Heart Rate Variability in Assessment of Autonomic Dysfunction in Patients With Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Dae Sung Cho, Jong Bo Choi, Young Soo Kim, Kwan Joong Joo, Sang Hoon Kim, Joon Chul Kim, and Hyun Woo Kim

OBJECTIVE  To determine and compare autonomic dysfunction in patients with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).

METHODS  The subjects were 30-60 years old and had no known systemic disease. Electrocardiographic signals in the patients in the resting state were obtained from 59 patients with CP/CPPS (age 46.5 ± 7.02 years) and 94 healthy subjects (age 48.4 ± 5.96 years), and heart rate variability parameters were compared.

RESULTS  The standard deviation of the N-N interval ($P < .001$), square root of the mean squared differences of the successive N-N intervals ($P = .004$), total power ($P = .004$), very low frequency ($P = .012$), and high frequency ($P < .001$) were lower in the patients with CP/CPPS. However, no significant differences were found in the low frequency and low frequency/high frequency ratios.

CONCLUSION  Patients with CP/CPPS exhibited lower heart rate variability parameters compared with normal controls, with the exception of low frequency and low frequency/high frequency ratios. Possible differences in autonomic nervous system between those with CP/CPPS and normal healthy subjects could exist and autonomic dysfunction might be one of the causes that aggravates CP/CPPS.


Prostatitis affects 9%-16% of men of any age and represents ≤12% of all outpatient visits to urologists in North America and Europe,1,2 compared with 5%-25% in Korea.3 Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) represents a significant proportion of physicians’ work among urologists and remains 1 of the most challenging urologic problems to treat. The etiology is still obscure, the therapy is empirical, and the treatment results are far from satisfactory.

Heart rate variability (HRV) is a noninvasive quantitative and qualitative technique that reflects autonomic imbalance of the cardiovascular system controlled by the autonomic nervous system (ANS), allowing the study of relationships between the ANS and diseases, such as diabetes mellitus, cardiovascular disease, obesity, and female urinary incontinence.4-8

The etiology of prostatitis, particularly for most patients diagnosed with CP/CPPS remains elusive but appears to be associated with ANS dysfunction when we consider the clinical symptoms, such as pelvic or perineal pain, because the lower urinary tract is innervated by the parasympathetic and sympathetic nervous systems that include afferent and efferent motor axons.

A recent study reported that CP/CPPS is initiated by an inflammation within the prostate, resulting in peripheral nervous system sensitization of the prostate and surrounding areas in the susceptible individual and induces some pain.9 Thus, some association exists between ANS imbalance and CP/CPPS. In addition, Yilmaz et al10 demonstrated that HRV suggests altered ANS responses in men with CPPS and concluded that HRV provides a basis for therapeutic manipulation of the ANS for the management of CPPS.

The present study aimed to determine and compare the autonomic dysfunction between patients with CP/CPPS and normal subjects.
The SDNN ($\pm$ 7.69 69.7 $\pm$ 24.5) and LF/HF ratios, the HRV parameters of the patients with CP/CPPS were significantly lower than those in the control group (Table 2).

**COMMENT**

CP/CPPS is a common condition diagnosed in the presence of chronic pelvic pain and lower urinary tract symptoms, which markedly impaired the quality of life. However, the etiology and pathophysiology of CP/CPPS are still unclear. The lower urinary tract, including the prostate, is innervated by 3 sets of peripheral nerves (the parasympathetic, sympathetic, and somatic nervous systems) that include afferent and efferent motor axons. A recent study reported that CP/CPPS is initiated by inflammation within the prostate gland that results in peripheral nervous system sensitization of the prostate and surrounding areas in the susceptible individual. Therefore, this might contribute to neuropathic pain with allodynia and hyperalgesia and could explain the inefficacy of treatment directed at prostatic inflammation with long-standing symptoms.

One of the most useful and least invasive methods to monitor the ANS is the HRV. HRV describes the spontaneous changes in the interval between 2 heartbeats. The heartbeat is not completely regular but fluctuates in a characteristic way, reflecting the continuous interplay between sympathetic and parasympathetic influences. A stable condition generally produces complicated HRV and exercise or stress normalizes HRV.

The Joint Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology established the measurement tool, pathologic analysis, and standard for clinical use of HRV in 1996. HRV analysis, as a monitor of ANS activity, can be performed using 2 main approaches: time domain analysis, which is a statistical calculation of how much variability exists; and frequency domain analysis, which is an analysis of the underlying frequencies and gives information about the autonomic balance and rhythm. The time domain includes average heart rate, SDNN, and RMSSD, and the frequency domain involves TP (total power for 5 minutes, including VLF, LF, and HF), VLF (frequency strength of 0-0.04 Hz for test times >5 minutes), LF (frequency strength of 0.04-0.15 Hz), and HF (frequency strength of 0.15-0.4 Hz). HRV reflects the function of intrabody ANS function. HF and RMSSD are predominantly a response to changes in parasympathetic activity, and LF and SDNN are dually influenced by cholinergic and adrenergic tones, as well as by other physiologic inputs. The TP values are similar to those of SDNN; they affect control of the ANS. Efferent vagal activity is a major contributor of the HF component, as seen in clinical and experimental observations of autonomic maneuvers, such as electrical vagal stimulation, muscarinic receptor blockade, and vagotomy. More controversial is the interpretation of the LF component.

### MATERIAL AND METHODS

We selected 59 men with CP/CPPS (age 46.5 ± 7.02 years) and 94 healthy male volunteers who had requested a health checkup (48.4 ± 5.96 years). None had any evidence of clinically significant signs of dehydration. Subjects with a history of neurologic disease, malignancy, coronary heart disease (CHD), arrhythmia, diabetes mellitus, and heart failure, which could influence ANS, were excluded. The HRV parameters were measured. All subjects underwent complete blood count, serum electrolyte, glucose, urea, creatinine, liver enzyme measurements, and urinalysis. They abstained from coffee, tea, or smoking before the study and were not receiving treatment with drugs, such as β-receptor agonists or antagonists, angiotensin-converting enzyme inhibitors, anticholinergics, or calcium channel blockers, which could influence the ANS. After the subjects had rested for 30 minutes, electrocardiography was done for 5 minutes with the patient seated and analyzed using SA-3000P (Medicore, Seoul, Korea). The heart rate, time domain index, and frequency domain index were compared. Standard deviation of the N-N interval (SDNN) and the square root of the mean squared differences of successive N-N intervals (RMSSD) were used to compare the time domain indexes. Frequency domain methods, including total power (TP), very low frequency (VLF), low frequency (LF), and high frequency (HF) were used to determine the sympathetic and parasympathetic heartbeat rate modulations at rest.

All results are expressed as the mean ± SD. Statistical evaluations were performed using the Statistical Package for Social Sciences, version 12.0.1 (SPSS, Chicago, IL). Comparisons were performed using the independent sample t test. $P < .05$ was considered significant.

### RESULTS

**Subject Characteristics**

The patients and normal subjects were similar in age (46.5 ± 7.02 vs 48.4 ± 5.96, $P = .076$). The laboratory results, including complete blood count, blood chemistry, and urinalysis of all patients were within normal limits, and no significant differences were found between patients and controls for age, weight, and body mass index (Table 1).

**Analysis of Time and Frequency Domain of HRV**

The SDNN ($P < .001$) and RMSSD ($P = .004$) of the patients with CP/CPPS were significantly lower by the time domain analyses. The TP ($P = .004$), VLF ($P = .012$), and HF ($P < .001$) were significantly lower using the frequency domain analyses. Thus, except for the LF and HF/HF ratios, the HRV parameters of the patients with CP/CPPS were significantly lower than those in the control group (Table 2).

### Table 1. Basic characteristics of patients with CPPS and healthy controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CPPS Group (n = 59)</th>
<th>Control Group (n = 94)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>46.5 ± 7.02</td>
<td>48.4 ± 5.96</td>
<td>.076</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.4 ± 7.69</td>
<td>69.7 ± 7.66</td>
<td>.808</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.2 ± 1.97</td>
<td>24.5 ± 2.47</td>
<td>.471</td>
</tr>
</tbody>
</table>

CPPS = chronic pelvic pain syndrome; BMI = body mass index. Data presented as mean ± standard error.
which is considered by some investigators to be a marker of sympathetic modulation (especially when expressed in normalized units) and considered by others to be a parameter that includes both sympathetic and vagal influences.\textsuperscript{16,18-22} However, VLF constitutes most of the TP in the HRV. VLF power in part reflects thermoregulatory mechanisms, fluctuation in activity of the renin-angiotensin system, and the function of peripheral chemoreceptors.\textsuperscript{18,23} VLF might thus reflect not only cardiac stress but also general systemic stress. Hubeaux et al\textsuperscript{24} reported a predominance of parasympathetic activity with the bladder emptied and a preponderance of sympathetic activity at the end of bladder filling in women with overactive bladder syndrome. They concluded that HF variations represented parasympathetic activity, and LF variations represented sympathetic activity. Finally, most investigators believe that LF and HF reflect the activity of sympathetic and parasympathetic activity in short-term HRV.

The clinical significance of HRV was first appreciated by Hon and Lee,\textsuperscript{25} who noted that fetal distress is preceded by alterations in the R-R intervals. In that study, they reported that fetal distress manifests itself as alterations in interbeat intervals before any appreciable changes occur in the heart rate itself. It is the first recognition that HRV indicates body changes or pathologic features.

HRV can be used to assess disease-associated mortality. In a community-based, elderly subsample of the Framingham Heart Study, frequency domain measures were significantly associated with all-cause mortality after adjusting for other risk factors. A total of 736 men and women with an average age of 72 years provided ambulatory time and frequency domain HRV data.\textsuperscript{26} Eight measures of HRV were examined, including 5 frequency domain measures. All 5 frequency domain measures were significantly associated with all-cause mortality and all but the LF/HF ratio (a putative measure of sympathovagal balance for which higher numbers indicate greater relative sympathetic dominance) remained so after controlling for other risk factors. A SD difference in the log-transformed LF power was associated with a 1.7 times greater relative risk of all-cause mortality in that study. Similarly, in the Atherosclerosis Risk in Communities study, the association between HRV and mortality was investigated in 11 654 men and women with an average age of 54 years.\textsuperscript{27} Two minutes of supine resting beat-to-beat heart rate data were collected, and the number of time and frequency domain indexes of HRV was calculated. The lowest quartile of HF power was associated with incident myocardial infarction, incident CHD, fatal CHD, and fatal non-CHD deaths in those with diabetes, with a hazard ratio of 1.27-2.03 during the 8-year follow-up period. In those individuals without diabetes, the effects were much less consistent. However, an examination of LF power indicated results consistent with the Framingham Heart Study, such that those without diabetes in the lowest quartile had a 1.33 greater risk of non-CHD mortality than those in the highest LF power quartile. The effect was even larger for fatal CHD, with those in the lowest LF power quartile having a 1.92 greater risk than those in the highest quartile.

Diabetes has also been associated with decreased HRV. Singh et al\textsuperscript{28} examined the relationship between HRV and blood glucose levels in 1919 men and women from the Framingham Heart Study. The first 2 hours of ambulatory heart rate recordings were used to calculate a number of time and frequency domain indexes of HRV. The fasting glucose levels were used to classify the subjects as having normal or impaired fasting glucose and to identify those with diabetes. Several indexes of HRV, including LF and HF power in the Framingham Heart Study were inversely associated with the fasting glucose levels and were significantly reduced in those with diabetes and those with impaired fasting glucose levels. The association between reduced HRV and diabetes remained significant after adjustment for age, sex, heart rate, body mass index, antihypertensive and cardiac medications, blood pressure, smoking, and alcohol and coffee consumption. Likewise, middle-age men and women from the Atherosclerosis Risk in Communities study in the lowest LF power quartile had a 1.2-fold greater risk of developing diabetes compared with those in the highest quartile, after adjustment for age, race, sex, study center, education, alcohol use, smoking, heart disease, physical activity, and body mass index.\textsuperscript{29}

In our study, all HRV parameters of the patients with CP/CPPS were significantly lower than those in the control group, except for the LF and LF/HF ratios. This evidence is consistent with the possibility of autonomic dysfunction in patients with CP/CPPS and suggests that abnormal autonomic function might correlate with pelvic pain in patients with CP/CPPS. It could also provide a clue toward the mechanism of CP/CPPS. Thus, additional research should evaluate the role of the ANS in the development and exacerbation of symptoms in patients with CP/CPPS.
CONCLUSIONS
Patients with CP/CPPS exhibited different HRV parameters compared with those of normal controls. With the exception of the LF and LF/HF ratios, all parameters in the patients with CP/CPPS were lower than those of normal controls. This suggests that some difference exists in the autonomic nervous system between patients with CP/CPPS and normal healthy subjects and might provide a clue that we should consider autonomic dysfunction as 1 of the causes that aggravate CP/CPPS.

References