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Assessment of cardiovascular autonomic functions in women with chronic pelvic pain

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ABSTRACT:

Background: Chronic pelvic pain (CPP) is a prevailing chronic painful condition in reproductive age group women. CPP is a burden on women with significant detrimental effects on health and personal life. Autonomic dysfunction is associated with several chronic painful conditions. However, there is limited knowledge of the autonomic status of women with chronic pelvic pain.

Aim: To study the effect of CPP on cardiovascular autonomic function in women.

Settings and Design: An analytical cross-sectional study.

Subjects and Methods: we recruited (n=60) patients of CPP in the age group of 18–45 years from the Gynecology outpatient department. The control group (n=30) comprised of age-matched healthy 30 female attendants.

Outcomes measures: Non-invasive cardiovascular autonomic tests performed were: Basal heart rate variability, E/I ratio: Heart rate variation with respiration, 30:15 ratio: Heart rate response to standing, Postural challenge tests, Cold pressor test, Sustained handgrip test.

Statistical Analysis: Unpaired t-test, p-value < 0.05 was considered significant.

Results: The values of BHRV, E:I ratio, and 30:15 ratio were found to be significantly lower in the CPP patients compared to controls. The rise in diastolic blood pressure during SHT and CPT was significantly higher in CPP patients as compared to controls ($p < 0.001$) suggesting sympathetic over-reactivity in CPP patients.

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Conclusions: From our study involving autonomic function testing on CPP patients, it was concluded that CPP patients have decreased parasympathetic tone and increased sympathetic tone compared to normal controls.

Keywords: Chronic pelvic pain; chronic pain, autonomic function tests, autonomic dysfunction

Introduction:

Most organs of the body exhibit dual innervations from both the sympathetic and the parasympathetic divisions of the autonomic nervous system (ANS) which often mediate opposite effects.[1] The ANS is affected by various chronic disorders and these changes may affect either the central nervous system or the peripheral ANS.[2] These changes either affect the ANS directly or the change may occur secondary to a chronic disorder like chronic renal failure or rheumatoid arthritis.[3] Studies that have been done in various chronic painful conditions have shown varying results, for example, migraineurs had decreased sympathetic tone and increased parasympathetic tone whereas the basal autonomic state of patients with fibromyalgia is characterized by increased sympathetic and decreased parasympathetic tones.[4,5] Dysmenorrheic women have shown an imbalance between sympathetic and parasympathetic components of the ANS and these females have a greater sympathetic than parasympathetic activity.[6] Lower parasympathetic activity has been associated with higher pain intensity in subjects with chronic widespread pain.[7] American College of Obstetrics and Gynecologists (ACOG) proposed a definition of chronic pelvic (CPP) pain as “non-cyclic pain of at least six months duration that appears in locations such as the pelvis, anterior abdominal wall, lower back, or buttocks and that is serious enough to cause disability or lead to medical care”. It was found that 15-20% of women aged 18-50 years have CPP of more than one year in duration.[8] It is a common condition in the reproductive age group of women, with limited knowledge of its pathophysiology. Causes of CPP can be gynecological (endometriosis, pelvic inflammatory disease, pelvic congestion syndrome), gastrointestinal (Constipation, inflammatory bowel disease, irritable bowel syndrome), urinary (Interstitial cystitis, bladder pain syndrome), musculoskeletal (abdominal wall myofascial pain, pelvic floor myalgia, fibromyalgia).[9] However, it was seen that in 61% of women with CPP symptoms, a clear diagnosis could not be established.[10] Hailan et al reported significant autonomic dysfunction in male patients of CPP due to chronic prostatitis, where chronic inflammation in the afferent nerves is responsible for the central sensitization resulting in reduced pain threshold, widespread pain, persistent abnormal pain, and altered autonomic responses to nociception.[11] There are studies in support

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of cardiovascular autonomic changes in women with CPP but it is difficult to say whether CPP leads to changes in autonomic function or vice versa.[12,13,14]

The literature survey has shown a scarcity of studies on autonomic status in CPP patients. Hence, we like to study the effect of CPP on cardiovascular autonomic responses through this study.

Subjects and methods:

After obtaining approval from the institute's ethics committee, the study was conducted in the Department of Physiology and Obstetrics and Gynaecology, University College of Medical Sciences and GTB Hospital, New Delhi.

As per our inclusion and exclusion criteria, we recruited women with CPP (n=60) from the Gynecology Outpatient Department. The control group (n=30) comprised age-matched normal healthy female attendants accompanying CPP patients.

Study design: Our study is an analytical cross-sectional study in a tertiary care setup.

Inclusion criteria: Women with CPP between 18 – 45 years of age.

Exclusion criteria: Females with Obvious gynecological and non-gynecological causes of CPP; Gynecological, abdominal, or pelvic malignancy; pregnancy/Desire to conceive/past pregnancy(within previous 12 months); any significant medical conditions like hypertension, diabetes mellitus, coronary artery disease; Severe low backache.

The subjects were allowed to familiarize themselves with the environmental conditions of laboratories. The procedure of the tests for assessment of autonomic status and the purpose of the study was explained in detail to the subjects and then written informed consent was obtained. Autonomic function tests of all subjects were recorded in the same phase of the menstrual cycle.

Outcome parameters recorded:

Autonomic function tests:[15,16]

Various autonomic function tests have been proposed, formulated, and standardized by various workers. The tests used for clinical assessment of autonomic functions.

Cardiac parasympathetic function

- **Basal heart rate variability:** Cyclical variation in heart rate variability (HRV) is due to sympathetic and vagal impulses to the sino-atrial node. The minimum and maximum R-R interval values were spotted in a continuous one-minute lead II ECG recording and

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then converted into heart rate. The difference between maximum and minimum values of heart rate was recorded as the heart rate variability in 1 minute.

- **E:I ratio**: Changes in respiration result in a rapid response in cardiac vagi and variations in heart rate often provide a good guide to their activity. The result was expressed in terms of a ratio of an average of 6 maximum R-R intervals during expiration to an average of 6 minimum R-R intervals during inspiration.
- **30:15 ratio:** The 30:15 ratio has been used as a means of quantifying the heart rate changes during standing. The 30:15 ratio was calculated by taking the ratio of the maximum R-R interval around the 30^{th} beat to a minimum R-R interval around the 15^{th} beat after standing.

Cardiac sympathetic function

- **Postural challenge test (PCT):** Standing up from a supine position causes the blood to pool from the thorax into the veins in the legs. The fall in blood pressure caused by standing up leads to the unloading of systemic baroreceptors and a rise in heart rate. Then reloading of the arterial baroreceptors causes an increase and overshoot of blood pressure and a rapid decrease in heart rate within 30 seconds after standing up. The maximum fall in the systolic blood pressure was calculated.
- **Sustained handgrip test (SHT**): Sustained isometric contraction of a skeletal muscle at more than 15% of its maximal contractile tension leads to a rise in blood pressure. This response is mediated via sympathetic afferents to the heart and blood vessels. The difference between the highest diastolic blood pressure during the test and baseline diastolic blood pressure was calculated.
- **Cold pressor test (CPT):** Assesses the integrity of a reflex arc, which includes afferent sensory nerves (pain), spinothalamic tracts, supra pontine and intra-thalamic relays; and efferent sympathetic pathways, peripheral sympathetic nerves, and vascular receptors. The subject has to immerse the hand in cold water (10°C) up to the wrist for 1 minute. The difference between the highest diastolic blood pressure during the test and baseline diastolic blood pressure was calculated.

Recording of ECG for autonomic function tests:

For the recording of autonomic function tests (Basal heart rate variability, E:I ratio, and 30:15 ratio), the lead-II ECG of each subject was recorded using the standard limb leads through BIOPAC–MP 36 data acquisition unit and AcqKnowledge 4.1 software of BIOPAC Systems, Inc. USA.

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Recording of blood pressure for autonomic function tests:

Blood pressure during PCT, SHT, and CPT was measured with a mercury sphygmomanometer by the standard Riva-Roci method.

Statistical analysis

Statistical analysis was done by IBM SPSS software version 20 (by IBM Corporation, USA). Unpaired- t-test to compare the autonomic function tests. The power of the study was kept at 90%, a p-value < 0.05 was considered significant. Data handling was done by MS Excel datasheet.

Results:

The mean ± standard deviation (SD) of the age of women in the control group was 30.63 ± 6.45 years and in the CPP group was 31.75±6.23 years. The difference between the CPP women and controls was non-significant statistically (p=0.869).

Table 1 and figures 1, 2, and 3 show the difference in the values for BHRV, E:I ratio, and 30:15 ratio between CPP patients and the control group. The values of BHRV, E:I ratio, and 30:15 ratio were found to be significantly lower in the CPP patients as compared to controls which is suggestive of a decreased parasympathetic tone in these patients.

Table 2 and figures 4, 5, and 6 show the values of changes in blood pressure during the postural challenge test, sustained handgrip test, and cold pressor test. During PCT, a fall in systolic blood pressure upon standing between CPP patients and controls was not statistically significant (P = 0.801). The rise in diastolic blood pressure during SHT and CPT was significantly higher in CPP patients as compared to controls (p < 0.001) suggesting sympathetic over-reactivity in CPP patients.

Table 1: Comparison of parasympathetic functions between CPP patients and normal controls.

Parasympathetic parameters	**CPP group (n = 60)**		**Control group (n = 30)**		**p-value** unpaired t-test
	MEAN	**± SD**	**MEAN**	**± SD**	
BHRV (beats/min)	15.67	2.92	17.87	2.3	0.01
E:I Ratio	1.24	.031	1.40	0.106	< 0.001
30:15 Ratio	1.078	0.040	1.219	0.100	< 0.001

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Table 2: Comparison of sympathetic functions between CPP patients and normal controls.

Sympathetic parameters	CPP group (n = 60)		Control group (n = 30)		p-value unpaired t test
	MEAN	± SD	MEAN	± SD	
PCT (mmHg)	7.50	2.87	7.33	3.12	.801
SHT (mmHg)	19.10	3.11	16.60	2.36	< 0.001
CPT (mmHg)	20.13	3.27	17.33	2.43	< 0.001

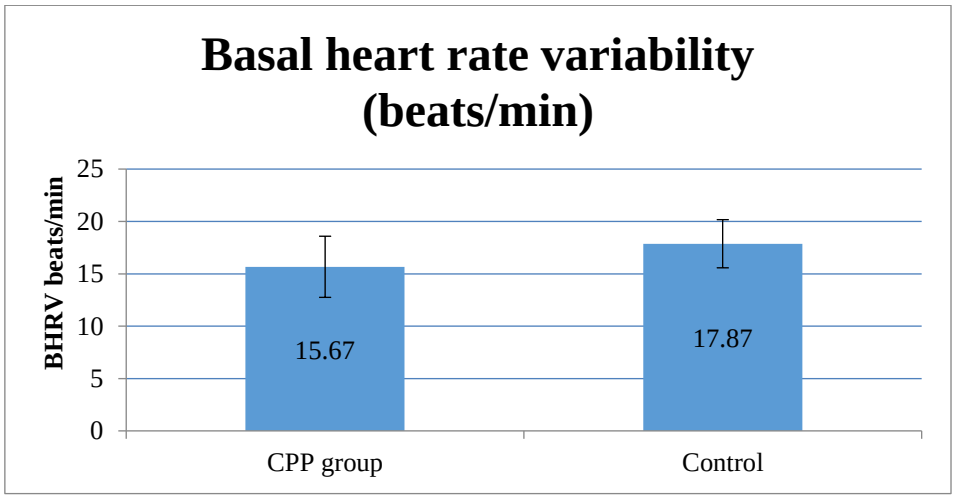

Figure 1: Comparison of basal heart rate variability between CPP patients and normal control.

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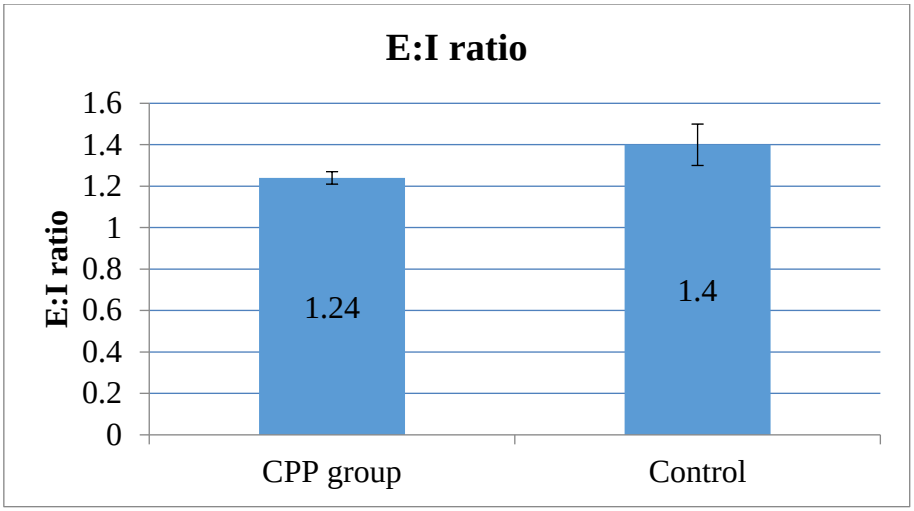

Figure 2: Comparison of E:I ratio variability between CPP patients and normal controls.

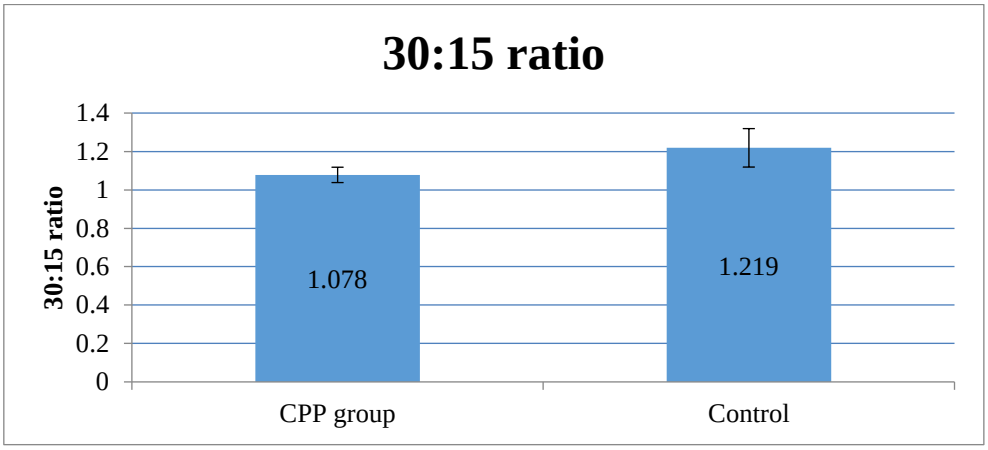

Figure 3: Comparison of 30:15 ratio variability between CPP patients and normal controls.

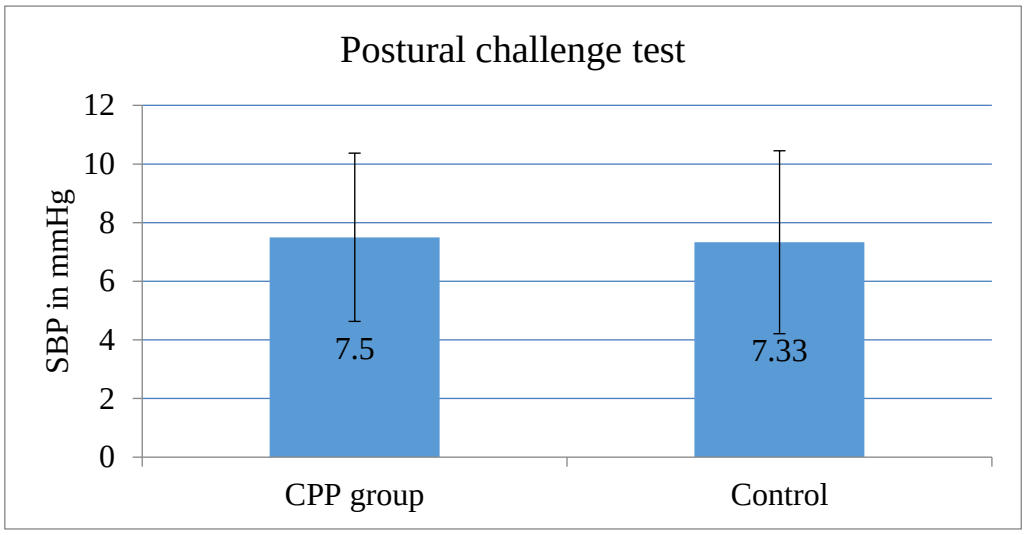

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Figure 4: Comparison of fall in SBP during postural challenge test variability between CPP patients and normal controls.

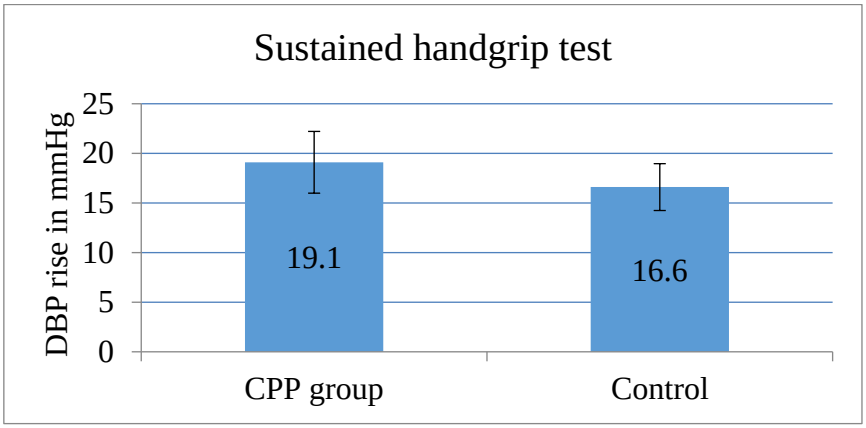

Figure 5: Comparison of rise in DBP during sustained handgrip test variability between CPP patients and normal controls.

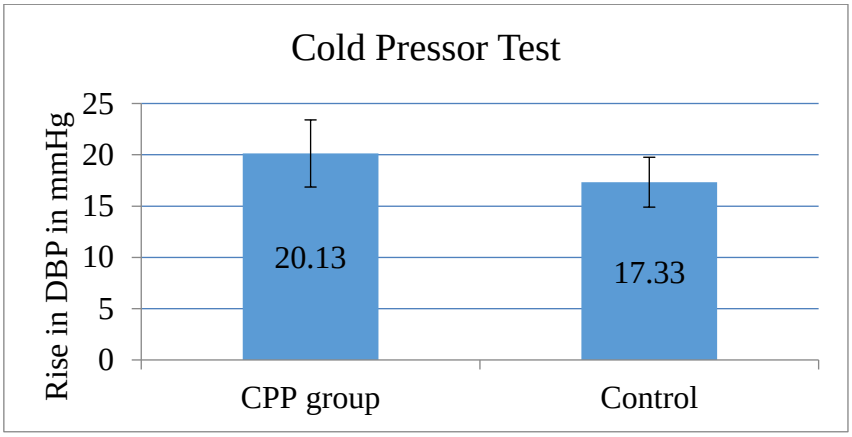

Figure 6: Comparison of rise in DBP during cold pressor test variability between CPP patients and normal controls.

Discussion:

In our study, basal heart rate variability, E:I ratio, and 30:15 ratio values in CPP patients were significantly lower as compared to controls. Decreased basal heart rate variability, E:I ratio, and 30:15 ratio indicates decreased parasympathetic function (decreased vagal tone) or it may be due to increased sympathetic outflow in CPP patients. Studies done on various other chronic painful conditions have shown similar results. E:I ratio was found to be significantly lower in women with irritable bowel syndrome (IBS) which is also one of the causes of CPP.[17] Evans et al observed that children with chronic pain (i.e. children with headaches, myofascial pain, fibromyalgia, complex regional pain syndrome, joint pain, and neurovisceral pain disorders) had decreased heart rate variability as compared to healthy children.[18] Similarly, Shankar et al

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found that E:I ratio and 30:15 ratio were significantly reduced in patients with chronic low back pain as compared to healthy controls indicating lower parasympathetic tone in CLBP patients.[19] The lower parasympathetic tone was also observed in patients with chronic non-inflammatory widespread pain (CWP).[6]

Cardiovascular responses to sustained handgrip test (SHT) and cold pressor test (CPT) are mediated by the sympathetic system. The present study showed that the rise in DBP during SHT and CPT was significantly higher in CPP patients as compared to controls. These findings are suggestive of increased sympathetic tone in CPP patients as compared to controls. A similar higher sympathetic tone in CPP patients has been reported in various studies. Granot et al showed that the rise in SBP during tonic pain stimuli was more in CPP subjects as compared to healthy females.[12] Likewise, Waring et al also found similar results in women with IBS; the LF:HF band ratio during SHT was higher in IBS patients indicating relative sympathetic excess during stimulated conditions as compared to age-matched healthy controls.[17] Tillisch et al found that IBS patients showed more skin conductance response due to visceral distension than healthy controls suggesting higher sympathetic activity in these patients.[20] Women with IBS had higher sympathetic activity as indicated by elevated LF/HF band ratio, during REM sleep because of vagal withdrawal.[21] In a study, women with CPP due to interstitial cystitis or bladder pain syndrome revealed changes in autonomic function with sympathetic dominance, diminished vagal activity, and altered autonomic responses to orthostatic stress.[22]

CPP is associated with significant central changes which include altered behavioural and central response to noxious stimuli, changes in brain structure, and altered activity of both the ANS and the hypothalamic-pituitary-adrenal axis as compared to pain-free women.[23]

Conclusion:

From our study involving autonomic function testing on CPP patients, it was concluded that CPP patients have decreased parasympathetic tone compared to normal controls as evidenced by decreased heart rate variability, E:I ratio, and 30:15 ratio. Secondly, increased sympathetic tone was seen by a greater increase in the rise in SBP during SHT and CPT as compared to controls.

Limitation of the study: Our study was conducted for a limited period and the sample size was small. Further long-duration follow-up studies need to be done with a larger sample size to get a better knowledge of the pattern of changes in autonomic status, autonomic dysfunctions, and their association with pain in CPP patients.

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Conflict of interest: Authors of this study have declared that, there is no any conflict of interest.

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References:

1. Komer Pl. Integrative neural cardiovascular control. Physiol Rev 1971; 51: 312-67.
2. McLeod JG, Tuck RR. Disorders of autonomic nervous system: part 1. Pathophysiology and clinical features. Ann Neurol 1987; 21: 419-30
3. Ewing DJ, Campbell IW, Clarke BF. Assessment of cardiovascular effect in diabetic autonomic neuropathy and prognostic implication. Ann Intern Med 1980; 92: 308-11.
4. Vijaylakshmi I, Shankar N, Bhatia MS, Saxena A, Gupta R. Evaluation of neurophysiological parameters: autonomic status and acute pain perception in migrainers; Del Psych J. 2010; 13(1): 79-85.
5. Cohen H, Neumann L, Shore M, Amir M, Cassuto Y, Buskila D. Autonomic dysfunction in patients with fibromyalgia: Application of power spectral analysis of heart rate variability. Semin Arthritis Rheum. 2000; 29: 217–27.
6. Oladosu FA, Hellman KM, Ham PJ, Kochlefl LE, Datta A, Garrison EF et al. Persistent autonomic dysfunction and bladder sensitivity in primary dysmenorrhea. Sci Rep. 2019 Feb 18;9(1):2194. doi: 10.1038/s41598-019-38545-3. PMID: 30778114; PMCID: PMC6379479.
7. Barakat A, Vogelzangs N, Licht CM, Geenen R, MacFarlane GJ, de Geus EJ. Dysregulation of the autonomic nervous system and its association with the presence and intensity of chronic widespread pain.; Arthritis Care Res (Hoboken). 2012; 64(8): 1209-16.
8. American College of Obstetricians and Gynecologists. Practice Bulletin No. 51. Chronic pelvic pain. Obstet Gynecol 2004; 103: 589-605.
9. Bordman R, Jackson B. Below the belt: Approach to chronic pelvic pain. Can Fam Physician 2006; 52: 1556-62.
10. Mathias SD, Kuppermann M, Liberman RF, Lipschutz RC, Steege JF. Chronic pelvic pain: prevalence, health-related quality of life, and economic correlates. Obstet Gynecol 1996; 87: 321-7.
11. He H, Luo H, Qian B, Xu H, Zhang G, Zou X, Zou J. Autonomic Nervous System Dysfunction Is Related to Chronic Prostatitis/Chronic Pelvic Pain Syndrome. World J

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 08, 2024

Mens Health. 2024 Jan;42(1):1-28. doi: 10.5534/wjmh.220248. Epub 2023 Apr 19. PMID: 37118962; PMCID: PMC10782122.

12. Granot M, Friedman M, Yarnitsky D, Zimmer EZ. Enhancement of the perception of systemic pain in women with vulvar vestibulitis. BJOG. 2002; 109(8): 863-6.
13. Janicki TI, Green A, Ialacci S, Chelimsky TC. Autonomic dysfunction in women with chronic pelvic pain. Clin Auton Res. 2013; 23(2): 101-3.
14. Chelimsky G, McCabe NP, Janata J, Elston R, Zhang L, Ialacci S et al. Autonomic testing of women with interstitial cystitis/bladder pain syndrome. Clin Auton Res. 2014; 24(4): 161-6.
15. Mathias CJ, Banister R. Autonomic failure. A textbook of clinical disorders of the autonomic nervous system. 5th ed. Oxford (UK): Oxford University Press, London. 2013. P.3-7.
16. Mathias CJ, Banister R, Low DA, Iodice V. Investigaion of autonomic disorders. In: Mathias CJ, Banister R (editors). Autonomic failure: A textbook of clinical disorders of the autonomic nervous system. 5th ed.Oxford University Press. Oxford (UK): 2013; P.259-89.
17. Waring WS, Chui M, Japp A, Nicol EF, Ford MJ. Autonomic cardiovascular responses are impaired in women with irritable bowel syndrome. J Clin Gastroenterol. 2004; 38(8): 658-63.
18. Evans S, Seidman LC, Tsao JC, Lung KC, Zeltzer LK, Naliboff BD. Heart rate variability as a biomarker for autonomic nervous system response differences between children with chronic pain and healthy control children. J Pain Res. 2013; 6: 449-57.
19. Shankar N, Thakur M, Tandon OP, Saxena AK, Arora S, Bhattacharya N. Autonomic status and pain profile in patients of chronic low back pain and following electro acupuncture therapy: a randomized control trial. Indian J Physiol Pharmacol. 2011; 55(1): 25-36.
20. Tillisch K, Mayer EA, Labus JS, Stains J, Chang L, Naliboff BD. Sex specific alterations in autonomic function among patients with irritable bowel syndrome. Gut. 2005; 54(10): 1396-401.
21. Thompson JJ, Elsenbruch S, Harnish MJ, Orr WC. Autonomic functioning during REM sleep differentiates IBS symptom subgroups. Am J Gastroenterol. 2002; 97(12): 3147-53.
22. Williams DP, Chelimsky G, McCabe NP, Koenig J, Singh P, Janata J, Thayer JF, Buffington CA, Chelimsky T. Effects of Chronic Pelvic Pain on Heart Rate Variability in

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 08, 2024

Women. J Urol. 2015 Nov;194(5):1289-94. doi: 10.1016/j.juro.2015.04.101. Epub 2015 May 9. PMID: 25963185; PMCID: PMC8753597.

23. Brawn J, Morotti M, Zondervan KT, Becker CM, Vincent K. Central changes associated with chronic pelvic pain and endometriosis. Hum Reprod Update. 2014; 20(5): 737-47.

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