

## AUTONOMIC SYMPATHETIC SYSTEM IS OVERACTIVE IN PATIENTS WITH BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS.

### Hypothesis / aims of study

The role of autonomic nervous system in the development of BPS/IC has been ignored during the last few years in favour of other pathologic mechanisms. However, some forms of chronic pain, as the chronic regional pain syndrome, have a relevant participation of the sympathetic system. In what concerns BPS/IC patients, high levels of urinary catecholamines have been reported before indicating an adrenergic overactivity (1). Furthermore, chronic bladder inflammation promotes nerve fiber sprouting (2). Finally, Onabotulinum Toxin A injection in the trigone of BPS/IC patients showed a decrease in pain and frequency, raising the possibility that impairment of sympathetic fibers, almost exclusively located in the trigone, play a role in such improvement (3). All together, these data may suggest that an abnormal sympathetic activity may occur in BPS/IC patients.

In this study the activity of the autonomic sympathetic nervous system in patients with Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) was evaluated.

### Study design, materials and methods

The activity of the sympathetic system was evaluated in 10 women with BPS/IC (ESSIC classification: 2a (1), 2b (1), 2c (5), 3b (1) and 3c (2)) and 10 healthy age matched women (38.1±6.9 vs 41±9.7 years). Body mass index was similar in the 2 groups (21.4±1.5 vs 22.3±2.3). Sympathetic (and parasympathetic) function was assessed through the Upright Tilt Testing (TILT) and by measurement of norepinephrine in the plasma and in 24-hour urine sample. The TILT protocol included positioning individuals 10 minutes in supine position, non-invasive assessment of EKG and hemodynamic parameters. Standard deviation of normal P wave intervals (SDPP, related to autonomic sympathetic nervous system tonus activity), root of the mean of the sum of successive differences in heart period series (RMSSD, related to autonomic parasympathetic nervous system tonus activity) and baroreflex sensitivity (BRS, related to autonomic parasympathetic nervous system reflex activity) were assessed. Patients and controls were then put at upright position in a 70° tilt table for 10 minutes and the same parameters were re-evaluated. Blood samples were collected for norepinephrine measurement in supine and after upright positioning. Twenty-four hour urine samples were also collected at another occasion to determine norepinephrine excretion.

BPS/IC patients were treated with intra-trigonal injection of Onabotulinum type A, 100 U injected in 10 trigonal sites. O'Leary Sant Score, Visual Analogue Scale (VAS) for Pain and QoL from IPSS were assessed in these patients before and 1 month after treatment. Blood samples and 24 hour urine were collected 1 month after treatment for norepinephrine measurements.

### Results

BPS/IC patients, after correction for systolic and diastolic blood pressures, heart rates, cardiac debits and peripheral blood resistances, exhibited higher basal sympathetic activity. Mean SDPP was lower in BPS/IC patients than in healthy individuals (40.0±12.2 vs 57.3±14.4 ms, respectively). Orthostatism increased SDPP in the 2 populations although in BPS/IC patients such increment was more modest (24.2±18.6 vs 57.2±23.0 ms in controls, p<0.05). Parasympathetic tonus and reflex activity (RMSSD and BRS) showed no significant differences among groups. Although within the normal range (below 750 µg/ml), basal plasmatic norepinephrine was increased in patients (397±36.4 µg/ml vs 204±46.4 µg/ml in controls, p<0.01). After upright positioning norepinephrine plasmatic concentration was similar in patients (596.3±30.4 µg/ml) and controls (579.3±69 µg/ml). The 24-hour urinary norepinephrine release was increased in all BPS/IC patients, the mean value being 151.3±21.2 µg/24h. Normal values are standardized in our laboratory, with an upper limit of 97 µg/24h. In healthy individuals, the mean value of 24-hour urinary norepinephrine was 71.3±36.2 µg/24h.

Intra-trigonal injection of 100 U of Onabotulinum Toxin A improved symptomatically all BPS/IC patients with a reduction in O'Leary Sant Score (from 29±6.4 to 18.1±3.6, p<0.05), VAS for Pain (from 5.8±1.8 to 2.5±1.3, p<0.05) and QoL from IPSS (from 5.1±0.9 to 1.3±1.7, p<0.05). These patients also had a decrease in the 24h urinary norepinephrine excretion (from 151.3±21.2 to 92.7±37.2 µg/24h, p<0.05). No changes were found in blood norepinephrine.

### Interpretation of results

This study shows an increase in sympathetic activity in patients with BPS/IC. In particular the high excretion of urinary norepinephrine suggests that lower urinary tract is under an intense adrenergic stimulation which may affect the urothelium and the bladder nociceptive fibres, as both express alpha1 receptors.

After treatment with OnaBotulinum Toxin A urinary norepinephrine decreased suggesting that local modulation of sympathetic activity might occur under the influence of the neurotoxin. It is well known that OnaBotulinum toxin A prevents the neurotransmitter release from sympathetic fibers.

### Concluding message

The eventual role of the sympathetic fibers in particular those innervating pelvic organs including the bladder should be further evaluated in order to clarify their contribution to BPS/IC

### References

1. Urology 1999, 53 (6): 1140-3
2. Neuroscience. 2006, 139(2): 671-85
3. European Urology 2010, 58 (3): 29-38

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<b><i>Is this a clinical trial?</i></b>	<b>No</b>
<b><i>What were the subjects in the study?</i></b>	<b>HUMAN</b>
<b><i>Was this study approved by an ethics committee?</i></b>	<b>Yes</b>
<b><i>Specify Name of Ethics Committee</i></b>	<b>Comissão de Ética para a Saúde do Hospital de São João</b>
<b><i>Was the Declaration of Helsinki followed?</i></b>	<b>Yes</b>
<b><i>Was informed consent obtained from the patients?</i></b>	<b>Yes</b>