

# Role of the Vesicoureteric Junction and Unstable Bladder in Vesicoureteric Reflux: Value of Bethanechol Chloride-aided Voiding Cystourethrography in Detecting Occult Reflux

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**Summary.** 1. The embryogenesis and anatomy of the vesicoureteric junction (VUJ) were reviewed and the role of the periureteric sheath was emphasized.

2. An unstable bladder was found to be associated with half of the cases of "primary" reflux. It was suggested that an unstable bladder somehow influences the integrity of the VUJ to cause reflux and/or its aggravation in the presence of an immature VUJ. When reflux is associated with an unstable bladder, its spontaneous cure is highly likely even if the reflux is severe. Conversely, unstable bladder is associated with a high risk of the failure or development of complications of antireflux surgery.

3. Our experience in 23 patients with the detection of occult reflux by bethanechol-aided VCU was presented. This appears to be a sensitive method for detecting occult reflux, as emphasized by our recent ureteroneocystostomy results in which postoperative contralateral reflux was hardly seen after unilateral surgery.

4. In contrast, the sensitivity of RI-VCU for detecting occult reflux seems to be low in both control and bethanechol-aided studies.

## EMBRYOGENESIS OF THE VESICoureTERIC JUNCTION (VUJ)

The embryogenesis of the VUJ is reviewed on the basis of the data provided by Matsuno.<sup>1)</sup> Differentiation of the ureteric muscle begins from the upper ureter at the 12th week and the muscle bundles grow to run in a spiral fashion. The purely longitudinal intramural ureteric muscle differentiates much later in gestation and begins to form bundles in the 17th week. Intra-luminal urinary flow appears to precede the process of myogenesis. The deep periureteric sheath and the trigonal muscle differentiate at a similar pace to the intramural ureteric muscle, while the detrusor muscle begins to differentiate from the apical dome of the bladder at the 7th week. A distinct

superficial periureteric sheath, which appears as a caudal extension of the detrusor muscle, is also seen from around the 12th week. The urethral striated muscle first appears in the 8th week and starts to show distinct striation by the 12th week, while the urethral smooth muscle appears in the 12th week and develops inside the striated muscle. Thus, VUJ is believed to form at a time when the urethral sphincter is already functioning.

## ANATOMY OF THE VUJ

Elbadawi stated that the VUJ is comprised of intravesical and juxtavesical ureteric portions surrounded by the outer deep and superficial periureteric sheath.<sup>2)</sup> The so-called Waldeyer's space is a distinct embryologic and anatomical space separating the superficial and deep periureteric sheaths at the VUJ. The normal function of the VUJ is to allow the smooth entry of urine into the bladder while preventing reflux. For this purpose, it is essential that all 3 components of the VUJ work together in an intimate and mutual fashion. Although further morphological and functional investigations are still required, we concur with Elbadawi that the ureteric sheath has a significant role in the function of the VUJ.

## ETIOLOGY AND MECHANISM OF REFLUX

The low pressure normally present in the resting bladder (8 to 15 mmHg) is sufficient to passively compress the roof of the intravesical ureter against the underlying detrusor and so prevent reflux. Peristalsis produces a pressure of between 20 and 35 mmHg in the extravesical ureter, which is sufficient to propel a bolus of urine rapidly and forcefully into the bladder with an abrupt spurt. The normal compli-

ance and elasticity of the intravesical ureter are crucial to physiological VUJ function and inflammation of the overlying bladder mucosa may affect the competence of the VUJ.

Two critical factors preventing reflux in humans are the length of the intravesical ureter relative to its diameter and the intrinsic longitudinal muscle coat of the submucosal ureter that inserts into the superficial trigone.<sup>3)</sup> Lyon et al.<sup>4)</sup> has reported that these factors are reflected in the appearance of the ureteric orifice. Ambrose and Nicolson<sup>5)</sup> as well as Stephens and Lenaghan<sup>6)</sup> have noted that as this orifice becomes more abnormal in appearance, it usually occupies a more lateral position (ureteral ectopia lateralis) and the intravesical ureter becomes progressively shorter. As a result, the more lateral the orifice, the more likely it is that reflux will occur. Recent work using color doppler imaging has shown that the distance of the ureteric orifice from the midline of the bladder correlates with reflux, since the mean distance in the reflux group was  $10.25 \text{ mm} \pm 2.40 \text{ [SD]}$  ( $p=0.004$ ).<sup>7)</sup> The length of the submucosal ureter when the bladder is full appears to be the single most useful guideline for estimating the probability that reflux will subside spontaneously.<sup>8)</sup>

Several other causes of reflux also exist. For example, lack of an adequate detrusor buttress under the intravesical ureter (paraureteral diverticulum) may result in reflux.<sup>9,10)</sup> If the VJU has only a marginal degree of competence intrinsically, infection may readily reduce the compliance of the roof of the intravesical ureter and permit reflux to occur. An ectopic ureter, an abnormally high intravesical pressure, and various iatrogenic causes can also lead to reflux.

## UNSTABLE BLADDER (UNINHIBITED BLADDER )

Koyanagi et al.<sup>11)</sup> first reported that reflux occurs synchronously with uninhibited contraction of the bladder, and that reflux is blocked by anticholinergic agents and aggravated by cholinergic drugs. The intrinsic neuromuscular antireflux mechanism of the VUJ appears to be affected in some unknown manners in the unstable bladder. The association of reflux with an unstable bladder was also reported by Koff et al.<sup>12)</sup> and Allen,<sup>13)</sup> while Terashima<sup>14)</sup> shed further light on their relationship. An unstable bladder is found in half of the patients with "primary" reflux and is more frequent in girls. The age distribution of "primary" reflux has 2 peaks, one of which is between

3 to 5 years and coincides with the age when an unstable bladder becomes symptomatic. He also noted that when the grade of reflux was compared among girls aged 3 to 7 years, it was more severe in those with an unstable bladder than in those with a normal bladder. In addition, Terashima stated that the grade of reflux does not correlate with the shape of the ureteric orifice in children with an unstable bladder, and that reflux in such children is likely to resolve spontaneously, even when it is of a high grade (III to IV, International Reflux Study Committee, 1981). In the recent study reported by Kakizaki et al.<sup>15)</sup> the overall rate of spontaneous resolution of reflux was similar in children with and without an unstable bladder, but the spontaneous resolution of high grade reflux was seen only in the children with an unstable bladder (Table 1). This suggests that an unstable bladder somehow influences the antireflux mechanism of the VUJ to cause reflux and/or its aggravation in the presence of an immature VUJ. Possible mechanisms involved included the excessively frequent elevation of intravesical pressure,<sup>12)</sup> detrusor-sphincter dyssynergia,<sup>13)</sup> and neuromuscular insufficiency of the VUJ itself.<sup>16)</sup>

It must be noted that antireflux surgery is particularly likely to result in failure or complications (especially diverticulum formation ) in patients with an unstable bladder.<sup>17)</sup> In addition, if antireflux surgery is performed, control of the unstable bladder is also mandatory. Treatment of an unstable bladder seems to be effective in preventing renal scarring and its progression.<sup>15)</sup>

To determine the chance of spontaneous resolution of reflux, the use of simultaneous cystometry and radionuclide ( $99 \text{ m Tc-Sn}$  colloid) voiding cystourethrography (RI-VCU) has been under trial at our hospital. It appears so far that reflux which occurs synchronously with uninhibited contraction of the bladder has a higher possibility of spontaneous resolution than that which does not do so.

**Table 1.** Rate of spontaneous resolution of reflux

Grade of VUR	Unstable Bladder	
	Positive	Negative
I	6/13(46.2%)	5/ 6(83.3%)
II	8/25(32.0%)	4/11(36.4%)
III	4/21(19.0%)	0/ 5 (0%)
IV	7/50(14.0%)	0/20 (0%)
V	0/14 (0%)	0/ 8 (0%)
Total	25/123(20.0%)	9/50(18.0%)

## DIAGNOSIS OF REFLUX

It has been common to perform voiding cystourethrography (VCU) in patients with a history of recurrent urinary tract infection. Although the technique of contrast-enhanced VCU has been standardized by eliminating many of the variables that can affect the result,<sup>18)</sup> problems are still posed by the patients with no reflux on conventional VCU in whom reflux is strongly suspected from the history, urographic changes, and/or cystoscopic findings.

The importance of detecting such elusive reflux has been stressed by Kogan et al.,<sup>19)</sup> who used isotope cystography for this purpose. However, although this sophisticated method has several advantages, it requires scanning apparatus that are not uniformly available. Through our experience of investigating reflux associated with unstable bladder, we surmised that bethanechol chloride-aided VCU might be helpful for detecting such occult reflux. Our experience with 23 cases of occult reflux investigated in this manner is summarized next.

### Materials and Methods

The 11 male and 12 female patients ranged from 1 to 28 years old, with 17 patients being 13 years old or less, were treated from January 1982 to June 1991. All patients had recurrent pyelonephritis. Routine diagnostic evaluations included intravenous pyelography (IVP), VCU, cystometry, and cystourethroscopy. The IVP films showed subtle pyelonephritic changes, such as mild renal scarring and calyceal blunting and/or deformity, as well as pyeloureteric folding (striation sign, Fig. 1) or ureteric dilatation, kinking or tortuosity. In some cases, a bladder diverticulum suggestive of reflux was noted. Cystometry was performed by the method of Lapedes, and the presence or absence of uninhibited detrusor contraction and super-sensitivity to bethanechol chloride were determined.<sup>20)</sup> At cystourethroscopy, after routine evaluation of the urethra and bladder outlet, the ureteric orifice configuration, position, and contractile force were examined carefully to assess the competence of the VUJ. When the initial routine contrast-enhanced VCU failed to document reflux (or showed only unilateral reflux) in patients strongly suspected of having it from the clinical history, IVP findings, and/or cystoscopic changes, then bethanechol chloride-aided VCU was performed. The dosage of bethanechol was 2.5 mg in adults and 0.04 mg/kg in children. Fifteen to 30 min after the subcutaneous administration of bethanechol, VCU was repeated in the same manner



Fig. 1. An example of the striation sign.

Table 2. Clinical profile of the 23 patients with occult reflux

Cause of Reflux	Children	Adults	Total
Primary Reflux			
(with Unstable Bladder)	11(4)*	0	11
(without Unstable Bladder)	3(2)*	5	8
Neurogenic Bladder	3	1	4
Total	17(6)*	6	23

\*Number of the patients with anterior urethral ring.

as in the routine study. In 8 patients, RI-VCU and/or bethanechol-aided RI-VCU was also performed.

### Results

The clinical profiles of the 23 patients are shown in Table 2. The grade of occult reflux was as follows: I, 2; II, 12; III, 8; IV, 2. These patients were divided into 2 groups. Group 1 included 9 patients (10 ureters) who did not have reflux on either side at any time in the conventional studies. In 8 of them, frank new reflux was induced unilaterally during bethanechol-aided

VCU, while 1 has frank new reflux bilaterally. Group 2 included 14 patients (14 ureters) who has only unilateral reflux in the conventional VCU. In this group with seemingly unilateral reflux, frank new reflux was induced on the contralateral side along with augmentation of the pre-existing reflux in all patients except 1. IVP abnormalities were not present in 8 kidneys and ureters, and the grade of reflux induced in these 8 ureters was milder than in the other 16. When the IVP findings were compared with the results of bethanechol-aided VCU in a larger group (including the other 14 patients who did not show occult reflux), positive and negative predictive value of this test was 66.7% and 85.7%, respectively (Table 3). Detection of occult reflux by RI-VCU was poor in both control and bethanechol-aided studies (Table 4). Of these 23 patients with occult reflux, 4 have neurogenic bladders, 10 underwent ureteroneocystostomy, and the remaining 9 are being followed up on anticholinergic therapy and/or transurethral resection of the urethral ring. Four of this last group have shown spontaneous resolution of their reflux.

#### Case Report

A 28-year-old nurse was referred to us for correction of right-sided reflux (Fig. 2) that was detected during diagnostic evaluation of recurrent urinary tract infection. IVP showed bilateral duplex kidneys with some pyelonephritic changes of the lower kidneys (Fig. 3). At cystoscopy, the duplex system was found to be complete on both sides. The left-sided ureteric orifices were juxtaposed with each other and appeared to be normal. On the right side, the orifice of the



**Fig. 2.** Film from a standard VCU procedure in a 28-year-old woman (case report).

**Table 3.** Value of bethanechol-aided VCU for detecting occult reflux

		IVP Findings		Total
		Suspected	Not suspected	
Bethanechol-Aided VCU				
	Reflux Positive	16	8	24
	Reflux Negative	3	18	21
	Total	19	26	45

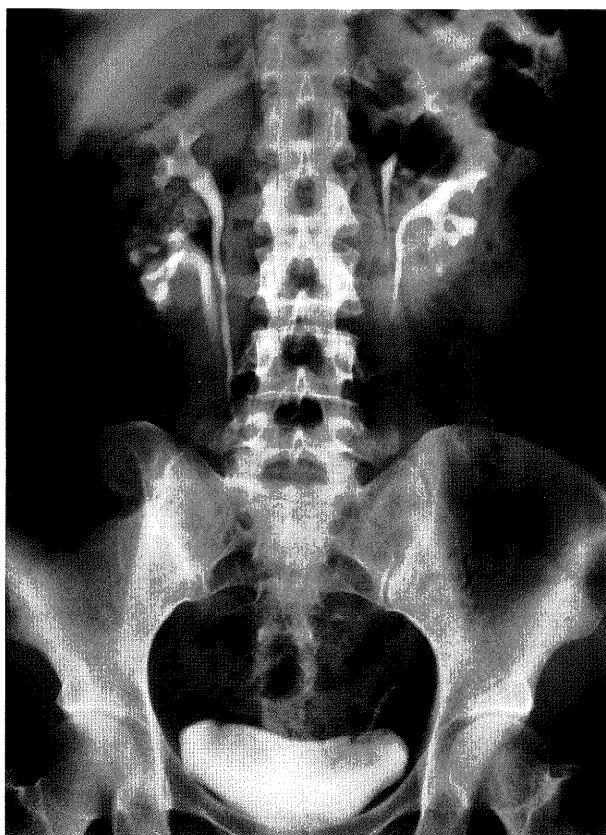
**Table 4.** Detection of occult reflux by RI-VCU

RI-VCU	Children	Adults	Total
Control	1/2	0/4	1/6(16.7%)
Bethanechol-Aided	1/1	1/5	2/6(33.3%)
Total	2/3	1/9	3/12(25.0%)

lower kidney of the duplex system was somewhat gaping, contracted poorly, and was located slightly cranio-lateral to the normal-appearing orifice of upper kidney. The bladder was normal on cystometry. Before a planned right ureteroneocystostomy, bethanechol-aided VCU was performed to rule out possible reflux on the left side. After bethanechol stimulation, the seemingly unilateral reflux was found to actually be bilateral, with frank new grade II reflux to the left lower kidney and aggravation of the pre-existing reflux to the right lower kidney from grade II to III (Fig. 4). Bethanechol-aided RI-VCU also showed reflux on the left side (Fig. 5). Subsequently, bilateral reimplantation of both duplex systems was successful.

#### APPLICATION TO UNILATERAL URETERONEOCYSTOSTOMY

The value of detecting occult reflux is best understood in the context of unilateral ureteroneocystos-



**Fig. 3.** IVP showing bilateral duplex kidneys.



**Fig. 4.** Bethanechol-aided VCU shows bilateral reflux to the lower kidneys of each duplex system.

tomy. Since the adoption of bethanechol-aided VCU (1982), determination of the correct therapeutic option has become easier. Only 1/33 patients who underwent unilateral ureteroneocystostomy showed postoperative contralateral reflux. This patient has such massive reflux (grade V) that bethanechol stimulation was apparently ineffective in demonstrating the contralateral abnormality. However, this is still an improvement on our previous experience, in which contralateral reflux was noted in 4/37 (11%) patients after a unilateral operation. Despite a similar incidence reported by other investigators, the current consensus seems to be that prophylactic bilateral surgery is too vigorous an option, since the rectified rate of treatment failure is reportedly less than 6%.<sup>21-24)</sup> A randomized prospective study appears to be warranted to determine whether bethanechol-aided VUC could lower this treatment failure rate to near zero.

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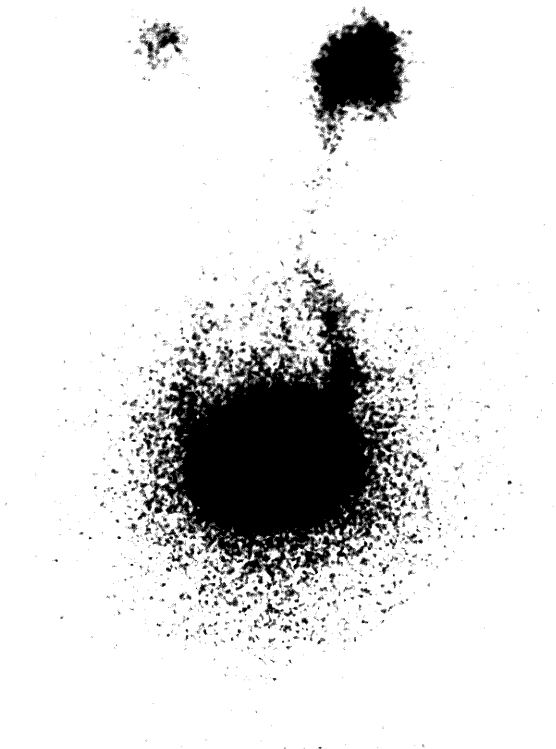


Fig. 5. Bethanechol-aided RI-VCU shows bilateral reflux.

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