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Physiological and pathophysiological implications of micromotion activity in urinary bladder function

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Abstract

‘Micromotions’ is a term signifying the presence of localized microcontractions and microelongations, alongside non-motile areas. The motile areas tend to shift over the bladder surface with time, and the intravesical pressure reflects moment-by-moment summation of the interplay between net contractile force generated by micromotions and general bladder tone. Functionally, the bladder structure may comprise modules with variable linkage, which supports presence of localized micromotions (no functional linkage between modules), propagating contractions (where emergence of linkage allows sequential activation) and the shifting of micromotions over time. Detrusor muscle, interstitial cells and intramural innervation have properties potentially relevant for initiating, coordinating and modulating micromotions. Conceptually, such activity could facilitate the generation of afferent activity (filling state reporting) in the absence of intravesical pressure change and the ability to transition to voiding at any bladder volume. This autonomous activity is an intrinsic property, seen in various experimental contexts including the clinical setting of human (female) overactive bladder. ‘Disinhibited autonomy’ may explain the obvious micromotions in isolated bladders and perhaps contribute clinically in neurological disease causing detrusor overactivity. Furthermore, any process that could increase the initiation or propagation of microcontractions might be anticipated to have a functional effect, increasing the likelihood of urinary urgency and detrusor overactivity respectively. Thus, models of bladder outlet obstruction, neurological trauma and ageing provide a useful framework for detecting cellular changes in smooth muscle, interstitial cells and innervation, and the consequent effects on micromotions.

Keywords autonomous activity, micromotions, whole bladder models.

The bladder is a large organ, generally serving as a reservoir for urine, but with intermittent expulsion of urine as perceived timely by the individual; this alternation between storage and voiding phases is known as the ‘micturition cycle’. Implicitly, effective storage implies that the reservoir is fully relaxed, and voiding indicates that the whole organ is contracting synchronously. The presumed general congruence of the reservoir (i.e. the whole organ is either relaxed or contracting) led to suggestions that the bladder musculature is a ‘functional syncytium’, so that behaviour of any part of the bladder could be taken as indicative of the state of the rest of it. However, this is now known to be incorrect, as clearly indicated by the
presence of micromotions (localized contractions and elongations) during urine storage (Drake 2007). Thus, to comprehend reservoir function of the bladder, and potentially voiding as well, understanding is needed of the motility properties of the whole organ, and how this translates into the pressure recorded from the bladder lumen. Such information cannot be obtained from conventional pharmacological muscle strip experiments.

In this review, we consider the knowledge of micromotions in various species, how these are changed pathophysiologically, and speculate on the relationship between this activity and the urodynamic properties of pressure and sensation.

**Functional properties of the bladder**

The lower urinary tract (LUT) consists of the urinary bladder, urethra and the urinary sphincter complex (Fig. 1). The bladder is a hollow smooth muscle organ. Conventionally, it is described as comprising the bladder body, located above ureteric orifices, and the base, lying between the ureteric orifices and the urethrovesical junction. The bladder is lined by transitional epithelium, referred to as the urothelium. Its muscularis wall is formed of the detrusor smooth muscle cells. Bladder wall thickness ranges between 1.8 and 4.7 mm in humans (Narumi et al. 1993) and tends to be greater in men than women (Hakenberg et al. 2000). The thickness of the bladder wall depends on the degree of distension by the contained volume. The different extents of wall stretch are coupled with corresponding changes in smooth muscle cell length.

The orientation and interaction between the smooth muscle cells in the bladder are important, as this will determine how the bladder wall behaves and what effect activity in the cells will have on its shape and intravesical pressure (Andersson & Arner 2004). In many species, detrusor cells are oriented longitudinally in the outer and inner layers and circularly in the middle layer (Andersson & Arner 2004). In the human detrusor, bundles of muscle cells of varying size are surrounded by connective tissue rich in collagen. The bundles are not clearly arranged in distinct layers, but run in various orientations, forming a meshwork (Drake et al. 2003b, Andersson & Arner 2004). The bundles vary in size, often a few millimetres in diameter, and composed of several smaller sub-bundles.

**Key features of the detrusor smooth muscle cells**

Detrusor muscle cells are spindle-shaped single nucleated cells which lack regular sarcomeric structures (Andersson & Arner 2004). Instead, α- and β-actin thin filaments, which are attached to dense bodies on the cell membrane, provide binding sites for myosin thick filaments (Andersson & Arner 2004). Interaction between actin and myosin filaments, initiated by an increase in intracellular Ca²⁺ levels, results in smooth muscle contraction (Fry et al. 2010). Ca²⁺ can enter the cytoplasm through the cell membrane via L- and T-type Ca²⁺ channels. It can also be released from intracellular stores through Ca²⁺-induced Ca²⁺ release via ryanodine receptors or Ca²⁺ release triggered by inositol triphosphate (IP₃) acting on IP₃ receptors expressed on the sarcoplasmic reticulum (Wu et al. 2002, Andersson & Arner 2004). The Ca²⁺ activation of the contractile proteins is considered to occur via a phosphorylation pathway where Ca²⁺ binds to calmodulin, and the Ca²⁺/calmodulin complex activates the myosin light-chain kinase, which in turn uses ATP to phosphorylate and activate myosin, resulting in cross-bridge formation with actin filaments. Contraction then occurs as cross-bridge cycling produces tension and shortening of muscle fibres. Dephosphorylation of the myosin light chain by myosin light-chain phosphatase results in relaxation of smooth muscle cell (Andersson & Arner 2004, Fry et al. 2010). Intracellular messengers that regulate the activity of these enzymes can therefore modulate contractile activity of detrusor smooth muscle cells.
Storage and voiding phases of the lower urinary tract

The bladder alternates between reciprocal ‘storage’ and ‘voiding’ phases, which signify two synergic coordinated states of the bladder and the urethra. Storage of urine signifies that there is no global bladder contraction, enabling the organ to function as a low-pressure reservoir. During the storage phase, there is probably background descending inhibition from higher CNS centres (Sadananda et al. 2013). At the same time, the bladder outlet (particularly the urinary sphincter) remains fully active, preventing flow of urine. Sympathetic nervous system storage reflexes result in contraction of the bladder neck and contribute to bladder relaxation at a peripheral level, thereby allowing the bladder to accommodate urine at low pressure throughout the filling range (de Groat 1997). A third state is evident in men at the time of ejaculation, when the synergic control maintains the bladder and urethral sphincter in the non-contracting state and the bladder neck contracted.

There are three crucial lower motor nuclei for LUT function: the parasympathetic nucleus of the sacral spinal cord controlling the detrusor, Onuf’s nucleus in the sacral spinal cord controlling the sphincter complex, and the sympathetic nucleus in the thoracolumbar spinal cord controlling the bladder neck. Maintenance of the synergic coordination of these nuclei as appropriate for storage, voiding and male ejaculation is regulated by the upper motor neurones. For voiding, it is the pontine micturition centre (PMC) which ‘switches’ the relevant spinal nuclei to the appropriate state for voiding. When voiding is instigated, bladder contraction results from activation of the parasympathetic nucleus, while opening of the channel for flow is achieved by inhibiting the sympathetic nucleus and Onuf’s nucleus, respectively, allowing the bladder neck and sphincter to relax (Fowler et al. 2008).

Afferent (sensory) information is sent via the pelvic nerve and the spinal cord to the periaqueductal grey (PAG) and onwards to higher centres responsible for conscious awareness (sensation). The PAG relays onto the PMC and receives the permissive input from the cerebrum which determines the timing of initiation of voiding (Fowler et al. 2008).

Terminology

Throughout this review, we emphasize the need to distinguish the bladder wall movements from their associated effects on pressure. As there is potential to confuse the numerous processes potentially relevant, we use the following descriptive terminology (Fig. 2).

1. Micromotions indicate the presence of localized motility, comprising microcontractions and microelongations. Any area that is not contracting or elongating can be referred to as ‘non-motile’.
2. Microcontraction indicates phasically decreasing separation between points. This can take the form of propagating microcontractions, which commence at an initiation point and spread directionally for a certain distance. Alternatively, there are non-propagating microcontractions, that is synchronous contraction of a defined area around a focal point.
3. Microelongation indicates phasically increasing separation between points. In theory, this could result passively, firstly as a consequence of distension by phasic increases in intravesical pressure, or secondly due to traction from adjacent microcontractions.
4. Shifting is used to signify that areas of motility tend to shift with time, so that there is discrepancy in focal and initiation points (for non-propagating and propagating microcontractions respectively) for the same bladder viewed at different times.

When alluding to bladder pressure, we use the following urodynamic terms:

1. Intravesical pressure is measured from within the bladder lumen.
2. Compliance relates bladder pressure to volume. A ‘compliant bladder’ signifies that minimal pressure change occurs over a substantial change in volume.
3. Baseline pressure indicates the lowest pressure at a stated time. Tonic pressure change indicates that there is a sustained increase (or decrease) in the baseline pressure.
4. Phasic pressure fluctuations are the term describing the pressure fluctuations above baseline commonly seen in the isolated bladder.

Clinical and experimental urodynamic studies often use the word ‘contraction’ when there is a change in intravesical (detrusor) pressure. For example ‘non-voiding contraction’ is a term used in several publications in the context of pressure recording. Clearly, the change in intravesical pressure must reflect some sort of contractile activity of the detrusor, but differing forms of contraction could have similar effects on intravesical pressure. For example, in theory, global bladder contraction might look similar to multi-focal synchronized non-propagating micromotions. For this reason, we use descriptive terminology for pressure observations (tonic and phasic pressure change), and we only use ‘contraction’ in the context of visible shortening of the bladder surface. ‘Voiding’? ‘non-voiding’ implies the activity is driven by the micturition reflex, so we feel it should be used primarily in
recordings from preparations in which the brainstem is still able to generate a voiding reflex, which is beyond the scope of the current review.

**Bladder wall movements and phasic pressure changes during the storage phase (non-pathological)**

It has long been generally assumed the bladder is inactive during the storage phase, with little motility and change in the intravesical pressure. After all, motility and pressure fluctuations appear counter-intuitive, as they would seemingly counteract reservoir function. However, small phasic fluctuations in pressure of the cat bladder prior to micturition were reported in 1892 by Sherrington (Sherrington 1892). Subsequently, in many species (Sugaya & de Groat 2000, Drake et al. 2003a), phasic fluctuations in pressure have been observed under conditions modelling the storage phase, generally increasing in amplitude and frequency as the bladder is filled (Sherrington 1892). In addition, bladder wall movements (micromotions) have been detected in various species, including the guinea pig, rat, pig and human (Levin et al. 1983, Maggi et al. 1988, Gillespie 2004, Lagou et al. 2006, Parsons et al. 2012). Most descriptions have used isolated whole

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**Figure 2** Schematic representation of micromotions. (a) external surfaces of the bladder seen from the anterior viewpoint, with the posterior wall portrayed as if hinged on the bladder’s left-hand side from the anatomical perspective. LUO = left ureteric orifice, RUO = right ureteric orifice. Both microcontractions (circles) and microelongations (rectangles) are illustrated. 1 and 2: localized microcontractions centred on a focal point (indicated by a star). 1. indicates that it is common to see such movements near one of the ureteric orifices in an unstimulated empty bladder, even when the rest of the bladder appears quiescent. 3: a propagating microcontraction, with the initiation point indicated by a star, from which contractions sequentially spread directionally. 4. A microelongation. As it is adjacent to the propagating microcontraction at 3, it can be speculated that the elongation is a result of traction from the initiation point. 5. A microelongation. As it is distant from any microcontractions, it can be speculated that the elongation may be a result of fluid shifts, that is, if part of the bladder wall contracts on a fixed volume of fluid, and areas that are relaxed will be expanded. (b) Pattern shifting. (i) At a given time, regions of motility appear consistent, but when the same bladder is re-examined a few minutes later, (ii) regions of motility have generally shifted.
bladders or bladder segments. For small animal species, these can be maintained in vitro using transmural oxygenation by diffusion. For large species, the larger tissue volume means that artificial perfusion is needed to maintain oxygenation and prevent ischaemia (Parsons et al. 2012). The use of models in which the CNS is either absent or altered means that the normal descending inhibitory influences may be lost, and it may be this ‘disinhibited autonomy’ that allows clearer expression of intrinsic properties such as micromotions in isolated bladder studies.

**Bladders from small animal species**

In isolated whole guinea pig bladders, using multiple-point motion analysis, it was illustrated that the bladder possesses micromotions, comprising discrete non-propagating and propagating microcontractions and localized microelongations (Drake et al. 2003a). Simultaneous measurement of bladder wall movements and intravesical pressure demonstrated phasic fluctuations in intravesical pressure which were associated with complex shifting movements within the bladder wall. Single microcontractions were associated with changes in intravesical pressure, although on some occasions, no pressure change was detected despite apparently substantial movements in the bladder wall (Drake et al. 2003a). It was postulated that where a microcontraction did not influence the pressure trace, the force produced by the contraction was mechanically damped (possibly by a synchronous microelongation elsewhere in the bladder). Where a microcontraction did elicit a detectable phasic fluctuation, it would indicate the bladder wall overall must have enough tone to permit transmission of force (Drake et al. 2003a). Accordingly, it was surmised that intravesical pressure reflects the net effect of summation of all movements of the bladder surface, both contraction and elongation.

In the isolated, unstimulated, fully empty rat bladder, a circumscribed area of microcontraction could be seen near one (not both) of the vesicoureteric junctions (VUJ) (Drake et al. 2003c). Simultaneous recording of phasic fluctuations and the micromotions demonstrated that these localized microcontractions did not cause any substantial change in intravesical pressure (Drake et al. 2003c). These baseline microcontractions, consistently being detected basolaterally, suggested that the region may have a specific role in vivo, and it was postulated that the proximity to the VUJ might represent a functional mechanism for the bladder at the location where urine boluses enter the organ from the ureter. For example, microcontractions could enable configuration of the bladder as it adapts to the arrival of successive urine boluses (Drake et al. 2003c). With ongoing filling, micromotion activity of the isolated bladder changed to propagating microcontractions, with shifting, and these were associated with low-amplitude phasic pressure fluctuations.

Video filming of mouse bladder in the absence of any pharmacological stimulus revealed the presence of localized micromotions throughout the bladder wall, except the trigone area (Lagou et al. 2006). These micromotions occurred at a similar frequency to phasic pressure fluctuations. The nature of surface movements was similar in different parts of the bladder wall and areas tended to maintain a constant phase relationship throughout the observation period (Lagou et al. 2006).

**Bladders from large animal species**

*In vitro* filming of pig bladder wall strips and simultaneous measurement of isometric tension demonstrated that micromotions were present in pig urinary bladder (Coolsaet et al. 1993). Coolsaet and colleagues reported that microcontractions and microelongations occurred independently at random over the bladder surface, with shifting of the patterns. On some occasions, micromotions did not influence the force of the bladder strips (Coolsaet et al. 1993), further emphasizing that micromotions do not always translate to changes in bladder wall tension. They also described the occurrence of antiphase activity in separated areas, meaning that one region would contract in alternation with another, with low- and high-frequency areas seen in the same specimen (Coolsaet et al. 1993).

Using isolated whole pig bladders and simultaneous measurement of bladder wall movements and intravesical pressure, micromotions were also detected throughout the bladder surface (Fig. 3) (Parsons et al. 2012). Within the filmed surface, frequencies of micromotions in different areas were not exactly the same, and two areas could show coincident in phase non-propagating microcontractions at some point in time and out of phase microcontractions at another time (Parsons et al. 2012). The correspondence between micromotions and whole bladder pressure fluctuations was variable. These micromotions occurred at a frequency similar to the recorded pressure fluctuations. However, on occasions, no obvious pressure changes were detected despite apparently substantial movements in the bladder wall, and it was concluded that changes in intravesical pressure will be the result of the summation of all bladder wall movements, not solely from the proportion of the bladder surface being filmed (Parsons et al. 2012).

**Human urinary bladder**

Studies using *in vitro* isolated whole human bladders have not been reported. However, a micromotion
detection catheter was developed, consisting of recording electrodes attached to a balloon mounted on a catheter. This was used to seek bladder micromotions in healthy female volunteers (Drake et al. 2005). Micromotions were detected in the bladder wall, with localized microcontractions characterized by gradual onset and decline, occurring at a frequency of about one contraction/min, and no apparent associated changes in intravesical pressure (Drake et al. 2005). Micromotions were only detected in a third of tested volunteers, which could indicate that only a subgroup of healthy women manifest micromotion activity or that the experimental approach was inhibitory or insufficiently sensitive (Drake et al. 2005).

The physiological implications of micromotions

The above studies indicate that the contractile activity of the bladder wall cannot simply be extrapolated solely from the intravesical trace (Drake et al. 2003a, 2005) and that substantial activity may occur in the bladder wall which is virtually unrepresented by pressure transients.

The nature of the bladder wall movements is loosely reminiscent of gastrointestinal peristalsis, including the observation of more than one type of movement. The cellular basis of peristalsis derives from the interstitial cells of Cajal, modulated and disseminated by intramural myenteric plexuses (Sanders 1996). Modulating circuits are found within these plexuses which receive diverse inputs and are capable of mediating local reflexes, conferring a modular structure (i.e. autonomous areas of smooth muscle controlled by dedicated integrative circuits). Thus, peristalsis includes segmentation and propulsive contractions, which is somewhat akin to localized and propagating bladder microcontractions. Furthermore, the bladder possesses cellular structures somewhat similar to the gut, namely interstitial cells (ICs) and intramural nerve plexuses (although substantially less complex than the myenteric plexuses). This functional and structural similarity led to the proposal that the whole bladder behaves as if comprised of linked semi-autonomous modules, which act as functional contractile units within the detrusor (Drake 2007). In this model, a module would be defined as the extent of a localized micromotion, while emergence of propagating contractions signifies functional linking leading to sequential activation of adjacent modules (Drake 2007). The linking may manifest as sequential activation, hence a propagating microcontraction. However, there is also reason to suppose more complex coupling, for example, where the activity in spatially separated modules shows a constant phase relationship or a phase cycling gradually passing from in-phase to antiphase and back again or the antiphase coupling of separate areas (Coolsaet et al. 1993). Propagating microcontractions are detected in bladders in response to an increase in intravesical volume or stimulation by applying a muscarinic agonist at low concentrations (Sui et al. 2003). The pattern shifting of micromotions

Figure 3 Micromotions and intravesical pressure in an isolated pig bladder. On the left is a photograph of the pig bladder, with added surface features highlighted to indicate the locations where micromotions were tracked. On the right, the pressure (above) and the micromotions (below) are plotted over a 3-min period. The micromotions are labelled (a), (b) and (c) in correspondence with the respective areas on the photograph, with downward deflection in each line indicating shortening. Note that in this example, micromotions generated only small pressure fluctuations, as indicated by the vertical dotted lines. The green dotted line at 100s shows obvious shortening in (a) and (b); the lack of pressure change with these contractions may reflect a damping effect of the elongation seen in (c).
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indicates that the modules are not structurally fixed, and the original premise that a module might be defined anatomically (Drake et al. 2001, Drake 2007) is probably not correct.

Micromotions, especially non-propagating microcontractions, do not always translate to evident changes in intravesical pressure, as discussed above. It can be assumed that several peripheral factors determine intravesical pressure, including the number and size of modules active, the extent to which their activity is showing coordinated linkage and overall intramural tension in the remainder of the bladder wall (Drake et al. 2003c). Thus, observed intravesical pressure properties are likely to reflect moment-by-moment summation of the interplay between net contractile force and tone.

Storage phase motility is a counter-intuitive property for a reservoir organ, but conceptually, it could facilitate two properties which are not fully understood: the generation of afferent activity (filling state reporting) in the absence of intravesical pressure change and the ability to transition to voiding at any bladder volume. Localized microcontractions are likely to cause focal distortion which will provide a substrate for sensory activity through direct stimulation of intramural afferents (Gillespie 2004). Correspondence between the pattern of afferent nerve firing and small-amplitude phasic pressure fluctuations has been reported in the rat (Iijima et al. 2009). As micromotions generally increase in frequency and amplitude with bladder volume, the associated ‘distortion-driven’ afferent stimulation will correlate with volume. Extrinsic influences on micromotion expression (e.g. from circulating hormones, or efferent innervation) could alter the gain (sensitivity) of the system. For example, reduced circulating adrenaline may allow greater expression of micromotions, which may explain the emergence of desire to pass urine people often experience when they return home (‘latchkey’ urgency). Alternatively, CNS efferents intermittently driving a transient increase in micromotions might enable a ‘sampling’ approach to gauging bladder volume. Peripheral sampling, as opposed to continuous monitoring, could explain the intermittent awareness of bladder filling experienced by individuals with normal LUT function. Regarding potential to transition to voiding at all bladder volumes, this ability implies that the bladder is maintained in a ‘state of readiness’ throughout the storage phase. Storage phase motility could serve to distribute tension and avoid localized over-distension, while helping configure detrusor muscle fascicles to the steady rise in urine volume delivered from the ureters throughout the storage phase. This avoids the non-uniform expansion and poorly configured musculature that could arise if the detrusor was quiescently passive during filling. Thus, micromotions theoretically could participate in two recognized properties of LUT function in the intact organism. Extrapolating to clinical pathophysiology, enhancement of micromotions and modular activity may result in exaggerated sensation from the bladder in absence of urodynamically detected increase in bladder pressure, resulting in pathological conditions such as sensory urgency (Drake et al. 2003c, Drake 2007). Conversely, loss of modular activity could lead to decreased sensation and increased post-void residual urine (Drake et al. 2003c).

The origin of microcontractions in the bladder

The mechanisms generating and coordinating the micromotions are not currently clear. The region between the basement layer of the bladder urothelium and the luminal surface of the detrusor muscle (lamina propria) has a complicated structure which may signify potential to contribute to generation of detrusor motility. This layer contains sensory nerves, ICs and a type of smooth muscle termed the muscularis mucosa (Andersson & Arner 2004, McCloskey 2011, Heppner et al. 2011).

The areas of bladder wall associated with non-propagating microcontractions involve several square millimetres at any given moment, suggesting that a large number of smooth muscle cells act as a functional working unit at that time. In a recent study, macroscopic electrical propagation was recorded in guinea pig bladder using a 64-electrode array positioned at various sites on the serosal surface (Hammad et al. 2014). It was reported that (1) electrical waves originated from different sites on the bladder and propagated predominantly in the axial direction for a limited distance before terminating spontaneously and (2) electrical activities occurred simultaneously in different areas of the bladder wall (patches) (Hammad et al. 2014). It was hypothesized that these electrical waves/patches may form the basis for microcontractions/microelongations (Hammad et al. 2014). As this method is fundamentally two-dimensional, as is video filming, it is not currently known whether all micromotion activity is co-planar with the bladder surface (x- and y-vectors) or whether micromotions may also occur in a perpendicular direction (z-vector; Fig. 4).

As myogenic transmission is limited, then the propagating waves might also involve other non-myogenic mechanisms (Drake et al. 2003a). In circumstances such as isolated bladder models, there is clearly no extrinsic innervation input, so the autonomous activity must represent an intrinsic property. As discussed earlier, the propagating waves of contraction in the
The intramural ganglia present in the bladder wall of smooth muscle cells within a circumscribed area. Each neuron must effectively make a connection with a number of smooth muscle cells, so that each neuron is associated in many patients with detrusor overactivity (DO), which is characterized as inappropriate detrusor contractions during the storage phase of the micturition cycle. DO is particularly evident in neurological diseases affecting the CNS above the sacral part of the spinal cord. In relation to the micromotion activity described above, alterations in such activity could be expected and may be mechanistically important (Coolsaet et al. 1993, Drake et al. 2001). For example, the isolation of the bladder from its innervation in suprasacral neurological disease may lead to disinhibited peripheral autonomy, that is enhanced micromotion activity due to loss of descending inhibition. Likewise, any process that could increase the initiation or propagation of microcontractions might be anticipated to have a functional effect, increasing the likelihood of urinary urgency and DO respectively.

Studies investigating bladder micromotions during pathological conditions are quite limited. In humans, some species could function as integrative circuits, receiving excitatory and inhibitory inputs, and the balance between these might either favour or hinder the contraction of the innervated extent of muscle (Drake et al. 2001). However, addition of neuronal inhibitory agents does not inhibit the micromotions in the isolated bladder (Drake et al. 2003a), indicating that any intrinsic innervation cannot be the main initiating factor.

Thus, both the ICs and intramural innervation have properties potentially relevant in pacemaker and integrative functions and may form the basis for initiating, coordinating and modulating micromotions of the bladder wall in some species either separately or together. This opens up the possibility of altering micromotion behaviour by moderating the activity of individual cellular contributors which may be active in its origin or propagation. For example, muscarinic and purinergic systems, transient receptor potential channels, the nitric oxide–cGMP–phosphodiesterase pathway and an increasing number of functional systems have been reported on one or more of the urothelium, innervation and ICs. Accordingly, these are potentially of interest to ascertain how they may influence micromotion activity (Grol et al. 2009, Rahnama’i et al. 2010, 2013, Birder 2011, Andersson & McCloskey 2014).

Pathophysiology

The motility of the bladder wall manifests a functional complexity which may have important implications in the aetiology and analysis of functional lower urinary tract disorders. Clinical problems affecting urine storage are highly prevalent and result in urinary urgency, frequency and urgency incontinence. These symptoms are associated in women with detrusor overactivity (DO), which is characterized as inappropriate detrusor contractions during the storage phase of the micturition cycle. DO is particularly evident in neurological diseases affecting the CNS above the sacral part of the spinal cord. In relation to the micromotion activity described above, alterations in such activity could be expected and may be mechanistically important (Coolsaet et al. 1993, Drake et al. 2001). For example, the isolation of the bladder from its innervation in suprasacral neurological disease may lead to disinhibited peripheral autonomy, that is enhanced micromotion activity due to loss of descending inhibition. Likewise, any process that could increase the initiation or propagation of microcontractions might be anticipated to have a functional effect, increasing the likelihood of urinary urgency and DO respectively.

Studies investigating bladder micromotions during pathological conditions are quite limited. In humans,
using the micromotion detection catheter (Drake et al. 2005), a significant difference in the prevalence of micromotions was detected between asymptomatic women (control group) and patients with increased bladder sensation (overactive bladder) (Drake et al. 2005) and bladder pain (Van Os-Bossagh et al. 2001). Patients with increased sensation on filling cystometry had a significantly higher prevalence of micromotion activity than the control group (Drake et al. 2005). As bladder afferents can be stimulated by local distortions of the bladder wall, exaggerated localized microcontractions and microelongations were associated with enhanced sensory return and sensation of urgency in these patients (Drake et al. 2005). The observation of patients in whom micromotions and strong urgency arose with no change in intravesical pressure suggests that pressure alone is not the main determinant of afferent activity (Drake et al. 2005). Importantly, the cellular structures which potentially influence micromotions are altered. Altered myogenic properties could underpin DO (Brading 1997), and changes within the smooth muscle cells or their pericellular environment can influence excitability and propagation (Chacko et al. 2014). For example, ICs become more numerous in the suburothelial and muscle layers after bladder outlet obstruction in the rat (Kim et al. 2011). Also in the rat, afferent activity and phasic pressure fluctuations are enhanced after spinal cord transection (Iijima et al. 2009). In human, there is increased numbers of suburothelial ICs, and reduced innervation seen in biopsies of the urothelium and suburothelial region in people with DO (Kuijpers et al. 2014).

Experimental partial bladder outlet obstruction (BOO) in rats resulted in coordinated micromotions during bladder stretch. Multiple areas of micromotion activity at baseline were detected in these rats compared to sham operated animals (Drake et al. 2003c). Increased coordination of micromotions was associated with enhanced phasic fluctuations detected in BOO rats. The linkage of enhanced micromotions to changes in bladder pressure could therefore be relevant in the context of DO.

With ageing, bladder problems clinically become substantially more prevalent, including DO and urinary urgency as mentioned above, but also voiding problems such as a weak urinary stream and incomplete emptying of the bladder. The latter can result from detrusor underactivity (DUA), which is defined clinically as a voiding contraction of reduced strength and/or duration, which prolongs urination and/or prevents complete emptying of the bladder within a ‘normal’ period of time (Abrams et al. 2002). The correspondence of micromotions with clinical bladder problems of ageing or DUA has not been undertaken. In aged mice, examination of the isolated bladder demonstrated a considerable reduction in the micromotion activity in all bladders, with some bladders failing to demonstrate any micromotions or phasic fluctuations (Lagou et al. 2006). Such loss of contractility would be worth evaluating in terms of the possibility that the autonomous activity of the bladder has a role in normal voiding (Drake 2007), such that deficient micromotions may be a feature of DUA. Although the correspondence between findings from studying the micromotion activity of the ageing bladder in animal models and clinical experience with the lower urinary tract symptoms in the geriatric population is a long way from being established, these studies could provide an insight into the potential complexity of the changes that occur in the ageing bladder.

Conclusions

To understand storage and voiding functions of the bladder, it is necessary to study the motility properties of the whole organ, and how this translates into the intravesical pressure. Bladder motility manifests as micromotions, comprising microcontractions and microelongations, alongside non-motile areas. This is most evident when input from the CNS is either absent or altered, so that the normal descending inhibitory influences are lacking; this ‘disinhibited autony’ allows clearer expression of intrinsic properties such as micromotions in isolated bladder studies. Simultaneous measurement of bladder wall movements and intravesical pressure shows phasic fluctuations in pressure associated with complex shifting movements. Sometimes, no pressure change is evident despite apparently substantial movements in the bladder wall. Thus, intravesical pressure reflects the net effect of moment-by-moment summation of all movements of the bladder surface, both contraction and elongation, and general bladder tone. The observations are consistent with a bladder structure comprising modules with variable linkage, which supports presence of localized micromotions (no functional linkage between modules) and propagating contractions (where emergence of linkage allows sequential activation of adjacent modules).

Storage phase motility is a counter-intuitive property for a reservoir organ, but conceptually, it could facilitate the generation of afferent activity as a result of bladder distortion and the ability to transition to voiding at any bladder volume. Detrusor muscle, ICs and intramural innervation have properties potentially relevant in pacemaker and integrative functions and may form the basis for initiating, coordinating and modulating micromotions of the bladder wall in some species. Thus, a change affecting structure or
properties of any of these structures could facilitate unregulated peripheral autonomy in dysfunction of the lower urinary tract.

**Conflict of interest**

We have no relevant conflict of interest.

**References**


