

# Autonomic Testing in Women with Chronic Pelvic Pain



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**Purpose:** We determined whether abnormal autonomic nervous system innervation of the bladder underlies IC (interstitial cystitis)/BPS (bladder pain syndrome) differently than other chronic pelvic pain.

**Materials and Methods:** In this institutional review board approved protocol 39 healthy controls and 134 subjects were enrolled, including 36 with IC/BPS, 14 with myofascial pelvic pain and 42 with IC/BPS plus myofascial pelvic pain. Three subjects were excluded from study. Autonomic nervous system evaluations included deep breathing, the Valsalva maneuver, and the tilt table and sudomotor tests. The latter evaluates autonomic neuropathy. A modified validated composite autonomic laboratory score was applied.

**Results:** Median age in the IC/BPS group was 47.5 years (range 21 to 78), greater than in healthy controls (34 years, range 20 to 75,  $p = 0.006$ ), the myofascial pelvic pain group (33 years, range 22 to 56,  $p = 0.004$ ) and the IC/BPS plus myofascial pelvic pain group (38 years, range 18 to 64,  $p = 0.03$ ). Body mass index did not significantly differ but the myofascial pelvic pain and IC/BPS plus myofascial pelvic pain groups had a higher body mass index than healthy controls ( $p = 0.05$  and  $0.03$ , respectively). Cardiovascular and adrenergic indexes did not differ. The tilt table test showed more orthostatic intolerance in all chronic pelvic pain groups. Tilt table test diagnoses (orthostatic hypotension, postural tachycardia syndrome and reflex syncope) were rare. Baseline heart rate was higher in all chronic pelvic pain groups ( $p = 0.004$ ). Compared to healthy controls all myofascial pelvic pain groups showed significantly more clear-cut autonomic neuropathy, defined as a sweat score of 3 or greater (vs IC/BPS plus myofascial pelvic pain  $p = 0.007$  and vs myofascial pelvic pain  $p = 0.03$ ).

**Conclusions:** Some chronic pelvic pain types show autonomic neuropathy and some show vagal withdrawal. In all types orthostatic intolerance likely reflects central sensitization and perhaps catastrophizing. Some of these findings suggest novel therapeutic targets.

**Key Words:** urinary bladder; cystitis, interstitial; chronic pain; pelvic pain; autonomic nervous system

AUTONOMIC abnormalities, including POTS, reflex syncope and autonomic neuropathy, may occur in functional disorders such as chronic fatigue syndrome,<sup>1</sup> functional gastrointestinal disorders<sup>2</sup> and headaches.<sup>3</sup> The typical symptoms of IC/BPS

(frequency, urgency and CPP depending on the bladder fill state<sup>4</sup>) suggest a pathophysiological role for a generalized cardiovascular and vasomotor ANS abnormality. We compared IC/BPS with another disorder, MPP with pain in the pelvis

## Abbreviations and Acronyms

ANS = autonomic nervous system

BMI = body mass index

CASS = Composite Autonomic Severity Score

CPP = chronic pelvic pain

HR = heart rate

MPP = myofascial pelvic pain

OH = orthostatic hypotension

POTS = postural tachycardia syndrome

QSART = quantitative sudomotor axon reflex test

TTT = tilt table test

VM = Valsalva maneuver

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unrelated to the bladder state, and hypothesized that it would harbor no cardiovascular or vasomotor autonomic dysfunction.

Preliminary findings showed no structural autonomic abnormalities in IC/BPS subjects except a higher baseline HR, supporting the concept of functional rather than structural change in the ANS.<sup>5</sup> Complicating that report, many subjects with IC/BPS had comorbid MPP. In the current full followup study we now have adequate power to determine whether autonomic abnormalities differ between these 2 overlapping but clinically distinct pelvic pain disorders, IC/BPS and MPP. We sought to determine whether the absence of structural abnormalities in the ANS persisted 1) when evaluating a larger cohort and 2) in subjects with IC/BPS without comorbid MPP. In addition, recent findings of autonomic neuropathy in fibromyalgia<sup>6</sup> led us to hypothesize that there are similar findings in MPP without cardiovascular or vasomotor autonomic dysfunction based on the concept of fibromyalgia of the pelvic musculature.

## METHODS

### Participants

This prospective institutional review board approved study (University Hospitals Case Medical Center, Cleveland, Ohio) was done to evaluate the structural integrity of the ANS of women diagnosed with IC/BPS and/or MPP (healthy control subjects) as a portion of the larger ICEPAC (Interstitial Cystitis: Elucidation of Psychophysiologic and Autonomic Characteristics) Study (ClinicalTrials.gov NCT01616992) using methods previously published.<sup>7</sup> All subjects were enrolled between February 2011 and December 2014, and provided informed consent before participating.

A diagnosis of IC/BPS required 6 months or more of pain clearly linked to the bladder fill state and study exclusion criteria aligned with IC/BPS NIDDK (National Institute of Diabetes and Digestive and Kidney Diseases) criteria.<sup>8</sup> In the absence of an accepted definition of MPP<sup>9</sup> the diagnosis required 1) 3 months or more of noncyclic

CPP unrelated to the bladder fill state and 2) a numerical rating scale pain score of 4 or greater of 10 in 2 of 5 pelvic floor muscles (bilateral puborectalis, obturator internus and midline perineal body) tested by applying 2 kg pressure with a gloved index finger to the relaxed muscle belly.<sup>10</sup>

In addition to general subject exclusions, healthy subjects were stringently screened to exclude any disorders commonly comorbid with pelvic pain (supplementary Appendix, <http://jurology.com/>). Fibromyalgia diagnosis required a history of diffuse pain and 11 or greater of 18 tender points on examination by a clinician.<sup>11</sup> By definition healthy subjects could not have fibromyalgia.

### Autonomic Testing

With rare exceptions that are explicitly discussed all autonomically active medications were stopped at least 5 half-lives prior to testing. Testing was performed in the morning or afternoon with several components that were previously described in detail.<sup>7,12</sup> Testing included the cardiovascular response to deep breathing (primarily testing cardiac parasympathetic integrity), VM (testing cardiac sympathetic, parasympathetic and vasomotor sympathetic integrity), TTT (testing cardiac and vasomotor sympathetic integrity) and QSART (testing post-ganglionic sympathetic cholinergic integrity). TTT was performed at 70 degrees for 30 minutes. VM (15 seconds and 40 mm Hg) and deep breathing (6 breaths per minute) were done at least 3 and 2 times, respectively, in each subject. Norms were used as described by Low and Sletten<sup>12</sup> except for QSART values, which were based on our laboratory norms. Subjects ate a light meal 2 hours before the tests.

### Data Analysis

As previously reported<sup>5</sup> we quantified ANS test results using a modified CASS with sudomotor, adrenergic and cardiovascular HR indexes (table 1).<sup>12</sup> The TTT baseline used the mean of the last 4 minutes of the 10-minute supine recording prior to tilt-up. Vital sign outliers accompanying fidgeting and talking were excluded. POTS required a greater than 30 bpm HR increase without hypotension in the first 10 minutes upright with associated orthostatic symptoms. Neurally mediated syncope required an abrupt decrease in blood pressure<sup>13</sup> and usually in heart rate. OH required a greater than 20/10 mm Hg blood pressure decrease in the first 3

**Table 1.** Modified CASS score

Score Points	Sudomotor Index	Adrenergic Index	Cardiovascular Index
1	Single QSART site decrease	Phase II early decrease less than 40-greater than 25 mm Hg or decreased phase II late or pulse pressure decreased to less than 50% of baseline, increased pressure recover time 4–5 secs, absent phase IV	Heart rate response to deep breathing or Valsalva ratio decrease but greater than 50% min
2	Single QSART site less than 50% of lower limit	Phase II late absent or increased pressure recover time 6–9 secs	Heart rate response to deep breathing or Valsalva ratio decrease but less than 50% min
3	2 or More QSART sites less than 50% of lower limit	Absent phase II late + phase IV, + increased pressure recovery time 10 secs or greater	Heart rate response to deep breathing + Valsalva response decrease but less than 50% min
4	Not applicable	Score 3 + OH, defined as systolic blood pressure decrease 30 mm Hg or greater, mean blood pressure decrease 20 mmHg or greater	Not applicable

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