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THE INFLUENCE OF CORTICOSTEROIDS ON HEART RATE VARIABLITY IN ACUTE CERVICAL SPINAL CORD INJURY

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SUMMARY – Heart rate variability (HRV) gives information on the sympathetic-parasympathetic autonomic balance. The aim of the study was to analyze sympathovagal balance after acute spinal cord injury (SCI), demonstrated by linear measures in time and frequency domain of HRV and to analyze the effect of corticosteroids on HRV parameters in SCI. The study included 40 tetraplegic patients with acute SCI and 40 healthy subjects as control group. In the SCI group, 29 patients received and 11 patients did not receive corticosteroid therapy. All patients underwent 24-hour Holter monitoring for evaluation of HRV. Cardiac autonomic balance was evaluated by analysis of HRV in time and frequency domain. Sympathovagal balance (LF/HF) was significantly reduced in the groups of acute SCI patients, both with and without corticosteroid therapy, as compared with controls. However, there was no statistically significant difference between the two SCI groups (1.74 (0524) with and 1.75 (0534) without corticosteroid therapy). This study showed the sympathovagal balance to be altered in the acute phase of cervical spinal cord trauma. Finally, there was no effect of corticosteroid therapy on HRV parameters in SCI patients.

Key words: *Cervical vertebrae – injuries; Spinal cord injuries; Heart rate; Adrenal cortex hormones – therapy; Sympathetic nervous system; Vagus nerve*

Introduction

Spinal cord injury (SCI) is an insult to the spinal cord resulting in a change, either temporary or permanent, in the cord normal motor, sensory, or autonomic function[1]. One of the most debilitating secondary consequences of SCI is alteration in autonomic cardiovascular control that, combined with paralysis, predisposes individuals with SCI to a higher incidence of cardiovascular disease. They frequently exhibit arrhythmias, reflex bradycardia and cardiac arrest[2].

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Patients having sustained complete injury, with no motor function or sensation below the level of the spinal cord lesion according to the American Spinal Injury Association (ASIA) standards[3] have a much higher incidence of autonomic dysreflexia (91% with complete injury *vs.* 27% with incomplete injury). Autonomic dysreflexia (AD) can lead to sequels of cardiovascular effects, such as myocardial infarction, intracranial hemorrhage, and even death[4].

Autonomic efferent pathways of cardiovascular regulation are severely impaired in patients with tetraplegia. SCI with resultant quadriplegia is associated with significant dysfunction of the sympathetic nervous system. Sympathetic preganglionic neurons in the thoracic and upper lumbar segment of the spinal cord lose supraspinal control due to cervical SCI. Parasympathetic preganglionic fibers passing through va-

gal nerves, which originate from the brainstem, remain intact[5].

The current ASIA standards for SCI assessment do not evaluate the severity of injury to autonomic pathways. The diagnosis of autonomic neuropathy depends on the results of tests that elicit reflex changes in heart rate[6]. One of the best noninvasive markers of autonomic nervous system function is analysis of the heart rate variability (HRV)[7]. Analysis of HRV has been used to assess autonomic function. It is altered in many diseases[8-11]. The parameters of HRV have been studied in patients with SCI and calculated from 24-hour Holter electrocardiogram (ECG)[12,13].

The aim of this study was to analyze sympathovagal balance after acute SCI as demonstrated by linear measures in time and frequency domain and to compare sympathovagal balance between tetraplegic patients administered and those not administered corticosteroid therapy. The aim was also to observe the effects of corticosteroids on HRV parameters.

Patients and Methods

The study included 40 patients (30 male and 10 female) with acute cervical SCI and 40 (31 male and 9 female) healthy subjects matched for age and sex. In the SCI group, 29 patients received and 11 patients did not receive corticosteroid therapy. Inclusion criteria were, as we previously reported[14], age under 70, cervical SCI with clinically complete motor and sensory loss under the level of injury, and sinus rhythm on ECG. Exclusion criteria were atrial fibrillation, AV block, diabetes mellitus, heart failure, and beta adrenergic blockers or antiarrhythmic drugs in therapy. None of the subjects had cardiopulmonary disease or used drugs that may influence HRV parameters.

The diagnosis of tetraplegia was made by neurological examination by a specialist according to the 1996 ASIA standards[3]. It is based on neurological responses, touch and pinprick sensations tested in each dermatome, and strength of the muscles that control key motions on both sides of the body, including, shoulder shrug (C4), elbow flexion (C5), wrist extension (C6), elbow extension (C7), finger flexion (C8) and small finger abductors (Th1), hip flexion (L2), thigh adduction, extension of leg at the knee (L2, L3, L4), thigh abduction, dorsiflexion of foot, extension of toes (L4, L5, S1), extension of leg at the hip, plantar flexion of foot and flexion of toes (L5, S1, S2). Total paralysis of motor strength was considered as complete lesion. Anesthesia and analgesia were considered as complete lesion. Traumatic SCI is classified into five categories on the ASIA Impairment Scale. The current standards for assessment of SCI (ASIA) examination do not evaluate the severity of injury to autonomic pathways[3].

Upon physical and radiographic examination to determine the degree and level of injury, some patients were administered anti-edematous therapy, as follows: methylprednisolone in high doses and 30 mg/kg bolus, followed by 5.4 mg/kg every hour. It is necessary to initiate treatment within 8 hours of injury and continue it for 23 hours[15]. Each subject provided a detailed medical history and all patients and controls were evaluated by physical examination and 24-hour Holter monitoring.

Analysis of HRV is a noninvasive and simple test to evaluate the autonomic nervous system function in patients with tetraplegia after SCI[16].

Linear analysis of 24-hour ECG recording was performed on the first day of hospital admission after acute SCI. The subjects were monitored with a 24-hour high resolution ECG recorder. Holter ECGs were carefully analyzed by cardiologists. HRV analysis was assessed over 24 hours in time domain and with power spectral analyses. Most of the variables proposed by the Task Force on the Heart Rate Variability were analyzed[17].

The following time-domain and power spectral parameters were calculated: time domain analysis included RR I – mean of R-R intervals; SDNN ms – standard deviation of all RR intervals; SDANN ms – standard deviation of the means of RR intervals in all 5-minute segments of the entire recording; RMSSD ms – square root of the mean of the sum of the squares of differences between adjacent RR intervals; SDNN index ms – mean of the standard deviations of all RR intervals for all 5-minute segments of the entire recording; SDSD ms – standard deviation of differences between adjacent RR intervals; NN50 count – number of pairs of adjacent RR intervals differing by more than 50 ms in the entire recording; and pNN50 – % NN50 count divided by the total number of all NN intervals.

Frequency domain analysis covered TP – total power; P – power; VLF – very low frequency (0.003-

0.04 Hz); LF – low frequency (0.04-015 Hz); HF – high frequency (0.15-0.4 Hz); and LH/HF – low to high frequency ratio named sympathovagal balance. LF and HF variables are expressed in mse2. All variables were measured over 23.1-hour period. ECG recordings were made by the CardioMem CM 3000 (Getemed, G.E., Teltow, Germany) 6-channel Holter recorders. HRV was computer analyzed using the CardioDay software.

R-R intervals that included ectopic beats were excluded and extrapolated by linear interpolation. Spectral analysis was computed using fast Fourier transformation[18].

Statistical analysis was performed using SPSS 17.5 (SPSS Inc., New York, USA) in MS Windows 7.

Means ± standard deviation (SD) were calculated. The groups were compared by use of Mann-Whitney U test. Between group differences in time domain variables were assessed by Student's t-test. Data were tested for normality using Kolmogorov-Smirnov distribution and Shapiro-Wilk test. The level of significance was set at $p<0.05$.

Results

Heart rate variability data derived from 24-hour ECG recordings are shown in Tables 1 and 2.

Table 1 illustrates HRV data in frequency and time domain in SCI patients with and without corticosteroid therapy.

Table 1. Data obtained by analysis of 24-hour ECG recordings; HRV in the frequency and time domain in two SCI groups (with and without corticosteroid therapy)

	Corticosteroid therapy				p
	Yes		No		
HRV in frequency domain:	$\bar{X}$	SD	$\bar{X}$	SD	
TP	1.6	(0.49)	1.4	(0.29)	0.254
p	1.6	(0.46)	1.7	(0.45)	0.385
VLF	1.7	(0.52)	1.8	(0.53)	0.860
LF	1.17	(0.249)	1.21	(0.145)	0.060
HF	3.38	(1.578)	2.94	(1.135)	0.550
LF/HF	1.74	(0.524)	1.75	(0.534)	0.858
HRV in time domain:					
RR I	777.82	(92.56)	792.01	(50.93)	0.765
Median RR I	764.9	(101.08)	792.0	(63.02)	0.570
SDNN	92.7	(31.48)	99.6	(19.55)	0.241
SDANN	63.0	(23.08)	64.2	(16.76)	0.612
RMSSD	113.1	(34.07)	119.6	(33.00)	0.570
SDNN index	42.2	(13.79)	44.5	(14.42)	0.633
SDSD	58.6	(13.85)	63.5	(24.66)	0.765
NN50	22983.4	(13252.08)	21002.6	(7960.58)	0.829
pNN50	24.7	(10.78)	22.7	(7.39)	0.812

ECG = electrocardiography; HRV = heart rate variability; SCI = spinal cord injury; p = test of statistical significance; values are expressed as mean ± standard deviation (SD); TP = total power; P = power; VLF = very low frequency; LF = low frequency; HF = high frequency; LF/HF = low to high frequency ratio; RR I = average value of R-R intervals; SDNN ms = standard deviation of all RR intervals; SDANN ms = standard deviation of the averages of RR intervals in all 5-minute segments of the entire recording; RMSSD ms = square root of the mean of the sum of the squares of differences between adjacent RR intervals; SDNN index ms = mean of the standard deviations of all RR intervals for all 5-minute segments of the entire recording; SDSD ms = standard deviation of differences between adjacent RR intervals; NN50 count = number of pairs of adjacent RR intervals differing by more than 50 ms in the entire recording; pNN50 = % NN50 count divided by the total number of all NN intervals.

Table 2. Data obtained by analysis of 24-hour ECG recordings; HRV in the frequency domain in SCI group and control group

	Group				p
	SCI		Control		
HRV in frequency domain:	$\bar{X}$	SD	$\bar{X}$	SD	
TP	1.6	(0.45)	3.8	(0.99)	<0.001
P	1.6	(0.45)	3.0	(1.08)	<0.001
VLF	1.7	(0.52)	2.7	(0.73)	<0.001
LF	1.18	(0.224)	2.16	(0.228)	<0.001
HF	3.26	(1.469)	1.28	(0.182)	<0.001
LF/HF	0.41	(0.158)	1.71	(1.875)	<0.001

ECG = electrocardiography; HRV = heart rate variability; SCI = spinal cord injury; p = test of statistical significance; values are expressed as mean ± standard deviation (SD); TP = total power; P = power; VLF = very low frequency; LF = low frequency; HF = high frequency; LF/HF = low to high frequency ratio.

Table 2 illustrates HRV data in frequency domain in SCI patients and control group.

In a previously published paper, we reported on the predominance of n. parasympathetic in SCI[14]. Time and frequency domain HRV indices were significantly reduced in the SCI groups with and without corticosteroid therapy, as compared with controls. In the present study, however, there was no statistically significant difference between the two SCI groups.

Low frequency (LF) in the SCI group with corticosteroid therapy was lower (1.17 (0249)) than in the SCI patients without corticosteroid therapy (1.21 (0145); p=0.060) but the difference did not reach statistical significance. High frequency (HF) in the SCI group with corticosteroid therapy was higher (3.38 (1578)) than in the group without corticosteroid therapy (2.94 (1135); p=0.550) but not significantly either. The sympathovagal balance, i.e. the low to high frequency ratio (LF/HF) was not statistically significantly different (p=0.858) between the two groups with cervical spine injuries.

All parameters monitored in time domain were not significantly different between the two groups with SCI. Analysis of the HRV parameters in time domain showed the standard deviation of average RR interval of five-minute recording (SDANN) and standard deviation of all RR intervals (SDNN) as a measure of total HRV to be lower, but not significantly, in the SCI group of patients having received corticosteroid therapy. The square root of the mean of the sum of the squares of differences between adjacent RR intervals (RMSSD) was also lower in the group having received corticosteroid therapy, while the number of adjacent RR intervals that differed by more than 50 ms (NN50) and the percentage of adjacent RR intervals that differed by more than 50 ms (pNN50) as measures of parasympathetic activity were higher in the SCI group having received corticosteroid therapy, but not significantly either. These results are contradictory, so further research is needed. However, there was no statistically significant difference between the two SCI groups.

Discussion

Autonomic dysreflexia is a potentially dangerous clinical syndrome that develops in individuals with SCI. Autonomic dysreflexia develops in individuals with a neurologic level of SCI at or above the level of sixth thoracic vertebra. The severity and neurological level of SCI have major impact on the autonomic nervous system function[19]. In individuals with intact central and peripheral nervous systems, a noxious stimulus results initially in a sympathetic response, leading to elevation in heart rate and blood pressure primarily through spinal reflexes. This response is modulated by the central nervous system and peripheral baroreceptors through the parasympathetic nervous system; it results in heart rate and blood pressure control both through direct responses by the vagus nerve and through inhibitory spinal cord signals. An appropriate balance of sympathetic and parasympathetic outflow is attained and modulated by both the central and peripheral nervous systems[20].

In tetraplegic individuals with complete lesions, disconnection of the spinal sympathetic neurons from cerebral control represents a unique possibility for analysis of the sympathetic influence on HRV[19]. The underlying pathophysiological changes that occur in the spinal cord and periphery causing autonomic dysreflexia have not been fully elucidated in a human model.

During the first week after SCI, disorder of autonomic functions can be life-threatening, especially due to development of bradycardia or even asystole. Cervical SCI has been associated with an increased risk of

mortality from several cardiovascular diseases, including both ischemic and non-ischemic heart disease[21]. Therefore, rhythm disorders and conduct disorders as the most common cardiovascular complications are still a major cause of mortality after trauma to cervical spine and spinal cord.

Tetraplegic patients are deprived of supraspinal sympathoadrenal control, but have intact efferent pathways. Interruption in the spinal cord of efferent sympathetic pathways from central centers leads to pathologic changes in the activity of the peripheral sympathetic nervous system. In complete high-level SCI, functioning in the isolated spinal cord below the lesion becomes independent of supraspinal control and has been termed 'decentralization' of the sympathetic nervous system[5].

Recently developed methods may be particularly useful in evaluating function of autonomic nervous system and the effects of certain drugs on the cardiovascular function in individuals with SCI. Specifically, power spectral analysis of HRV has become commonly used as a noninvasive method to quantify autonomic control of the cardiovascular system[12]. Permanent changes in the sympathetic and parasympathetic autonomic nervous system cause changes in heart rate and fluctuations in the average heart rate.

In our study, HRV was calculated from 24-hour Holter ECG, which is the optimal index of neural control of the heart[12].

In a previously published paper, we have reported on the predominance of n. parasympathetic and altered sympathovagal balance in acute SCI. In their study, Malmqvist *et al*. demonstrated a lower mean LF/HF ratio in the C1-T5 group as compared with the T6-T12 group, indicating that diminished sympathetic activity in these patients results in lower values of LF, which could reflect a less affected sympathovagal balance in the latter group. Their results were similar to ours, suggesting that LF is partly mediated by sympathetic fibers, which supports the assumption that LF/HF ratio can serve as a measure of the sympathovagal balance since HF is mediated entirely by vagal control[19].

In high-level SCI, the sympathetic nervous system is disproportionately involved when compared with the parasympathetic nervous system[5]. However, the fact that LF is not absent after complete injury to cervical spine suggests that the sympathetic control of the heart is modulated by rhythmic discharges by spinal sympathetic neurons, although without supraspinal control.

Previous studies on the effects of certain drugs on HRV did not provide definitive conclusions when HRV is directly related to the effect of certain medications. It is known that beta-receptor antagonists, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers affect HRV and are not administered without previous testing[22-26]. The antiarrhythmics propafenone and flecainide reduce HRV[27].

Inflammation can cause further damage to the spinal cord and patients are treated with drugs to reduce swelling.

The National Acute Spinal Cord Injury Studies (NASCIS) II and III, and a Cochrane Database of Systematic Reviews article of all randomized clinical trials have verified significant improvement in motor function and sensation in patients with complete or incomplete SCI treated with high doses of methylprednisolone within 8 hours of injury[28,29].

We tried to see if corticosteroids had influence on HRV. Analysis of the HRV parameters in the time domain showed that SDANN and SDNN as measures of total HRV were slightly but not significantly decreased in the group with SCI having received corticosteroid therapy as compared with the SCI group without therapy. RMSSD was also decreased in the group on corticosteroid therapy, while NN50 and pNN50 as measures of parasympathetic activity were also slightly but not significantly increased in the SCI group having received corticosteroid therapy.

Reduced HRV is associated with increased morbidity and mortality. It can be assumed that reduced HRV could also be a predictor of morbidity and mortality in subjects after trauma of the cervical spine[30]. Analysis of the HRV parameters in the frequency domain showed that low frequency was lower and high frequency higher in the SCI group on corticosteroid therapy as compared with the SCI group without corticosteroid therapy, but the difference did not reach statistical significance. The low to high frequency ratio (LF/HF) did not differ statistically significantly ($p=0.858$) between the two SCI groups. Accordingly, analysis of the HRV parameters in the time and frequency domains showed no significant difference between the groups of SCI patients having and not having received corticosteroid therapy.

Stein *et al*. analyzed HRV in patients with systemic lupus erythematosus with and without corticosteroid treatment. Time and frequency domain HRV indices were significantly reduced in the systemic lupus erythematosus groups with and without corticosteroid therapy, as compared with controls. However, the indices were not significantly different between the two systemic lupus erythematosus groups[31].

In conclusion, SCI causes dysfunction of the autonomic cardiovascular regulation demonstrated by the spectral measures of HRV. Analysis of autonomic function is related to clinical measures of autonomic nervous system after acute SCI and provides a useful noninvasive clinical marker that can help assess the severity of damage to the autonomic pathways. These measures may also prove useful in evaluating changes in the autonomic function over time or due to interventions aimed at improving autonomic function after SCI and particularly in assessing the effects of certain drugs on the autonomic nervous system.

Finally, a high dose of methylprednisolone can improve motor function and sensation in patients with complete or incomplete SCI[28,29], but cannot improve the sympathovagal balance. We did not find any effects of corticosteroids on HRV parameters. However, additional research is needed in the field.

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Sažetak

UTJECAJ KORTIKOSTEROIDA NA VARIJABILNOST SRČANOGA RITMA KOD AKUTNE OZLJEDE VRATNE KRALJEŽNICE

A. Krstačić, G. Krstačić i *D. Gamberger*

Varijabilnost srčanoga ritma (VSR) daje informacije o simpatičko-parasimpatičkoj autonomnoj ravnoteži tijela. Cilj rada bio je analizirati simpatovagalnu ravnotežu nakon akutne ozljede vratne kralježnice prikazom rezultata VSR linearnim metodama u vremenskoj i frekvencijskoj domeni te procijeniti učinak kortikosteroida na parametre VSR. Istraživanje je provedeno na 40 ispitanika s akutnom ozljedom vratne kralježnice i kralježnične moždine i 40 zdravih ispitanika kontrolne skupine. U skupini s ozljedom kralježnice 29 ispitanika je primalo kortikosteroidnu terapiju, a njih 11 nije primalo tu terapiju. U svih bolesnika provedeno je 24-satno praćenje Holterom za procjenu VSR. Analizom parametara VSR u vremenskoj i frekvencijskoj domeni praćena je autonomna kontrola srca. Simpatovagalna ravnoteža ukazala je na značajno snižen omjer niskih i visokih frekvencija (LF/HF) u bolesnika na kortikosteroidnoj terapiji i onih bez ove terapije zbog akutne ozljede vratne kralježnice u odnosu na kontrolnu skupinu. Međutim, nije bilo statistički značajne razlike između dviju skupina s ozljedom kralježnice [(1,74 (0524) u skupini na kortikosteroidnoj terapiji i 1,75 (0534) u skupini bez ove terapije]. Ovo istraživanje je pokazalo da je simpatovagalna ravnoteža poremećena kod bolesnika u akutnoj fazi traume vratne kralježnične moždine. Akutna ozljeda dovodi do poremećaja autonomne kardiovaskularne regulacije i modulacijske aktivnosti n. simpatikusa na kardiovaskularni sustav. Međutim, nije nađen učinak kortikosteroida na paremetre VSR nakon akutne ozljede vratne kralježnice.

Ključne riječi: *Vratna kralježnica – ozljede; Kralježnična moždina, ozljede; Srčani ritam; Adrenalni korteks, hormoni – terapija; Simpatički živčani sustav; Nervus vagus*