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Provisional chapter

Functional Anatomy of the Vesicoureteric Junction: Implication on the Management of VUR/ UTI

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Additional information is available at the end of the chapter

1. Introduction

The detailed anatomy and the nature of the anti-reflux mechanism of the human vesicoureteric junction (VUJ) are still unknown and controversial. VUJ is traditionally thought to be a passive valve; however, recently there is increasing evidence to support the theory of a functional active neuro-muscular sphincter present at the VUJ. In this chapter, we sought to describe different forms of ureteric jet that can be visualized in both grey-scale and color Doppler ultrasound. We are going to summarize the results of a number of original studies based on large number of human subjects. From the observations of these studies, we propose the dual mode of action and an active functional sphincter at the VUJ.

2. Anatomy of Vesicoureteric Junction (VUJ)

The VUJ can be recognized as a small convex, bulging-out structure on the mucosal surface of the urinary bladder. The function of the VUJ is to allow unhindered antegrade passage of urine bolus from ureter into the bladder while prevent the reflux of urine into the ureter from the bladder, during both normal bladder filling and voiding.

2.1. Histology and histochemical study of the VUJ

The anatomical studies of human VUJ were first started around year 1800. To date, the mechanism of how VUJ functions is still poorly understood and controversies exist among different theories.

The generally accepted anatomical presentation of the VUJ is illustrated in a diagrammatic form as follows: (Fig 1).

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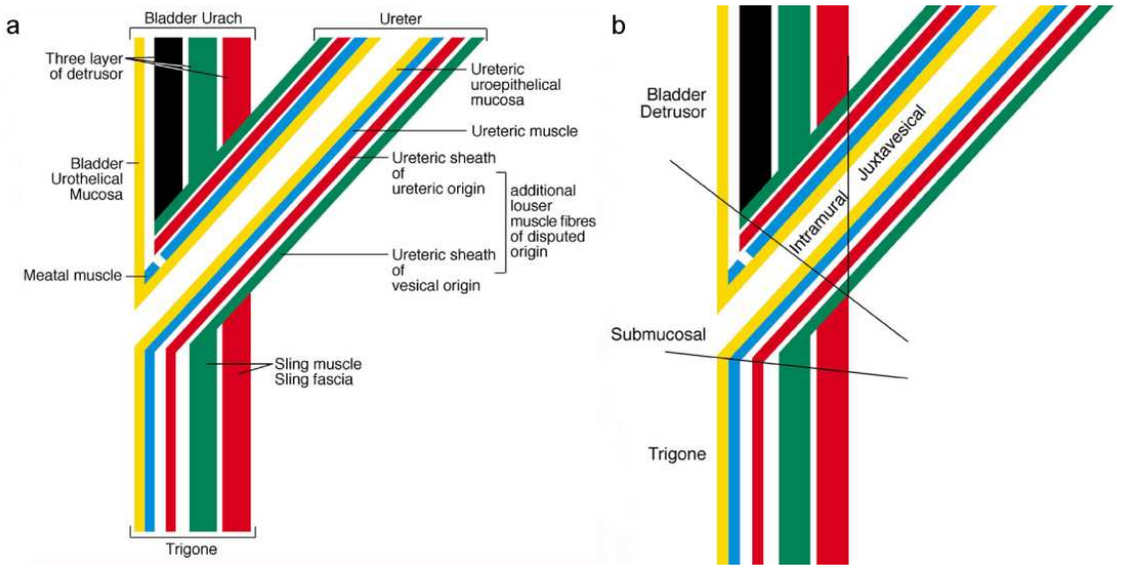


Figure 1. Schematic diagram of the anatomical layers in (a) ureteric and urinary bladder wall and (b) VUJ in human

2.1.1. Histology of the VUJ

VUJ involves three anatomical components: the ureteric wall, urinary bladder wall and the ureteric sheath. They are described as follows:

Three layers of ureteric and urinary bladder wall (Fig. 1a)

The wall of the ureter and urinary bladder consists of three layers: the outer adventitia, middle muscular layer and the inner mucosal layer.

The adventitia is the outermost layer composes of mainly fibrous connective tissues.

The muscular layer of the ureter consists of non-striated muscle which is uniform in thickness. When approaching the VUJ the muscle coat composes predominately longitudinally orientated muscle bundles (Gearhart et al., 1993). The ureteric muscle then fans out with fibers splitting around the orifice before becoming part of the superficial trigone. Some of the fibers extend to the urethra thereby creating connection between the urethra and the ureter (Bell's muscle) (Gearhart et al., 1993; Hutch et al., 1961; Juskiewenski et al., 1984; Noordzij & Dabhoiwala, 1993; Roshani et al., 1996; Stephens & Lenaghan, 1962; Tanagho & Pugh, 1963; Tanagho et al.,1968).

The muscular layer of the urinary bladder is also known as the detrusor muscle. It is composed of interlacing large bundles of non-striated muscle cell in a criss-cross arrangement. Different regions of the bladder have different muscle arrangements. There are anastomoses between different muscles in the form of complex reticular or netlike muscular meshwork. Four regions can be identified: the detrusor muscle proper, trigone, VUJ and the bladder neck.

The detrusor muscle proper consists of three ill-defined layers: an inner longitudinally orientated layer of muscle bundles, a substantial middle circular layer and an outer longitudinally orientated layer (Hunter, 1954; Uhlenhuth et al., 1953). The muscle fibers of the

internal layer originate behind the ureteric orifice. The outer longitudinal bundles continue with the capsules of adjacent pelvic organs and the pubovesical ligament (Noordzij & Dabhoiwala, 1993). Three muscle layers of the detrusor form the superior part or roof of the VUJ. The inferior part or the floor is formed by only two layers of detrusor. They are the outer longitudinal layer (sling muscle) and the inner circular layer (sling fascia). They play an important role in the physiology of the VUJ by providing a firm support to the structures of the intravesical ureter and preventing reflux. They also form part of the trigone (Hutch et al., 1961; Tanagho & Pugh, 1963).

Finally the innermost mucosal layer of the ureter and the urinary bladder consists of a transitional epithelium (also known as the urothelium) and the lamina propria, the underlying supportive layer, consists of loose connective tissue. The urothelium is usually extensively folded, giving the ureteric lumen a satellite outline in histological specimens. However, this satellite pattern is not readily seen with ultrasound and may reflect a different process of collapse of the urothelium in vivo (Dyson, 1995; Motola et al., 1988; Tanagho, 2000).

Ureteric hiatus

The gap in the bladder wall through which the ureter passes is known as the ureteric hiatus. There are two gaps: outer and the inner hiatus. The outer hiatus is slightly higher and lateral to the inner hiatus. A roof and floor can also be identified. Thus the lower end of the ureter becomes oblique in position as it pierces through the bladder wall. The diagonal angle of passage of the ureter through the bladder wall in eight fresh human cadavers was 11^0 when using the endoluminal ultrasound method (Roshani et al., 1999). This cannot be confirmed in vivo because the angle of entry is only noticeable near the VUJ where the intramural channel is around 4-5 mm and more sharply angled than 11^0.

Different portion of the VUJ (Fig 1b)

There are two portions of ureter: The part outside the bladder muscle is known as the juxtavesical portion while inside is known as the intravesical portion. At birth, the intravesical ureter is 0.5 cm in length while in adulthood it is 1.5 to 2.6 cm. The intravesical ureter has two parts: the intramural and submucosal portion. The submucosal portion is covered by mucous membrane only. The intramural portion measures 0.9 cm while the submucosal part measures 0.7 cm in length. They are of approximately equal length in 80% at all ages (Cussen, 1967; Gruber, 1929; Hutch, 1961; Roshani et al., 1999; Tanagho & Pugh, 1963).

Ureteric Sheath (Fig. 1a)

There is an additional group of looser muscle fibers closely related to the adventitia of the intravesical and juxtavesical ureter, which is known as the ureteric sheath. This connective tissue sleeve separates the ureteric muscle coat from the bladder wall. However, the origin of this sheath is of great dispute. Some studies have suggested that the ureteric sheath is a separable structure. It is ureteric in origin and made by a fibromuscular layer wrapped around the intramural ureter (Disse, 1902; Tanagho & Pugh, 1963; Tanagho et al., 1968; Versari, 1908). Other studies have suggested that the sheath is vesical in origin, which is composed of longitudinal muscle fibers ascending from the bladder onto the juxtavesical part of the ureter (Hutch et al., 1961; Noordzij & Dabhoiwala, 1993; Uhlenhuth et al., 1953; Waldeyer, 1892).

Elbadawi and Ruotolo supported the dual sheath concept. They found two muscular sheaths surrounding the distal end of the ureter, superficial and deep periureteric sheaths. The superficial one was vesical in origin and the deep one was both ureteric and vesical in origin (Elbadawi, 1972; Ruotolo, 1949).

Other areas of the VUJ

There are also other areas about VUJ that are in dispute, including whether there is direct continuation of the trigone with ureter and the number of layers in trigonal muscle.

Some studies have suggested that the trigone is direct continuation with the ureter. The muscle fibers of the intravesical ureter fan out and become continuous with the superficial trigonal muscle. On the other hand, the ureteric sheath also fans out and joins the muscle bundles from the contralateral ureter forming the middle or deep trigone and extended to the urethra. This is called the Bell's muscle (Gruber, 1929; Juskiewenski et al., 1984; Noordzij & Dabhoiwala, 1993; Roshani et al., 1996; Tanagho & Pugh, 1963; Tanagho et al., 1968).

However, Disse, Uhlenhuth found that the ureteric muscle stopped abruptly in the VUJ thus they has proposed that the trigonal muscle is not of ureteric origin but represents submucous musculature (Disse, 1902; Uhlenhuth et al., 1953).

There is an isolated report on the existence of a sling muscle and meatal muscle in the VUJ (Fig 1a). Hutch has reported the existence of the sling muscle and sling fascia. They are the outer longitudinal and inner circular bladder muscles that form the floor of the VUJ and are thin but tough strip of muscle. These muscles lie underneath and provide firm support to the intravesical ureter, whichmight play a role in preventing reflux (Hutch et al., 1961).

Both Zaffagnini and Korner have reported the existence of the meatal muscle. There are transureteric vesical muscle bundles and extension of the deep periureteric sheath superficial to the ureteric muscle in the roof of the submucosal segment. The bundles of the two periureteric sheaths are cross or decussate with each other in the roof of the submucosal segment. This has been described as the meatal muscle (Zaffagnini & Mangiaracina, 1955) or a double perimeatal muscular sling (Korner, 1962).

Despite the controversies in different studies about the origin and relationships of the muscles, all studies do support the presence of muscle in the VUJ, thus suggesting that a potential functional muscular sphincter might be present.

2.1.2. Histochemical study of the VUJ

The VUJ has a dual sympathetic-parasympathetic innervation. It is richly supplied by noradrenergic and cholinergic nerves (Dixon et al., 1992, 1994, 1998a, 1998b; Gearhart et al., 1993; Gosling et al., 1999). The nerves supplying the ureterotrigonal and vesical component of the VUJ have the same origin: the ureterovesical ganglion complex. Therefore, theoretically the activity of the two components can be synchronized and regulated in relation to each other (Elbadawi & Schenk, 1971).

Both Jen and Roshani have shown that detrusor and deep trigone receive cholinergic innervation while the ureteric and superficial trigonal muscles receive noradrenergic innervation (Jen et al., 1995; Roshani et al., 1996) (Fig 2).

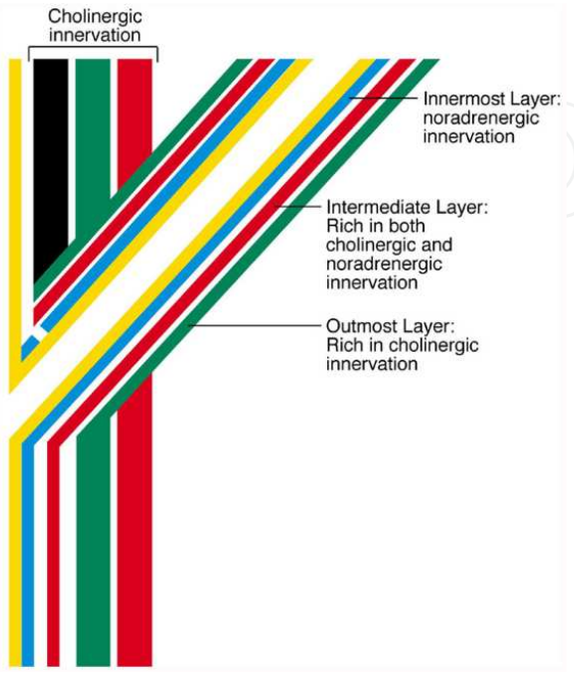


Figure 2. Histochemical study of the VUJ in human (according to Gearhart et al., 1993)

Gearhart have found three distinct smooth muscle components in the VUJ. The innermost layer is the ureteric muscle which is rich in pseudocholinesterase (PChE) and this muscle fans out and continues with the trigonal fiber. The intermediate layer of muscle is a distinct layer rich in both acetylcholinesterase (AChE) and PChE. It is not derived from the ureter or the detrusor but it continues with the trigonal fiber. The outermost layer is the detrusor muscle and is rich in AChE (Gearhart et al., 1993).

These additional informations further support our hypothesis that VUJ is likely to possess functional active sphincteric mechanism rather than just a passive flap valve.

2.2. Anti-reflux mechanism at VUJ

There are three well known schools of though for the anti-reflux mechanism: passive valve mechanism, mixed active and passive valvular action and sphincteric mechanism. However the exact nature of the anti-reflux mechanism of VUJ is unresolved and the existence of a valvular action is controversial.

2.2.1. Passive valve mechanism

Passive valve mechanism is a purely passive one which depends on the length and obliquity of the intravesicular ureter. When the intravesical pressure increases during bladder filling or

voiding, there is an increase in length of the intravesical ureter and a one way "flap-valve" at the ureteric orifice is produced. The ureter is then compressed and flattened thus preventing regurgitation (Hutch, 1952; Hutch et al., 1955; Juskiewenski et al., 1984; Paquin, 1959).

2.2.2. Mixed active and passive valvular action

In this theory, the anti-reflux action depends on both the sphincter action of the bladder muscle and the obliquity of the ureter. The anti-reflux mechanism is brought by the dynamic relationship between bladder wall, intravesical ureter and trigone. (Blok et al., 1985, 1986; Hutch, 1952; Hutch et al., 1955, 1961; Roshani et al., 2000a, 2000b; Tanagho & Pugh, 1963; Tanagho et al.,1968).

2.2.3. Sphincteric mechanism

In this theory, the integrity of the VUJ is based on the sphincter action produced by the ureteric function and tone, and or urinary bladder action alone. The sphincteric action is brought by the muscular activity of the ureteric muscle, sling muscle, sling fascia and the Waldeyer's sheath and the intricate muscular meshwork of the trigonal region of the bladder (Hutch et al., 1961; Noordzij & Dabhoiwala, 1993; Stephens & Lenaghan, 1962; Stewart JC 1937; Tanagho & Pugh, 1963; Tanagho et al., 1968; Uhlenhuth et al., 1953).

3. Review of previous studies on ureteric jet

3.1. What is ureteric jet?

Ureteric jet is the forceful ejection of urine through the VUJ into the bladder and it can be detected by gray scale as a stream or burst of low-intensity echoes emerging from the ureteric orifice. The jet lasts for few seconds and it is fast enough to produce a frequency shift; thus both colour and Doppler waveform can be obtained at real-time (Fig 3)

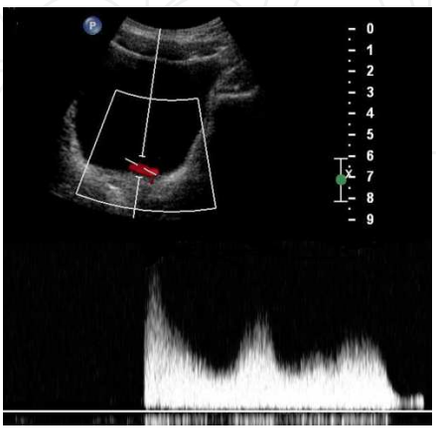


Figure 3. Colour and Doppler waveform of the ureteric jet.

Ureteric jet can be further characterized by its pulse wave Doppler waveform. In the next section, detailed literature review on ureteric jet in both human and animal studies will be outlined.

3.2. Previous work on the ureteric jet in human

Ureteric jet has been reported as early as 1955 (Kalmon et al., 1955) using the X-ray method (intravenous urography, IVU) while the first one to document the sonographic appearance of jet was Dubbins (Dubbins et al., 1981). The reported incidence of the visualization of jet ranged from 5.7% to 100% (Blomley et al., 1997; Cox et al., 1992; Eklöf & Johanson, 1980; Elejalde& de Elejalde, 1983; Gothlin, 1964; Marshall et al., 1990; Nevin et al., 1962). There is a higher chance of visualizing jet using ultrasound than radiography. Recently, the reported rate of visualization of ureteric jet in 1341 normal subjects using ultrasound is 99% (Leung et al., 2007b).

There are a number of theories why ureteric jet can be visualized on ultrasound, as follows: i) miniature bubbles produced in a rapidly moving fluid (Kremkau et al., 1970), ii) turbulent flow of urine into a static fluid in the closed bladder and the continual changes in the shear forces between the jet and the adjacent static urine was the caused for the Doppler signal (Dubbins et al., 1981), iii) difference in specific gravities of the injected fluid and the fluid within the bladder (Kremer et al., 1982), iv) differences in density and compressibility changes between urine in bladder and in the ureter (Baker & Middleton, 1992; Price et al., 1989).

3.2.1. Characteristics of ureteric jet

Pattern of the jet

There are many descriptions about Doppler waveform such as crescendo and decrescendo forms, single-hump and multiple-hump (as many as four) curves, turbulent form of jet pattern, discrete jets, ureteric streaming, rest periods (ie, period of undetected flow). Jet pattern could be divided into three phases: Firstly, initial phase can be visualized as pulsed oozing or flattened type or combination of both. It is then followed by a steady phase as uniform Doppler waveforms at regular intervals and a final phase as uneven waveforms at irregular intervals (Cox et al., 1992; Jequier et al., 1990; Wu et al., 1995). The pattern of jet alters with physiological changes. After large fluid load, there is eitheris an increase in jet frequency or the pattern is converted to an almost continuous signal with absent humps (Jequier et al., 1990). This temporal variation also occurs in velocity, duration and amplitude of the jet (Blomley et al., 1997; Burge et al., 1991; Cox et al., 1992; Wu et al., 1995).

On the contrary, during inadequate hydration or in diseased patients, the waveform becomes flattened (Wu et al., 1955).

Jets are usually directed anteriorly, anteromedially, with or without crossing of the jets. Sometimes they can also be perpendicular to the mucosal surface. There is not much difference in the jet direction bewteenboth paediatric and adult groups (Burge et al., 1991; Catalano et al., 1998; Cox et al., 1992; Dubbins et al., 1981; Elejalde & de Elejalde, 1983; Jequier et al., 1990; Patel & Kellett, 1996; Sweet et al., 1995).

Parameters of the jet

The extension of jet varies from 1 to 5 cm into the bladder but sometimes extended more than 5 cm or less than 1 cm (Dubbins et al., 1981; Elejalde & de Elejalde, 1983; Kremer et al., 1982).

The mean jet velocity in the paediatric group varies between 18 to 31.6 cm/s (from 26 days to 17 years old) while in the adults it varies from 32.1 to 60 cm/s (from 18 to 49 years old (Cox et al., 1992; Jequier et al., 1990; Marshall, 1990; Matsuda et al., 1995; Matsuda& Saitoh, 1995; Sperandeo et al., 1994;). The duration of jet ranges from 0.6 to 7.5 s (Jequier et al., 1990) in paediatric and from 3.5 to 15 s in adult (Catalano et al., 1998; Cox et al., 1992; Kremer et al., 1982; Matsuda et al., 1995). The frequency of jet ranges from 2.4 to 5.4 jets/min in adult (Burge et al., 1991; Catalano et al., 1998; Kremer et al., 1982; Matsuda & Saitoh, 1995). The interjet interval ranges from 2 to 150 seconds (Catalano et al., 1998; Cox et al., 1992).

Adult subjects have a higher velocity (20 vs. 16 cm/s), duration (2.5 vs. 1.8 s) and frequency (1.2 vs1 jets/min) than children (Matsuda & Saitoh., 1995).

There is symmetry in jet frequency, jet parameters of velocity and duration between right and left side in healthy subjects (Burge et al., 1991; Cox et al., 1992; Matsuda & Saitoh, 1995).

Under the condition of forced diuresis, the jet hasa higher velocity (32.1 vs. 20 cm/s), duration (6.7 vs. 2.5 s) and frequency (2.4 vs. 1.2 jets/min) than in the normal physiological state (Matsuda & Saitoh, 1995).

3.2.2. Clinical implication of ureteric jet

It has previously been suggested that the presence of ureteric jet implies concurrenturinary tract infection (UTI) (Kalmon et al., 1955; Nevin et al., 1962) and absence of vesicoureteric reflux (VUR) (Kuhns, 1977). Subsequent studies prove that the presence of ureteric jet is just a normal physiologic phenomenon and cannot be used to diagnosis UTI or exclude VUR (Eklöf & Johanson, 1980; Gothlin, 1964; Gudinchet et al., 1997; Jequier et al., 1990; Marshall et al., 1990).

However, the presence of jet could be used to exclude ureteric obstruction. The complete absence of jet or a continuous low-level waveform is diagnostic for high-grade obstruction from ureteric calculi (Abulafia et al., 1997; Burge et al., 1991; Catalano et al., 1998; Elejalde & de Elejalde, 1983; Laing et al., 1994; Tal et al., 1994; Timor-Tritsch et al., 1997; Wu et al., 1995; Yoon et al., 2000).The difference in jet velocity has been used to study the effect of drug treatment on benign prostatic hyperplasia (Sperandeo et al., 1994, 1996) and to study the physiology of the kidney and ureter, includingthe glomerular filtration rate (Blomley et al., 1997; Burke & Washowich, 1998; Chiu et al., 1999; Han et al., 1996, 1997; Patel et al., 1996; Summers et al., 1992; Wachsberg, 1998)

3.3. Previous work on the ureteric jet on animals

Lamb et al has found that ureteric jet can be consistently visualized in the dogs. The ureteric jets show variable frequency and duration. Lamb has suggested that the non-visualization of the ureteric jet might be helpful in diagnosing ectopic ureter (Lamb & Gregory, 1994).

In our institution, we have also studied the ureteric jet in 16s female pigs at the age of two to three monthsserially. The first scan was the baseline study, after that the pig underwent the process of deroofing of the intravesical portion on one of the ureters. The second scan was done one month after deroofing. The third scan was done when the pigs were four to five months old. The data from the pigs was compared with a group of 31 girls up to four years old. In this study, the incidence of monphasic waveform does not decrease as the pigs become mature. There is no association between reflux and monophasic waveform.

This observation is quite different from that in the human studies, as discussed in laterl part of this chapter.

4. Doppler waveform of ureteric jet

4.1. Pattern of the ureteric jet

Ureteric jets areclassified according to the number of peaks within that particular Doppler waveform. Six basic patterns are identified: monophasic (with only one peak), biphasic (two peaks), triphasic (three peaks), polyphasic (number of peaks exceeding three), "square" (a plateau waveform in which no distinct peak be identified but of average duration); and "continuous" when the waveform lasts longer than 20 seconds which can be either polyphasic or plateau form. These waveforms are further classified as three categories. Monophasic jet is classifies as the first category of simple and immature pattern (Fig. 4).

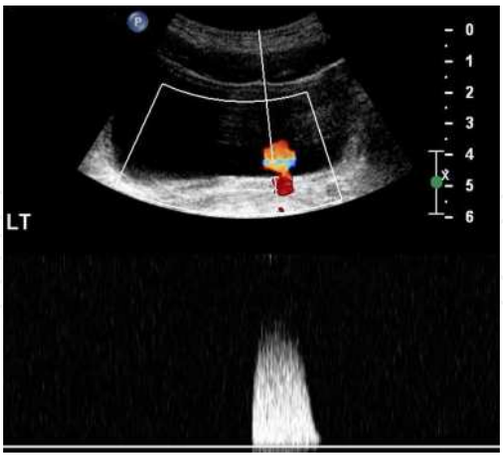


Figure 4. The simple, immature monophasic pattern of the ureteric jet

The bi, tri- and polyphasic patterns are classified as the complex and mature pattern (Fig 5).

The last two patterns are the square and continuous forms. These are modified waveform under the state of forced diuresis. They are classified as the diuretic pattern (Fig. 6).

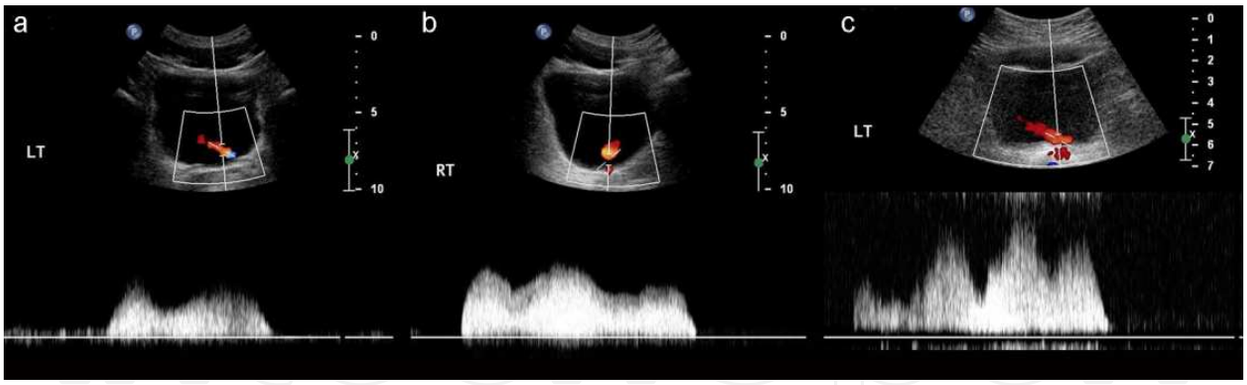


Figure 5. The complex and mature pattern of the ureteric jet: bi (a), tri (b), polyphasic (c)

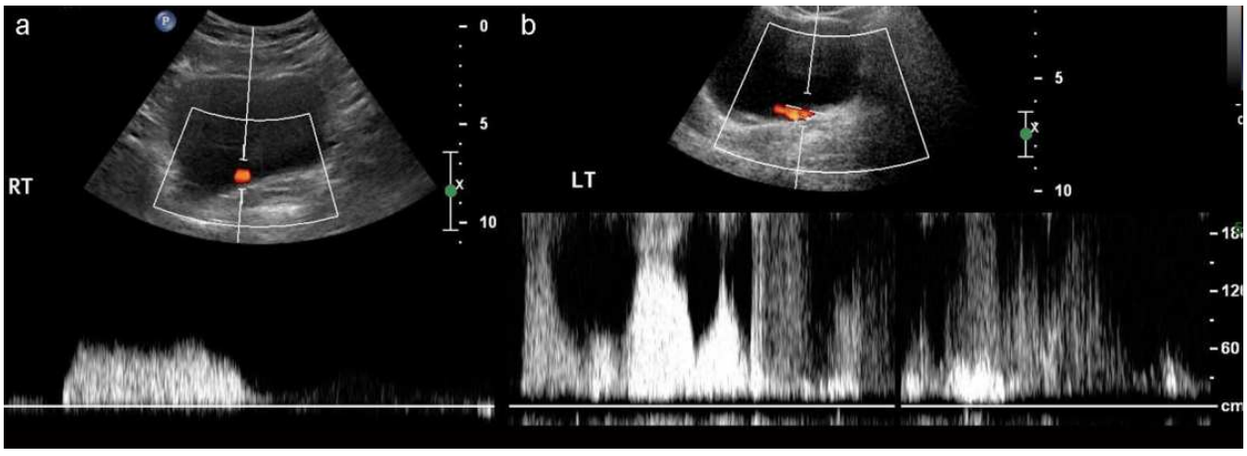


Figure 6. The diuretic pattern of the ureteric jet: square (a), continuous (b)

4.2. Measurement of ureteric jet

On the Doppler waveform, the maximum velocity (peak velocity), jet duration and initial slope can be measured (Fig 7).

4.3. Uncommon modification of the jet

There are three uncommon but interesting modifications of the jet. They are: presence of breaks, multispike pattern and change in direction of the jet. These patterns are relatively uncommon in the normal population but they provide indirect supportive evidence for the hypothesis of functional sphincter action at the VUJ.

Presence of breaks meant there is a total absence of signal between peaks within the duration of that particular wave (Fig 8). Most of the breaks are observed in the maximally full bladder and the incidence is found to be 5.7% of the study population (Leung et al., 2007b).

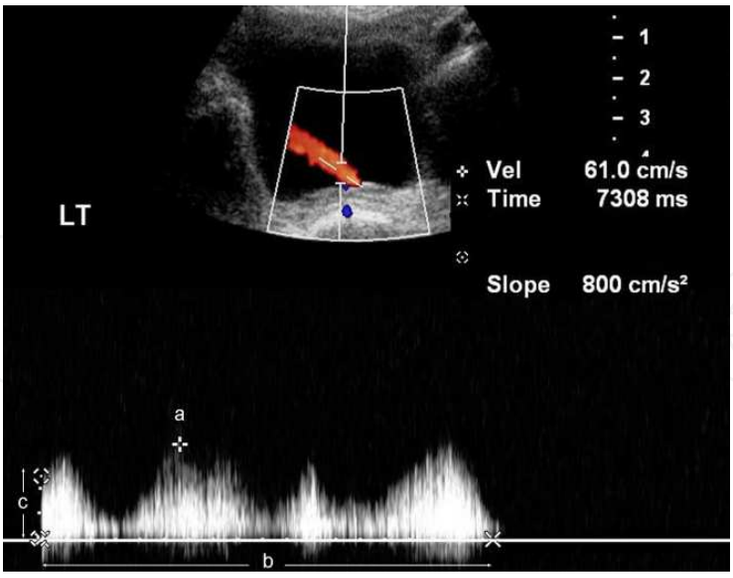


Figure 7. Doppler measurement of the ureteric jet: peak velocity (a), duration (b) and initial slope (c)

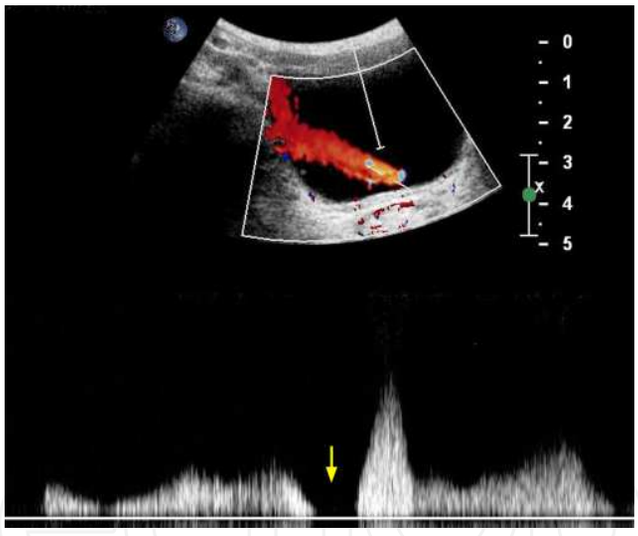


Figure 8. Presence of break (arrow) within the ureteric jet

Multispike pattern is defined as the pulsation in the jet pattern as a result of the pulsation transmitted from the adjacent arteries (Fig 9). This pattern is more commonly observed when bladder is maximally full and the incidence is found to be 1.9% of the study population (Leung et al., 2007b).

Change in angle of the jet meant there was a change in the direction of the jet at the beginning and at the end (Fig. 10). This pattern could be observed at any diuresis status. The incidence is found to be 4.3% of the study population (Leung et al., 2007b).

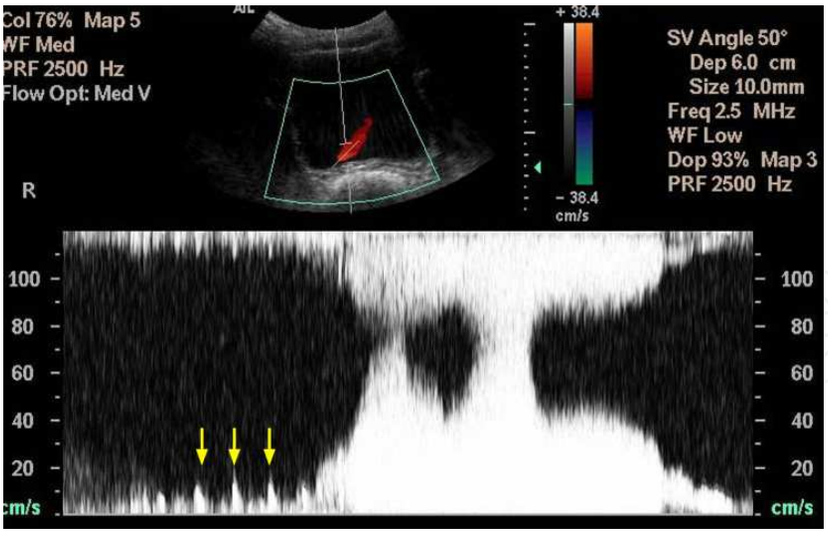


Figure 9. Multispike pattern (arrows) of the ureteric jet.

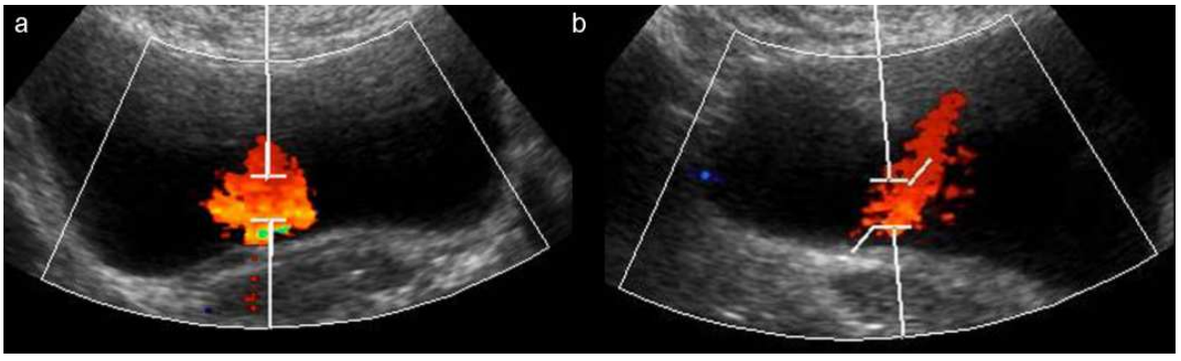


Figure 10. Changing of angle in the ureteric jet: from vertical at the beginning (a) to slightly inclined at the end (b) of the jet.

5. Our observation on Doppler waveform of the ureteric jet

In our institution, we have studied the pattern and physical properties of the ureteric jet in the normal population. The characteristics of ureteric jet are studied under specific physiological conditions such as pregnancy, pharmacological effect under general anaesthesia and after structural ureteric modification following renal transplantation. The characteristics of jet are also assessed under different pathological conditions such as: children with VUR and UTI, children with nocturnal enuresis and children with neurogenic bladder.

5.1. Physical properties of ureteric jet in normal population

This part of study is based on a normal population of 1,341 subjects with age ranging from 15 days to 82 years old (Leung et al., 2002a).

5.1.1. General properties of jet

In the normal population, four common patterns can be identified: monophasic, biphasic, triphasic and polyphasic (Table 1). The square and continuous patterns occur under force dieresis, which contributes only 1.5% of cases in the normal population. With increasing age from infancy, the proportion of monophasic waveform decreases while the more complex patterns prevail.

Age (year)	Incidence (%)			
	Monophasic	Biphasic	Triphasic	Polyphasic
0-9.9	30	30.6	23.3	16.1
10-19.9	3.3	28.7	41.1	26.9
20-29.9	0	35.6	40.7	23.7
30-39.9	2.0	35.6	35.1	27.3
40-49.9	2.5	34.1	32.7	30.7
50-59.9	3.8	38.7	30.8	26.7
60-69.9	0	38.0	35.5	26.4
70-79.9	4.7	37.2	37.2	20.9

Table 1. Incidence of the four patterns in different age groups of the normal population.

In the normal population, there is strikingly larger number of monophasic patterns in children (22%) than in adult (1.9%) (Table 2).

	Children		Adult	
	Number	Incidence (%)	Number	Incidence (%)
Monophasic	83	22	18	1.9
	$P < 0.01$			

Table 2. Incidence of monophasic jet in children and adult.

For the mean velocity, it is 34.03 cm/s for the monophasic jet and 61.82 cm/s for the complex pattern in children. While in adult, the mean velocity of the monophasic jet is 57.65 cm/s and 78.89 cm/s for the complex pattern.

For the mean jet duration, it is 1.17 s for children with monophasic pattern and 5.26 s for the complex pattern. In adults, the mean jet duration is 1.91 s for monophasic jet and 6.9 s for complex pattern.

For the mean initial slope, it is 211.82 cm/s^2 for monophasic jet and 293.32 cm/s^2 for the complex pattern in children. While in adults, the mean initial slope of the monophasic jet is 195.54 cm/s^2 and 271.21 cm/s^2 for the complex pattern.

The direction of flow of the jet can be directed anteriorly, anteromedially (with or without crossing of the jets), or in amore vertical direction or perpendicular to the bladder base.

5.1.2. Different effects on ureteric jet

The laterality differences, effect of age, gender and bladder filling status on the pattern of ureteric jet have been investigated.

In general, there is no significant difference in waveform pattern, initial slope, velocity and duration of ureteric jet between the right and left sides in both children and adults.

For the effect of age, children have a higher incidence of monophasic jet. This immature pattern occurs constantly in the first 6 months of life and becomes mature at the age of 4.54 years. There is no significant gender difference for the mean age of VUJ maturity in children (Leung et al., 2007a). Adults have higher jet velocity and longer duration of jet than children for both the monophasic and complex patterns. However, the initial slope of the jet shows no significant difference between children and adults.

For the gender effect, in children, there is no significant difference in velocity, duration, initial slope or number of peaks within a single jet between boys and girls. In adults, male subjects have a higher incidence of polyphasic waveform than females involving both right and left side. Male subjects also have a higher velocity and longer duration of the jet than female on both sides.

Finally, as for the effect of bladder filling status on the jet, 42.2% of subjects show no change in the number of peaks within a single jet waveform, 28.9% show a decrease and 26.5% show an increase, and 2.4% has square and continuous jet when the bladder becomes very full (Leung et al., 2002a). In all subjects, the initial slope, velocity and duration of the jet are not affected by different stages of bladder filling. In conclusion, the stage of bladder filling should have little effect to determine whether a subject has an immature or complex pattern.

5.2. Characteristic of the jet in different physiological conditions

5.2.1. Physiological effect

Hormonal changes of pregnancy are thought to cause smooth muscle relaxation (Hundley et al., 1942; Kumar, 1962). In our institution, we sought to investigate whether this hormonal effect on the smooth muscle exists within the maternal urinary tract, if the hypothesis of a functional active sphincteric mechanism at the VUJ is sound. A longitudinal study has been used to illustrate this physiological change. A total of 107 pregnant women have performed Doppler study of the ureteric jet at 20, 32 weeks' gestation, and 3 months postpartum. The incidence of monophasic jet (immature jet) is significantly higher at 20 weeks' gestation (18.7%), and even higher at 32 weeks' gestation (41.1%) when compared with non-pregnant

women (1.9%). However, the incidence drops to again and becomes comparable to the non-pregnant women (1.6% vs. 1.9%) after 3-month postpartum (Leung & Metreweli, 2002a).

In the above study, we conclude that pregnancy does modify the ureteric jet pattern. One possible explanation is that the VUJ reverts to the simpler mechanism to produce the monophasic pattern by the myogenic component when the mature neural component fails or is inactivated to produce complex jet pattern. Therefore the complex ureteric jet is subject to an on-off switch. If it is switched off then the ureter reverts back to a monophasic jet. The above observation leads to the hypothesis about a myogenic origin related to the monophasic waveform and a neurogenic origin related to the complex waveform.

5.2.2. Pharmacological effect

Another study has been set to investigate for any effect of the anaesthesia drug on functional sphincteric action of the VUJ. If so, this will be reflected by changes in the Doppler waveform of the ureteric jet after application of anaesthesia. We have studied a total of 16 children while they underwent surgery under general anaesthesia. Before anaesthesia, 14 of them showed a complex pattern and two showed a monophasic pattern. However, after anaesthesia, all of them showed a monophasic waveform (Leung et al., 2003).

This observation confirms that the change in the ureteric jet from a complex to a monophasic waveform is brought by the effect of the drugs acting on the functional sphincteric action of the VUJ. This observation again supports the hypothesis of a functional active sphincter and supports the dual components of the VUJ sphincter. In this scenario, the neural component of the VUJ is inactivated by the anaesthesia, leaving only the myogenic component to function, hence producing the monophasic jet pattern.

5.2.3. Structural modification effect

Ureteric peristalsis in the transplanted ureter should be the same as that in the normal subject. The traditional concept about VUJ competence is mechanical in origin, so that during re-implantation of the donor ureter into the native bladder, the structure or function of the native VUJ is destroyed and the equivalent of a mechanical flap valve is "re-created" (Paquin, 1959; Politano et al., 1958). However, no one has studied whether the surgical VUJ behaves in a similar manner as a native VUJ. In our institution, we have assessed for any change in the ureteric jet after ureteric transplantation for renal transplantation, so as to demonstrate the effect of structural change at VUJ.

The ureteric jets from 55 renal transplant patients have been compared with 817 healthy subjects. The Doppler waveform of transplant ureters is distinctly different from those of healthy adult ureters. Only two patterns can be identified in transplanted ureters: more commonly a short monophasic waveform (66.1% vs. 2.6% in the health ureters), and less commonly a longer multiphase pattern but does not resemble the patterns of the healthy ureter (Leung & Metreweli, 2002b).

In conclusion, the ureteric jet patterns associated with transplant ureters are very different from those ureters with an intact VUJ, but resemble the pattern expected from simple

efflux of urine secondary to ureteric peristalsis. On the other hand, this jet pattern of transplanted ureter also has little resemblance to the normal monophasic pattern because the latter requires some functional sphincteric type activity, referred as myogenic component in the dual component theory that we have described earlier. Furthermore the more complicated transplant jet bears no resemblance to the normal complex category. This can be explained by the loss of the proposed neural component. Inherent ureteric muscular peristalsis has been shown to be preserved in transplanted ureter, which is likely to be the vis-a-tergo producing the jet. In conclusion, there is a loss of functional active sphincter mechanism of the VUJ in the transplanted ureter as a result of the operative procedure. This observation again supports the hypothesis that VUJ is a functional active sphincter.

5.3. Characteristic of the ureteric jet in different pathological condition

Characteristic of Doppler waveform of the ureteric jet in different pathological groups have also been investigated, as illustrated below.

5.3.1. Children with VUR and UTI

We have previously shown that young children have a much simpler monophasic immature pattern. A study has been carried out to study whether there is any correlation between the presence of such immature pattern with UTI and VUR.

We have studied 98 children with UTI and VUR and compared with 241 healthy children. The incidence of monophasic jet (immature pattern) is 29% in healthy children overall, but varies greatly according to age. The immature pattern is universal in the first 6 months of life, but drops significantly to below 15% in late childhood. This immature pattern is more commonly seen in children with UTI (37.5%) and VUR (90.5%) than in healthy controls of the same age (Leung et al., 2002b).

An immature pattern of ureteric jet is seen predominantly in three groups of subjects: (1) neonatal and infant group, (2) children with UTI and (3) children with VUR,. However in older children between 2-14 years of age, there is a higher tendency of persist immature pattern in both UTI and VUR groups. The persistence of immature jet pattern suggests that developmental immaturity might be a feature of children with UTI and VUR.

As immature ureteric jet pattern is associated with immaturity of ureteric function during infancy, a similar pattern observed in UTI / VUR groups lead to a hypothesis that this developmental immaturity of VUJ might be a contributing/ predisposing factor to urinary infection and the reflux problem in children.

Previous studies have been that majority of children with VUR do not have an anatomically defined congenital anomaly at the VUJ, (Dixon et al., 1998a), however, a functionally immature or transitory phase of developmental immaturity of VUJ might be present and predispose the affected children to VUR and UTI.

5.3.2. Children with nocturnal enuresis

In our institution, a study has been set to investigate whether immature ureteric jet pattern is present in children with nocturnal enuresis.

We have studied 511 children presenting with primary nocturnal enuresis. There was a higher incidence (19%) of immature waveform observed in children with nocturnal enuresis as compared with normal children within the same age range (7.4%) (Leung et al 2006). This study suggests that there is a lower level of maturity in the VUJ in enuretic children. Another interesting finding is that the immature jet is more commonly seen in enuretic children with markedly thickened bladder wall and multiple urodynamic abnormalities. This observation suggests that monophasic waveform is associated with abnormalities of the detrusor muscle as well as an increase in detrusor pressure. All these parameters might be indicators of immaturity of the VUJ-detrusor complex, which predispose affected children to the development of primary enuresis.

5.3.3. Children with neurogenic bladder

As discussed previously, VUJ has a nervous component with hitherto unknown functions. Patients with inactivated neural component within the VUJ due to drug effects or surgery have a higher incidence of monophasic jet pattern. It is well known that patients with neurogenic bladder have high incidence of secondary VUR while VUR is associated with monophasic ureteric jet. In our institution, we sought to investigate whether there is a prevalence of monophasic jet in patients with neurogenic bladder.

In a study of 27 children with neurogenic bladder, the frequency of monphasic jet is much higher in neurogenic bladder group (40.7%) when compared with normal population within the same age range (7%). Despite the small number of subjects, the observation again supports the theory of functional active sphincteric mechanism of VUJ. In this scenario, monophasic pattern prevails when the neural component within the VUJ is deactivated.

6. Dual mode of action of the functional sphincter at the VUJ

In summary, combining the anatomical and histochemical data, as well as the observations from Doppler ultrasound studies of ureteric jets, a functional sphincter with dual mode action at the VUJ is proposed. This sphincter is not a passive valve. On top of the monophasic ureteric peristaltic wave within the ureters as demonstrated by M-mode, a more complex pattern is observed in the ureteric jet emanating from VUJ demonstrated by Doppler waveform. The reason for the change in waveform pattern of the ultimate ureteric jet is due to modification of jet by an active sphincter mechanism at the VUJ.

In brief, six patterns of ureteric jet and three uncommon variations are identified. They are classified as the monophasic, mature complex (bi, tri and polyphasic) and diuretic pattern. In the normal population, a higher incidence of the monophasic pattern is seen in immature neonate and in children under four years old. The monophasic pattern occurs constantly in

the first six months of life. There is a significant drop in the incidence of monophasic pattern by the age of four. The complex waveforms prevail in older children and normal adults. There are two components in the dual mode action of such functional sphincter. They are the "myogenic" (primary or immature) component and the "neurogenic" (secondary or mature) component. We postulate that the monophasic jet pattern is the result of contraction caused by the myogenic component of the VUJ, while the complex pattern is the result of modulation of the myogenic component of the jet by the neurogenic component in response to the distal intrauretetic pressure (Fig 11). The mode of the functional sphincteric action of the VUJ and the subsequent ureteric jet waveform vary depending upon whether or not the neurogenic component is active.

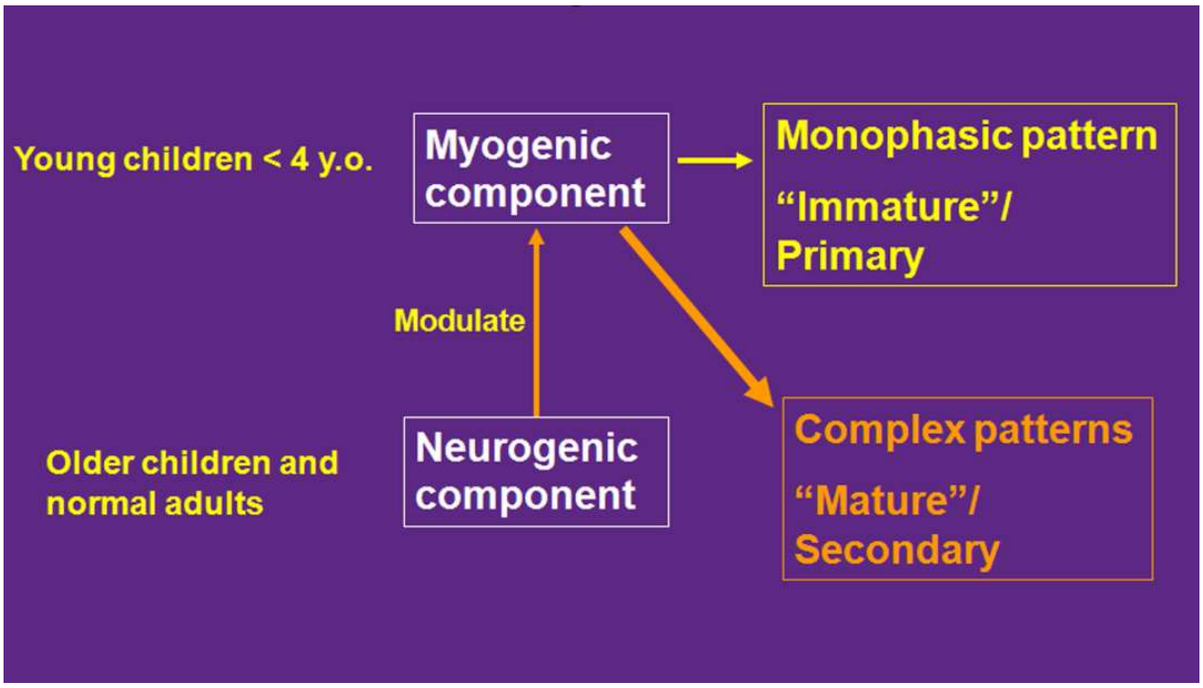


Figure 11. Diagram showing the dual mode of action of the VUJ in the normal population

The presence of the less frequently observed modifications of the ureteric jet pattern is also contributed to the dual mode action of VUJ. The multispike pattern appears to be a premature relaxation of the VUJ that precedes the ureteric jet proper. It is related to the relaxation mechanism found in forced diuresis. Forced diuresis is probably caused by permanent relaxation of the VUJ functional sphincter allowing free flow of urine modified by ureteric peristalsis. These modifications are under the control of neural mechanism. The breaks modification is found under condition of maximum bladder filling hence increased intravesical pressure. This is probably a result of the pressure wave of the ureteric jet generating apparently lower velocities and intervening with zero flows.

Whenever the neurogenic component is switched off, only the myogenic component operates and thus results in a reversion to the monophasic pattern of the ureteric jet. The above holds true under three physiological conditions. During pregnancy, the hormonal

effect temporarily inactivates the neurogenic component. Once the hormonal effect is lost, the neural component is activated again. In the anaesthetized (GA) children, the drug effect also temporarily inactivated the neurogenic component. In patients undergoing renal transplantation, the normal VUJ mechanism in the transplant ureter is altered or completely lost as a result of the operative procedure, thus a totally different ureteric jet pattern is observed (Fig 12).

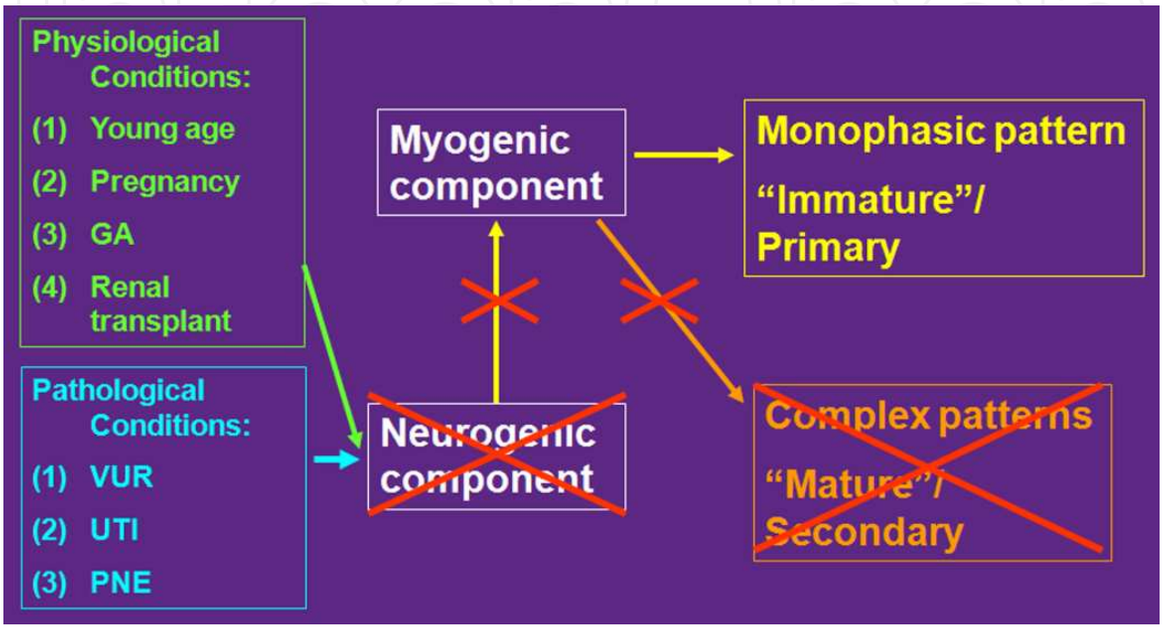


Figure 12. Diagram showing the inactivation of the neurogenic component under different physiological and pathological conditions

Under pathological conditions, there is strong correlation between the presence of VUR and the immature monophasic waveform. This suggests that the more mature complex jet pattern is associated with a more efficient anti-reflux mechanism than the simple immature pattern. The immature jet pattern may represent a temporary developmental immaturity of the VUJ, which predisposes children to the risk of VUR. Monophasic jet is also found in children with nocturnal enuresis associated with detrusor immaturity. A higher incidence of monophasic waveform is also found in children with neurogenic bladder, consistent with loss of the neural component. This might also explain why there is a higher incidence of VUR and UTI in children with neurogenic bladder when the anti-reflux mechanism is lost at the VUJ (Fig 12).

7. Conclusion

The concept of dual mode action (myogenic and neurogenic component) of a functional active sphincter at human VUJ has the following implications:

1. Human VUJ function takes time to mature.

2. It is important for understanding the physiology of VUJ and the mechanism for predisposition to certain pathological conditions, such as VUR and UTI in children

3. This may change the traditional thinking and management of VUR and UTI in children and adults. For example, as the normal physiology of the functional sphincter action of the VUJ is affected by anaesthesia, any VUR study performed in an anaesthetized child should be abandoned (The situation in adults is not known).

4. It is a potentially useful clinical tool for identifying children who are at risk of developing VUR and UTI. This mightlead to more aggressive intervention that will protect the upper urinary tract before any damage is sustained.

5. It is a potentially useful non-invasive investigation to assess bladder abnormalities in children with nocturnal enuresis. It may also enable evaluation of the efficiency of pharmacological interventions.

6. As the VUJ functional sphincter share components of the detrusor muscle, study of ureteric jet may also reflect detrusor activity and the effects of pharmacological intervention on the detrusor.

As a conclusion, the implication of this chapter is that it will alter the scientific basis in the understanding of VUJ and related pathological conditions.. Doppler ultrasound study of ureteric jet provides a non-invasive, physiological and ethical method to study the physiology and pathophysiology of VUJ. In the future, this is valuable for evaluating the therapeutic approach in different kinds of pathological conditions related to VUJ and bladder detrusor activity.

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