of motor and sensory nerve impairment. Sympathetic lesions alone may cause incontinence due to impaired internal sphincter closure. Patients with peripheral nerve diseases usually complain of suprapubic fullness and inability to void, showing urodynamic findings of detrusor areflexia.

Urinary symptoms and signs may differ from expectations because of incomplete suprapontine, spinal, sacral, and peripheral lesions, coexisting involvement of central and peripheral neurological pathways or other factors, such as drugs, prostate obstruction, or cognitive impairment.

3.2 Neural Control of Intestinal Tract

Bowel activity and secretion in the gastrointestinal (GI) tract are connected and modulated by the cortical activity and controlled by intrinsic and extrinsic GI innervation of smooth muscle layers and glands. Intrinsic innervation relays on the enteric nervous system (ENS), which is the largest nerve cells accumulation outside the brain, having about 100 million neurons and extending throughout the length of GI tract. The neurons of the ENS are organized into two plexuses, myenteric or Auerbach plexus, between the longitudinal and circular smooth muscle layers, and submucosal or Meissner plexus, that influences the absorptive and secretory functions of the enteric mucosa. Extrinsic innervation depends on parasympathetic and sympathetic preganglionics. Sympathetic output originates in the prevertebral ganglia, while parasympathetic innervation is allowed by dorsal motor vagal nucleus (DMV) of the medulla oblongata and sacral parasympathetic nucleus of the spinal cord.

Despite the close anatomical relationship between the rectum and anal canal, there are clear differences in their innervation. Afferent innervation of the rectum derives from the pelvic nerve (Aδ and C fibers), sensitive to rectal distension. Aδ fibers rapidly adapt to changes in rectal distension, while C fibers are slowly adapting and respond to the intensity of rectal distension [2]. Sensations from the rectum can be poorly localized, while the high density of afferent pathways and receptors in the anal canal allows localization of the sensations and sensory definition of the quality of content.

The motor control of anorectum and pelvic floor results from parasympathetic, sympathetic, and somatic nerves. Parasympathetic pathways originate from the parasympathetic nucleus located at S2–S4 segments, having both excitatory and inhibitory components. The excitatory part induces colonic propulsive activity during defecation, while the inhibitory part permits adaption of colonic volume to the content and relaxation of the colon ahead of fecal material.

Rectoanal inhibitory reflex, consisting of anal relaxation, induced by rectal distension, is mediated by a nitric oxide pathway involving intrinsic nerves. Tonically active sympathetic excitatory neurons that innervate internal anal sphincter allow closure of the anal canal at rest. Anal sphincter and pelvic floor somatic innervation originates from Onuf's nucleus motor neurons at S2–S4 levels. The external anal sphincter (EAS) contributes 30–50 % of resting anal tone, while internal anal sphincter (IAS), regulated by sympathetic nerves, provides most of the resting anal pressure. The puborectalis muscle (PRM) is, moreover, tonically active and permits maintenance of the resting anorectal angle. PRM contraction in fact is fundamental to preserve fecal continence, and its relaxation is necessary for normal bowel emptying. The rectum is functionally different from colon because of its function as a reservoir opposed to a transit function. The rectal compliance is the adaptive capacity of this reservoir to increase its distension to luminal content.

Small volumes of feces propulsed slowly to an almost empty rectum result in an increased rectal compliance, while rapid and large masses distending the rectal wall induce activation of rectoanal inhibitory reflex and the desire to void.

Defecation is mediated by a coordinated relaxation of pelvic floor, IAS and EAS, and an increase in rectal pressure. However, evidence is emerging of an existing association between symptoms of impaired defecation and psychological state.

Gastrointestinal symptoms are also the most important non-motor manifestation of Parkinson disease (PD) and parkinsonism, with constipation as the most prominent manifestation resulting from poor colonic peristalsis and defecatory dysfunction [3]. A wide pattern of cortical areas is involved in anorectal stimulation, including areas that process cognitive and affective aspects of sensation (prefrontal cortex, anterior cingulate cortex and insula) and areas activated during spatial discrimination (primary and secondary somatosensory cortex). Anal canal stimulation results in activation of similar cortical areas than those involved during rectal stimulation, but the former results in activation at a more superior level of primary somatosensory cortex without anterior cingulate cortex activation. It seems that viscera have a greater limbic cortex representation than somatic structures, thus explaining the greater autonomic responses evoked by visceral sensation in comparison with somatic sensation [4].

3.3 Neurophysiological Evaluation of Pelvic Floor

Neurophysiological evaluation of patients affected by urinary, fecal, and sexual disorders usually follows surgical and clinical evaluation and, almost always, other investigations. Although neurophysiological investigations are performed worldwide, their application to pelvic floor disorders is limited to a few centers. In patients with pelvic floor disorders, EAS EMG is the single most useful diagnostic test, particularly for focal sacral lesions. EAS muscle is, in fact, readily accessible and evaluated without discomfort. However, no consensus statement for a standardized approach to LUT and anorectal neurogenic disorders has been reached, and the role of different tests has not been clearly defined yet.

Clinical history and neurological examination should always be performed to propose a diagnosis of neurogenic pelvic dysfunction and to plan further electrophysiological tests [5, 6]. Examination usually includes anal sphincter tone, strength in the S1–S2 innervated muscles (gastrocnemius, gluteal muscles), sensation extending from the soles of the feet to the perianal area, and presence of anal and bulbocavernous reflexes. Anal reflex is induced by pricking or scratching the perianal skin area, whereas bulbocavernosus reflex is evoked by a nonpainful clitoral or gland squeeze [7, 8]. Clinically elicited reflexes may be extinguished by mild or severe nerve lesions, whereas the same reflexes can be recorded neurophysiologically, though with a prolonged latency and reduced amplitude, also in almost complete nerve lesions.

Extensive neurophysiological investigations should be performed in any patient with LUT and anorectal disorders of suspected central or peripheral neurogenic etiology. These tests include concentric needle EMG of different pelvic floor muscles, measurement of sacral reflex latency (pudendo-anal or bulbocavernosus reflex) [9], pudendal and anal somatosensory-evoked potentials (SEPs), and motor-evoked potentials (MEPs) from pelvic floor and EAS muscles by transcranial and lumbosacral magnetic stimulation. Pudendal nerve terminal motor latency (PNTML) has been used in different clinical conditions, but its clinical value has been questioned because the reproducibility, sensitivity, and specificity are uncertain. The recording of a sympathetic skin response (SSR) from the saddle region is useful for testing the lumbosacral autonomic sympathetic system. Unfortunately, a clinically useful test for evaluating the sacral parasympathetic system, which is crucial for LUT and anorectal functioning, has not been found yet.

Tests are usually capable of demonstrating neuropathic lesions and helping to define the specific affected sensory, motor, or autonomic pathway. Severity of lesions can be also assessed, and the underlying mechanisms can be revealed. Even when all other functional tests do not show altered findings, the electrophysiological tests can be positive, therefore leading to a surgical or conservative approach and assessing the prognosis.

3.3.1 Electromyography (EMG)

Needle EMG is the most important neurophysiological technique for evaluating patients with suspected neurogenic etiology of pelvic floor dysfunction [10]. EMG assessment of the pelvic floor, EAS, and EUS muscles is mainly indicated to evaluate: (1) the presence of pathological spontaneous activity, fibrillation potentials and positive sharp waves, and denervation of muscle fibers, (2) the presence of muscle fiber reinnervation [11], (3) normal mild continuous tonic contraction in the EAS, PRM [12], and EUS and adequate contraction or relaxation during squeeze or straining, and (4) recruitment pattern and motor-unit potential (MUP) waveform [13]. It is sometimes difficult to discriminate MUPs from fibrillation potentials and positive sharp waves in partial denervation of sphincter muscles during relaxation; in this case, the needle evaluation of bulbocavernosus muscle is useful as no ongoing activity of motor units is recorded [14]. The most important parameters in the analysis of MUP are amplitude,

duration, area, number of phases and turns, and firing rate that can be automatically evaluated by advanced EMG systems provided with special software of analysis.

However, in the EAS muscle the best diagnostic parameters seem to be MUP duration, area, and number of turns [15]. Completely or partially denervated pelvic muscles may be reinnervated by axonal regrowth from the proximal nerves; thus a recording of bi and triphasic motor units, soon becoming polyphasic with prolonged duration, can be shown. The EAS muscle needle EMG examination is the test most commonly used to assess the functional state of pelvic floor and sacral myotomes; in fact EAS is easy to access, its needle evaluation is not very painful and very useful information can be acquired. EAS examination holds the central position in Podnar and Vodusek's algorithm for electrodiagnostic evaluation of the sacral nervous system [6]. With the patient in a comfortable Sims position with knees and hips flexed, after grounded electrically at the thigh, a standard concentric needle EMG electrode is inserted into the subcutaneous portion of the EAS muscle to a depth of 3–5 mm under the mucosa, 1 cm from the anal orifice [6, 16]. Both left and right halves of the subcutaneous EAS muscle must be examined separately, starting on the side with the clinical evidence of sphincter dysfunction (episiotomy scar tissue, patulous anus). If partial or complete atrophy of the subcutaneous EAS muscle is appreciated, a concentric needle electrode can be introduced 1–3 cm deeper through the skin to evaluate spontaneous activity, recruitment pattern, and functional contractile capacity of the deeper EAS and 4–5 cm deeper for examination of the PRM. In the presence of fibrosis, there is a loss of pelvic floor muscle contractile capacity, and consequently, no spontaneous activity or MUP is recognized. When the needle advances in the EAS muscle, continuous firing of low-threshold MUPs is normally appreciated, and during a brief period of relaxation, the presence of spontaneous activity, fibrillation, or jasper potentials can be recorded.

EMG recordings from the EAS are performed at rest and during squeezing, coughing, and straining that simulates rectal evacuation. In healthy subjects, squeeze and cough increase the MUP recruitment pattern, whereas strain decreases or inhibits MUP firing.

Needle examination of the bulbocavernosus muscle is indicated when no EMG signals are recorded in the subcutaneous or deeper EAS muscles [17].

Kinesiological EMG (KEMG) is used to assess and record patterns of individual anterior or posterior muscles during functional maneuvers. An abnormal pattern during bladder filling or emptying, anal closure, squeezing, coughing, and straining can be recorded by surface or needle electrodes. The utility of this technique is to reveal possible dyssynergic contraction pattern of EUS concomitant with detrusor contraction (during urodynamic test) and analogous inappropriate PRM activation on attempt of evacuation. In patients with anal incontinence, during manometric balloon retaining test, KEMG can show absent or insufficient EAS activation.

3.3.2 Sacral Reflexes

Sacral reflexes are motor responses, derived from pelvic striated floor and sphincter muscles, to electrical stimulation of the dorsal penile or clitoral nerve, perianal skin, bladder neck, or proximal urethra. Sacral reflexes evaluate the functional status of

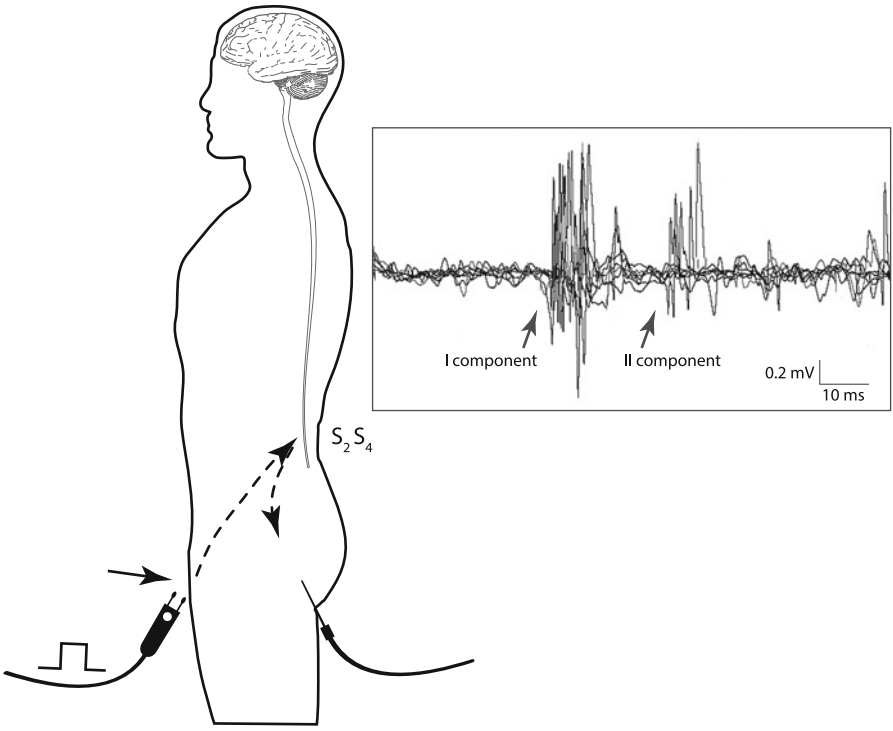

Fig. 3.4 Neurophysiological recording of the pudendo-anal reflex elicited in a healthy man by single electrical stimulation of the dorsal penile nerve. Responses are recorded by a concentric needle electrode inserted in EAS muscle. Note the two different components of the sacral reflex

the afferent neural fibers of the clitoris or penis, the S2–S4 spinal segments, and the efferent pathways to EAS and bulbocavernosus muscles [7, 9, 18]. The central circuit at the spinal level is complex and probably involves many sacral interneurons.

The motor response in EAS and BC muscle is recorded either with a concentric needle or wire electrodes and can be analyzed separately for each side of both muscles. These sacral reflexes, named pudendo-anal and bulbocavernosus reflex, reveal two components with different thresholds at the electrical stimulation: a first component with a shorter latency of 28–45 ms, probably oligosynaptic, and a second component with a longer latency at about 50–75 ms, typical for a polysynaptic response (Fig. 3.4). The first component is morphologically constant, is stable, and does not habituate, while the second component or long latency response is not always demonstrable and rapidly habituates [19]. The cutaneoanal reflex, described in 1891 by Rossolimo, like the other two reflexes consists of two or three motor contractions (early response at 5 ms, intermediate at 15 ms, and late at about 50 ms) of EAS muscle in response to scratching or pricking the perianal skin. This reflex, which is abolished by transection of the posterior S4 roots, shows marked habituation, is quite variable (35–80 ms), and therefore cannot be used as a diagnostic tool [20].

Vesicourethral and vesico-anal reflexes are described following stimulation of the bladder neck and mucosa, but their usefulness as a diagnostic tool is considered to be limited.

Recently, a technique for transcutaneous electrical stimulation of the S3 motor root, recording from EAS muscle, has also been described [21].

Method: A common scheme of sacral-evoked responses consists in the anterior electrical stimulation (penile/clitoral, bladder neck site) and recording by needle electrode from different pelvic muscles (BC, EAS, levator ani). Sacral reflexes are useful in different pelvic floor disorders and have been recommended for the assessment of cauda equina, conus, and medullaris lesions. In the presence of unilateral/asymmetrical lesions of pudendal nerves, sacral roots, or lumbosacral plexus, these reflexes may show a reduction of responses amplitude and/or increased latencies.

Only the largest myelinated, fastest fibers convey the neurophysiological signals traveling in the afferent limb of these reflexes. Many disorders of bladder, bowel, and sexual function are unfortunately the result of unmyelinated fiber dysfunction; therefore, conduction in these fibers is not tested by these procedures, and autonomic and small-fiber neuropathies may not be revealed by these tests.

3.3.3 Somatosensory-Evoked Potential (SEP)

Pudendal SEP is a method for evaluating the afferent sensory pathway to the parietal cortex, and it is used in investigating central and peripheral neurological diseases that affect pelvic floor functional integrity. SEPs findings may help in showing lesions in somatosensory pathways, localizing them and defining a prognostic value.

In a similar way to the other neurophysiological tests, pudendal SEPs may be normal in latency and amplitude also in case of an underlying organic disease. The peripheral electrical stimulation used to obtain an SEP activates predominantly, if not entirely, the large diameter fast-conducting group Ia muscle and group II cutaneous afferent fibers. Loss of posterior, dorsal column or lemniscal sensory pathways is invariably associated with abnormal SEPs, indicating that within the spinal cord the SEPs are mediated predominantly via these tracts. Generally SEPs are best recorded over the somatosensory cortex, and several of their components are widely distributed over the scalp [22]. The pudendal SEPs technique, first described by Haldeman in 1983 [23], depends on the recording by a disk electrode affixed to the scalp of a typical "W-shaped" waveform, as a response that appears with a given latency depending on site stimulation. Although several studies have shown that SEPs can effectively be recorded after dorsal penile and clitoral stimulation [23–27], only few investigations have been published concerning anal somatosensory-evoked responses [28, 29]. It is necessary to remind that pudendal SEPs after anal and dorsal penile/clitoral nerve stimulation cannot be considered to produce equivalent results due to separate branches of the pudendal nerve innervating the pelvic region. Therefore, obtaining separate reference values in both sexes for anal and penile/clitoral latencies when evaluating pelvic floor neurophysiology is considered to be relevant [30]. The analogous morphology of pudendal and tibial SEPs might suggest a common neurophysiological mechanism to produce both responses.

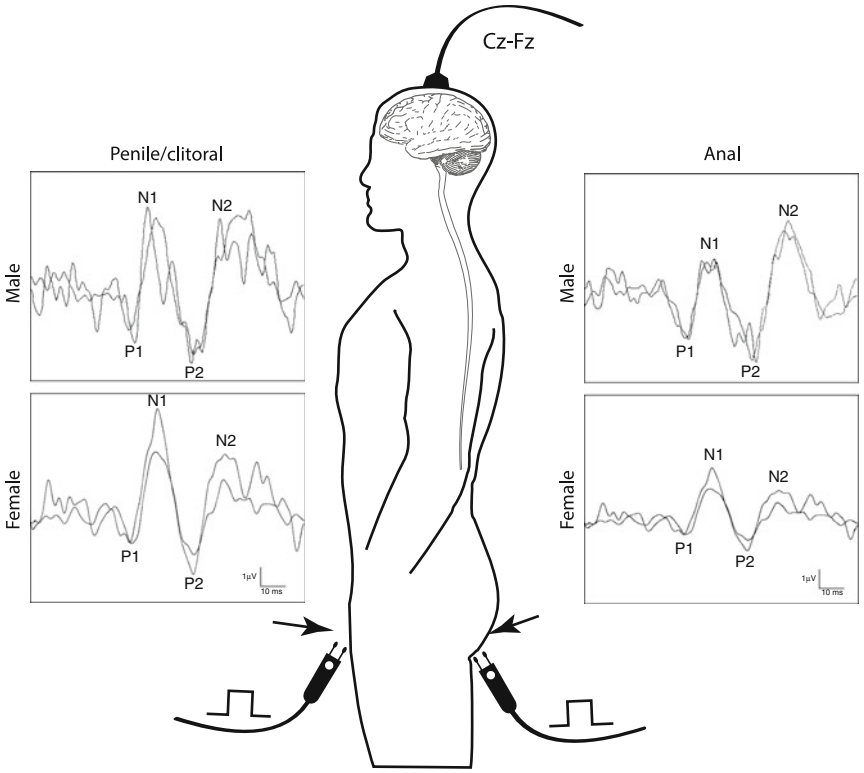

Fig. 3.5 Superimposed waveforms of pudendal SEPs after anal (*right*) and penile/clitoral (*left*) stimulation in a male and a female healthy subject. SEPs responses are bipolarly recorded using surface electrodes from the scalp. SEPs are analyzed by visually determining *P1*, *N1*, *P2*, and *N2* latencies

Method: The responses are bipolarly recorded using surface electrodes from the scalp, 2 cm behind Cz, referred to Fz or Fpz (10–20 EEG International System), roughly overlying the sensorimotor cortex for the genital and anal area. Electrical stimulation is performed by means of a bipolar surface electrode positioned at the anal orifice, at the base of the penis or cranial to the clitoris. The typical recording consists of a series of waves that reflects sequential activation of neural structures along the somatosensory pathways. A first positive peak can be recorded in normal subjects at about 42 ms using a stimulus intensity of two to four times the sensory threshold. Later negative and positive peaks show a large variability in amplitude between individuals (Fig. 3.5). SEPs amplitudes have, however, not been found to differentiate between normal and pathologic responses. SEPs can be used in perineology to confirm and localize sensory abnormalities affecting anal or genitourinary neural pathways [6, 10]. Some authors [25] have already discussed the limitations of pudendal SEPs, showing that sometimes in pathological conditions penile/clitoral SEPs are normal. Pudendal SEPs are considered to be useful in diagnosing impotence associated with spinal cord injury [31] and diabetic neuropathy [32], while in case of primary erectile dysfunction, their utility is debated [33].

3.3.4 Motor-Evoked Potential (MEP)

Conventional electrophysiological methods that activate the descending corticomotoneuronal pathways use the electrical and magnetic stimulation technique. However, transcranial magnetic stimulation (TMS) has the advantages of being painless and capable of stimulating also the more deeply situated nervous structures; electrical stimulation is therefore mainly reserved for intraoperative monitoring. TMS has been commonly used to assess the central and peripheral conduction time to skeletal muscles of the upper and lower limbs and to evaluate the integrity and function of the corticospinal pathways [34, 35]. TMS is also applied to study the corticospinal pathway to the pelvic floor muscles, including EAS, which is the most common target muscle from which MEPs are recorded [36, 37], and EUS and PRM, whose recordings are poorly reproducible [38]. The intensity of TMS necessary to obtain an EAS MEP is much higher than the intensity to elicit a MEP in the limbs. This fact can be explained by the cortical representation of the anogenital area that is localized deep within the motor strip in the interhemispheric fissure.

This method investigates the motor efferent pathway from the brain and lumbosacral roots to the EAS, allowing to determine the total conduction time and the lumbosacral latency. Cortical magnetic stimulation is usually performed in two conditions: at rest, with EAS relaxed (MEPs mean latency of about 27 ms), and during facilitation (MEPs mean latency of about 23 ms) due to a voluntary mild contraction of pelvic floor and EAS muscles. The magnetic stimulation applied over the lower lumbar spine is known to activate the lumbosacral ventral roots at their exit from the vertebral canal. MEPs from lumbosacral magnetic stimulation are obtained only during rest condition at about 6 ms [37], since facilitation does not modify latencies during peripheral nerve stimulation (Fig. 3.6).

Method: Magnetic shocks are delivered by a magnetic simulator; different shapes of coils exist, each of which produces different magnetic field patterns. The coil produces, normally, a peak magnetic field strength of 1.5 T, being placed flat on the scalp, centered on Cz (10–20 I.E.) to stimulate the motor cortex and on the lumbosacral region (L3–L4 interspace) to stimulate the lumbosacral roots. EMG recordings are taken from EAS using a needle electrode placed approximately 1 cm lateral to the anal orifice. The ground electrode is located around the upper portion of the leg. The different types of MEP abnormalities, i.e., responses with decreased amplitude or delayed latency, may imply axonal or demyelinative impairment underlying the different clinical pathological conditions. Corticospinal abnormalities detected by this method in patients with neurogenic bladder and bowel disorders have been reported [39–41].

3.3.5 Sympathetic Skin Response (SSR)

SSR is a technique that records changes in skin conductance after activation of sweat glands in skin areas rich in eccrine glands (commonly palmar, plantar, saddle sites) under the neural control of sympathetic cholinergic (sudomotor) fibers. SSR is the only neurophysiological technique directly testing sympathetic fibers.

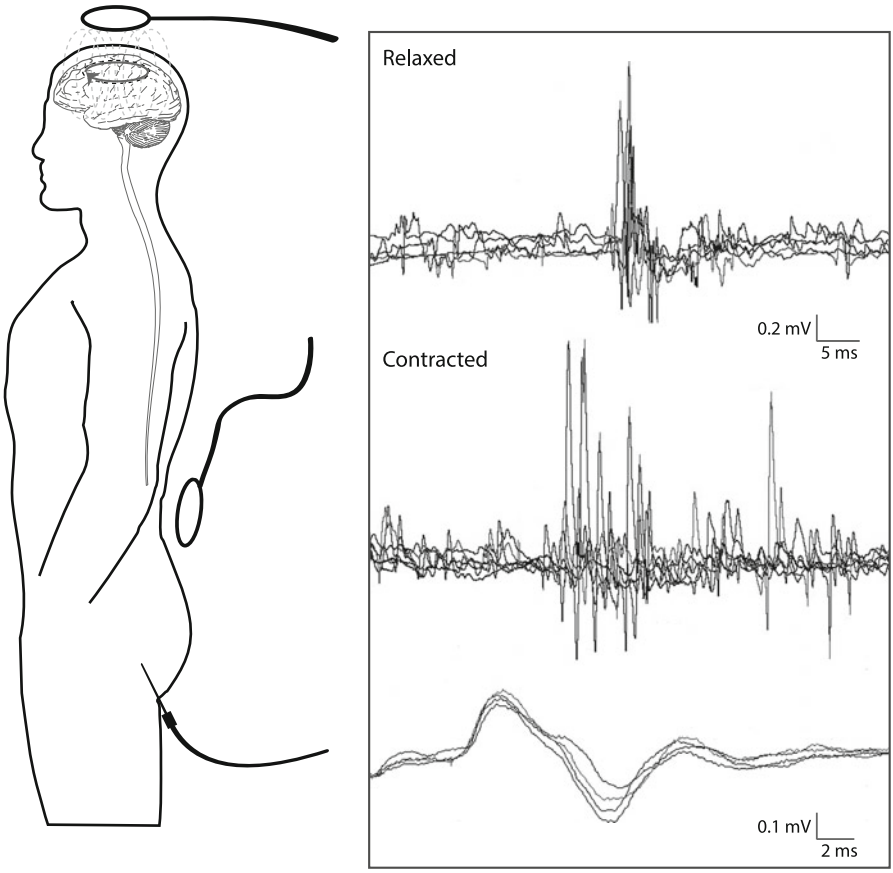

Fig. 3.6 Motor-evoked potentials from EAS after transcranial magnetic stimulation of the motor cortex and after lumbar magnetic stimulation. Upper two traces represent cortical motor superimposed responses at rest and during facilitation, bottom traces show MEPs from EAS muscle after magnetic stimulation applied over the lower lumbar spine

Potentials generated by SSR can be recorded in response to various stimuli; these include electrical peripheral nerve stimulation, acoustic stimuli, and magnetic stimulation of the nerves or brain, although magnetic stimulation lacks specificity in terms of sensory pathways involved [42, 43]. SSR is dependent on integrity of peripheral sympathetic cholinergic pathways, as it is preserved in selective sympathetic adrenergic failure, and it is absent in pure autonomic failure (PAF) (with sympathetic adrenergic and cholinergic failure) and in pure cholinergic dysautonomia. Different areas in cerebral cortex and in the brainstem have been proposed as generator sites for the sensory signals of the SSR [44].

Method: SSRs are recorded from palmar, plantar, and saddle surfaces, both left and right, using surface electrodes. Electrodes are placed on the volar site and on the corresponding area of the dorsal aspect of the hand or foot. For perineum

recordings, the active electrode is attached to the perineum (below the scrotum) and the reference electrode to the iliac crest with the ground on the leg. This kind of recording from the perineal region increases the diagnostic sensitivity when evaluating sympathetic function within the thoracolumbar spinal cord [45]. Only few studies exist regarding the relationship between bladder dysfunction and SSR anomalies. In particular a lack of SSR in bladder neck dyssynergia and in foot following spinal cord injury has been shown [46].

3.3.6 Pudendal Nerve Terminal Motor Latency (PNTML)

Pudendal nerve inferior rectal branches can be evaluated measuring PNTML, which is the technique most commonly used for assessment in patients with idiopathic neurogenic fecal incontinence [16]. PNTML technique, first described in 1984 by Kiff and Swash, is determined by recording the anal sphincter motor potential evoked by stimulation of the pudendal nerve into the rectum with a special bipolar surface electrode known as St. Mark's electrode. The stimulating electrode is fixed on the tip of a gloved index finger, while the two recording electrodes, which pick up the contraction response of EAS, are placed at the base of the finger. On insertion of the finger into the rectum, an electrical stimulation is given near the ischial spine.

Pudendal nerve is therefore stimulated as it leaves the pelvis, before branching into perineal nerve and inferior rectal nerve, which innervate periurethral striated muscle and anal sphincter respectively.

Mean latencies of the responses from the anal sphincter are 2.1 ± 0.2 ms; however, PNTML using St. Mark's electrode permits to stimulate the terminal pudendal nerve branches only near their motor points, preventing complete evaluation of pudendal nerve (Fig. 3.7). Moreover the recorded response is frequently of low amplitude and impaired by stimulus artifact. The test owes its popularity to different studies showing abnormal latencies in various clinical situations [47–49]. In fact, pudendal neuropathy is seen in up to 70 % of patients with fecal incontinence and in more than 50 % of patients with sphincter injury [50].

However, PNTML clinical value has been questioned, and two consensus statements, uroneurological and gastroenterological, did not propose this test for evaluating patients with bladder and bowel dysfunction [17, 51]. American Gastroenterological Association medical position statement in 1999 concluded that PNTML cannot be recommended for evaluating patients with fecal incontinence because: (a) PNTML has a poor correlation with clinical symptoms and histologic findings, (b) the technique does not discriminate between muscle weakness caused by pudendal nerve injury and muscle injury in patients with fecal incontinence, (c) there is a lack of sensitivity and specificity for detecting EAS weakness, (d) it is considered to be an operator-dependent technique, and (e) the test does not predict surgical outcome [51, 52].

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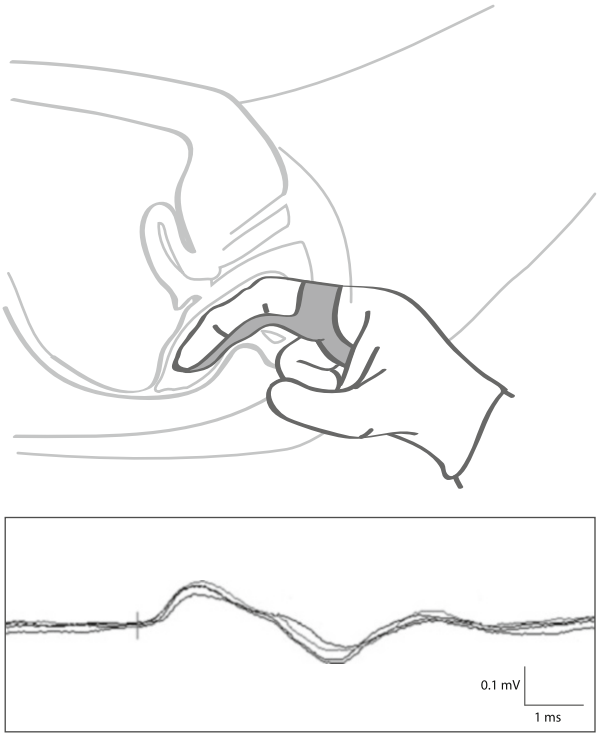

Fig. 3.7 St. Mark's electrode, used to stimulate the pudendal nerve at the level of the ischial spine, transrectally or transvaginally and to record the response at the EAS muscle. Typical pudendal nerve terminal motor latency response in a healthy subject

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Basic Concepts in Electricity and Electrotherapy

4

Jacopo Martellucci

4.1 Introduction

Electrotherapy is the use of electrical energy as a medical treatment. Although electrotherapy has been a component of clinical practice since the early days, its delivery has changed remarkably and continues to do so. The most popular modalities used these days are quite dissimilar to those of 50 or more years ago even if they are based on the same principles. Modern electrotherapy practice needs to be evidence based and used appropriately. Used at the right place and at the right time for the right reason, it has a phenomenal capacity to be effective. Used unwisely, it will either do no good at all or possibly make matters worse, as would be true for any other therapy. The skill of the practitioner using electrotherapy is to make the appropriate clinical decision as to which modality to use and when, and to use the best available evidence when making that decision.

The electrotherapy modalities involve the introduction of some physical energy into a biological system. This energy brings about one or more physiological changes, which are used for therapeutic benefit. Clinically, it is probably more useful to determine first the nature of the problem to be addressed and then establish the physiological changes that need to take place in order to achieve these effects and, lastly, the modality which is most able to bring about the changes in the target concerned [1].

The term "electrotherapy" is generally used in the widest sense. However, some modalities (e.g., ultrasound and laser) do not strictly fall into an "electrotherapy" grouping (they do not deliver an electric current), which is why some authorities prefer the term electrophysical agents [2].

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4.2 Electrotherapeutic Window

It has long been recognized that the amount of a treatment is a critical parameter. This is no less true for electrotherapy than for other interventions. There are literally hundreds of research papers that illustrate that the same modality applied in the same circumstances but at a different dose will produce a different outcome.

For example, an energy delivered at a particular amplitude has a beneficial effect, while the same energy at a lower amplitude may have no demonstrable effect.

Along similar lines, "frequency windows" are also evident. A modality applied at a specific frequency (pulsing regime) might have a measurable benefit, while the same modality applied using a different pulsing profile may not appear to achieve equivalent results.

Electrical stimulation frequency windows have been proposed, and there is clinical and laboratory evidence to suggest that there are frequency-dependent responses in clinical practice. Transcutaneous Electrical Nerve Stimulation (TENS) applied at frequency X appears to have a different outcome to TENS applied at frequency Y in an equivalent patient population. Studies by Sluka et al. [3], Kararmaz et al. [4], and Han et al. [5] are among the numerous studies that have demonstrated frequency-dependent effects of TENS.

Also for sacral nerve modulation, there are several examples of attempts to identify the best therapeutic window using the stimulation parameters [6–9].

It can be suggested that if the right amplitude and the right frequency are applied at the same time, then the maximally beneficial effect will be achieved. Unfortunately, there are clearly more ways to get this combination "wrong" than "right." A modality applied at a less than ideal dose will not achieve best results. Again, this does not mean that the modality is ineffective, but more likely that the ideal window has been missed.

The situation is complicated by the apparent capacity of the windows to "move" with the patient condition. The position of the therapeutic window in the acute scenario appears to be different from the window position for the patient with a chronic version of the same problem. A treatment dose that might be very effective for an acute problem may fail to be beneficial with a chronic presentation.

Moreover, many other parameters need to be considered, such as the treatment characteristics (number of sessions, treatment intervals, energy, and time of exposure) or the patient's features (age, sex, comorbidities).

In conclusion, despite the general rules, the best therapeutic outcome can be achieved only by selecting the best possible stimulation parameters individualized to each patient.

Moreover, when applying electromodalities to patients, it is essential to respect the electrical nature of the human body.

4.3 The Bioelectric Body and the Bioelectric Cell

The electrical activity of the body has been used for a long time for both diagnostic and monitoring purposes in medicine, largely in connection with the "excitable" tissues. Examples include ECG, EMG, and EEG. More recent developments have begun to look at the tissues which were not regarded as excitable, but in which

endogenous electrical activity has been demonstrated. The endogenous electrical activity of the body arises from a variety of sources, some of which are well documented, while others remain more obscure in their origins and control mechanisms. The relationship between endogenous electrical activity (not exclusively potentials), injury, and healing has been researched in several areas of clinical practice and has been well documented in several publications [10].

Every living cell has a membrane potential, with the inside of the cell being negative relative to its external surface. Typically, the resting membrane potential of a healthy cell will be −60 to −80 mV, and during an action potential, the membrane potential might reach +40 mV. Relatively to the size of the cell, the membrane potential is massive. The membrane is on average 7–10 nm thick. The equivalent voltage is somewhere in the order of ten million volts per meter.

The cell membrane potential is strongly linked to the cell membrane transport mechanisms, and much of the material that passes across the membrane is ionic (charged particles); thus, if the movement of charged particles changes, then it will influence the membrane potential. Conversely, if the membrane potential changes, it will influence the movement of ions.

Membrane currents are the result of opening ion selective channels which causes ions to flow across cell membranes. This flow is spontaneous because all ion types are distributed unevenly between cellular and extracellular compartments. In general, cells contain high loads of K+, but low Na+ and Ca++ ions, while extracellular fluids contain high Na+ and Ca++ ions, but low K+ concentrations. When channels are activated, ions will always start diffusing through the pores in either direction, although more ions will flow from the high to the low concentration. This ion diffusion is an important part of bioelectricity maintaining resting potentials and generating action potentials. It is also used to couple the transport of secondary solutes that can be upconcentrated inside or outside according to metabolic needs. Finally, ATP-hydrolyzing pumps reverse the flow of ions regenerating the gradients dissipated by the activity of channels and secondary transporters.

Different cells and tissues respond preferentially to different types of energy and at different doses.

Given the natural energy systems of the living cell, there are two approaches to the application of electrotherapy modalities. First, one can deliver sufficient energy to overcome the energy of the membrane and thereby force it to change behavior. Second, one can deliver much smaller energy levels, and instead of forcing the membrane to change behavior, it can be just stimulated. Low-energy membrane stimulation produces membrane excitement, and membrane excitement produces cellular excitement (upregulation).

Electrical potentials exist across the membranes of virtually all cells of the body. In addition, some cells, such as nerve and muscle cells, are capable of generating rapidly changing electrochemical impulses at their membranes, and these impulses are used to transmit signals along the nerve or muscle membranes. In still other types of cells, such as glandular cells, macrophages, and ciliated cells, local changes in membrane potentials also activate many of the cells' functions.

The resting membrane potential of large nerve fibers when not transmitting nerve signals is about −90 mV.

Nerve signals are transmitted by action potentials, which are rapid changes in the membrane potential that spread rapidly along the nerve fiber membrane. Each action potential begins with a sudden change from the normal resting negative membrane potential to a positive potential and then ends with an almost equally rapid change back to the negative potential. To conduct a nerve signal, the action potential moves along the nerve fiber until it comes to the fiber's end.

An excitable membrane has no single direction of propagation, but the action potential travels in all directions away from the stimulus, even along all branches of a nerve fiber, until the entire membrane has become depolarized.

The large fibers are myelinated, and the small ones are unmyelinated. The average nerve trunk contains about twice as many unmyelinated fibers as myelinated fibers.

The central core of the fiber is the axon, and the membrane of the axon is the membrane that conducts the action potential. Surrounding the axon is a myelin sheath (Schwann cell rotates around the axon many times, laying down multiple layers of Schwann cell membrane containing the lipid substance sphingomyelin, which is an excellent electrical insulator that decreases ion flow through the membrane about 5,000-fold) that is often much thicker than the axon itself. About once every 1–3 mm along the length of the myelin sheath is a node of Ranvier, a small uninsulated area only 2–3 μm in length where ions still can flow with ease through the axon membrane between the extracellular fluid and the intracellular fluid inside the axon.

Even though almost no ions can flow through the thick myelin sheaths of myelinated nerves, they can flow with ease through the nodes of Ranvier. Therefore, action potentials occur only at the nodes (saltatory conduction).

A new action potential cannot occur in an excitable fiber as long as the membrane is still depolarized from the preceding action potential (refractory period).

Some signals need to be transmitted to or from the central nervous system extremely rapidly; otherwise, the information would be useless. An example of this is the sensory signals that apprise the brain of the momentary positions of the legs at each fraction of a second during running. At the other extreme, some types of sensory information, such as that depicting prolonged, aching pain, do not need to be transmitted rapidly, so that slowly conducting fibers will suffice.

A fibers are myelinated afferent or efferent fibers of the somatic nervous system having a diameter of 1–22 μm and a conduction velocity of 5–120 m per second. They include the alpha, beta, delta, and gamma fibers. Alpha fibers are motor and proprioceptive fibers, having conduction velocities of 70–120 m/s and ranging from 13 to 22 μm in diameter. Beta fibers are motor and proprioceptive fibers, having conduction velocities of 30–70 m/s and ranging from 8 to 13 μm in diameter. Gamma fibers conduct at velocities of 15–40 m/s and range from 3 to 7 μm in diameter, comprising the fusimotor fibers. Delta fibers are sensory and nociceptor fibers and conduct at velocities of 2–30 m/s and range from 2 to 5 μm in diameter.

B fibers are myelinated preganglionic autonomic axons having a fiber diameter of ≤ 3 μm and a conduction velocity of 3–15 m/s. They are both afferent and efferent and are mainly associated with visceral innervation.

C fibers are unmyelinated postganglionic fibers of the autonomic nervous system, at the dorsal roots and at free nerve endings, having a conduction velocity of 0.6–2.3 m/s and a diameter of 0.3–1.3 μm, that conduct impulses of prolonged, burning pain sensation from the viscera and periphery.

Basically, any factor that causes sodium ions to begin to diffuse inward through the membrane in sufficient numbers can set off automatic regenerative opening of the sodium channels. This can result from mechanical disturbance of the membrane, chemical effects on the membrane, or passage of electricity through the membrane. All these are used at different points in the body to elicit nerve or muscle action potentials: mechanical pressure to excite sensory nerve endings in the skin, chemical neurotransmitters to transmit signals from one neuron to the next in the brain, and electrical current to transmit signals between successive muscle cells in the heart and intestine.

When excitatory synapses are repetitively stimulated at a rapid rate, the number of discharges by the postsynaptic neuron is at first very great, but the firing rate becomes progressively less in succeeding milliseconds or seconds. This is called fatigue of synaptic transmission. Fatigue is an exceedingly important characteristic of synaptic function because when areas of the nervous system become overexcited, fatigue causes them to lose this excess excitability after a while [11].

4.4 Fundamental Concepts of Electricity

4.4.1 Electric Charge

In order for electricity to exist, there must be a source of electric charge. There are two types of charges, called positive and negative.

Ancient cultures around the Mediterranean knew that certain objects, such as rods of amber, could be rubbed with cat's fur to attract light objects like feathers. Thales of Miletos made a series of observations on static electricity around 600 BC, from which he believed that friction rendered amber magnetic, in contrast to minerals such as magnetite, which needed no rubbing.

Some further experimenters speculated that invisible "fluids" were being transferred from one object to another during the process of rubbing and that these "fluids" were able to effect a physical force over a distance. Charles Dufay was one of the early experimenters who demonstrated that there were definitely two different types of changes wrought by rubbing certain pairs of objects together. The fact that there was more than one type of change manifested in these materials was evident by the fact that there were two types of forces produced: *attraction* and *repulsion*.

The hypothetical fluid transfer became known as a *charge*.

Benjamin Franklin came to the conclusion that there was only one fluid exchanged between rubbed objects and that the two different "charges" were nothing more than either an excess or a deficiency of that one fluid.

Following Franklin's speculation of the wool rubbing something off of the wax, the type of charge that was associated with rubbed wax became known as

"negative" (because it was supposed to have a deficiency of fluid), while the type of charge associated with the rubbing wool became known as "positive" (because it was supposed to have an excess of fluid). Precise measurements of electrical charge were carried out by the French physicist Charles Coulomb in the 1780s using a device called a *torsional balance* measuring the force generated between two electrically charged objects. The results of Coulomb's work led to the development of a unit of electrical charge named in his honor, the *coulomb* (C).

The coulomb is defined as the quantity of charge that has passed through the cross section of an electrical conductor carrying one ampere within one second.

It was discovered much later that this "fluid" was actually composed of extremely small bits of matter called *electrons* (J. J. Thomson, 1897), so named in honor of the ancient Greek word for amber. Experimentation has since revealed that all objects are composed of *atoms* and that these atoms are in turn composed of smaller components known as *particles*. The three fundamental particles comprising most atoms are called *protons*, *neutrons*, and *electrons*.

The tight binding of protons in the nucleus is responsible for the stable identity of chemical elements and the failure of alchemists to achieve their dream of creating gold from other minerals.

Neutrons are much less influential on the chemical character and identity of an atom than protons, although they are just as hard to add to or remove from the nucleus, being so tightly bound. If neutrons are added or gained, the atom will still retain the same chemical identity, but its mass will change slightly and it may acquire strange *nuclear* properties such as radioactivity.

However, electrons have significantly more freedom to move around in an atom than either protons or neutrons. In fact, they can be knocked out of their respective positions (even leaving the atom) by far less energy than what it takes to dislodge particles in the nucleus. If this happens, the atom still retains its chemical identity, but an important imbalance occurs. Electrons and protons are unique in the fact that they are attracted to one another over a distance. It is this attraction over distance which causes the attraction between rubbed objects, where electrons are moved away from their original atoms to reside around atoms of another object.

Electrons tend to repel other electrons over a distance, as do protons with other protons. Because of this attraction/repulsion behavior between individual particles, electrons and protons are said to have opposite electric charges. Each electron has a negative charge and each proton a positive charge. In equal numbers within an atom, they counteract each other's presence so that the net charge within the atom is zero.

An excess or a deficiency of electrons on an object gives that object a static electric charge, also called electrostatic charge. If an object contains more number of total electrons than the total protons, then that object is said to be negatively charged. If an object contains a fewer number of total electrons than the total protons, then that object is positively charged.

So "charge" is the technical term used to indicate that an object has been prepared so as to participate in electrical forces.

An electric field is a field around charged particles and changing magnetic fields which exerts a force on charges within the field. All charged objects create an

electric field that extends outward into the space that surrounds it. The charge alters that space, causing any other charged object that enters the space to be affected by this field. The strength of the electric field is dependent upon how charged the object creating the field is and upon the distance of separation from the charged object.

4.4.2 Conductors and Insulators

The electrons of different types of atoms have different degrees of freedom to move around. With some types of materials, such as metals, the outermost electrons in the atoms are so loosely bound that they chaotically move in the space between the atoms of that material by nothing more than the influence of room-temperature heat energy. Because these virtually unbound electrons are free to leave their respective atoms and float around in the space between adjacent atoms, they are often called *free electrons*. Charged particles, such as electrons in metals or ions in solution, will tend to move or change position as a result of their interaction with other charged particles. In other words, charged particles will tend to move in matter when electrical potential differences exist.

This relative mobility within a material is known as electric *conductivity*. Conductivity is determined by the types of atoms in a material (the number of protons in each atom's nucleus, determining its chemical identity) and how the atoms are linked together with one another. Materials with high electron mobility (many free electrons), in which charged particles readily move when placed in an electric field, are called *conductors*, while materials with low electron mobility (few or no free electrons), which do not tend to allow free movement of ions or electrons, are called *insulators*.

Metals such as copper, silver, or gold are good conductors; rubber, glass, porcelain and many plastics are good insulators.

The atoms of metals tend to give up electrons from their outer orbital shell quite readily when placed in an electric field. If a negatively charged substance is brought near one end of a long metal wire, electrons closest to the substance will be displaced along the wire away from the mass of similar charge.

Biological tissues contain charged particles in solution in the form of ions such as sodium (Na+), potassium (K+), calcium (Ca++), or chloride (Cl–). Human tissues are conductors because the ions there are free to move in aqueous body fluids when exposed to electromotive forces. The ability of ions to move in human tissues varies from tissue to tissue. Muscle and nerves are good conductors, whereas skin and fat are poor conductors.

4.4.3 Electrical Current: Ampere and Voltage

The properties of electric charges in motion are more important to the understanding of therapeutic electrical stimulation than are properties of charges at rest. The movement of charged particles through a conductor in response to an applied

electric field is called *current*. The conduction of electrical charge through matter from one point to another is the transfer of energy that brings about physiological change during the clinical application of electrical stimulation. Producing electrical current requires the presence of freely movable charged particles in some substance and the application of a driving force to move the particles. In metal circuits, electrons are the movable charged particles, whereas in biological systems, ions in body fluids (electrolytic solutions) are the charged particles. The forces that induce current in biological fields are the applied voltages. The magnitude of current induced in a conductive medium is directly proportional to the magnitude to the applied voltage.

Current is defined as the amount of charge moving past a plane in the conductor per unit of time.

The standard unit of measurement for current is the ampere (A). One ampere is equal to the movement of 1 C of charge past a point in a second. The current used in electrotherapeutic application is often very small and is generally measured in milliamperes (mA: 10^{-3}A) or in microamperes (μA: 10^{-6}A).

Electrons in a conductor can flow only if the electric charge at the extremities of the conductor differs, that is, when there is a potential difference between the two ends. When the charge builds up, with positive polarity (shortage of electrons) in one place and negative polarity (excess of electrons) in another place, a powerful electromotive force exists. The difference can also be provided by a buildup of electrostatic charges, as in the case of a lightning stroke. This force, also known as voltage or electrical potential, is expressed in volts (V). Without the presence of a voltage between the two extremities of a conductor, there can be no flow of electrons. Under this condition, current flow is equal to zero.

Current has a direction, and the direction could be defined as either the net rate of flow of negative charges or the net rate of flow of positive charges. The arbitrary convention is that current is the net rate of flow of positive charges. This convention is why diagrams are drawn showing current flowing from positive (+) leads to negative (−) leads.

4.4.4 Resistance and Conductance

The magnitude of charge flow is determined not only by the size of the driving force (voltage) but also by the relative ease with which electron or ions are allowed to move through the conductors.

The property of a conductor to oppose to movement of charged particles is called resistance (R), and, conversely, the property to ease the charged particles' movement in a medium is called conductance (G).

The standard unit of resistance is the ohm (Ω), and the magnitude of the current induced in a conductor is inversely proportional to the resistance of the conductor.

The standard unit of conductance is the siemens (S).

The relationship between voltage and resistance that determines the magnitude of current (I) is expressed in Ohm's law:

$$I = V / R \text{ or } V = I \times R$$

Ohm's law simply states that the current induced in a conductor increases as the applied driving force (V) is increased or as the opposition to charge movement (R) is decreased.

Alternatively, Ohm's law may be expressed in terms of conductance (G) rather than resistance:

$$I = V \times G \text{ or } V = I / G$$

4.4.5 Capacitance and Impedance

In order to understand current in biological tissues, two other electrical concepts must also be introduced. Capacitance is the property of a system of conductors and insulators that allows the system to store charge. Currents produced in biological tissues are influenced not only by tissue resistance but also by tissue capacitance.

The capacitance is expressed in farads (F); 1 F is the magnitude of capacitance as 1 C of charge is stored when 1 V of potential difference is applied.

The term impedance (Z) describes the opposition to alternating currents, analogous to the way resistance describes the opposition to direct currents, that a system presents when a voltage is applied. Alternating current could be defined as a continuous or uninterrupted bidirectional flow of charged particles.

Impedance takes into account both the capacitive and resistive opposition to the movement of charged particles. When dealing with clinical electrical stimulation, it is more appropriate to express the opposition to current in terms of impedance, because human tissues are better modeled as complex resistor and capacitor networks.

Because impedance depends on the capacitive nature of biological tissues, its magnitude depends on the frequency of applied stimulation. In general, the higher the frequency of stimulation, the lower the impedance of tissues. The standard unit of impedance is the ohm.

4.5 Intuitive Approach to Electric Parameters

The concepts of voltage, current, and impedance are easily related to more intuitive parameters, allowing basic understanding to grow from a conceptual basis as well as from quantitative analysis.

Mechanical systems, fluid flow, heat transfer, and electric systems are all described by the same differential equations. To understand any one of these processes is equivalent to understanding them all. The only difference is the parameters. Substituting voltage for pressure and electric current for fluid flow allows an electric engineer to work in fluid mechanics [12].

Voltage is a measure of electric potential energy just as height is a measure of gravitational potential energy in the approximately constant gravitational field near the earth's surface. The gravitational potential energy of an apple is realized when it drops from the tree. The apple's velocity, when it hits your head, depends on the difference between the original height of the apple and the height of your head. Both height and voltage are measured as a difference between two locations, rather than as absolute numbers.

Current is a measure of flow. A river current corresponds to the volume of water that flows in some amount of time (e.g., liters per second). The current is determined by the steepness of the river grade (voltage) and the friction of the water and riverbed (resistance). A wide river flowing from a steep mountain passes huge amounts of water, just as a small resistor and a large voltage results in a huge electric current.

The electrons in a conductor that are free to move are also analogous to water in a long, straight, horizontally positioned pipe. The water has the capability of flowing through the pipe, but it will only dribble out the ends as long as the pipe is exactly level. Only when one end of the pipe is raised above the other end will a flow occur.

For direct currents (DCs), impedance is the same as resistance and simply corresponds to friction in a mechanical system. When alternating currents (ACs) are used, however, some of the energy from one cycle can be stored for use in later cycles. This concept of energy storage forms the basis of capacitance and impedance. A classic example of capacitance/impedance could be considered the Newton's cradle. If one ball is pulled away and is let to fall, it strikes the first ball in the series and comes to nearly a dead stop. The ball on the opposite side acquires most of the velocity and almost instantly swings in an arc almost as high as the release height of the last ball. This shows that the final ball receives most of the energy and momentum that was in the first ball, with the results of bouncing forever. In this system, friction is virtually eliminated. This is impedance without resistance. Energy is simply shifted back and forth between the first and the last ball. If friction is introduced, then energy is dissipated as heat and, over time, the bouncing subsides.

In complete analogy to the electrical impedance could be defined the acoustic impedance, a complex number which describes how a medium absorbs sound by relating the amplitude and phase of an applied sound pressure to the amplitude and phase of the resulting sound flux.

4.6 Stimulation Parameters

4.6.1 Frequency

Frequency is the number of occurrences of a repeating event per unit time. The standard international unit for frequency is the hertz (Hz), named after the German physicist Heinrich Hertz; 1 Hz means that an event repeats once per second.

Electrical frequency refers to the pulses produced per second during stimulation (e.g., 40 Hz = 40 pulses per second).

Nerve activation in applications for functional electrical stimulation is usually restricted to frequencies below 50 Hz. It has been suggested that frequencies above 50 Hz may predispose to nerve damage with continuous stimulation [13]. Frequencies above 100 Hz have been defined as high frequency and such frequencies have often been reported to result in the failure of evoked neural responses [14, 15]. The blocking effects of high-frequency alternating current (HFAC) waveforms have been variously reported since 1939 [16]. Bowman and McNeal evaluated the effect of voltage-controlled biphasic rectangular pulses between 100 Hz and 10 kHz and achieved a nerve conduction block above 4 kHz [17]. Stimuli at 300 Hz applied to the pudendal nerves have been reported to show a pressure reduction of the urethral sphincter by 30–45 % [18]. Li et al. have used 200–300 Hz stimuli to cause sphincter fatigue prior to evoked voiding and suggested that the optimal parameters to induce sphincter fatigue were 3 V, 100–500 Hz, and 100 microseconds for 15–20 s [19, 20]. Applied frequencies of 600 Hz have been claimed to produce a conduction-type block [21]. Tai et al. have shown that in the pudendal nerve, isolated from the spinal cord, evoked responses could be blocked with HFAC above 7 kHz [22].

The changes in anal pressure could be obtained without fatigue at stimulation frequencies of 10–20 Hz [23].

The effect of sacral nerve stimulation on bladder function has been suggested to be dependent on stimulation frequency, with bladder excitation dominating at frequencies of 2–5 Hz and bladder inhibition dominating at 10 Hz [24].

Low-frequency TENS stimulation induces the selective release of endorphins in the central nervous system [25].

4.6.2 Pulse Width

Electrical stimulation devices deliver pulses in waveform patterns that are often represented by geometric shapes such as square, peaked, or sine wave. These shapes characterize electrical current that rises above a zero baseline for the extent of the stimulation paradigm (uniphasic; e.g., direct current) or current that alternates above and below the baseline (biphasic or alternating current) [26]. The time span of a single pulse is known as the pulse width or pulse duration, so the pulse width is how wide each pulse is. It is measured in microseconds. Generally speaking, the higher the pulse width, the more "aggressive" the stimulation feels.

Dudding and colleagues, which examined changes in rectal compliance following acute changes in stimulation parameters, observed an increase in rectal compliance when the pulse width was decreased to 90 μs or the frequency increased to 31 Hz, from the conventional SNS settings of 14 Hz and 210 μs [27].

Dinning and colleagues [28] found no differences between stimulation with a pulse width of 300 and 400 μs about colonic motor responses.

Alteration of amplitude, pulse width, and frequency will have different effects on different fiber types depending on their diameter and the presence or absence of

myelination. Pulses of short duration will tend to excite large axons with fewer small fibers recruited [29].

The pulse width on TENS devices usually range from 1 to 250 μs. Walsh and colleagues [30] showed that TENS delivered at a frequency of 110 Hz and pulse width of 200 μs could better mediate hypoalgesia by increasing both peripheral nerve conduction latency and mechanical pain threshold compared to lower a frequency (4 Hz) and a shorter pulse width (110 μs).

4.6.3 Amplitude

Amplitude is sometimes called magnitude, level, or intensity and refers to the width of the electric wave. Depending on the quantity being measured, the magnitude of an ac wave might be given in amperes (for current), volts (for voltage), or watts (for power).

The peak amplitude of an AC wave is the maximum extent, either positive or negative, that the instantaneous amplitude attains. In many waves, the positive- and negative-peak amplitudes are the same. The peak-to-peak (pk-pk) amplitude of a wave is the net difference between the positive-peak amplitude and the negative-peak amplitude.

To simplify this, the amplitude is what you feel when you "turn the unit up." It is what causes the "buzzing" sensation of the stimulation to go higher or lower.

The higher the intensity, the stronger the depolarizing effect in the structures underlying the electrodes [31].

Intensity will also factor into patient comfort with higher intensities being typically less tolerated. For this reason, it is usually set at the patient threshold.

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Acupuncture for Pelvic Floor Disorders

5

Marco Scaglia, Mattia Tullio, Ines Destefano, and Leif Hultén

5.1 Acupuncture: A Traditional Technique Moving from Empiricism to a Modern Era

Acupuncture is a traditional Chinese method of medical treatment involving the insertion of fine, single-use, sterile needles in acupoints according to a system of channels and meridians that was developed by early practitioners of *traditional Chinese medicine* (TCM) over 2,000 years ago [1].

The needles are stimulated by manipulation, electrical stimulation, or heat [2]. The general theory of acupuncture is based on the premise that there are patterns of energy flow (Qi) through the body that are essential for health. Disruptions of this flow are believed to be responsible for disease. Acupuncture may correct imbalances of flow at identifiable points close to the skin. There is a considerable body of international literature on the risks and benefits of acupuncture, and the World Health Organization lists a variety of medical conditions that may benefit from the use of acupuncture or moxibustion [1].

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Acupuncture with an empirical basis has been used in the treatment and prevention of disease for centuries. A lack of scientific studies to prove or disprove its claimed effects led to rejection by many of the Western scientific community. For a long time, acupuncture was not accepted by physicians in the Western world, in part due to the mysterious and unexplainable mechanisms of traditional Chinese acupuncture. Through pioneering work to clarify the neurophysiological mechanism of acupuncture, the technology became scientifically approved, and it has been considered on par with other medical treatments in many healthcare systems [3].

In addition to a variety of disorders, acupuncture has been shown to be effective for management of bladder disturbances and even for treatment of irritable bowel and fecal incontinence.

Now that the mechanisms and functional background of the acupuncture effects on disease and pathological conditions can be partly explained in terms of endogenous facilitating and/or inhibitory systems, the integration of acupuncture with conventional medicine has become possible. Its use for pain relief has been supported by clinical trials, and this has facilitated its acceptance in pain clinics in most countries. Acupuncture effects must devolve from physiological and/or psychological mechanisms with biological foundations, and needle stimulation could represent the artificial activation of systems obtained by natural biological effects in functional situations. Acupuncture and some other forms of sensory stimulation elicit similar effects in man and other mammals, suggesting that they bring about fundamental physiological changes. Acupuncture excites receptors or nerve fibers in the stimulated tissue which are also physiologically activated by strong muscle contractions, and the effects on certain organ functions are similar to those obtained by protracted exercise. Both exercise and acupuncture produce rhythmic discharges in nerve fibers and cause the release of endogenous opioids and oxytocin essential to the induction of functional changes in different organ systems. Experimental and clinical evidence suggest that acupuncture may affect the sympathetic system via mechanisms at the hypothalamic and brainstem levels and that the hypothalamic beta-endorphinergic system has inhibitory effects on the vasomotor center. Post-stimulatory sympathetic inhibition reaches its maximum after a few hours and can sometimes be sustained for a considerable time after cessation of stimulation, as demonstrated in both man and animals. Experimental and clinical studies suggest that afferent input in somatic nerve fibers has a significant effect on autonomic functions.

5.2 Acupuncture in Functional Gastrointestinal Disorders

The prevalence of one or more functional *gastrointestinal disorders* is estimated to be as high as 70 % in general population using Rome diagnostic criteria. Since functional gastrointestinal disorders are diagnosed based on symptoms and the exact etiologies for most of functional gastrointestinal disorders are not completely known, the treatment for these disorders is often unsatisfactory, and alternative therapies become attractive to both patients and practitioners. During the last decades, a considerable number of studies focused on acupuncture as treatment of functional gastrointestinal disorders and its underlying mechanisms.

Table 5.1 Cleveland clinic continence score

Type of incontinence	Never	Rarely	Sometimes	Usually	Always
Solid stools	0	1	2	3	4
Liquid stools	0	1	2	3	4
Gas	0	1	2	3	4
Wears pad	0	1	2	3	4
Altered lifestyle	0	1	2	3	4

The sum of continence defects may be interpreted as follows: IC 0 = perfect continence, IC 1–7 = good continence, IC 8–14 = moderate incontinence, IC 15–20 = severe incontinence

Human and animal studies were conducted to explore the effects of acupuncture on gastrointestinal secretion, sensation, motility, and myoelectrical activity.

In the following paragraphs we will narrow our interest on functional gastrointestinal disorders and pelvic floor dysfunctions. There are very few studies on acupuncture and fecal incontinence, more on constipation and irritable bowel syndrome. We will describe the studies and the unpublished experience performed by our group on this subject during the last decade.

Traditionally, symptoms of *fecal incontinence* are thought of as an imbalance in the circulation of the kidney meridian; this, translated for the Western culture, corresponds to a deficit in the kidney and adrenal function (in the ancient time they could not differentiate between the adrenal gland and the kidney). Therefore, the aim of treatment with acupuncture is to balance the corticosteroid output in order to relieve the patient from fecal incontinence. While for decades surgeons only aimed at reinforcing or substituting the sphincter function, the use of acupuncture focused on increasing the sphincter function as well as regularizing the bowel function and restoring the autonomic nervous control of the pelvic floor.

We conducted a study [4] on 15 female patients, mean age 60 years. The defects of anal continence were assessed before the treatment and at regular intervals after the acupuncture sessions (Table 5.1). Anorectal function was determined through anorectal manometry. Each patient received one acupuncture treatment per week for a 10-week period. Subsequently, a control session was repeated once per month up to 7 months for six patients. The final functional assessment was performed at 18 months.

Dr. Scaglia, who is well trained in the procedure, performed the acupuncture.

The sterile and disposable acupuncture needles were 40 mm long and 0.3 mm in diameter and had stainless wire at the tip and copper wire at the handle. After insertion in the acupoint, the needles were gently stimulated by rotation and then left in place for 20 min.

During the trial the selection and localization of these points were mainly based on traditional Chinese medicine (TCM), and the following points were used: RM 3 (Zhong ji) and RM 6 (Qi Hai), both located at the midline of the lower abdomen; DM 4 (Ming Men) and BL 23 (Shen Shu) in the lumbar region; BL 32 (Ci Liao) in the 2nd sacral foramen; LI 4 (He Gu) in the hand between the first and second metacarpal bones; ST 36 (Zu San Li) at outer side of the leg below the knee; and K (Tai Xi) at the inner side of the ankle.

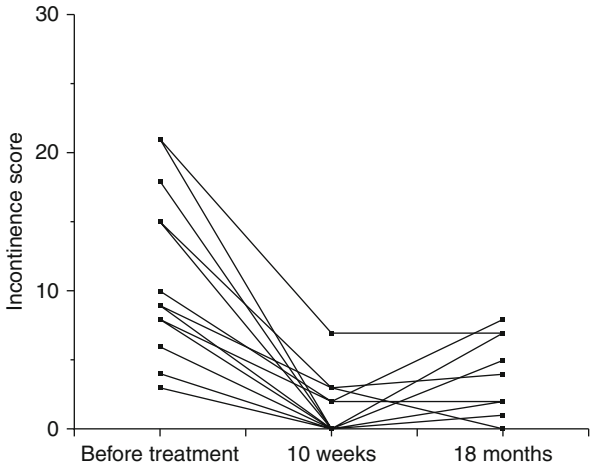

Fig. 5.1 Individual fecal incontinence score before and at intervals after acupuncture sessions

The results were presented as a median and interquartile range. Data was analyzed with Student-Fisher t-test ($p<0.05$).

The overall mean continence score of all patients changed from 10 (3–21) estimated before treatment to zero (0–7) ($p<0.05$) at 10 weeks, reflecting a significant improvement in continence. The continence index available in 14 patients at 18 months from the start of the treatment was 1 (0–8) ($p<0.05$) (Fig. 5.1).

Before acupuncture fecal incontinence occurred in nine of the 15 patients, with a mean incontinence score of 17 (9–18). After 10 weeks of treatment, these showed a significant improvement, with a median score of 0 (0–3), and when assessed at a later stage (18 months), they still scored favorably, with a median score of 1 (0–6).

The six patients who did not have fecal incontinence before the treatment had less severe incontinence (flatus and/or soiling), with a mean score of 4 (3–5) before starting the sessions. At 10 weeks these improved considerably, as reflected in the mean score of 0 (0–0).

The improvement – observed after the third acupuncture treatment – remained persistent for a long time after cessation of treatment in some patients.

Sporadic episodes of soiling were observed, mainly associated with irregularity in bowel movements, in patients regularly checked for a 7-month period after the completion of acupuncture.

As shown in Fig. 5.2, the majority of patients that suffered irregularity in bowel habits when entering the study improved significantly at 10 weeks and quite a few experienced a prolonged favorable state even at longer follow-ups. At 18 months bowel habits still remained regular in eight out of 14 patients, and 12 had firm stools.

At 10 weeks after acupuncture, resting *anal pressure* had increased from 25 (17–35) mmHg to 36 (20–42) mmHg ($p=0.05$). While maximal sphincter squeeze pressure remained uninfluenced, the ability to sustain the squeeze pressure increased from 41 (32–68) mmHg to 60 (40–100) mmHg ($p<0.05$). Prior to the acupuncture sessions, the sensation of *rectal filling* was absent or blunt in six patients, and the defecation urge sensation was blunt or absent in two patients. These defects in rectal

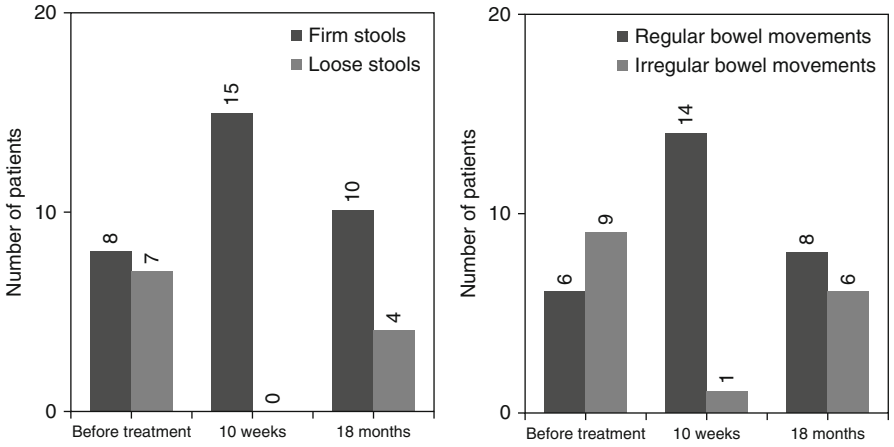

Fig. 5.2 Bowel habits (*left panel*) and stool consistency (*right panel*) before and after acupuncture

Table 5.2 Manometric results

	Pre-	Post (10 weeks)	Post (18 weeks)
Anal pressures (mmHg)			
Resting press	25 (17–35)	36 (20–42)	37 (18–48)
Squeeze	87 (58–117)	87 (55–132)	65 (54–118)
Sustained squeeze (at 15 s)	41 (32–68)	60 (40–100)	45 (30–59)
Rectal sensibility (distension pressure cm H_2O)			
Threshold	15 (10–20)	15 (11–20)	10 (9–15)
Urge	20 (20–25)	20 (20–25)	20 (14–21)
Rectal volume (ml)			
Rectal volume (40 cm H_2O dist press)	348 (340–402)	334 (299–369)	342 (311–358)

$p < 0.05$

sensory function remained unchanged. The average *rectal volume* 348 (340–402) ml also remained unchanged (Table 5.2).

At 18 months resting anal pressure was still well retained, whereas the ability to sustain the anal squeeze had returned to pretreatment levels. Rectal volume and the rectal sensory variables were unchanged.

An important concept in TCM is *point specificity*, which implies that stimulation of some acupoints is effective in treating certain clinical conditions, whereas other acupoints are less/not effective.

A systematic review designed to evaluate whether there are points specific to diseases concluded that approximately half of the trials produced evidence for point specificity and half did not [51].

This raises the interrogative: if point specificity does not exist, can appropriate controls on the inactive acupoints of certain conditions be developed for acupuncture? If rigorous studies that show clear point-specific responses were conducted,

what was the underlying mechanism? In a study examining potential answers to these questions from a pelvic floor perspective, we collected data suggesting that point-specific responses to EA at different points exist. Stimulation of certain points (KI 3, 36 ST, DM 1, RM 1) results in a significant raise in anal pressure and in rectal contraction, while stimulating others (RM 3–6) causes more modest changes or no change at all (BL 32).

The stimulation of somatic nerves that project indirectly to regions of the brain concerned with regulation of sympathetic outflow underlies the capability of certain acupoint to raise the pelvic floor tonus effectively.

During a pilot study, we tried to investigate whether the electrical stimulation of sacral acupoints had any effect on the anorectal motility, recorded simultaneously to the treatment, since manual stimulation of BL 32 alone, located at the level of the second sacral foramen, was not producing any change.

Ten female patients, mean age 59, presenting various fecal continence defects were studied.

Eight acupuncture needles were placed bilaterally at the level of the sacral roots S1, S2, S3, and S4 and connected to an external neurostimulator delivering unipolar monophase rectangular impulses. Each couple of needles was consecutively electrostimulated with an increasing frequency and intensity up to the maximum amplitude the patient can tolerate. A anorectal mano-volumetry assessment was performed before and during the electrostimulation. The stimulation caused a significant rectal relaxation, ranging from 180 (137–231) ml before the experiment to 227 (188–254) ml ($p<0.05$) during stimulation, corresponding to a 25 % increase of rectal volume. No effects were observed in anal resting pressure. When the second sacral root was stimulated, a rectal motility activation could be observed: in basal condition the maximum rectal volume displacement recorded was 5 (4–25) ml and during transcutaneous electrical stimulation at the second sacral foramen was 18 (13–38) ml (p 0.05).

The mechanism of action of electric acupuncture and its effects on the anorectal function remains unknown but could be similar to how sacral nerve stimulation achieves favorable results. The general rectal relaxation induced during the acute electrostimulation, for example, could be due to a parasympathetic effect.

Because the theory behind acupuncture as treatment of incontinence explains that it is intended to tackle the hypothetic subclinical adrenal dysfunction, we performed a pilot study on 12 patients to explore the effects of manual acupuncture on the endocrine function.

We are not the first to investigate this, as a recently published study on the beneficial effects of acupuncture in the irritable bowel syndrome (IBS) shows how the treatment is linked with a detectable change in salivary cortisol [5].

In our pilot study we utilized the same manual acupuncture schema and incontinence scoring system of the study on fecal incontinence previously described.

We observed an improvement in the incontinence mean score, with an initial value of 11.5 (sd 6.8) that significantly decreased to 5.8 (sd 4.9), and a significant reduction of salivary cortisol (h 8) changing from 8.6 (2.2) to 10.9 (5.9) µg/ml (Student t-test $p<0.05$), after 10 sessions of acupuncture.

These results suggest that more than one mechanism might be involved in the beneficial influence of acupuncture.

An analysis of the *urinary 8-isoprostanes* was performed as well; these are specific products of lipid peroxidation, which is a consequence of oxidative stress and peroxynitrate formation, measurable by *enzyme-linked immunosorbent assay* (ELISA). Nitric oxide might influence the internal sphincter function, acting as a neurotransmitter. Although the antioxidant action of acupuncture was never reported in animal studies, this test aims to evaluate the possible anti-inflammatory effect of acupuncture in vivo and its relationship with cortisol levels.

Urinary isoprostane levels lowered from 1.8 (sd 0.6) to 1.5 (0.4); however, these changes were not statistically significant, supposedly due to an inverse relationship between isoprostane and cortisol levels.

Irritable bowel syndrome (IBS) comprises a group of functional bowel disorders in which abdominal discomfort or pain are associated with defecation or a change in bowel habit and with features of disordered defecation. A lowered sensory threshold to rectal distention is a hallmark of IBS patients. The effect of acupuncture on IBS is elusive. In an open-design pilot study, the 101 patients with IBS that received a 4-week course of acupuncture presented an improvement in overall well-being and in bloating but not in abdominal discomfort or defecation frequency. A double-blind trial in patients with IBS showed no significant difference in the improvement of IBS symptoms between acupuncture and sham acupuncture, although the improvement seemed more consistent with acupuncture.

Little effort was made to investigate the efficacy of acupuncture on *constipation*, and there is scarce information in the literature. One study of 17 children with chronic constipation demonstrated that acupuncture gradually increased the plasma opioid level as well as the frequency of bowel movement to a value similar the control during a 10-week treatment period [6]. However, his findings were not confirmed in adult patients with constipation [7].

An acupoint considered very important for the treatment of constipation is Tianshu (ST25) [52]; the effects of manual stimulation were significantly superior to those obtained with medication, increasing the number of patients whose defecation was up to four times per week together with the rise in constipation score and patients' satisfaction. In another study on 100 patients with chronic functional constipation, the total positive results with moxibustion and acupuncture were 74 and 52 %, respectively [53].

The effect of electric acupuncture at "Tianshu" (ST 25) on colonic smooth muscle structure and interstitial nerve plexus was studied in rats with slow transit constipation [54]: the results showed that electrical stimulation of ST 25 improved the slow transit colon inducing structural changes too.

The efficacy of auricular therapy as treatment of constipation [55] was also reviewed, and 29 relevant studies, from 1994 to 2008, were considered. All articles reported positive results, but their findings cannot be generalized because of two significant methodological flaws: the uncertainty in acupoint identification and inconsistent protocols.

Our experience in this regard is summarized in a pilot study on ten patients with *multiple sclerosis* and *bowel dysfunctions* with prevalent constipation and, as a control group, ten patients with functional constipation. We investigated functional scores, quality of life, anorectal manometry scores, and bowel transit time after 2–4 weeks of acupuncture performed twice a week. The results were recapitulated as percentages of patients with up to four defecations per week after acupuncture: 70 % of severe functional constipation and 50 % of multiple sclerosis patients had normal bowel habits at the end of treatment; these results decreased respectively to 40 and 30 % at the 3-month follow-up, suggesting that a maintenance protocol of regular acupuncture session was needed.

5.3 Acupuncture for Urinary Tract Diseases

The use of acupuncture and electric acupuncture in the context of diseases of the urinary system has been and still is the subject of numerous experimental and clinical studies.

The efficacy of traditional Chinese acupuncture for *nocturnal enuresis* (NE) was reported to range from 76 to 98 %. Asian researchers identified the presence of nocturnal detrusor instability in up to one third of all "enuretic" children [56, 57], and NE failed to respond to standard treatment in 44 % of patients [58, 59] (the standard treatments include the bed-wetting alarm, used to facilitate waking up children with monosymptomatic enuresis, and the synthetic antidiuretic hormone that aims to reduce the volume of overnight urine or the antimuscarinic medication and urotherapy). Acupuncture therapy was reported to suppress uninhibited bladder contractions and to significantly improve wetting where there is urodynamic evidence of detrusor over activity.

The acupuncture points used to treat bladder dysfunction were located in areas innervated by spinal sacral segments S2 through S4 and were stated in the treatment protocols. The points BL 23, BL 28, BL 32, RN 3, RN 4, RN 6, and RN 12 were shown to influence the spinal micturition centers and parasympathetic innervation of the urinary tract [60], while the stimulation of scalp acupoints DU 20 and DU 14 modulated brain function via the inner temporal, thalamencephalon and prefrontal cortical systems [61]. The stimulation of the acupoints UB 20, UB 13, SP 6, ST 36, KI 3, and LU 9 was considered to invigorate the spleen, vital energy, and blood, thereby facilitating the normalization of the bladder function. The high concentration of neuroendocrine transmitters and hormones at acupuncture points was released and spread after needling and other stimulation [62, 63]. Functional magnetic resonance imaging (fMRI) and PET scan performed during natural or conventional bladder filling in healthy subjects showed activation of specific brain regions: the pons, midbrain periaqueductal gray, thalamus, hypothalamus, and frontal cortex [64]. During acupuncture at ST 36, fMRI indicated the activation of the hypothalamus and of the bilateral prefrontal cortex [65], suggesting that acupuncture utilized the neural brainstem–thalamus–cortex reticular system. The sustained activation of the hypothalamus was observed, as

well as the increase in concentration of some neurotransmitters, such as 5-HT [65, 66].

Therefore acupuncture may affect micturition or excitation through the descending serotonergic system. Simultaneous *electronencephalography* (EEG) and cystometric monitoring in urethane anesthetized male rats undergoing acupuncture showed that, after acupuncture stimulation on the sacral segment, bladder activity was suppressed in 53 % (36/68) trials and that in 61 % (22/36) of animals this was accompanied by an increased EEG amplitude [67]. A systematic review of both Western and Eastern studies, in which acupuncture was compared to other treatment(s), suggested encouraging results for children with enuresis. However, the quality of the reports limited identification of key parameters [68]. The study of Karaman et al. demonstrated that laser acupuncture therapy was significantly more beneficial compared to placebo in terms of complete dryness, partial improvement, and decrease in the mean number of weekly bed-wetting episodes.

Another use of acupuncture and electric acupuncture can be observed in the treatment of moderate and severe *benign prostatic hyperplasia (BHP)*. The prevalence of BPH is as high as 40 % in men in their 50s and 90 % in men in their 80s [8]. Current treatment options for BPH include watchful waiting, lifestyle modifications, alpha-blockers, 5-alpha-reductase inhibitors, phytochemicals, and BPH-related surgery [9]. Although most of the aforementioned therapies have various documented degrees of effectiveness in the management of BPH, their use is limited to specific patient populations or has side effects that interfere with the patients' quality of life [10].

Acupuncture is a traditional Chinese medicine treatment that has been commonly used in the management of *lower urinary tract symptoms* (LUTS) in China for thousands of years. The effects of acupuncture on LUTS are well documented in Chinese medicine textbooks and are supported by modern research studies too [11–13].

Ricci et al. [14] found that electric acupuncture (EA) had effects in decreasing urinary urgency and the number of voiding times that persisted after transurethral resection of the prostate [15]. found that EA could significantly increase the sphincter closing pressure in women with stress incontinence as compared with placebo, and [16] showed how acupuncture increased bladder capacity in patients with bladder instability. Besides its beneficial influence on urinary storage problems, acupuncture was found effective in the prevention of recurrent lower urinary tract infections in adult women [15, 16], in improving the quality of life of patients with chronic prostatitis [17] and in ameliorating primary monosymptomatic nocturnal enuresis [18]. Wang et al. found that acupuncture at point BL 33 had better effects than terazosin in improving International Prostate Symptom Score (IPSS), postvoid residual urine (PVR), and maximum urinary flow rate (Qmax) in patients diagnosed with mild to moderate BHP [19, 20]. They also found that acupoint EA at BL 33 had better effects on IPSS, but no difference on PVR and Qmax as compared with nonacupoint EA [21].

A particular use of acupuncture has been also experienced in *stroke survivors*. This patient group experiences a high prevalence (44–69 %) of *bladder dysfunction*;

this includes urinary retention, incomplete bladder emptying (IBE), detrusor external sphincter dyssynergia, and bladder hyperactivity [22]. Urinary retention may occur in approximately 29 % of the stroke patients in rehabilitation wards [23]. Catheterization is commonly performed to manage episodes of acute urinary retention in stroke survivors. However, indwelling catheters may affect rehabilitation activity or daily living, lead to urinary infection, and interfere with the reestablishment of a normal voiding pattern [24]. A significantly higher rate of urinary infection is observed in individuals with IBE [25]; thus, indwelling catheters should be removed as soon as possible. The incidence of IBE in stroke patients is initially 56 %, but it decreases to 32 % over time [25]. The use of α-blockers may increase emptying, but side effects such as orthostatic hypotension may affect patient rehabilitation.

Intermittent catheterization is another option for IBE management [26], but this procedure depends on patient ability and family support. Several studies on stroke survivors suggest that acupuncture therapy provides significant benefits for stroke patients [27–32]. Animal experiments demonstrated that EA could improve the bladder emptying function too [33, 34]. Only a few high-quality studies focused on this subject, most reports lack the appropriate inclusion criteria or objective tools to assess the treatment effects of EA. One randomized trial demonstrated that the stimulation of acupuncture points could improve poststroke urinary symptoms, but only moxibustion therapy was mentioned in their study [35].

Yu et al. [36] noted the beneficial effects of EA in stroke survivors with IBE, thereby making EA a potential safe modality with which to improve urinary function.

Acupuncture could improve the voiding function by regulating the peripheral afferent nerve system. The locations of the two acupoints, BL 28 and BL 32, are similarly distributed along the S2–S4 dermatomes. The voiding reflex center lies at the level of S2 to S4. BL 28 and BL 32 were stimulated by acupuncture to directly increase the excitability of the pelvic nerve, which innervates the detrusor muscle. In addition, SP 6 indirectly raises the excitability of the pelvic nerve. The increased detrusor pressure was previously observed after acupuncture treatment in animal experiments. The improvement in voiding function as an effect of acupuncture treatment was proven by clinical studies.

Bladder dysfunction is also a common problem associated with *multiple sclerosis* (MS), affecting up to 80 % of patients [36]. Current drug treatments, e.g., anticholinergics, are only partially effective and have substantial adverse effects [37]. Catheterization, although effective, is at the expense of the quality of life (QoL). The advantage of acupuncture is its safety because side effects rarely occur [38]. Two case reports described MS patients with bladder symptoms who were favorably treated with EA [39]. Furthermore, electrical stimulation of the acupuncture point SP 6, known as percutaneous tibial nerve stimulation (PTNS), was effective with regard to voiding dysfunction and QoL in patients with overactive bladder [40]. After inserting bilaterally two stainless steel needles (0.22 mm × 25 mm, single use), on acupuncture points SP 6 (posterior border of tibia) and SP 4 (medial edge of foot), connected with the EA device (20 Hz, for 30 min once a week for 10 weeks),

SH Tjon Eng Soe, DJ Kopsky et al. hypothesized that EA could provide a useful tool in MS patients with mild bladder dysfunction who do not wish to take medication or are unable to because of side effects [41].

5.4 Acupuncture for Sexual Dysfunction

Premature ejaculation (PE) is the most common male sexual complaint, affecting 20–30 % of all men [42]. Clinicians tend to use definitions of PE as described in one of the major guidelines [43–45]. The large array of definitions can be summarized in three main qualifications: short time interval between penetration and ejaculation, little or no voluntary control of ejaculation, and negative consequences, such as distress [46]. Daily selective serotonin-reuptake inhibitors (SSRIs) are the first choice of treatment in PE; however, this use is off label. Paroxetine, sertraline, and fluoxetine have all been evaluated in patients with PE, and paroxetine was found to have a substantially greater efficiency [47]. Recently, dapoxetine, a new SSRI with a short half-life, has become available in some countries for on-demand treatment of PE [48].

However, only one study has investigated acupuncture for the treatment of PE (Chen) [49]. A randomized controlled trial [50] was performed on ninety patients with PE, in the absence of other sexual diseases. The patients were randomly assigned to the paroxetine (20 mg/day), acupuncture (twice a week for 4 week in acupoints: ST 36, LI 4, KI 3, LR 3, EX-HN 3, CV 3 for 20 min), and placebo (sham acupuncture) groups. The results demonstrated that although less effective than daily intake of paroxetine, acupuncture had a significantly stronger ejaculation-delaying effect than placebo.

5.5 Conclusions

In conclusion acupuncture offers good opportunities for improving fecal incontinence, constipation, and genitourinary dysfunctions. Considering the high hospital costs associated with sacral nerve stimulation, acupuncture might be an alternative. Even if acupuncture requires repeated sessions in order to gain control of the symptoms, many patients would accept this inconvenience once the technique has been clearly explained.

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Electrical Stimulation, Biofeedback, and Other Rehabilitative Techniques

6

Filippo Pucciani

6.1 Fecal Disorder Rehabilitation

The conservative management of defecation disorders in adults is based on education and lifestyle interventions, diet and fluid intake, bowel management, and retraining programs. The rehabilitative treatment of fecal incontinence and obstructed defecation is the first-line therapy in patients who have not responded to simple dietary programs and medication [1, 2]. Anal electric stimulation, biofeedback, pelvic floor muscle training, and sensory retraining have been used to treat the symptoms of people with these fecal disorders. Nevertheless, because there are no international agreements on the use of these various rehabilitative techniques, the main problems in this field are related to the absence of standards and guidelines. Moreover, rehabilitation requires a highly trained therapist and is time-consuming both for the therapist and the patient. Therefore, the patient must be strongly motivated. In spite of these negative factors, rehabilitative treatment has a high success rate of about 70 %, and the patient's quality of life after treatment is significantly better than it was before [3, 4].

The aim of this chapter is to describe rehabilitative techniques and their clinical impacts on fecal incontinence and obstructed defecation.

6.2 Anal Electrical Stimulation

Anal electrical stimulation was first described about 50 years ago for the treatment of fecal incontinence [5, 6]. Skin or intra-anal plugs, connected to clinical work stations or portable devices, have been used, and the rehabilitative treatment is usually

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performed daily for some months by the patient in a home environment. The purpose of anal electrical stimulation is to induce muscle contraction by direct stimulation or indirectly via peripheral nerve stimulation. The device delivers a square wave of current alternating between a period of a few seconds of work and a double rest period, according to a standard sequence of pulses (width in ms; frequency in Hz) reported in a printed instruction sheet that is given to patients. There is at present no experimental evidence to guide optimum electrical stimulation parameters for different symptoms and clinical conditions. Therefore, there is no universally accepted protocol, and electrical parameters that can be used for anal stimulation vary among centers: the work and rest periods, width and frequency of pulses, and ramp up and ramp down of waves are not standardized. A stimulator is usually used for 20 min daily, but it can be applied twice/day: however, regular outpatient monitoring is needed to verify the application of electrical stimulating protocol. How electrical stimulation works on anal function has not yet been defined. It is postulated that chronic axonal stimulation increases the efficacy of neuromuscular transmission, activates dormant axons, and increases the conduction rate of pudendal nerves [7]: the effect seems to be an improvement in anal and perineal awareness [8]. Several uncontrolled studies have reported clinical benefit of anal electrical stimulation when used in patients affected by fecal incontinence [9–11]. On the contrary, other studies have not shown any therapeutic advantage and have underlined the superiority of biofeedback when compared to electrical stimulation [12–14]. A Cochrane review of trials of electrical stimulation for fecal incontinence concluded that "At present there are insufficient data to allow reliable conclusions to be drawn on the effects of electrical stimulation in the management of fecal incontinence. There is a suggestion that electrical stimulation may have a therapeutic effect, but this is not certain" [15]. So, on the basis of currently available evidence, it is not possible to recommend electrical stimulation for fecal incontinence [2]. On the other hand, electrical stimulation, when used in combination with biofeedback and sphincter exercises, enhances their effects [16–19]. A recent review concluded that there is sufficient evidence of the efficacy of the combination of biofeedback plus electrical stimulation in the treatment of fecal incontinence [20].

Isolated reports point to the positive use of electrical anal stimulation in patients affected by obstructed defecation [4, 21, 22]. The same remarks, made for electrical anal stimulation used in patients affected by fecal incontinence, are valid also for this topic.

6.3 Biofeedback

Biofeedback is considered to be an operant conditioning technique for the defecation reflex [23]. It consists of sphincteric coordination exercises together with visual/verbal feedback training: it employs a trial-and-error process whereby learning takes place and the patient must be aware of the desired response (signals). Biofeedback training is aimed at improving voluntary external anal sphincter contraction and relaxation [24, 25] and restoring the synchrony of internal and external

sphincter response during rectal distension [26]. Biofeedback may make use of electromyographic or pressure devices in the clinic using a working station or at home by means of portable electronics, but there is no standardization: instrumentation, training procedures, and operative protocols differ between one center and another. Because of this, it is very difficult to compare rehabilitative outcomes. Biofeedback, either alone or in combination with other rehabilitative techniques [27, 28], is generally attempted only after pharmacological therapy has failed in the treatment of defecation disorders. The response rate, which includes both symptom improvement and cure rates, ranges from 50 to 80 % in the treatment of fecal incontinence [2] and from 35 to 75 % in patients affected by obstructed defecation [29, 30]. Clinical improvement is maintained in the long term, but continuing exercises are needed to sustain the success rate [28, 31].

6.4 Pelvic Floor Muscle Training

The aim of pelvic floor muscle training is to improve performance, extension, and elasticity of the levator ani and perineal muscles. The main targets of pelviperineal rehabilitative exercises are on resting tone and voluntary contraction/relaxation of the puborectalis muscle that becomes strengthened and coordinated. Post-defecatory reflex and the stress abdominoperineal reflex also become more effective. These results are achieved by means of sequential exercises performed weekly in outpatient sessions. Usually, pelvic floor muscle training is combined with biofeedback [27, 32]. The variety and sequence of pelviperineal exercises are not standardized and each clinic dedicated to pelvic floor rehabilitation has its own treatment protocol. However, some rehabilitative steps may be proposed. After a preliminary lesson on relaxed breathing and corporeal consciousness, the patient is taught to locate and focus on agonist, antagonist, and synergic muscles on the perianal plane. The next main steps of pelvic floor training are anteversion and retroversion pelvic movements, anal contractions/relaxations, perianal and perivaginal stretching, stretch reflexes of the puborectalis muscles, abdominopelvic synergy, and finally anal corticalization [19, 27]. Pelvic floor muscle training is mainly used in patients with obstructed defecation who have pelvic floor dyssynergia, because it is specific training for uncoordinated pelvic floor muscles [27, 33]. It is also used in patients with fecal incontinence and pelvic floor defects [19] or descending perineum syndrome [34]. The success rate is high: symptom severity and quality of life improve in about 90 % of patients affected by pelvic floor dyssynergia, and the results are long-lasting [4, 33].

6.5 Sensory Retraining

Defective rectal sensitivity may be involved in obstructed defecation and fecal incontinence [35, 36]. Intact rectal sensation plays a key role in fecal continence and normal defecation: a normal perception of fecal bolus and gas sustains basal

continence and is decisive in triggering and maintaining defecation. Rectal hyposensitivity [37] and rectal hypersensitivity [38] are the pathophysiological mechanisms which impair rectal sensation. Sensory retraining is thus aimed at restoring the defective rectal sensitivity. Hyposensitivity and hypersensitivity occur when sensory threshold values fall outside normal limits: hyposensitivity is detected when the manometric sensory threshold is higher than normal values, hypersensitivity when the threshold is lower. Retraining of the rectal sensory threshold, restoration of elastic properties of the rectum, and retraining of external anal sphincter response to rectal distension are the targets of sensory retraining. Such rehabilitation treatment may be performed through biofeedback [39], an inflated balloon [40], or water enemas of decreasing/increasing volume [19]. Unfortunately, evidence of targeted therapy on defective rectal sensitivity is lacking, with no randomized controlled trials available. However, sensory retraining has been shown to objectively improve symptoms in up to 92 % of patients [37] and subjectively improve obstructed defecation [29, 41] and incontinence [42] with sustained improvement for at least 12 months [43].

In conclusion, the rehabilitative treatment of fecal disorders is a good therapeutic option: many patients improve and some of them become symptom-free. Moreover, rehabilitation offers a harmless mode for identifying those "nonresponder patients" who should be next in line for more invasive and expensive therapeutic procedures (sacral neuromodulation, surgery).

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Functional Electrical Stimulation (FES) in Micturition Disorders

7

Aldo Tosto

7.1 Introduction

Functional electrical stimulation (FES) was based on observation that any neural structure submitted to electrical stimulation produces a propagation of the stimulus to all the neuromuscular somato-scheletric or visceral areas depending on their neural control or influence [1, 2]. A great number of contribution have been published since the second half of the nineteenth century with a lot of neurophysiological explanations about this phenomenon and the possible clinical applications in multidisciplinary dimensions. Our experience with FES, as "functional urologist," began taking note of a general agreement regarding the evidence that FES applied to a tissue conductor (as skin or mucosa) produces not only neuromuscular excitation and analgesia but also a facilitator effect on voluntary motility. This evidence could explain the subsequent better neuromuscular control observed in the area submitted to electrical stimulation [3]. This assumption was established as starting point of therapeutic or rehabilitative employment of the technique. In fact we can define electrical stimulation as "functional" when it is used as prosthetic-substitutive or therapeutic-rehabilitative procedure [4]. Do not take into consideration some enthusiastic reports published in the early 1900s; in the last century, until the first half of 1950s [5–7], many authors have proved the applicability of the technique in neurology, urology, or gynecology disorders especially as part of conservative management of stress urinary incontinence (SUI) in women and also in men with post-prostatectomy SUI. This employment still continues today with continuous progress in neurophysiologic and urodynamic knowledge about neural control of

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pelvic floor musculature and pelvic organ functions. Actually there is a great debate on short- and long-term results of the FES, with particular regard to a different representation of outcome measures not always strictly recommended. Another source of misunderstanding factors seems to originate from all the possible combinations of materials (current type, intensity and frequency, electrode types) and operative methodology (perineal superficial, endocavitary, and others). For these reasons "EStim" (as has been defined in the last years as FES) [8] requires further and more qualitative studies regarding widely accepted standardization of terms, methods, and outcome measures.

In this chapter we describe some of the materials, methods, and indications of FES that resulted, which are widely employed and accepted among the scientific community approaching the micturitional disorders.

7.2 Neurophysiologic Basis of FES Employment in Micturition Disorders

FES (or EStim) has been proposed to treat micturition disorders as a rehabilitative tool with the aim of conservative management of these disorders especially in rehabilitative treatment of stress urinary incontinence (SUI), lower urinary tract symptoms (LUTS), and urge and mixed urinary incontinence (UUI, MUI).

In SUI the aim of the technique's employment was to obtain a better function of pelvic floor muscles through chronic long-term stimulation. This objective stated on the basis of a postulated normalizing activity on the stretching receptors of the pelvic floor muscles producing an improvement of muscular force and resistance to fatigue. Moreover this type of electrical stimulation should produce another effect as the increase of number and size of the slow twitch fibers producing a better response in terms of endurance especially in long-term program of treatment [9, 10]. In other disorders as UUI, MUI, or LUTS (as those characterizing the overactive bladder syndrome) and successively even in the treatment of chronic pelvic pain (CPP), the adopted technique was, at first, the acute maximal functional electrical stimulation (AMFES) or short-term stimulation. For a neurophysiological explanation of this activity, the primary hypothesis of inhibitory effect of contractility of detrusor muscle smooth cells due to high-intensity and high-frequency electrical stimulation did not receive a conclusive demonstration. But the more sophisticated hypothesis of a proper capacity of this type of stimulation to reorganize the sacral reflex mechanisms involving the interrelation between afferent and efferent pathways, from and to the detrusor walls and spinal centers, has not received a clear or definitive confirmation. Actually acute maximal electrical stimulation is less used in our clinical practice and often replaced by other treatments [11].

Another example of FES used in micturition disorders as unbalanced bladder emptying (underactive bladder expressed by chronic urinary retention) is the intravesical electrical stimulation (IVES) also known as transurethral electrical bladder stimulation (TEBS), at first purposed by Katona [12] and successively popularized by Madersbacher and others [13–15].

The neurophysiologic basis of this kind of stimulation presume, as postulated by Katona, that facilitative process directs the impulses generated at the bladder receptors toward the central nervous system by vegetative afferentation is of primary importance to generate efferent responses. When these afferent pathways result in damaged "low-intensity" input, discharge could be because of poor efferent response. This fact represents the first pathophysiologic mechanism of "impaired" bladder contractility and subsequently unbalanced void. The effectiveness of intravesical electrical stimulation presumes nevertheless a substantial integrity of the neural pathways of the sacral reflex arc. The primary objective in fact was identified on the possibility to restore vegetative afferentation resulting in a better perception of bladder sensibility and normal desire to void. This "restoration" should determine an adequate contractile response of the detrusor muscle. But the clinical use of IVES remains a matter of debate because of poor results in the long-term and subsequent considerations of this technique as a "time-consuming" and "profitless" methodology.

7.3 FES in Micturition Disorders: Materials and Methods

The effectiveness and safety of FES requires the knowledge of some physical properties of the electrical current when applied to human care. The tissue impedance is of primary importance to define characteristics of the electrodes and other stimulation parameters as type of current, current intensity, pulse shape and duration, frequency, and work time (or duty cycle). Impedance could be defined as the resistance that the current faces up through a tissue: a low tissue impedance corresponds to a better transmission of electrical stimulus (for instance, the bone tissue has a strong impedance (160 Ω), while striated muscles have an impedance from 1.5 to 18 Ω and nervous tissue 5.8 Ω). Knowledge on tissue impedance guided the construction criteria of the electrodes in accord with the clinical use of FES. A general principle stated that electrodes must be mounted on the devices, as much as possible, proximal to the stimulating areas.

For this reason devices used in urology has a "plug" shape for vaginal or anal employment. Usually these devices have one or more ring electrodes mounted in the middle-upper tract (Fig. 7.1). About the parameter of stimulation, the first difference regard the type of current that could be monophasic or biphasic, pulsed or intermittent, and faradic or interferential. Each type of current should be employed according with physical property and objective of stimulation.

Current intensity depends on the patient's tolerance (usually the maximum intensity tolerable), and it could range in a scale between 10 and 100 mA. The pulse shape afterward can be variable between rectangular, quadratic (square), symmetric, or asymmetric. Duration of stimulus (measured in ms) varied between 0.2 and 1 ms. The proper value depends on the statement that a long-term impulse ($\geq$1 ms) electively stimulates sensory fibers, while an impulse $\leq$0.2 ms stimulates the motor fibers. The stimulation time (also described as "duty cycle" or "work time") was

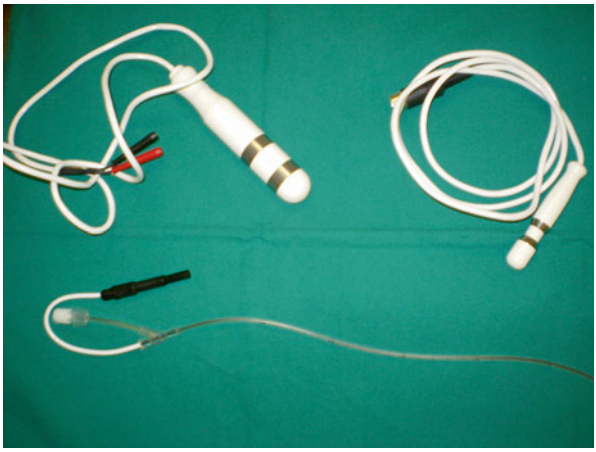

Fig. 7.1 On the *top* some devices (vaginal and anal plugs) adopted for FES/EStim. *Lower* the electrode catheter used for intravesical electrical stimulation

Table 7.1 Indications and contraindication to a clinical use of FES/EStim techniques

Indication	Contraindication
SUI with sphincter weakness	(A) Genitourinary tract infections
Impaired pelvic floor balance	(A) Pregnancy
Overactive bladder (wet or dry)	(A) Pacemaker conductors
Postpartum urinary incontinence	(A) Hemorrhagic diseases
Recurrent pelvic surgery fails	(R) Vesicoureteral reflux, spasmophilia
	(R) Vaginal atrophy
	(R) Anal strictures or lesions

Legend: *A* absolute, *R* relatives

commonly set in 1:2 ratio, and commonly the rest time is double the stimulation time. However, the most important stimulation parameter of FES (EStim) remains the frequency, which could be defined as the cycle number or electrical phases per second and is expressed in hertz (Hz). A common adopted criterion in urologic rehabilitative trials provides a range of frequencies varying from 20 to 50 Hz for application in stress urinary incontinence treatment, while lowest frequencies (5–20 Hz) have been adopted for the treatment of urge urinary incontinence or overactive bladder syndrome and detrusor overactivity. The physiologic basis of the different values depends on physical property of the neural fibers. In fact tonic fibers (less diameter) discharge at a frequency of 10–20 Hz, while phasic fibers (greater diameter) discharge at a frequency of 30–60 Hz. Some authors suggested an alternation of frequencies into the same program in order to reproduce a natural succession of motor neuron discharge [16]. In Table 7.1 we summarized indications and contraindication to functional electrical stimulation, while in Tables 7.2 and 7.3, we resumed some of the EStim programs reported by the most recent literature revision as benchmarks [22].

In the following schedule the operative methodology adopted in our clinical practice for each FES/EStim application is reported.

Table 7.2 EStim procedures in urinary incontinence in women

Author	Indication	Frequency (Hz)	Electrodes	Duty cycle	Trial duration		
Bo et al. [17]	SUI	50	Vaginal	(10" on/30" off)	30'	1/day	6 months
Brubaker et al. [18]	SUI/DO	20	Vaginal	(2" on/4" off)	20'	2/day	8 weeks
Godec et al. [19]	SUI/MUI	20	Vaginal	(10" on/10" off)	15'	1/day	8 weeks
Castro et al. [24]	SUI	50	Vaginal	(5" on/10" off)	20'	3/week	6 months

Table 7.3 EStim procedures for urinary incontinence in men post RRP

Authors	Indication	Frequency (Hz)	Electrodes	Trial duration	Associated treatment
Marchiori et al. [20]	SUI post RRP	30–50	Anal	10 + 10 2/week 6 months	PFME + BFB
Yamanishi et al. [21]	SUI/MUI	50	Anal	Not reported	PFME + BFB

(a) *Stress urinary incontinence in women*
(Sphincteric weakness, PC test 0–1)
(Usually associated with biofeedback in preparation or association with pelvic floor muscle trial with the aim to ameliorate consciousness raising of pelvic floor muscles)
Vaginal plug double ring electrodes
Current biphasic rectangular: intensity in a range of 30–80 mA (mean 50 mA)
Duration 0.2–1 ms (mean 0.5 ms); Duty cycle 1:2 ratio (5 s on/10 s off)
In these patients program treatment provides a series of 30 min sessions, 3 times/week for 12 times and 3–6 months of home EStim + PFMT with monthly clinical control.

(b) *Post-prostatectomy stress urinary incontinence in men*
(Associated with pelvic floor muscle trials)
Anal plug double ring electrodes
Current biphasic rectangular: intensity 10–25 mA
Type 1: biphasic, 30 Hz, 0.3 ms, 10 min (1:1, 10 s on, 10 s off × 10 min)
Type 2: biphasic, 50Hz, 0.5 ms, 10 min (1:2, 5 s on, 10 s off × 10 min)
In these patients program treatment provides a series of 30 min sessions, three times/week for eight to ten times and 6 months of home PFMT with monthly clinical control.

(c) *Urge urinary incontinence or LUTS (overactive bladder) in women*
(Associated with bladder retraining and other behavioral treatment)
Vaginal plug double ring electrodes
Current biphasic quadratic (square): intensity 30–150 mA (progressive according with tolerance); Duration 1 ms; Frequency 10–20 Hz

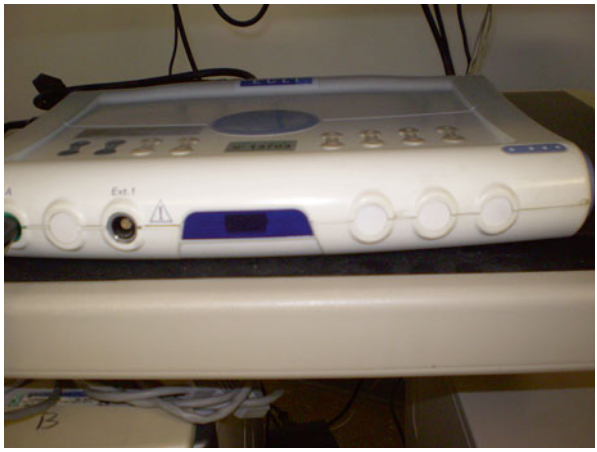

Fig. 7.2 Our module for electrical stimulation and biofeedback. It is connected with a computer with running operative software

Duty cycle 1:2 (10 s on, 20 s off), 30 min/session
In these patients the program is strictly individualized because of precocious dropout or less tolerance. Three times/week for 4 weeks, as a result, is the ideal schedule of the procedure, while home EStim was extremely variable (3–9 months) depending on tolerance and perceived results. A monthly clinical control is recommended for each treatment choice.
All programs of FES/EStim in our center provide a full clinical evaluation with accurate perineal balance and uroflowmetry with stop test and ultrasonographic post-voiding residue determination, at the beginning and during all the scheduled follow-ups.

(d) *Intravesical electrical stimulation (IVES or TEBS)*
In this application the electrical therapy adopted in our center is the TEBS [15, 16] consisting in a series of intravesical electrical impulses transmitted to the bladder walls through a liquid medium (bladder should be filled at half of cystometric capacity) when an electrode mounted on the tip of a specific catheter (Fig. 7.1) is connected to the source (Fig. 7.2). In our experience we preferred the procedures proposed by Primus et al. [15] or:
Current intensity 5–15 mA; Frequency 10–20 Hz; Pulse duration 4 s on, 8 s off (or 6–8), 90 min session (3 × 30′)

In these patients we perform the sessions for 5–6 consecutive days with a simultaneous cystometric registration during all the time of the session. The procedure requires from the beginning an accurate preliminary urodynamic evaluation (pressure-flow study or video-urodynamics). A continuous cystometric monitoring could have a predictive role in order to control the effectiveness of treatment and of urodynamic evidence changes. Successively, in the responding patients, it could be a sufficient simplified follow-up based on seriate uroflowmetric and ultrasonographic control of post-voiding residue and upper urinary tract integrity.

7.4 FES in Micturition Disorders: Clinical Results and Remarks

In the last 10 years, the largest literature review on this topic has been provided by the International Consultation on Incontinence [8, 22, 23]. In the last issue (2013 edition), the 12th Committee introduced the argument as follows: "the literature concerning EStim in the management of Urinary Incontinence remains difficult to interpret because the lack of a well substantiated biologic rationale underpinning the use of Estim…" and this statement could be interpreted as a conclusive (and negative) sentence. But afterward, in the same report, we can read that the principal cause of this "lack" remains the wide variety of material and methods and analysis of results proposed. This fact reduces the possibility to establish comparative criterions according to evidence-based medicine. Nevertheless, the percentage of subjective care or improvement in urinary incontinence patients results between 55 % [24] and 77 % [17] in women with SUI and of 50 % (main value) in men with SUI post radical prostatectomy [21].

So, actually, the role of FES/EStim in female stress urinary incontinence has been widely achieved and confirmed as a complementary tool in pelvic floor muscle trials, alone or associated with others (biofeedback, vaginal cones), with the aim of a precocious pelvic floor muscle response to physical exercises [9, 10, 23]. For the same reasons the technique has been employed for a precocious recovery of continence in male patients with post-prostatectomy stress or mix urinary incontinence.

Weakness of evidences, instead, persists to justify the employment of FES/EStim in urge urinary incontinence and detrusor overactivity [11, 25]. But otherwise, as shown in the Tables 7.2 and 7.3, this application is still employed. In general all the studies considered for systematic literature reviews [23–25] were assessed as having a high risk of bias. But otherwise, the pooled data regarding women with predominant stress urinary incontinence showed cure rates higher in patients who underwent FES/EStim compared with patients who have no active treatment. In our personal experience results obtained in women with stress urinary incontinence, treated from the beginning with functional electrical stimulation as single therapy, showed a lower rate of improvement when compared with the patients who received a complete PFMT cycle with or without FES or BFB (55 % versus 78 % of objective improvement to the pad test).

In general urologic experience, supported from the largest literature review, it is observed that adverse events or effects depending on FES/EStim are uncommon, but tenderness, bleeding, and vaginal irritation and infection with pain have been reported. For these reasons an accurate hygiene and continuous control in patients who use EStim devices, especially in home practice, are strongly recommended. Another lack of well-documented data has been signalized in regard to interpretation of results with particular emphasis to the instruments used for outcome measures. For this reason reports on percentage of care or improvement have raised some doubts and the last and largest consensus conference (I.C.I. 2013) [23]. recommended the need of further and more qualitative studies on this topic.

Finally, in regard to the result of IVES or TEBS, Decter [16] concluded his review concerning this matter emphasizing the observation that the success rate of this kind of electrical stimulation reported by Katona (71 %) was not achieved even closely in other contributes, and for this reason the benefit of IVES/TEBS has been judged "modest" with particular regard to the relation cost/benefit.

Such considerations induced Decter to put himself between those who judged IVES/TEBS as a modality with limited clinical efficacy and not justifying the time and efforts of the patients and staff.

More recent experience, instead, showed that this technique could be taken into consideration in all subject with urodynamic evidence of unbalanced nonobstructive micturition often present in incomplete or "occult" neurologic lesion. Moreover, IVES/TEBS should be taken into consideration before neurostimulation or modulation implants [26].

7.5 Conclusions

Functional electrical stimulation (FES/EStim) represents actually a complementary tool in conservative management of urinary incontinence. It maintains a role in all pelvic floor muscle rehabilitative trials when it is indicated on the basis of the patient's predominant symptoms, signs, and individual compliance. All the techniques described above, in the hands of a competent staff, are important to achieve a therapeutic objective, but this assumption should be verified through more qualitative contributes because a persistent lack of outcome instruments is widely accepted. The literature on this topic, even in the last years, presents a large number of well-conducted and controlled studies, but often it failed to give us definitive answers to questions as follows: "Is EStim surely effective in the prevention of urinary incontinence and other micturition disorders? Is EStim by itself better than other treatments in patients with urinary incontinence and LUTS? Is one type of EStim better than the other?" Unfortunately we have obtained only a conclusive answer regarding the observation that FES/EStim results surely better than no active treatment, but it is not yet sufficient to encourage new researches. In our opinion this fact seems to be related to a progressive limitation of resources and spaces for "low-profit" medical activity that it translates in a reduction of investments in this sector.

But otherwise for those who continue to believe on the clinical utility of rehabilitative support to prevent worsening or complications of micturition functional disorders, electrical stimulation, despite some contradictory or undefined aspects, should be considered a further possibility to improve the results of pelvic floor muscle training.

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Transcutaneous Electrical Nerve Stimulation

8

Filippo Murina and Stefania Di Francesco

8.1 Introduction

Transcutaneous electrical nerve stimulation (*TENS*) is a simple, noninvasive analgesic technique that is used extensively in health-care settings by physiotherapists, nurses, and midwifes.

TENS was originally developed in the early 1970s as a screening technique for the selection of women with chronic pain most likely to achieve satisfactory pain relief by the implant of an electrical stimulator.

A significant number of women with chronic pain achieved pain relief through the screening itself and less stimulators needing to be implanted [1].

By definition, any stimulating device which delivers electrical currents across the intact surface of the skin is TENS, although the technical characteristics of TENS parameters cause the desired clinical effect.

The management of chronic pain such as in chronic neuropathies, postherpetic neuralgia, and trigeminal neuralgia by TENS is supported by a large number of clinical trials [2].

It has been demonstrated that TENS is of significant benefit in the management of vulvar and sexual pain (*vulvodynia*), and it can also have a relevant role in the treatment of pelvic floor dysfunction where we have the development of hypertonic muscles [3].

The pelvic floor represents the neuromuscular unit that provides support and functional control for the pelvic viscera. Its integrity, both anatomic and functional, is the key in some of the basic functions of life: storage of urine and feces, evacuation of urine and feces, support of pelvic organs, and sexual function. When this integrity is compromised, the results lead to many of the problems seen by clinicians.

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Pelvic floor dysfunction can involve weakness and result in *stress incontinence*, fecal incontinence, and pelvic organ prolapse. The pelvic floor is controlled by a delicately balanced set of neuromuscular reflexes that have the ability to be modified by a process known as neuroplasticity.

TENS can be used to strengthen pelvic muscles in the management of hypotonic pelvic floor dysfunction.

This chapter will focus on the current and previous literature that has begun to elucidate the basic science mechanisms of TENS and how these mechanisms can be applied to the pelvic floor disorders.

8.2 TENS Mechanisms

The electrical characteristics of TENS are chosen with a view to selectively activate different populations of nerve fibers as this is believed to produce different outcomes.

Mammalian nerves are divided into A, B, and C groups. Group A is further subdivided into α, β, δ, e, and ϒ fibers.

In general, the greater the diameter of a given nerve fiber, the greater its speed of conduction.

Aβ fibers, the largest ones, mediate the sensations of touch at a conduction velocity above 2 μs. Aδ fibers mediate the sensation of cold and the first components of the sensation of pain, at a conduction velocity between 2 and 30 μs. C fibers mediate the sensation of warmth and the main component of the sensation of pain, at a conduction velocity above 100 μs.

Two mechanisms are claimed for TENS effectiveness. One is the "pain gate control" that is blocking the information travelling along the nociceptive fibers through stimulation of the large-diameter afferent Aβ fiber. The other, called "extrasegmental TENS," is based on the release of the body's endogenous opioids by stimulation of the small diameter afferent and motor fibers. According to the gate control theory, the stimulation of the large afferent fibers Aβ inhibits the small nociceptive fibers Aδ and C, by activating the inhibitory interneurones in the substantia gelatinosa of the spinal cord dorsal horn [4] (Fig. 8.1).

TENS-induced activity in Aδ and C afferents has also been shown to produce extra-segmental analgesia through the activation of structures which form the descending pain inhibitory pathways, such as periaqueductal gray (PAG), nucleus raphe magnus, and nucleus raphe gigantocellularis.

Furthermore this type of TENS activates opioid receptors located peripherally, in the spinal cord and in areas involved in descending inhibition including the nucleus raphe magnus in the rostral ventral medulla and the PAG [5].

The normal function of the pelvic floor muscles is essential for supporting the pelvic visceras and maintaining urinary and fecal continence.

The etiology of urinary incontinence is multifactorial with the most common cause being dysfunctions of the pelvic floor muscles. Therefore, weakened pelvic floor muscles may be assumed to predispose women to an increased risk of developing urinary continence.

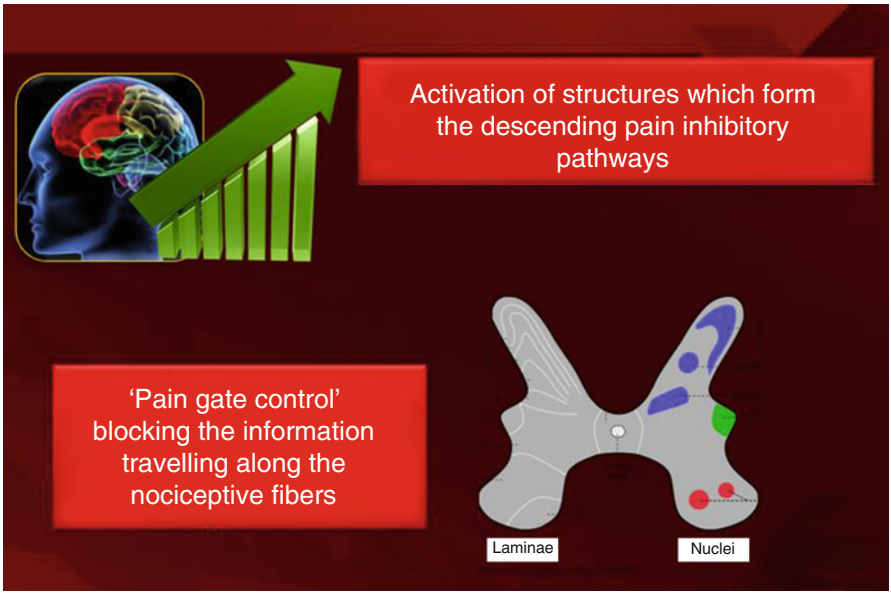

Fig. 8.1 Mechanisms claimed for TENS effectiveness

TENS aims to strengthen the pelvic floor muscles in an attempt to recover urinary continence mechanisms.

The effect of electrical stimulation on pudendal afferents in the treatment of urinary incontinence has been described and can be reassumed as follow [6]:

- Reflex activation of sympathetic inhibitory neurones
- Reflex central inhibition of parasympathetic excitatory neurons

TENS can be used in the treatment of *fecal incontinence*. It is postulated that stimulation of the skin in the distribution of the S3 dermatome excites mainly the Aβ fibers, thereby modulating signals to and from the pelvic organs with a possible effect on continence.

Essentially, there are four broad categories of anatomical site to which TENS electrodes can be applied: painful area, peripheral nerve, spinal nerve roots, and other specific points (acupuncture, trigger, and motor points). Irrespective of the electrode site that is chosen, stimulation will ultimately result in the passage of afferent information into the central nervous system [7].

Vaginal electrodes are the most commonly used devices for applying electrical currents for pelvic floor muscle problems in women (Fig. 8.2). The vagina offers a route of low impedance, because of the low resistance of the vaginal mucosa and proximity to branches of the *pudendal nerves*.

Anal electrodes are suitable for patients with anal sphincter weakness. Anal electrodes can also be used in narrow vaginas, where a vaginal electrode is too big and painful to insert. Electrodes suitable for electrical stimulation may also be used for electromyography (EMG) biofeedback.

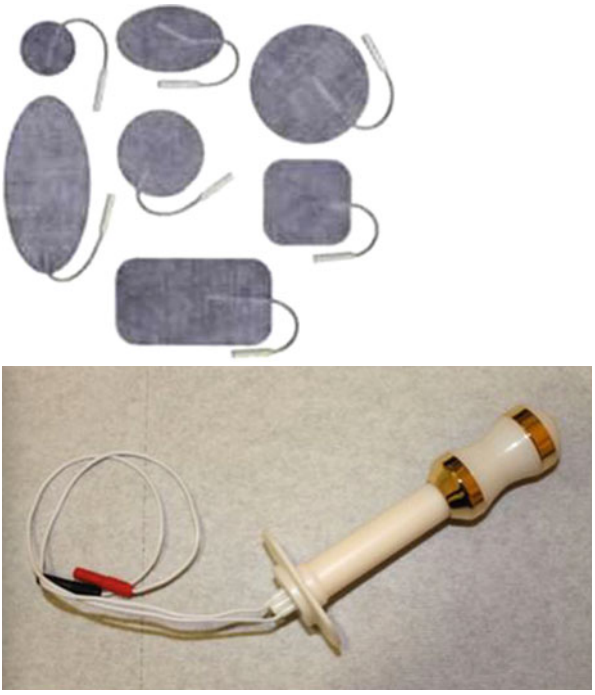

Fig. 8.2 TENS electrodes: patches and vaginal probes

8.3 TENS Parameters

The stimulation parameters that are set on the TENS unit determine the type of nerve fibers stimulated and thus its mechanism of action.

8.3.1 Frequency

The frequency of a current refers to the number of pulses delivered per second; therefore, a frequency of 200 Hz means that 200 pulses are delivered per second.

Both high (50–100 Hz) and low (5–10 Hz) frequencies can be applied and are thought to work by different mechanisms. High-frequency TENS is thought to selectively activate large-diameter non-noxious Aβ afferents to reduce nociceptor cell activity and sensitization at a segmental level in the central nervous system [8]. Low-frequency TENS can be applied and activates small diameter motor afferents to elicit extra-segmental analgesia [8].

Concentrations of β-endorphins increase in the bloodstream and cerebrospinal fluid of healthy subjects after administration of either high- or low-frequency TENS. This suggests that at the spinal level there are different opioids released with different stimulation frequencies and thus possibly different opioid receptors activated to produce analgesia with high- or low-frequency TENS [9].

Low-frequency TENS activates μ-opioid receptors in the spinal cord and the brainstem, whereas high-frequency TENS activates δ-opioid receptors in the spinal cord and the brainstem [9].

It is also generally thought that large-diameter fibers are activated by high-frequency TENS and that low-frequency TENS at motor intensity activates Aδ afferent fibers [8].

Furthermore, basic science studies show that simultaneous activation of μ-opioid and δ-*opioid receptors* prevents the development of tolerance. Thus, providing low- and high-frequency TENS simultaneously, to activate μ-opioid and δ-opioid receptors, should similarly prevent tolerance to TENS [8].

8.3.2 Pulse Duration

The unit of pulse duration is usually given in microseconds (μs) which are units of time; hence, it is more correct to use the term "duration" rather than "width." The pulse duration is usually defined as the duration of only the positive component of the waveform. TENS pulse durations are in the μs range ($1\ \mu s = 1 \times 10^{-6}$ s).

Pulse duration currents of 30–100 μs activate large-diameter fibers without activating smaller nociceptive fibers. Wider-intensity pulses (around 100 μs) simultaneously stimulate "sensitive" and "pain" fibers. In this case, analgesic action is not derived from a gate control mechanism, but from the activation of the descending pain inhibitory pathways [10].

A pulse duration of 50–100 μs is well within the range which is expected to activate Aβ fibers.

The recommended pulse width for muscle stimulation is approximately 250, and 500 μs.

These pulse width leads to conversion of fast to slow twitch muscle fibers with the results in a muscle which is less susceptible to fatigue [6].

8.3.3 Duty Cycle

The duty cycle is the time the current is on and off. Typically, most TENS units allow the user to choose between continuous, burst, and modulated outputs. If the output is set for amplitude modulation, a cyclic modulation in amplitude is produced which increases from zero to a preset level and then back to zero again. The modulated output has been demonstrated to overcome accommodation of nerve fibers, hence providing more comfort to the patient [11].

8.3.4 Stimulation Intensity

Intensity refers to the magnitude of current or voltage applied by the TENS unit. Aarskog et al. [12] used pressure pain threshold (PPT) to compare two intensity levels of high-frequency TENS (100 Hz) applied simultaneously for 20 min to the hand/forearm on both sides. The intensity levels were either the lowest intensity at

which the participant first perceived the electrical stimulation on the skin (sensory threshold) or at a level that the participant described as strong but comfortable. There was a statistically significant increase in PPT on the strong-but-comfortable intensity side but not on the sensory-threshold intensity side.

The relevance of stimulus intensity was also highlighted in a study by Claydon et al. [13].

These authors found that TENS at a high intensity (to tolerance) using different frequencies at each site produced the greatest hypoalgesia. These results indicate that the high-intensity currents (irrespective of the applied frequency) are the key parameter in TENS applications.

Sjolund found that stimulation at high frequency (80 Hz) and high intensity (10× sensory threshold) of the plantar and sural nerves produced maximal suppression of the C fiber-evoked flexion response in a rat [14].

In the TENS treatment protocol, the pulse has to be increased rapidly until the patient reports the onset of any sensation under the electrodes. The intensity is then increased slowly until this sensation reaches a level described as the maximum tolerable, without experiencing pain.

8.4 TENS and Vulvar Pain

Vulvodynia is a complex, common, and multifactorial condition manifesting pain in the vulvar area with an estimated prevalence of up to 16 % [15].

The disease, most often described as a burning pain, occurring in the absence of relevant visible findings or a specific, clinically identifiable, neurological disorder. It is classified according to the site of the pain, whether generalized or localized and whether provoked, unprovoked, or mixed. *Vestibulodynia* defines the most common localization, which is at the vulval vestibule [16]. Introital dyspareunia, the intensity of which may inhibit or prevent intercourse, is often the presenting symptom.

The etiology of vulvodynia is not fully understood. Many findings suggest that neuropathic mechanisms may underlie the clinical symptoms of the disease including neural hyperplasia, inflammation, central or peripheral nociceptive dysfunction, and involvement of contiguous pelvic floor muscles [17].

Central and peripheral sensitization seems to be responsible for perpetuation of the symptoms long after any "triggering factor" (infections, trauma, allergy, hormonal factors,etc.) has been resolved.

These sensitized afferent nerve fibers discharge more readily and at lower thresholds, helping to explain why apparently imperceptible or minimal stimulation sometimes causes pain [17].

In light of the complex neuropathology of this syndrome, an effective therapeutic approach should target both peripheral and central neural sensitization.

It has been demonstrated that TENS is of significant benefit in the management of vestibulodynia, in fact it provides a therapeutic *neuromodulation* based on presynaptic inhibition in the dorsal horn of the spinal cord; moreover it acts on direct inhibition of an abnormally excited nerve and on restoration of afferent input explained by the "gate control theory" [17].

Contextually, electrical stimulation delivered by a TENS unit activates sovraspinal inhibitory systems and it increases the release of endogenous morphine-similar substances (amplification of endogenous descending system for analgesia), but it is essential to use appropriate and validated stimulation parameters [17].

Electroanalgesia with diphasic currents of frequencies between 2 and 100 Hz and 50–100 μs pulse duration has been used in the treatment of localized vulvodynia, with a high improvement (75 %) superior to placebo [3]. In all trials using TENS in vulvodynia, the stimulation was delivered through plastic vaginal probe inserted in into the vagina for 20 mm.

The number of treatment sessions and interval between sessions are also worth discussion.

A daily regimen consisting of a period of 2 weeks of daily TENS applications (10–14 sessions) was considered appropriate to assess the efficacy of the treatment [18].

We think that a twice-weekly or an alternate-day regimen was preferred to the commonly reported daily regimen in relation to the site of application of the TENS electrode.

In fact, the vagina is more delicate and thinner than the skin, which is the site where TENS was applied in many reports. Irritation or reddening beneath or around the TENS probe may result in areas of broken or damaged skin. A twice-weekly or alternate-day regimen were also preferred to a daily treatment to minimize for a possible decline in response due to tolerance to TENS analgesia [5].

This effect has been interpreted as an adaptive change by the nervous system to the TENS regular repetitive stimuli.

TENS treatment can also be self-administered in the privacy of a woman's home after a short period of supervision, using an inexpensive device. Our experience with a large series of *provoked vestibulodynia* patients (480 women) showed that there is a positive response after 10–15 sessions (symptom reduction >50 %) which tends to peak after 25–35 sessions [17].

Furthermore, we observed that nociceptive system is best suited to the new situation through a gradual increasing of day numbers between TENS sessions.

Pelvic floor hypertonic dysfunction is found in 80–90 % of patients with vulvodynia [19].

The leading opinion indicates that vulvar pain can produce spasm of the levator ani muscle, and pelvic floor hypertonicity contributes to self-maintenance of pain.

It is not important what starts the process (muscle or nerve), but it is important how alteration of the pelvic muscles is responsible for the severity of symptoms. Indeed, "the weight of the muscle" may be different between patients with vulvodynia, and this is the only important target of the treatment program.

TENS can also help to reduce the pelvic floor hypertonicity working through the following two main modes:

- Directly with an electrical muscle stimulation, in fact the levator ani muscles are innervated by the levator ani nerve, while no evidence of innervation by the pudendal nerve can be found. The levator ani motor neurons are diffusely distributed in the sacral ventral horn, while the pudendal motor neurons are concentrated in Onuf's nucleus (a group of neurons located in the ventral part of laminae

IX of the anterior horn). However, there is a great deal of overlap between the dendrites of levator ani motor neurons and pudendal motor neurons, and both nerves contain primary afferent fibers that project into the sacral spinal cord [20]. Thus, there is great potential for interaction between the sensory and motor nerve fibers that control the levator ani muscle, the vulva, and the vestibule.

- Indirectly because TENS reduce the vulvar pain with the results in a secondary decrease in muscle activity and spasm. One of the more common neuropathic reflexes that occur is visceromuscular hyperalgesia. This results in muscular instability and a hypertonic contractile state within the muscles of the pelvic floor.

The ideal approach of vulvodynia, however, is a multimodal interventions with the use of more than one type of therapy for the care of patients with chronic pain.

Physical therapy is an important complement to any therapy for the vulvodynia associated with levator ani hypertone and myalgia.

A retrospective study in Italy assessed a total of 145 women diagnosed with vulvodynia who were treated with weekly biofeedback and TENS, in association with functional electrical stimulation and home therapy with stretching exercises for the pelvic floor [21].

The authors applied the standard protocol for TENS consisting in a biphasic pulse with modulation 1/4/1 (001–004 Hz) of frequency and 300/100/300 μs of pulse duration.

An improvement of vulvar pain was seen in 75.8 % of subjects. The study concluded that pelvic floor relaxation with biofeedback and electroanalgesia is safe and effective in improving vulvar pain and dyspareunia in women with vulvodynia.

In a multimodal treatment strategy, TENS was used in combination with palmitoylethanolamide (PEA) combination in patients with vestibulodynia [22].

The premise was that PEA may contribute to a downregulation of hyperactivated *mast cells* responsible for the proliferation and sprouting of vestibular *pain fibers*.

The study confirms that TENS is of significant benefit in the management of vestibulodynia, also in a home environment, and PEA can be a value-added treatment adjunct when the onset of vestibulodynia is more recent or when the disease relapses.

Postpartum perineal pain and entry *dyspareunia* have been reported to affect 42 % of women within the first 2 weeks after their first vaginal delivery [23]. It has been attributed to post-episiotomy tenderness, a result of spontaneous laceration and reactive algic spasm of the perineal muscles, assessed by a vaginal physiatric visit and electromyography.

Dionisi et al. applied the standard TENS protocol, consisting of a 30-min weekly session of biphasic pulses with modulation 0/10–50 Hz of frequency and 300/100/3,000 μs of pulse duration, in addition to a physical therapy program [24].

After five sessions of TENS, 84.5 % of woman improved, and at the end of the treatment period (ten sessions in total), 95 % of women had achieved a complete resolution of symptoms.

8.5 TENS and Urinary Dysfunction

TENS can be effective alone or combined with other therapies in the treatment of urinary incontinence, but there is no consensus on the electrical parameters to be used.

Parkkinen et al. [25] have recommended an interferential current with a frequency of 2,000 Hz, modulated at 50 Hz and a pulse width of 250 μs.

Laycock and Jerwood [26] used frequencies of 35–40 Hz and a pulse width of 250 μs as effective and tolerable for women, while other authors have recommend a frequency of 50 Hz and pulse width of 300 μs [27, 28].

Another study [29] compared two TENS intravaginal protocols for the treatment of *stress urinary incontinence* in women. Patients were randomly divided into two groups, one received TENS with medium-frequency current, while the other received a TENS with low-frequency current, and no significant differences were found between groups for any of the variable assessed; the patients received 20 min at maximum tolerable intensity TENS twice a week for 6 weeks adding to a total of 12 sessions.

Urinary tract infection and atrophic vaginitis should be treated before a course of electrical stimulation.

Transvaginal pelvic floor electrical stimulation was found to be a safe and effective therapy for genuine stress incontinence.

Sand et al. [27] in a placebo-controlled trial showed that stress incontinence was improved by at least 50 in 62 % of patients using an active device compared with only 19 % of patients using sham devices. Voiding diaries showed at least 50 % improvement in 48 % of active-device patients compared with 13 % of women using the sham device, and no relevant adverse effects were noted in either group.

Dysfunctional voiding (also called discordant voiding) is common in patients with various pelvic pain disorders.

We now know that this represents an upregulated guarding or "holding" reflex and is referred to as idiopathic urinary retention. Fowler and colleagues [30] described a unique type of urinary retention associated with abnormal urethral sphincteric electromyography (EMG) activity and polycystic ovaries. The symptom of urinary retention is often triggered by a significant life event that may have been emotional or surgical. TENS has been found to be very beneficial for these patients with urinary retention and has a long-term success rate of 68 %.

Bladder pain syndrome/interstitial cystitis (BPS/IC) is characterized by urinary frequency, urgency, irritable voiding dysfunction, and pelvic pain. It is associated with a number of other pain disorders including vulvodynia and irritable bowel syndrome.

The prevalence of hypertonic pelvic floor dysfunction is thought to be 50–87 % in patients with BPS/IC [31]. Seventy-six percent of patients with BPS/IC are also found to have voiding dysfunction and very high urethral pressures, which are both manifestations of the pelvic floor hypertonic component of their symptoms. Hypertonic pelvic floor dysfunction can cause symptoms of frequency and pain.

It can induce bladder pain with bladder C-fiber upregulation and urothelial dysfunction because of its effect on voiding. It can also be a secondary pain generator triggered by the bladder pain of IC and by holding urine because of the constant urge to void.

After the identification of hypertonic pelvic floor dysfunction, treatment using physical therapy, like TENS, directed toward relaxation technique, can be very effective.

TENS was applied to 24 women with PBS in the form of ten 30-min applications, two or three times per week [32]. Stimulation was effective in alleviating pain, as evaluated at the end of treatment and 2 weeks, 4 weeks, and 7 months after completion of treatment.

8.6 TENS and Bowel Dysfunction

It was demonstrated the feasibility and effectiveness of sacral TENS (S-TENS) in the treatment of *fecal incontinence*, primarily assessing patient continence scores.

The scientific basis behind the success of TENS in the management of fecal incontinence is poorly understood. TENS activates myelinated sensory α- and β-fibers, thereby inhibiting C-fiber transmission to the thalamus. This potentially has an effect on signal modulation to the pelvic organs.

It is possible that TENS leads to a "resetting" of nervous pathway(s) that increases rectal sensitivity either temporarily or permanently.

Patients having received percutaneous sacral nerve stimulation for their fecal incontinence treatment generally report favorable outcomes: 80 % of patients had more than 50 % continence improvement after a 16 months follow-up [33]. The stimulation was set at a frequency of 10 Hz, pulse width of 250 ms, and conventional continuous TENS mode.

The potential advantage of sacral over tibial TENS, however, is that the stimulation pathway is shorter and closer to the S3 nerve. This may reduce the chance of dissipation of the signal strength and thus increase its effectiveness.

These results appear better than another recent study [34]: 53 % of patients had more than 50 % continence improvement after a mean follow-up of 19.7 months.

Of the ten patients recruited in the study of the St. Marks group [35], two achieved complete continence. In their experience there was a statistically significant reduction in the median frequency of incontinent episodes per week and in the median frequency of defecation per week. There was a statistically significant improvement in the median ability to defer defecation. There was also a statistically significant improvement in the St. Marks Incontinence Score and in the bowel habit satisfaction visual analogue scale from 8.5 (20) to 45 (33) ($P=0.008$). However, there was no change in the Rockwood FI QOL or SF-36 QOL scores.

Constipation is a symptom complex with many different causes. *Pelvic floor dysfunction* is certainly a common cause of constipation, and symptoms of lifelong constipation should alert the clinician to the possibility of lifelong pelvic floor dysfunction.

TENS was shown to improve bowel function in slow-transit constipation children [36], with significantly faster colonic transit on nuclear transit scintigraphy.

In a pilot study of STC children trained by the physiotherapist to use a battery-powered interferential machine at home, TENS increased defecation frequency and reduced soiling; of the 32 STC children, 38–69 % achieved some treatment success [37].

Two self-adhesive 4-cm^2 electrodes were placed on the anterior abdominal wall at the level of the umbilicus of the child, and two other electrodes were placed on the back between T9 and L2 on either side. The current from the electrodes was crossed diagonally from front to back. Interferential treatments delivered a 4-kHz carrier frequency, a beat frequency of 80–160 Hz with an intensity of less than 33 mA as previously described. Stimulation was performed or monitored by the parent(s) at home (1 h daily for 3–6 months).

In principle, electrical stimulation could activate sensory nerve fibers in the skin, sensory and motor nerves in the spinal nerves, sympathetic and parasympathetic nerves, enteric nerves in the bowel wall or pacemaker cells in the intestine (interstitial cells of Cajal), and intestinal muscle cells [38].

The stimulation parameters were similar to those used on bladder that produced diarrhea as a side effect.

8.7 Conclusion

TENS is used extensively in health care to manage pelvic painful conditions because it is cheap, is safe, and can be administered by patients themselves. Success with TENS depends on appropriate application of the technique; experimental pain studies and clinical trials are beginning to refine parameters of stimulation to obtain the best pain relief. Furthermore electrical stimulation is becoming accepted as a useful therapy for urinary and fetal incontinence.

Multimodal therapy is very important in the treatment of patients with visceral pelvic pain disorders; for this reason, TENS should be combined with biofeedback and pelvic floor muscle exercises for muscle strengthening and with bladder drill and medication for detrusor hyper- and hypoactivity and incontinence.

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Tibial Nerve Stimulation

9

Iacopo Giani and Stefania Musco

9.1 Introduction

The tibial nerve stimulation (TNS) was firstly introduced by Mcguire in 1983 to treat lower urinary tract symptoms (LUTS) using transcutaneous adhesive electrodes [1]. Currently, it is the lowest risk and the least invasive form of neuromodulation.

Later on, in 1990, Dr M. Stoller described the Stoller Afferent Nerve Stimulation (SANS) as a minimally invasive procedure for the treatment of overactive bladder syndrome using a needle electrode for the percutaneous stimulation of the posterior tibial nerve (PTNS) [2].

The posterior tibial nerve is a mixed nerve containing motor and sensory fibers which originate from the L4–S3 nerve roots. Its mechanism of action is still unclear, but it's suggested that the posterior tibial nerve stimulation modulates the afferent and efferent signals through the sacral plexus (S2–S3) [3, 4]. Compared to sacral nerve stimulation (SNS), the direct retrograde (or afferent) stimulation of S3 root avoids to generate painful electrical currents nearby the pelvic area, and it doesn't need of surgical procedure for definitive implant.

Several studies would suggest both sensory and motor neuromodulatory effects. Cortical changes during PTNS similar to those reported for continuous stimulation in SNS have been described warning an important role for the central nervous system [5, 6]. Moreover, according to the "gate control" theory, the perception of pain is related to peripheral signals. The plastic reorganization of cortical network triggered by peripheral neuromodulation can be hypothesized as a mechanism of action

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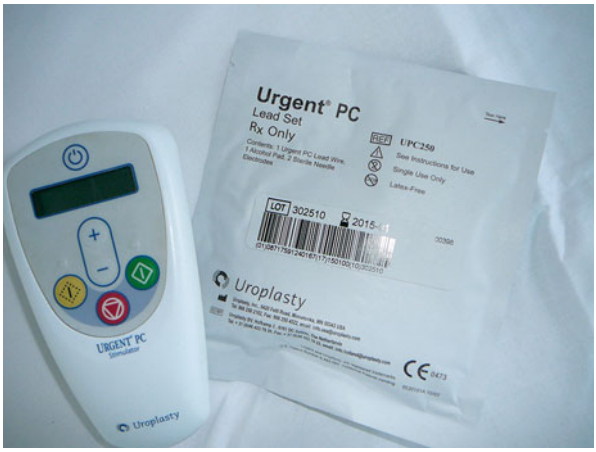

Fig. 9.1 Urgent PC Neuromodulation System (Courtesy of Uroplasty, Inc., Minnetonka, MN)

of PTNS. Long-term potentiation could be one of the mechanisms of action of PTNS as reported by Finazzi et al. based on the modifications on the long latency somatosensory evoked potential after PTNS [7].

The use of PTNS, for the treatment of overactive bladder (OAB) syndrome, was approved by FDA in 2000.

Nowadays, the only specific device commercially available, which received the CE mark for OAB and fecal incontinence in 2005, is the Urgent PC Neuromodulation System (from Uroplasty, Inc., Minnetonka, MN) (Fig. 9.1).

9.2 PTNS Technique

The Stoller technique (SANS protocol) consists in the electrical stimulation of the posterior tibial nerve by a fine metallic needle 34 gauge inserted into the lower part of the leg, 3–5 cm cephalad to the medial malleolus [2]. Interestingly, the place where the needle is inserted had been already known by traditional Chinese acupuncture as the Sanyinjiao (SP6) point for the pelvic floor organ dysfunctions [8–10]. Patients lie supine with the soles of the feet together and their knees abducted and flexed ("frog position"). A grounding pad is placed in the medial face of the ipsilateral calcaneus. The needle electrode is then connected to an external low-voltage (9 V) pulse generator which delivers the electrical pulse (Fig. 9.2).

Once the electrode needle is correctly placed and the electrical impulse is on, the motor response consists in an involuntary toe flex or an extension of the entire foot while the sensory response results in a sensation in the ankle area or across the sole of the foot. The toe flex is obtained by a direct stimulation (retrograde or afferent) of the S3 nerve root, mostly responsible for the bladder innervation: this confirms the presence of S3 fibers in the tibial nerve.

A current level of 0.5–9 mA at 20 Hz at a fixed frequency of 20 Hz and pulse width of 200 μs is selected based on the subject's motor and/or sensory responses.

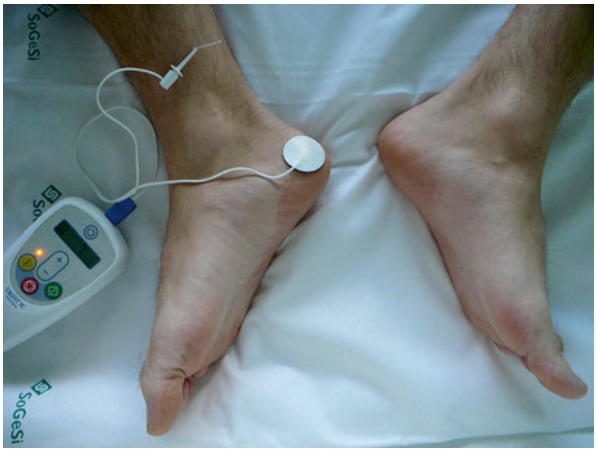

Fig. 9.2 Needle and pad positions

Each session lasts 30 min, and it's repeated for 10–12 times usually on a weekly basis. Some authors have investigated more frequently stimulation or longer lasting session, reporting the advantage to obtain the same results in less time [11, 12].

Daily treatment may be more effective than twice weekly treatment [13].

PTNS is a low-risk procedure: only minor bleeding, mild pain, and skin inflammation resulting from the placement of the needle are reported [14].

On the basis of McGuire, transcutaneous stimulation of the tibial nerve (TTNS) using adhesive electrodes has also been demonstrated to be effective for either urinary and bowel dysfunction. However, it has been suggested that PTNS is more effective than surface stimulation probably because the needle electrode is closer to the tibial nerve [15].

In the study of George Percutaneous, transcutaneous and sham transcutaneous posterior tibial nerve stimulation was compared in a prospective blinded randomized placebo-controlled trial. Patients undergoing percutaneous nerve stimulation had a greater reduction in the number of incontinence episodes and were able to defer defecation for a longer interval than those undergoing transcutaneous and sham stimulation. These improvements were maintained over a 6-month follow-up period [16].

Adequately powered RCTs of PTNS vs TTNS stimulation are necessary to establish the short- and long-term effects on both techniques.

9.3 Results

9.3.1 The Urological Experience

9.3.1.1 Overactive Bladder (OAB) Syndrome

Over the last decades, several case studies have been published about the use of PTNS for the treatment of OAB syndrome. There is evidence that PTNS

significantly improves OAB symptoms such as urinary frequency, urgency, and urgency urinary incontinence with a positive impact on QoL [17]. The percentage of success, in patient's refractory to previous conservative treatments, after a PTNS round is about 60–80 % [18]. A multicenter double-blind controlled prospective study (SumiT) compared the efficacy of the active (54.5 %) and the sham therapy (20.9 %) [19]. Another multicenter RCT documented comparable efficacy of PTNS vs drug therapy (OrBiT trial). At 3 months, 79.5 % of the patients after PTNS vs 54.8 % of patients on tolterodine were improved [20]. Further the clinical results, urodynamic data were also reported by some authors [21–23]. According to Vandonick et al., the absence or the presence of a mild detrusor overactivity with normal bladder capacity seems to be a possible predictive parameter of success [23].

PTNS seems to be effective even in childhood. Hoebeke et al. reported a significant reduction (60 %) of LUTS, and 17 % resulted dry after treatment. These data have been confirmed by De Gennaro et al. observing an improvement of OAB symptoms in 80 % of children with a good acceptance to treatment and tolerability assessed by VAS scale. Moreover, considering the urodynamic outcomes, a normalization of cystometric capacity was seen in 62.5 % of patients [24, 25].

OAB and Long-Term Efficacy

Although the evidence of significant improvement in OAB symptoms with short-term use of PTNS, there is not yet a standardized protocol for maintenance therapy. Regimes varied between weekly and monthly stimulations depending on the patients' and clinicians' perception of symptoms control [26]. Two long-term follow-ups, The OrbiT and the Step trials, have showed that the majority of patients maintained a responder status, respectively, at 12 and 24 months with a mean interval of treatment of about 3 weeks. The withdrawal rate was 30–33 % [23, 27]. Considering these results, PTNS is an attractive alternative to drugs or implantable sacral nerve stimulation (SNS) for the long-term treatment. In contrast to SNS, patients can simply discontinue PTNS with no need to undergo surgery when become refractory to therapy. It's been proposed a home-based transcutaneous tibial nerve stimulation (TTNS) as an attractive cheaper option for chronic treatment [28]. Despite that, the long-term use of PTNS therapy and its cost-effectiveness need to be examined further.

9.3.1.2 Neurogenic Bladder

Since the first study of McGuire, several trials have been published to better clarify the clinical and urodynamic effects of TNS in patients affected by neurogenic bladder [1, 29–35]. Finazzi Agrò et al. showed an improvement of urodynamic data in 9/14 patients affected by neurogenic detrusor overactivity (NDO) due to multiple sclerosis (MS), incomplete spinal cord lesion (SCL), and Parkinson disease (PD). Particularly in this paper by Finazzi Agrò et al, people with incomplete SCL showed to respond more than patients with central lesions [33]. De Seze et al. observed a significant improvement of LUTS and urodynamic filling parameters after daily 20 min sessions of TTNS for three months [35]. Gobbi et al. looked at the effect on QoL in patients

suffering from MS. Eighty-nine percent of subjects reported a treatment satisfaction of 70 % with a significant improvement in most of QoL domains [31]. On the other hand, the use of PTNS is neurogenic voiding dysfunction is still more controversial.

9.3.1.3 Non-Obstructive Urinary Retention

Similarly to SNS, also PTNS has been proposed in patients affected by idiopathic or neurogenic non-obstructive urinary retention. The experience in this field of application is limited. On the basis of literature, the percentage of clinical success varied from 41 to 67 %. Vandoninck has reported an improvement of urodynamic parameters during voiding phase [36, 37].

9.3.1.4 Chronic Pelvic Pain

Only more recently, few studies have been published to assess the PTNS efficacy in treating chronic pelvic pain (CPP) syndrome. Based on literature, PTNS may be considered a treatment option in those "complicated" patients non-responder to standard conservative therapies. In particular it has been seen a reduction of VAS scale and an improvement of QoL questionnaire scores. Despite that, the percentage of responders in CPP patients seems to be lower (about 40–42 %) than that one reported in OAB patients [38, 39].

9.3.2 The Colorectal Experience

Extrapolation from SNS and urological evidence would suggest both sensory and motor neuromodulatory effects evaluated through anorectal physiology studies. These putative effects include upregulation of afferent rectal sensory perception and striated muscle function, allowing generation of increased maximum squeeze and resting pressure [40, 41]. There is also evidence of a reduction in spontaneous anal relaxations and rectal contractions [42–44]. Furthermore enhancement of rectal mucosal blood flow (as a surrogate marker of autonomic nervous function) has also been demonstrated as an alteration in the central neurotransmitter environment [45, 46].

Furthermore, it is well known from experimental data that somatic afferents from the skin are involved in neuromodulation of various autonomic functions. Afferent stimulation of the sciatic nerve inhibits gastrointestinal motility and that of the splanchnic nerves is responsible for mediating the inhibitory response [47].

In addition, with acupuncture needles placed either over the sacrum or perineal area, a stimulation regimen of 30 min per week for 10 weeks, followed by maintenance therapy after 1–3 months, a 50–85 % reduction in fecal incontinence episodes has been reported similar results to those after SNS and PTNS. The effects have sometimes been reflected even in the manovolumetric markers, with an increased tone in the internal sphincter, elevation of sensory thresholds, and an increased rectal volume capacity [48].

Upon these considerations, PTNS has been applied for several different coloproctological diseases.

One of the first experience was reported by Shafik et al. in 2003 who obtained an improvement in fecal incontinence scores in 78.2 % of the 32 cases treated [42]. Four years later Mentes et al. reported its application on partial spinal injury patients to be successful [49]. PTNS also showed its effectiveness in 28 patients included in the SUmit Trial who were also diagnosed for fecal incontinence: 45.5 % of PTNS patients improved, while only 18.2 % of sham subjects improved [27]. De la Portilla F in 2010 gave its contribution with a study conducted on 16 fecal incontinence patients: 10 of 16 improved in the short term, while only 5 of 16 maintained good results after 6-month period without treatment [50]. Govaert in a multicenter study reported improvement with >50 % decreased in incontinence episodes, in 59 % of patients treated at 1-year follow-up [51]. Boyle et al. obtained an important improvement in 68 % of 48 subjects treated with median number of incontinence episode per week decreased from 4 to 0 ($p > 0.0001$) [52]. The same year Findaly et al. evaluate the efficacy of PTNS on 13 patients with fecal incontinence of variable etiology: idiopathic, obstetric, and iatrogenic, and demonstrated subnormal physiology, but by contrast, all patients had intact sphincter complexes. Incontinence improved in all patients, with reduction in median episodes of wind, liquid, and solid to 0 episodes per month with 12 weeks treatment [53]. This was sustained for wind, but not liquid and solid, 1 month later. Although not presented in the initial paper, 10 of the 13 patients had a greater than 50 % reduction in incontinence. In common with Govaert et al., improvements were seen in those who had previously failed surgical intervention (sphincteroplasty and PTQ implants) [51, 53]. Another contribution derives from the experience of Hotouras et al., who published in 2012 his experience with 88 female incontinence patients showing a statistical improvement in the short term of Cleveland Clinic incontinence score, median deferment time, and median number of weekly incontinence episodes, and also that sphincter damage and altered rectal sensation did not appear to influence the outcomes. Hotouras enlarged his study to 100 patients affected by urge, passive, and mixed fecal incontinence: purely passive fecal incontinence did not show a significant improvement, while patients with urge FI ($n = 25$) and mixed FI ($n = 60$) demonstrated a statistically significant improvement in the mean CCF-FI score (11.0 ± 4.1 to 8.3 ± 4.8 and 12.8 ± 3.7 to 9.1 ± 4.4) with an associated improvement in the QoL score [54].

A pilot study from the St. Mark's Hospital was realized in 2012 on 18 slow transit constipation patients: Wexner constipation score improved significantly as the PAC-QOL, stool frequency increased, and the use of laxatives decreased while there was no change in colonic transit time [55]. Again, Hotouras et al. (2012) published its approach to 20 unresponsive patients to PTNS over a complexive number of 100 patients treated: these patients were treated with sacral nerve stimulation (SNS), and 14 of them reported a significant therapeutic benefit with an improved incontinence score [56].

In conclusion the colorectal experience with PTNS showed encouraging results, mainly in the short term. The lower cost and invasiveness attribute to PTNS a possible future role in the flowchart treatment of fecal incontinence.

Enlarged cohort studies and high focused selected type of fecal incontinence patients need to clarify its effectiveness.

9.4 Conclusions

PTNS is nowadays a feasible option to treat pelvic floor organ dysfunctions as first- or second-line treatment. It is considered as a less invasive, safer alternative to SNS and more effective than transcutaneous stimulation. TTNS may have the advantage to be easily managed by patients at home.

No serious AEs have been reported in literature after PTNS. The majority of subjects, including children and frail older patients, seem to well tolerate the needle placement and the subsequent electrical stimulation.

Ongoing investigations improving our knowledge of neuromodulation mechanism of action are needed to increase the success rate.

New information about which factors may favor the time-duration efficacy, leading to a cost-effective treatment with impact on QoL, would afford specialists the opportunity to pursue a more appropriate individual treatment course.

Data from adequately powered comparative double-blind trials for PTNS treatment for both urinary and colorectal dysfunctions are necessary to be added to the existing evidence.

Although the sustained PTNS success, long-term follow-up is required to verify the ability of this neuromodulation technique to maintain benefits.

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Sacral Nerve Modulation: Techniques and Indications

10

Michele Spinelli

10.1 Introduction

Impaired bladder and sphincter function can be altered by various treatment modalities. Electrostimulation is one of the therapeutic options that has been used in urology for many years. The sites where the stimulation is applied have included anal, intravaginal, intravesical, tibial, and transcutaneous locations on a body surface. The success rate of those stimulation techniques varies to some degree, and this may be the reason why most of the stimulation treatment options did not gain wide acceptance. Thanks to the work of Tanagho and Schmidt first and later other urologists, chronic stimulation of the sacral nerves became one of the most accepted stimulation treatment modalities in functional urology today.

Sacral neuromodulation (SNM) uses mild electrical pulses to activate or inhibit neural reflexes by continuously stimulating the sacral nerves which innervate the pelvic floor and lower urinary tract; it is also referred to as the pacemaker for the bladder. SNM has been introduced in 1979 by Tanagho and Schmidt at the University of California in San Francisco, USA [1, 2]. From this first experimental use of SNM by surgically implanting an electrode around selected sacral nerves in dogs, InterStim™ Therapy was developed by Medtronic Inc. (Minneapolis, USA) for use in humans. It first received CE marking in Europe in 1994 and obtained Food and Drug Administration (FDA) approval for the first urological indication in October 1997. Since then, InterStim Therapy has continuously evolved in terms of knowledge of its mode of action as well as in technical and surgical aspects. Although its mode of action is still not completely known and research indicates that it involves not just efferent electrostimulation of sacral nerves but also neuromodulation due to somatosensory bladder afferents projecting into the pontine micturition center in the brainstem [3].

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No other treatment in the area of lower urinary tract dysfunctions has undergone such a wide dissemination in the last few years as the sacral neuromodulation (SNM). Major hardware developments, published literature with good clinical results, FDA approvals, and increased knowledge on the physiological mechanisms of action, played a major role in the growth of the therapy acceptance.

Many studies have described the advantage of having a test stimulation (often described as PNE) available that allows patient selection through the acute and subchronic phase of the test. The use of this acute and subchronic test stimulation in candidates for SNM therapy has always been an integral part of the method. However, exception to this approach became obvious when shown that some patients did not have a successful test but still could respond well to the therapy and have sustained clinical benefit after the permanent implantation. This was the turning point where alternatives to test stimulation and thus alternatives to patient selection would start to develop.

10.2 One-Stage vs. Two-Stage Implant of InterStim Therapy

The InterStim Therapy procedure at the beginning was proposed with the use of a test (percutaneous needle evaluation PNE) with a subsequent open surgical implant of the system.

To assess viability of SNM and to allow selection of responsive patients, testing consists of an acute stimulation period followed by a subchronic stimulation period with home evaluation.

Initially, the peripheral nerve evaluation (PNE) technique was used for the testing phase. With this technique, an insulated thin wire is placed into the third sacral nerve (S3) foramen in the vicinity of S3 with the patient under local anesthesia. This temporary unipolar lead is connected to an external neurostimulator and taped to the skin surface. Patients with at least 50 % symptom improvement proceed to removal of the temporary lead followed by implant of a quadripolar permanent lead and implantable neurostimulator (INS) placement. This is referred to as the one-stage implant because the permanent quadripolar lead and the INS are implanted at the same time. Remarkably, some patients do not have a successful test but still respond well to permanent SNM therapy with sustained clinical benefit.

An explanation for this false-negative result with the 1-stage implant procedure is that the temporary electrode is prone to migration during the subchronic test phase. The displacement probability is even higher due to the unipolar structure of the temporary lead compared to the quadripolar permanent lead. In addition, the duration of this test is limited to a maximum of 2 weeks as longer implant of temporary leads increases the probability of bacterial infection. Significant restrictions, such as no showering, also dictate short-term testing.

Furthermore, up to 33 % of the patients who have a beneficial test stimulation with a temporary lead do not continue to have a successful outcome when implanted with the INS or in other words are false-positive responders.

Therefore, better patient selection reducing false-negative and false-positive responders was considered essential for further improvement of SNM outcome. It was believed that this could be achieved by finding predictive factors and/or by improving the classical testing technique.

To minimize technical-related failures and increase test efficacy, several successive modifications have been made in the technology, which finally led to the development of currently practiced InterStim Therapy in our institutions. The most significant change was the shift from PNE (one-stage implant) to a two-stage procedure. The first stage refers to the implanting of a permanent lead for testing the response to SNM.

In the second stage, patients who are responsive after testing have the INS implanted.

The latter only consists of a minor surgical intervention.

10.3 Development of the Tined Lead

At first, the permanent lead placement was secured by fascial fixation with the patient under general anesthesia. A refined fixation method with twist locks or silicone anchors allowed a smaller incision under conscious sedation and, as such, a less invasive approach.

To further improve the technical features of the lead, a self-anchoring tined lead was designed, which received CE marking and FDA approval in 2002 [4]. The tined lead comprises four sets of silicone tines proximal to the electrodes as an integral part of the lead body, with each tine element consisting of four flexible, pliant tines (Fig. 10.1).

The system engages subcutaneous tissue, particularly muscle tissue, to decrease axial movement of the lead and consequent dislodgment of the stimulating electrodes.

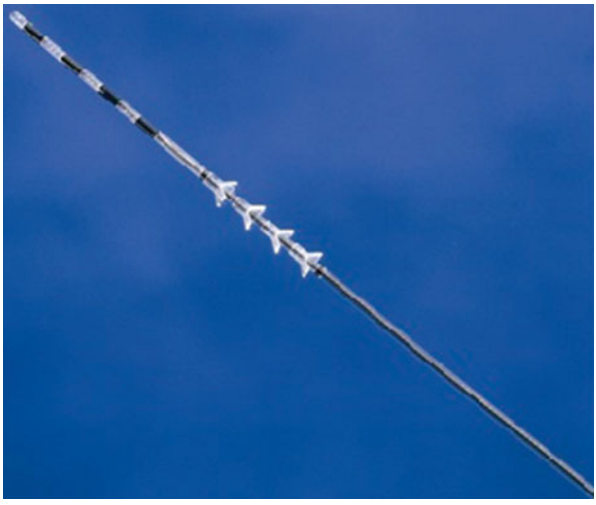

Fig. 10.1 Self anchoring tined lead

The particularity of the tined lead is that the two-stage implant can be conducted in a fully percutaneous and simplified way.

Furthermore, this technique does not preclude other treatment options, and, in contrast to surgical interventions, it can be easily reversed. So it offers the advantage of a truly minimally invasive approach for SNM, performed under local anesthesia in an outpatient setting. As such, additional to fluoroscopy of radiopaque markers on the lead and motor responses (bellows contractions of the perineum, plantar flexion of the great toe), the patient's conscious sensory responses (vaginal, perineal, or rectal) are accessible. These sensory responses are helpful to allow a more accurate placement of the permanent tined lead.

A positive outcome during screening with the tined lead was reported for 77–90 % of the tested patients [5, 6]. SNM with the tined lead resulted in permanent implant of the INS in significantly more urinary urge incontinent patients than with PNE (88 % vs. 46 %, $p=0.02$).

The minimally invasive operative procedure to test and apply InterStim Therapy with the tined lead is performed with an insertion kit consisting of a foramen needle, a directional guide wire, a dilator with a concentric plastic sheath, and the tined lead [5]. The patient is placed in the prone position with a 45° flexion of the hips and knee joints. By using local anesthesia and intravenous conscious sedation, the foramen needle is inserted in the S3 foramina.

After ensuring correct sensory and motor responses, the inner stylet of the needle is removed and replaced with the directional guide. The foramen needle is then replaced by the dilator and introducer sheath, and thereafter the directional guide and dilator are removed, leaving the introducer sheath in position. Finally, the tined lead is inserted until the proximal electrode enters the foramen (Fig. 10.2).

To verify the lead's position, an electrical signal is applied to evoke motor and sensory responses by the patient. While testing the electrodes, the position of the lead is also confirmed by fluoroscopy. With the lead held in place, the introducer sheath is retracted. The tined lead is tunnelled subcutaneously to the future implant pocket of the INS. Through a small incision at that ipsilateral place, an extension cable is introduced for connecting the tined lead subcutaneously to a pulse generator. The latter is situated at the contralateral side and is external during the first stage. This transposition with long tunnelling is chosen to prevent infection. In the second stage, the INS is implanted into the upper gluteal region in a subadipose pocket.

At the end of the each stage of the procedure and whenever there is a decrease in symptomatic response, it is recommended to perform sacral x-rays.

Buttock placement of the INS has become an alternative to subcutaneous implant in the lower part of the anterior abdominal wall because of the lower incidence of adverse events, shorter (approximately two times) operation time, and avoidance of patient repositioning during the operation.

In a prospective European multicenter study in 94 patients with different types of voiding dysfunction, screening with the tined lead was performed for on average 30 days [6]. This led to success in 72 patients (76.6 %) according to the physicians and at 6 weeks in 70 patients (74 %) when defined as ≥ 50 % improvement in symptoms compared to baseline; these 70 patients received the INS. After

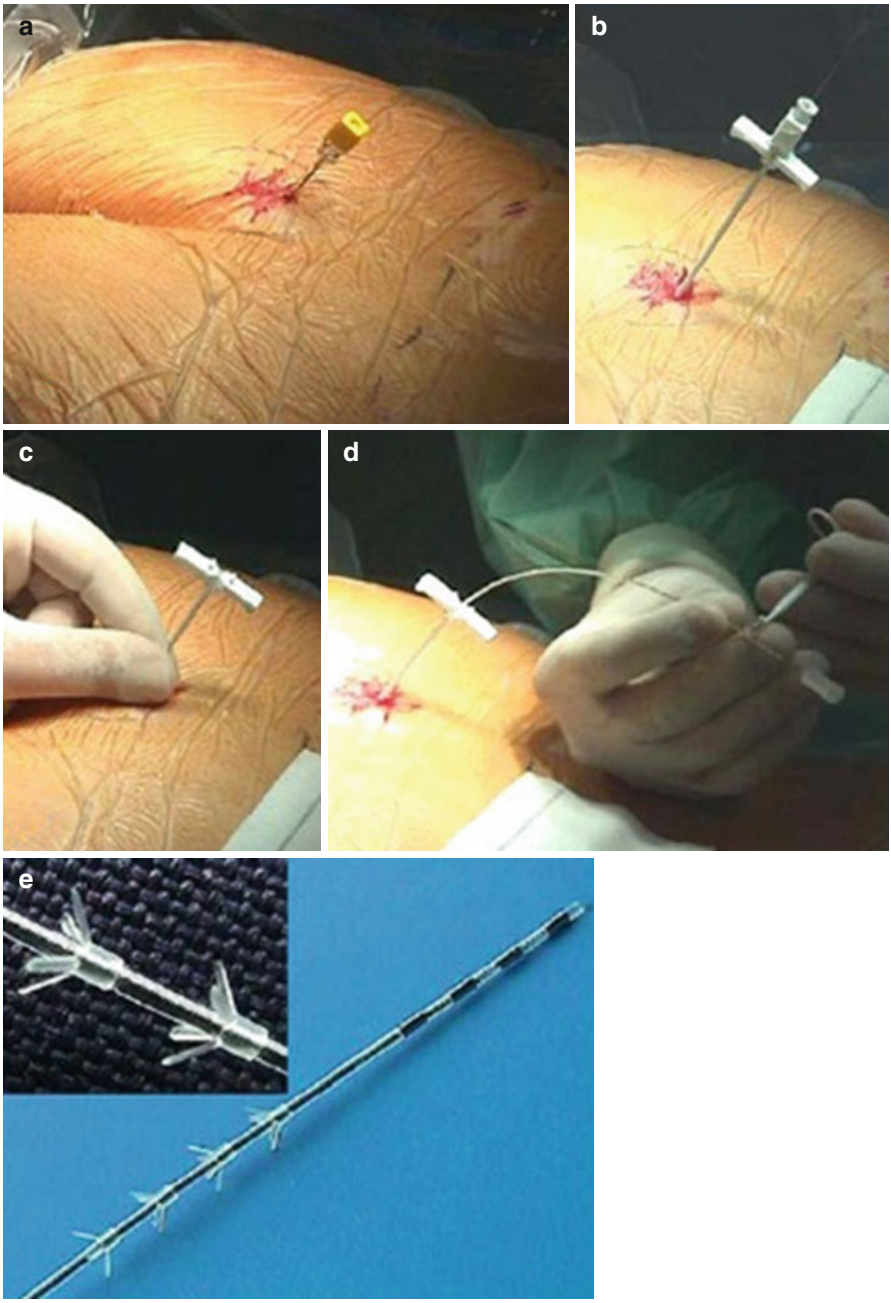

Fig. 10.2 Implant technique

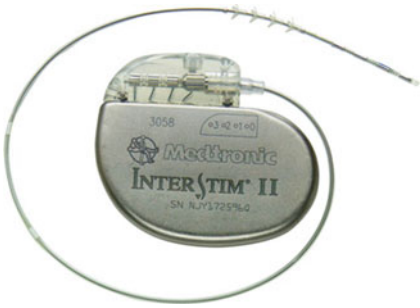

Fig. 10.3 InterStim II (Courtesy of Medtronic Inc., USA)

6 months, follow-up data were available for 20 patients with UUI and 21 patients with UR. Patients with UUI had a significant reduction in the number of daily voids ($p<0.001$), incontinent episodes ($p<0.005$), and replaced pads ($p=0.0069$). Patients with UR experienced improvements in the number of self-catheterizations ($p<0.001$), voids per day ($p<0.001$), and the catheterization volume ($p<0.001$).

A small but longer-term study with the tined lead showed that 31 of 39 patients with OAB or UR (79 %) responded; 90 % of these 31 patients had >50 % improvement in at least one of the relevant voiding dairy variables after a mean follow-up of 15.5 months. In the 21 patients with UUI or urgency-frequency, the mean number of voids and incontinence episodes per day decreased; the difference was probably not significant due to the small sample size. The mean voided volume increased significantly with 44 %.

Several technical aspects of SNM with InterStim Therapy were improved tremendously. This led to the development of the InterStim II system that has been designed to eliminate the need for extension cables, and it is also almost 50 % lighter and smaller in volume compared to the initial INS model (Fig. 10.3) [7].

The new screwdriver with only one instead of four screws aims to simplify the connection between the INS II and the tined lead. Also a new InterStim iCon patient programmer has become available with as main change the possibility to choose from four preset programs. In addition, the software of the physician programmer has been updated.

The lack of an extension cable allows for an easier and shorter implant. The data also convincingly reveal that the new screwdriver is a real improvement resulting in more connection reliability and a reduced risk of screw damage and is making the physician feel more comfortable in doing the procedure. The new iCon patient programmer is an additional advance for the patient as it is considered more patient friendly due to the amplitude being visible on the display and is providing better control of stimulation by the patient.

10.4 Conclusions

Over the last decades, SNM has proven to offer therapeutic benefit to patients suffering from chronic lower urinary tract dysfunction. SNM with InterStim Therapy is an effective treatment modality which has evolved from an elaborate technique to a minimally invasive, fully percutaneous and reversible treatment, which can be performed under local anesthesia in an outpatient setting. This has been established by several technical and surgical improvements, such as the development of the tined lead and the new INS II. In the first phase of the 2-stage implant procedure, the self-anchoring tined lead is percutaneously and permanently implanted and used to select patients for definitive INS implant. The prolonged test period and the lower risk of lead migration make this test method more reliable than the classic PNE in terms of success rate in follow-up. This has almost been doubled from approximately 50–80 %. Several studies with the tined lead have shown a favorable short- and long-term efficacy and impact on QoL for patient with different urological conditions. The tined lead procedure is also considerably safe as the risk of migration and adverse events have been reduced and are more easily manageable with troubleshooting. The reduced size of the INS II and the lack of an extension cable have made the implant easier and the operation shorter and provide more comfort to the patient. Therefore, it can be stated that SNM with InterStim (II) Therapy using the tined lead is a very valuable treatment in patients refractory to conservative treatment.

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Sacral Nerve Modulation for Urinary Disorders: Overactive Bladder

11

Marzio Angelo Zullo

11.1 Introduction

Overactive bladder (OAB) syndrome is a combination of complex urinary symptoms and is defined as urinary urgency with or without urgency urinary incontinence, usually accompanied by frequency and nocturia, in the absence of urinary tract infection or other obvious pathologies [1].

OAB syndrome affects more than 400 million people worldwide [2]. The estimated prevalence is between 12 and 17 %, and one-third of patients experience urgency urinary incontinence [3, 4]. The prevalence increases with age, affecting 30–40 % of the population >75 years of age [2]. Frequency is the most commonly reported symptom (85 %), while 54 % complained of urgency and 36 % of urgency urinary incontinence [4]. Also this syndrome has an important impact on the patient's quality of life.

OAB symptoms are due to involuntary contractions of the detrusor muscle during the filling phase of the micturition cycle. These involuntary contractions are termed detrusor overactivity and are mediated by acetylcholine-induced stimulation of bladder muscarinic receptors [5]. It has been estimated that 64 % of patients with OAB have urodynamically proven detrusor overactivity and that 83 % of patients with detrusor overactivity have symptoms of OAB [6].

11.2 General Principles of Treatment

The treatment of patients with OAB is complex, and international guidelines suggest lifestyle interventions, pelvic floor reeducation, bladder retraining, and antimuscarinic drugs as first-line treatment options.

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11.2.1 Medical Treatment

While a conservative approach is justified initially, drug therapy is the main treatment in the management of women with OAB syndrome. The most recent systematic review [7], including six different drugs, supports the efficacy of antimuscarinic therapies in patients with OAB syndrome. They have been proven to be more effective than placebo, confirming a grade A of level of recommendation for OAB in women. Nevertheless, all types of antimuscarinic agents cause side effects, with dry mouth (30 %) and constipation (8 %) as the most frequent. Consequently, the compliance with immediate release preparations has been reported to be low, with only 18 % of patients continuing therapy at 6 months [8]. This has not improved despite the introduction of long-acting slow-release drugs. A recent retrospective study has shown persistence rates with the antimuscarinic therapy at 12 months ranging from 14 to 35 %, with little difference among different preparations [9]. The high discontinuation rate of antimuscarinic treatment may be due to intolerable side effects and insufficient improvement of symptoms. However, it is well known that younger patients were more likely to stop using antimuscarinic agents.

An important role has been proposed for the beta 3-adrenergic receptor in promoting urine storage in the bladder by inducing detrusor relaxation [10]. Mirabegron is a beta 3-adrenergic receptor agonist that has been developed for the treatment of OAB and represents a new class of drug therapy with proven efficacy and good tolerability [11]. Further long-term studies are needed to demonstrate the true efficacy and safety of the drug.

When conservative therapies fail, alternative treatments should be considered.

11.2.2 Minimally Invasive Techniques

New and minimally invasive techniques are available such as percutaneous tibial nerve stimulation (PTNS), intradetrusor injection of botulinum toxin (BTX), and sacral neuromodulation (SNM).

PTNS involves stimulation of afferent fibers of the posterior tibial nerve (L4–S3) accessed just above the ankle. In a recent meta-analysis on the effectiveness of PTNS, the subjective success rate was 61.4 % (95 % CI 57.5–71.8), and objective success rate was 60.6 % (95 % CI 49.2–74.7) [12], but the maintenance treatment was necessary to successfully treat the patients with OAB [13].

BTX is a neurotoxin derived from *Clostridium botulinum*, and its effect is to inhibit the release of acetylcholine, adenosine triphosphate, and substance P from the urothelium. The BTX injected into multiple sites in the detrusor muscle via cystoscopy should lead to bladder paralysis and consequently may reduce the symptoms of OAB, but its exact action is not completely understood [14]. A recent study on botulinum toxin type A (200 units) injected in the detrusor muscle showed that 31 % of patients with OAB were continent after 6 months, but urinary tract infection (31 %) and self-catheterization (16 %) were common [15]. Furthermore the effect

of BTX may last between 3 and 12 months, but robust evidence on long-term outcome is lacking [16].

11.3 Sacral Neuromodulation

SNM has been approved by the Food and Drug Administration (FDA) in 1997, and more than 150,000 patients have already received this treatment worldwide [17]. SNM is currently recommended by expert panels for the treatment of intractable OAB syndrome [18].

SNM therapy involves the use of mild electrical pulses to stimulate the sacral nerves. During the test phase of peripheral nerve evaluation (PNE), a temporary lead is placed, with patient under local anesthesia, next to the sacral nerve, usually S3, that gives intraoperatively the better motor response on the patient's pelvic floor. A positive motor response with or without a sensory response has been shown to be a better predictor than a sensory response alone of a positive test stimulation [19]. The subchronic phase is usually considered successful when there is at least 50 % improvement of symptoms. Patients with a successful treatment receive a permanent implant, which consists of a definitive electrode connected to an implantable pulse generator.

Migration of the temporary lead and failure of this technique to identify responders to permanent SNM led to the development of a two-stage implant technique [20]. With this technique a permanent tined lead is implanted under local anesthesia and connected to an external "screener" and left in place for 4–8 weeks. If the symptoms of patient improve by at least 50 %, the permanent implantable pulse generator is implanted in the soft tissue of the patient (usually in the buttock). The reoperation rate appears to be decreased with the introduction of tined lead technique [21].

11.3.1 Efficacy

The results of seven randomized trials have been reported in the literature [22–28], and they are consistently in favor of the implant. When complete continence was studied, almost 50 % of the implanted patients were continent at 6 months as opposed to 1.6 % in patients in the delay group, while a total of 87 % showed an improvement more than 50 % in the number of leakage episodes as opposed to 3 % in the delay group [29] (Table 11.1).

Weil et al. [28], Schmidt et al. [26], and Hassouna et al. [25] showed that the daily number of leakage episodes and of pads used was significantly lower 6 months after implantation in the stimulation group compared with baseline. Weil et al. [28] also observed that mean bladder capacity assessed by cystometry increased at 6 months compared with baseline in the stimulation group.

Although evidence from case series studies can be less reliable than evidence from randomized trials, because of the risk of confounding, it is notable that these results are similar to those of the randomized trials. In more than 40 case series

Table 11.1 Success rates at 6 months in the randomized trials

	Stimulation group (%)		No treatment group (%)	
References	Cured	Improved	Cured	Improved
Weil [28]	9/16 (56)	Not reported (29)	1/22 (5)	0/22 (0)
Schmidt [26]	16/34 (47)	10/34 (29)	0/42 (0)	2/42 (5)
Hassouna [25]	–	22/25 (88)	–	8/25 (32)

studies, about 39 % of patients with urgency urinary incontinence were cured following implantation, and 67 % of patients achieved 50 % or greater improvement in incontinence symptoms [29]. In addition, in the case series studies, the benefits of neuromodulation were reported to persist at follow-up periods 3–5 years after implantation.

Results of persistence of the clinical success in the long term appear to be conflicting. A randomized study [30] suggested some reduction of efficacy with time: a similar proportion (46 %) of patients with urgency urinary incontinence remained dry at 3 years and 6 months after SNM, but only 59 %, as opposed to 87 %, showed greater than 50 % improvement in the number of leakage episodes. Further, a multicenter 5-year prospective trial showed reduction of the number of leakage episodes and pads used in patients with urgency urinary incontinence and decrease in frequency and urgency and increase in mean voided volume per micturition episode in OAB dry patients [31].

By contrast, a 5-year follow-up study [24] on 121 patients with refractory OAB showed persistence of the clinical success in the long term: 84 % of the patients with urgency urinary incontinence and 71 % of the patients with urgency/frequency who had a successful outcome 1 year after implantation continued to have a successfully outcome after 5 years.

The use of SNM may also be recommended for particular populations such as the elderly. Despite age over 55 years and the presence of three or more chronic comorbidities were considered as negative predictive factors for successful outcome with SNM in urinary urge incontinence [32]; in our study [33] on 18 patients over 65 years affected by intractable OAB, 15 women obtained an overall success rate of 83 %. Among all women who underwent implantation of SNM, there was also a statistically significant improvement in the health-related quality of life. No major long-term complications occurred; minor ones happened in two patients (13.3 %) who complained of pain at the pulse generator site; in both cases the event resolved after 3 months using anti-inflammatory treatment. SNM can be considered a viable alternative for treating OAB syndrome in well-selected elderly women.

11.3.2 Quality of Life

Satisfaction and quality of life after SNM have also been studied. Quality of life improvements have been reported in patients with detrusor overactivity, and a strong

correlation was identified between the number of incontinence episodes and quality of life index.

Cappellano et al. [34] showed a significant improvement in the quality of life score in patients with urgency urinary incontinence who underwent SNM: at 18 months of follow-up, 90 % of subjects gave a positive response to treatment and 100 % of patients recommended it to a relative or friend. In addition, Foster et al. [35] showed that the majority of patients (84 %) were satisfied with SNM treatment.

11.3.3 Adverse Events

Adverse events associated with SNM implant have been extensively discussed in the literature. A recent study reported an explantation rate of 21 % and a surgical revision rate of 39 % [36]. The most common complications [25, 28, 31] are pain at the implant site (3–42 %), lead migration (1–21 %), wound problems (5–8 %), bowel dysfunction (4–7 %), infection (4–10 %), and pulse generator problems (5 %). The majority of adverse events do not require surgical intervention, but conservative treatment. The introduction of the tined lead and the two-staged procedure have positively affected the adverse event and reoperation rates. Lower incidences of pain (2.5 %), lead migration (0.6 %), and infection (2.5 %) were reported in a follow-up study [37]. Surgical revision was required in 16 % of patients including those with reduced efficacy (10 %) [37]. The learning curve and patient selection may have an additional beneficial effect on the reoperation rates [31].

11.3.4 SNM Versus Botulin Toxin

Studies comparing the effectiveness of the SNM versus BTX have produced conflicting results [15, 31]. A decision analysis model was constructed using values for efficacy and complications from the literature and the personal series. Markov state transition modeling was used with health states and transitions between states designed to fully account for the complex interplay of therapeutic efficacy and multiple possible complications. Overall outcomes and complications for the two operations (SNM vs. BTX injection) were yearly compared (Fig. 11.1), and the probability of success of the SNM was higher than the BTX injection (59 % vs. 48 %, $p < 0.05$, respectively).

11.3.5 Cost-Effectiveness

Few studies have examined the cost-effectiveness of SNM. Siddiqui et al. [38] suggested that SNM treatment strategy was more expensive ($ 15743 vs. $ 4392) but also more effective (1.73 vs. 1.63 quality-adjusted life years – QALYs) than BTX injections in the first 2 years of therapy. However Leong et al. [39] showed that SNM treatment was cost-effective after 5 years compared to BTX injection.

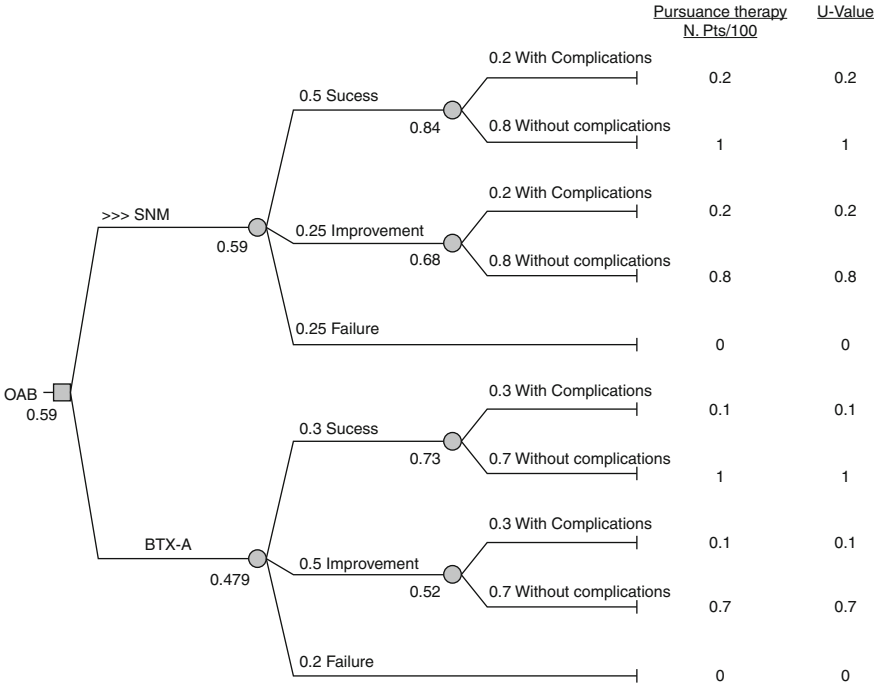

Fig. 11.1 Decision-makers on the clinical benefits between SNM and BTX

11.4 Conclusions

In conclusion, current evidence supports the short- and long-term efficacy of SNM in treating intractable OAB syndrome, and, in addition, there is a low incidence of adverse events, many of which do not require reoperation. Currently SNM stands as the single licensed second-line treatment for OAB, but more research is needed to improve the selection of patients and the identification of more prognostic factors and to clarify the reduction in effectiveness over time.

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Sacral Nerve Modulation for Urinary Disorders: Urinary Retention

12

Maria Paola Bertapelle

12.1 Introduction

Sacral nerve modulation (SNM) represents a well-established treatment for urinary symptoms suggestive of a low urinary tract dysfunction (LUTD). Either storage symptoms or voiding ones can be restored by SNM therapy. Among voiding symptoms, straining and poor stream are often associated with a certain degree of urinary retention. This last condition may either be due to detrusor dysfunction during voiding (detrusor underactivity, acontractile detrusor) or to abnormal urethral function (dysfunctional voiding or non-relaxing urethral sphincter obstruction) [1]. Sacral nerve modulation therapy may restore voiding either in urinary retention sustained by detrusor underactivity (or acontractility) or by urethral dysfunction. The Food and Drug Administration (FDA) approved the InterStim® (Medtronic, Minneapolis, Minnesota, USA) device for nonobstructed urinary retention in 1999. The condition "nonobstructed urinary retention" was mentioned to exclude urinary retention associated with obstructed voiding in benign prostatic hypertrophy (BPH), urethral strictures, or genital prolapse from SNM therapy.

Dysfunctional voiding and non-relaxing urethral sphincter obstruction can be considered, from a functional perspective, as causes of obstructed voiding and are often associated with urinary retention. They represent a major indication for SNM therapy. This is the reason why it should have been better to clearly refer to anatomical or organic obstruction as a contraindication for SNM.

Since the first report of the technique for the functional evaluation of sacral nerve root integrity by Tanagho and Schmidt in 1990 [2], which got off SNM surgery, thousand of papers have been written about SNM therapy. The first clinical report by Siegel in 1992 hypothesized a common denominator for storage and voiding

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dysfunction to be highlighted in interference with normal patterns of reflex coordination between the bladder, sphincter, and pelvic floor. The rationale for SNM had to be found in the observation by Tanagho and Schmidt (1988) that stimulation of the sacral nerves via an electrical implant could inhibit inappropriate neural reflex behavior [3]. Preliminary clinical results reported by Tanagho and Schmidt [4] and Siegel [5] showed the most successful to be patients whose presentation included dysfunctional voiding symptoms and urinary retention. The Sacral Nerve Stimulation Group (1999) conducted a prospective randomized study about SNM therapy, in accordance with regulatory requirements of the 16 contributing worldwide centers. Positive results of SNM for the treatment of urinary retention were lesser (38.4 %) than those reported in a highly selected group of young women who had urinary retention and associated dysfunctional voiding (68 %) [6]. The underlying condition had therefore to be considered as essential to gain an optimal result of SNM therapy.

12.2 Urinary Retention. Two Main Actors: The Detrusor and the Urethral Sphincter

Bladder voiding is described in terms of detrusor and urethral function and assessed by measuring the urine flow rates and voiding pressures. Pressure flow study of voiding is the method by which the relationship between the pressure in the bladder and urine flow rate is measured during bladder emptying. Normal voiding is achieved by a voluntarily initiated continuous detrusor contraction that leads to complete bladder emptying within a normal time span and in the absence of obstruction. Normal urethra function during voiding is defined as the urethra that opens and is continuously relaxed to allow the bladder to be emptied at a normal pressure [1]. Coordination between detrusor contraction and urethral relaxation is therefore essential for a coordinated and complete bladder voiding. Whenever bladder contraction fails or urethra relaxation does not happen, urinary retention may occur. Bladder contraction may fail in neurogenic lesions, due to pharmacological interference, after surgery or whenever a detrusor myogenic damage occurs (bladder acontractility). Detrusor myogenic damage is the most common consequence of prolonged or acute bladder overdistension. In ICI-RS 2011 [7], the authors analyzed the nature of acute overdistension occurring in an individual where the bladder becomes anatomically overdistended for a prolonged period of time. The problem with acute bladder overdistension is that a primary, usually temporary, neurogenic dysfunction associated with decreased or absent bladder sensation combined with temporary neurogenic detrusor underactivity is present. If not treated rapidly, overdistension causes secondary myogenic damage to the bladder due to changes in architecture and function, along with edema in the lamina propria and the smooth muscle of the bladder indicating tissue damage [8].

Detrusor may also fail to contract due to detrusor inhibition resulting from a failure of urethra relaxation. As far as urethra failing to relax is concerned, it may occur in neurogenic lesions and in dysfunctional voiding (neurologically normal individuals). In 1998, Fowler [9] described a syndrome characterized by urinary retention in young females with endocrine dysfunction and, in a good percentage of

cases, polycystic ovary. In these women abnormal needle electromyographic signals of the urethral striated sphincter were recorded: both complete repetitive discharges and decelerating bursts. The hypothesis was that the state of contraction of the urethral sphincter during voiding could inhibit detrusor contraction and lead in time to detrusor acontractility. Dysfunctional voiding is often observed in young females, not Fowler's syndromes, as a consequence of acute emotional stress, sexual abuse, etc.

Dasgupta et al. [10] examined the changes in brain activity in eight women with urinary retention due to sphincter overactivity (Fowler's syndrome) treated with SNM. Patients underwent brain imaging with positron emission tomography (PET) in order to identify regions of brain activity related to perception of bladder fullness and their modulation by SNM. In healthy controls, bladder fullness increased activity in the brainstem (midbrain) and limbic cortical regions. In contrast, women with urinary retention showed no significant brainstem activity, but did show increased limbic cortical activity. The application of SNM therapy in this group of women resulted in a normal pattern of midbrain activity and decreased cortical activity.

12.3 How to Manage Urinary Retention: From Conservative Options to Functional Therapy

Self intermittent bladder catheterization represents the gold standard to manage urinary retention. Whenever voiding still occurs (reduced volumes spontaneously or by abdominal straining), completion catheterization allows bladder emptying. Training to perform self intermittent catheterization is mandatory in patients with either complete or incomplete urinary retention. A compliant patient regularly performing intermittent bladder draining by catheterization is the best candidate for functional therapeutic options. In urinary retention, either sustained by detrusor or sphincteric dysfunction, no radical surgical procedures are recommended (whenever good anatomical bladder condition is assured). Pharmacological treatment in the case of detrusor acontractility is limited to the provisional use of muscarinic receptor agonists (choline esthers). Bethanechol can be used not lesser than 100 mg/day for not more than a week to stimulate residual bladder contractility in urinary retention due to acute recent overdistension. Pharmacological properties of bethanechol are to stimulate the urinary tract as well as the gastrointestinal tract rather selectively. The choline esters increase ureteral peristalsis, contract the detrusor muscle, and increase the maximal voluntary voiding pressure [11].

Pharmacological treatment of dysfunctional voiding implies the use of muscle relaxants such as baclofen (low doses of 10–20 mg a day), a $GABA_B$ agonist. Benzodiazepines may also be used as muscle relaxants, with little clinical effect.

Sacral nerve modulation represents a well-established functional therapy for urinary retention. With more than 20 years of clinical application, SNM treatment represents the best functional therapeutic option to reserve for urinary retention patients. Optimization of patient selection is mandatory to obtain the best result from SNM therapy. Optimizing patient selection also means to be able to introduce them into the world of functional therapy. Since results of chronic SNM may vary in time, depending on multiple factors (periodical bladder relaxation, adaptation of

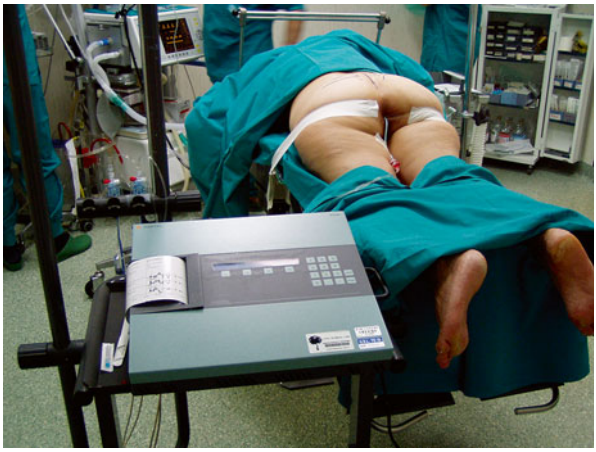

Fig. 12.1 DCT: manometric control of the bladder and bowel pressures

nervous system to chronic electrical stimulation), patients have to be trained to periodically control complete voiding by self-catheterization.

As far as detrusor failing to contract is concerned, we need to know whether detrusor acontractility depends on a myogenic damage. In this case, self intermittent catheterization will be the only option since the reappraisal of a potential detrusor contractility. A tool to highlight the presence of myogenic detrusor damage, not to be treated by SNM, is detrusor contractility test (DCT) [12]. The original technique of DCT was performed in general anesthesia, now performed in sacrally restricted anesthesia: with the patient in the sitting position, a 27–29 gauge spinal needle is introduced at L4–L5 spinal level and 1 ml solution of 0.5 % hyperbaric bupivacaine and sufentanil two to three micrograms injected. Sitting position is maintained up to 20 min. The patient refers a sensation of warmness and voluntarily moves his/her lower limbs, normal touch sensitivity. The patient is then placed in a 30° head down supine position; the bladder is filled with 250 ml saline solution. A 9 Ch 2 channel urodynamic catheter and rectal probe are then placed. DCT is performed under manometric control of the bladder and bowel pressures (Fig. 12.1) in the prone position. Ground patch is placed at the level of the foot, to avoid burning sensation during electrostimulation. Using an external electrostimulator (1–30 V, 3–30 Hz, Fig. 12.2), somatic (3 V, 3 Hz) contraction is evoked to assess the integrity of nerve conduction. Autonomic (30 V, 30 Hz) contractions are monitored during and at the end of acute electrostimulation of S2 and S3 nerves, bilaterally (Fig. 12.3). In the case of lack of bladder contraction, whereas a bowel contraction occurs, a detrusor myogenic damage is suspected. The patient is then informed about the necessity of continuously performing intermittent catheterization and draining the volume to lesser than 400 ml of urine, and SNM therapy has to be postponed.

Dysfunctional voiding with urinary retention can be regarded as the most suitable dysfunction to be treated with SNM. Negative control exerted toward the bladder by a contracted urethral sphincter (hyperexcitability of vesico-urethral reflex) maintains urinary retention. SNM modulates this dysfunctional reflex. The statement by

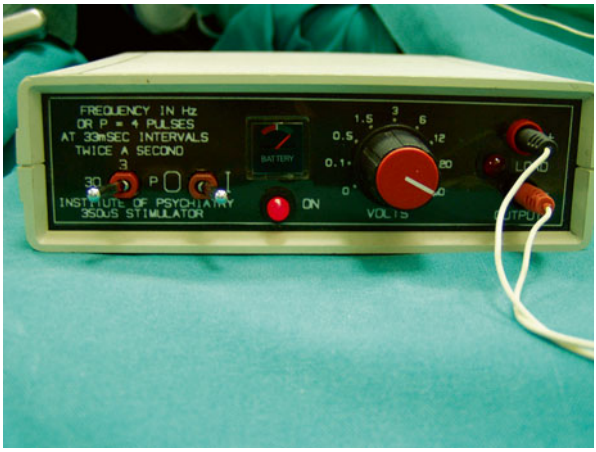

Fig. 12.2 DCT: external stimulator

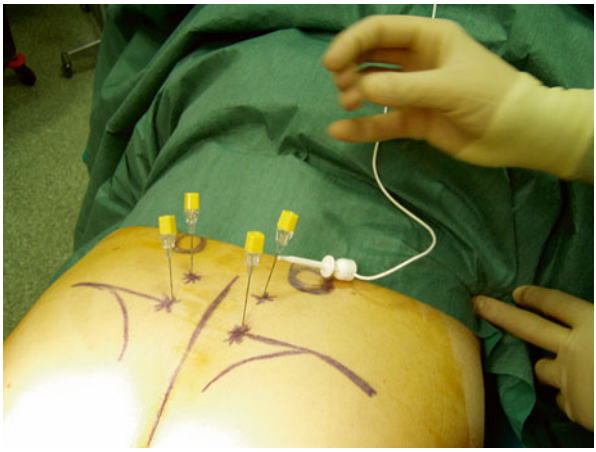

Fig. 12.3 DCT: testing needles in S2 and S3 foramina, bilaterally. Patient cable stimulating right S2

Tanagho and Schmidt in 1991 [13] that "neuromodulation through foraminal stimulation of the sacral nerve depends on electrical stimulation of afferents axons that modulate sensory processing of the voiding reflex pathways of the central nervous system" is still up-to-date. During the last 15 years, research in the field of electrical modulation of the nervous system through the sacral nerves has refined and completed this initial hypothesis.

12.4 Sacral Neuromodulation: From Testing Its Efficacy to Follow-Up of Permanent Implant

Patients with urinary retention selected to receive SNM therapy have to be tested for the efficacy of functional treatment. Percutaneous needle testing of nerve functional integrity followed by placement of a temporary wire electrode (percutaneous nerve

evaluation, PNE) has been used for years as the only tool for patient selection. The duration of the stimulation test varied from a few days to a week; wire electrode displacement occurred even in informed and properly nursed patients. In well-selected patients with dysfunctional voiding, spontaneous micturition often occurred within few hours from electrode placement. In other cases, spontaneous voiding did not occur, and in most of cases, suboptimal nerve stimulation was suspected. PNE revealed in time as a non-reliable tool for the selection of patients. This observation stimulated the research of a more reliable electrode placement to test the patients. Janknegt (1997) suggested the use of surgically implanted permanent electrode to test the patients [14], proposing for the first time a two-stage technique. Permanent electrode was connected through a temporary extension to external screener. The two-stage technique allowed longer stimulation test. The need for open surgery to implant (and to remove, in case of unsuccessful test) permanent electrode represented the main limit of the two-stage technique. The ardent research of a more feasible system to test the patient led to the development of a percutaneously implantable electrode [15], the tined lead system. Since then permanent tined lead electrode was used to test the patient in a two-stage implant. In case of positive follow-up of the first stage, the tined lead is connected to permanent InterStim® device. The flexibility of percutaneous tined lead implant and removal increased the number of tested patients and the percentage of positive results of SNM therapy, especially in the retention group of patients. A first randomized prospective study [16] evaluated PNE technique versus a surgical first stage tined lead placement to better predict whether a patient would progress to an implantation of permanent device. The study was conducted in a cohort of older urge incontinent women; the authors concluded that the first stage procedure using the tined lead electrode better predicted progression to implantable pulse generator placement than PNE in that cohort of patients.

The implant of the InterStim® device (second stage of SNM implant procedure) requires accurate nursing to instruct the patients how to manage their symptoms with implanted device. Since urinary retention may happen again, it is important to train the patient to recognize eventual incomplete voiding or signs of bladder overdistension and to perform intermittent catheterization. Voiding diary is a mandatory tool for nurses to follow up patients immediately after surgery; it becomes a precious tool for the patient to check voided volumes in time. In patients with urinary retention that may be eligible for SNM, strict control of the urinary bladder capacity is essential. Patients with bladder capacities of more than 500 mL often request immediate SNM testing. However, before the SNM evaluation, the regular use of clean intermittent self-catheterization with a 400-mL bladder capacity limit is mandatory to remodel the detrusor muscle as a base for efficacy.

InterStim® device is programmed by an external device to optimize the quality of chronic stimulation. The patient needs to be trained to the use of a personal device (i-Con® patient's programmer) to communicate with InterStim® device. i-Con® device is a relatively new tool in which utility is conditioned by the quality of training to use it.

12.4.1 Results

A report of the use of SNM in UR was published in 2001 by Jonas et al. [6] in which 177 patients with UR refractory to conservative therapy were enrolled between 1993 and 1998. Thirty-seven patients were assigned to treatment and 31 to the control group. At 6 months the stimulation group showed 69 % elimination of catheterization and an additional 14 % with greater than 50 % reduction in catheter volume per catheterization. Temporary inactivation (3 days) of SNM therapy resulted in significant increase in residual volume. The effectiveness of SNS therapy was sustained for18 months after implantation.

Recently, the 5-year follow-up results of patients included in the trial in order to obtain FDA approval were analyzed. Of 163 patients enrolled, 152 have been implanted. Of the 163 patients, 103 (64 %) had UI, 28 (17 %) UF, and 31 (19 %) UR. Voiding diaries were collected annually over 5 years. In the UR group, the average number of catheterizations per day decreased from 5.3 at baseline to 1.9 at 5 years post implant [17]. However, an important finding in this study is the high correlation between 1- and 5-year success rates. Of the implanted patients, 78 % with UR continued to have a successful outcome at 5-year follow-up, if successful at 1 year.

This result was confirmed in the study of White and colleagues [18]. At a mean follow-up of 40 months, 85.7 % of patients with refractory, nonobstructive urinary retention demonstrated greater than 50 % improvement in symptoms with SNM.

The presence of Fowler's syndrome is a positive predictive factor for SNM in female urinary retention. Idiopathic urinary retention patients can benefit as well, but the success might be less predictable. This was suggested in the study of De Ridder and colleagues [19], in which 62 women were implanted, 30 with Fowler's syndrome, and 32 with idiopathic retention. Twenty-eight patients failed: 9 with Fowler's syndromes and 19 without ($p=0.04$). Kaplan-Meier analysis showed that patients with Fowler's syndrome benefitted significantly longer from SNM (log-rank test, $p=0.005$). Moreover, considering a validated psychological questionnaire, in those with Fowler's syndrome, 26.6 % screened positive for somatization, as did 43.8 % in the idiopathic group (not significant). Screening for depression was positive in 30 and 18.8 %, respectively (ns). There was no correlation with the outcome.

12.5 Conclusions

Urinary retention without an identifiable urological cause presents a diagnostic and therapeutic challenge. Patients with nonobstructive chronic urinary retention usually have to rely on intermittent self-catheterization or indwelling suprapubic or transurethral catheters, which significantly affect quality of life. Sacral nerve stimulation is a minimally invasive treatment for nonobstructive urinary retention, with 10 years of data documenting its long-term safety and efficacy. The evolution of SNM devices and improvements in surgical and testing techniques, especially the

introduction of the two-stage tined lead procedure, have considerably reduced the failure, adverse event, and surgical revision rates associated with SNM, ensuring that this modality is an effective minimally invasive treatment for urinary retention. However, SNM therapy in urinary retention needs dedicated specialists to accurately select and follow up the patients and adequate nursing by dedicated and trained staff.

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Sacral Nerve Modulation for Fecal Incontinence

13

Donato F. Altomare, Simona Giuratrabocchetta, Ivana Giannini, and Michele De Fazio

13.1 Background

Sacral nerve stimulation is an innovative, mininvasive approach to fecal incontinence and other pelvic floor dysfunctions based on the delivery of electrical stimuli to the pelvic nerves through an electrode percutaneously positioned through the sacral foramen (usually S3) and connected to an implantable pulse generator. This technique has the unique advantages to affect continence without performing operations on the anal sphincter and to have the possibility to pretesting the outcome of the definitive implant with a low-cost temporary stimulation. Its reliability and effectiveness is nowadays recognized by the FDA [1], by the NICE [2], and by the main Coloproctological scientific societies (ASCRS, ESCP, ICS) and systematic reviews [3].

13.2 Indication for SNS Therapy

The indication for using sacral nerve stimulation started in urinary incontinence, particularly in patients with detrusor instability [4], but its application has been extended to several other pelvic floor disorders, particularly in fecal incontinence after the first demonstration by Matzel in 1995 [5]. Since its mechanism of function was poorly understood, SNS has been applied to several types of fecal incontinence. At the beginning, only patients with major fecal

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incontinence and with integrity of the hypothesized target organs (anorectum and anal sphincters) and neural pathways were included, but with the growth of experience and the evidence of the importance of the central sensory effects of SNS, the procedure was applied successfully to several new types of fecal incontinence.

Although unofficially, the excluding criteria originally included congenital anorectal malformations, previous rectal surgery, rectal prolapse, chronic diarrhea, irritable bowel disease, neuropathies like SLA, multiple sclerosis, Parkinson's disease, spinal cord injury, ulcerative colitis, anal fistulas, pregnancy, and mental or physical inability to adhere to treatment.

Although urge fecal incontinence was believed to be the best indication, several reports indicate that the type of incontinence, passive or urge, does not affect the success rate of SNS [6, 7]. A series of reports demonstrated that SNS could benefit even to patients complaining fecal incontinence after the resection of the rectum for cancer [8, 9] and those with some degree of anal sphincter lesion [10]. The latter is of paramount importance since it is a further demonstration that SNS affects the continence mechanisms more through a centrally mediated sensory effect than a peripheral muscular contraction.

13.3 Technical Evolution

Electrical stimulation of the pelvic nerves was originally intendant to help paraplegic patients in the rehabilitation of their lower extremities and to assist micturition [11, 12]. The approach to the pelvic nerves was originally performed anteriorly by means of a difficult and risky operation, but it became soon clear that they could have been easily stimulated posteriorly through the sacral foramens. Since the end of the last century, a demanding operation under general anesthesia was necessary to expose the 3rd sacral foramen through a 10 cm paramedian sacral incision and to place the electrode through it, securing its position by non-resorbable sutures to the sacral periosteum (Fig. 13.1). To avoid this invasive approach, there has been an attempt to fix the electrode to the fascia of the gluteus maximum after its percutaneous position through the sacral foramen, but still there was a high risk of displacement (Fig. 13.2).

The procedure was made easier and reliable by Spinelli [13] after the introduction of a tined quadripolar lead (model 3889, Medtronic, USA) provided with special plastic wings to prevent accidental displacements, which can be placed by means of a total percutaneous access with an introducer kit (Fig. 13.3). This method is nowadays used all over the world and, because of the higher reliability compared to the monopolar wire electrode, is used also for the percutaneous nerve evaluation (PNE) temporary testing [14] (Fig. 13.4).

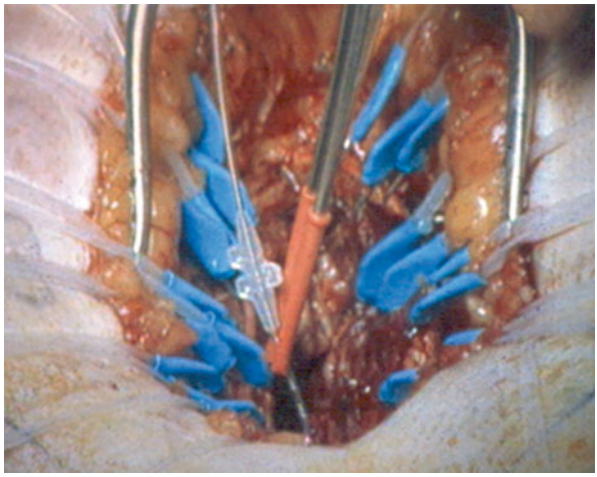

Fig. 13.1 Open surgical approach to the S3 foramen

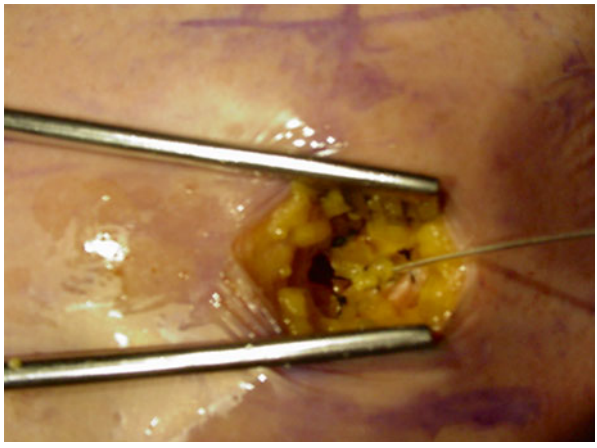

Fig. 13.2 Sacral electrode fixed to the fascia of the gluteus maximum

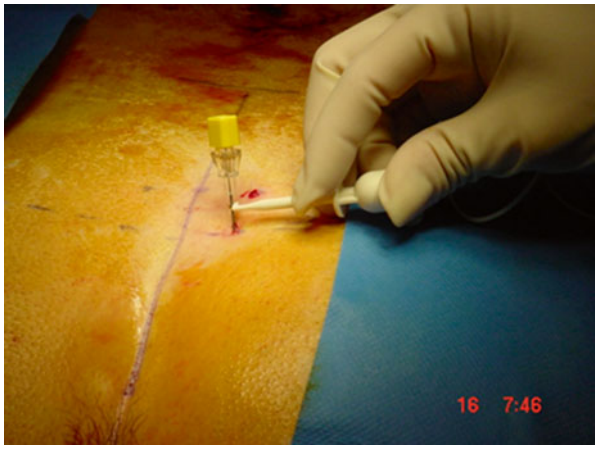

Fig. 13.3 The percutaneous nerve evaluation (PNE) test

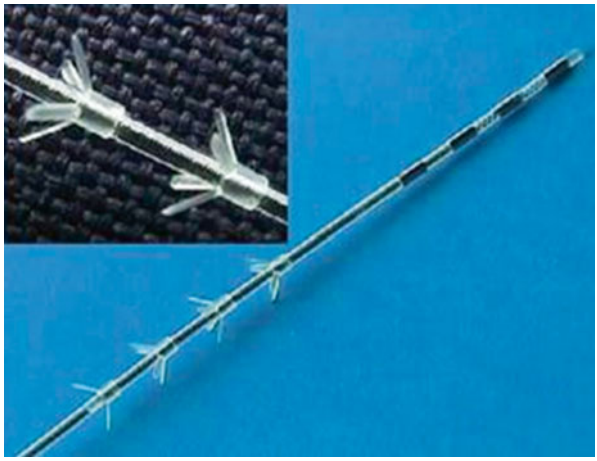

Fig. 13.4 Tined lead quadripolar electrode

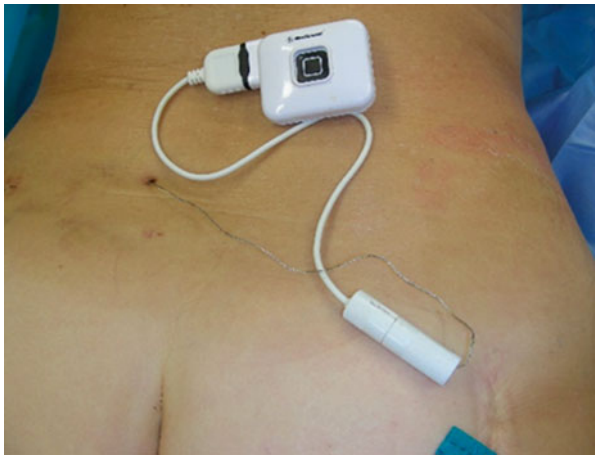

Fig. 13.5 Verify™ External neurostimulator (mod 3531 Medtronic, USA)

The traditional screener for the temporary test period was changed with a new patient's è programmer (mod 3537 Medtronic, USA) (Fig. 13.5) connected via Bluetooth to a new interactive screener which can be programmed by the patient and the doctor (Fig. 13.6).

Finally, the implantable pulse generator also was made smaller and thinner (InterStim™ II, model 3889, ©Medtronic, USA, Fig. 13.7) with an easy and simple direct connection to the electrode compared to the earlier model which also needed an extension wire to connect the electrode to the pulse generator. The patient portable programmer (iCon™ model 3037, ©Medtronic USA) was made compact and with an interactive display (Fig. 13.8).

Fig. 13.6 Patient's programmer (mod 3537, courtesy of Medtronic Inc., USA)

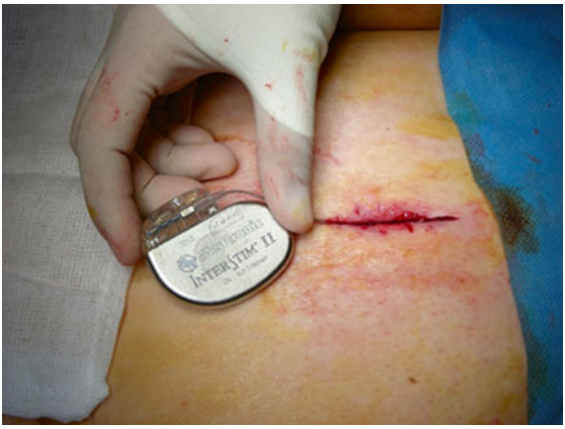

Fig. 13.7 Implantable neurostimulator InterStim II® (mod 3058, courtesy of Medtronic Inc., USA)

Fig. 13.8 Patient's programmer iCon® (mod 3037, courtesy of Medtronic Inc., USA)

13.4 The Procedure of SNS

The usual approach consists of a two-step procedure which has recently been modified together with the changes of the technical devices.

Nowadays, in most of the centers for SNS, the first step is performed under local anesthesia and short-term antibiotic prophylaxis with the patient in prone position and consists of the percutaneous positioning of the tined quadripolar electrode through one of the S3 foramens previously identified on the skin of the sacral region on the base of some bone landmarkers. The exact lead position is controlled under fluoroscopy and by stimulating a test needle (Fig. 13.3) before placing the electrode, which is then tunneled under the skin and connected, through an extension, to the new Verify™ device. The latter is connected via Bluetooth to the patient's programmer (model 3537 Medtronic, USA). The stimulation parameters are then optimized according to the patient sensation in the perineum.

During the next 2–3 weeks, the patient will fill in a dedicated stool diary in order to record any episodes of incontinence and to recalculate the scores of incontinence. If at least one of these tools will show at least 50 % improvement, the patient is rescheduled for the definitive implant of the pulse generator (InterStim II, mod. 3889, Medtronic, USA) which will be connected directly to the electrode and placed under the skin of the gluteus region.

13.5 Stimulation Parameters

This aspect of the SNS has poorly been investigated, and there are no trials comparing different parameters, despite the change of voltage, frequency, and pulse width is frequently performed in the follow-up of these patients searching the best combination for success stimulation.

While the pulse width is rarely modified from the default of 210 μs during the follow-up of these patients, the frequency is often changed ranging from 14 to 31 Hz, even if the best combination with other stimulation parameters has never been established. Usually urologists are more prone to use higher frequencies than coloproctologists.

The voltage is normally set to the minimum required to reach the patient sensory threshold because this can spare the battery life and reassure the patient about the active function of the stimulation. Actually, the voltage value is dependent of the proximity of the electrode to the pelvic nerves and of the integrity of the neural pathways.

The only paper dealing with manipulation of the stimulator parameters was carried out on 14 incontinent patients and concluded that short pulse duration (210 μs) and higher frequency (31 Htz) gave the best results in this series [15].

13.6 Outcome Evaluation

Most of the papers on this topic define the success of this therapy with more than 50 % improvement of the incontinence scores (Cleveland Clinic Score [16], St. Marks' score [17], etc.) and/or at least 50 % reduction of the number of the episodes of major fecal incontinence written down a stool diary sheet in the last 2–4 weeks.

An ad hoc subcommittee of the European Society of Coloproctology has recently discussed the choice of the best incontinence scoring system, and one of the score, which reached the best performance, was the Revised Faecal Incontinence Score by Sansoni et al. [18] where the authors have attempted to improve on the Cleveland Clinic score's weaknesses. In fact the flatus item was deleted and two other items for urgency and leakage were added. The reliability of this new score was tested showing higher performance compared to the Cleveland Clinic score and the St. Marks' score.

Another even more important way to evaluate the outcome of this therapy is the measure of the changes in patient's quality of life. While generic indices like SF36 are not being used anymore because of their poor sensitivity in detecting QoL changes in follow-up after intervention for fecal incontinence, the use of a disease-specific index like FIQL [19] is increasing including its validation in different languages. Another useful and reliable index is the ICIQ B score [20], which combines symptoms and QoL variables, however, is rarely used in studies dealing with fecal incontinence.

13.7 Mechanisms of Action

At the beginning of this therapy, the peripheral effects on the pelvic musculature were believed important, but, although present, the effect of SNS on the anal sphincter tone is inconstant, or irrelevant, insufficient to explain any changes in fecal continence [21–24]. Furthermore, it was demonstrated that the latency between the stimulation and the pelvic muscle contraction was about ten times more than expected as a result of the activation of the reflex arc, indicating that it was the result of a medullary polysynaptic reflex [25].

An effect on rectal compliance and on colorectal motility was hypothesized, but never clearly demonstrated [15, 26].

Several studies carried out in patients with urinary and fecal incontinence using different techniques (PET scan [27], evoked sensory potential [28], and functional magnetic resonance [29]) have demonstrated an activation or inhibition of the central brain areas involved in the control of micturition and continence. Furthermore, the only type of incontinent patients where SNS has never shown to give positive results is the complete spinal patients; on the contrary good results can be achieved even in patients with demonstrated anal sphincter defects indicating that a central, sensory-type effect is more important than any peripheral motility activation.

Finally, a recent study has demonstrated that in most of fecal incontinent patients with long-term successful SNS, the effect is maintained for long term even when the pulse generator has switched off, suggesting that a long-lasting SNS could induce a form of the brain neuroplasticity [30].

13.8 Long-Term Outcome

While the early success rate after SNS for fecal incontinence ranges around 80 % [31–33], its long-term outcome tends to decline with time as for all the other types of treatment for fecal incontinence [34–36]. Few single center [37–41] and

multicenter [42, 43] experiences have been carried out looking at the long-term outcome of SNS for fecal incontinence. Taking into consideration the report concerning patients with at least 5 years of permanent implant, the success rate ranges between 89 and 55 %. In this regard, however, it should be emphasized that the success rate is always considered an at least 50 % improvement if the baseline condition, which does not correspond to be cured by fecal incontinence. If the percentage of patients with fully continent after SNS is considered, the success rate ranges between 61 and 36 %.

Finally, there is a debate whether the success rate should be related to the patients selected for SNS (Intention to treat criteria) or just those who succeeded the temporary test and underwent permanent implant of the electrostimulation. Based on the ITT criteria, only 42–54 % of the patients maintained the long-term success [41, 44] and only 26 were cured [44]. Similar results were recently reported on a large series of patients recorded in a European survey [45].

Confirming these results, a total of 57.3 % of the patients offered SNS therapy were satisfied at 4 years follow-up despite their continence status. However, although patient satisfaction was clearly related to the number of FI episodes and patients experiencing full continence were all satisfied, and the satisfaction rate decreased as the number of FI episodes increased, 46 % of the patients with more FI episodes at follow-up than at baseline were still satisfied. In total, 74.7 % of the patients receiving active SNS therapy reported a reduction of ≥50 % in FI episodes, and only 10.3 % of whom were dissatisfied after 4 years of follow up. Therefore, functional outcome of SNS therapy cannot be based only on bowel-habit diaries and bowel scores [46].

In conclusion, although an approximately 10 % loss of effectiveness was demonstrated within 5 years, SNS still appeared to be an effective long-term treatment option. To put this figure into context, most patients seeking treatment for FI can be managed successfully with conservative measures alone; in more than half of the remainder, SNS can provide at least a 50 % improvement in continence maintained into the long term [3].

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Sacral Nerve Modulation for Constipation

14

Marco Franceschin, Jacopo Martellucci, and Alfonso Carriero

14.1 Introduction

Severe chronic constipation is disabling with an estimated incidence of 3–15 % [1]. Patients may experience a combination of difficulty in evacuation, decreased bowel frequency, abdominal pain, and bloating. Primary constipation involves three pathophysiologic subtypes [2, 3]. *Slow-transit constipation* is characterized by prolonged delay of stool transit through the colon. *Obstructed or dyssinergic defecation* is characterized by either difficulty or inability to evacuate stool from the rectum.

Constipation-predominant irritable bowel syndrome is characterized by symptoms of constipation with discomfort or pain as a prominent feature [4]. Secondary constipation is caused by a myriad of factors such as diet, drugs, behavioral, lifestyle, and endocrine, metabolic, neurological, psychiatric, and other disorders.

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In the Rome III criteria [5, 6] for functional constipation, the following criteria have to be fulfilled for the last 3 months with symptoms onset at least 6 months prior to diagnosis:

1. At least two of the following symptoms have to be present in more than 25 % of all defecations:
   (a) Straining
   (b) Lumpy or hard stool
   (c) Sensation of incomplete evacuation
   (d) Sensation of anorectal obstruction or blockage
   (e) Manual maneuvers to facilitate defecation
   (f) Fewer than three bowel movements per week
2. Loose stools are rarely present without the use of laxatives.
3. Insufficient criteria for irritable bowel syndrome.

In clinical practice, differentiation of constipation from constipation-predominant irritable bowel syndrome may be difficult, despite the criteria given in the Rome III criteria, and in many patients psychological factors can be strongly correlated with the disease [7].

Bowel problem adversely affected family life in 33 %, sexual life in 56 %, work life in 69 %, and social life in 76 % of patients [8].

Only a minority of patients with severe constipation fail conventional pharmacological and behavioral treatments, but unfortunately traditional surgical operations, such as subtotal colectomy with ileorectal anastomosis, are associated with substantial morbidity (15–30 % of patients develop diarrhea and fecal incontinence, 10 % remain constipated, 10–20 % reported bowel obstruction episodes, 40 % suffer from abdominal pain, and another 5–10 % progress to a permanent ileostomy) and a variable outcome [9–12]. Modulation of the extrinsic neural control of the large bowel and pelvic floor may provide an alternative to direct bowel surgery for treating intractable idiopathic constipation. Continuous low-amplitude electrical stimulation of sacral nerve roots is an established treatment for urinary voiding disorders and fecal incontinence [13–15]. In a combination of early studies of 250 patients undergoing sacral nerve stimulation (SNS) for urinary voiding disorders, 28 (78 %) of 36 subjects with coexisting symptoms of constipation reported increased frequency of defecation at 6-month follow-up [16, 17]. Some preliminary studies of the St. Mark's group have reported successful short-term SNS for treating idiopathic constipation [18–20]. In the European prospective multicenter study of 62 patients with refractory constipation, constipation was defined as two or fewer bowel evacuations per week on average, and⁄or straining to evacuate in over 25 % of attempts to evacuate, and⁄or sensation of incomplete evacuation after defecation on over 25 % of occasions, or any combination of these symptoms [21]. The results of this series show that trial stimulation was successful in 73 % of cases. Success was measured by comparing prestimulation with 3-week post-stimulation patient diaries. The primary outcome measures of treatment success in each patient were defined as (1) improvement in bowel frequency, changing from two or fewer to three or more evacuations per week, (2) reduction in the proportion of defecation episodes associated with straining, and (3) reduction in the proportion of defecation episodes

associated with a sense of incomplete evacuation. All symptoms had to show an improvement of at least 50 % to qualify as a treatment success. The 45 (73 %) successfully tested patients subsequently underwent implantation of a permanent electrode and stimulator. The frequency of defecation increased significantly from a baseline median of 2.3 (range 0–20) evacuations per week at the start of treatment to 6.6 (1–16) evacuations per week at the end of the follow-up period.

These data suggest and confirm the possible role of SNS for the treatment of chronic constipation.

14.2 Mechanism of Action

The mechanism of action in which SNS affect transit time and defecation is unclear. It is likely to involve multiple physiological effects, in particular modulation of afferent and local reflex pathways [22, 23]. Stimulation of the S3 root is often the preferable option for therapy (the S2 root has the greatest afferent outflow from the sacral plexus [24], but often leads to activation of sciatic motor fibers that can lead to buttock and leg pain) providing maximal sacral afferent stimulation in the absence of unwanted side effects [22]. Many studies have described changes in anorectal sensory and motor function as a result of SNS, although there does not appear to be a consistent pattern to these changes [25]. A double-blind randomized study assessing the effect of SNS on rectal sensation in patients with rectal hyposensitivity suggested that modulation of afferent pathways may be important as improvement in threshold and maximum tolerated volumes to balloon distension occur with therapy [26].

Giani and colleagues [27] demonstrated an increase in the latency of cerebral somatosensory evoked potentials in patients with fecal incontinence and constipation undergoing SNS. Griffin and coworkers [28] found an increase in amplitude of primary cortical evoked potentials was seen during stimulation. These findings suggest that SNS alters the representation of the lower gastrointestinal tract in the sensory cortex. The effects of SNS on colonic motility were investigated by Dinning and colleagues [29]. They showed that SNS at suprasensory threshold significantly increased the antegrade pancolonic wave sequence in patients with slow-transit constipation. However, even if they suggest that stimulation at subsensory threshold, as used routinely in clinical practice, may not have an effect on motility [30] Kamm and coworkers [21] showed normalization of whole-gut transit time at 6-month follow-up in half of patients undergoing SNS for slow-transit constipation using stimulation at subsensory threshold. This corresponded to an increase in frequency of defecation. In contrast, SNS in patients with fecal incontinence may reduce antegrade colonic transit [31]. The difference in the effect of stimulation under different conditions remains unclear, but SNS may act to normalize transit by modulation of the enteric nervous system or reflex pathways at the spinal cord level.

The only statistically significant changes noted in the study of Ganio et al. [32] about manometric evaluation were an increase in amplitude of maximum squeeze pressure during sacral nerve stimulation and a reduction in the rectal volume for the urge threshold. Moreover, they fail to demonstrate any effect on the rectoanal inhibitory reflex and rectal compliance did not change significantly with sacral nerve stimulation. These data were not completely confirmed in the study of Knowles and colleagues [26].

14.3 Selection of Patients

14.3.1 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria varied between studies. All studies included patients with chronic symptoms and failure of conservative measures. The need for digital manipulation was an indication in two studies [32, 33], whereas fulfillment of the Rome III criteria was used in three studies [19, 21, 33]. Three of the studies selected only those patients who had slow-transit constipation [19, 34, 35].

Exclusion criteria included previous abdominal surgery, a history of psychiatric or psychological illness, and pregnancy or attempt at pregnancy in many studies. The presence of rectal prolapse was a contraindication in four studies [21, 26, 33, 35]. All studies are reported in Table 14.1.

Table 14.1 Inclusion and exclusion criteria

Authors	Inclusion criteria	Exclusion criteria
Kenefick et al. [20]	Failed conventional therapy, bowel frequency 2 or less per week, straining > 25 % of time, minimum duration 1 year	Previous abdominal surgery, hysterectomy, current or planned pregnancy, significant psychological disturbance
Kamm et al. [21]	Failed conventional therapy, bowel frequency 2 or less per week, straining > 25 % of time, minimum duration 1 year	Previous large bowel surgery. Current or planned pregnancy, significant psychological disturbance. Presence of Stoma, rectal prolapse, congenital or organic bowel pathology. Alternating constipation and diarrhea
Malouf et al. [19]	Long-standing constipation with slow gut transit, failed conservative treatment (included biofeedback), Rome III criteria	Previous surgery for constipation. Significant psychological disturbance
Sherma et al. [36]	Failed conventional therapy (included rectal irrigation and biofeedback), bowel frequency 2 or less per week, straining > 25 % of time, minimum duration 1 year	Not described
Ganio et al. [32]	Feeling of incomplete evacuation for > 50 % of bowel movements during previous year. Failed conventional therapy	Sphincteric defect, current or planned pregnancy, inflammatory bowel disease, cardiac disease
Holzer et al. [33]	Failed conventional therapy, bowel frequency 2 or less per week, Severe constipation with pathologic colonic transit study	Congenital anorectal malformations, rectal prolapse, chronic bowel disease, presence of stoma, neurologic disease, bleeding complication

Table 14.1 (continued)

Authors	Inclusion criteria	Exclusion criteria
Carriero et al. [34]	Failed conventional therapy (included biofeedback and laxative), Rome III criteria	Symptoms of ODS[a] at defecography, previous abdominal surgery, congenital malformation, neurologic disease
Naldini et al. [35]	Failed conventional therapy, bowel frequency < 1 per week without laxative, minimum duration 1 year. Slow transit	ODS, anorectal dyssynergism, congenital anorectal malformation, external rectal prolapse. Current or planned pregnancy, significant psychological disturbance. Chronic inflammatory bowel disease
Humphreys et al. [37]	6 to 15 years old with presenting symptoms of dysfunctional voiding, enuresis, incontinence, urinary tract infections, bladder pain, urinary retention, urgency, frequency, constipation, and/or fecal soiling	Not described
Govaert et al. [38]	Failed conventional therapy, bowel frequency < 1 per week without laxative, minimum duration 1 year. Slow transit	Any organic pathology causing constipation, previous large bowel surgery, inflammatory bowel disease, erratic bowel habit (alternating constipation and diarrhea, or irritable bowel syndrome), congenital anorectal malformations, stoma in situ, neurologic diseases (such as complete spinal cord transection, multiple sclerosis, spina bifida, or Parkinson disease), Current or planned pregnancy, significant psychological disturbance
van Wunnik et al. [39]	10–18 years patients who fulfill Rome III criteria, failed conventional therapy	Organic pathology, chronic IBD, previous large bowel surgery, congenital anorectal malformations, or neurological disease (complete spinal cord transection, multiple sclerosis, or spina bifida). Current or planned pregnancy, significant psychological disturbance
Knowles et al. [26]	Failed conventional therapy. Failure to evacuate more than 60 % of instilled rectal contrast in 3 min using a standard defecography protocol. Absence of delayed colonic transit, megarectum or significant dynamic structural obstructions (rectocele and intussusception)	Congenital anorectal anomalies or absence of native rectum due to surgery; present evidence of external full-thickness rectal prolapse; stoma in situ; chronic bowel diseases such as inflammatory bowel disease. Current or planned pregnancy

[a]ODS: obstructed defecation syndrome)

Table 14.2 Investigations before sacral neuromodulation

Authors	Investigation before NMS	Additional Insights
Kenefick et al. [20]	Colonoscopy, proctography, transit study, anorectal physiology	Wexner constipation score, SF-36 quality of life assessment
Kamm et al. [21]	Sigmoidoscopy, anorectal physiology, whole-gut transit study (before and 6 months after permanent implant)	Cleveland Clinic constipation score, SF-36, subjective questionnaire
Sherma et al. [36]	Colonic visualization, anal physiology, colonic transit study, defecation proctogram	Not described
Ganio et al. [32]	Barium enema/colonoscopy, anal ultrasound, anal manometry, pudendal nerve terminal motor latency, transit study, defecography	Not described
Holzer et al. [33]	Clinical examination, colonoscopy, colonic transit study, defecography	Wexner constipation score, SF-36 quality of life assessment
Carriero et al. [34]	Colonscopy, anorectal manometry, and endoanal ulrasound	Wexner constipation score, SF-36 quality of life assessment, MMPI-2
Naldini et al. [35]	Colonscopy, anorectal manometry and anal sphincter electromyography, colonic transit time, cysto-colpo defecography	Wexner constipation score, SF-36 Quality of life assessment
Govaert et al. [38]	Physical examination, colonic transit time study, defecography, and anorectal physiology testing	Wexner constipation score, bowel habit diary
van Wunnik et al. [39]	Whole-gut transit time study, defecography, MRI, anorectal manometry, rectal sensitivity	Bowel diary, Cleveland Clinic constipation score
Knowles et al. [26]	Colonic transit study, defecography, anal manometry	Bowel diary, SF-36 quality of life assessment

14.3.2 Investigations

Preoperative investigations included in most of the studies a colonic transit studies, barium enema, colonoscopy, study of anorectal physiology, and defecography. All the preoperative assessments for each study are reported in Table 14.2.

14.3.3 Clinical Predictors

Psychological evaluation has shown to be a significant predictive method for the selection of patients with constipation suitable for SNS treatment, reaching a success rate of 85 % [34].

Using MMPI, Wexner and colleagues found in constipated patients a significant elevation on the hypochondriasis and depression scales [40]. They concluded that constipated patients may benefit greatly by adding a psychological component to the treatment regime.

Another study carried out in 40 patients with ODS who underwent transanal rectal prolapsectomy, a recurrence of constipation occurred in 52 % of cases at a median follow-up of 3 years [41]. This decreased to 20 % when patients with psychoneurotic disorders were excluded, suggesting that the underestimated occult-associated disease, such as anxiety and depression, might be associated with a poor result.

In the study proposed by Carriero et al. [34], the essential role of psychological evaluation was confirmed when the results of the group of patients who were initially excluded due to their psychological conditions were added, causing a significant drop of the success rate and making it comparable to the lowest success rates reported in literature.

In another study, Martellucci and Naldini [42], performing a retrospective analysis of patients with STC with pathologic colonic transit time that underwent SNM test, evaluated the success of the treatment related to the preoperative bowel preparation protocols.

In their study, 20 patients underwent no preparation, 7 patients underwent to a preoperative enema, and 11 patients underwent to a complete preparation with sodium phosphate. Twenty-five patients (65 %) were definitively implanted: 12/20 (55 %) patients in the first group, 4/7 (57 %) in the second group, and 9/11 (82 %) in the third group underwent to definitive SNM, respectively, suggesting that preoperative bowel preparation could help to improve the results during the screening period of SNM for STC.

14.4 Efficacy

General results are included in Table 14.3.

In the Malouf and Kenefick patients [18, 19], four of the ten tested patients demonstrated a successful increase of symptoms and where definitively implanted. An increase in the number of spontaneous defecations was demonstrated at 6-month follow-up. Improvement in the Cleveland Clinic constipation score was reported. Ganio et al. [32] described 40 patients with functional anorectal and urinary disturbances, of whom 12 had constipation. After 10 days of peripheral nerve evaluation (PNE), ten completed the course of stimulation. This group showed an improvement in initiating evacuation and a reduction of time required to evacuate. In the Naldini et al. [35] study, 15 patients with slow-transit constipation underwent temporary SNS. Of these, nine managed to have permanent implant. At 6 months, there was an increase in the number of bowel movements per week. In the Holzer et al. [33] prospective study, 19 patients underwent to temporary SNS. Eight of these had slow-transit constipation, and nine had evacuatory dysfunction. Eight patients (four with slow-transit and four with evacuatory dysfunction) undergone to permanent

Table 14.3 Results of published studies of sacral nerve stimulation for constipation in adult patients

Authors	Year	Study type	Tested	Permanent	% success	Selection
Kenefick et al. [20]	2002	Prospective	10	4	40	
Malouf et al. [19]						
Holzer et al. [33]	2008	Prospective database	19	8	42	
Kamm et al. [21]	2010	Prospective	62	45	72.5	
Naldini et al. [35]	2010	Prospective database	15	9	60	
Carriero et al. [34]	2010	Prospective database	13	11	84.5	MMPI test
Sharma et al. [36]	2011	Prospective database	21	11	52.5	
Govaert et al. [38]	2012	Prospective database	117	68	58	
Knowles et al. [26]	2012	Double-blind crossover	13	11	85	Rectal hyposensitivity
Ortiz et al. [43]	2012	Prospective database	48	23	48	

stimulation and it results in a reduction of Cleveland Clinic constipation scores and short form 36 (SF-36) quality of life (QoL) scores. Kamm et al. [21] in 2010 performed a multicenter prospective study with 62 patients underwent test stimulation of whom 45 (73%) progressed to permanent stimulation with a follow-up median of 28 months. Thirty-nine (87 %) of the 45 who had undergone permanent stimulation showed an improvement in frequency of defecation, straining, sensation of incomplete evacuation, abdominal pain, and bloating. There was an improvement of the Cleveland Clinic constipation score from 18 at baseline to 10. The colonic transit time in half of the patients with slow gut transit had normalized by 6 months. Govaert et al. [38] reviewed 117 patients who had undergone temporary test for SNS. Of these 68 proceeded to permanent SNS. Some of the patients in this report were part of the multicenter study published by Kamm et al. [21]. There was an initial significant improvement in the Cleveland Clinic constipation score from mean 17 to 10,2 at first follow-up, maintained at a 37 months. Sharma et al. [36] submitted 21 patients to temporary stimulation, 18 of whom had slow-transit constipation. Of these, 11 went on to have a permanent implant. Eight of these 11 patients stopped using laxatives. Carriero et al. [34] proposed a psychological assessment for the selection of patients. In this study, 68 patients with slow-transit constipation underwent Minnesota Multiphasic Personality Inventory (MMPI)-2 questionnaire, but only 45 completed the questionnaire. Thirteen had a normal score and underwent temporary screening phase. Of these, 11 proceeded to permanent stimulation. Interestingly, nine of the patients who had refused to complete the MMPI-2 questionnaire, or had an abnormal score, requested to be with tested despite the psychological evaluation results. Of these, only three (33 %) progressed to permanent stimulation.

In the prospective randomized double-blind placebo-controlled crossover trial of Knowels et al. [26], 14 female patients with proctographically defined evacuatory dysfunction (ED) and demonstrable rectal hyposensitivity were studied. In this study, 13 patients completed the trial, and 11 were definitively implanted. Defecatory desire volumes to rectal balloon distension were normalized in 10 patients and maximum tolerable volume in 9. There was a significant increase in the number of successful bowel movements per week and in the Cleveland Clinic constipation score. It has to be shown that after a follow-up of 19 months, only 9 patients still benefit from the treatment, partially influencing the good success rate.

In the two centers study of Ortiz et al. [43], 23/48 patients (48 %) were implanted with a permanent stimulator. However, considering an intention-to-treat basis, only 14 of 48 patients (29.2 %) met the definition of a successful outcome at the latest follow-up period (25.6 months).

Few studies have reported the effects of SNS in children with constipation. Van Wunnik et al. [39] described 13 adolescent girls (10–18 years), underwent PNE for constipation. Twelve had placement of a permanent implant. At follow-up of 6–12 months, there was an improvement in the number of defecations per week, abdominal pain, straining, and in Cleveland Clinic constipation score. In the second study, performed by Humphreys et al. [37], 23 children were described (6–15 years old), of whom 15 had constipation-type symptoms. After a mean follow-up of 13 months, constipation symptoms improved in 12 of the 15 patients treated with permanent SNS. Also Roth et al. [44] reported about dysfunctional elimination syndrome (a spectrum of functional disturbances involving the urinary and lower gastrointestinal systems in the absence of any obvious anatomical or neurological deficiency in children) 17 children with constipation-type symptoms; in 12 children, these symptoms resolved or improved following SNS.

14.5 Clinical Considerations

Constipation should be managed initially using a pharmacological agents, rectal irrigation, and/or behavioral treatments. In some paper [22, 41, 45], SNS find a significant role in algorithms for the treatment of constipation.

SNS appears to be an effective treatment for constipation; however, research to date has been predominantly confined to small, low-level evidence studies with most lacking a coherent definition of constipation. There are no standardized inclusion or exclusion criteria for the use of SNS for constipation. Severe slow-transit constipation is the most frequent indication for neuromodulation across all studies. Although SNS appears to have great potential in treating patients with slow-transit constipation its mechanism of action is still not completely clarified.

The study of Knowles et al. [26] suggests that patients with rectal hyposensitivity could be a group of patients with a higher success rate compared to slow-transit constipated patients.

The technique for temporary and permanent neuromodulation was similar across studies. S3 was the most common nerve root used for neuromodulation, and both

leg and perineal responses were measured. Four studies used local anesthesia for temporary leads, although one group changed to general anesthesia in their second reported study. Insertion of temporary leads under local anesthesia is technically possible; however, patient preference and pain tolerance may play a role for decision making about anesthesia type. In a recent study performed by Martellucci [46], ultrasound-guided electrode placement was performed in eight consecutive patients, enrolled for SNM, with a linear subcutaneous probe. At the end of the procedure, a control fluoroscopy was performed in all the cases. The procedure was performed under local anesthesia, and sensory and motor responses were evaluated in every patients. The position was considered successful when the electrode was placed in S3 foramen, with three of the four poles located outside the sacrum and the poles 2 and 3 straddle the posterior bone table. The electrode was correctly placed in S3 sacral foramen in all the patients. The depth of the electrode was correct in 7/8 patients. In one patient, with body mass index >35, the posterior bone table was between poles 1 and 2. The sensory and motor responses were detected in every patients without complications.

The author concludes that even if ultrasound-guided lead placement is a feasible, safe, and reproducible possibility for SNS therapy, a thick and dense subcutaneous tissue could be considered as a limiting condition, above all for the difficulty to visualize the internal sacrum line.

Computed tomography (CT)-guided lead placement for sacral neuromodulation was also described, preferentially used in patients with a complicated access to S3 foramina [47–49].

Maeda et al. [49] reported that nearly 60 % of patients who received sacral nerve stimulation for constipation experienced at least one reportable event, including lack or loss of efficacy, pain, and undesired change of sensation.

The most common adverse events were related to electrodes requiring revision. Pain was the second most common adverse event including back, leg, anal, pelvic, thigh, stimulator site, and vaginal pain, and pain with defecation.

Reprogramming successfully managed 50 % of adverse events, and only in 7 % of patient's adverse events (including loss of efficacy) led to interruption of the treatment.

Also in the data reported by Martellucci and Naldini [50], in the follow-up period 45 % of patients required at least one modification of the initial stimulation parameters: five patients required changing of the initial parameter settings within 6 months from the definitive implantation and three after 6 months from the implantation. All the five patients that required earlier the change of the parameter need more than one modification (range 2–8). Four of these patients (80 %) removed the stimulator after a median time of 12 months (range 3–16). The three patients adjusted after 6 months did not require other changes in the stimulation parameters.

The main first adjustment tested was on the polarity configuration of the electrodes (7/8 patients), in three patients the frequency was changed, and only one

Table 14.4 Stimulation parameters

Author	Pulse width (ms)	Frequency	Amplitude	Stimulation
Kenefick et al. [20]	210	14 Hz	1.7 (range 0.2–2.0)	Continuous
Holzer et al. [33]	210	16 Hz	Below the threshold	Continuous
			5 (range 1.5–8.5)	
Kamm et al. [21]	210	14 Hz (10–21)	Below the threshold	Continuous
Naldini et al. [35]	210	14 Hz	Below the threshold	Continuous
			2.3 (range 0.6–4.5)	
Sharma et al. [36]	210	10–21 Hz	Below the threshold	ns
Govaert et al. [38]	210	14–16 Hz	Below the threshold	ns
Knowles et al. [26]	210	15 Hz	Below the threshold	ns

patient was reprogrammed with pulse width adjustment. Amplitude was always regulated at the lowest value required to feel the stimulation.

The authors concluded that the success rate of SNM could be increased by changing stimulation parameters but the need for early changes in the stimulation settings could be considered as a predictor of a negative outcome.

The stimulation parameters used in the analyzed studies are reported in Table 14.4 and are consistent between the studies.

14.6 Conclusions and Future Perspectives

SNS appears to be an effective treatment for chronic constipation. Larger clinical and studies comparing SNS with alternative treatments are required. Data regarding selection of patients for temporary neuromodulation are unclear and further research into predictive factors for success would improve patient selection.

Lee et al. [51] reported that magnetic sacral dermatome stimulation may offer potential for therapeutic benefit for a subset of patients with idiopathic slow-transit constipation, particularly constipated patients with rectal hyposensation or hindgut dysfunction.

Transcutaneous stimulation using sticky pad electrodes over the lumbosacral region or acupuncture points has been reported to improve constipation symptoms [52].

Also direct colonic pacing seems to be feasible and shows positive results in the treatment of slow-transit constipation [53].

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Pudendal Nerve Modulation

15

Michele Spinelli

15.1 Electrical Modulation of the Pudendal Nerve

As the pudendal nerve is one of the major nerves which stimulates the pelvic floor muscles, the external urethral and anal sphincters and the pelvic organs, this nerve is being increasingly investigated as a treatment option, particularly patients with neurogenic OAB.

The pudendal nerve is composed of nerve fibers originating from S2 to S4 nerve roots which innervate the pelvic floor muscles, the external urethral and anal sphincters, and the pelvic organs. It is a mixed nerve that contains somatic and autonomic nerve fibers.

The pudendal nerve leaves the pelvis via the intra-piriform foramen and passes dorsally in an arc around the ischial spine through the lesser sciatic foramen into the ischiorectal fossa and before leaving Alcock's canal (pudendal canal) divides into two terminal branches: the perineal nerves and the inferior rectal nerves.

These nerves supply motor and sensory innervations to the striated muscles (bulbocavernosus muscle and external anal sphincter) and partly to the urethra and the dorsal nerve of the penis or clitoris. The caudal portion of the pudendal nerve runs through the pudendal canal, which lies against the sidewall of the pelvis and duplicates the fascia of the obturator internus muscle.

Anatomy, physiology, and neurophysiology of the pudendal nerve have been studied extensively, particularly when its role in continence mechanisms has been more elucidated [1, 2]. One of the first works investigating the clinical significance of pudendal nerve anatomy was performed by Juenemann et al. [3]. The authors

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demonstrated that in patients with neurogenic lower urinary tract dysfunction, electrostimulation of the sacral root and pudendal nerve markedly increased intraurethral closure pressures.

Today, there is much knowledge obtained on the pudendal nerve anatomy and innervations' role. New studies continue to be performed to further assist physicians operating in close proximity to this nerve or when using this nerve for various therapeutic applications. These studies should also help to get a better understanding of the underlying neuronal mechanism and the involved pathways in humans when the pudendal nerve is stimulated.

Due to the anatomy of Alcock's canal, surgical exposure of the nerve has been difficult in the past due to the increased risk of damage to the nerve itself, but with recent developments in the implant procedure and equipment, chronic pudendal nerve stimulation (PNS) can now be easily achieved. Anatomy of the pudendal nerve and its terminal branches from a cadaver was published by Schraffordt SE et al. in 2004 [4]. This study documented the anatomy of the pudendal nerve by looking into 28 cadavers, in order to examine the course of the pudendal nerve and its branches in the perineum. The study concluded that a sound knowledge of the anatomical variations of the pudendal nerve and its branches is essential for all surgeons operating in the perineal region.

Today, chronic pudendal nerve stimulation can easily be performed using the existing InterStim device. The treatment is minimally invasive by using a percutaneous approach to reach Alcock's canal [5]. A permanent tined lead can be implanted in the first implant stage to evaluate the clinical efficacy; this avoids any risk of efficacy changes when the permanent INS is implanted. The tined lead, which was originally developed for sacral nerve stimulation, to create a more secure lead position has also contributed to making pudendal nerve stimulation a safe option for surgeons and patients [6]. Additionally, neurophysiological monitoring helps to implant the lead in the correct position and helps to verify effective stimulation.

This monitoring is done by assessing electromyographic activity (EMG) of the external anal sphincter (EAS). A cadaver study, published by Reitz in 2007 [7], provides data which indicates safe needle placement via the posterior approach, which is the approach used by author.

15.2 Surgical Technique

15.2.1 Lead Implant

The patient is placed in prone position. Bony topography is drawn with the use of a fluoroscopy x-ray device in order to spot the greater trochanter and the ischial tuberosity (Fig. 15.1) These two reference marks are used to find the two points as schematic images shown below (Fig. 15.2).

This technique is recommended to stay clear of veins and arteries and to avoid possible needle punctures or injections of anesthesia directly into the vascular

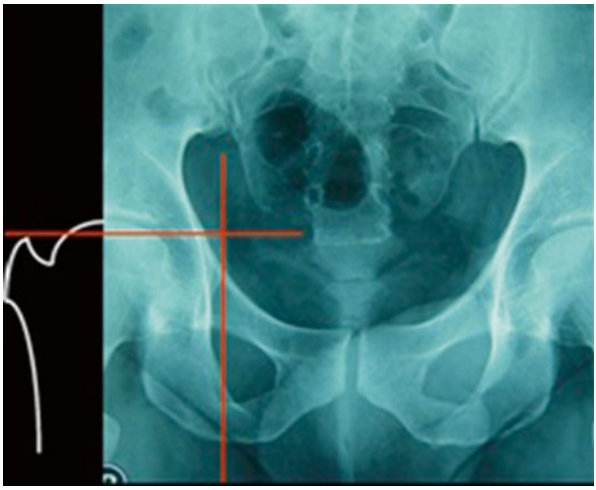

Fig. 15.1 X-ray showing lead insertion position

Fig. 15.2 Diagrammatic view of lead puncture insertion position

system. The x-ray C-arm should be ready to perform anterior-posterior image of the pelvis. Locate the ischial tuberosity tip (*ITT*) and the greater trochanter (GT) with a pair of 90° angle crossed stylets placed on the patient's skin, mark with a dot where the stylets cross.

Puncture the intersection of the lines drawn vertically from the ITT and horizontally from the GT, as demonstrated in Fig. 15.4:

15.2.2 Preparation for Lead Insertion

Anesthesia should be administered to the patient only if proceeding with lead implant after skin drawing. Muscle relaxants should not be used. Avoid general anesthesia. Anesthetic choices include lidocaine solution for injections, maximum dose is 500 mg for healthy patients and bupivacaine with maximum recommended dose of 200 mg. Dosage should be minimized to preserve nerve response. Minimize the risk of vascular absorption by injecting slowly and in small boluses local anesthetic or chemotoxic substances, aspirate before injecting.

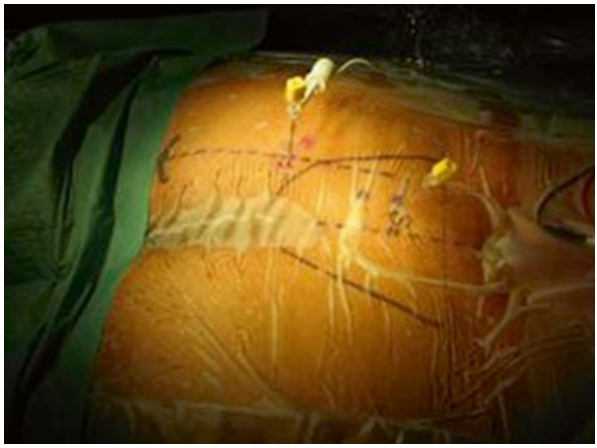

Fig. 15.3 Acute test with test needle

15.2.3 Acute Test with Test Needle to Locate Optimal Position

Place patient in a prone position, prepare the patient's lower quadrant and connection site, and prepare perineum, gluteus, and sacrum for sterile surgery. Drape to allow observation of the pelvic floor for muscle response to test stimulation. Clean dry skin area, and affix the ground pad to it. Electromyography recording needle is gently inserted in the anal sphincter stimulation. Patient stimulation cable is connected to electromyography output. Vertically insert the insulated foramen test needle. Connect the mini-hook from the patient cable to the non-insulated part of the foramen needle and stimulate; see Fig. 15.3.

A 1 mA step increasing pulse current from 0 is used to locate the tip of the needle adjacent to the pudendal nerve by comparing the generated CMAP with the reference trace. An acceptable CMAP should be within a variability of 2 ms compared with the reference trace.

When satisfied with the needle position, replace needle stylet with the directional guide. Holding the directional guide, remove the foramen needle. Make a small incision on either side of the directional guide. Fit the dilator and introducer sheath over the directional guide and advance to the third most proximal depth marker on the directional guide with the top of the dilator; see Fig. 15.4.

15.2.4 Tined Lead Insertion

While holding the lead in place, retract the introducer sheath until the second visual marker lines up with the top of the introducer sheath handle (Fig. 15.5). A 1 mA step increasing pulse current from 0 is used to locate the tip of the needle adjacent to the pudendal nerve by comparing the generated CMAP with the reference trace. Stimulate the various electrodes and observe the generated CMAP; see Fig. 15.6.

Hold sheath and lead together when adjusting lead position.

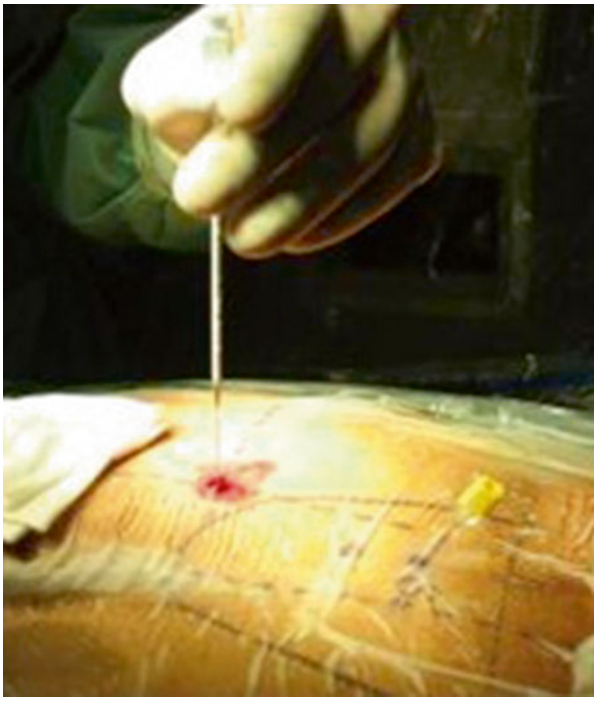

Fig. 15.4 Preparation for tined lead insertion

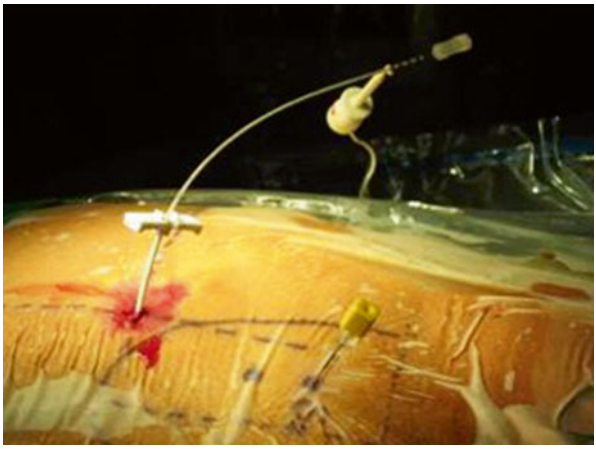

Fig. 15.5 Tined lead insertion

When satisfied with the lead position, hold the lead in place and carefully withdraw the introducer sheath and the lead stylet. Ensure the lead is in the correct position before deploying the tines. Do not dislodge the lead as tines are deployed. Stimulate the four electrodes to confirm the CMAP previously observed. If you need to advance lead after tines are deployed, do so after lead stylet is inserted. If you need to retract, do so completely using gentle traction and place it again.

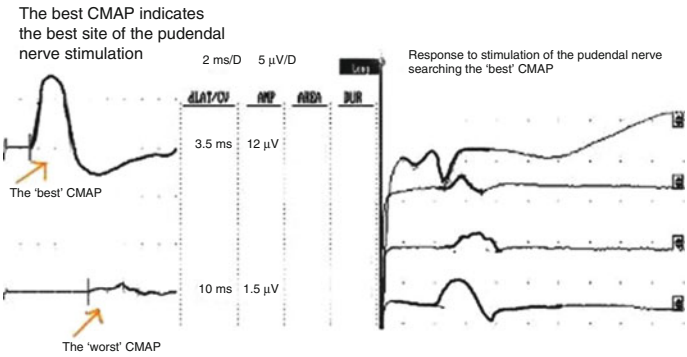

Fig. 15.6 Review of CMAP to locate the best tined lead position

15.2.5 Tunnelization from Pocket Site to Incision Site and Lead Connection to the Test Stimulator

Identify the site for the neurostimulator subcutaneous pocket. Make a small opening large enough for the percutaneous extension lead connector at the future neurostimulator pocket site. Either the abdomen or buttocks are suitable sites. Make a tunnel from the pocket site to the incision site. Lead tunneling should not be too deep. Gently feed the lead through the tube, remove the tube and keep the lead in place, close the lead implant incision, and dress the wound appropriately. Make a small incision contralateral to the neurostimulator pocket site where the percutaneous extension will exit the skin, and tunnel at the subcutaneous level from the pocket to the stab wound. Connect the lead and the percutaneous extension, and position the lead and extension in order to avoid sharp bends or kinks. Insert lead into percutaneous extension screw set connector. The connection to the test stimulator is now available for test stimulation. Tunnel the lead to the future neurostimulator pocket site. Close the initial incision and staple the wound leaving only the fine percutaneous extension wires and pin connector protruding from the skin.

15.2.6 Parameter Settings

Suggested parameter settings in the test stimulator are bipolar stimulation between the best stimulating electrodes, frequency of 5 Hz, pulse width 210 ms, continuous mode, and amplitude as low as possible (1–5 V below patient's sensitivity). It is not suggested to seek for patient sensory responses.

The patient should be carefully instructed about hygienic and general conduct during the test phase. In addition to providing the patient manual, explain the procedure for managing the test stimulator.

If any adverse events occur during the first-stage implant, these will be recorded and documented.

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Dynamic Graciloplasty

16

Claudio Fucini, Filippo Caminati, and Niccolò Bartolini

16.1 Historical Background

The idea to find a substitute or support for a damaged failing anal sphincter in incontinent patients with skeletal muscles of the thigh dates back to the beginning of the last century [1–3]. Pickrell et al. in 1952 described the technique of transposition of the gracilis muscle with its nerve supply in children with neurogenic incontinence, reporting excellent results [4]. The gracilis muscle appeared to be an ideal muscle to isolate and encircle the anus for several reasons (Table 16.1). The operation gained discrete popularity among pediatric surgeons who reported satisfactory results in early childhood which, however, declined with time possibly due to disuse atrophy [5, 6]. Anecdotal experiences of graciloplasty in adult subjects for fecal incontinence in extensive destruction of sphincters have been reported by several authors [7, 8]. Good results were reported by Corman in 1985 in patients with severe perineal trauma and fecal incontinence [9]. In 1976, Simonsen et al. had proposed graciloplasty as a substitute of anal sphincters in perineal colostomy after abdominoperineal excision (APE) [10]. However, the results of graciloplasty reported in other experiences were quite controversial varying from 0 to 84 % of success [11, 12]. What emerged from these experiences was that the muscle, despite being trained with adduction exercises of the leg, eventually acted simply as a passive obstacle to defecation; in fact, for its intrinsic twitch characteristic of a long muscle composed of type II "fast twitch" fibers without tonic activity, it could not sustain protracted contraction and behave as an anal sphincter composed of type I "slow

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Table 16.1 Characteristics of the gracilis muscle

Superficial position in the medial aspect of the upper thigh
Main neurovascular bundle in the upper part of the muscle which can allow to free its body for all the entire length as far as the insertion of its tendon to the tibial plate
Proximal attachment to the pubic bone far from the insertion of the main neurovascular bundle
No functional problem after detachment from the leg being an auxiliary muscle for adduction, flexion, and extrarotation of the hip and knee

twitch" fibers. So far graciloplasty as a substitute of anal sphincter never gained wide popularity. Transposition of the gracilis muscle has been used in the treatment of rectovaginal or rectoprostatic fistulas [13] or as coverage and sphincteric support after extended excision or destructive infection of the perineal region. The reports of Eisenberg and Salmons in 1980 [14] and Salmons and Henriksson in 1981 [15] demonstrating the functional adaptation of type I "fast twitch" fatigable muscle fibers to type II "slow twitch" fatigue-resistant muscle fibers, when the former is stimulated electrically at low frequency, renewed the attention toward the gracilis muscle for the possibility of training it to sustain long-term contraction and act as a real sphincter. Cavina in 1987 reported his experience with 32 patients in which, after APE for rectal cancer, he performed an anorectal reconstruction with both gracilis muscles, one as a puborectalis sling and the other as a neo-anal sphincter wrapped around a perineal colostomy [16]. For the first time, he introduced in this clinical setting the concept of electrostimulation. In this experience, electrostimulation was applied with external stimulator connected to the muscle with transcutaneous electrodes. The aim was to avoid postoperative atrophy of the muscle. Despite stimulation had been applied empirically for some hours a day, without defined protocols, the results reported regarding the tone obtained by the muscles and defecatory function were excellent. However, thanks to the works of Baeten et al. [17] and Williams et al. [18] who introduced the concept of dynamization that the interest toward graciloplasty as a support or substitute of anal sphincter had a great renewal. In fact to obtain a lasting conversion from fast twitch to slow twitch muscle, a temporary electrical stimulation did not appear to be sufficient; only a continuous and indefinitely protracted stimulation (dynamic) could achieve the conversion. The authors demonstrated that it was possible, by an implantable stimulator, to maintain continuous stimulation and contractions of the muscle to make it behave as a real sphincter. At defecation the stimulator was switched off allowing relaxation of the muscle and passage of the feces. The stimulator could be switched off/on with a magnet which is, nowadays, replaced by a handheld telemetry equipment (iCon mod.3037, Medtronic Inc., USA). For these reasons dynamic graciloplasty (DGP) gained wide popularity in the 1990s, especially in Europe, for the treatment of end-stage fecal incontinence and in the construction of continent perineal colostomies after APE [19, 20]. Since its introduction, however, the indications for dynamic graciloplasty have greatly reduced despite the satisfactory results in the treatment of end-stage fecal incontinence reported by an important multicentric experience [21] and by other authors [22, 23]. Indeed, long-term results, measured as continence scores, were poor in other reports, and obstructed defecation has been

a relevant problem in most experiences [24]. The introduction of artificial bowl sphincter (ABS) [25] which overlapped most of the indications for DGP and principally the introduction of sacral nerve stimulation (SNS) [26] had limited greatly the indications of DGP. In a survey of 20 relevant studies on ABS (444 patients) and DGP (934 patients), Belyaev et al. [27] found similar success rate (43 % vs. 49 %), rate of surgical revision (45 % vs. 46 %), and explantation (33 % vs. 32 %). However, the high number of complications registered for both approaches (654 for DGP and 746 for ABS) had favored the emerging role of sacral neuromodulation whose introduction in the surgical management algorithm for fecal incontinence has demonstrated to be more effective and less costly than DGP or ABS [28].

16.2 Current Indications for DGP

In the treatment of selected cases of end-stage fecal incontinence, DGP can be offered as an option to those patients in whom a major defect of the external sphincter is the main reason of the problem. Usually these lesions are of traumatic or iatrogenic origin, and sphincter's defect involves half or more of its circumference preventing the possibility of a direct muscular and anal repair. ABS is not indicated in the presence of a massive tissue defect (Fig. 16.1). Patients with anorectal agenesis submitted to pull-through procedure in whom electromyographic mapping or perineal sonography demonstrates the absence of anal sphincters are also possible candidates to DGP. In patients strongly determinate to avoid a terminal abdominal stoma after APE, the so-called total anorectal reconstruction (TAR) can be an option. The operation consists in performing, after an APE, a perineal colostomy and encircling it with a neosphincter represented by a stimulated gracilis muscle. In end-stage fecal incontinence, a complete workup of the anorectal function of the patient to rule out the extent and type of damage should have been primarily done to evaluate possible conservative or alternative surgical treatments like sphincteroplasty, SNS, and ABS (Table 16.2). Contraindications to DGP are reported in Table 16.3. As regards TAR, the almost unique indication derives from the desire of the patients to avoid a terminal abdominal stoma. Advances in surgical techniques and increasing adoption of neoadjuvant treatment have determined in the last years a steep increase of sphincter-sparing procedures with subsequent decreasing number of patients with permanent abdominal colostomy [30]. Therefore, the indications for offering a TAR procedure are nowadays quite limited (Table 16.4). As regards the approach to patients with rectal cancer, some authors [31, 32] sustain that it is correct to offer the option of TAR only after an adequate period of follow-up (at least 2 years) to minimize the risk of a recurrence and to allow selection of patients really determine to avoid an abdominal stoma. Indeed, in most of the reported series, TAR was performed as primary reconstruction. Deferred reconstruction is feasible but with high morbidity [33]. The operation should be reserved to patients with long life expectancy. Patients with advanced age, with metastatic disease, or very advanced rectal cancer; those who do not respond to preoperative chemoradiation; and those with no curative resection should not be considered for TAR. Patients must have complete information of the operation with the possible complications and rate of failure. Functional results are

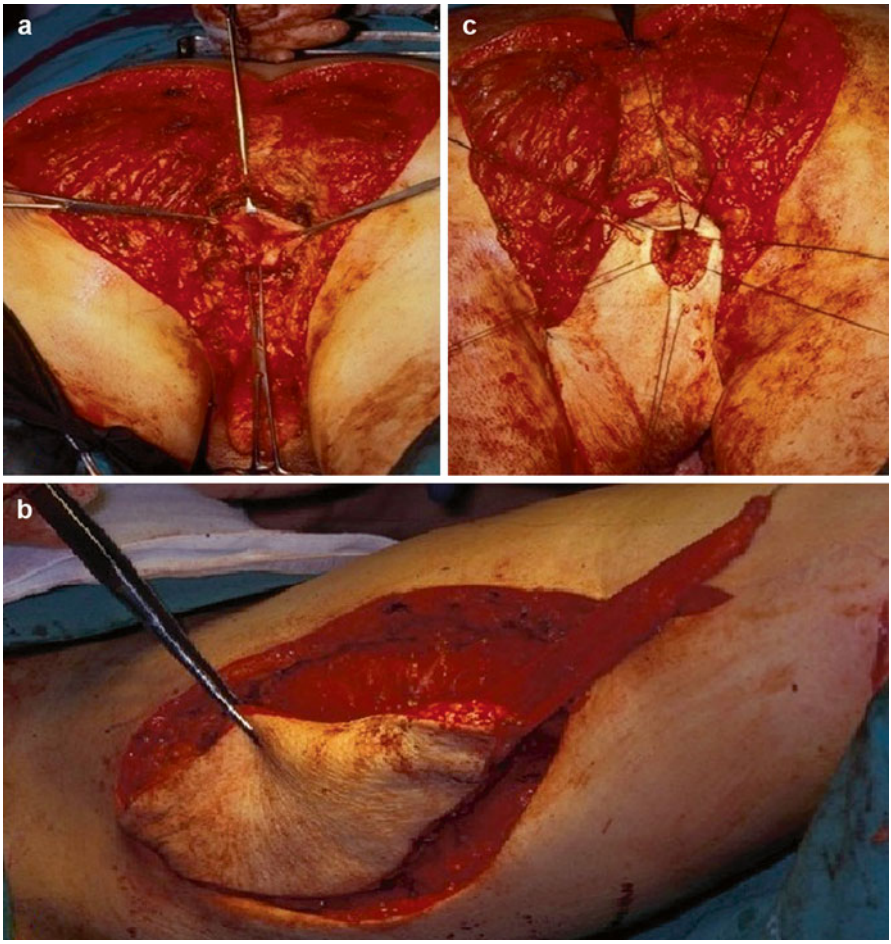

Fig. 16.1 (**a**) Wide perineal and anal sphincter excision for destructive Verneuil disease. (**b**) Preparation of myocutaneous gracilis flap. (**c**) Transposition of the flap to the perineum with the gracilis muscle encircling in γ fashion the neoanus; anastomosis between the rectum and the skin of the flap. Dynamization of the muscle was performed after 6 months

Table 16.2 Examinations for evaluation of fecal incontinence

Colonoscopy/proctoscopy	Anorectal sensitivity tests
Endoanal sonography	Anal reflexes examination
Anal manometry	Electromyography of the anal sphincter with PNTML (pudendal nerve terminal motor latency)
Clinical evaluation and incontinence scores (Jorge/CCFI/Williams) [23, 29]	Defecography

Table 16.3 Contraindications to DGP

Intussusception	Enterocele
Rectocele	Rectal prolapse
Constipation	Perianal sepsis or Crohn's disease
Causes of potentially damaged gracilis muscle (sclerosis, myopathic diseases)	Cardiac pacemaker (relative)

Table 16.4 Possible indications for APE + TAR

T2–T3 very low rectal cancer (*2–3 cm from a.m.*) not suitable for an intersphincteric excision and coloanal anastomosis (history of episodes of fecal incontinence and/or partial response to preoperative chemoradiation)
Anal cancer partially responsive to chemoradiotherapy
Extensive damage of anal structures for advanced fibrosis and stenosis after radiochemotherapy for anal cancer
Complete traumatic or infective destruction of anorectal structures (car accident, gun wounds, sex abuse, Verneuil disease, etc.)

not always good. They must be advised that a fairly acceptable outcome in the long term can be obtained in 50 % of the cases and that defecation will not be the same as before the surgery. Quite often they will experience defecatory difficulties requiring enemas to empty the neorectum. The surgeon must evaluate the manual dexterity of the patients to use the magnet or handheld telemetry equipment which controls the stimulator. Of high relevance is the meeting with one or more patients of similar age and sex who had undergone the procedure especially TAR.

16.3 Technique of Dynamic Graciloplasty: General Aspects

As regards isolation of the gracilis muscle, the technique has been well standardized after the works of Pickrell, and it is the same either in the presence of intact rectum or in the case of TAR after APE [4]. Conversely, other technical aspects related to timing of graciloplasty after APE as well as the timing and method of electrical stimulation have been and in part are still controversial issues. The different surgical approaches are summarized in Table 16.5.

16.4 Dynamic Graciloplasty in Fecal Incontinence

The patient is placed on the operating table in the modified Lloyd-Davis position with the interested leg abducted and extended. This leg will be, if necessary, adducted during the operation to favor the encirclement of the anorectum or neorectum by the gracilis. A single longitudinal incision is made on the medial aspect of the thigh following a line going from the medial femoral condyle to the inferior pubic ramus. Alternative access to the muscle can be obtained through a series of small incisions

Table 16.5 Reported surgical approaches to DGP

Graciloplasty for fecal incontinence with intact rectum	Synchronous vs. deferred insertion of stimulating electrodes Immediate vs. deferred stimulation Neuronal vs. muscular stimulation	With or without protective stoma
APE with synchronous perineal colostomy	Synchronous mono- or bilateral graciloplasty Synchronous or deferred insertion of the electrodes Neuronal vs. muscular stimulation Immediate vs. deferred stimulation	With or without protective stoma
Deferred perineal colostomy after late refusal of terminal abdominal stoma	Synchronous or deferred mono- or bilateral graciloplasty Synchronous or deferred insertion of electrodes Neuronal vs. muscular stimulation Immediate vs. deferred stimulation	With or without protective stoma

following the same line. Taking care not to damage the main saphenous vein, the muscle is easily identified being the most superficial muscle in that area, sharply dissected and gently encircled with a finger (Fig. 16.2a). Small feeding vessels are identified, tied, and cut to reach the tendon in its distal part, remembering that, at this level, the sartorius muscle covers the tendon and it must be separated. The tendon is followed as far as its insertion in the tibial tuberosity and cut 4–5 cm distal to the muscular body. The gracilis is proximally isolated as far as its main neurovascular bundle containing arteries arising from the profunda femoris and nerve from the obturator nerve. The main vascular pedicle and nerve enters in the lateral aspect of the muscle at the junction of the proximal with the distal two thirds of it at about 7–8 cm from the origin of the muscle at the pubic bone and emerging under the abductor longus muscle. The pedicle can be checked with the help of a disposable nerve stimulator (Fig. 16.2b). Some authors have suggested to clear the vascular pedicle from areolar tissue with careful dissection and mobilize the muscle as far as its origin in the pubis [18]. This maneuver would help in obtaining a complete encirclement of the anal canal by the body of the muscle and in identifying the main nerve of the gracilis proximal to the main vascular bundle. This can also allow the positioning of the stimulating electrode directly on the nerve that lies on the abductor magnus muscle. Since preservation of the main neurovascular bundle is the mandatory step of the operation, most of the authors do not isolate the main nerve to the gracilis muscle for the risk of damaging it, preferring to place the electrodes distally to the nerve entrance (Fig. 16.2c) [34]. The muscle with intact neurovascular bundle is repositioned in the thigh.

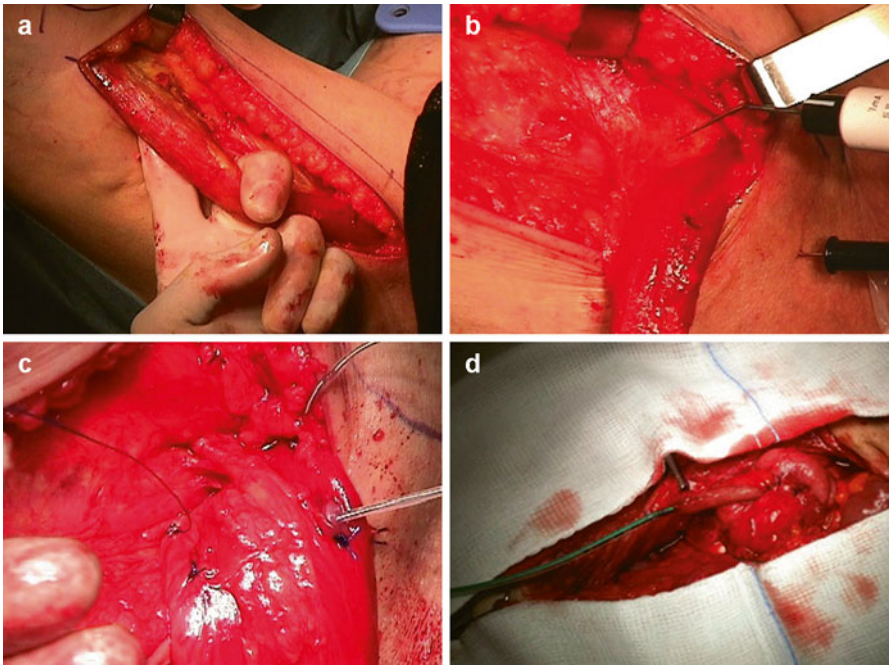

Fig. 16.2 (**a**) Isolation of the gracilis muscle. (**b**) Identification of the neurovascular bundle with electronic stimulator. (**c**) Final position of the electrodes for neuromuscular stimulation. (**d**) Preparation of Malone-type appendicostomy for antegrade continence enema

16.4.1 Preparation of Native Anorectum in Fecal Incontinence

Two curvilinear incisions 3–4 cm long are made lateral or anterior/posterior to the anus. A subcutaneous tunnel around the anal canal, external to the sphincters, is created. It must allow at least the passage of two to three fingers for easy accommodation of the gracilis muscle to avoid its entrapment when transposed. A communication is created between the perineum and the wound in the thigh with sharp dissection dividing the strong Scarpa's fascia. Also this tunnel must allow the passage of, at least, three fingers.

16.5 Graciloplasty and TAR

Graciloplasty, as part of immediate TAR, is done much the same as for fecal incontinence. It is done under general anesthesia being carried out after TME abdominoperineal resection with perineal colostomy. Sometimes two gracilis muscles have been transposed [33, 35]; however, in most experiences, only one gracilis has been isolated and transposed [31, 36]. The operation is made in the classic Lloyd-Davis position as for APE with access to both thighs. The abdominal operation can be performed laparoscopically and it is slightly different from a standard APE. In fact

to allow the descending colon to reach the perineum, it is necessary to mobilize the splenic flexure. A temporary loop ileostomy is prepared in the lower right abdominal quadrant. In the perineal phase, after excision of the anorectum and having encountered the abdominal dissection, the anorectum and sigmoid colon are delivered outside the perineal wound as in a pull-through maneuver. The descending colon is transected with a stapler in a well-vascularized area a few cm outside the perineum and the specimen removed. Some long stitches are positioned in the proximal stump to avoid its sliding in the pelvic cavity. Alternatively, a longer proximal stump 10–15 cm is left to protrude outside the perineum. The preparation of the gracilis is performed in the same manner as described above. A subcutaneous tunnel is created between the incision of the thigh and perineal wound.

16.6 Positioning of the Gracilis Muscle and Dynamization

Using a long strong clamp passed from the perineal wound to the incision in the thigh, the free tendon is grasped and the muscle is transposed in the perineum taking care not to twist it. Different configurations of looping the anus with the muscle can be adopted to use as much as possible muscular tissue rather than tendon (Fig. 16.3). Gamma or epsilon loop is created when the muscular part is long. Alpha loop is preferred in case of short muscular part or in double transposition. Rosen suggested a split technique in which the tendon is brought through the muscle belly itself to shorten the way around the anal canal [36]. After deciding the configuration of the loop, the muscle is repositioned in the thigh to allow easier placements of the electrodes and to pass the fixing stitches in the periosteum of the homolateral or contralateral pubic bone (ischium). During this maneuver, if patients are under general anesthesia, no muscle relaxant must be used. Electrodes (Platinum-Iridium, mod.435045/mod.435055, Medtronic Inc., USA) must be placed to allow maximum contact with muscular fibers and nerves. The first electrode (anode), with a special designed needle, is passed through the body of the muscle orthogonal to its main axis a few cm distal to the nerve entrance. The other electrode (cathode) is positioned close to the entry of the nerve in the muscle with the help of an auxiliary electrode connected to the needle used for insertion. Stimulating this electrode and the needle, it will be easy to find out the best place for insertion that is where the muscle contracts at the lowest voltage. Both electrodes are fixed to the epimysium. In the case of double graciloplasty, the electrodes (cathodes) are positioned close to the nerve entrance of both muscles. The dynamized muscle(s) is/are now repositioned around the anus according to the best configuration, while the tendon(s) is/are anchored by the stitches placed in the periosteum of the ischial tuberosity(ies). The electrodes are passed subcutaneously from the thigh(s) to a pocket prepared in the lower abdomen and connected to a pulse generator (InterStim mod.3023, Medtronic Inc., 710 Medtronic Parkway N.E. Minneapolis – MN 55432 – USA) placed and fixed to the muscular fascia. The wounds are closed. Some authors create a temporary loop ileostomy in the lower right abdominal quadrant also in the procedure for fecal incontinence [23]. In TAR the colonic stump (neoanus) is

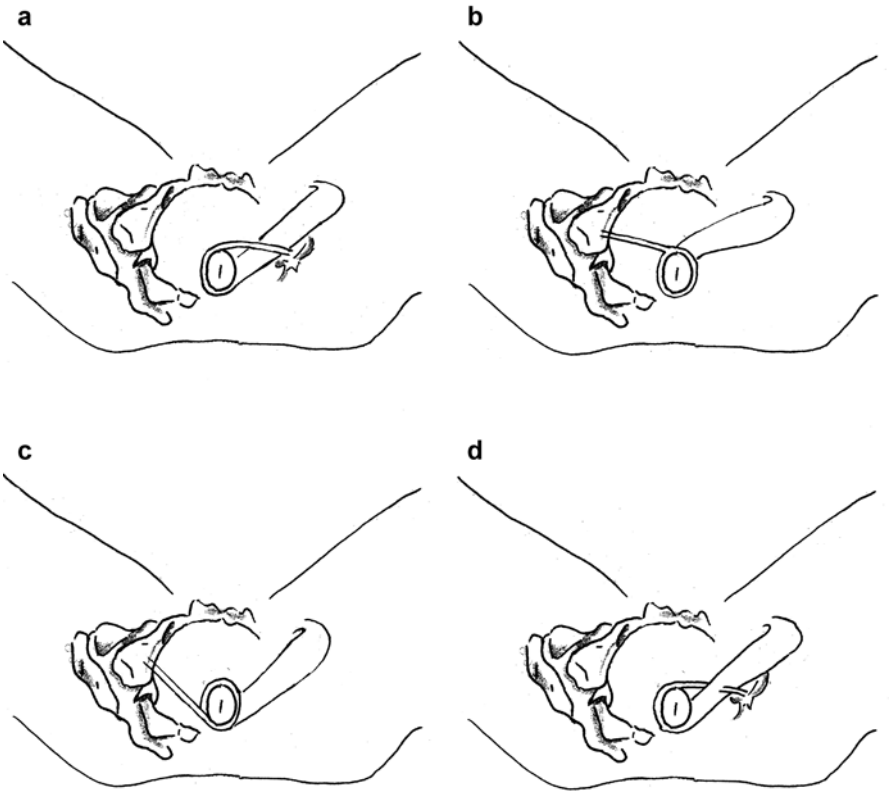

Fig. 16.3 Possible loops of the gracilis muscle around the anus. (**a**) Alpha (α). (**b**) Gamma (γ). (**c**) Epsilon (ε). (**d**) Split-sling-technique

opened and sutured to the perineal skin. When a longer stump has been left protruding from the perineum, this can be left in situ for 1 week as far as it has adhered to the perineal skin. At that moment, the excess of the colon will be resected and the coloperineal anastomosis performed.

16.7 Electrostimulation Training

The electrostimulation can be usually started after 1 month, when the wounds have healed and the tendon is sealed to the ischiatic tuberosity. The stimulation can be done continuously or cyclically according to the established parameters programmed with a portable neuroprogrammer (N'Vision Medtronic) to reach the frequency (at the minimum voltage for full muscle contraction) of 15 Hz in 6–8 weeks to be maintained permanently. This is sufficient for achieving a fast-to-low switch conversion and transformation of the gracilis muscle into a fatigue-resistant muscle. Temporary ileostomies are closed at the end of muscle training.

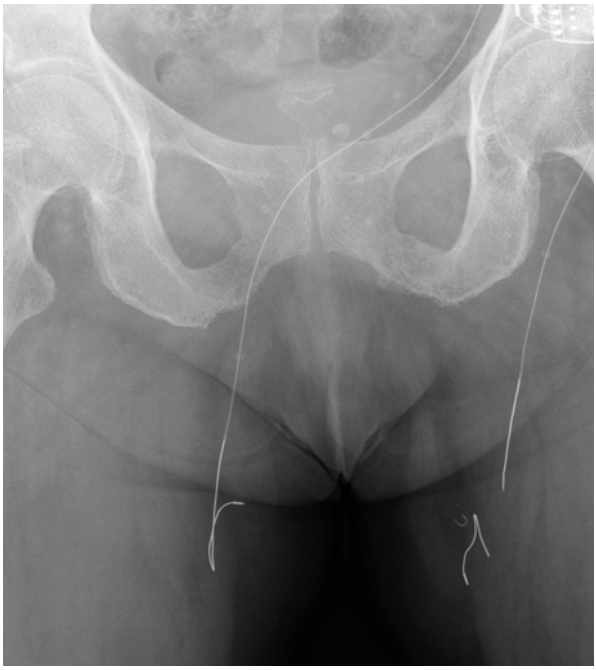

Fig. 16.4 Spontaneous rupture of electrodes after 15 years from implant

16.8 Complications

Immediate and delayed postoperative morbidity after dynamic graciloplasty is high especially when the operation is associated to APE and TAR. Many experiences report very high rates and variety of complications, averaging 2–2.9 per patient [21, 37, 38]. Complications are related to the complexity of the operation and possibly to the experience of the operator with this procedure. Table 16.5 listed the complications observed in different experiences varying from the frequent infection at the sites of implanted prosthetic devices, at times requiring explantation, to the serious colon necrosis demanding abdominal reoperation to the bizarre late spontaneous rupture of stimulating electrodes (Fig. 16.4). Corrective surgery is often necessary. Definitive removal of the electronic devices and transformation of TAR in a perineal or abdominal colostomy have been reported to occur from 10 to 30 % of the cases (Table 16.6) [27, 31].

16.9 Functional Results

The functional results of DGP are quite different when the operation is done for the treatment of fecal incontinence in patients with intact anorectum or in patients submitted to TAR. Success rates in 60–70 % of patients treated for fecal incontinence have been obtained in many experiences [21, 23, 39] despite a relevant number of

Table 16.6 Complications of stimulated graciloplasty

Stimulator sepsis	Lead displacement
Tendon and muscular necrosis	Rectal injury
Detachment of tendon	Lead injury
Stenosis of neosphincter	Perineal hernia
Colon necrosis (in TAR)	Anal stricture
Lead rupture	Skin erosion
Rectocele	Constipation

complications. Sometimes the failures to achieve fecal continence are related to complications (detachment of tendon from the ischium, lead displacement) that can be easily managed with minor surgery. Nevertheless, as already mentioned, the increased adoption of SNS has progressively confined the treatment with DGP to very selected cases of fecal incontinence. As regards the functional results of dynamic graciloplasty in TAR, it is difficult to have a reliable evaluation for several reasons: high number and variability of postoperative complications, small series of patients treated with different techniques, use of different types of stimulation, and above all different evaluations of the outcome. Satisfactory continence has been reported to occur in 50 % [32] to 85 % of the cases [35]; soiling from exposed mucosa of perineal colostomy is very common. Of more difficult treatment is the common presence of obstructed defecation [23, 31, 40]. In some cases, it can be due to the presence of a stenotic neoanus that can be treated with a simple V-Y plastic surgery. In most cases, however, the difficulty to evacuate is possibly due to the loss of all reflexes triggered by the sensitive receptors present in the anal mucosa and in the pelvic floor. To solve this relevant problem, some authors have proposed to associate a defunctioning continent colon conduit [41] or a Malone-type appendicostomy [42] to TAR to allow antegrade continence enema to control defecation (Fig. 16.2d). Satisfactory results have been reported with this procedure; however, satisfactory functional results have been reported also by other experiences with Malone antegrade continence enema associated to perineal colostomy after APE without TAR and DGP [43].

16.10 Quality of Life (QOL)

It is evident that dynamic graciloplasty, especially when it is part of a TAR, cannot allow a physiological defecation. In addition, many patients can have episodes of incontinence together with difficulties to defecate requiring daily enemas. It would be important to know how much these problems can affect negatively the quality of life when compared with the presence of a terminal abdominal stoma. Cavina et al. [44] carried out a study comparing, through several validated instruments, the QOL of 21 patients with TAR and dynamic graciloplasty with the QOL of 27 normal subjects. He did not find significant difference in the QOL of the two groups. Fucini et al. [45] using the EORTC C30 and C38 QOL questionnaires compared the QOL of 5-year survivor patients with an abdominal stoma with that of 5-year survivor

patients with TAR and dynamic graciloplasty. The global QOL of this group resulted to be better than that of patients with a terminal abdominal stoma. Interestingly similar results were reported by Farroni et al., who compared the QOL of 14 patients with an abdominal stoma with that of 13 patients with perineal colostomy and Malone appendicostomy using the same EORTC questionnaires [43].

16.11 Comment by the Authors

After 25 years from its introduction in the clinical practice, it is still difficult to give an exhaustive evaluation of dynamic graciloplasty. The expectations that this sophisticated and technologically advanced procedure had created in the beginning have been mostly frustrated. The physical and mental engagement of the patients in a complex and sometime multistage procedure with high morbidity does not seem to be paid by the results obtained; in particular this is true for dynamic graciloplasty after TAR. Nevertheless, in very selected cases of fecal incontinence or in patients absolutely determined to avoid a terminal abdominal stoma, dynamic graciloplasty could have a role. Since these cases represent a small number of subjects, it would be wise to concentrate their treatment in specialized centers.

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Electrical Stimulation in Sexual Dysfunction

17

Jacopo Martellucci

17.1 Introduction

Masters and Johnson were some of the first researchers to study and describe the sexual response cycle in their 1966 book *Human Sexual Response* [1].

The cycle begins with excitement as blood rushes into the genitals, then reaches a plateau during which they are fully aroused, which leads to orgasm, and finally resolution, in which the blood leaves the genitals.

Desire and arousal are both part of the excitement phase of the sexual response.

Sexual dysfunction (SD) refers to a problem occurring during any phase of the sexual response cycle that prevents the individual or couple from experiencing satisfaction from the sexual activity.

Sexual dysfunctions are highly prevalent, affecting about 43 % of women and 31 % of men [2, 3], even if it is a topic that many people are hesitant to discuss.

Moreover, in addition to their widespread prevalence, sexual dysfunctions have been found to impact significantly on interpersonal functioning and overall quality of life in both men and women, as confirmed by a large study involving 27,500 men and women in 29 countries (aged 40–80 years), which was conducted to assess the importance of sex and the prevalence of sexual dysfunction. In the results, 82 % of men and 76 % of women agreed with the statement that "a satisfactory sex life is essential to maintaining a relationship" and the majority disagreed with the statement that "older people no longer want sex" [4].

Several factors (physical, hormonal, psychological, social) contribute to sexual dissatisfaction or dysfunction, and these factors tend to be interrelated. Age was an

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important correlate of lubrication difficulties among women and of several sexual problems, including a lack of interest in sex, the inability to reach orgasm, and erectile difficulties among men.

Factors involved in sexual functions associated with chronic diseases and cancer are reported in Table 17.1.

The traditional sexual response cycle including excitement, plateau, orgasm, and resolution set the foundation for studying and categorizing sexual dysfunctions in men and women.

Sexual dysfunction generally is classified into four categories:

- *Desire disorders—lack of sexual desire or interest in sex:* Sexual desire disorders or decreased libido (also known as hypoactive sexual desire disorder; HSDD) are characterized by reduction or absence for some period of time of sexual desire or libido for sexual activity or of sexual fantasies. The condition ranges from a

Table 17.1 Factors involved in sexual functions associated with chronic diseases and cancer

Type	Mechanisms	Examples
Direct	Change in sexual desire from disease	Typically reduced, e.g., from high prolactin and anemia of chronic renal failure [1]. May be increased, e.g., from some brain disorders [2]
	Disruptbn of genital response from disease	ED from multiple sclerosis [3], hypertension [4], orgasmic disorder from multiple sclerosis [5]
	Disruptbn of genital response from surgery	Radical prostatectomy and ED [6], radical hysterectomy and reduced genital congestion/reduced lubrication [7], orgasmic disorder after radical vulvectomy [8]
	Disruptbn of genital response from radiation	ED from vascular (and also likely nerve) damage after radiotherapy for prostate cancer [9]; vaginal stenosis and friability from radiation for pelvic cancer [10]
	Dyspareunia and disruptbn of sexual desire and response from chemotherapy	Sudden ovarian failure after chemotherapy for breast cancer [11]; testicular failure after intensive chemotherapy for hematopoietic transplantation [12]
	Disruptbn of sexual desire and response from antiandrogen treatment	GnRH therapy for prostate cancer [13]
	Disruptbn of genital response from aromatase inhibitors	Loss of sexual genital sensitivity, and exacerbation of vaginal atrophy from aromatase inhibition post breast cancer [14]
	Disruptbn of sexual desire and response from pain	Pain from any chronic condition is a potent sexual distraction
	Disruption of sexual desire and response from nonhormonal medications	Narcotics can depress desire through gonadotropin suppressbn [15]; selective serotonin reuptake inhibitors reduce desire and response [16]

Table 17.1 (continued)

Type	Mechanisms	Examples
Indirect	Reduction of self-image	Reduced by disfiguring surgeries, stomas, incontinence, altered appearance (e.g., drooling and altered faces of Parkinson's, altered skin color and muscle wasting of renal failure)
	Depressed mood	Depression and mood lability commonly accompany chronic illness; depression major determinant of sexual function in women with renal failure [17] or multiple sclerosis [18]; strong link between ED and subsequent depression [19]
	Impaired mobility	Reduced ability to caress, hug, and hold a partner; to sexually self-stimulate, to stimulate a partner, to move into positions for intercourse, to pelvically thrust in spinal cord injury, Parkinson's, brain injury, postamputation
	Reduced energy	Fatigue may take its toll on sexuality especially desire, e.g., from renal failure or chemotherapy
	Partnership difficulties	Difficulties finding a partner, dysfunction in the partner who assumes a care giver role, institutionalization, fear of becoming a burden to a partner, lack of independence. Relationship discord from stressors of living with medicalized lives (e.g., three times weekly hemodialysis)
	Sense of loss of sexuality from imposed infertility	From surgery removing gonads or uterus, from chemotherapy or radiotherapy causing gonadal failure
	Fear of sex worsening medical condition	Avoiding sex fearing a further stroke

From Basson et al. [5]
ED erectile dysfunction

general lack of sexual desire to a lack of sexual desire for the current partner, and it may have started after a period of normal sexual functioning or the person may always have had no/low sexual desire. Hypoactive sexual desire disorder has been reported in approximately 30 % of women and 15 % of men in population-based studies and is associated with a wide variety of medical and psychologic causes.

- *Arousal disorders—inability to become physically aroused or excited during sexual activity:* Sexual arousal disorders, including erectile dysfunction in men and sexual arousal disorder in women, are found in 10–20 % (arousal and lubrication disorders are reported in 8–28 % of women) and are strongly age-related in men. They are characterized by a normal desire for sex but a difficulty or inability to become aroused or maintain arousal during sexual activity.
- *Orgasm disorders—delay or absence of orgasm (climax), ejaculation disorders (for male):* Orgasmic disorder is relatively common in women, affecting about 10–25 % in community-based studies. In contrast, premature ejaculation is the most common sexual complaint of men, with a reporting rate of approximately 30 % in most studies. These conditions consist in a persistent or recurrent

difficulty in achieving orgasm after sufficient sexual arousal and ongoing stimulation (anorgasmia or delayed ejaculation).

- On the contrary, premature ejaculation (PE) occurs when a man experiences orgasm and expels semen soon after sexual activity and with minimal penile stimulation. However, there is no uniform cutoff defining "premature," and values between 15 s and one minute are reported. Men's typical ejaculatory latency is considered approximately 4–8 min [6].
- Another uncommon ejaculation disorder is retrograde ejaculation, which occurs when semen enters the bladder instead of going out through the urethra during ejaculation. The main reason is an incomplete or ineffective closure of the bladder neck. It can be caused by medications, health conditions, or surgeries that affect the nerves or muscles that control the bladder opening.
- *Pain disorders—pain during intercourse*: Sexual pain disorders have been reported in 10–15 % of women and less than 5 % of men. Dyspareunia (painful intercourse), vaginismus (an involuntary and painful spasm of the muscles of the vaginal wall that interferes with intercourse), and vulvodynia (burning vulvar pain not necessary related to sexual activity) are common sexual pain-related conditions. Dyspareunia may be caused by insufficient lubrication (vaginal dryness) in women. Poor lubrication may result from insufficient excitement and stimulation or from hormonal changes caused by menopause, pregnancy, or breast-feeding. It is unclear exactly what causes vaginismus, but it is thought that past sexual trauma (such as rape or abuse) may play a role.

However, there is considerable overlap between sexual dysfunctions, especially in women [7]. In patients with hypoactive sexual desire disorder, 41 % of women had at least one other sexual dysfunction and 18 % had diagnoses in all three categories (excluding pain disorders) [8].

17.2 Sexual Dysfunction and Pelvic Pain Disorders

Urinary voiding disorders have been strongly associated with sexual dysfunction. In women with urinary incontinence, 60 % had urinary incontinence during sexual intercourse, which significantly impacted their sex life [9]. Similarly, others have reported greater degrees of incontinence correlating with lower scores on the sexual function survey [10, 11].

The landmark National Health and Social Life Survey established a strong association between urinary tract symptoms and arousal disorders (odds ratio 4.2; 95 % confidence interval 2.75–5.89) and sexual pain disorders (odds ratio 7.61; 95 % confidence interval 4.06–14.26) [12]. The prevalence of sexual dysfunction secondary to sexual and pelvic pain ranges from 7 to 58 % [13].

In addition, women with genitourinary hypersensitivity disorders, classified by the International Continence Society as "genitourinary pain syndromes," account for a large percentage of female patients who present to urogynecologic and sexual medicine practices [14].

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a potential cause of SD and should be considered in the differential diagnosis for dyspareunia. Dyspareunia is estimated to occur in 49–90 % of women with IC/PBS, and urinary and pain symptoms are exacerbated following sexual activity [15].

Using the Female Sexual Distress Scale (FSDS), Peters et al. reported that IC/PBS patients had significantly more dyspareunia (74.6 % vs.29.9 %), more fear of pain (50.2 % vs. 13.5 %), and significantly less sexual desire and ability to achieve orgasm compared with healthy controls [16].

The prevalence of SD among women affected by laxity disorders of the pelvic floor is estimated to be 25–63 %. An estimated 11 % of these women undergo pelvic surgery for their laxity disorder, and the surgical repair procedure may either enhance or further impair their sexual function [12, 17].

Coital urinary incontinence (CUI) is another significant factor that affects sexual function and may be underdiagnosed in the clinical setting. Unless women are asked directly about its occurrence, they rarely report CUI spontaneously. Bachmann et al. noted that only 3 % of women self-reported sexual disturbances (including CUI); however, the prevalence increased to 20 % after direct questioning in an outpatient setting [18].

Surgical repair of pelvic organ prolapse or stress urinary incontinence, while generally beneficial for a woman's quality of life, can also have negative effects [19]. Depending on the extent of surgical dissection, tissue damage, devascularization, and denervation involved, the result can be decreased vaginal blood flow and increased fibrosis, ultimately resulting in increased dyspareunia.

Sexual function improves in women following pelvic reconstructive surgery, but the improvement is more substantial following anterior repair either alone or in combination with a vaginal hysterectomy when compared with posterior repair [20].

For upper vaginal prolapse (uterine or vault), abdominal sacral colpopexy was associated with a lower rate of recurrent vault prolapse on examination and painful intercourse than with vaginal sacrospinous colpopexy [21].

The association between vaginal mesh and dyspareunia is well documented, especially after posterior repair, and the incidence of dyspareunia was increased associating levator myorrhaphy to posterior vaginal repair, with a de novo dyspareunia rate up to 20 % [22].

Despite the good functional results achieved by expert surgeons, large multicenter studies show that urogenital dysfunction remains a common problem after rectal cancer treatment. More than half of patients experience a deterioration in sexual function, consisting of ejaculatory problems and impotence in men and vaginal dryness and dyspareunia in women. Radiotherapy seems to have a role in the development of sexual dysfunction, without affecting urinary function [23].

Laparoscopic or robotic total mesorectal excision for rectal cancer is associated with significantly less deterioration in sexual function compared with open surgery. This effect is particularly pronounced in women [24].

Prostate cancer by itself reduces sexual desire and the frequency of sexual intercourse. Additionally, surgery or hormonal therapy to block testosterone

further increases the frequency of erectile dysfunction. Erectile dysfunction following radical prostatectomy is primarily attributable to nerve injury caused by intraoperative nerve traction, thermal injury, ischemic injury, and local inflammatory reactions [25].

Women with fecal incontinence were as likely to engage in sexual relations as women without fecal incontinence; however, sexually active women with fecal incontinence had poorer sexual function and reported more dyspareunia, fear, and avoidance of sexual activity with greater partner problems than women without fecal incontinence [26].

17.3 General Treatment Principles

Treatment of sexual dysfunction is complicated by the lack of a single causative factor, limited proven treatment options, physician unfamiliarity with available treatments, overlap of different types of dysfunction, limited availability of treatment, and limited expertise in the treatment [27].

Most types of sexual dysfunction can be corrected by treating the underlying physical or psychological problems. Sexual therapy and education (e.g., cognitive behavior therapy, individual and couple therapy, physiotherapy) form the basis of treatment in most cases. The success of treatment for sexual dysfunction depends on the underlying cause of the problem and the outcome is good for dysfunction that is related to a treatable or reversible physical condition.

Substantial advances have occurred in the understanding of the pathophysiology of erectile dysfunction that led to the development of successful oral therapies, namely, the phosphodiesterase type 5 inhibitors, even if with limitations [28].

With the advent of phosphodiesterase type 5 inhibition as oral therapy, intracavernous injection of vasoactive agents has been relegated to second-line therapy for most patients with erectile dysfunction. However, the future of this category of agents remains attracting and an ever-expanding number and combination of agents are under investigation, making intracavernous injection more appealing as greater efficacy and tolerability and more rapid onset are attained [29].

Developments in the treatment of male erectile dysfunction have led to investigation of pharmacotherapy for the treatment of female sexual dysfunction, even if the benefit of hormonal and nonhormonal drugs is less demonstrated. Testosterone improves sexual function in postmenopausal women with hypoactive sexual desire disorder, although data on its long-term safety and effectiveness are lacking. Estrogen improves dyspareunia associated with vulvovaginal atrophy in postmenopausal women. Phosphodiesterase inhibitors have been shown to have limited benefit in small subsets of women with sexual dysfunction [30].

The myriad of therapeutic modalities for the treatment of female sexual dysfunction are summarized in Table 17.2, underlining the difficulties and the variability of the treatment of these diseases.

Table 17.2 Therapeutic modalities for the treatment of female sexual dysfunction

Behavioral therapy	Pharmacological therapy to bladder	Nonpharmacological therapy to pelvic floor	Therapy to vagina and vulva
Dietary modifications	Pentosan polysulfate sodium	Physical therapy	Lubricants
Stress reduction	Hydroxyzine hydrochloride	Myofascial massage	Estrogen creams
Relationship counseling and sex therapy	Amitriptyline hydrochloride	Thiele massage	Cromolyn
Lifestyle modifications	Cyclosporin A	Pharmacological therapy to pelvic floor	Capsaicin
Planned timing for intercourse	Intravesical bladder therapy/cocktails (dimethyl sulfoxide, heparin, lidocaine, Marcaine, steroids)	Muscle relaxants (Valium suppository)	Lidocaine gel
Pre- or postcoital bathing	Antispasmodics and antimuscarinics	Trigger point injections with local anesthetics and anti-inflammatory medications	Trigger point injections with local anesthetics and anti-inflammatory medications
Changing sexual positions	Botulinum toxin A	Botulinum toxin A	
Noncoital sexual alternatives	Neuromodulation		
Pre- and postcoital ice pack applied to genital and suprapublic areas	Medical: Gabapentin, Pregabalin		
Vaginal diators	Surgical: Peripheral and sacral nerve stimulation		

From Wehlbe et al. [31]

17.4 Electrotherapies for Sexual Dysfunctions

In this wide field, electrotherapies could have a potential role for treating specific symptoms in specific patients.

The principles of using electrical stimulation of peripheral nerves or nerve roots for restoring useful bladder, bowel, and sexual function after damage or disease of the central nervous system have been extensively reported in literature.

17.4.1 Neuromodulation for Female Sexual Dysfunction

Since the 1990s, sacral neuromodulation (SNM) is used in patients with refractory idiopathic symptoms of overactive bladder or nonobstructive urinary retention and then for fecal incontinence ad constipation. During routine follow-up for SNM, a

number of patients spontaneously reported improved sexual functioning in comparison to before their SNM implantation.

The rationale of this result can be highlighted considering the common innervation of the involved structures through the pudendal and the hypogastric nerves.

However, even if the associations between lower urinary tract symptoms (LUTS) and female sexual dysfunction (FSD) are well documented, the question remains as to whether improved sexual function following SNM results from a reduction in LUTS and/or the associated improvement in quality of life (QoL) or if it occurs independently of changes in urinary function.

In the study of Gill et al. [32] in 33 patients affected by overactive bladder (OAB), a statistically significant improvement in urinary and sexual function occurred according to multiple metrics. Female Sexual Function Index (FSFI) and female sexual health questionnaire (FSHQ) were used to assess the sexual status and function of the patients, and also urinary function was assessed using validated instruments. Of the 33 patients only 10 where sexually active, and all the patients were in a menopausal status.

Validated urinary symptom and quality of life scores improved significantly. After treatment, most patients were incontinent less often with sexual activity and felt less restricted from sexual activity by fear of incontinence. Validated quantification of sexual function demonstrated significant improvements in overall sexual function, arousal, and satisfaction. In their results, improved sexual function was not significantly associated with improved urinary function after SNM despite apparent trends between the two.

Opposed to this result, studying a possible correlation between OAB symptoms improvement and sexual function improvement, Signorello et al. [33] analyzed the correlations between differences in Female Sexual Function Index (FSFI) scores and in clinical outcome and correlations between differences in FSFI, short form 36 (SF36), and incontinence quality of life index (IQoL) scores in 16 sexually active patients treated for OAB with SNM (15/16 were in menopause).

A significant correlation was found between clinical improvement and improvement in sexual function. No significant correlation was found between differences in FSFI and quality of life index (IQoL and SF36).

The authors suggest that improvement in the quality of sexual function in female patients with OAB correlates with improvement in urinary symptoms.

Pauls et al. [34] reported improvement in the FSFI score in 11 female patients with an SNM implant for LUTS. Significant improvement with regard to desire, lubrication, orgasm, satisfaction, and pain was found. No increase in score was noted for the arousal domain. Sexual arousal is a response to a sexually attractive stimulus and has both a physiological and a subjective component.

Interestingly, all patients in Pauls' study improved on the FSFI, while only three subjects reported subjective improvement in sexual functioning.

Lombardi et al. [35] presented the results of their study on the effect of SNM on sexuality in 31 female patients. In this study, both patients with idiopathic and with neurological causes for their LUTS were included. Improvement in Female Sexual Distress Scale and FSFI after SNM was found in both patient groups.

Also Yih and colleagues [36] suggest a possible positive role of SNM, observing that sexual function improves along with urinary symptoms after neuromodulation in 167 patients with voiding symptoms evaluated with FSFI and Interstitial Cystitis Symptom-Problem Indices (ICSI-PI). Improved FSFI domains included desire, orgasm, satisfaction, and pain. Of the 74 sexually inactive patients at baseline, 10 became sexually active during the follow-up.

On the contrary Ingber et al. [37] used the FSFI on 54 female patients (27 sexually inactive) affected by OAB or painful bladder syndrome (PBS), who were scheduled to receive a neuromodulation implant. They administered the FSFI before and after 6 months from implantation, and they found no significant improvement in female sexual function.

Both neuromodulation by SNM and by pudendal implant techniques were used in their study.

Pudendal nerve stimulation for SD was also described in the paper of Peters [38], focusing on the technique and according to the original technique described by Spinelli [39].

Also the study of van Voskuilen et al. [40] on 8 patients treated with SNM for urgency symptoms (6 patients), urinary retention (1), and fecal incontinence (1) did not show a clear effect of SNM on sexual function, although there seems to be an improvement in orgasm scores. However, the lack of response on psychological questionnaires (5 questionnaires: Questionnaire for Screening for Sexual Dysfunctions, the Golombok-Rust Inventory of Sexual Satisfaction, the Symptom Checklist-90, the Maudsley Marital Questionnaire, and the McGill-Mah Orgasm Questionnaire) and the increase in vaginal pulse amplitude at plethysmography after SNM implantation could indicate that the improvement seems to be more physiologically than psychologically mediated.

Jarrett et al. [41] administered a self-written sexual questionnaire to patients with fecal incontinence before and after SNM implantation.

Nine of the 16 patients were sexually active. All nine patients reported that their sex life had been affected by fecal incontinence prior to SNM, and seven had felt benefit from implantation. The median improvement in their sex life was 40 %, and the percentage of improvement was inversely correlated to age.

Another study on the effects of SNM for LUTS on female sexual function was carried out by Zahibi et al. [42].

A characteristic of this study was that a large proportion of the patients had pelvic pain as well as LUTS. The study group chose to perform bilateral SNM and to position the electrodes epidurally in the sacral canal, thus stimulating the nerves of S2 and S4 as well as S3. A significant improvement in the FSFI was found. Results were better in patients who underwent the treatment for voiding dysfunction compared to those who had pain as their primary complaint. Domains with no significant improvement were desire and pain.

A concomitant improvement of LUTS and SD was noted even after percutaneous tibial nerve stimulation. Patients most likely to benefit were women, patients with an OAB, and subjective responders. The aspects of sexual life which mostly improved were overall satisfaction, libido, and frequency of sexual activities [43].

In front of these conflicting results, some factors need to be considered.

One of the most obvious causes for a not consistent concordance between the studies is the low number of patients tested. A reason for this might be that many patients with prolonged LUTS or fecal symptoms are not sexually active because of their complaints, and current sexual activity was not always an inclusion criterion. Considering sexually inactive patients in the measurement could be a selection bias.

Moreover, a large proportion of the group of patients who have urinary or fecal symptoms and are considered for SNM therapy are postmenopausal patients, as evident in the described papers.

Postmenopausal women report a relatively high rate of sexual dysfunction (higher than men). There is a marked decline in sexual interest and frequency of sexual activity. Lower estrogen levels after menopause may lead to changes in genital tissues and sexual responsiveness, and in this group considerable comorbidity can be found such as hysterectomy, vascular disease, diabetes, or arthrosis that might also preclude patients from engaging in sexual activity [44].

Previous pelvic surgery could be another influencing factor, as well as the lack of dedicated studies about SNM for SD, with SD as the main indication for the treatment.

There has been one case report on the use of sacral neuromodulation for the treatment of refractory vulvar vestibulitis syndrome.

Sacral neuromodulation was used, and at 6 weeks postoperatively, the patient reported that her pain had decreased from a 10/10 to a 2/10. At 24 months postimplantation, the patient continued to report decreased pain, was able to resume coitus, noted an increase in pain-free days, and a decrease in the intensity of pain during flares [45].

In another case report, a 51-year-old patient that presented with symptoms of lower urinary tract dysfunction and clitoral pain after an abdominal hysterectomy treated with SNM was described.

During test stimulation, she experienced only moderate improvement in voiding symptoms, but a striking improvement in clitoral pain symptoms. She underwent a two-stage implantation of a neurostimulator with a successful outcome after 6 months follow-up [46].

Govaert et al. [47] shows that SNM has an effect on uterus contractility. A decrease in frequency of contractions is seen with the SNM system switched on. However, as the measurements were performed in patients in the resting state, it is not clear what the effect of SNM on the uterus is while the patient has an orgasm.

Lastly, there are case reports on female patients who received lumbar epidural electrical stimulation, who have spontaneous orgasms when the simulator is turned on.

Through standard techniques, quadripolar or octopolar leads were placed in the epidural space percutaneously. The lead was maneuvered initially to an L1–L2 position and then repositioned based on feedback from the patient. The patients were allowed to utilize the device ad libitum for up to 9 days. These women described a greater frequency in sexual activity, increased lubrication, and overall satisfaction. A return of orgasmic capacity was found in 80 % (4/5) of patients

having secondary anorgasmia with an average intensity of ≥3/5 while using the device. Once the device was removed, the patients returned to their previous anorgasmic status [48, 49].

17.4.2 Neuromodulation for Erectile Dysfunction

Anecdotally, most men report improved erectile functioning after neuromodulation for concomitant pelvic floor diseases. Research in monkeys, dogs, and rats has shown that electrical stimulation of the cavernous nerve results in an erection by causing increased arterial flow, relaxation of the cavernous muscles, and venous outflow restriction [50–52].

Shafik [53] implanted a cavernous nerve stimulation device in a series of 15 men for the treatment of erectile dysfunction. Cavernous nerve stimulation at a frequency of 10 Hz led to penile tumescence and an increase in intracavernous pressure but poor rigidity. When the stimulation frequency was increased to 60 Hz, penile tumescence and rigidity and intracavernous pressure increased, and full erection was achieved.

Additionally, Shafik's study demonstrates that unilateral cavernous nerve stimulation is sufficient to induce erection.

Erectile dysfunction is a recognized, common adverse consequence of radical prostatectomy as well as various other pelvic surgeries. While a host of management options have been considered to decrease this complication, neuromodulatory therapy has recently been advanced as an intervention that may be applied for this purpose. Neuromodulatory therapy offers a therapeutic approach for addressing the neuropathic changes of the penis that occurs in this context with the goal of maximally preserving erectile function postoperatively [54].

In 16 men undergoing retropubic radical prostatectomy and in 6 undergoing penile surgery for venous leakage, Lue et al. [55] applied electrical stimulation to the prostatic apex bilaterally (prostatectomy group) or to the hilum of the penis (venous surgery group). Electrical stimulation produced visible erection in 8 of the 16 prostatectomy patients and an increase in intracavernous pressure in 5 of the 6 venous surgery patients.

Burnett et al. [56] explored the feasibility of using an implantable electrode array for cavernous nerve stimulation for patients undergoing nerve-sparing prostatectomy. The implantable electrode array was placed over the neurovascular bundles (20 Hz frequency, 260 μs pulse width, 5–60 mA amplitude up to 10 min) in 12 patients undergoing open retropubic radical prostatectomy, and penile circumference increases were measured. Six of 12 (50 %) patients demonstrated a significant increase in penile circumference after stimulation.

To determine if intraoperative stimulation of the cavernous nerves while monitoring changes in penile tumescence could be useful to map the course of these nerves and would result in an improvement in nerve sparing and erectile function after radical prostatectomy, Klotz and Herschorn [57] studied 23 patients.

A cavernous nerve stimulator and tumescence-monitoring device was used during radical prostatectomy to identify the course of the cavernous nerves and guide the surgeon in avoiding nerve damage. Nineteen of 21 patients reported erectile function preoperatively. Seventeen (89 %) of 19 patients demonstrated a tumescence response during surgery. Sixteen (94 %) of the 17 patients who demonstrated a response to nerve stimulation and for whom the surgery was guided by the tumescence response reported the ability to have erections after surgery.

The same author confirmed the results in a multicentric prospective, randomized, single-blinded study, performed on 61 patients at 6 centers [58]. Patients had elected to undergo nerve-sparing prostatectomy and had normal preoperative erectile function documented by the Sexual Function Inventory Questionnaire (SFIQ) and RigiScan parallel testing. At 1 year, there was substantial improvement in erectile function in the group in which the procedure was performed assisted by the neurostimulation mapping. This group had a mean of 15.9 min of greater than 60 % nocturnal tumescence compared to 2.1 min in the conventional nerve sparing group ($p < 0.024$).

However, as suggested by Holzbeierlein and colleagues [59], a response to neurovascular bundle stimulation does not necessarily correlate with the precise anatomical location of the cavernous nerves and that a considerable background variability related to anesthesia, surgical manipulation, and other undefined factors that may cause minor but measurable changes in penile circumference and need to be considered.

To evaluate if SNM could improve erectile function, Lombardi et al. [60] studied 22 males that underwent a permanent SNM for LUTS of neurogenic or idiopathic origin. International Index of Erectile Function (IIEF-5) was used. Postoperatively, seven of the 22 showed an improvement in their IIEF-5 scores maintained until the last follow up.

17.4.3 Functional Electrical Stimulation and Rehabilitative Techniques

The sphincteric and supportive functions of the pelvic floor are fairly well understood, and pelvic floor rehabilitation (PFR) has demonstrated effectiveness in the treatment of urinary and fecal incontinence.

However, the role of the pelvic floor in the promotion of optimal sexual function has not been clearly elucidated.

It has been proposed that the pelvic floor muscles are active in both male and female genital arousal and orgasm and that pelvic floor muscle hypotonus may impact negatively on these phases of function. Hypertonus of the pelvic floor is a significant component of sexual pain disorders in women and men. Furthermore, conditions related to pelvic floor dysfunction, such as pelvic pain, pelvic organ prolapse, and lower urinary tract symptoms, are correlated with sexual dysfunction [61].

The role of functional electrical stimulation (FES) in treating LUTS with regard to sexual dysfunction and quality of life has been reported, suggesting a remarkable enhancement in sexual health and satisfaction in all the FSFI domains, particularly evident for the desire, arousal, satisfaction, and orgasm domains [62]. The FES represented an important part of PFR, even if a complete rehabilitation program, including biofeedback, pelvic floor muscular exercises, and vaginal cones, should be considered [63].

The FSFI, administered before and after transvaginal electrical stimulation, showed a significant improvement in desire, lubrication, sexual satisfaction, and pain, whereas arousal and orgasm domains were not significantly affected [64].

The normalization of muscle tonus provided by PFR could be one of the possible explanations of these outcomes. As a result, rehabilitation represents the basis for satisfying orgasmic sensation [65]. In fact, ischiocavernous attachment to the clitoral hood results in clitoral engorgement; the bulbocavernous muscle, when contracted, places pressure on the deep dorsal vein of the clitoris, preventing venous escape.

Additionally, specific rehabilitation programs can improve arousal, reducing the inhibition caused by leakage during orgasm [66].

Women with vulvar pain, dyspareunia, or vaginismus have limited ability to function sexually and often present with musculoskeletal and neurological findings appropriately addressed by a trained physiotherapist [67].

Some benefits of the rehabilitative approach, performed with a portable electromyographic biofeedback instrumentation for daily, at-home, biofeedback-assisted pelvic floor muscle rehabilitation exercises, were reported for the treatment of vulvar vestibulitis syndrome [68].

Confirming these results, in the study of McKay and colleagues [66], 29 patients with moderate to severe vulvar vestibulitis syndrome were analyzed. Each patient was given a computerized electromyographic assessment of pelvic floor muscles and provided with a portable electromyographic home trainer biofeedback device, and specific instructions were given to perform biofeedback-assisted pelvic floor muscle rehabilitation exercises. Fifteen of the 29 treated patients (51.7 %) demonstrated markedly decreased introital tenderness, and 14 of them (93.3 %) were able to resume sexual activity without discomfort. Nine patients (31.0 %) demonstrated a significant decrease in introital tenderness and pain, and six of the nine (66.7 %) resumed sexual activity. Thus, 20 of the 29 women (69 %) became sexually active. Following completion of treatment, 24 (88.9 %) reported negligible or mild pain.

17.4.4 Electroejaculation for Ejaculatory Dysfunction

Ejaculatory dysfunction is an uncommon cause of male infertility; however, in some groups, such as patients with spinal cord injury, anejaculation is very prevalent and is the major cause of infertility [69]. Other causes of anejaculatory infertility include retroperitoneal lymph node dissection, diabetic neuropathy, multiple sclerosis, transverse myelitis, and psychogenic anejaculation.

Regaining sexual function is the highest priority among paraplegics [70]. However, only 10 % of men with spinal cord injury (SCI) can father children without medical assistance, owing to potential impairments in erection, ejaculation, and semen quality [71].

Before the 1980s, the options for retrieving sperm from men with SCI were limited, owing to a lack of safe, consistent, and effective methodologies. Electroejaculation (EEJ) was first described in humans by Learmonth in 1931 [72]. Horne et al. [73] in 1948 reported the first use of EEJ in SCI persons, resulting in successful ejaculation in nine of 15 men. In the 1980s, the procedure of EEJ was commercialized for semen retrieval in humans [74]. Adapted from devices used in veterinary medicine, EEJ came into wide use for retrieval of sperm from anejaculatory men, the majority of whom were men with SCI [75–77].

Electroejaculation is carried out with an electrical probe, which is inserted rectally and is positioned with the electrodes in contact with the anterior rectal wall in the area of the prostate gland and the seminal vesicles. The electrical stimulation is administered in a wave-like pattern with voltage progressively increasing in 1–2 V increments until ejaculation occurs.

Antegrade ejaculation is not produced in a projectile fashion but rather as an intermittent release of semen during the course of the procedure. Between 15 and 35 stimulations are usually needed to ensure emptying of the semen. The voltage and current that have been reported to successfully produce ejaculation range from 5 to 25 V and 100–600 mA, respectively [78].

In the 1990s, the method of penile vibratory stimulation (PVS) became the method of first choice for semen retrieval in men with spinal cord injuries (SCIs). Because vibratory stimulation is very simple in use, less expensive, and noninvasive, it does not require anesthesia and is preferred by the patients when compared with EEJ; PVS is recommended to be the first choice of treatment in spinal cord injured men [79, 80].

The majority of spinal cord injured men are not able to produce antegrade ejaculation by masturbation or sexual stimulation. However, approximately 80 % of all spinal cord injured men with an intact ejaculatory reflex arc (above T10) can obtain antegrade ejaculation with PVS. Electroejaculation may be successful in obtaining ejaculate from men with all types of SCI, including men who do not have major components of the ejaculatory reflex arc. Furthermore, EEJ has been successfully used to induce ejaculation in men with multiple sclerosis and diabetic neuropathy. Any other conditions which affect the ejaculatory mechanism of the central and/or peripheral nervous system including surgical nerve injury may be treated successfully with EEJ. Finally, for sperm retrieval and sperm cryopreservation before intensive anticancer therapy in pubertal boys, PVS and EEJ have been successfully performed in patients who failed to obtain ejaculation by masturbation [78].

Confirming these indications, Kafetsoulis and colleagues [81] administered a survey to professionals for the evaluation of the current treatment methods for infertility in couples with SCI male partners.

Because EEJ was reserved as a second-line of treatment, it was performed only after PVS failures. Electroejaculation was performed 845 times on a total of 185

men with SCI whose level of injury ranged between C3 and L3 (4.6 procedures per patient). Of the 185 men, 175 (95 %) could ejaculate with EEJ. Of the 845 EEJ procedures, 95 % resulted in ejaculation. Of the 5 % of men who did not ejaculate with EEJ, all were patients with retained pelvic sensation who experienced pain at low voltages (1–4 V) on their first trial of EEJ and did not want to continue with further trials of EEJ under sedation or general anesthesia.

The most common reasons cited by respondents for not offering EEJ was a lack of EEJ equipment (60 % of respondents) and a lack of training in EEJ (42 % of respondents).

Sperm retrieved by EEJ is characterized by abnormal sperm motility (asthenospermia) and normal count. This was the case in patients with spinal cord injuries as well as those who suffered from psychogenic anejaculation. The asthenozoospermia may be related to increased scrotal temperature, urinary infection, stasis of seminal fluid, neural effects on physiology of the testis and epididymis, sperm autoimmunity, some factors in the seminal plasma, disordered storage of spermatozoa in the seminal vesicles, and external testicular pressure effects of the "closed-leg" position [82–84].

However, the concentration and the motility of sperm obtained by electroejaculation were not significantly different from sperm obtained naturally, suggesting a disease-related alteration rather than alterations caused by the procedure [85].

Several successful pregnancies have been reported using spermatozoa obtained by PVS or EEJ combined with assisted reproduction techniques such as intrauterine insemination or in vitro fertilization with or without intracytoplasmic sperm injection.

Ohl et al. [86] published a large study in which several aspects of EEJ in combination with assisted reproductive technology in the treatment of anejaculatory infertility were investigated. They studied 121 consecutive couples, in which 87 male partners had SCI. Intrauterine insemination was the route of sperm delivery in all insemination cycles. For those couples that did not conceive within 3–6 cycles of intrauterine insemination (IUI), gamete intrafallopian transfer (GIFT) or in vitro fertilization (IVF) procedures were recommended. Among couples with an SCI male partner, in 479 completed cycles of EEJ with IUI, 41 pregnancies were obtained. This represents an 8.6 % pregnancy rate (PR) per cycle and 32.2 % PR per couple.

Chung et al. [87] reported their experience in EEJ combined with IUI and IVF-ET. A group of 26 men participated, 23 SCI patients and 3 patients who had retroperitoneal lymph node dissection for testicular cancer. Female partners received 50 mg/day (days 3–7) clomiphene citrate during IUI cycles to improve PRs. Electroejaculation was performed on the day of insemination, and both antegrade and retrograde specimens were processed by swim-up technique. A total of 50 IUIs were performed in 10 couples, resulting in 5 pregnancies in 3 couples, with 2 couples conceiving twice. This constitutes a PR of 10 % per IUI and 30 % per couple.

In spite of the lower fertilization rate in psychogenic patients, combination of EEJ and ICSI gives adequate results to couples with psychogenic anejaculation similar to the results obtained for SCI patients [88].

The overall pregnancy rate per cycle from those studies averages about 25 %. It should be noted that this rate is similar to the pregnancy rate per cycle during natural procreation in healthy couples wanting to become pregnant (25–30 %) [89], although assisted ejaculation procedures and reproduction techniques are required for SCI men and their partners. If assisted ejaculation procedures fail or yield insufficient motile or viable spermatozoa for assisted reproductive techniques, surgical procedures of sperm retrieval are indicated.

17.4.5 Acupuncture for Sexual Dysfunction

Although new pharmaceutical agents have been identified for male erectile problems, sexual desire, and orgasm disorders, individuals with sexual dysfunction often seek alternative therapies, including traditional Chinese medicine.

Acupuncture is an ancient Chinese healing method. Despite its existence for many centuries, many Western physicians still tend to dismiss its efficacy by arguing that this is caused by a placebo effect. However, such an argument is no longer in line with current neuroscientific knowledge of the underlying mechanisms of actions of acupuncture.

It has been shown that manipulation of strictly defined energetic trigger points results in potent sensory stimulation that produces various changes in the central and peripheral nervous system.

Interestingly, various studies have shown that acupuncture facilitates the release of endogenous opioids in the central nervous system and that several classes of molecules, such as neurotransmitters, cytokines, and growth factors, are possible mediators for specific acupuncture effects [90]. Particularly interesting is the effect of acupuncture in the release of β-endorphin, an endogenous opioid that influences a variety of hypothalamic and autonomic functions and involved in the regulation of pain perception, stress response, mood, and immune functions [91].

Moreover, acupuncture has been reported to alleviate the sensory discriminative aspect and affective component of pain [92]. Physiologically, the afferent stimulation of acupuncture has been attributed to its effect on A-δ and C-fiber sensory nerve fibers and activation of descending pain-inhibiting pathways. As these nerve fibers are sensitive to the light touch of mechanoreceptors in the skin, further research of acupuncture may perhaps lead to better insight into the still unanswered question of why some men only ejaculate rapidly intravaginally, whereas their ejaculation time is seemingly undisturbed during masturbation. Interestingly, neuroimaging studies in humans have validated that acupuncture modulates a widely distributed network of brain regions involved in pain perception and have shown that the amygdala, insula, and hypothalamus modulation may demonstrate some acupuncture specificity [93].

Acupuncture therapy has been used by many researchers both in male and female sexual dysfunction; however, the results are conflicting. Emerging research is establishing that acupuncture may be an effective treatment modality for sexual dysfunction including impotence, loss of libido, and inability to orgasm. Moreover,

acupuncture reduces inflammation, increases sperm motility, improves semen parameters, modulates the immune system, and improves sexual and ejaculatory dysfunction in male infertility [94].

Khamba et al. [95] shown a significant improvement in all areas of sexual functioning as well as in both anxiety and depressive symptoms among male affected by SD secondary to antidepressants (including selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs)). Female patients reported a significant improvement in libido and lubrication.

Aydin et al. [96] examined the effects of acupuncture and hypnotic suggestions, compared with placebo, in the treatment of male sexual dysfunction. Men who received placebo had a 43–47 % improvement in sexual function. The success rates of acupuncture and hypnotic suggestions were 60 and 75 %, respectively.

Although the improvement was not statistically significant compared to the placebo, the authors suggested that treatment with acupuncture could be used as an adjuvant therapy in nonorganic male sexual dysfunction.

Kho et al. [97] investigated the use of acupuncture in erectile dysfunction (ED) and found that acupuncture did not influence the profile of the stress and sex hormones but did improve the quality of erection and restored the sexual activity in some patients, with an overall effect of 39 %. An improvement of the quality of erection was experienced by 15 % of patients, while 31 % reported an increase in their sexual activity.

In contrast, Yaman et al. [98] reported a success rate of acupuncture of 69 % in 29 patients, all patients being diagnosed with psychogenic erectile dysfunction.

However, in the review by Lee et al. [99] that analyzed the four studies of acupuncture therapy for ED, one randomized controlled trial showed beneficial effects of acupuncture compared with sham acupuncture in terms of response rate [100], while another found no effects of acupuncture and the remaining two studies were uncontrolled clinical trials. The authors concluded that the evidence was insufficient to suggest that acupuncture is an effective intervention for treating ED.

Few other papers which described the effect of acupuncture therapy on male sexual dysfunction were focused on premature ejaculation (PE).

Chen [101] compared therapeutic effects of acupuncture and medication (oral Sailete 20 mg/day) on primary, simple PE and found the total effective rates were 82.1 % in the acupuncture group and 63.6 % in the medication group.

Sunay [102] compared acupuncture with paroxetine (20 mg/day) and placebo. Median scores of paroxetine, acupuncture, and placebo groups were 17.0, 16.0, and 15.5 before treatment, and 10.5, 11.0, and 16.0 after treatment, respectively ($p=0.001$, $p=0.001$, and $p=0.314$). Increases of intravaginal ejaculation latency times with paroxetine, acupuncture, and placebo acupuncture were 82.7, 65.7, and 33.1 s, respectively. Extent of ejaculation delay induced by paroxetine was significantly higher than that of acupuncture ($p=0.001$). The authors concluded that although less effective than daily paroxetine, acupuncture had a significant stronger ejaculation-delaying effect than placebo.

The authors hypothesized that the observed effectiveness of this revolutionary approach to PE could be due to a central effect of acupuncture on neurotransmitters such as serotonin or endorphins, which are frequently involved in sexual behavior.

However, other authors [103] suggested a possible role of a peripheral reflex. This reflex is mediated by a spinal control center, referred to as the spinal ejaculation generator (SEG). The SEG coordinates sympathetic, parasympathetic, and motor outflow to induce the two phases of ejaculation: emission and expulsion. In addition, the SEG integrates this outflow with inputs conveying biochemical or mechanical information from the accessory sex organs, producing sequential contractions of the epididymis, vas deferens, seminal vesicles, and prostate [104].

Some positive results of acupuncture were found also in the treatment of functional retrograde ejaculation [105, 106] and vestibulodynia.

Curran et al. [107] studied 8 women with vestibulodynia. A significant decrease in pain with manual genital stimulation and helplessness was found. A strong (though nonsignificant) effect for improved ability to have intercourse and sexual desire was also noted, as an improvement in perceived sexual health, reduced pain, and improved mental well-being in the majority of participants.

In the series of Powell and Wojnarowska [108], 12 patients who had not responded to conventional treatment were studied. Two patients felt so much improved that they declared themselves "cured"; three believed their symptoms had improved and wished to continue acupuncture; four felt slightly better and judged acupuncture more effective than any other treatment; and three noted no effect at all. A large part of its beneficial effect, as recognized by the authors, may come from the regular specialist contact.

According to these results, the guidelines for the management of vulvodynia of the British Society for the Study of Vulval Diseases recommended that acupuncture may be considered in the treatment of unprovoked vulvodynia (grade of recommendation C; level of evidence IIb) [109].

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Electrical Stimulation for Pelvic Pain

18

Francesco Cappellano

18.1 Introduction

The role of *electrical stimulation* for the treatment of pain has a long history.

Stimulation-produced analgesia has been used by the Chinese for many centuries, including the use of an electric current applied to acupuncture needles [1].

Electrical stimulation of *peripheral nerves* using implanted electrodes for the therapy of intractable pain has been used over the past 30 years [2]. Difficulties faced have included defining the appropriate indications, utilizing approved device technology, and standardizing surgical techniques.

Failure to effectively diagnose and treat patients with pelvic pain often leads to the development of a chronic pelvic pain syndrome (*CPPS*). These patients usually have undergone multiple surgical procedures; show signs of drug dependence, depression, inappropriate affect, and limitation of activity; and have been evaluated by a large number of physicians previously (Fig. 18.1). There are three main categories of chronic pain: neuropathic, nociceptive, and idiopathic pain [3, 4].

The conditions that are responsible for *neuropathic pain* are mechanical trauma, ischemia, and degeneration or inflammation of the peripheral or central pain pathway.

In most of cases neuropathic pain is the cause of a CPPS: it is caused as believed in the past by entrapment or more recently by neurogenic inflammation of the pudendal nerve and alteration of pain receptors and central pain pathways by surgery, radiotherapy, or inflammatory diseases [5].

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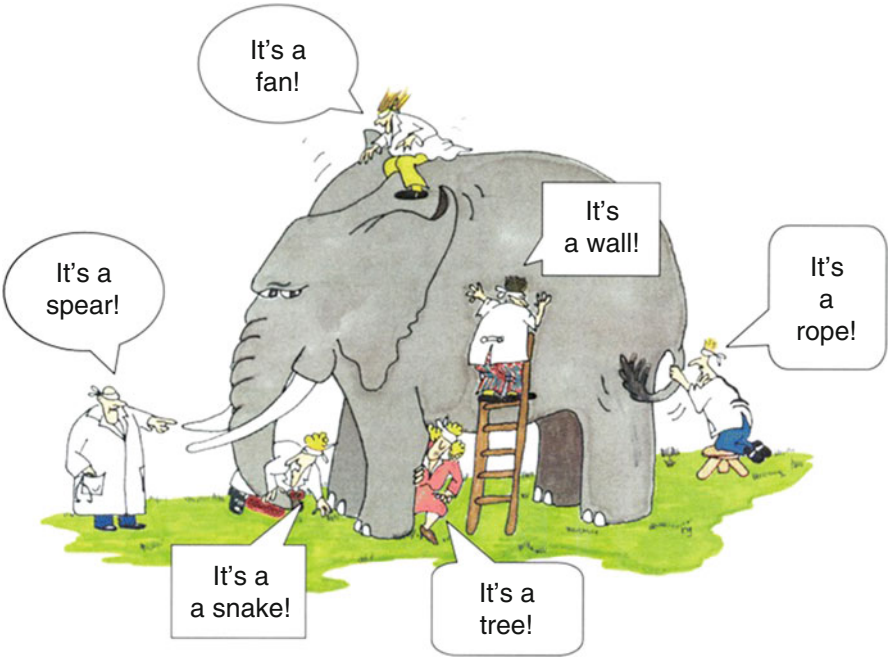

Fig. 18.1 *Blind Men and the Elephant* by John Godfrey Saxe (1816–1887). The story of the blind men and an elephant has been used to illustrate a range of truths and fallacies. At various times it has provided insight into the relativism or inexpressible nature of truth, the behavior of experts in fields where there is a deficit of information. (Reproduced with permission from Himmelfarb J, et al. (2002) The elephant in Uremia, Nature 62:5)

The diagnosis of CPPS is made by exclusion: after ruling out endometriosis, chronic pelvic inflammatory disorders, uterine or ovarian pathology in women, prostatitis in men, urological pathology, interstitial cystitis, or irritable bowel syndrome, remaining patients are diagnosed with a CPPS. Multiple factors are assumed to be involved in the pathogenesis of CPPS, such as chemical irritants, endocrine factors and pelvic floor muscle irregularities, as well as immunological and neurological aspects. The exact pathogenesis of CPPS remains unknown: however, in these patients, pelvic floor hyperactivity and pelvic congestion are common phenomena [6]. CPPS is often related to the dysfunction of the pelvic floor, with associated symptoms such as voiding dysfunction, urinary retention, constipation, and dyspareunia. The pain cycle theory explains why pelvic floor spasms and pelvic pain are linked physiopathologically [7, 8].

No diagnostic tests for peripheral neuropathy are available today for patients with CPPS: somatosensory-evoked potentials of the pudendal nerve and EMG (pudendo-anal reflex) have not been validated at today for this purpose.

Neuropathic pain and CPPS are currently treated with spinal cord and peripheral nerve stimulation by pain clinicians. Several neurophysiological mechanisms of

action have been proposed [9]: these include simple blocking of pain transmission by a direct effect in the spinothalamic tracts, activation of descending inhibitory pathways, effect on central sympathetic systems, segmental inhibition through coarse fiber activation and brain stem loops, inhibition by increasing GABA levels in the dorsal horn, and activation of a thalamocortical mechanism masking the nociceptive input.

18.2 Transcutaneous Electrical Nerve Stimulation (TENS)

TENS is a noninvasive therapy used to stimulate peripheral nerve fibers using surface electrodes on the skin. It is a non-pharmacological treatment option in the management of chronic pain. TENS was proposed in the treatment of pelvic pain with simple operation for the patient which is to put self-adhesive electrodes on the skin and then connecting the electrodes to an external stimulating device and to stimulate 20–30 min/day. The electric frequency rate varies from 1 to 100 Hz, depending on the more or less painful response with optimal values around 50 Hz. The position of the electrodes is the most significant variable depending on the painful zone: they can be located on the abdominal wall as well as at the suprapubic level or at a perineal level but also in the inguinal zone. The principle of action is based on the "gate control" theory with a stimulation and recruitment of large myelinated afferent nerve fibers having a fast conduction, inhibiting pain at the spinal level. Sikiru et al. [10] conducted a randomized study versus placebo to evaluate the role of TENS in *chronic pelvic pain* in men suffering from abacterial prostatitis. TENS stimulation was performed five times a week for 4 weeks for 20 min. The conclusion was that there was a significant improvement in pain in the TENS group ($p<0.005$). Fall and Linsdtrom [11] reported their experience on 60 patients testing the efficacy of TENS in the management of "interstitial cystitis." The stimulation was applied 30 min to two hours twice daily with a follow-up of 9 months to 17 years. They observed a better effectiveness of TENS on pain than in voiding frequency. Similarly, the effectiveness of TENS was 81 % for non-ulcerative interstitial cystitis (27 % remission) against 54 % in case of ulcerative lesion (with 15 % remission).

Schiotz et al. [12] treated 21 patients with "dysmenorrhea" with TENS. Patients were evaluated on the basis of VAS score and analgesic consumption. They observed a significant decrease in VAS score from 6.7 to 5.18 ($p=0.0009$) and consumption of analgesics ($p=0.03$) with no side effects. Kaplan et al. [13] also showed a decrease in dysmenorrhea pain in 61 patients, with a marked decrease in 30 % and moderate in 60 %. A review of the Cochrane Database [14] was performed in 2002 to assess the effectiveness of TENS and acupuncture in the treatment of dysmenorrhea. The finding was that the high-frequency TENS was effective but that the number of studies were small in size. However, the evidence to conclude about the effectiveness of low-frequency TENS or acupuncture was insufficient.

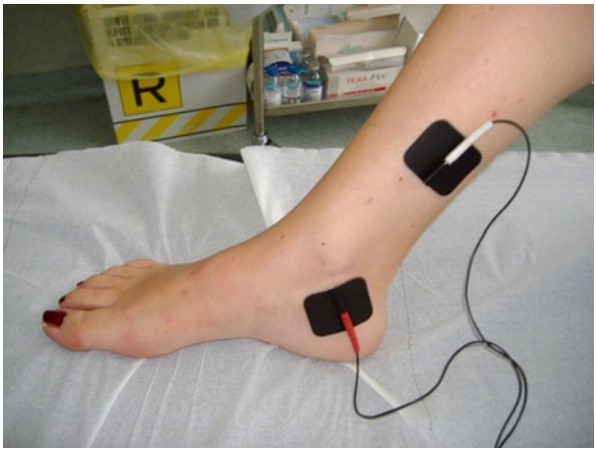

Fig. 18.2 Self-adhesive electrodes positioning for home chronic PTNS

18.3 Percutaneous Tibial Nerve Stimulation (PTNS)

Nerve stimulation may be performed percutaneously, directly stimulating the nerve fibers. It requires a medical procedure by puncturing with an acupuncture needle and the nerve is then stimulated with an external battery-operating device with fixed parameters (20 Hz, 210 μs, 0–10 V). This stimulation is usually performed on ambulatory basis and can be repeated at home for chronic stimulation with self-adhesive electrodes (Fig. 18.2). The most frequently used stimulation pattern for pelvic pain is the stimulation of the *posterior tibial nerve* (former popliteal sciatic internal nerve [SPI]) also called percutaneous tibial nerve stimulation (*PTNS*). The stimulation needle is positioned on the posterior tibial nerve behind the medial malleolus. McGuire et al. [15] were the first to describe this kind of stimulation of the nerve to treat detrusor overactivity. This technique has also been proposed for the treatment of fecal incontinence. In a newer way it is used for the treatment of pelvic pain. Van Balken et al. [16] published in 2003 the first series of the posterior tibial nerve stimulation in the management of pelvic pain. They published a prospective multicenter study in 33 patients with *chronic pelvic pain*. A subjective response was observed in 42 % of cases. Objectively, a reduction in VAS score more than 50 % was observed in 21 % and a decrease in VAS score more than 25 % in 18 % of cases. They concluded for a small effectiveness of this therapy, but it was considered for future controlled studies.

The same authors [17] have published another series trying to evaluate the prognostic factors for the clinical response with the percutaneous nerve stimulation. One hundred thirty-two patients were included in this study: 83 patients with overactive bladder, 16 for chronic non-obstructive retention, and 33 for *chronic pain*. The overall objective success rate was 32.6 and 51.5 % the subjective rate. The only prognostic objective and subjective factor was poor mental health (depression) assessed by the SF-36, in particular SF-36 Mental Component Summary (MCS).

In another article on a subpopulation of 121 patients in this series [18], they also highlighted a significant improvement in sexual function with PTNS.

Kim et al. [19] also made a prospective study on 15 patients treated with intermittent PTNS for chronic pelvic pain. The conclusions were that after 12 weeks pain improved less than 50 % (assessed by VAS score) in 60 % of cases and improved more than 25 in 30 % of cases with the PTNS.

Similarly Zhao et al. [20] treated 18 patients with painful bladder syndrome/interstitial cystitis with PTNS twice a week for 30 min per session with a total of ten sessions. They did not find significant difference in terms of pain. However, eight patients (44 %) reported improvement in the voided urine volume and found the treatment effective.

More recently Kabay et al. [21] published a controlled study in 89 patients with syndrome chronic pelvic pain/chronic prostatitis treated by PTNS. Patients were randomized to have a *nerve stimulation* ($n=45$) or a treatment with sham ($n=44$). An objective response was noted after 12 weeks of stimulation in the group having PTNS with an improvement in pain in 40 % of cases and improvement of symptoms in 66.6 % of cases. No change was observed in the sham group. To date, there is insufficient evidence to determine the role of PTNS in the treatment of chronic pelvic pain. Although initial results seem promising, the populations are small and follow-up durations are relatively short.

18.4 Neuromodulation of Sacral Roots (*SNM*)

The most accepted neuromodulatory technique is spinal cord stimulation, in which electrical signals are delivered to the spinal cord by electrodes in the epidural space.

Peripheral nerve stimulation is likely to recruit a larger number of nerve fibers for the purpose of activating inhibitory interneurons than spinal cord stimulation, which exerts its effect through layers of dura and cerebrospinal fluid [22]. It also recruits primary afferent delta fibers, which project to the spinothalamic tract and in all probability not to the dorsal column.

There are evidences that dysregulated central nervous system responses may have a major role in the etiology of CPP [23]. These dysregulated responses may maintain the perception of pain in the absence of acute injury. In addition, these changes may enhance perception in such a manner that nonpainful stimuli are perceived as painful and painful stimuli may be perceived as stronger than normal (allodynia and hyperalgesia) [23]. Therefore, it has been suggested that therapies aimed at modulating the nervous system such as centrally acting medications, *PTNS,* and *SNM* might be effective.

A possible working mechanism for neuromodulation in the treatment of chronic pain is based on the gate control theory. This theory states that pain perception depends on a pattern of peripheral nervous input. It is supposed that a mechanism at the spinal segment level is present which regulates the interaction between afferent nerve signals and pain sensation [24]. Interneurons of the spinal cord dorsal horn create gating components, and inhibition or facilitation of afferent fibers modulates

the input to the spinal transmission neurons. It is also believed that the impulses from the dorsal horn are controlled by a descending system containing fibers from the brainstem, thalamus, and limbic lobes [25]. *Neuromodulation* is believed to restore the control at the spinal segmental gate as well as at supraspinal sites such as the brainstem and the limbic system nuclei.

Several articles reported on SNM in the treatment of bladder pain syndrome/interstitial cystitis [26–33] with an overall 60 % success rate. Some publications reported about the efficacy of SNM in patients with nonspecific intractable pelvic and/or urogenital pain. Everaert et al. [34] performed a percutaneous nerve evaluation (PNE) in 26 patients after failure of conservative treatment for intractable chronic pelvic pain (including genital, urethral, inguinal, and perineal pain). Patients with interstitial cystitis were excluded from analysis. Significant pain relief was obtained in 16 patients (62 %). Pain relief was significantly better in patients with symptoms of voiding dysfunction than in those with dyspareunia. Relief was also better with decreasing age ($p<0.0001$) and better in men than in women ($p<0.05$). Of the 11 implanted patients, 8 (73 %) were satisfied with the treatment. Siegel et al. [35] measured the efficacy of SNM in patients with a history of pelvic and/or urogenital pain that persisted for at least 6 months and was refractory to any conventional treatment. Surgical implantation of a definitive neuromodulation device was performed in 10 patients. At a median follow-up of 19 months, 60 % of the patients reported significant improvement in pelvic pain symptoms. Eight patients (80 %) had a decrease in the number of hours of worst pain and nine had an increased number of hours of least pain at long-term follow-up. At baseline the average rate of pain was 9.7 vs. 4.4 at long-term follow-up.

Martellucci et al. [36] analyzed 27 patients affected by pelvic pain tested for sacral nerve modulation. Sixteen patients (59 %) were definitively implanted with a mean follow-up of 37 months. Mean preoperative VAS was 8.1 and decreased to 2.1 ± 1.2 at 6 months follow-up ($p<0.0001$), persisting at 1.9 ± 1.3 after 60 months, suggesting that SNM could be effective in the treatment of some patients affected by chronic pelvic pain and the effect persists over time. They also suggested that a positive screening phase and a positive response to gabapentin or pregabalin showed to be predictors of a successful response. Multiple localizations of pelvic pain and pain appeared after stapler surgery seem to be negative factors for the success of the treatment.

Govaert et al. [37] and Falletto et al. [38] reported some favorable results in 4 (9 tested) and 12 patients (27 tested) respectively, affected by anal pain. In the patients with a successful screening phase, visual analog pain score had significantly improved and SF-36 physical component scores increased.

In the reported series a large number of patients had previously undergone pelvic surgery and the association between pelvic surgery and pelvic pain is well known in the clinical practice.

However, Falletto et al. [38] reported previous pelvic surgery in 9/12 patients but in only five (41.5 %) the onset of pain occurred after surgery.

In the paper of Govaert et al. [37] seven previous pelvic surgical procedures were performed in nine patients, but no data were given about the number of intervention per patient or the relation between pain and surgery.

A positive effect of SNM was also reported for the treatment of pain after discectomy (unspecified level) and after L1 burst fracture [39], but unfortunately this data was not confirmed other series.

Martellucci et al. [40] evaluated the efficacy of SNM in the treatment of CPP appeared after pelvic surgery for benign diseases. In the study, 8/17 patients (47 %) were definitively implanted after the success of the screening phase. Mean follow-up was 39 months. Mean preoperative VAS was 8.2 (±0.9) and 1.9, 2.1, 2.0, and 1.8 after 6, 12, 24, and 36 months, respectively.

In the reported results, a positive result of the stimulation during the screening phase for more than 4 weeks seems to have a high predictive value. Also age less than 60 years and duration of symptoms less than 24 months proved to be good predictors for the success of SNM treatment.

SNM has proved to be ineffective in patients with CPP related to stapler surgery, while it has proved useful in the treatment of post-hysterectomy-related pain.

In a retrospective study by Peters et al. [41], 84 patients underwent *pudendal nerve stimulation* for IC/PBS and overactive bladder. An overall positive pudendal response (greater than 50 % improvement on the pudendal lead) was obtained in 71.4 %. Almost all subjects (93 %) with a history of failed sacral neuromodulation responded to the pudendal neuromodulation. The potential benefit of stimulating the pudendal nerve is an increased afferent stimulation through the S2–S4 nerve roots. Another technique that provides stimulation of the S2–S4 nerve roots is the caudal epidural approach. Using an introducer, a quadripolar lead is positioned in a retrograde fashion under fluoroscopy over the S2–S4 sacral nerve roots. Zabihi et al. [42] evaluated the efficacy of bilateral caudal epidural SNM for the treatment of refractory chronic pelvic pain and PBS/IC. Twenty-three patients (77 %) had a successful trial stimulation and underwent permanent implantation. Mean follow-up was 15 months, and in these patients, the pain score improved by 40 %. On average, patients reported a 42 % improvement in symptoms. Future studies should evaluate the clinical utility of different neuromodulatory treatments in well-defined patient populations.

18.5 Conclusion

Although CPP pain is in most of cases accompanied by voiding symptoms, SNM currently has no FDA approval for the treatment of chronic pelvic pain despite an overall success rate of about 60 %. Since many patients with CPP syndrome have an insufficient effect of conservative treatment, minimally invasive alternatives such as SNM and PTNS have been advocated to prevent major and unnecessary surgery. At this time, electrical stimulation should only be considered as a treatment for patients with refractory pelvic pain when all other treatment options have failed. Still the results are suboptimal and explant or revision of the devices are relatively common. The currently published results might suggest that SNM and PTNS could be used as an effective alternative treatment option in patients with refractory chronic pelvic pain. *Chronic pelvic pain* is a comprehensive generic term that includes a group of

patients with pain arising from different heterogeneous mechanisms. This makes comparisons difficult. Clear and well-defined inclusion criteria are required to evaluate which patients with chronic pelvic pain are most likely to benefit from peripheral nerves *electrical stimulation*, and which predictive factors can help physicians to select the most suitable candidates.

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Pelvic Floor Neuromodulation in Neurologic Patients

19

Giulio Del Popolo, Jacopo Martellucci, and Stefania Musco

19.1 Background

Patients with lesions above the pons usually continue to have reflex contractions of the detrusor, but the cerebral regulation of voiding and defecation is often lost. This is the case in lesions as from stroke, head injury, etc., which mostly continue to have a normal coordinated sphincteric function. However these patients may purposely increase sphincter activity during an overactive detrusor contraction to prevent urinary incontinence which would otherwise occur. This has been termed "pseudodyssynergia" because it is indistinguishable from true dyssynergia on a urodynamic record. Urinary incontinence in suprapontine lesions, such as stroke, Parkinson's disease, and multiple sclerosis, is due to bladder overactivity.

Most frequent suprasacral lesions are spinal cord injury and multiple sclerosis. A spinal cord injury (SCI) is damage or trauma to the spinal cord that results in a loss or impaired function causing reduced mobility or feeling. Common causes of damage are trauma (car accident, gunshot, falls, sports injuries, etc.) or disease (transverse myelitis, poliomyelitis, spina bifida, Friedreich's ataxia, etc.). In SCI, bowel and bladder dysfunction have significant lifelong consequences, and neurogenic voiding dysfunction is a major contributor to the morbidity and mortality.

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Spina bifida and myelomeningocele are equally debilitating conditions that have a similar spectrum of symptoms including voiding and bowel dysfunction.

Multiple sclerosis (MS) is a chronic autoimmune neurodegenerative disease with symptoms dependent on the clinical type and the site of lesions, in which demyelination results in the ensuing physical disability.

Bowel symptoms are reported to be common in MS, including constipation (29–43 %) and fecal incontinence (over 50 %), and 34 % of patients spending more than 30 min a day managing their bowel movement [1]. Urinary urgency was reported in 65 % of patients and detrusor hyperreflexia, detrusor sphincter dyssynergia, and detrusor hyporeflexia were found in 27, 25, and 6 %, respectively [2].

Parkinson's disease (PD) is considered as a disorder involving dopaminergic, noradrenergic, serotonergic, and cholinergic systems, characterized by motor and nonmotor symptoms, in which gastrointestinal dysfunction is the most common nonmotor symptom (which comprises swallowing disorders, dysphagia, pyrosis, constipation, incomplete rectal emptying, need for assisted defecation and oral laxatives) [3] and urinary symptoms are reported in 27–39 % of patients [4].

Historically, renal disease has been the major cause of death in the paraplegic due to poor bladder management [5].

More recently, as a better understanding of low-pressure storage and efficient emptying has been gained and new devices for the management of voiding and bowel dysfunction had been introduced, paraplegics in developed countries now primarily die from pneumonia, septicemia, heart disease, accidents, and suicide [6]. However, functional pelvic disorders still significantly affect the patients' quality of life.

Sacral nerve modulation (SNM) is a well-established treatment for non-neurological patients with refractory lower urinary tract and bowel dysfunction. Although SNM was originally not considered an option for neurogenic pelvic floor dysfunction, there is evidence that SNM is effective and safe for treating also neurological patients [7, 8]. Moreover, SNM has shown positive results also regarding sexual dysfunction with improvement in both male and female with neurogenic pelvic floor dysfunction [9, 10]. Besides SNM, other neurostimulation techniques have been reported, with possible indication in these patients. However, the lack of randomized controlled trials and the evidence about which neurological patients should be treated (spinal cord injury, spina bifida, multiple sclerosis, etc.) still leaves many questions unanswered.

19.2 Neurogenic Lower Urinary Tract Dysfunction

Neurogenic bladder (NGB) has been found in 40–90 % of patients with MS, 37–72 % of patients with PD, and 15 % of patients with stroke. It is estimated that 70–84 % of patients with spinal cord injuries have at least some degree of bladder dysfunction [11].

Neurogenic voiding patterns range from bladder atony to neurogenic detrusor overactivity (NDO). Uncoordinated voiding or high storage pressures can cause upper tract deterioration, while high residual urine volumes can lead to recurrent

urinary infections. The use of anticholinergics, clean intermittent catheterization (CIC), and intradetrusor botulinum neurotoxin A (BoNT-A) injection has led to significant improvements in the urologic health of these patients with proven efficacy and low complication rates [12, 13]. Despite these gains, persistent issues with regard to urinary tract infections, urethral strictures, upper tract deterioration, cost, and compliance continue to plague this patient population.

The control of the lower urinary tract is a complex, multilevel process that involves both the peripheral and central nervous systems, and neurogenic LUTD is a challenge, because all available treatment modalities may fail. Although a large number of neurologic diseases and injuries may affect lower urinary tract function, the consequences are widely consistent (i.e., chronic urinary retention, urgency–frequency syndrome, urgency incontinence, or a combination).

19.2.1 Sacral Nerve Modulation

Originally, SNM was not considered an option for neurogenic LUTD; however, some studies have suggested that SNM is also effective in these patients [14, 15]. Taking into account that SNM is minimally invasive and completely reversible, it is of great interest whether this treatment option is valuable for patients with neurogenic LUTD before resorting to more invasive procedures.

Chartier-Kastler et al. [14] studied nine women treated for refractory neurogenic urge incontinence with SNM. Neurological spinal diseases included viral and vascular myelitis in one patient each, multiple sclerosis in five, and traumatic spinal cord injury in two. All patients had clinically significant improvement of incontinence, and five were completely dry. Average number of voids per day decreased from 16.1 to 8.2. Urodynamic parameters at 6 months after implant improved significantly from baseline, including maximum bladder capacity from 244 to 377 ml and volume at first uninhibited contraction from 214 to 340 ml. Maximum detrusor pressure at first uninhibited contraction increased in three, stabilized in two, and decreased in four patients. Urodynamic results returned to baseline when stimulation was inactivated. All patients subjectively reported improved visual analog scale results by at least 75 % at last follow-up.

In the study of Lombardi and Del Popolo [16], 24 SCI patients, tested using mini-invasive approach with percutaneous technique and tined lead, were enrolled and divided into two groups: 13 individuals in the urinary retention category and 11 suffering from overactive bladder syndrome. All the subjects underwent definitive SNM implantation and maintained a clinical improvement of more than 50 % compared with baseline. Four subjects with urinary retention needed a new implant in the contralateral S3 sacral root because of loss of efficacy. The authors concluded that SNM is a therapy to consider in the treatment of NLUTS for partial SCI patients, even if the loss of clinical benefits for patients with retentive NLUTS must be taken into account.

Also in the experience of Hohenfellner and colleagues [17], SNM has been reported to be effective in the treatment of neurogenic bladder dysfunction.

Their patient population consisted of 27 patients with bladder storage failure due to detrusor hyperreflexia and/or bladder hypersensitivity (15), failure to empty due to detrusor areflexia (11), and combined bladder hypersensitivity and detrusor areflexia (1). Twelve patients underwent chronic sacral neuromodulation with unilateral electrode implantation into one of the dorsal S3 foramina. However, they reported a high loss of efficacy rate after 54 months of follow-up, suggesting that the treatment could be temporary.

These results were confirmed by Chaabane et al. [18] in 62 patients (detrusor overactivity in 34 cases and chronic urinary retention in 28 cases). Out of the 62 patients, 41 patients (66.1 %) had more than 50 % improvement on urodynamic evaluation and bladder diary and 37 were implanted. With a mean follow-up of 4.3 years, results remained similar to the evaluation phase in 28 cases (75.7 %), were partially altered in three cases (8.1 %), and lost in six cases (16.2 %), suggesting that results depend on the type of the underlying neurologic disease and in particular whether it may progress or not.

In patients suffering from chronic neurogenic nonobstructive urinary retention (N-NOR), SNM is highly efficacious in the medium follow-up. Thirty-six/85 patients (42 %) responded to percutaneous first stage of SNM. Eleven out of 34 patients at follow-ups were "inconstant responders" because they returned to similar baseline voiding symptoms, but responded again with an implant on the contralateral S3 sacral root. Two failed twice and responded once again after an S4 sacral root implant [19].

The inherent course of the neurologic disease or injury (i.e., stable or progressive disorder) certainly greatly influences the LUTD and consequently the effect of SNM.

Moreover, SNM may be initially successful in a patient with MS but may stop working after MS relapses. In addition, early SNM in patients with complete spinal cord injury during spinal shock (i.e., the bladder areflexia phase) could prevent detrusor overactivity and urinary incontinence [20], whereas SNM has been attempted without success in complete chronic spinal cord injury patients [21], emphasizing the significance of the time point of SNM. In the case that the benefits of early SNM in patients with complete spinal cord injury may be reproduced in randomized trials and if these findings can be conveyed to patients with other neurologic diseases or injuries, this will completely revolutionize the management of neurogenic LUTD.

However, a pooled success rate of 68 % for the test phase and of 92 % for permanent SNM indicates that SNM may be effective and safe for the treatment of patients with neurogenic LUTD [5].

Discussing the efficacy and safety of SNM for neurogenic LUTD, it is important to be aware of the fact that these patients usually have undergone multiple failed previous treatments. Thus, a pooled success rate of 68 % for the test phase is more than just some benefit. After failed conservative treatment, SNM testing seems worthwhile in patients with neurogenic LUTD before more invasive treatments are considered. In addition, patients with neurologic disease or injury often suffer not only from LUTD but also from bowel dysfunction; because SNM may be beneficial

for both conditions, patients with combined dysfunctions appear to be good candidates for SNM, with a high impact on the associated QoL.

Moreover, the overall results in patients with neurogenic LUTD are in line with the findings in patients with non-neurogenic LUTD and success rates are probably not lower than for established indications of SNM in non-neurogenic voiding dysfunction. This is also consistent with the fact that in some patients, non-neurogenic LUTD may actually be neurogenic but not yet be discovered.

Sacral neuromodulation (SNM) represents a promising option for managing treatment-refractory neurogenic bladder dysfunction. It remains to be seen, however, which types of neurogenic bladder dysfunction and which underlying neurological disorders best respond to SNM. However, it should be noted that high frequency diathermy and unipolar electrocauterization are contraindicated in patients with neuromodulators, that during extracorporeal shock wave lithotripsy the focal point should not be in the direct vicinity of the neuromodulator or the electrode, that ultrasound and radiotherapy in the region of the implanted components should be avoided, that the neuromodulation should be discontinued in pregnancy, and that MRI examinations should only be conducted when urgently indicated and the neuromodulator is turned off.

19.2.2 Pudendal and Dorsal Genital Nerves Modulation

The pudendal nerve is a major contributor to bladder afferent regulation and bladder function. Because the pudendal nerve carries such a large percentage of afferent fibers, neuromodulation of the pudendal nerve is an attractive option for refractory detrusor hyperreflexia.

Dorsal genital nerve (DGN) stimulation has shown to be able to suppress undesired detrusor bladder contractions in patients with both neurogenic detrusor overactivity (NDO) and detrusor sphincter dyssynergia (DSD) [22] and repeated conditional short duration electrical stimulation significantly increased cystometric capacity in patients with spinal cord injury [23]. The increase was mainly caused by an inhibition of detrusor contractions.

Opisso et al. [24] investigated whether patients with neurogenic detrusor overactivity can sense the onset of bladder contraction and in turn suppress the contraction by electrical stimulation of the dorsal penile–clitoral nerve. A total of 17 patients with neurogenic detrusor overactivity underwent three cystometric filling trials. The first cystometry was used to determine bladder capacity. The second cystometry was done with automatic electrical stimulation of the pudendal nerve when the bladder reached a threshold pressure of 10 cm H_2O above the mean detrusor pressure. The third filling cystometry was done with patients controlling the pudendal stimulation and asked to begin stimulation when they could sense the onset of an uninhibited bladder contraction. Compared to peak pressure for cystometry, 1 average peak pressure during suppressed contractions for cystometries 2 and 3 was 49 and 26 % lower, respectively. The average delay of the onset of stimulation during cystometry 3 with respect to cystometry 2 was 5.7 s. They concluded that patient-controlled

genital nerve stimulation is as effective as automatic controlled stimulation to treat neurogenic detrusor overactivity, increase bladder capacity, and prevent uninhibited detrusor contractions, although patients must be trained in the technique.

Spinelli and colleagues [25] described their experience with pudendal nerve stimulation using a device with a quadripolar tined lead placed at Alcock canal in 15 patients with neurogenic bladder. In this study, the average number of incontinent episodes among this group of patients decreased from seven to three episodes per day. Eight patients became continent during the screening phase of the study, and four patients had a greater than 50 % improvement in the number of incontinent episodes experienced per day. Urodynamic evaluation in seven patients revealed a significant increase in detrusor capacity and a decrease in maximum detrusor pressure. The authors suggest that based on these preliminary data, pudendal nerve stimulation is an effective therapeutic alternative for neurogenic overactive bladder particularly in nonresponder patients to antimuscarinic drugs and in whom traditional sacral neuromodulation failed, before to consider more invasive procedures such as bladder augmentation.

19.2.3 Tibial Nerve Stimulation

Posterior tibial nerve stimulation (PTNS) was found to be effective in 37–100 % of patients with overactive bladder (OAB), in 41–100 % of patients with nonobstructive urinary retention, and in up to 100 % of patients with chronic pelvic pain/painful bladder syndrome (CPP/PBS), children with OAB/dysfunctional voiding, and patients with neurogenic pathologies [26]. Moreover, there is evidence that the improvement in OAB symptoms using PTNS is comparable to the effect of antimuscarinics but with a better side effect profile [27]. Acute urodynamic effects of PTNS were observed in a mixed population of OAB patients, most of whom neurologically impaired (multiple sclerosis, spinal cord injury, Parkinson's disease).

During stimulation, an increase of first involuntary detrusor contraction volume and of cystometric capacity was found [28]. In this study, a total of 44 consecutive patients with urge incontinence, frequency, and urgency secondary to overactive bladder were studied. Of the patients, 37 had detrusor hyperreflexia due to multiple sclerosis (13), spinal cord injury (15), or Parkinson's disease (9), and 7 had idiopathic detrusor instability. Routine cystometry at 50 ml/min was done to select the patients with involuntary detrusor contractions appearing before 400 ml maximum filling volume. Repeat cystometry was performed immediately after the first study during left posterior tibial nerve stimulation using a surface self-adhesive electrode on the ankle skin behind the internal malleolus with shocks in continuous mode at 10 Hz. frequency and 200 ms wide. Volume comparison was done at the first involuntary detrusor contraction and at maximum cystometric capacity. The test was considered positive if the volume at the first involuntary detrusor contraction and/or at maximum cystometric capacity increased 100 ml or 50 % during stimulation compared with standard cystometry volumes.

Mean first involuntary detrusor contraction volume on standard cystometry was 162.9 ± 96.4 ml, and it was 232.1 ± 115.3 ml during posterior tibial nerve stimulation.

Mean maximum cystometric capacity on standard cystometry was 221 ± 129.5 ml, and it was 277.4 ± 117.9 ml during stimulation. Posterior tibial nerve stimulation was associated with significant improvement in first involuntary detrusor contraction volume ($p < 0.0001$) and significant improvement in maximum cystometric capacity ($p < 0.0001$). The test was considered positive in 22 of the 44 patients.

Although some studies suggested that PTNS could be effective in the management of severe OAB in multiple sclerosis (MS), without compromising bladder emptying or inducing side effect and even in the absence of an acute cystometric effect [29–32], these results were not confirmed by other authors [33] that failed to obtain acute urodynamic reductions of detrusor overactivity.

Other studies suggested that PTNS could also be effective to suppress detrusor overactivity in patients with Parkinson's disease [34].

However, low evidence studies (only prospective nonrandomized trials are available), short study periods, heterogeneous indications, and treatment modality make it difficult to draw any definitive conclusions, and in order to recommend PTNS as a practical treatment option, randomized controlled trials, long-term data, and health economic analysis are needed.

19.2.4 Sacral Rhizotomies and Electrical Bladder Stimulation

In 1969, Brindley developed a device to stimulate sacral roots at the level of the cauda equina. The first Brindley stimulator was implanted in a patient in 1978. Although the first implants did not involve posterior sacral rhizotomy, lesions to these nerves during surgery led to the advantage of leaving the patient's bladder completely areflexic and restoring normal bladder compliance and curing reflex incontinence. Subsequently, placement of the Brindley stimulator was combined with sacral posterior rhizotomy [35]. The denervation step is skipped in cases of genital sensation and reflex erections.

The objective of the Brindley technique is to improve both voiding and effective continence. Any patient with a stable supra-sacral spinal cord lesion (paraplegia, tetraplegia) with a reflex bladder (incontinence, vesico-sphincter dyssynergia resistant to medical treatment with the risk of upper urinary tract involvement) can benefit from the Brindley technique. The electrodes are placed on the anterior sacral roots in order to obtain the desired micturition. Posterior sacral rhizotomies are indispensable to the technique as they suppress detrusor and sphincter hyperreflexia and improve continence, thereby protecting the upper urinary tract.

Ninety percent of patients gain satisfactory continence and no longer require an incontinence appliance, with a significant improvement of the quality of life. Bladder capacity and compliance increase dramatically. As a consequence, urinary infection rate decreases. The majority of patients remain dry, and more than 80 % have a complete voiding or a post-void residue of less than 50 ml and do not require any catheterization [36]. Over a retrospective review of 500 patients with a Brindley stimulator, 411 were still in use with the patients pleased [37].

Ergon and colleagues [35] reviewed their experience with 93 SCI patients with sacral anterior root stimulators combined with posterior sacral rhizotomy.

They reported that 83 patients used their stimulators for micturition, and 82 were fully continent.

Van Kerrebroeck et al. [38] reported that complete continence during daytime was achieved in 73 % of patients and in 86 % at night in 52 patients in which complete posterior sacral root rhizotomies were performed and a Finetech–Brindley sacral anterior root stimulator implanted. Significant increase in bladder capacity and bladder compliance was achieved in all patients. Residual urine was reduced significantly, resulting in a decrease of the incidence of urinary tract infections.

However, the major limitation to this form of neuromodulation is that it requires an intact neural pathway between the sacral cord nuclei of the pelvic nerve and the bladder. Furthermore, the irreversibility of the sacral deafferentation may limit future treatment options.

19.2.5 Intravesical Electrical Stimulation

Since 1975 intravesical electrical stimulation (IVES) has been used as a rehabilitative technique for children with myelodysplasia [39, 40]. Worldwide, several other investigators have used IVES to treat neurogenic bladder dysfunction secondary to a variety of factors, including SCI, myelodysplasia, and other neurologic diseases [41]. Impressive results from IVES have been reported, including the restoration of bladder sensation with filling and stimulation of the detrusor contraction, conscious urinary control, and a significant increase in bladder capacity. These benefits have been achieved without harmful effects on the upper urinary tract.

In experimental studies it was shown that IVES involves the direct activation of the Aδ afferents from the low threshold bladder mechanoreceptors, the sensory system responsible for initiating and maintaining the micturition reflex [42].

Moreover, IVES might affect voiding contractions in addition to inhibiting C-fiber activity and it seems to have a more complex effect on the bladder control pathway. For synaptic neurotransmission in the spinal cord, IVES could possibly shift the balance between excitation and inhibition towards inhibition [43].

In a 15-year study, Lombardi et al. [44] evaluated the clinical and urodynamic impact of intravesical electrostimulation (IVES) on incomplete spinal cord injury (SCI) patients suffering from chronic neurogenic nonobstructive urinary retention (N-NOR). Thirty-eight subjects (37.2 %) responded to IVES, and of those, 83.3 % recovered the first sensation of bladder filling after the IVES round. Nineteen responders repeated IVES within 1 year, owing to loss of efficacy. They obtained similar voiding symptoms improvement and urodynamic results as after the first IVES cycle. A period of <2 years from SCI to IVES and the presence of first sensation of bladder filling at baseline represented significant predictive parameters for IVES success.

However, although a strict correlation in terms of clinical and urodynamic patterns was demonstrated in patients with incomplete SCL and N-NOR, following IVES compared to SNM, voiding improvement through IVES was short term when

compared with the effects of permanent SNM. In fact, following the two procedures, the first sensation of bladder filling was either maintained or recovered by all responders, but the IVES responders lost their clinical benefits in a mean follow-up of 9.6 months [45].

Improvement in constipation scores was also noted in an elderly patient affected by incomplete cauda equina syndrome that underwent IVES to improve impaired bladder emptying. One month after IVES treatment, which consisted of 20 daily sessions, cystometrography evidenced a normalization of urinary pattern and a concomitant improvement of constipation (Wexner score from 22 to 4) was reported [46].

19.3 Neurogenic Bowel Dysfunction

Exciting new features have been described concerning neurogenic bowel dysfunctions (NBD), including interactions between the central nervous system (CNS), enteric nervous system (ENS), neurotransmission of noxious and non-noxious stimuli, and involving the fields of gastroenterology and neurology.

Bowel dysfunctions (e.g., fecal incontinence, infrequent or difficult defecation) are both frequent and severely troubling problems for patients with spinal cord injury, multiple sclerosis, myelomeningocele, and Parkinson's disease. Fecal incontinence in SCI, MMC, and MS is mainly due to abnormal rectosigmoid compliance and rectoanal reflexes, loss of rectoanal sensibility, and loss of voluntary control of the external anal sphincter. Constipation in SCI, MMC, and MS is probably due to immobilization, abnormal colonic contractility, tone and rectoanal reflexes, or side effects from medication. In PD, dystonia of the external anal sphincter causes difficult rectal evacuation, and the loss of dopaminergic neurons in the enteric nervous system probably causes slow-transit constipation. Interestingly, in recent years, it has become evident that PD affects several neuronal structures outside the substantia nigra, between which are the ENS. Recent reports have shown that the lesions in the ENS occur at a very early stage of the disease, even before the involvement of the CNS, suggesting a possible critical role in the pathophysiology of PD, as it could represent a point of entry for a putative environmental factor to initiate the pathological process [47]. The etiology of symptoms after stroke still needs to be clarified; however, cerebral insults may impair supraspinal control of defecation resulting in both constipation and FI.

The etiology of these symptoms is complex; there may be autonomic and pelvic nerve dysfunction (with attenuation of voluntary motor function and impaired anorectal sensation and anorectal reflexes), or generalized systemic factors (e.g., altered diet and behavior, impaired mobility, psychological disturbances, or drug adverse effects). The mainstay of current treatment is adapting a conservative approach towards reversing the systemic effects and optimizing the mechanics of defecation through the use of laxatives and irrigation approaches. When successful, this approach improves both evacuation and incontinence symptoms, with associated improvements in the quality

of life and independence. Stoma formation remains an option for patients refractory to other approaches. Therapies directed at modulating pelvic innervation through electrical stimulation constitute the main hope for the future [48, 49].

19.3.1 Sacral Nerve Modulation

Schurch et al. measured an early segmental and a late polysegmental reflex mediated by afferent pathways during PNE test in patients with complete SCI, but none of the patients experienced any effect on symptoms [21]. Despite successful foramina lead placement, none of our complete SCI patients showed any improvement of neurogenic incontinence after 5 days of treatment by sacral nerve stimulation. The findings confirm that the anal contractions observed during peripheral nerve evaluation are reflex responses mediated by afferent pathways. Both the early and late reflex responses are of spinal origin, since they were obtained in complete SCI patients in whom all spino-bulbo spinal loops are supposed to be interrupted. The finding that neuromodulation is working in non-neurogenic patients but is less successful in complete SCI patients could give evidence that preserved spino-bulbo spinal loops contribute to the positive effects of neuromodulation.

In contrast, several studies have shown a positive clinical outcome of SNS in patients with incomplete SCI.

In line with studies of SNS in non-neurologic patients, SNM may also reduce symptoms of neurogenic constipation. Generally, the number of involuntary bowel movements decreases during stimulation, and the effect remains at medium-term follow-up.

Lombardi et al. [50] reported that 23/37 incomplete spinal cord injured patients (59 %) were submitted to definitive SNM maintaining their clinical benefits after permanent implantation with a median follow-up of 38 months. The length of time since neurological diagnosis to SNM therapy represents the only factor related to the success of the implantation. In subjects with constipation (12), the median number of evacuations shifted from 1.65 to 4.98 per week, whereas the Wexner score changed from 19.91 to 6.82. In subjects with fecal incontinence (11), the median number of episodes per week was 1.32 compared with 4.55 pre-SNM. The general and mental health of both groups were measured with the SF-36 questionnaire and consistently showed statistical improvement ($p<0.05$). Anorectal manometry showed no important variation compared with baseline. In this regard, the effects of SNM on anorectal physiology in patients with NBD are conflicting and most studies found no effect.

In the study of Gstaltner et al. [51], a total of 11 patients suffering from flaccid paresis of the anal sphincter muscle and fecal incontinence caused by cauda equina syndrome underwent PNE, which was successful in 8 patients. Two of these patients were eliminated from the procedure at the end of the temporary SNS period; one patient refused the permanent implantation. Therefore, five patients proceeded to permanent implantation, which led to an improved continence in all the cases

The benefits of SNM in patients with spinal cord surgery, spinal cord trauma, poliomyelitis, spastic paresis, spinal stroke, Friedreich's ataxia, syringomyelia, and in other patient group with NBD were reported [52–55].

Since SNM has an effect in patients with incomplete but not in those complete SCI, future studies are needed to clarify which spinal pathways are necessary for the clinically important effects of SNM.

19.3.2 Tibial Nerve Stimulation

Posterior tibial nerve stimulation (PTNS) was first introduced for bladder dysfunction. However, many patients suffer from both urinary incontinence and FI (double incontinence), and some also experienced improvement of FI. Stimulation has been done, using either self-adhesive surface electrodes or by needle electrodes placed distal on the leg near the medial malleolus and a ground surface electrode placed on the ipsilateral leg. As for bladder dysfunction, in studies with PTNS, pulse width is 0.2 ms, and the frequency used is 10 or 20 Hz. The amplitude setting differs from below the motor threshold to maximal tolerable current, but generally stimulation amplitude is below 10 mA. Various treatment protocols have been applied ranging from 4 to 12 weeks of treatment with scheduled stimulation sessions from daily to every third to fourth day.

Several studies suggests a positive effect of PTNS in various non-neurogenic patients, and PTNS and transcutaneous tibial nerve stimulation (TTNS) resulted in significant improvements in some outcome measures [56]; however, TTNS was not superior to sham stimulation in a large, adequately powered, randomized controlled trial [57].

Mentes et al. [58] examined two SCI patients with an incomplete lesion and reported improvement of the Wexner incontinence score and suggesting a possible role of PTNS in treating fecal incontinence caused by partial spinal cord injury.

19.3.3 Sacral Rhizotomies and Electrical Bowel Stimulation

The clinical indication for sacral anterior roots stimulator (SARS) is exclusively related to bladder function where the effect is well documented. However, beneficial effects on defecation and constipation are described. Many patients use SARS for stimulated defecation either alone or in combination with laxatives. Thus, SARS may alleviate constipation, as most patients treated defecate daily or every other day and various studies demonstrated significantly reduced time used for defecation after SARS [35, 59–62].

In the study of Valles and colleagues [61], there was a clinical improvement in constipation and most patients reported being more satisfied with bowel function after implantation of the sacral anterior root stimulator. However, fecal incontinence did not change after the procedure, and no correlation was found between objective and subjective responses to the sacral anterior root stimulator and manometric or colonic transit times before implantation.

Furlan et al. compared SARS to Malone antegrade continence enema (MACE) and stoma. The MACE procedure gave the best long-term outcome with respect to bowel function, quality of life, and complication rate [63].

19.4 Conclusion

Pelvic floor electrical stimulation represents ways to reestablish neurogenic control and thereby alleviate NLUTS and NBD symptoms. While several studies have demonstrated proof-of-concept of these treatments, larger randomized studies are lacking, and long-term effects should be evaluated. Such studies are mandatory to define the indications for each of the techniques and to clarify the right place for each modality in a treatment algorithm.

In fact, for example, in the European Association of Urology (EAU) guidelines, sacral neuromodulation still has a low level of recommendation in neurogenic patients affected by NLUTS [64] and in the International Consultation on Incontinence (ICI) guidelines there is no recommendation for SNM in NLUTS, but it is recommended in neurogenic fecal incontinence.

However, advances in neuromodulation techniques may allow the clinician to abandon irreversible demolitive surgical procedures favoring minimally invasive and well-tolerated functional approaches.

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New Frontiers: Electrical Stimulation in Urinary Disorders

20

Michele Spinelli

The discovery of electricity brought enormous changes to the human civilization, but true medical advantages were only gained in the eighteenth century when the first relationship was made between electricity and nerves. Since then, knowledge on muscle stimulation, discoveries on the connection between electricity and magnetism, and creation of first electric generator and later electric oscillators, stimulators, and amplifiers for neuropsychological studies in the early twentieth century led the way to modern electrical stimulation and its use in the urological field.

The first report on bladder treatment with the use of electrical stimulation is dated from the year 1878. Interestingly, it was urinary retention that the Danish surgeon Saxtorph MH treated by using a metal electrode and placing it transurethrally into the bladder. Ancient reports on urinary incontinence hardly exist in contrast to frequent diseases like bladder stones, urinary retention, and fistulas. Reports on surgical treatments of urinary incontinence can be found in the nineteenth century, while other modern techniques were introduced much later, in the second half of the twentieth century.

Real interest in the use of electrical stimulation for control of bladder function started in the 1950s and 1960s with the stimulation of the pelvic floor, the detrusor, the spinal cord, or the pelvic and sacral nerves.

In 1963, two articles of importance were published that cannot pass unmentioned. Caldwell and his équipe used the electrical stimulation to control sphincter incompetence by using the first pelvic floor stimulator. The device was designed for the treatment of fecal incontinence, but he also succeeded in treating urinary incontinence.

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The milestone in sacral nerve stimulation in humans has been marked with the implantable Brindley system, through which bladder voiding was restored in complete spinal injury with a direct intradural or extradural stimulation of S2, S3, and S4 bilateral.

According to Brindley's lessons, physicians involved in this field have learned what it is possible to obtain with a direct stimulation of the sacral area, in terms of efferent responses.

Today, this approach is less used as deemed too invasive, also because of the necessity to perform a posterior rhizotomy.

The revolution of the concept of modulation has been at the basis of all knowledge in urological field in the last 20 years.

When speaking about neuromodulation and indications for this treatment, we always use an old concept: SNM is not a treatment for incontinence, voiding difficulties, or urgency frequency but is the method to restore a normal control of the lower urinary tract—SNM is the treatment of sensory and motor diseases because of its possibility to reorganize peripheral and central control of the sacral area function.

Nowadays, according to guidelines, SNM is approved in so-called "idiopathic" situations that are sometimes called "nonneurogenic." This term is inappropriate: we are in a paradox where we use an electrical treatment applied on the nervous system and we obtain the resolution of different symptoms. This means that even if we are confronted to a neurological condition such as spinal injury, we are certainly confronted to a neurological disorder.

The real history of sacral root simulation starts at the University of California, in San Francisco, where Prof. Tanagho and his group developed various experimental models to evaluate the feasibility of stimulation of various sacral root components. They developed many experimental models and have done research on both normal and paraplegic animals and elucidated the anatomy of the whole sacral plexus before moving to clinical practice. Based on their findings that bladder contractions could be achieved separately from sphincteric activity, it was possible to work on and develop a true bladder pacemaker. Thanks to their work it was possible to treat neurogenic bladder dysfunctions and make a true new step forward in functional urology.

SNM is actually one of the most important tools in the hands of urologists involved in functional problems, but, keeping in mind published data, we have also had an interesting evolution on the method of lead implantation. Nothing has much changed so far to resolve problems of suboptimal results and to treat bladder symptoms more effectively in spinal injured population or in neurogenic bladder syndromes due to multiple sclerosis or other neurogenic diseases. The introduction of minimally invasive staged procedures with tined lead method now allows a complete reversible approach and this has been the reason of a large use of this approach: despite this well-codified procedure, there are still a lot of open issues related to different aspects.

The history of neurostimulation in urology is related to the efforts in finding a solution for spinal injured patients. Actual techniques of stimulation and electrical

modulation are recognized as a second-choice approach. After coming through the spinal shock phase, 80 % of patients with spinal cord injuries develop "automatisms" involving both somatic and vegetative components, generally in the presence of an upper motor neuron injury. The current work of the neuro-urologist is principally concerned with the symptomatic treatment of these events, which are responsible for sense and motor overactivity.

During the past 20 years, experience in the use of chronic sacral nerve stimulation techniques involving the sacral area has proven to have an effect in chronic modulation patients regarding phenomena secondary to the activation of the primary sensory component (C fibers), responsible for bladder overactivity with the prevalent modulation of A-delta afferent component capable of reactivating normal control mechanisms at a central cortical and subcortical level. However, the effect is sometimes scarce when the phenomenon becomes chronic.

The sacral area provides an access point for chronic stimulation leads which are mini-invasive and reversible and involves both the pelvic area functions and the motor functions of the lower limbs. The early use of nerve stimulation of the sacral area (sacral roots and pudendal nerves) prior to the appearance of responses are not in line with the use of the current approach and of the approach on the pudendal nerve represent the goal in the future. Nothing is really known about what the most reliable parameters would be to obtain the best stimulation, and this is one of the goals for the coming years. Another issue to be solved is the necessity of a continuous or a cycling stimulation, as it is still to be soundly understood if loss of responses might sometimes be related on a habit of the nerves.

There is no evidence as to the use of a bilateral stimulation. A real pudendal approach may prove interesting, although one would not argue that pudendal stimulation is better than sacral stimulation. Pudendal nerve stimulation is a better target in case of neurogenic overactive bladder in incomplete spinal cord lesions, and responses during acute stimulation are different than in the sacral one.

The promise for the future is to achieve the possibility of a mixed direct stimulation with a continuous modulation.

All these new approaches are related to the development of different leads and generators with the possibility to maintain a modulation to restore a central balance of the nervous system along with the possibility to stimulate the sacral area in order to achieve a synergic voiding of the bladder.

New Frontiers: Electrical Stimulation in Colorectal Disorders

21

Jacopo Martellucci

Electrical stimulation techniques are changing the future of pelvic floor treatment.

The common surgical procedures provided anatomical corrections also for functional disorders, taking the risk to be ineffective, dangerous, and to compromise further treatments.

Electrical therapies are often minimally invasive and, above all, reversible, and represent a true functional treatment for functional diseases.

The rise of new effective technologies created new evidences and more physiopathological questions, and the attempts to answer are representing the real new frontier.

21.1 Colonic Electrical Stimulation (Colonic Pacing)

Electrical stimulation of the gastrointestinal (GI) tract is an attractive concept. Since these organs have their own natural pacemakers, the electrical signals they generate can be altered by externally delivering electric currents by intramuscular, serosal, or intraluminal electrodes to specific sites in the GI tract.

Different methods of electrical stimulation have been derived from the variation of stimulation parameters, including long-pulse stimulation, short-pulse stimulation, and stimulation with a train of pulses. Electroacupuncture may also be considered as a methodologic variation of electrical stimulation because electrical stimuli are delivered by needles inserted into acupuncture points associated with the gastrointestinal tract [1].

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Patients with slow transit constipation accounted from 5 to 15 % of the constipated population [2], and severe constipation (e.g., bowel movements only twice a month) is seen mainly in young women.

Several studies showed the positive effects of direct colonic stimulation in animal models [3–6].

A recent paper of Martellucci and Valeri [7] reported the first description of a permanent colonic pacing in two young female patients affected by severe slow transit constipation.

The number of bowel movements per week increased from 0.3 to 3.5 in the first patient and from 0.5 to 2.5 in the second patient. Both patients no longer needed laxatives, enemas, or any other treatments.

The two electrodes were placed laparoscopically and under endoscopic control in the muscular layer of the rectosigmoid junction, and then connected to a left inguinal subcutaneous stimulator.

According to the results of Shafik, the presence of a rectosigmoid junction pacemaker and a colosigmoid functional sphincter, regulated by rectosigmoid and recto-colic reflexes, suggested a possible target site for electrical stimulation [8].

The role of the sigmoid colon in the pathophysiology of slow transit constipation is well known, even if not completely clear, considering that megacolon (mainly left) is the main clinical finding in Hirschsprung's disease, that a dolichomegacolon (mainly left) is a common feature of patients affected by chronic slow transit constipation, that diverticular disease manifests in left and sigmoid colon, and that an incomplete sigmoid resection for diverticulitis exposes to a higher recurrence rate.

Even if the extent of colonic innervation is still under debate, it is generally believed that vagal innervation to the large bowel terminates at the level of the splenic flexure, while the remainder of the colon, including the rectum, receives parasympathetic input from the pelvic nerves (PN).

A pattern of dual, coordinated, parasympathetic innervation in the left colon may regulate motor activity between the proximal colon and rectum.

The distal colon and rectum also receives sympathetic input from the hypogastric nerves (HGN), mainly derived from the lumbar preganglionic outflow that runs to the inferior mesenteric ganglia (hypogastric ganglion). The innervation and functional role of the HGN on the internal anal sphincter has been well studied. However, it still remains unclear how the HGN regulates colorectal motility.

All these observations suggested that slow transit constipation (or certainly some cases) could be related to conflicting neurogenic input received by the left/sigmoid colon and maybe associated with (or the cause of) hypogangliosis and interstitial cell alteration.

Even if the results are promising, deeper neurophysiopathological studies are needed for a better understanding of the colonic motor function, and further studies with a larger number of patients and a longer follow-up are required.

21.2 Dorsal Genital Nerve Stimulation

Dorsal genital nerve (DGN) stimulation has also been investigated as a method against bowel dysfunction. The pudendal nerve dorsal genital branch carries afferent fibers, and it is easily accessible peripherally.

Some studies have analyzed the effect of DGN stimulation for the treatment of fecal incontinence in patients with pudendal neuropathy and idiopathic FI.

In the results of Binnie and colleagues [9], this stimulation results in an immediate rise in the pressure in the anal canal and a significant increase in the electromyographic activity of the external anal sphincter. Maintenance of the stimulus over a 2-month period raised the mean resting pressure significantly in the anal canal and increased the reflex and voluntary responses of the external anal sphincter to coughing and squeezing actions, respectively. The length of the sphincter was not affected. There was widening of the mean motor unit potential duration, though this was not significant. The resting electromyogram was enhanced after the course of treatment, indicating greater spontaneous activity in the external sphincter. In their series, seven of the eight patients studied became continent at the end of the treatment.

Only after about 15 years, Frizelle et al. [10] confirmed these results. In their study biofeedback using a pudendal nerve stimulator comprising a bipolar electrode was applied to the base of the clitoris or penis. Electrical pulse voltage was self-titrated and defined periods of treatment were prescribed. Anorectal manometry and Cleveland incontinence scores were assessed.

There was a significant reduction in incontinence symptom score after pudendal nerve stimulator treatment in the 42 patients treated. This was accompanied by significant improvements in anal sphincter tone, maximal tolerated rectal volume, and the sustained rectoanal inhibitory reflex.

However, Worsøe and colleagues [11] confirmed the efficacy of the treatment but found conflicting functional results. Stimulation was applied twice daily for 3 weeks at the maximal tolerable stimulation amplitude (pulse width, 200 μs; pulse rate, 20 Hz). FI severity scores, FI Severity Visual Analogue Score (VAS), FI Quality of Life Score (FIQL), sphincter function, and rectal volume tolerance were assessed at baseline, immediately after stimulation and 3 weeks after stimulation.

The Wexner score and the St. Mark's score improved after stimulation in seven and six of the patients and improvement was maintained 3 weeks after stimulation. The number of incontinent episodes was reduced in seven out of nine patients. Improvement was maintained for 3 weeks after stimulation. Interestingly, subjective assessments of FI severity using the VAS score and the FIQL score did not improve during stimulation. Sphincter function and rectal volume tolerability were unaffected.

Moreover the same authors, comparing stimulated with unstimulated phasic distension, found no significant difference in the median rectal cross-sectional area (CSA) measured with impedance planimetry. Comparing stimulated with unstimulated stepwise distension, there was no significant difference in the median rectal CSA. Neither the rectal pressure-CSA relationship (CSA/P(R)) nor the rectal wall

tension changed during stimulation. No acute effect on rectal CSA during pressure-controlled distension was demonstrated during DGN stimulation [12].

However, these results were not confirmed in patients with spinal cord injury in which DGN stimulation results in an acute decrease of rectal CSA and rectal pressure-CSA relation [13].

21.3 Magnetic Stimulation

It has been reported that sacral pathways can be stimulated by means of functional magnetic stimulation, and positive effects were described for voiding dysfunctions [14–17]. A magnetic field can induce an electric field, creating a current which can stimulate neuromuscular tissue as if it had been produced by electrodes. Therefore, the mechanism of action by magnetic stimulation seems to be quite similar to that of electrical stimulation. The application of magnetic pulses on the sacral roots was found to evoke motor potentials in the pelvic sphincter muscles and produce contractions of pelvic floor muscles [18, 19]. The magnetic fields generated from the magnetic coil are able to pass through high-resistance structures such as bone, fat, and skin without harm to the body. Compared with electrical stimulation, magnetic stimulation has some potential advantages: is noninvasive, not painful, and easy to use.

Magnetic sacral root stimulation produces an increase in anal and rectal pressure and a decrease in rectal volume in healthy subjects and patients with fecal incontinence or a spinal cord injury [20] and induces frequency specific changes in cortico-anal excitability [21].

Moreover Gallas et al. [22] suggested a potential role of sacral magnetic stimulation in affecting colonic motility.

This was confirmed by Lee et al. [23] who found potential benefit from magnetic sacral dermatome stimulation for a subset of patients with idiopathic slow transit constipation, particularly in constipated patients with rectal hyposensation or hindgut dysfunction.

During the stimulation period (3 week), the frequency score of spontaneous bowel movements decreased in eight of the 14 patients, whose threshold volumes for urge to defecate and maximum tolerable volumes were significantly greater than those of the nonresponders, and significantly decreased at the end of treatment. The degree of straining on defecation also significantly decreased in the responders. Responders had shorter right colonic transit time and longer left colonic transit time compared to the nonresponders.

In the study of Kubota and colleagues [24] on pediatric patients, 13 controls and 20 patients with chronic constipation were studied. The sphincter response to magnetic stimulation was biphasic in the controls, consisting of an initial rise followed by a decrease in the sphincter pressure, while it varied among the patients with chronic constipation including a biphasic response in 16 patients, no response in three patients, and only a transient rise in pressure in one patient. In nine preoperative patients with Hirschsprung's disease, no rectoanal reflex was observed;

however, the sphincter pressure increased due to magnetic stimulation in six patients, while three patients exhibited no recordable responses. These results suggest that the repetitive magnetic stimulation technique is a valuable modality for investigating the neural interaction between the sacral nervous system and the anorectum.

Kubota and colleagues [25] also suggested that sacral magnetic stimulation might be a useful modality to improve postoperative bowel or bladder dysfunction in children with anorectal malformations.

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