Urethral Function During a Woman's Lifetime

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Insights, Imaging, and Clinical Implications

By

J.M. van Geelen

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LIST OF ABBREVIATIONS (ALPHABETICAL ORDER)

(M)UCP:	(Maximum)Urethral Closure Pressure
17-OH-P:	17-Hydroxy-Progesterone
A(V)LPP:	Abdominal (Valsalva) Leak Point Pressure
AFC:	Air-charged catheter
AUL:	Anatomic Urethral Length
BBT:	Basal Body Temperature
CEE:	Conjugated Estrogens
CNS:	Central Nervous System
E_2:	Estrogen
FSH:	Follikle Stimulating Hormone
FUL:	Functional Urethral length
HERS:	Heart and Estrogen-progestin Replacement Study
HRT:	Hormone Replacement Therapy
ICS:	International Continence Society
IP/10:	Integrated Urethral Pressure
ISD:	Intrinsic Sphincter Deficiency
IUGA:	International Urogynecologic Association
LH:	Luteinizing Hormone
LUT:	Lower Urinary Tract
MUI:	Mixed Urinary Incontinence
NHS:	Nurse's Health Study
P:	Progesterone
PMP:	Distance Internal Meatus to Point of MUP
PTR:	Pressure Transmission Ratio
SUI:	Stress Urinary Incontinence
TBP:	Total Bladder Pressure
UGS:	Urogenital Symptoms
UPP:	Urethral Pressure Profile
UPR:	Urethral Pressure Reflectometry
UPV:	Urethral Pressure Variations
URP:	Urethral resistance Pressure
UUI:	Urge Urinary Incontinence
WFC:	Water Perfusion Catheter
WHI:	Women's Health Initiative

PREFACE

Lower Urinary Tract disorders including urinary incontinence represent a major health problem that affects about 25% to 45 % of the adult female population and are associated with a negative impact on quality of life and considerable costs in health care. In western countries, incontinence care represents 2 to 3% of the total national health care budget. In the USA, total costs go up to 16 billion a year (figures for year 2010). In the elderly, urinary incontinence is frequently the main reason for admission in nursing home. The impact on health care is likely to expand as prevalences of these disorders increase with a growing population of elderly women. In the second half of the last century, increasing public awareness of this trivial but embarrassing condition and the development of sophisticated investigational techniques have stimulated research and increased medical knowledge of physiology and pathophysiology of this stigmatizing disorder.

Large population based epidemiological and observational studies have documented, not only the high prevalences of this disorder in women of reproductive age and after menopause, but also the relationships between major events throughout a woman's lifetime and their causal relation to the onset of urinary incontinence. This book presents up-to-date insights in urethral functioning, new investigational methods and risk factors during woman's life that initiate incontinence or may worsen the condition. Three prospective studies, carried out in asymptomatic nulliparous women constitute the core of this monography. The impact of oral contraceptives and of reproductive hormones (estradiol and progesterone) during the normal menstrual cycle on urethra continence mechanism was assessed and correlated with the variables of the simultaneously recorded urethral pressure profile. A prospective longitudinal study including asymptomatic nulliparous women from early pregnancy till 8 weeks after childbirth, calculated the correlation of serum levels of estrogens and progesterone in pregnancy with variables of urethral function, measured during the same study session, The effects of obstetrical factors on the urethral sphincter function are analysed separately. Each chapter concludes with a list of references to relevant articles. The last chapter summarizes the natural course of urethral function during a woman's lifetime. We trust that the contents of this book, based upon objective data and obtained with validated research techniques will contribute to better understanding of urethral function and the aetiology of urethral dysfunction. I like to acknowledge the support of my son Nicolas van Geelen in preparing this monography.

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CHAPTER 1

ANATOMY

The bladder and urethra act as a functional unit, whose purpose is the storage of urine in the bladder and its timely and complete expulsion per urethram under voluntary control. In the healthy continent female, the urethra, almost over its entire length, acts as the urinary sphincter but does not have the anatomic characteristics of a functional sphincteric structure. The intraurethral pressure or urethral closure pressure exceeds total bladder pressure from the bladder neck to almost as far as the external meatus. Two sphincter mechanisms can be discerned.

Histologic characteristics of urethral sphincter mechanisms:

1.1 Bladder neck or proximal urethral sphincter mechanism

Embryologically the trigone and urethra have a separate origin from the rest of the bladder. The musculature of the deep trigone and proximal urethra begins to differentiate from the mesodermal tissue independently from and at a later stage (i.e.11-20 cm CRL stage) than the detrusor muscle. At the bladder outlet transversely oriented muscle fibers of the middle circular layer of the detrusor fuse with the deep trigone and encircle the internal urethral orifice: “Heiss ring” or “the trigonal ring”. From its position and fiber orientation, the trigonal ring is the only anatomic structure that could be considered to be an internal urethral sphincter. On its ventral and lateral aspect, the trigonal ring is covered by U-shaped bundles of the outer longitudinal layers of the detrusor which loop around the bladder neck forming the detrusor loop (Fig.1.1). Together with urethral smooth muscle the trigonal smooth muscle constitutes the proximal urethral or the bladder neck sphincter mechanism. Caudally the deep trigone extends in the dorsal wall of the urethra as a plate-like continuation of transversally oriented smooth fibers and collagenous tissue, “the trigonal plate” (Hutch JA, 1972, Butterworth Appleton Century Crofts. London. pp.62-133; Huisman AB,1983, Thesis RUG. The Netherlands. pp.1-31).

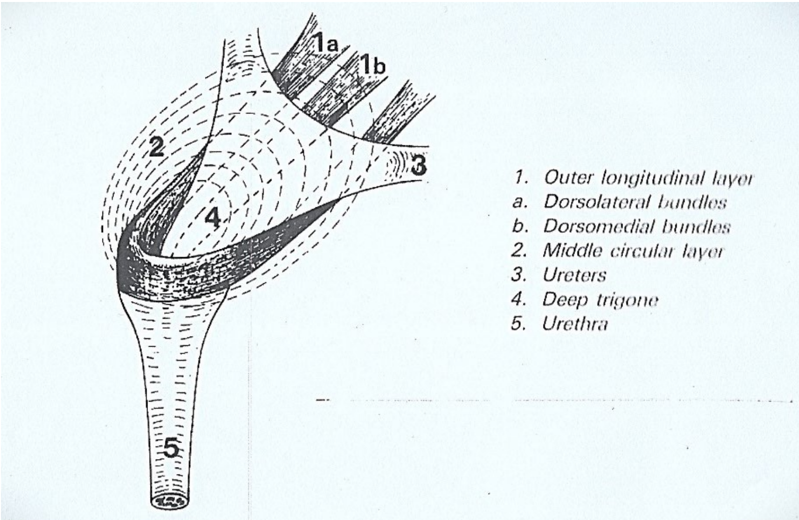

Fig. 1.1: schematic representation of the female bladder neck and proximal urethra. (Redrawn and modified from J.A. Hutch. "Anatomy and Physiology of the bladder, trigone and urethra". With permission of Butterworth Appleton. Copyright 1972).

1.2 Distal urethral sphincter mechanism

The female urethra is a multilayered muscular tube, approximately 3 cm to 4 cm long, that extends below the bladder neck to the external meatus. The urethral wall consists of mucosa, submucosa, two smooth muscle layers and an intramural striated urethral muscle. Together with the periurethral striated musculature these components constitute the distal or intrinsic urethral sphincter.

- The urethral mucosa and richly vascularized submucosa constitute a compressible and easily deformable layer which under external compression will ensure complete occlusion of the urethral lumen: "inner urethral softness" (Zinner et al.,1980, pp. 115-117). Squamous epithelium found in the distal urethra changes more proximally to transitional epithelium in the bladder neck and bladder. The urethral epithelium and the submucosal vascular bed are hormonally -i.e. estrogen- sensitive. Cytological changes like those found in the vaginal epithelial cells are observed in the urethral epithelium during the reproductive years and fluctuations in estrogen levels have a demonstrable effect on vascular pulsations (Smith, 1972, pp. 667-670). Clinical and experimental studies indicate that the urethral vascular bed contributes approximately up to 30% to the intra-urethral pressure (Rud et al.,1980, pp. 343-347). The urethral vascular bed is most fully developed in the reproductive period and declines after menopause (Huisman AB,1983, pp. 1-31).

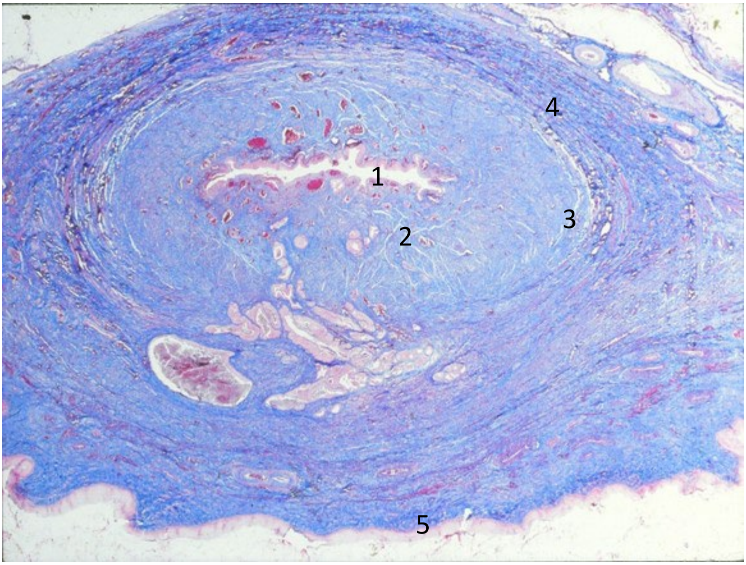

Fig. 1.2: transverse section mid-urethra: pre-menopause. AZAN staining (presented 42nd IUGA Annual Meeting. Vancouver 2017. Van Geelen) 1. urethral lumen. 2. Longitudinal smooth muscle layer 3. Circular smooth muscle. 4. Striated urethral muscle. 5. Vaginal mucosa.

- The urethral smooth muscle layer forms a tough and compact tubular structure surrounding the urethral mucosa and submucosa and consists of relatively small smooth muscle bundles embedded in dense fibroelastic collagenous tissue. The more prominent inner longitudinal layer and the smaller outer circular layer surround the urethra almost for its entire length. Distally the marked layering is gradually lost and the smooth muscle bundles fan out in the periurethral connective tissue which surrounds the external meatus. The contribution of the smooth muscle component together with its binding fibroelastic connective tissue to the resting urethral closing pressure varies according to different investigators and accounts for ± 40% of the intra-urethral pressure, whereas the striated urethral muscle and the urethral vascular bed contribute each ± 30% (Fig.1. 2). (Rud et al. 1980. pp.

343-347; Tanagho et al.1969. pp. 136-149; Donker et al. 1976," Scientific foundations of urology", London).

- Outside the smooth urethral musculature, below the bladder neck, circularly arranged striated muscle bundles surround the urethra in a horseshoe-like pattern over about 20% to 80% of the urethral length. Dorsally the fibers fuse with the transversely oriented tissue of the trigonal plate and. The striated urethral muscle, sometimes also called urogenital sphincter or rhabdosphincter, is most marked in the middle-one third of the urethral wall i.e. the region where generally maximum urethral closure pressure (MUCP) is recorded (Fig.1.3). The location of MUCP is according to studies using simultaneous urethro-cystometry and voiding urethro-cystography approximately 5 mm proximal to the urogenital diaphragm (Westby et al. 1982. pp. 408-412. The small-diameter slow-twitch fibers of the urethral striated muscle are functionally capable of maintaining tone over prolonged periods without fatigue. The intrinsic striated urethral muscle is separated from the extrinsic periurethral striated muscle by endopelvic connective tissue (Gosling et al.,1981, pp. 35-41; Delancey JOL ,1988, pp. 296-301). The term "external sphincter", often applied to this distal urethral sphincter mechanism, is confusing as the urethral striated muscle is clearly separated from the extrinsic peri-urethral striated muscles in the pelvic floor by a continuous connective tissue septum: the pubo-vesico-cervical or endopelvic fascia.

- Periurethral striated muscles of the pelvic floor encompass the urethra at the level where the urethra traverses the urogenital diaphragm: the urethrovaginal sphincter and compressor urethrae (Delancey, 1988). The pelvic floor musculature not only supports the pelvic organs, bladder base and urethra but also has a role in initiating voiding when appropriate and in the coordination of the micturition process. The large-diameter fast-twitch and slow-twitch fibers allow for rapid forceful muscle contraction and thus seem ideally suited to increasing intraurethral resistance during sudden increases in intraabdominal pressures e.g. coughing and sneezing (Gosling et al.,1981).

1.3 Functional Anatomy

Urethral activity involves two functions: maintenance of continence and a compliant urinary conduit. The concept of the functioning of the complex bladder neck sphincter mechanism was presented by Hutch (1972) and still holds to this day. Under normal conditions, during the filling phase, the base

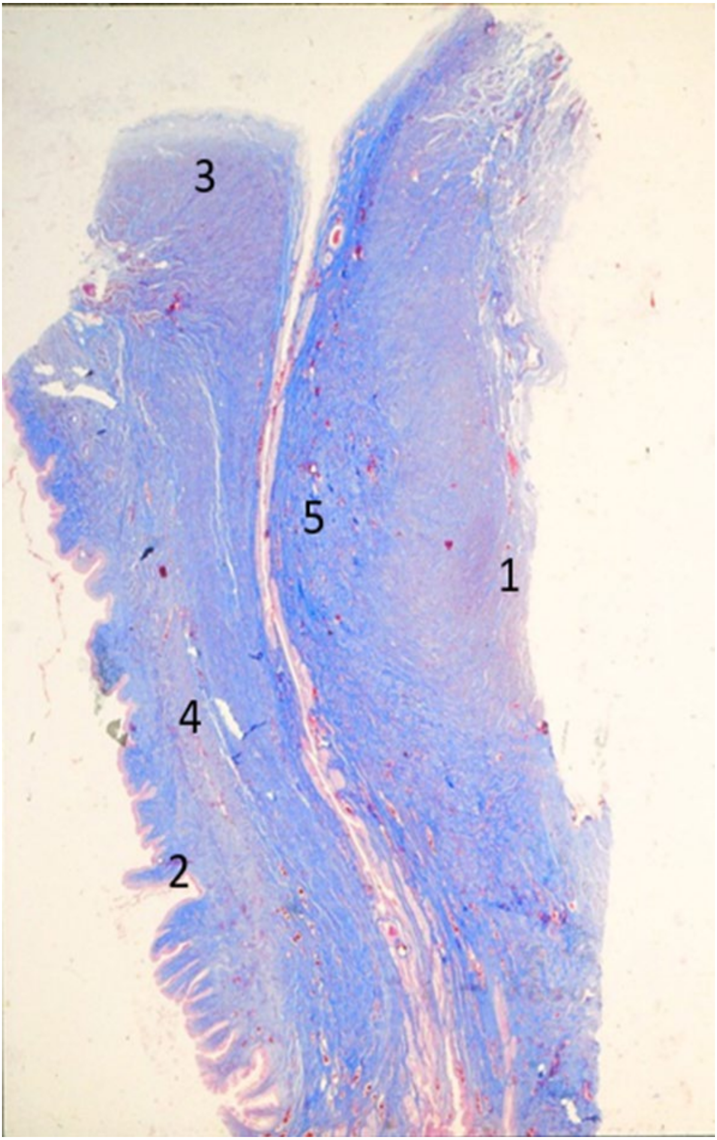

Fig. 1.3: longitudinal section female urethra: AZAN staining (presented 42 IUGA Annual Meeting 2017, Vancouver. Van Geelen). Legends. Longitudinal section Urethra: 1. striated urethral muscle. 2. Vaginal mucosa. 3. Deep trigone. 4. endopelvic fascia. 5. urethral smooth muscle.

of the bladder remains flat, and urine is retained at the level of the bladder neck. The circularly oriented muscle fibers of the middle circular layer, the "trigonal ring", pull the apex of the deep trigone inward to keep the bladder neck closed. It is unlikely, however, that the trigonal ring contributes significantly to urinary continence as it represents only a small and relatively weak sphincteric structure. The detrusor loop is so positioned that the apex of the deep trigone fits into its concave surface. Since the detrusor loop continues into the posterior surface of the bladder as the right and left lateral posterior outer layer, it exerts a backward directed force in direct opposition to the base plate of the bladder, thus increasing the closure function of the bladder neck. Passive continence is maintained at the level of the bladder neck: the atypical sphincteric structure is competent, cough and strain proof and maintains continence without the assistance of the distal sphincteric mechanism. However, bladder neck competence is not a prerequisite for urinary continence: studies using cystourethrography together with synchronous pressure monitoring have shown that about half of continent climacteric women have an open bladder neck, "funneling" (Versi et al., 1990, pp.579-59). The distal urethral sphincter mechanism has an ancillary role in the maintenance of continence and functions as a "back-up" mechanism to ensure continence in women with an incompetent bladder neck. Recent studies show evidence that presence of an open bladder neck is due to laxity of the supportive tissue of the pelvic floor (Delancey JOL,1994, pp. 1713-1723). At the initiation of voiding, contraction of the detrusor moves the bladder base out of its flat position whereas synergistic relaxation of the striated urethral and peri-urethral muscles allows complete evacuation of the bladder.

Female urinary incontinence is often part of or concomitant with a wider range of health problems involving the pelvic floor: laxity of pelvic floor supportive structure, genito-urinary prolapse, neurologic disorders, obstetric or surgical lesions and functional incontinence due to impaired mobility. This monograph focuses on urinary incontinence caused by laxity of the pelvic floor supportive tissue and/or by an incompetent urethral closure. Stress urinary incontinence resulting from intra-abdominal pressure rise e.g. coughing, jumping, laughing is the most common type of incontinence and is caused by loss of anatomic support of the pelvic supportive structures in combinations with decreased urethral closure pressure. In the last decade of the 20th century, anatomic, video-radiological and dynamic studies have clarified the complex mechanisms by which the pelvic floor muscles control urinary continence and voiding function. "The integral theory" by P. Petros and Ulmsten (Petros P and Ulmsten U, 1990, pp.1-79) and the “Hammock hypothesis” by J.O. Delancey (1994) are complementary.

Both theories, based on different investigational techniques, have shown that the stability of the endopelvic fascia and its firm attachment to the arcus tendineus fascia pelvis and levator ani muscle are essential for adequate urethral support and urethral closure during stress. In healthy asymptomatic women the proximal two-thirds of the urethra lies within the abdominal cavity. An increase in intra-abdominal pressure will be almost equally transmitted to the bladder and proximal urethra. The pressure rise in the urethra during a cough is frequently higher than the pressure rise in the bladder leading to a pressure transmission ratio (PTR) of over 100%. The rise in urethral pressure precedes the intra-abdominal pressure rise by approximately 200ms (Constantinou and Govan, 1982, pp.964-969). These observations indicate that contraction of the pelvic floor muscle is a compensatory reflex that aids to maintain continence during periods of increased intra-abdominal pressure. Based on the concepts of the Integral Theory and the Hammond Hypothesis, Ulmsten et al. developed the sub urethral sling procedure nowadays known as the TVT procedure (Ulmsten U and Petros P, 1995, pp.75-82).

A small polypropylene vaginal tape is placed - tension free - under the pubo-vesico-cervical fascia, via a minimal incision in the anterior vaginal wall at the level of the midurethra. The ends of the tape are loosely fixed in the musculature of the abdominal wall or foramen obturatorium. This minimal invasive procedure has become the treatment of choice in anti-incontinence surgery and underlines the important role of the pelvic floor supportive tissue in the pathogenesis of stress urinary incontinence. Although this surgical strengthening of urethral support is clearly effective, randomized trials and longitudinal studies reveal that 2 years after surgical correction 10 to 20 % still suffer from urinary incontinence. (Nilsson et al., 2004, pp. 1259-1262; Ward and Hilton, 2004, pp.324-331; Schraffordt Koops 2006, pp.65-74).

Three factors are involved in the mechanism of stress incontinence: laxity of urethral support, decreased resting urethral closure pressure, and decreased transmission of increased abdominal pressure. Continued studies have shown that maximum urethral closure pressure (MUCP) is the predominant factor associated with stress incontinence. In general, almost all studies using urethral profilometry show a lower MUCP in stress incontinent women compared with asymptomatic continent counterparts. (DeLancey et al. 2008. 2286-2290).

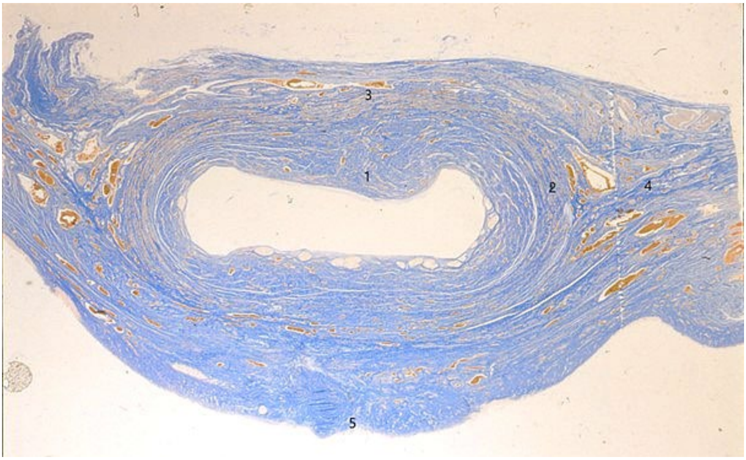

Fig.1.4: transverse section Urethra and Anterior vaginal wall: 73year old female: the urethral lumen and anterior vaginal wall. 1.longitudinal smooth muscle. 2. circular smooth muscle. 3 striated urethral muscle. 4. Peri-urethral striated muscles. 5, vaginal mucosa. (Azan staining: Van Geelen 1983).

1.4 Neuroanatomy

The function of the lower urinary tract is under control of both divisions of the autonomic nervous system. The bladder and urethra are supplied by parasympathetic fibers by way of the pelvic nerves and by sympathetic fibers by way of the hypogastric nerves. Both the pelvic and the hypogastric nerves are mixed nerves and contain motor or efferent to and sensory or afferent fibers from the bladder and urethra.

There is no consensus as to the peripheral innervation of the striated urethral muscle. Some authors indicate that the intramural striated muscle receives its motor innervation by branches of the pelvic nerve other investigators conclude that the somatic innervation of the urethral striated muscle is supplied by the pudendal nerve (Gosling et al.,1977, pp.302; Tanagho et al., 1982, pp.405). The striated musculature of the pelvic floor receives its somatic afferent and efferent innervation through the pudendal nerves (fig.1.5).

1.5 Pelvic nerve

The pelvic nerve is the principal motor supply to the detrusor muscle. The preganglionic parasympathetic fibers in this nerve originate in the intermediolateral cell column in the sacral segments S_{2-4} of the spinal cord. The pre-ganglionic axons pass through the ventral roots and pelvic nerves and synapse in the ganglia of the autonomic pelvic and vesical plexus. In humans the density of the parasympathetic nerve endings decreases distally in the bladder neck and urethra. Acetylcholine is the principal neurotransmitter at the cholinergic nerve endings. Recent observations suggest the presence of a second non-cholinergic neurotransmitter, most probably purinergic in nature, at the neuro-effector sites in the mammalian bladder.

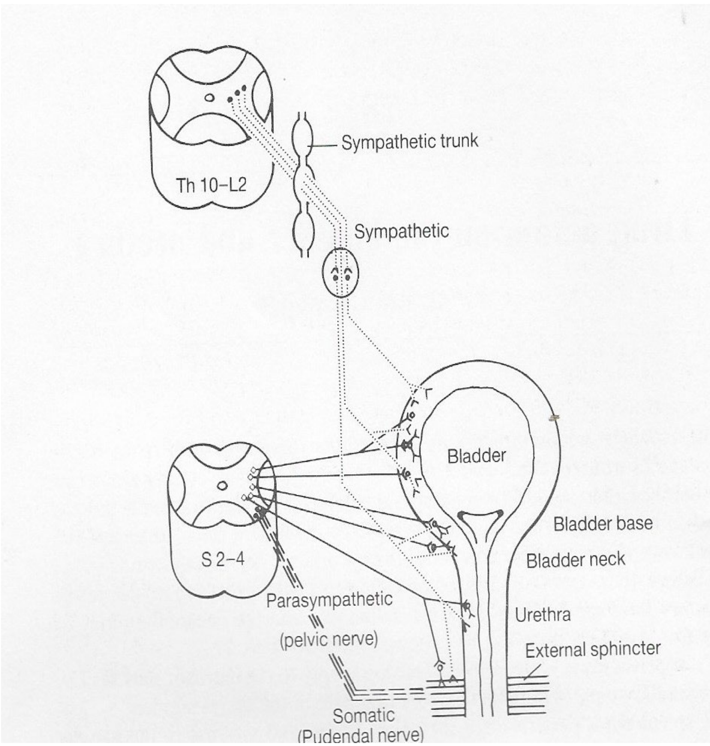

Fig.1.5: spinal cord and the efferent innervation of the lower urinary tract and pelvic floor. (Proc. XII World Congress.1988. Advances in Gynecology and Obstetrics. Chapter 28.).

1.6 Hypogastric nerve

The preganglionic sympathetic -adrenergic- fibers to the lower urinary tract stem from the thoracolumbar segments Th_{10}-L_2, pass through the splanchnic nerves and most of them synapse in the ganglia of the superior hypogastric plexus. The pre- and postganglionic sympathetic fibers continue to terminate in the ganglia of the pelvic and vesical plexus. Some of the postganglionic sympathetic fibers accompany the blood vessels in the wall of bladder and urethra, while others terminate on detrusor and urethral smooth muscle. Still other postganglionic sympathetic fibers terminate on the postganglionic parasympathetic neurons. Noradrenaline released from postganglionic synaptic nerve endings may thus interfere with the cholinergic transmission in the parasympathetic ganglia. The presence of interganglionic connections between the adrenergic and cholinergic systems provides for functional interaction of sympathetic and parasympathetic system in the innervation of the lower urinary tract. In man both alpha- and Beta-adrenergic receptors are present in the bladder and urethra. Beta-adrenergic (i.e. relaxation-mediating) receptors predominate in the detrusor muscle. Alpha-adrenergic (i.e. contraction-mediating) receptors predominate in the bladder base, bladder neck and in the urethra (fig 1.5). The increased sympathetic activity recorded during the storage phase acts to promote bladder filling and simultaneously increases urethral resistance by stimulation of the alpha-adrenergic receptors in the bladder base and proximal urethra. There is no unanimity among investigators with regard to the density of the sympathetic innervation of the bladder neck and trigone area, but all studies indicate a scanty adrenergic innervation of the female urethra (Gosling et al.1977; Tanagho et al. 1982). The actual role of the autonomic nerve system in bladder control is undoubtedly more complex than the simplistic model suggested in the foregoing paragraph (Fig.1. 6).

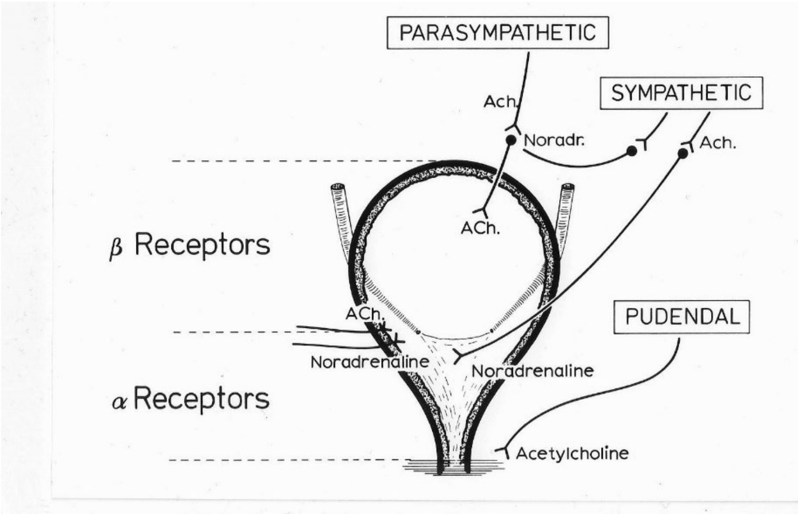

Fig. 1.6: schematic representation of the peripheral innervation of bladder and urethra. (reprint from Int. Urogynecol J. 1990; 1:19-24).

1.7 Summary

In spite of the differing opinions which still exist with regard to some aspects of the anatomy and innervation of the bladder neck and urethra, it is generally agreed that the closure function of the bladder neck and proximal urethra is determined by the tonus of the sympathetically innervated smooth muscle bundles together with the inherent tension exerted by the binding fibroelastic tissue. At mid-urethra, the urethral smooth muscle combines with the urethral striated and periurethral striated muscle systems to maintain adequate urethral closure pressure. Resting urethral resistance, transmission of intraabdominal pressure rise to bladder and urethra and the contractility of the striated muscles in the pelvic floor co-operate to maintain urinary continence both at rest and under stress. Recording of the urethral closure pressure under static and dynamic conditions, known as urethral pressure profile (UPP), is a valuable tool in the assessment of urethral sphincter function.

1.8 References

Constantinou C, Govan D. spatial distribution and timing of transmitted and reflexly generated urethral pressure in healthy women. J Urol. 1982; 127: 964-969.

Delancey JOL. Structural support of the urethra as it relates to stress incontinence: the hammock hypothesis. Am. J Obstet. Gynecol. 1994; 170:1713-1723.

Delancey JOL. Structural aspects of the extrinsic continence mechanism. Obstet. Gynecol. 1988;72: 296-301.

Delancey JOL, Trowbridge E, Miller JM, Ashton Miller A et al. Stress urinary incontinence: relative importance of Urethral support and Urethral closure pressure. J Urol. 2008; 179: 2286-2290.

Donker PJ, Dröes JT, van Ulden BM. Anatomy of the musculature and innervation of the bladder and urethra. In Williams D.I and Chisholm G.D. (eds). Scientific foundations of Urology Vol II. William Heineman medical books Ltd London: 1976.

Gosling JA, Dixon JS. Critchley HOD, Thompson SA. A comparative study of the human external sphincter and periurethral levator ani muscles. Brit J Urol. 1981; 53: 35-41.

Gosling JA, Dixon JS, Lendon RG. The autonomic innervation of the human male and female bladder neck and proximal urethra. J Urol.1977; 118: 302-305.

Huisman AB. Aspects on the anatomy of the female urethra with special relation to urinary continence. Contr. Gynecol. Obstet. 1983;10: 1-31.

Hutch JA. Anatomy and physiology of the bladder, trigone and urethra. Butterworth Appleton Century Crofts, London. 1972; 62-133.

Nilsson CG, Falconer C, Rezapour M. seven-year follow-up of the tension free vaginal tape procedure for treatment of urinary incontinence. Obstet. Gynecol. 2004; 104:1259-1262.

Petros P, Ulmsten U. An integral theory of female urinary incontinence. Acta Obstet. Gynecol. Scand. (suppl 153) 1990; 69:1-79.

Rud T, Andersson KE, Asmussen M, Hunting A, Ulmsten U. factors maintaining the intraurethral pressure in women. Invest. urol. 1980;17: 343-347.

Schraffordt Koops SE, Bisseling TM, van Brummen HJ, Heintz PM, Vervest HAM. What determines a successful TVT: A prospective multicentre cohort study, results from the Netherlands TVT data base. Am. J Obstet. Gynecol. 2006; 194: 65-74.

Smith PCM. Age changes in the female urethra Brit. J Urol. 1972; 44: 667-670.

Tanagho EA, Meyers FH, Smith DR. Urethral resistance: its components and implications I. Smooth muscle components. Invest. Urol. 1969; 7:136-149.

Tanagho EA, Schmidt RA, Gomes de Araujo C. Urinary striated sphincter. What is its nerve supply. Urology 1982; 20: 415 -416.

Ulmsten U, Petros P. Intravaginal sling plasty (IVS): an ambulatory surgical procedure for treatment of female urinary incontinence. Scand. J. Urol. Nephrol. 1995; 29:75-82.

Versi E, Cardozo L, Studd J et al. Distal urethral compensatory mechanism in women with incompetent bladder neck who remain continent and the effect of the menopause. Neurourol. Urodyn. 1990; 9: 579-590.

Ward Kl, Hilton PA. Prospective multicenter randomized trial of tension-free vaginal tape and colposuspension for primary urodynamic stress incontinence. Am J Obstet. Gynecol. 2004;190: 324-331.

Westby M, Asmussen M, Ulmsten U. Location of maximum intraurethral pressure related to the urogenital diaphragm in the female subject as studied by simultaneous urethracystometry and voiding urethrocystography. Am J Obstet. Gynecol. 1982; 15: 408-412.

Zinner NR, Sterling AM, Ritter RC. The role of inner urethral softness in urinary continence. Urology 1980; 16: 115-117.

CHAPTER 2

EVALUATION OF URETHRAL FUNCTION

2.1 The Urethral Pressure Profile: UPP variables

The interaction between the continence mechanism and the micturition process involves several coordinated reflexes operating between bladder, urethra and striated muscles of the pelvic floor on one hand and the reflex centers in the sacral spinal cord on the other hand. In addition to these short neural pathways several long neural tracts, both ascending and descending, mediate the influence of higher central nervous system (CNS) centers on the functioning of the lower urinary tract (LUT) (Chai and Steers ,1997, 85-97).

Stimulated by the high prevalence of LUT disorders and the clinical problems encountered in the differential diagnosis and treatment of incontinence, urodynamic investigational techniques have been developed. Several techniques for simultaneously measuring intravesical pressure in relation to urethral closure pressure are at present available: open catheter systems, fluid or air-filled balloons, membrane catheters and microtip transducer catheters. With the aid of a mechanical puller a dual sensor measuring device is withdrawn, at a constant speed, from the bladder to the external meatus urethrae, thus allowing to record the urethral closure pressure at every point throughout the urethra in relation to the bladder pressure under both static and dynamic conditions, coughing, squeezing: Urethral Pressure Profile (UPP). By subtraction the difference between the Maximum Urethral Pressure (MUP) and total bladder pressure can be calculated: Maximum Urethral Closure Pressure (MUCP).

Simultaneous urethro-cystometry i.e. simultaneous measurement of the intravesical pressure and the urethral pressure profile (UPP), provides recording of the following parameters of urethral function. Definitions are according to the Standardization Committee of the International Continence Society (ICS) (Bates et al.1977,49: 207-210).

- Functional urethral length (FUL): the length of the urethra along which the intraurethral pressure exceeds the total bladder pressure.
- Anatomic urethral length (AUL): the distance between the point in the urethra where the intraurethral pressure exceeds the total bladder pressure and the point where the intraurethral pressure falls to atmospheric pressure.
- Bladder pressure or total bladder pressure (TBP): pressure within the bladder in relation to atmospheric pressure.
- Maximum urethral pressure (MUP): the maximum pressure of the urethral pressure profile recorded in relation to the atmospheric pressure.
- Urethral closure pressure (UCP or MUCP): the difference between the maximum urethral pressure and the simultaneously measured total bladder pressure.
- Point of Maximum urethral pressure (PMP): distance from the internal meatus to the point of maximum urethral pressure.
- Integrated pressure (IP/10): surface of the area between the urethral pressure curve and the bladder pressure level divided by 10.
- Pressure transmission ratio: urethral pressure rise in relation to increase in bladder pressure during coughing or Valsalva maneuver: PTR = $\Delta P_{ura}/\Delta P_{ves}$ x 100%.
- These definitions are further illustrated in Figure 2.1.

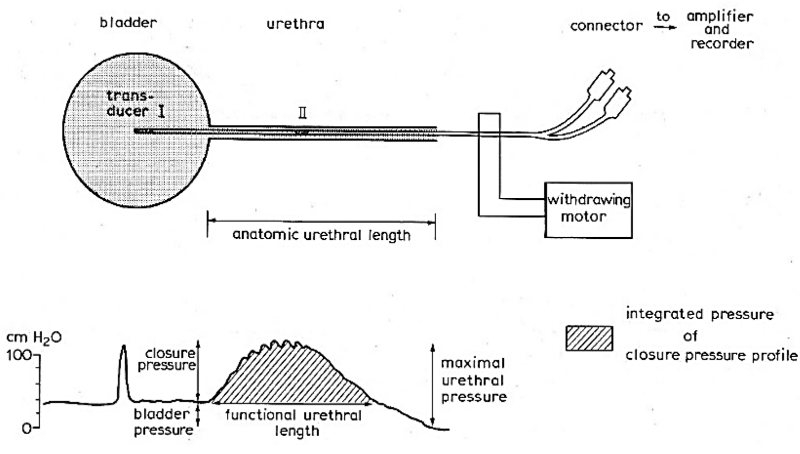

Fig. 2.1: representation of urethral pressure profile and UPP variables.

2.2 Techniques for measurement of urethral function

-The open catheter perfusion system (WFC) with its external strain gauge transducer has been most used for recording urethral pressure profile. This investigational technique measures the resistance by the urethral wall to flow output from one or more side holes in the catheter together with the pressure needed to maintain a constant flow within the system (Brown and Wickham, 1969, pp. 211-217). The accuracy and reliability of this system for pressure recording in the LUT have been well documented (Griffiths DJ, 2000, pp. 61-77). The correlation coefficient comparing each water perfusion measurement at rest with the other water perfusion measurements in the same patient was excellent at r=0.95 (Kuhn et al.,2007, pp. 932-935). A disadvantage in routine measurement of the UPP with a fluid perfusion system is the slow frequency response of the system to sudden changes in intraabdominal pressures (e.g. coughing), rendering this technique useless for dynamic recordings. Technical difficulties with fluid or gas perfusion systems such as air bubbles, coagula, and artefacts induced by patient movements led to the development of new investigational techniques.

-Asmussen and Ulmsten introduced a dual channel technique for measuring simultaneously the total bladder pressure and the intraurethral pressure over the entire urethral length: simultaneous urethro-cystometry (Asmussen and Ulmsten, 1975, pp. 83-103). Two 2 silicon strain gauge pressure transducers are mounted, 6 cm distance from each other, in a 7 Fr. semiflexible Dacron catheter. The proximal pressure sensor is located at 6 cm from the tip where the catheter has an outer diameter of 7 Fr (2.33mm). The distal sensor is at the tip of the catheter, where the outer diameter is 5 Fr.(1.65mm) (Millar and Baker, 1973, pp. 86-87). During a recording session the distal sensor is situated in the bladder and registers the intravesical pressure whereas the proximal sensor measures directly the compressive force of the urethral wall on the transducer membrane as it is withdrawn from the bladder through the urethra. The transducers are connected to a differential amplifier which also calculates the difference between urethral pressure and bladder pressure, i.e. urethral closure pressure (UCP). The correlation coefficient comparing each microtip measure with the other microtip measures in the same patient was also good ranging from r=0.70 to 0.80 (Kuhn et al. 2007).

Two micro-transducer catheters are available: The “Millar “micro-transducer Catheter, described above (Millar Instruments Inc. Houston, Texas) and the “Gaeltec” catheter, a silicone rubber coated 7 Fr. gauge catheter bearing 2 micro-transducers, one at the tip and one 6 cm proximally (Gaeltec Ltd, Dunvegan Scotland). The Gaeltec catheter is more flexible than the Millar catheter, the recording techniques and the measurements by these 2 catheters are comparable.

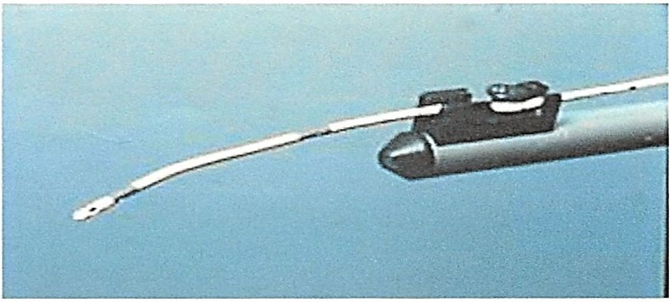

Fig. 2.2: microtip catheter with two pressure sensors.

Three parameters are of importance when measuring the urethral pressure profile: 1. outer diameter of the catheter between 4-10 Fr. 2. A withdrawal rate of the catheter from the bladder through the urethra of 3-4 mm/sec. 3. In-case of open-end catheters the infusion rate of the system kept to approximately 1-2 ml/min (Asmussen 1976,10; pp.1-6). The fluid filled perfusion catheter, and the dual micro-tip transducer catheter are reliable recording systems and currently the most widely used and studied catheters for urodynamic studies. If performed according to these criteria and standardized methodology, the coefficients of variation (CV=SD/mean x 100%) of the urethral closure pressure measurements as determined by the two techniques are comparable and vary between 3-11%." *In vitro"* studies assessing the test-retest variation and reproducibility of water perfusion systems and microtip pressure recording catheters may demonstrate excellent accuracy and reliability, they do not reflect biologic variations that occur in - *in vivo* -recordings. In addition, as the physical properties of the two UPP recording techniques used for the evaluation of urethral function differ, the UPP variables measured with the different techniques cannot be compared and are not interchangeable (Schmidt et al. 1977,10, pp. 390-397; Hilton P, 1982,1, pp. 303-311). There is currently no accepted gold standard technique for urethral pressure profilometry. Weber (2001) expressed accurately the criteria for a reliable diagnostic test: 1. Measurements must be performed in a standardized way: 2. results must be reproducible: 3. Calculated parameters for health and disease must be sensitive and specific, with clear cut-off levels and without overlapping values: 4. Calculated parameters must contribute to differential diagnosis and choice of treatment: 5. calculated parameters must correlate with the outcome of treatment

(Weber AM, 2001,56, pp.720-735). The available and most currently used techniques for urethral pressure profilometry do not fulfill the criteria of a useful diagnostic test but they have considerably contributed to better understand the physiology and pathophysiology of lower urinary tract functioning. During the last two decades new investigational techniques have been introduced as alternatives to the conventional UPP measurements.

These techniques include:

- T-doc dual-sensor air-charged catheter (AFC) is a single use disposable catheter system allowing for simultaneous pressure measurement in the bladder and in the urethra. This technology uses two miniature pressure-sensing air-filled balloons placed circumferentially around a polyethylene 7 Fr. catheter which communicates the pressure signal to an external semiconductor transducer. The two balloons, 6 cm apart, assess bladder pressure and circumferentially urethral pressure. Laboratory data demonstrate AFC catheters to exhibit strong linearity with minimal hysteresis and adequate frequency response up to 5 Hz which, according to the manufacturer, complies to capture clinically relevant pressure changes (Couri et al. 2018, pp. 619-625). T-doc catheters are disposable, cheap and currently the most widely used catheters in the USA. A few studies compared the performance of T-Doc catheters with open catheter perfusion systems during cystometry. The data show statistically significant differences in bladder pressure recorded by the two catheters, but the causes of these differences are unknown (Abrams et al., 2017, pp.1234-1242). In a prospective, single-blind, randomized trial, including 64 women referred for urodynamic investigation, measurements of urethral function obtained by air-charged and micro-transducer catheters were compared. Both techniques demonstrated a high concordance in UCP and Valsalva Leak Point Pressures (LPP) measurements: Lin's concordance coefficients of air-charged and microtip catheters were r= 0.82 and r= 0.79 respectively. The measurements of FUL had lower concordance. The air-charged catheter is as reliable as the microtip catheter but generally gives higher readings. Consequently, these techniques cannot be used interchangeably for clinical investigations (Zehnder et al., 2008, pp. 1013-1017). AFC's offer several advantages over existing catheters; they are cheap, disposable, easy to use and offer circumferential measuring capacity. A disadvantage is that the resistance of the balloon may lead to it being expelled during investigation. There is a lack of good quality research studies designed to evaluate the effectiveness of air-charged catheters in clinical practice (Abrams, 2017). To the best of my knowledge, there are no – or not yet - urodynamic studies including urethral pressure profiles, comparing UPP measurements obtained by water perfusion catheters with Air-charged catheters.

- Fiberoptic catheters: The technique is based on two miniature size optical fiber pressure sensors, with a diameter of 0,2 mm, embedded in a single catheter. The fiberoptic pressure sensor is sealed with a pressure sensing diaphragm that translates the amplitude of a reflected light signal into an electrical signal. These catheters are available in both disposable and reusable forms, are less fragile and less expensive than micro-transducer systems. The number of studies that assessed the validity and reproducibility of this technique for urodynamic investigation is limited. The results show that measurements of UCP and Pressure transmission ratio (PTR) with the fiberoptic catheter are significantly lower than those obtained with the micro-transducer technique. No significant difference was found between the two systems in the measurement of Valsalva Leak Point Pressure (LPP) (Elser et al., 1999, 371-374; Culligan et al., 2001, pp.253-257).

- Urethral pressure reflectometry (UPR): UPR was introduced as a novel technique for simultaneously recording of urethral pressure and the cross-sectional area in the female urethra. The technique uses a 45 cm-long polyvinyl chloride tube connected to a thin, highly flexible poly-urethane bag, inserted into the urethra using a Ch 8 feeding tube as introducer. The bag is 6 cm long and occupies only 0.4 mm^2 when placed in the urethra and a diameter of 5 mm when fully dilated. A digital signal processor generates wide band sound waves (100Hz to 16KHz) via a probe into the polyurethane bag. The acoustic reflections from the cavity are relayed to a computer which in turn converts the reflections and calculates the cross-sectional area. A syringe, used to pump air, and a transducer are connected to the system enabling to measure different pressures in the poly-urethane air bag simultaneously with continuous measurement of the cross-sectional area along the entire length of the urethra both at rest and during stress (Khayami et al., 2016, pp.1449-1458). The transducer measures the pressure in the system and the computer registers it. The air-pressure required to force the urethra open is the urethral pressure, which agrees with the physical definition of pressure (Lose et al., 2002, pp. 258-260). UPR measures the same pressures as conventional UPP systems but is not hampered by artifacts encountered with conventional methods and is – in vitro and in vivo – more reproducible (Klarskov and Lose. 2007, pp. 351-356). It is most of all a research tool, its clinical relevance has not yet been validated.

- Urethral Retro-Resistance Pressure (URP, Monitor[tm]): To find a more physiologic testing condition, a non-invasive technique was developed to measure urethral resistance to retrograde infusion of sterile fluid. URP is defined as the pressure required to achieve and maintain an open urethral sphincter. This method eliminates the need for a catheter insertion during the measurement of UCP and the risk of a systemic artifact (Slack et al., 2004, pp. 109-114). The system uses a cone-shaped measuring device placed 5 mm into the external meatus urethrae. The device infuses fluid at a controlled rate of 1 ml per second. The URP is the pressure required to open the sphincter urethrae. A large multicenter randomized study, including 258 stress incontinent women, comparing URP with MUCP measured during multichannel urodynamics and leak Point Pressure (LPP), showed a consistent relationship between URP and incontinence severity: the mean values of URP decreased with increasing severity of incontinence, whereas the mean values of MUCP and LPP did not. The data suggest that URP is a physiological measure of urethral function, the test has a good reproducibility and may have clinical utility as a diagnostic tool (Slack, 2004. pp. 109-114). These observations are at variance with the results of a multicenter study, including 52 women with stress incontinence studied using the Brown and Wickham technique, which found that MUCP and LPP modestly correlate with each other (r= 0.50-0.62, $P < 0.001$), and MUCP and LPP both demonstrated significant decreases with increasing severity of incontinence ($P< 0.01$). There was no significant correlation of these urodynamic parameters with objective outcome measures (pad -test) or other subjective outcome measures (QOL) (Nager et al., 2001, pp 395-400). The predictive value of URP, MUCP and LPP measurements in terms of incontinence severity and cure rates remains to be defined.

- Abdominal leak point pressure (ALPP). This is a dynamic test. ALPP is defined as the lowest value of intravesical pressure at which urine leakage occurs because of increased intra-abdominal pressure in the absence of a detrusor contraction. The increased intra-abdominal pressure can be induced by coughing or the Valsalva maneuver (VLPP). In an anatomically normal urethra with a competent sphincter mechanism increased intra-abdominal pressure does not cause urine leakage. Urine loss provoked by coughing and/or Valsalva maneuver, or by jumping is characteristic for the clinical diagnosis stress urinary incontinence (SUI) and as such ALPP can be helpful as a diagnostic tool for assessment of urethral sphincter competence. ALPP is commonly used as an adjunct to UPP for assessment of urethral function but cannot be used as a single test to grade the severity of UI. ALPP does not meet the criteria for a useful diagnostic test because of lack of standardization, biologic variation and large overlap in ALPP