

TREATMENT OF AUTONOMIC NEUROPATHY

TREATMENT OF PERIPHERAL AUTONOMIC DYSFUNCTION OF THE URINARY BLADDER (Part Two)

Roy Freeman, MD
Associate Professor of Neurology
Harvard Medical School
Boston, MA USA

The bladder wall is comprised of three layers of interdigitating smooth muscle and serves as a receptacle for the storage and appropriate evacuation of urine. This smooth muscle—the detrusor muscle—forms the internal sphincter at the junction of the bladder neck and urethra while the external sphincter is formed from the striated muscle of the urogenital diaphragm and is a true anatomical sphincter. Higher centers involved in bladder control include the anterior and medial frontal lobes, limbic regions, basal ganglia, thalamus, hypothalamus, and brainstem.¹⁻⁴ These regions receive afferent fibers from and send efferent fibers to "micturition centers" in the lower spinal cord. The bladder has parasympathetic, sympathetic, and somatic innervation.⁵

The innervation of the bladder described above provides the basis for understanding bladder autonomic dysfunction. There are several different schemas classifying voiding dysfunction.⁶ The classification of Krane and Siroky (see Table 1) incorporates a functional description of detrusor muscle and sphincter function and provides a logical basis for instituting therapy. Therapies directed at reducing bladder hyperreflexia and maintaining urinary continence may alternately modify bladder contractility, bladder outlet resistance, or employ other means to bypass vesicular or sphincteric abnormalities. Therapies for bladder hypomotility, conversely, attempt either to increase bladder contractility, to decrease outlet resistance, or to achieve both.⁷

The non-pharmacologic interventions that include toileting regimens, Credé maneuver, intermittent catheterization, indwelling foley catheterization, palliative or definitive surgical interventions, and biofeedback are often used in concert with medications. The patient's customized therapy is best pursued with the aid of urologic consultation. Individualized treatment regimens should be guided by the history, examination, urodynamic studies, and measurement of the post-void residual volume.⁸

Bladder dysfunction and peripheral neuropathy

In cases of peripheral denervation, sensory, motor, sympathetic, and parasympathetic nervous system dysfunction of the bladder occurs in varying combinations.^{1, 9} The parasympathetic nervous system is the primary innervator of the detrusor muscle and deficits result in detrusor areflexia. Although detrusor muscle contraction initially may be normal in patients with sensory dysfunction, afferent deficits lead to bladder overdistention and secondary detrusor dysfunction. Dysfunction of the sympathetic

nerves leads to deficits in internal urethral sphincter control that may result in incontinence. Similarly, somatomotor nerve dysfunction may result in incontinence due to impaired external urethral sphincter closure.

Patients complain of suprapubic fullness and voiding difficulties. Some patients may report urinary frequency, urgency, and incontinence. These symptoms are a consequence of urinary retention with overflow incontinence. Examination reveals an overdistended bladder with high post-void residual and, on occasion, detrusor instability.^{10, 11}

Diabetes mellitus is the most common cause of urinary dysfunction secondary to peripheral nervous system pathology.^{12, 13} Development of symptoms is insidious, often manifesting years after onset of diabetes. Symptoms of bladder dysfunction have been observed in 37–50% of patients, and urodynamic evidence for vesicular malfunction has been described in 43–87% of insulin-dependent patients.^{14–17} The most common abnormalities were impaired detrusor contractility and detrusor areflexia.¹⁷ Although some diabetic patients, particularly the elderly, may have uninhibited bladder contractions¹⁸ and detrusor hyperreflexia.¹⁹ Mechanical obstruction of the bladder neck, as in cases of benign prostatic hypertrophy or cystocele, also may account for some instances of hypotonic, distended bladders in diabetics.

Impaired afferent conduction is thought to result in diminished sensation of bladder filling, increased bladder capacity, and reduced detrusor contractility as a result of overdistention injury.¹⁰ The term "diabetic cystopathy" has been applied to this disorder, especially the detrusor areflexia, that results from impaired bladder sensation. Patients with bladder hypomotility and high residual urine volumes may be at greater risk for the development of an increased risk for infection,¹⁵ although not all authors are in agreement.²⁰ A neurogenic bladder has also been associated with the DIDMOAD or Wolfram's syndrome.²¹

Other peripheral neuropathies that are associated with bladder dysfunction include amyloid neuropathy,²² Guillain-Barré syndrome,^{23–25} chronic demyelinating neuropathies,²⁶ Lyme disease,²⁷ HIV neuropathy,²⁸ and herpes zoster infections.^{29,30}

Treatment of bladder hypomotility

Initial therapy should emphasize timed voiding schedules with bladder contractions enhanced by a Valsalva's maneuver and Credé maneuver. Clean intermittent self-catheterization, however, is the primary therapy for impaired or absent detrusor muscle activity. The interval between catheterizations should be designed to maintain a residual volume of less than 100 cc and avoid incontinence. The majority of patients performing self-catheterization will develop bacteruria; however, antibiotic therapy is only necessary if symptomatic urinary tract infections occur. Patients who present with overflow incontinence and an overdistended bladder may regain bladder tone with the temporary use of an indwelling catheter.

Pharmacotherapy has a limited role in the treatment of detrusor areflexia. Stimulation of muscarinic, postganglionic receptors results in enhanced bladder contractility. Bethanechol chloride is a parasympathomimetic drug with relatively selective action at the urinary bladder. This agent may be effective in chronic states of detrusor atony or hypotonicity. It has also been used to facilitate reflex bladder contraction in patients with suprasacral cord injury.⁷ Dosing and route of administration of bethanecol vary with the clinical indications for its use. Typical oral doses range from 25–100 mg four times daily. The cholinergic agonist, carbachol chloride, which may have additional ganglion stimulating properties, also may enhance bladder motility.⁷

Other agents reported to enhance detrusor contractility include alpha-methyl-dopa, phenoxybenzamine, prostaglandins, and narcotic antagonists. During normal bladder filling, reflex inhibition of parasympathetic ganglia is thought to be mediated by sympathetic efferent activity and, specifically, by action at alpha-adrenergic receptors. Blockade of these receptors may disinhibit parasympathetically mediated bladder contraction. Trials using alpha-methyl-dopa³¹ and phenoxybenzamine³² have reported some benefit. Prostaglandins,^{33, 34} thought to act as excitatory neurotransmitters at the level of bladder smooth muscle, and narcotic antagonists, thought to block tonic inhibition of micturition by endogenous opioids,^{33,35,36} have been studied as other therapeutic options. These agents provide limited clinical benefit. For a complete list of agents used to treat bladder hypomotility, see Table 2.

TABLE 1

Classification of Bladder Dysfunction

- Detrusor hyperreflexia (or normoreflexia)
 - Coordinated sphincters
 - Striated sphincter dyssynergia
 - Smooth muscle sphincter dyssynergia
 - Nonrelaxing smooth muscle sphincter

- Detrusor areflexia
 - Coordinated sphincter
 - Nonrelaxing striated sphincter
 - Denervated striated sphincter
 - Nonrelaxing smooth muscle sphincter

TABLE 2

Therapy of Bladder Hypomotility

Behavioral therapy

- Timed bladder emptying
- Biofeedback

Catheterization and collecting devices

- Clean intermittent self-catheterization
- Urine collection devices
- Condom catheters
- Indwelling catheters
- Diapers and pads

Compressive and reflex maneuvers

- Credé maneuver
- Valsalva's maneuver
- Trigger zone stimulation

Pharmacotherapy to enhance bladder contractility

- Parasympathomimetic agents
- Prostaglandins
- ? – adrenergic antagonists
- Opioid antagonists
- Metoclopramide

Pharmacotherapy to relax the smooth muscle sphincter

- ? – adrenergic antagonists
- ? – adrenergic agonists

Pharmacotherapy to relax the striated muscle sphincter

- Centrally acting muscle relaxants
- Baclofen
- Dantrolene

Electrical stimulation of the paralyzed bladder

- Direct stimulation
- Stimulation of the spinal bladder innervation
- Conus medullaris
- Pelvic nerve
- Anterior roots

Surgery

- Reduction cystoplasty
- Bladder neck and sphincter surgery

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