

Decreased Intravesical Adenosine Triphosphate in Patients with Refractory Detrusor Overactivity and Bacteriuria

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Purpose: Although several studies have examined the relationship between adenosine triphosphate release from the urothelium and bladder sensations including painful filling and urgency, the association between bacteriuria and urothelial adenosine triphosphate release has not been well studied. We evaluated women with refractory detrusor overactivity who were experiencing an acute exacerbation of detrusor overactivity symptoms including frequency, urgency and nocturia (and/or urge incontinence). We measured changes in intravesical adenosine triphosphate levels in these women with and without bacteriuria.

Materials and Methods: In this prospective cohort study women with refractory detrusor overactivity were invited to our unit during acute symptomatic exacerbation. On presentation a catheter urine specimen was collected and 50 ml normal saline instilled into the bladder to evoke gentle stretch, with removal after 5 minutes. Adenosine triphosphate concentrations were determined on fresh washings using a bioluminescence assay.

Results: The incidence of bacteriuria 10^3 cfu/ml or greater was 27% (15 of 56 specimens) during the 16-month study period. Adenosine triphosphate concentrations were lower during episodes of bacteriuria in the overall cohort ($p = 0.0013$) and paired samples from individual patients ($p = 0.031$) compared to episodes of sterile urine.

Conclusions: In the first study on the subject to our knowledge, we demonstrated a striking difference between adenosine triphosphate levels measured in the presence and absence of bacteriuria in this patient group.

Abbreviations and Acronyms

ATP = adenosine triphosphate
CSU = catheter specimen of urine
DO = detrusor overactivity
OAB = overactive bladder
UTI = urinary tract infection

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Key Words: adenosine triphosphate; bacteriuria; urinary bladder, overactive

INVESTIGATION into the mechanisms involved in the sensation of urinary urgency has revealed the importance of a bladder purinergic system involving nonadrenergic, noncholinergic neurotransmission.¹ In the healthy bladder, stretch of the bladder wall stimulates the release of ATP from the urothelium,² which interacts with purinergic P2X_{2/3} receptors located on the suburothelial afferent nerves, giving

rise to a normal sensation of bladder fullness.³ However, in bladder disease states this mechanism is altered and enhanced purinergic neurotransmission is believed to contribute to an abnormal sensation of urgency.⁴

To date, most studies on ATP release in bladder dysfunction have focused on women with bladder dysfunction characterized by painful filling, for example patients with interstitial cystitis⁵⁻⁷ and

painful bladder syndrome.⁸ Purinergic dysfunction in diseases such as detrusor overactivity characterized by urinary urgency in the absence of pain has been examined to a lesser extent.^{9,10} Despite the fact that UTI is one of the most common causes of urinary urgency in women, the relationship between ATP concentrations and bacteriuria has not been well studied.

The purinergic system is well-known to trigger inflammatory responses via activation of purinergic receptors located on cells of the innate immune system.¹¹ In addition, cyclophosphamide induced cystitis is associated with hypersensitivity of bladder afferent nerves to ATP in rat bladders.¹² Several studies have confirmed high rates of bacteriuria (25% to 40%) in women with urodynamic refractory DO¹³ and a wider group with clinical overactive bladder syndrome.^{14,15} A significant proportion of women with detrusor overactivity are refractory to conventional treatment modalities.¹⁶ In this study we examine the levels of intravesical ATP in patients with refractory DO who are experiencing an acute exacerbation of DO symptoms. Intravesical ATP levels were correlated with the presence or absence of bacteriuria.

MATERIALS AND METHODS

A 16-month prospective cohort study was performed at a tertiary urogynecology unit. Women with urodynamically proven detrusor overactivity refractory to the standard therapeutic strategies of behavioral modification and anticholinergic agents were considered eligible for study inclusion. We defined refractory DO as failure to respond to 2 or more anticholinergic agents coupled with outpatient bladder training for 1 year or more, with persistent disabling symptoms on frequency-volume chart.¹⁷

In December 2009 our departmental database was searched for eligible women. A total of 68 women with refractory DO were identified and were mailed a personal letter inviting them to participate in the study. Women were invited to attend our unit whenever their OAB symptoms were acutely worsened, ie frequency, urgency, nocturia (with or without urge incontinence). On presentation, participants completed a validated 4-point (0, 1, 2, 3) urgency score (see table).¹⁸ All patients signed written consent upon recruitment, and the study was approved by the South Eastern Sydney Human Research and Ethics Committee (reference 09/STG/72).

After recruitment, patients were catheterized by an experienced study nurse using standard aseptic technique

and a standard 14Fr Nelaton catheter. A catheter specimen of urine was retrieved, and forwarded immediately to the microbiology laboratory for formal culture and sensitivity. After emptying the bladder, 50 ml sterile 0.9% NaCl was instilled to evoke gentle bladder stretch and the catheter clamped. After 5 minutes in situ, the saline was collected for ATP analysis and the catheter was removed. The decision to prescribe empirical antibiotic treatment on the day of specimen collection was made on an individual basis according to patient symptoms. All women whose CSU specimens cultured bacteriuria 10^3 cfu/ml or greater at 48 hours were treated with a 1-week course of appropriate antibiotic therapy according to sensitivity testing. All study participants were invited to return on any subsequent occasions whenever OAB symptoms were acutely worsened.

CSU specimens from study participants were cultured using horse blood agar incubated at 35C in 7% CO₂ and MacConkey's agar incubated at 35C in air. These culture media grow all known pathogens and contaminants. Pyuria was determined using hemocytometer counts on uncentrifuged urine specimens with counts of more than 10 white blood cells per μ l considered significant. Any bacteriuria 10^3 cfu/ml or greater was considered a positive urine culture, in accordance with recent guidelines.¹⁹ Specimens with bacteriuria less than 10^3 cfu/ml were considered sterile.

Saline samples were immediately stored at 4C and then assayed for ATP within 30 minutes. ATP analysis was performed immediately on 100 μ l specimens taken from the top of the 50 ml saline bladder wash using a routine luciferin/luciferase bioluminescence assay (Sigma) and a GloMax® 20/20 Luminometer.⁹ A standard ATP calibration curve was constructed before and after performing the study assay using serial dilutions of ATP created from stock solution to allow correction for background reagent values.

Median ATP concentrations were compared using the Mann-Whitney test for nonparametric data. Paired analyses were performed using the Wilcoxon sign rank test. Two-tailed p values are reported throughout and the 5% level was considered significant. Statistical analysis was performed using Statsdirect 2.7.2.

RESULTS

Between January 1, 2010 and March 31, 2011, 33 women with refractory DO were recruited and they supplied 56 study specimens. The median (IQR) age of women recruited was 70 (60–74) years. Study participants were a severely affected group with a median duration of OAB symptoms of 20 (8–24)

Table

Urge Score	Definition	No. Sterile (%)	No. Bacteriuric (%)	Median nM ATP (IQR)
0	None—no urgency	1 (2)	0	
1	Mild—awareness of urgency but is easily tolerated	2 (5)	4 (27)	49.8 (9.3–64.4)
2	Moderate—enough urgency discomfort that it interferes with or shortens usual activities	13 (33)	5 (33)	39.1 (27.3–56.5)
3	Severe—extreme urgency discomfort that abruptly stops all activities	24 (60)	6 (40)	37.0 (9.5–60.8)

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