

# PREDICTING REFRACTORY DETRUSOR OVERACTIVITY: ARE THERE ANY CLUES AT DIAGNOSIS?

Kylie J Mansfield,<sup>1</sup> Tim Cowan,<sup>2</sup> Ying Cheng,<sup>3</sup> Wendy Allen,<sup>4</sup> Kate H Moore<sup>5</sup>

1. Senior Physiology Lecturer, University of Wollongong, Australia

2. Research Assistant, Pelvic Floor Unit, St George Hospital, Sydney, Australia

3. Postdoctoral Researcher, Pelvic Floor Unit, St George Hospital, Sydney, Australia

4. Research Nurse, Pelvic Floor Unit, St George Hospital, Sydney, Australia

5. Director, Pelvic Floor Unit, St George Hospital, Sydney, Australia

**Disclosure:** No potential conflict of interest

**Citation:** *European Medical Journal - Urology*, 2013; 1, 87-91

## ABSTRACT

Approximately one-third of patients diagnosed with detrusor overactivity (DO) will be refractory to treatment with antimuscarinic drugs. In this study, we examined baseline clinical details and history of urinary tract infection (UTI), urodynamics parameters, urinary pH and ATP in voided urodynamic fluid for any prognostic factors that would allow prediction of the refractory state at the time of diagnosis. At follow-up (2 to 5 years), patients were characterised as responders or non-responders based on a >50% decrease in urge leaks and voids per 24 hours. Of the 61 patients who met the inclusion criteria, follow-up revealed that 25% of these did not respond to antimuscarinic therapy. There were no significant differences in urodynamic parameters in responders compared to non-responders. Patients with a greater number of leaks/week at baseline and a history of UTI were more likely to be non-responsive to antimuscarinic therapy. There was no difference in urinary pH or ATP concentration in voided urodynamic fluid in the two groups. The results indicate that severity of leakage at baseline history and a history of recurrent UTI appears to be poor prognostic features in patients with DO. These may be associated with the development of the 'refractory' state.

**Keywords:** Detrusor Overactivity, refractory, urinary tract infection, bacteriuria, adenosine triphosphate

## INTRODUCTION

Overactive bladder (OAB) is a syndrome complex characterised by urge incontinence, that is, leakage with a severe urgent desire to urinate.<sup>1</sup> This debilitating condition affects approximately 17% of people over the age of 40,<sup>2</sup> with increasing economic consequences worldwide.<sup>3,4</sup> Urodynamic testing reveals detrusor overactivity (DO) resulting from involuntary contractions of the detrusor muscle during filling. The main treatment for DO is with antimuscarinic drugs, which are thought to work by interacting with muscarinic receptors located on the detrusor muscle or mucosa of the bladder.<sup>5-7</sup> Antimuscarinic therapy does not generally cure the condition but gives immediate benefit in about 65% of patients. Thus, 35% of patients do not respond to antimuscarinic therapy and are termed 'refractory', defined as failure to respond to detailed bladder training with more than two antimuscarinic agents for more than 12 months on frequency volume chart.<sup>8</sup> Poor outcomes were reported from a longitudinal follow-up of patients

with DO (over a 5 to 10 year period) which found that long-term improvement was only achieved in 35% of women.<sup>9</sup> In addition, OAB symptoms have been reported to last for more than 10 years in 88% of patients with DO,<sup>10</sup> indicating that this is a disease syndrome with chronic implications for sufferers.

The underlying cause of DO has not been elucidated. Recent theories have focused on abnormalities in the purinergic signalling from the bladder urothelial cell layer, resulting in changes in afferent nerve impulses from the bladder that increase the sensation of 'urgency'. Increased release of adenosine triphosphate (ATP) from the bladder urothelium has been demonstrated in conditions of bladder dysfunctions characterised by pain, such as painful bladder syndrome (including interstitial cystitis).<sup>11-12</sup> In 2010, we examined the release of ATP into intravesical fluid from patients with DO at urodynamic testing.<sup>13</sup> We found a correlation between the first desire to void (FDV) and the concentration of ATP present in the intravesical fluid.<sup>13</sup> Similarly, we have

recently reported that intravesical ATP concentration correlates with the FDV in patients with OAB syndrome (without urodynamically proven DO).<sup>14</sup> Taken together, these studies indicate a role for ATP in bladder sensation. However, whether the magnitude of ATP release during bladder filling can predict treatment response has never been studied.

Several recent studies have described high rates of bacteriuria (25-40%) in women with urodynamic refractory DO<sup>15</sup> and a wider group with clinical overactive bladder (OAB) syndrome.<sup>16-17</sup> Despite this, infection has largely been ignored as a contributor to the aetiology of refractory DO.<sup>18</sup> The aims of the current study were to evaluate patient response to antimuscarinic therapy in relation to 1) patient history of bacterial cystitis at the first visit and 2) ATP concentration in voided urodynamic fluid at baseline urodynamics.

## METHODS

Patients who had presented for urodynamic testing between January 2008 - April 2011 at our regional Department of Urogynaecology who had been recruited into a study of ATP levels in voided urodynamic fluid (n=118)<sup>13</sup> were considered for this study. Three weeks prior to urodynamics testing patients had an initial visit when history was taken together with screening mid-stream urine for detection of bacterial cystitis. Any patients with a positive result for bacterial cystitis were treated with appropriate antibiotics before urodynamics

was performed. Only patients who were not symptomatic for urinary tract infection (i.e. absence of foul-smelling urine and dysuria) were eligible for urodynamics. Patients who had a urodynamic diagnosis of idiopathic DO, that is involuntary detrusor contractions during the filling phase which were either spontaneous or provoked (n=61), were followed-up. Patients who were either urodynamically normal or pure urodynamic stress incontinence with no urge symptoms were excluded from this follow-up study as treatment response would not equate to antimuscarinic efficacy (n=48). Patients with neurological disorders (n=1), any voiding dysfunction (n=2), or previous deep pelvic radiotherapy (n=3) were excluded. In addition, women who were unable to receive antimuscarinics (i.e. Dementia/Glaucoma n=3) were also excluded.

Following urodynamic diagnosis patients with idiopathic DO received routine clinical care including bladder training and antimuscarinic therapy. Patient response to antimuscarinic therapy was determined by frequency volume chart (urge leaks and voids per 24 hours, nocturia). 'Response' was denoted as greater than 50% benefit on urge leaks and voids per 24 hours. Additional patient history was recorded, including age, duration of symptoms, menopausal status, number of pregnancies/births, number of antimuscarinic agents tried, and urodynamic parameters. Comparison of findings in responders compared with non-responders was undertaken using a Mann-Whitney test.

Patient history of bacterial cystitis was defined as either

**Table 1. Clinical history for patients with DO characterised as responders or non-responders.**

|   | Responders<br>(n=37) | Non-Responders<br>(n=11) | Significance |
|---|----------------------|--------------------------|--------------|
| Age (range)                                     | 66.00 (32-92)        | 66.50 (33-87)            | NS           |
| Leaks/week (IQR)                                | 7 (3-18)             | 21 (12-29)               | p=0.014      |
| Post menopause (%)                              | 78%                  | 83%                      | NS           |
| Pregnancies (range)                             | 3 (0-6)              | 3 (0-5)                  | NS           |
| Births (range)                                  | 2 (0-6)              | 3 (0-5)                  | NS           |
| UTI ever  | 48.5%                | 91%                      | p=0.015      |
| Any recurrent UTI                               | 21%                  | 63.5%                    | p=0.013      |
| No history of UTI                               | 46%                  | 8%                       | p=0.01       |
| Duration of symptoms<br>(range, years)          | 6.38 (2-29)          | 7.83 (2.5-25)            | NS           |
| Number of antimuscarinic drugs<br>tried (range) | 1 (1-4)              | 2.5 (2-7)                | p=0.0026     |

‘recurrent UTI’ which was more than 3 proven episodes of infections in 5 years;<sup>19</sup> “any UTI”, that is any proven UTI during the patient’s adult life, or no history of UTI. Comparison of the prevalence of UTI in responders and non-responders was undertaken with a chi-squared test. In addition, laboratory findings of urinary pH and concentration of ATP in voided urodynamic fluid was collated and compared by Mann-Whitney U test. Because a correlation between ATP in voided urodynamic fluid and the FDV has previously been reported,<sup>13</sup> we also examined this relationship in the responders and non-responders using linear regression. All statistical analyses were undertaken using GraphPad Prism (version 6).

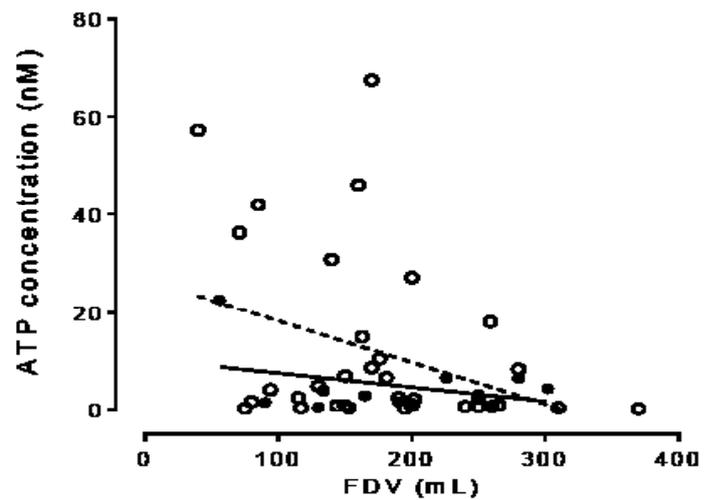
## RESULTS

Of the 118 patients who had ATP determinations at the time of their diagnosis, 61 met the inclusion criteria. Nine patients were lost to follow-up (despite contacting the GP) and three were completely non-compliant with therapy, thus 49 patients underwent treatment and could be traced. Follow-up revealed that 37 of these (75%) had responded to antimuscarinic therapy and 12 (25%) were non-responders. The follow up period for this study was ranged from 2 to 5 years.

In examining the clinical history (collected at first presentation) there were no significant differences between responders and non-responders in relation to age, parity, menopausal status, or duration of symptoms (Table 1). However, baseline severity of leakage gave some significant prognostic information in that severity of leakage was greater in non-responders (median 21 leaks/

**Table 2. Patient data collected at urodynamic diagnosis (Median, IQR).**

|   | Responders (n=37) | Non-Responders (n=12) | Significance |
|---|-------------------|-----------------------|--------------|
| First desire to void (FDV, mL)          | 170 (135-235)     | 190 (130-260)         | NS           |
| Maximum Cystometric Capacity (MCC, mL)  | 410 (312-492)     | 417 (367-473)         | NS           |
| Maximum Detrusor Pressure (pDET, mm Hg) | 35 (24-45)        | 42 (27-55)            | NS           |
| Urinary pH                              | 6.41 (5.53-7.02)  | 5.98 (5.54-6.33)      | NS           |
| ATP concentration (nM)                  | 2.4 (0.6-14.9)    | 2.95 (1.5-5.88)       | NS           |



**Figure 1. Correlations between ATP concentration in voided urodynamic fluid and FDV in patients with DO who respond to antimuscarinic therapy (open circles, p=0.039) and in patients who are non-responders (p=0.25, closed circles).**

week) compared to responders (median 7 leaks/week, p=0.01, Mann-Whitney, Table 1). Interestingly, there was a difference between UTI history and the clinical outcome (p<0.0001, chi-square). A significantly higher percentage of the non-responders had a history of both recurrent UTI (p=0.013, Mann-Whitney) and any UTI episode (p=0.034, Mann-Whitney, Table 1) while a significantly higher percentage of responders had no UTI history (p=0.0005, Mann-Whitney, Table 1). The non-responders had been treated with a median of 2.5 antimuscarinic agents (ranging from 2 to 7). This was significantly greater than the number of antimuscarinic agents than the responders had been treated with (p=0.03, median 1, range 1 to 4, Table 1).

In examining urodynamic parameters of responders compared to non-responders there was no significant difference between FDV, maximum cystometric capacity (MCC) and maximum detrusor pressure (Table 2). The ATP concentration in voided urodynamic fluid did not differ between responders and non-responders (Table 2). A significant correlation between ATP in voided urodynamic fluid and FDV (Figure 1) was seen in the responders (p=0.039, r<sup>2</sup>=0.12) but not in the non-responders (p=0.25, r<sup>2</sup>=0.14).

Urodynamic parameters and ATP concentration in voided urodynamic fluid was also analysed in relation to patients who had a history of UTI (n=31) and those with no proven episodes of infection (n=18). In this instance there was again no significant difference in FDV, MCC and

|   | UTI (n=31)       | No history of UTI (n=18) | Significance |
|---|------------------|--------------------------|--------------|
| First desire to void (FDV, mL)          | 167 (133-250)    | 193 (121-232)            | NS           |
| Maximum Cystometric Capacity (MCC, mL)  | 389 (300-440)    | 422 (365-500)            | NS           |
| Maximum Detrusor Pressure (pDET, mm Hg) | 40 (26-45)       | 32 (20-55)               | NS           |
| Urinary pH                              | 6.255 (5.5-6.49) | 6.46 (5.45-7.05)         | NS           |
| ATP concentration (nM)                  | 3.9 (1.4-10.4)   | 0.9 (0.36-4.66)          | p=0.049      |

**Table 3: Effect of a history of UTI on urodynamic parameters (Median, IQR)**

maximum detrusor pressure (Table 3). However the ATP concentration in voided urodynamic fluid was significantly higher in patients with a history of UTI ( $p=0.049$ , Mann-Whitney, Table 3).

## DISCUSSION

In this study we have found that both baseline severity of leakage and history of UTI are important prognostic features. Increased severity of leakage was seen in patients who were not responsive to antimuscarinic therapy. Similarly, Morris and associates reported in 2008 that severe urge incontinence at presentation was associated with treatment failure,<sup>9</sup> although the cause of this leakage has not been determined.

For the past 30 years, the possible role of subclinical infection/inflammation in the etiology of DO has largely been ignored. A number of studies have reported an increased prevalence of bacteriuria in patients newly diagnosed DO.<sup>20-23</sup> Similarly, bacterial cystitis has been described in patients with OAB syndrome, who had not had urodynamics.<sup>17</sup> Thus several authors have now shown that the incidence of bacteriuria/bacterial cystitis is more common in new onset DO (or incontinent women with OAB) than in controls, although a relationship between cystitis and refractory DO has not previously been reported.

In this study we report that the likelihood of a patient having a history of recurrent UTI was three-fold greater in patients who failed to respond to antimuscarinic therapy (non-responders) compared to those who respond to therapy. Thus, our results suggest that recurrent UTI,

or indeed a history of UTI, may have importance in the acquisition of a 'refractory' state. In the last 2 years there have been two preliminary studies of antibiotic therapy in patients with OAB. In both trials, antibiotic therapy (in combination with antimuscarinic drugs and bladder training<sup>24</sup>) or antibiotics alone<sup>25</sup> was seen to significantly improve the treatment response, as indicated by a reduction in voids per day<sup>24-25</sup> or urgency scores.<sup>25</sup>

One proposed mechanism is that bladder inflammation, associated with bacteriuria, evokes increased afferent nerve activity in response to bladder distension.<sup>26-28</sup> Patients with refractory DO have been found to have increased expression of nociceptive neuropeptides such as substance P.<sup>29</sup> Similarly, nerve growth factor (NGF) is increased in biopsies and urine of refractory patients.<sup>30</sup> In addition to NGF, elevated levels of pro-inflammatory cytokines have been reported in OAB patients.<sup>31-32</sup>

The second aim of this study was to determine if the ATP concentration in voided urodynamic fluid was able to prognosticate the response to antimuscarinic therapy. Our results indicate that this was not the case, with ATP concentration in voided urodynamic fluid not being able to be used as a useful biomarker to predict response to antimuscarinic therapy for patients with DO. It is of interest that the previously observed correlation between FDV and ATP in voided urodynamic fluid<sup>13</sup> was preserved in the patients who responded to antimuscarinic therapy, but was lost in the non-responders, although it is likely that this is related to the small number of patients in the latter group ( $n=12$ ). Also of interest is the finding that the ATP concentration in voided urodynamic fluid from patients with a history of UTI is significantly higher ( $p=0.049$ ) than that in patients who had no history of infection. This is in contrast to our findings of decreased ATP in patients with a current bacterial infection.<sup>33</sup> It is possible that a history of infection alters the long-term response of the urothelium to stretch, leading to increased release of ATP as opposed to a current infection decreasing ATP release possibly through a decrease in urothelial cell viability.<sup>34</sup> These differences in ATP release in patients with a current infection and a history of infection need to be further investigated to fully understand the way in which infection alters urothelial responses.

## CONCLUSION

Results from this study indicate although ATP remains an important molecule for the signalling of afferent impulses in the urinary bladder, it is not useful as a prognostic indicator for responsiveness to antimuscarinic therapy. Severity of leakage at baseline history and a history of UTI appears to indicate a poor prognostic significance in patients with DO possibly being associated with the development of the 'refractory' state.

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