Detrusor Instability and Low Compliance May Represent Different Levels of Disturbance in Peripheral Feedback Control of the Micturition Reflex

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Background. Detrusor instability is a major cause of urinary incontinence in females. Its cause is unknown. Diagnosis is made with cystometry. A phasic pressure rise during cystometry diagnoses the unstable detrusor, and a non-phasic pressure rise the stable "low-compliance" detrusor. The aim was to test the hypothesis that such cystometric findings may represent different levels of disturbance in peripheral feedback control of a prematurely activated, but otherwise normal micturition reflex. Of 169 neurologically normal female incontinent patients (mean age, 50; mean parity, 3) urodynamically tested, 40 had detrusor instability and 16 had low compliance. Digital support of bladder base tested the peripheral control mechanism, and hand-washing the central control mechanism. The data were applied to a non-linear feedback equation with one variable, X_{NEXT} = cX(1 - X), where c = central inhibition and X = fraction of possible nerve impulses in the micturition circuit.

Results. During filling, all 16 low-compliance patients had a bladder in the activated but stable closed state. Fourteen of the detrusor instability group could not suppress the micturition reflex and lost urine. During hand-washing, unexpectedly greater urine loss was noted in the low-compliance group (13 of 16) than in the detrusor instability group (24 of 40), χ^2 (P < 0.005). With digital stretching, urge symptoms disappeared within a few seconds in 18/20 patients, and detrusor instability was suppressed in six patients. Interpretation. The bladder has two stable states: open and closed. Closure is regulated by central and peripheral components. In the female, the peripheral component is controlled by the pelvic floor stretching the vagina to support the urine column. This prevents inappropriate activation of the micturition stretch receptors. In patients with low compliance, this peripheral control mechanism was sufficient to maintain the micturition reflex in an activated but stable closed state. In patients with detrusor instability, the micturition reflex could not be suppressed, swinging between the open and closed states. Conclusions. Demonstration of a peripheral musculoelastic control mechanism unlocks a new direction for management of female patients with non-neurological bladder instability. It is possible, using simple clinical methods based on digital vaginal stretching, to predict cure of instability by surgical tightening of the vagina and its supporting ligaments. Neurourol. Urodynam. 18:81–91, 1999.

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INTRODUCTION

Feedback control of micturition involving central and peripheral control mechanisms was demonstrated in the cat model by Barrington [1921]. Despite ever increasing complexity involving the influence of sympathetic and parasympathetic systems [de Groat and Saum, 1976], it is known that below a certain pressure threshold, activation of parasympathetic efferents is ineffective, and above which, parasympathetic discharge to the bladder can be evoked following electrical stimulation of afferents in the pelvic nerves [Morrison, 1990]. In patients without neurological damage, detrusor instability (DI) is a major cause of urine loss in the female [Abrams et al., 1988]. DI is diagnosed by detection of a phasic pressure rise during cystometry. The etiological basis of DI is unknown but is generally attributed to either a neurological defect or to some abnormality within the bladder itself [Ingelman-Sundberg, 1952; Lapides et al., 1960; de Groat and Kawatani, 1985; Malone-Lee, 1996]. Low compliance describes a stable non-phasic pressure rise also detected during cystometry. Its cause is also unknown.

More recently, it was proposed that bladder instability in the female may be mainly a prematurely activated micturition reflex [Petros and Ulmsten, 1993a,b, 1997a]. It was hypothesized that the mechanism for premature activation of the bladder base stretch receptors was the inability of a lax vaginal membrane to be stretched sufficiently by the pelvic floor muscles to support the column of urine. The critical ‘firing off’ pressure [Morrison, 1990] was therefore reached prematurely, at a lower bladder volume. Thus a vaginal membrane adequately stretched by pelvic floor contraction constituted a peripheral neurological feedback control mechanism, interacting with previously described central control mechanisms.

Cystometry gives a one-off resultant of all the factors creating detrusor pressure, central and peripheral. Hand-washing has the potential to interrupt one of these factors—central control of the micturition reflex.

The aim was to test the hypothesis that in the non-neurological patient, cystometric abnormalities may represent an abnormality of peripheral neurological feedback control of a normal micturition reflex. The mathematical feedback equation \( X_{\text{NEXT}} = cX(1 - X) \) was used to correlate observed urodynamic patterns with mathematical predictions.

MATERIALS AND METHODS

One hundred and sixty-nine neurologically normal women with urinary incontinence were urodynamically tested with supine fast-fill cystometry (100 ml/min) using methylene blue–colored saline at room temperature. Mean age was 50 years (range, 35–71) and mean parity was three. No patient was under any drug or other treatment at the time of testing. Hysterectomy had been performed in 10% of these women, and 16% had undergone vaginal repair or incontinence surgery. Gaeltec microtransducers, standardized before use, were inserted into the bladder and posterior vaginal fornix. A dry pad was applied to the perineum, and the now standing

\(^{1}\)Bladder instability, in contradistinction to DI is not defined by the ICS, but by convention, it describes the involuntary loss of urine due to uninhibited contraction of the detrusor.
patient washed her hands in running water for 60 sec. ICS standards and recommendations were followed, except where otherwise specified.

Urine loss on hand-washing provocation was assigned as the gold standard, on the basis that urine loss is the end point of an unstable bladder. For the purposes of this study, a 15-cm rise in detrusor pressure was taken as the cut-off point for diagnosis of DI.

On a separate occasion, 20 patients with both urge incontinence and bladder instability were tested with a full bladder in the supine position. The vagina in the area of the bladder neck was, in turn, supported by one finger, gently stretched forward, then markedly upward toward the superior surface of pubic symphysis. The time taken for urge symptoms to disappear and reappear was recorded. This was repeated three times, with and without double Gaeltec microtransducers in the midurethra and bladder.

Mathematical testing of feedback control of the micturition reflex was carried out by applying known neurological functions to the classical feedback equation

\[ X_{\text{NEXT}} = cX(1 - X), \]

where \( c \) is a variable representing the degree of inhibition of the micturition reflex, both peripheral and central and \( X \) = the fraction of maximum possible neurological impulses in the micturition circuit. \( X \) was given the same initial value (0.5) for all iterations, equivalent to the afferent signals from a moderately full bladder.

RESULTS

**Interpretation According to ICS Definitions**

The results are summarized in Table I. In 40 patients, there was a phasic detrusor pressure rise\(^2\) to 15 cm H\(_2\)O during filling cystometry. Of these, 24 (60\%) lost urine\(^2\) after hand-washing provocation, and 14 (35\%) during filling. Sixteen patients with a low-compliance bladder,\(^3\) did not lose any urine during filling cystometry, but 13 (81\%) of these lost urine on provocation with hand-washing test that followed. Using the \( \chi^2 \) test, \( \chi^2 = 23.59 \) with 1 df \((P < 0.005)\), the difference between the DI and low-compliance groups was highly significant. Mean volume (cystometric capacity) was 448 ml (range, 191–545). For the patients with low compliance, the mean volume was 459 ml (range, 381–500). There was no history of neurological disease, irradiation therapy or infection in either group.

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\(^2\)With a urodynamic pattern consistent with the ICS description for DI.

\(^3\)With a urodynamic pattern consistent with the ICS description for a low compliance bladder.
Demonstration of a Peripheral Control Mechanism

The only reliable and reproducible finding was abatement of urge symptoms on digital support of the vagina and reappearance of urge on withdrawing that support. In 18 of the 20 patients, the urge disappeared between 3 and 8 sec (mean, 5.4) and returned on removal of that support in a comparable period of time. Stretching also reliably abolished the urge symptoms but often gave quite different results within the same patient. In one patient, return of urge symptoms was delayed 30 sec on release of vaginal stretching but only 4 sec on withdrawing support of bladder base. Over-stretching the vagina upward consistently worsened the urgency. The cystometric patterns fluctuated considerably with digital stretching, indicating a very sensitive peripheral control mechanism. In six of the 20 patients, it was possible, with some effort, to demonstrate temporary abatement of the instability pattern (Fig. 1).

Mathematical Testing of Feedback Control of the Micturition Reflex

Normal patient. With reference to Fig. 2, all control systems are assumed to be functioning perfectly, stimulation of N is controlled, and the equation is iterated with a low c value of 0.2.

First iteration. \( X_{\text{NEXT}} = 0.5 \times 0.2 \ (1-0.5) = 0.05 \).
Second iteration. \( X_{\text{NEXT}} = 0.05 \times 0.2 \ (1-0.05) = 0.009 \).
Third iteration. \( X_{\text{NEXT}} = 0.019 \times 0.2 \ (1-0.019) = 0.0037 \). X becomes virtually extinct by the third iteration (Fig. 3, retention).

Low-Compliance Group

On iteration of the equation. As bladder contraction is an accepted cause of low compliance [Abrams et al., 1988] and no urine was lost during filling, c needed a value that reflected an activated but stable closed state (Fig. 3). The equation was iterated with a c value of 2.0 to reflect a constant X value.

First iteration. \( X_{\text{NEXT}} = 0.5 \times 2 \ (1-0.5) = 0.5 \).
Second iteration. \( X_{\text{NEXT}} = 0.5 \times 2 \ (1-0.5) = 0.5 \).
Third iteration. \( X_{\text{NEXT}} = 0.5 \times 2 \ (1-0.5) = 0.5 \). X remains at 0.5, a steady state at the third iteration (Fig. 3, stable closed).

Bladder Instability Group

On iteration of the equation. X (Fig. 2) is clearly much less controlled and more numerous in this group. As c must be in the region of >3.0 [May, 1976] to reflect fluctuation between the unstable open and unstable closed states, the equation was iterated with a c value of 3.6.

First iteration. \( X_{\text{NEXT}} = 0.5 \times 3.6 \ (1-0.5) = 0.9 \).
Second iteration. \( X_{\text{NEXT}} = 0.9 \times 3.6(1-0.9) = 0.324 \).
Third iteration. \( X_{\text{NEXT}} = 0.324 \times 3.6 \ (1-0.324) = 0.788 \).
Fourth iteration. \( X_{\text{NEXT}} = 0.788 \times 3.6 \ (1-0.788) = 0.601 \).
Fifth iteration. \( X_{\text{NEXT}} = 0.601 \times 3.6 \ (1-0.601) = 0.864 \).
Sixth iteration. \( X_{\text{NEXT}} = 0.864 \times 3.6 \ (1-0.136) = 0.423 \). X is clearly swinging between two states (Fig. 3, unstable open and unstable closed).
DISCUSSION

Feedback control exists in all natural systems and can be expressed by simple mathematical formulae [May, 1976]. In this context, the bladder has only two stable states, open and closed. The unstable bladder by definition has difficulty in maintaining the closed state during filling and so swings inappropriately into the open state.

It is difficult to explain hand-washing urine loss with either detrusor muscle...
abnormality or neurologically based theories. A local lesion cannot be influenced by
hand-washing. A neurological lesion causes bladder instability precisely because it is
not subject to the body’s neurological control systems.

Selective stimulations and ablations in the M and L regions of pontine tegmen-
tum [Griffiths et al., 1990] caused many of the manifestations depicted in Figs. 2 and
3: urethral striated sphincter contraction (Cm, Cu), detrusor overactivity (Od) (Fig. 2)
and urinary retention (Fig. 3). Extrapolating the findings of Griffiths et al., the central
facilitatory and inhibitory systems present in all parts of the brain [Feneley and
Harrison, 1992] act as Boolean gatekeepers, opening or closing the gates (Fig. 2) for the neurological impulses, X, as they pass up and down the central nervous system, depending on whether the micturition system is in the open or closed state.

In the normal patient, peripheral control of micturition by voluntary pelvic floor contraction was described by Denny-Brown and Robertson [1933], but they could not explain the mechanism for this. The data appear to sustain a hypothesis for a sensitive peripheral musculoelastic neurological control mechanism: as the bladder fills, stretch and volume receptors (N, Fig. 2) are stimulated, and the urethral pressure reflexly rises due to a simultaneous "extrinsic muscle contraction" [Lose, 1990] (Cm, Fig. 2); this stretches the vaginal membrane to support the urine column. The increased vaginal tension prevents activation of the stretch receptors N (Fig. 2) at the bladder base. Muscle-activated vaginal stretching during "holding on" (Cm, Fig. 2) was demonstrated radiologically [Petros and Ulmsten, 1997b]. With reference to Fig. 3, with each succeeding iteration of the positive feedback circuit, the number of impulses, X, rapidly diminishes. The bladder relaxes, and the system returns to the closed retention state.

In the low compliance group, as no urine was lost during filling, we can deduce that the micturition reflex was in a state of controlled activation, and the detrusor was contracting against a urethra closed by striated muscle contraction. The broken line in Fig. 3 denotes each point of the iterated equation with only one variable, the central

Fig. 3. Pictorial representation of iteration of the feedback formula $X_{\text{next}} = cX(1 - X)$. This graph is directly adapted from works on chaos theory. $X_{\text{next}}$ is equated to detrusor pressure. Normal suppression of the micturition reflex $c$ is low, the patient develops retention. Low compliance (unbroken lines). $c$ is in the stable closed range, and the micturition reflex, although activated, remains controlled. Unstable bladder. Because of the large number of afferent impulses X, c rises beyond a factor of 3. The system becomes unstable, and the micturition reflex swings between the unstable open and unstable closed states. As $c$ continues to increase, the system splits into larger fractions (4, 8, 16, etc.) and enters the chaotic zone.
mechanism. The different slope of the low compliance graph (unbroken lines) is attributed to the influence of an additional variable, the peripheral neurological control mechanism. This becomes exhausted as the bifurcation into unstable open and unstable closed is reached. A comparable instability pattern commencing at the peak of low compliance is not an uncommon observation during cystometric testing [Stephenson and Wein, 1984]. With reference to Fig. 3, $X_{\text{NEXT}}$ is equated to detrusor pressure, which is created by the number of nerve impulses, $X$, acting on the detrusor and the amount of urethral resistance. The transition from the closed to open mode (urine loss in 13 of 16 patients) on hand-washing can only be explained by sudden interruption of the central and peripheral control mechanisms, allowing uninhibited passage of $X$ (Fig. 2). This relaxed the urethra (Ou), further stimulated the detrusor (Od), and activated Om, to stretch open the urethra, as in normal micturition [Tangho, 1978].

The results suggest that during filling, there is a lower level of micturition reflex control in the DI group than in the low-compliance group. $N$ (Fig. 2) was stimulated during filling, producing $X$ in sufficient numbers to overcome central inhibition and to cause 14 patients to lose urine. When $X$ was lower (as in the second, fourth, and sixth iterations), it is likely that the peripheral control mechanism was sufficiently activated to maintain the system in the closed state, controlling urine loss. When $X$ was high, it was more likely that urine would be lost. As $c$ continues to rise beyond 3 in the iteration formula (Fig. 3), the system splits into 2, 4, 8, 16, 32, etc., modes and proceeds into the chaotic zone [May, 1976]. This may explain why some patients with very severe DI have apparently random periods of prolonged or intermittent irregular urine loss, and some short periods of complete dryness. Urodynamically, the struggle between the closed and open modes is suggested by the bell-shaped bladder pressure variations (Fig. 1), characteristic of both DI and a classical feedback system.

Given that the micturition reflex was not fully controlled in the DI group during filling, it can be assumed that all the body’s inhibitory mechanisms were fully activated. This potentially cut down the lag time necessary for the brain to bring the micturition reflex back under control after interruption of central control by hand-washing. That urine was lost in only an additional 10 of 26 patients during hand-washing appears to sustain this hypothesis.

### Application of the Feedback Equation to Other Conditions Causing DI

Other abnormal bladder conditions can be expressed with the feedback equation. Bladder inflammation or tumor may stimulate $N$ (Fig. 2), causing excess afferent $X$ impulses (urgency symptoms). Multiple sclerosis or other lesions may interfere with $c$ at all levels in the brain and spinal cord, causing uninhibited passage of $X$ through the brain and urine loss. Spinal cord transection may block both afferent (Oa) and efferent $X$ impulses (Oe), causing neurogenic retention.

### Bladder Instability Is a Complex Urodynamic Process, Not a Singular Condition

The unstable bladder cannot be summarized in a single reading DI, taken at a singular point in time. The control mechanism in patients afflicted with an unstable bladder is a complex, non-linear dynamic process that extends over the full 24 hr of
their day. The cycling of the detrusor and urethral pressures consistently noted in urodynamic testing represents a struggle for control between the open and closed states. The urodynamic manifestations of this struggle fits very well into the conclusions of this work, that bladder instability represents an abnormality in a complex micturition feedback control system.

Some of the urodynamic components of a prematurely activated micturition reflex were reported previously [Petros and Ulmsten, 1993b]. It was demonstrated that the urodynamic events occurring in non-neurological bladder instability are similar to those seen in normal micturition [Tanagho, 1978], encompassing four potential passes of the micturition reflex. With reference to Fig. 2 and Table II, these are sensory urgency (Oa, n = 109), urethral relaxation (Ou, n = 91), detrusor contraction (Od, n = 56), and urine loss (n = 52), each separated by a time delay of a few seconds. The peripheral and central control mechanisms have the capacity to alter each particular manifestation of the reflex.

Peripheral Control Is Regulated by Striated Muscle

The anatomical components concerned with micturition in the female comprise not only the traditional smooth muscle/neurological circuits of Barrington, but a recently described external mechanism that assists opening and closure of the outflow tract [Petros and Ulmsten, 1997b]. This is a musculoelastic mechanism. During closure, forward, backward, and downward forces combine to stretch the vagina tightly against its supporting ligaments, much like the membrane of a drum. The stretched vagina supports the urine column, preventing activation of the stretch receptors at bladder base. In this experiment, the vagina was digitally stretched to mimic stretching by the pelvic muscles in the normal woman.

During vaginal support (Fig. 1). There is evidence of cycling in the urethral pressure without sensory urgency. This can be interpreted as follows: the central inhibitory mechanism C (Fig. 2) acts above the pons to suppress consciousness of Oa. Nevertheless, the impulses pass through the pons in sufficient numbers to activate Ou (Fig. 2), causing a cyclic fall and rise in urethral pressure (urethral instability).

On removing vaginal support to the stretch receptors, the afferents (Oa) increase to the point where the central mechanism cannot inhibit the impulses (X), and the cortex interprets this as sensory urgency. Furthermore, the micturition reflex has strengthened to the point where the detrusor pressure now starts to rise cyclically, with a typical instability pattern.

Impact on ICS Definitions and Descriptions

In the above experimental context, DI is interpreted as the second urodynamic limb of a prematurely activated micturition reflex. This, in turn, may be caused by

| TABLE II. Manifestations of the Micturition Reflex on Hand-washing in 115 Patients with a History of Bladder Instability [Petros and Ulmsten, 1993b] |
| --- | --- |
| Manifestation | Percentage of total (n = 115) |
| Sensory urgency | 93 |
| Urethral relaxation | 79 |
| Detrusor contraction | 49 |
| Urine loss | 45 |
vaginal laxity that prevents the muscle forces Cm from stretching the vagina sufficiently to prevent production of afferent impulses X (Fig. 2). Interpreting the concept of DI in this way also removes the inconsistencies associated with DI as an index of pathogenicity. It is perfectly reasonable for DI to be present in 70% of normal women [van Doorn et al., 1992].

Impact of the Peripheral Micturition Control Mechanisms on Treatment Options

The data demonstrate that an adequately tight vaginal membrane can abolish abnormal urge symptoms and control DI.

Surgical Treatment

The technique of digital support constitutes a virtual operation. It can be used routinely as a pre-operative test and gives a rationale for the virtual absence of de novo urgency with tension-free vaginal repairs to the anterior, middle, and posterior compartments of the vagina [Petros, 1997]. These minimally invasive operations predictably cure manifestations of bladder instability (frequency, urgency, and nocturia) in up to 85% of patients. It was demonstrated that excessive stretching of the membrane from below can cause de novo urgency. This explains the frequent observation of de novo onset of urgency after bladder neck elevation surgery. It follows that every effort should be made during surgery to avoid anatomical distortion and change of vaginal geometry.

Nonsurgical Treatment

Pelvic floor training. Strengthening the pelvic floor muscles would improve the ability of Cm (Fig. 2) to stretch the vaginal membrane and decrease X and therefore Oa.

Intravaginal devices. These may work by stretching the vaginal membrane. Thyssen et al. [1997] demonstrated reduced urgency with an intravaginal device.

REFERENCES

Peripheral Control of Micturition