Impaired Detrusor Contractility: Anything New?

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Current Urology Reports 2002, **3:**373–377
Current Science Inc. ISSN 1527-2737

Impaired detrusor contractility (IDC) is a poorly defined entity that represents a treatment challenge for the urologist. The etiology of IDC is variable and may include neurologic disorders, inflammatory conditions, and pharmacologic and psychogenic causes. The gold standard for the treatment of IDC is clean intermittent catheterization (CIC). Although well-established as efficacious and safe, CIC may be conceived as a major burden on a patient's quality of life and has been associated with urinary tract infections and urethral and/or bladder injury. Alternative treatment modalities for IDC can be divided into interventions at the nervous system supplying the bladder, the bladder itself, or the bladder outlet. We review and discuss novel and creative treatment options for patients with IDC that have been developed or tested over the past decade.

Introduction

Multiple classification systems have contributed to difficulties in defining and investigating the problem of the underactive and the acontractile detrusor, here collectively referred to as impaired detrusor contractility (IDC). According to the International Continence Society, voiding dysfunction can be divided into detrusor and urethral dysfunction. Detrusor function during voiding is further classified into normal, overactive, or underactive (including acontractile) conditions, while urethral function can be normal, underactive, or overactive. Overactive urethral function can be obstructive with the obstruction either caused by an overactive urethral function or by mechanical factors. These definitions are based on the results of urodynamic studies. An acontractile bladder is defined as one that cannot contract during urodynamic studies, whereas an underactive detrusor is defined as a muscle that produces contraction of either inadequate magnitude or duration to effect complete bladder emptying in the absence of urethral obstruction [1].

An older urodynamic classification proposed by Krane and Siroky [2] divides voiding dysfunction into detrusor normoreflexia, hyperreflexia, and areflexia [2]. According to this classification, detrusor areflexia can occur with coordinated sphincter function, nonrelaxing or denervated striated sphincter, or with nonrelaxing smooth sphincter.

Classification of voiding dysfunction can also be based on a simple functional basis. Wein and Barrett [3] describe voiding dysfunction in terms of whether the deficit is primarily one of the filling or the emptying phase of micturition. According to this classification failure to empty can be caused by a bladder dysfunction or an outlet dysfunction. Bladder dysfunction that produces failure to empty is further classified into neurogenic, myogenic, psychogenic, and idiopathic causes.

Other definitions related to IDC are acute and chronic retention. Inability to void over 12 hours necessitating catheterization, ultimately yielding a urine volume equal to or greater that normal bladder capacity, is defined as acute retention. Acute retention may be painful or painless, depending on the neurologic status of the patient. Chronic retention is an insidious and painless failure of bladder emptying. Catheterization may yield volumes equal to at least 50% of normal bladder capacity [4]. Chronic urinary retention can lead to recurrent urinary tract infections, stones, and overflow incontinence. Both acute and chronic urinary retention can be caused by a detrusor dysfunction, urethral dysfunction, or a combination of these factors.

A variety of conditions can lead to poor detrusor contractility, resulting in impaired bladder emptying. Diseases may cause permanent or temporary detrusor dysfunction by damaging the detrusor muscle itself (detrusor myopathy) or its nerve supply (lower motor neuropathy). Among the many causes for IDC are neurologic diseases, spinal disc protrusion, severed pelvic nerve, chronic bladder outlet obstruction, diabetes mellitus, and metabolic and myopathic disorders. Impaired detrusor function can be also iatrogenic either resulting from surgical trauma or idiopathic in origin. The standard treatment options to facilitate bladder emptying include clean intermittent catheterization (CIC), chronic indwelling catheter in the form of either suprapubic cystostomy or urethral Foley catheters, and urinary diversions such as ileal or colonic conduits. The traditional treatment of choice for patients who wish to avoid an indwelling catheter is CIC. Although considered the gold standard, this mode of treatment is

Table 1. Responses elicited by electric stimulation at different locations

Needle position	Pelvic floor	Foot/calf/leg	Sensation
S2; primary somatic contributor to pudendal nerve	Clamp of anal sphincter (contraction of anal sphincter)	Leg/hip rotation, plantarflexion of entire foot, contraction of calf	Contraction of base of penis/clitoris
S3; pelvic autonomic functions and levator ani	Bellow of perineum (lifting and dropping of pelvic floor)	Plantarflexion of great toe (sometimes other toes)	Pulling in rectum, radiating forward to scrotum or labia
S4; pelvic autonomic and somatic, no lower extremity	Bellow	No leg or foot motor stimulation	Pulling in rectum only

highly bothersome to the patient or his caregiver and is not free of complications [5–8]. New alternatives to the use of indwelling catheters, CIC, and urinary diversion can be divided into interventions at the neural system innervating the bladder, the detrusor muscle itself, or the bladder outlet. Treatment modalities that were introduced or significantly improved in the past decade in each of these groups are presented and discussed.

Interventions at the Nervous System

Attempts to elicit detrusor contraction by electrodes implanted at the bladder wall, pelvic nerve, sacral nerve root, and spinal cord as a treatment for voiding dysfunction have been described in the literature [9–11]. These attempts produced artificial micturition patterns with high intravesical pressures and involuntary movements of the lower limbs. The only electric stimulation technique used for the treatment of IDC that has passed the test of time and is still in use today is sacral nerve (S3) neuromodulation. Sacral nerve neuromodulation is used for the treatment of lower urinary tract dysfunction. An electric current is delivered through the S3 foramen to the sacral nerve, the primary somatic innervation of the levator ani and primary autonomic innervation of the detrusor. The clinical efficacy of this method is believed to rely on modulation of sacral micturition reflexes, but the exact mechanism of action is not fully understood. Indications for the use of neuromodulation include urgency-frequency symptoms (overactive bladder), urge incontinence, and urinary retention. The technique is thus used both in cases of detrusor overactivity and hypoactivity, therefore the term neuromodulation and not neurostimulation is used.

This mode of treatment is delivered in three stages: acute, subacute, and chronic. The acute phase consists of percutaneous localization of the sacral spinal nerves with a needle electrode. If a positive response is observed a wire electrode is left in place for the subacute phase. In the subacute phase the wire electrode is left in place for a few days and neuromodulation is applied. Clinical response is tracked by the patient keeping a recording with a voiding diary. Significant improvement in symptoms in the subacute phase is an indication for permanent implantation of the neuromodulation device (chronic phase).

The acute phase is performed under local anesthesia. A needle electrode is introduced into the S3 foramen (uni- or bilaterally). The correct placement of the needle electrode is verified by observing the effect electric stimulation has on the leg, foot, and pelvic floor. Correct location of the needle tip at the S3 foramen will produce flexion of the toe and bellow (a "sucking in" movement) of the perineum. Incorrect placement of the needle tip at the level of S2 or S4 will result in different response (Table 1). Once the proper response is elicited a stimulation wire is put through the needle electrode and its correct position verified by repeated electric stimulation. The wire electrode is then connected to an external hand-held neurostimulator and the device is left in place for a few days. The patient continues to fill out a voiding diary over several days during the subacute neurostimulation period. A reduction of clinical symptoms by at least 50% in the case of urgency-frequency and urge incontinence or a voiding with postvoid residual volume of less then 50 mL in patients with urinary retention is considered a success. If the subacute neurostimulation is proven successful the permanent device is implanted. The permanent device consists of a neurostimulator, extension lead, and an electrode. The neurostimulator and the electrode are implanted through a midline sacral incision over S4 up to S1 and a separate buttock incision, respectively. A subcutaneous tunnel is created between the incisions over the sacrum and the buttock. An extension wire is then passed through the tunnel and is used to connect the neurostimulator and the electrode. Electric stimuli can be adjusted to the patient's specific need using a remote control unit placed over the implanted neurostimulator.

Sacral nerve neuromodulation has been extensively used for the treatment of urgency-frequency symptoms and urge incontinence. Reports on its value in urinary retention are sparse. Shaker and Hassouna [12•] have recently reported on the results of sacral nerve neuromodulation (S3 foramen implant) in 20 patients (19 women, one man) with nonobstructive, non-neurogenic, chronic urinary retention. All patients reported subjective improvement in all symptoms. All patients had at least 50% improvement in voided and postvoid residual volume. Furthermore, urinary tract infection rates decreased significantly and associated pelvic pain improved substantially.

Interpretation of these results is difficult because only limited follow-up is presented, with only eight and five patients being followed for periods of 1 year and more than 18 months, respectively [12•]. Furthermore, sacral nerve stimulation is not devoid of complications such as implant failure, battery failure, implant infection, electrode migration, pain at the implant site, and wound infection and dehiscence. Similar outcomes were reported by the national register of Italy [13]. One hundred and ninety-six patients in two different registers (prospective and retrospective) were studied. Of the 196 patients, 45 had urinary retention and an additional 10 of the 45 patients had neurogenic urinary retention. In patients with idiopathic retention the average residual urine decreased from 277 to 108 mL, 50% of patients stopped catheterization, and another 13% catheterized once daily at 1 year of postimplantation follow-up [13]. The early results of sacral nerve neuromodulation for the treatment of impaired bladder contractility are thus encouraging. Longer follow-up and patient stratification according to the etiology of IDC may contribute to identification of subgroups of patients that may benefit more from this treatment.

Interventions at the Detrusor Muscle: Electromotive Intravesical Bethanechol

The value of bethanechol for the treatment of impaired bladder emptying has always been controversial. Conflicting evidence exists as to its efficacy [14,15]. The effect of bethanechol is induced by its binding to the muscarinic M_3 receptor in detrusor muscle cells. Once bound to the receptor a chain of events occurs. A second messenger mediates the release of calcium from intracellular stores, causing a phosphorylation of actin-myosin filaments, leading to detrusor contraction. This excitatory impulse is transmitted via intercellular junctions to adjacent cells to produce a coordinated contraction of the detrusor muscle. A report on electromotive administration of intravesical bethanechol in patients with acontractile detrusor was recently published [16]. Urinary retention and detrusor areflexia were cystometrically diagnosed in 25 women and 20 men. Patients were further divided into four groups according to the cause of their areflexia. Neurologic disease, chronic bladder dilatation, idiopathic disease, and acute bladder overdistention was observed in 26, 11, five, and three patients, respectively. Bethanechol (20 mg in 150 mL of 0.3% NaCl solution) was instilled into the bladder. Electromotive administration of bethanechol was facilitated using pulsed electric current (2.5 kHz, gradually increased to 20 mA) using a intravesical catheter electrode (anode) and an abdominal skin electrode (cathode) for 12 minutes. Response was evaluated by measuring the intravesical pressures. No change in intravesical pressures were revealed in the control groups, including patients treated with bethanechol instillation with no electric current or electric current without bethanechol instillation. Significant difference in the intravesical pressure was evident between different groups of patients, with 92% of the patients with neurologic disease and only 27% of patients with chronic bladder distention responding to the test. A positive response to the electromotive administration of bethanechol was correlated with response to oral administration of bethanechol. Nine of the 11 responders and none of the nonresponders restored their spontaneous voiding after oral administration of bethanechol. Riedl *et al.* [16] have suggested that chronic bladder dilatation may contribute to intracellular changes, thereby rendering bethanechol treatment ineffective. The clinical applicability of electromotive administration of bethanechol as a treatment modality or a diagnostic test allowing better patient selection for oral bethanechol treatment remains to be seen. The main finding may be that patients with acontractile bladder represent a wide group of pathologic processes with defects at different levels of the neuromuscular chain. Reclassification of patients according to their pathologic process may help to provide better treatment to different patient groups.

Detrusor Myoplasty and Electrically Stimulated Detrusor Myoplasty

The concept of using skeletal muscle to support the function of nonskeletal muscles is not new. A pedicled latissimus dorsi flap was used to support cardiac function in selected patients presenting with severe cardiopathy as early as the 1980s [17]. Restoring bladder emptying by wrapping the bladder with a skeletal muscle with its own vascular supply has been reported in cadavers, animal models, and recently in humans. Different muscles have been used for this procedure including rectus abdominis, rectus femoris, and latissmus dorsi. Successful restoration of bladder emptying was reported in patients with a congenital malformation, such as prune belly syndrome, or with post-traumatic lower motor neuropathy [18–20,21•,22,23]. Stenzl *et al.* [21•] report on their early experience with microneurovascular free transfer of autologous latissimus dorsi muscle in three male patients (two patients with spinal cord injury and one patient with chronic overdistention). A flap of latissimus dorsi muscle (at least 75% of the muscle) was removed together with a pedicle consisting of the thoracodorsal vessel and nerve. Microvascular end-to-end anastomosis to the inferior epigastric vessels and nerve was then performed. Through an abdominal incision the latissimus dorsi muscle was wrapped around the bladder, covering about 75% of the bladder. No catheterization was required as soon as 16 to 30 weeks after surgery. Urodynamic evaluation performed 12 months after surgery revealed bladder capacities of 600 to 650 mL and residual urine volumes of 0 to 90 mL. Flow rates were also within normal limits. The authors

concluded that microneurovascular free transfer of the latissimus dorsi muscle can functionally restore a deficient detrusor muscle.

Detrusor myoplasties are designed to enable bladder emptying when the detrusor muscle itself is dysfunctional. Detrusor myoplasties require a neural input that will enable proper bladder contraction. There are situations, however, in which neural input to the bladder muscle or to the myoplastic detrusor is impaired, and in these cases the question remains where the neural impulse will come from. A suggested solution is the electrically stimulated detrusor myoplasty, recently reported in human cadaver and dog models [20]. The rectus abdominis muscle is surgically dissected with preservation of its insertion to the pubic bone. The deep inferior epigastric vessels and the most caudal intercostal nerves are preserved. A complete wrapping of the bladder is achieved with this technique. Two pairs of bipolar electrodes are then inserted next to the nerve entrance and used to stimulate the muscle, resulting in an increase in intravesical pressures and reasonable bladder emptying. Potential advantages of electrically stimulated detrusor myoplasty over S3 neuromodulation and detrusor myoplasty alone are that it works independently of the nerve supply to the bladder or bladder dysfunction etiology [20].

Detrusor myoplasties require expertise in tissue transfer and microsurgical technique. Their place in the treatment of IDC will have to be determined in larger groups of patients. Their value and effect on patient quality of life should be weighed against simpler measures such as self-performed CIC or the more involved neuromodulation techniques. The choice of the best flap to be used also remains to be established.

Interventions at the Bladder Outlet

Interventions at the bladder outlet for the management of IDC attempt to circumvent the problem of disturbed bladder innervation or impaired detrusor musculature. Here the outlet is manipulated so that urine is expelled without an active driving force produced by the bladder itself.

Clean intermittent catheterization was first described by Lapides [24] in 1972 as a treatment for neurogenic conditions. Since its introduction it has become the treatment of choice for many neurogenic bladder conditions including IDC. Sterile intermittent catheterization is still considered the treatment of choice for patients with neuropathic bladders in the hospital environment to prevent cross infections; however, many patients find CIC to be a significant psychologic burden. In this procedure a catheter should be introduced into the bladder every 3 to 4 hours each day, usually for life. Moreover, this treatment is not free of complications. Symptomatic urinary tract infections have been found in 10% of patients treated with CIC. Urethral and bladder injury, although far less common, are also among the possible complications [5–8].

The ideal treatment should allow the patient to completely evacuate his or her the bladder and to remain continent between voidings with minimal disturbance to routine daily life. A solution consistent with these goals of treatment was recently suggested by Nativ *et al.* [25] who reported on their early experience with a temporary remote-controlled intraurethral insert. The intraurethral insert (InFlow; Influence Medical Inc., Ramat Gan, Israel) is a short silicone catheter with an internal valve and pump mechanism that is introduced into the urethra using a disposable inserter. The insert is fixed in position by flexible silicone fins at the level of the bladder neck and by a flange at the external urethral meatus. The catheter is easily removed by pulling its external flange or by manipulating the flange, causing collapse of the flexible silicon fins. Periodic replacement of the insert is performed by a caregiver or by the patient. The valve and pump mechanism contains a tiny magnet in its core that is remotely energized by the InFlow activator. To initiate urination the activator is held at the pubic area near the urethral opening and its "on" button is pressed. The valve of the device opens and the miniature rotor spins so that the pump draws urine from the bladder, allowing the patient to "void" with a urine flow of 10 to 12 mL/second. At the end of urination the pump ceases to rotate and the valve closes to regain continence. The results of bladder management with the InFlow device were described by Madjar *et al.* [26•,27] in two separate studies. The first study [26•] was conducted in Germany and Israel. Of the 92 women with urinary retention and voiding dysfunction who were recruited to the study, 51% continued to use the device for a mean follow-up period of 7.6 months (range, 2 to 26 months). Early withdrawal from treatment was recorded in 49% of the patients. Patients who stopped the use of the device early (a mean of 7.1 days) did so because of local discomfort or urinary leakage around the catheter. The second study [27] provides longer follow-up on a separate set of 92 female patients. Early discontined treatment rates were similar to those reported in the first study (52 patients, 56.5%) [26•]. Late discontinuation of the device use was recorded in 19 patients (20.6%). The reasons for delayed discontinuation of the device were unrelated to the medical aspects of the insert in nine of the 19 late quitters (two patients died of unrelated causes, three patients deteriorated physically or mentally, two patients improved spontaneously, and two other patients found the device to be too costly). Local discomfort, dyspareunia, and spontaneous expulsion of the device were reasons for discontinuation by another 10 patients. Twenty-one patients (22.8%) continued to use the device for more than a year with a follow-up time of 12 to 44 months (mean 24.6 months). Complications in this group of patients included device migration into the bladder (four patients), asymptomatic bacteriuria (15 patients), and symptomatic urinary tract infections (four patients, including one patient who had pyelonephritis). Two patients complained of episodic inconvenience

between their legs during walking. All patients who continued treatment were satisfied with the device and preferred it to previous treatment modalities used. The authors concluded that the InFlow intraurethral insert can serve as a long-term treatment for the management of women with voiding difficulties, and that women who continue treatment for prolonged time are satisfied with the device use [27]. Presntly the device awaits the approval of the US Food and Drug Administration and recertification (CE Mark) in Europe, and is limited to use by women only. The role of the InFlow device in the treatment of IDC will be determined by further research, and perhaps improvements in its design to allow better patients tolerance and lower complication rates.

Conclusions

Impaired detrusor contractility represents a challenge to the urologist. The traditional treatment for patients with IDC is CIC. CIC is safe and effective but carries a considerable inconvenience to patient's daily life and may lead to complications such as urinary tract infections and urethral and bladder injury. Numerous innovative and exciting treatment alternatives to CIC have been described. Present studies are limited by a relatively small number of patients and short follow-up periods. The future of these treatment modalities will be determined based on the results of studies with larger cohorts of patients, longer follow-up time, and proper stratification of patients according to the etiology and pathophysiology of their IDC.

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