ABSTRACT

Neurourology is applicable to urinary incontinence and obstructive uropathy in the general population. In most neurogenic conditions, incontinence is related to a loss of coordination of the bladder with the urethral sphincter mechanism. This article discusses possible causes and risk factors for stress incontinence and gives several clinical examples of patients with incontinence of varying causes.

No medications have been approved by the US Food and Drug Administration for the treatment of stress incontinence. Alpha receptor agonists, tricyclic antidepressants, and estrogen have all been used to treat the condition, with varying degrees of success. A new pharmaceutical agent targeting the unique motor neurons in Onuf's nucleus, which specifically innervate the striated urethral sphincter, shows promise as an effective treatment for motor urge incontinence and possibly certain types of stress incontinence. The types of stress incontinence for which the agent may be effective, however, must be carefully defined.

Neurourology, especially the video urodynamic study of urinary tract function and dysfunction in patients with known neural lesions, is applicable to urinary incontinence and obstructive uropathy in the general urologic population. It was first established in neurogenic conditions that risk is related to abnormal bladder compliance or the ability of the bladder to store urine at low pressure. This abnormality is the result of bladder outlet obstruction. In most neurogenic conditions, this obstruction is related to a loss of coordination between the bladder and the urethral sphincter mechanism. Abnormal bladder storage function also results from any significant obstructive process involving the bladder outlet, such as benign prostatic hypertrophy or urethral obstruction after stress incontinence surgery (Figure 1). Obstruction, structural or neurogenic, has the same effect on compliance, which in turn determines risk.

URETHRAL FUNCTION

According to a body of opinion, urinary continence depends primarily on reflex and volitional contractility of the striated muscle portion of the urethral sphincter. The part of the urethral closure mechanism with the highest pressure is the midurethral area. The function of this area is putatively abnormal in men with postprostatectomy incontinence and in women with stress incontinence. Thus, strengthening this area with exercises or direct electrical stimulation is advocated for both postprostatectomy and stress incontinence.

In women, pelvic floor dysfunction is a broad term that includes vaginal prolapse conditions as well as uri-
nary and fecal incontinence associated with childbirth injuries to the urethral and anal sphincter and the levator musculature during labor and delivery. The term also broadly includes stress incontinence conditions related to the same kinds of injury or functional alteration.

**Childbirth and Levator Muscle Function**

Occasionally, labor and delivery are associated with acute onset of severe stress incontinence, such that even minimal effort is associated with gross leakage (Figure 2). Vaginal prolapse and fecal incontinence also occasionally seem to result from labor and delivery. These conditions were once thought to be transient and to improve with time. All of these conditions probably do not improve with time, however. Recovery instead seems to be related to the nature and extent of the injury.

Magnetic resonance imaging (MRI) studies by DeLancey et al at the University of Michigan suggest that serious levator muscle injuries, with partial or total loss of levator mass can be incurred during childbirth (Figure 3). These conditions are associated with vaginal prolapse and incontinence. When severe stress incontinence occurs immediately postpartum, however, video study shows an open nonfunctional internal sphincter mechanism or one that leaks at very low abdominal pressures.

Levator muscle injury and intrinsic sphincter dysfunction do not always occur together. Stress incontinence may occur alone, without levator muscle injury, and vice versa. Although the mechanism of injury for both conditions appears to be trauma associated with labor, levator muscle injuries do not cause stress incontinence; isolated stress incontinence can occur independent of levator muscle injury.

**Urethral Function Associated With Certain Neural Lesions**

Specific findings in patients with certain neural conditions suggest that our ideas about the role of the striated sphincter in urethral incontinence may not be completely accurate. Total loss of striated urethral sphincter activity associated with complete sacral root transection does not cause stress incontinence per se, although with time both uterine and other vaginal prolapse conditions may develop (Figure 4). However, total loss of internal sphincter function associated with
specific neural disease or injury does cause severe stress incontinence, even if normal reflex and volitional function of the external sphincter are preserved. This occurs in some patients who sustain a pelvic neural plexus injury during abdominal-perineal resection for rectal carcinoma (Figure 5). This type of injury is intrapelvic; thus, the pudendal nerves are spared and the external sphincter functions normally. This also occurs occasionally after radical hysterectomy. As in the former condition, the striated sphincter functions normally, but the bladder is decentralized and areflexic, and the smooth sphincter is nonfunctional. These patients have severe stress incontinence.

Unlike sacral cord or root injuries, spinal cord injury at the 12th thoracic and first lumbar cord levels is associated with total loss of proximal urethral closure and severe stress incontinence. A similar situation exists in as many as 85% of patients with myelodysplasia (Figure 6). In patients with myelodysplasia, some function of the striated sphincter is preserved (although function is certainly not normal), but there is no function of the internal sphincter. These individuals have severe stress incontinence. Thus, certain neural lesions associated with loss of proximal urethral sphincter function result in severe stress incontinence, even if the striated sphincter retains function.

A further interesting aspect to these conditions is that function of the striated sphincter is not linked to phases of bladder activity as it is in normal states. As a result of pelvic neural injury, the bladder is decentralized; thus, there is no neural mechanism to support coordination of the bladder with the striated sphincter. In this case, persistent closure of the urethra by the striated sphincter, which is the only part of the urethra that remains functioning, is obstructive. Depending on the strength of urethral closure, this obstruction can induce progressive loss of bladder compliance and pose a risk to ureteral and renal function. The obstruction induces destructive behavior with a progressive loss of bladder compliance and higher ambient bladder pressures at progressively smaller bladder volumes (Figure 7). This happens despite coexistent severe stress incontinence. The process can be ameliorated by a surgical procedure that lowers outlet resistance. These findings suggest that resistance to abdominal pressure as an expulsive force is mainly the province of the internal sphincter.

Loss of internal sphincter function—even if the striated sphincter functions normally—is associated
with severe stress incontinence. On the other hand, the bladder faces the totality of urethral resistance (the highest being in the striated sphincter area) in the absence of the usual neural mechanism to open the urethra with detrusor expulsive activity. The bladder responds to the fixed outlet resistance offered by the striated sphincter, and compliance progressively deteriorates. A certain degree of resistance is required for adverse effects on the ureters to be produced (Figure 8). A urethral closure mechanism that requires a detrusor pressure of 40 cm H₂O to induce leakage is dangerous to bladder, ureteral, and renal function.

**Treatment of Incontinence Associated with Proximal Urethral Failure**

Closing the urethra stops stress leakage, but one does not want to increase the detrusor pressure required to induce voiding. Obviously, this is not voiding in the sense of coordinated bladder contraction and urethral relaxation, but leakage across a relatively fixed striated sphincter mechanism driven by increased detrusor pressure resulting from increased volume. Closure of the proximal sphincter is only safe when it does not change the detrusor–striated sphincter relationship, which determines risk to the upper urinary tract (Figure 9). Slings are quite safe here, because the increase in luminal pressure in the urethra after a sling procedure is less than 10 cm (Figure 10). This is not true for buried urethral segments or a submucosal neourethra where the efficiency of the valve mechanism increases with volume and with detrusor pressure, nor for the artificial sphincter placed at the bladder neck, which can increase the detrusor leak-point pressure to values above 40 cm H₂O.

These findings suggest that a small pressure advantage of the proximal urethra over the bladder is associated with stress competence. The exact role of the striated sphincter in resistance to abdominal pressure as an expulsive force is thus difficult to estimate, but function of the striated sphincter alone, without smooth muscle closure, does not provide continence. The striated sphincter clearly has a role as reflex-activated back-up system to prevent stress leakage. However, whether isolated loss or weakening of striated sphincter function itself causes stress incontinence remains to be proven. In clearly defined neural conditions, stress incontinence does not result from isolated loss of striated sphincter activity.
CONDITIONS ASSOCIATED WITH ABNORMAL FUNCTION OF THE STRIATED SPHINCTER

Fowler et al described a peculiar abnormality of the striated sphincter in young women with partial or complete urinary retention. They recorded specific abnormalities by sphincter electromyography in these women, clearly indicating that the inability to initiate detrusor contraction is related to a neural problem that prevents relaxation of the striated sphincter. These patients were previously thought to have emotional problems; although the lack of striated sphincter relaxation has been noted by other workers, it was attributed to volitional factors. Clearly, there is some real abnormality. In these cases, a bilateral pudendal blockade was transiently associated with involuntary voiding, in some measure confirming the observations of Fowler et al in such patients.

Neural modulation is effective in treating this condition on an empirical basis thus far. This syndrome emphasizes the critical relationship of the sphincter to the control of detrusor contractility. The bladder is a smooth muscle organ under cortical control; it makes sense that this control is exerted through a striated muscle group innervated by alpha motor neurons connected to the pyramidal tract—a fast system with direct cortical connections.

VOLITIONAL SPHINCTER FUNCTION

Onuf’s nucleus in the anterior sacral horn is a collection of unique motor neurons that supply the striated urethral sphincter. Generally, the urethral sphincter, anal sphincter, and levator muscles work together, but the neurons in Onuf’s nucleus specifically innervate the striated urethral sphincter. Activity of this area is associated with sphincter tone, contractility, and continence. Inhibition of the detrusor motor neurons is associated with activity of
the volitional sphincter. Relaxation of the external sphincter is the first event in a reflex bladder contraction and seems to be required to free the detrusor motor neurons from inhibition.

Horseradish peroxidase neural tracing studies, later supplemented by rabies viral tracing, demonstrated the anatomical relationship between the striated sphincter and Onuf’s nucleus.13 The striated sphincter and the detrusor motor neurons have a reciprocal relationship.14 Striated sphincter activity is associated with detrusor motor neuron inhibition. Voluntary interruption of detrusor contraction in progress is associated with a contraction of the striated sphincter and, within 1 to 2 seconds, cessation of the contraction. This relationship underpins one of the effects of sacral neural stimulation in the modulation of uninhibited detrusor reflex activity. By the variation of stimulus parameters, a sphincteric relaxation can be induced—with resumption of detrusor contractility.

Even suprasacral spinal cord injury, which separates the sacral cord centers from the brain-stem micturition center, does not destroy the reciprocal relationship between the bladder and the striated sphincter. Both bladder and sphincteric responses are poorly phased and the normal sequence of events in bladder filling and contractility is lost, but the basic relationship is maintained. After suprasacral spinal cord injury, there is a poor reflex striated sphincter response to bladder filling (the guarding reflex), but the detrusor response, when it occurs, is immediately associated with a sphincteric contractile response, in the face of which the detrusor response fades. Sphincter relaxation occurs as the bladder contraction stops. Another detrusor contraction occurs with a sphincteric response, and on and on. This can generate high pressures and can be dangerous, but the basic relationship is the same.

In addition to control of the detrusor reflex, the striated sphincter is thought to be weakened in patients with stress incontinence. Pelvic floor exercises and direct electrical stimulation have been used to stimulate and strengthen the striated sphincter.15 Electrical stimulation was found to have an inhibitory effect on reflex detrusor contractility, which is easy to understand in retrospect. The effects of electrical stimulation on stress incontinence are less well established. Pelvic floor exercises, however, do have a beneficial effect, and many women so treated feel further treatment with surgery is unnecessary. One of the problems here is to determine which patients may benefit from muscle reeducation and strengthening. DeLancey et al concluded that their technique of precontraction of the striated sphincter as a method to stop stress leakage was not effective in patients with no levator muscle function. An individual with a nonfunctional proximal sphincter would most likely receive no benefit from pelvic floor muscle reeducation, but data by specific type of stress incontinence does not exist.

Most clinicians who treat incontinence think pelvic floor exercises are unsuccessful in patients with severe intrinsic sphincter deficiency (ISD). The definition of ISD, however, is problematic. Gynecologists generally define ISD in terms of a low urethral pressure, and urologists define ISD by video studies showing an open proximal sphincter or a very low abdominal leak-point pressure. These are clearly different conditions. A patient with a very low urethral closing pressure related to a very weak striated sphincter may not respond to pelvic floor

Figure 10. An 11-Year-Old Girl With Severe Stress Incontinence Associated With an Open Bladder Neck

The patient is shown before (A) and after (B) a crossed sling procedure. She is continent but requires intermittent catheterization.
exercises or to electrical stimulation, and perhaps neither would a patient with a nonfunctional internal sphincter. Nevertheless, these are not identical conditions.

**Medication for Stress Incontinence**

No medications have been approved by the US Food and Drug Administration for the treatment of stress incontinence. Alpha receptor agonists, tricyclic antidepressants, and estrogen have all been used to treat the condition. Alpha receptor agonists do increase urethral closing pressure in the proximal urethra experimentally and clinically. Anecdotal reports have shown successful treatment of stress incontinence with these agents. Adverse effects are troublesome, and include hypertension, palpitations, tachycardia, dry mouth, anxiety, and tachyphylaxis. Thus, these agents should not be used in elderly patients—the patients in whom the agents were most often used.

There are also anecdotal reports of estrogen for the treatment stress incontinence. These agents are effective, but only in patients with long-term estrogen deficiency and a relatively immobile urethra with a very low leak-point pressure. Estrogen is more effective when combined with a tricyclic antidepressant. Controlled double-blind studies of estrogen replacement in postmenopausal women with stress incontinence have not shown any beneficial effect. This finding is expected because most kinds of stress incontinence would not likely respond to estrogen replacement.

Tricyclic antidepressants, such as imipramine, have direct inhibitory smooth muscle effects in vitro; in vivo, imipramine has weak anticholinergic effects. The agent positively affects poor bladder compliance and can be effective in enuretic children. Imipramine is also known to prolong norepinephrine reuptake centrally and peripherally. Norepinephrine release in the pelvic ganglia increases the pelvic nerve preganglionic activity required to effect a postganglionic contraction, and thus, proximal urethral relaxation and a detrusor contraction. Imipramine then seems to delay ganglionic transmission.

Imipramine, alone or in combination with estrogen, has been used to treat stress incontinence and is occasionally effective for that indication. No studies conclusively show the agent's effect on stress incontinence, and there have been no controlled studies of its efficacy. To treat detrusor hyperactivity, imipramine can be used in combination with standard anticholinergic agents with which it has an additive and perhaps synergistic effect. This is especially easy to determine in patients with spinal cord injuries who are maintained on intermittent catheterization protocols and develop reflex detrusor contractility and incontinence while taking medication, such as extended-release oxybutynin chloride, 30 mg daily. The addition of imipramine usually resolves the incontinence; however, even if the incontinence is not resolved, there is a measurable effect on bladder capacity.

**New Pharmaceutical Agents**

Duloxetine, a new antidepressant, has demonstrated in vivo effects on Onuf's nucleus. The agent increases motor neural activity in the nucleus, which in turn drives contractility of the striated urethral sphincter (see Figure 1 from Dr. Thor's article, page 678). This effect is due to prolonged reuptake of norepinephrine and serotonin in the nucleus. This agent would then be expected to facilitate bladder storage and strengthen the urethral mechanism, which resists abdominal pressure as an expulsive force. The effects on bladder storage activity have been demonstrated experimentally, but not yet clinically (Figure 11). Duloxetine is potentially a very useful agent that will likely have effects on the pelvic ganglia that are similar to the effects seen in Onuf's nucleus. If so, beneficial effects on urethral function in both the proximal and striated sphincter areas, as well as modulation of detrusor reflex contractility thresholds, would be expected.

Norton et al used duloxetine in a clinical study of 553 women with stress incontinence. Some of these women had symptoms of urge incontinence, but stress incontinence was the primary problem. None of the women had previous surgery and all had a positive cough stress test. The outcome was determined by reduction in incontinence episodes compared with placebo and by quality-of-life testing. The study compared 3 dose levels (20 mg, 40 mg, and 80 mg daily) with placebo. The group taking 80 mg daily had a significant improvement in quality of life and a 64% median reduction in incontinence episodes (Figure 12). Side effects were minimal, and were similar to those associated with other selective serotonin reuptake inhibitors and selective
norepinephrine reuptake inhibitors. Nausea was the most common side effect.

This study included a large group of patients and was performed with proper selection and a control group. The results are impressive, but it is difficult to determine how many patients were completely dry during the study. Nevertheless, this is the first controlled trial of an agent to treat stress incontinence. Duloxetine will likely be useful for both stress and urge incontinence, alone or in combination with other agents.

REFERENCES

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