CONTROL OF HEART RATE BY THE AUTONOMIC NERVOUS SYSTEM IN ACUTE SPINAL CORD INJURY

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SUMMARY – Spinal cord injury may cause loss of cardiovascular reflexes mediated by sympathetic drive due to interruption in the supraspinal control of spinal sympathetic motoneurons. The aim of this study was to analyze sympathovagal balance after acute spinal cord injury demonstrated by linear measures in time and frequency domain of heart rate variability (HRV). The study included 40 tatraplegic patients after acute spinal cord injury and 40 healthy subjects as controls. Cardiac autonomic balance was evaluated by HRV analysis in time and frequency domain. The ratio of low to high frequencies (LF/HF) was statistically significantly (Mann-Whitney U=0.0; Z=-7.7; *P*<0.001) different between the group with cervical spine injuries 0.41 (0158) and control group 1.71 (1875). LH/HF was significantly reduced in the group of patients with acute trauma. This study established HRV analysis by linear methods as an objective measure of normal and abnormal function of the autonomic nervous system. In conclusion, spinal cord injury causes dysfunction of the autonomic cardiovascular regulation and leads to disturbances of the modulatory sympathetic activity on the cardiovascular system. The HRV parameters analyzed indicate decreased but still present sympathetic activity and suggest that descending and ascending fibers of the sympathetic nervous system in isolated segment are undamaged, although without supraspinal control after acute spinal cord injury.

Key words: *Cervical vertebrae – injuries; Spinal cord injuries; Autonomic nervous system – physiopathology; Sympathetic nervous system – physiopathology; Heart rate – physiology; Sympathovagal balance*

Introduction

Spinal cord injury (SCI) is associated with abnormal cardiovascular control and is related to the level and severity of injury to efferent sympathetic pathways. One of the leading causes of morbidity and mortality in individuals with tetraplegia after SCI is cardiovascular disease. They frequently exhibit arrhythmias, reflex bradycardia, and cardiac arrest[1,2]. It has been shown that after severe cervical spine injury according to the American Spinal Injury Association standards (ASIA A and B), almost all patients develop bradycardia, 68% have hypotension, and 16% of patients experience cardiac arrest. Patients with moderate spinal injury (ASIA C and D) develop permanent bradycardia in 35%-71% of cases, while cardiac arrest occurs rarely[3,4].

The diagnosis of autonomic neuropathy depends on the results of tests that elicit reflex changes in heart rate[5]. Autonomic efferent pathways for cardiovascular regulation are severely impaired in patients with tetraplegia. Sympathetic preganglionic neurons in the thoracic and upper lumbar segment of the spinal cord lose supraspinal control because of the cervical SCI. Parasympathetic preganglionic fibers through the vagal nerves, which originate from the brain stem, remain intact[6]. Permanent changes in the sympathetic

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and parasympathetic autonomic nervous system lead to changes in heart rate and cause fluctuations in the average heart rate.

One of the best noninvasive markers of autonomic nervous system is analysis of the heart rate variability (HRV)[7]. HRV is an established method to assess the beat-to-beat neural heart rate modulation and its alterations in a number of diseases[8-12].

It is known that certain drugs such as the antiarrhythmics propafenone and flecainide reduce VSR[13,14].

The aim of this study was to establish the degree of impaired cardiac autonomic balance after acute cervical SCI in patients with complete motor and sensory lesion.

Patients and Methods

The study included 40 consecutive patients after acute cervical SCI (30 male and 10 female) and 40 healthy subjects (31 male and 9 female). Inclusion criteria were age under 70 years, cervical SCI with clinically complete motor and sensory loss under the level of the injury, and sinus rhythm on electrocardiogram (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 and none took medications likely to affect the results of the study.

In the control group, there were 40 healthy subjects without acute and chronic morbidity and medication that can affect the parameters of HRV; they were also reviewed at Department of Traumatology.

Neurologic examination was performed by a neurologist according to the 1996 ASIA standards. Motor function was examined by using muscles for the C5-Th1 and L2-S1 levels. Total paralysis of motor strength was considered a complete lesion. Sensory function was examined by touch and pinprick at each dermatome. Anesthesia and analgesia were regarded as a complete lesion. The current standard of SCI assessment according to ASIA does not evaluate severity of injury of autonomic pathways[3].

Patients were also analyzed according to the parameters obtained by physical examination (blood pressure, body temperature), analysis of blood (electrolytes such as potassium, sodium, calcium, complete blood count, the parameters of renal and hepatic functions) and acid-base status determination. All deviations were corrected by a physician.

One noninvasive and simple test to perform in patients with tetraplegia after SCI to evaluate autonomic nervous system is analysis of HRV[15]. 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. HRV was calculated from 24-hour Holter electrocardiogram by using a commercial system. Cardiac autonomic balance was evaluated by HRV analysis in time and frequency domain. Most of the variables proposed by the Task Force on the Heart Rate Variability were analyzed[16]. Time domain analysis included average value of R-R intervals (RR I); standard deviation of all RR intervals (SDNN ms); standard deviation of the averages of RR intervals in all 5-minute segments of the entire recording (SDANN ms); square root of the mean of the sum of the squares of differences between adjacent RR intervals (RMSSD ms); mean of the standard deviations of all RR intervals for all 5-minute segments of the entire recording (SDNN index ms); standard deviation of differences between adjacent RR intervals (SDSD ms); number of pairs of adjacent RR intervals differing by more than 50 ms in the entire recording (NN50 count); and % NN50 count divided by the total number of all NN intervals (pNN50).

In all patients, HRV in the frequency domain was analyzed in short time series over a 5-min recording at rest in supine position. Frequency domain analysis included total power (TP; power (P); very low frequency (VLF; 0.003-0.04 Hz); low frequency (LF; 0.04-015 Hz); high frequency (HF; 0.15-0.4Hz); and low to high frequency ratio (LH/HF) named sympathovagal balance. LF and HF variables are expressed in mse2.

All variables were measured during a 23.1-hour period. ECG recordings were made by CardioMem CM 3000 6-channel Holter recorders (Getemed, G.E., Teltow, Germany). HRV was analyzed by a computer 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[17].

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

7. Means and standard deviations (SD) were calculated. The groups were compared by means of Mann-Whitney U test. Group differences in time domain variables were assessed by Student's t-test. Data were tested for normality using Kolmogorov-Smirnov distributions and Shapiro-Wilk test. The level of significance was set at $P<0.05$.

Results

There were no statistically significant differences according to sex and age (Mann-Whitney test, U=721; Z=-0.76; $P=0.447$). Median age was 52 (range, 42-62) in the group with SCI and 51 (range, 42-60) in the control group. HRV data derived from 24-hour ECG recordings are shown in Table 1.

Table 1 shows HRV data in the frequency and time domains in control subjects and SCI patients. All parameters monitored in the frequency domain were significantly different between the group of SCI patients and control group of healthy subjects. LF in the group with SCI of 1.18 (0224) was statistically significantly lower (Mann-Whitney U=7.0, Z=-7.6; $P<0.001$) than LF in the control group (2.16 (0228)). HF in the group with SCI of 3.26 (1469) was statistically significantly higher (Mann-Whitney U=45.0, Z=-7.3; $P<0.001$) than HF in the control group (1.28 (0182)). The LH/HF ratio was statistically significantly (Mann-Whitney U=0.0, Z=-7.7; $P<0.001$) different between the group with cervical SCI (0.41 (0158)) and control group (1.71 (1875)). Analysis of the HRV parameters in the time domain showed that the SDANN and SDNN as measure of total HRV were significantly lower in the SCI group, while the RMSSD, NN50 and pNN50 as measures of parasympathetic activity were significantly higher

Table 1. *Data obtained by analysis of 24-hour ECG recordings; HRV in the frequency and time domains*

	Group				
	SCI		Control		
HRV in frequency domain	$\overline{X}$	SD	$\overline{X}$	SD	*P*
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
HRV in time domain					
RRi	781.7	(82.81)	835.5	(87.59)	0.014
Median RRi	772.4	(92.22)	822.6	(95.03)	0.039
SDNN	94.6	(28.62)	154.3	(30.69)	<0.001
SDANN	63.3	(21.33)	135.7	(32.48)	<0.001
RMSSD	114.9	(33.48)	62.1	(23.13)	<0.001
SDNN index	42.8	(13.82)	46.3	(16.00)	0.303
SDSD	59.9	(17.28)	57.1	(20.04)	0.500
NN50	22438.7	(11963.93)	12054.8	(7356.01)	<0.001
pNN50	24.2	(9.92)	12.6	(7.97)	<0.001

P = test of statistical significance; SCI = spinal cord injury; 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.

in the SCI group as compared with control group of healthy subjects.

Discussion

This study offered data on linear parameters of HRV derived from 24-hour ECG analysis obtained in patients with acute SCI. 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. Efferent fibers linked with the cervical and upper thoracic sympathetic ganglia originate from the spinal cord between Th1 and Th4, and among other areas innervate the heart. The cell bodies of these neurons originate in the intermediolateral cell column between T3 and L3, with the major portion of the innervations between T5 and T9[6].

Permanent changes in the sympathetic and parasympathetic autonomic nervous system lead to changes in heart rate and cause fluctuations in the average heart rate. One of noninvasive markers of autonomic nervous system activity is analysis of HRV. HRV was calculated from 24-hour Holter electrocardiogram, which represents the optimal index of neural control of the heart. Heat rate variability is a useful noninvasive measure of the autonomic nervous system[18-20].

All parameters in the frequency domain were significantly different between the groups. The TP and P values were significantly lower in the group of SCI patients. The parameter of sympathetic activity, the mean value of LF spectrum in the group of patients with acute spinal cord trauma was significantly lower than the mean value of LF spectrum in the control group of healthy subjects. The sympathovagal balance and LF/HF ratio were significantly reduced in the group of patients with acute trauma. On the other hand, the parameter of parasympathetic activity and the mean HF spectrum value were significantly higher in the group with acute injuries.

These findings were consistent with those found in the literature. In the study conducted by Patil *et al*., a lower LF/HF ratio in patients with SCI was confirmed by reduced HRV and disrupted sympathovagal balance as compared with a control group of healthy subjects[21]. In the study by Claydon and Krassiooukov, the analysis of HRV in subjects with chronic cervical or thoracic spinal and spinal cord injuries showed that LF values were significantly lower in the group with cervical injuries compared with a control group of healthy subjects and subjects with thoracic spine injury, while HF values were significantly higher in the group with cervical spine injury than in the other two groups of subjects. The sympathovagal balance (LF/HF) was lower in the group with cervical injuries compared to subjects with thoracic spine injury and control group[15].

Decreased values of LF in subjects with cervical spinal injuries probably reflect reduced sympathetic control of heart rate. The fact that LF is not absent after complete injury to the cervical spine suggests that sympathetic control of the heart is modulated by rhythmic discharges by spinal sympathetic neurons, although without supraspinal control. Previous studies examining HRV in chronic cervical spine injuries recorded lower LF values[22-24].

There was a significantly higher value of HF in the SCI group as compared with the group of healthy subjects. Elevated HF values suggest an increased activity of vagus nerve after acute trauma. Low values of sympathovagal balance with elevated HF indicate parasympathetic predomination after acute cervical spine and spinal cord trauma and suggest that reduced sympathetic activity is not balanced by reduced parasympathetic activity in the acute phase of trauma. The mean value of VLF spectrum was significantly lower in the group of patients with acute spinal cord trauma than in the control group of healthy subjects. Total HRV was reduced after acute cervical spine trauma, mainly due to VLF reductions. The finding suggests a reduced cardiovascular diurnal oscillation after cervical spine injury. Reduced HRV is associated with increased morbidity and mortality, and reduced VLF is a strong independent predictor of all-cause cardiovascular mortality[25-27]. We can assume that reduced HRV could also be a predictor of morbidity and mortality in subjects after cervical spine trauma[28]. Analysis of HRV in the time domain showed that the mean values of RR interval, median, SDNN and SDANN were significantly reduced in the group of patients with acute cervical spine trauma. The RMSSD and NN50 as measures of sympathetic activity in the time domain were significantly elevated

in the group of subjects with quadriplegia compared to control group of healthy subjects, indicating parasympathetic predominance and increased activity of vagus nerve in acute SCI.

There were no statistically significant between-group differences in the values of SDNN index and SDSD.

In conclusion, this study showed the sympathovagal balance to be altered in quadriplegic patients in the acute phase of cervical spinal cord trauma. 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 the autonomic nervous system after acute SCI; it provides a useful noninvasive clinical marker that can help assess the severity of damage to the autonomic pathways. The use of these measures may also be valuable in evaluating changes in autonomic function over time or due to interventions aimed at improving autonomic function after SCI.

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Sažetak

AUTONOMNA KONTROLA SRČANE FREKVENCIJE KOD AKUTNE OZLJEDE VRATNE KRALJEŽNICE

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Ozljedom vratne kralježnice može doći do gubitka simpatički posredovanih kardiovaskularnih refleksa zbog prekida supraspinalne kontrole spinalnih simpatičkih motoneurona. Cilj rada bio je analiza simpatovagalne ravnoteže nakon akutne ozljede vratne kralježnice prikazom rezultata varijabilnosti srčanog ritma (VSR) linearnim metodama u vremenskoj i frekvencijskoj domeni. Istraživanje je provedeno na 40 ispitanika s akutnom ozljedom vratne kralježnice i kralježnične moždine i s posljedičnim neurološkim deficitom tipa tetraplegije te na 40 zdravih ispitanika kontrolne skupine. Analizom parametara varijabilnosti srčanog ritma u vremenskoj i frekvencijskoj domeni praćena je autonomna kontrola srca. Omjer niskih i visokih frekvencija (LF/HF) bio je statistički značajno (Mann-Whitney U=0,0; Z=-7,7; P<0,001) različit između skupine s ozljedom vratne kralježnice 0,41 (0,158) i kontrolne skupine 1,71 (1,875). Ispitivanje parametara VSR ukazuje na značajno snižen LF/HF nakon akutne ozljede kralježnice. Provedeno istraživanje potvrđuje ispitivanje varijabilnosti srčanog ritma linearnim metodama kao objektivnog pokazatelja normalne i poremećene funkcije autonomnog živčanog sustava. U zaključku, akutnom ozljedom vratne kralježnice dolazi do poremećaja autonomne kardiovaskularne regulacije i poremećaja modulacijske aktivnosti n. simpatikusa na kardiovaskularni sustav. Analiza parametara VSR pokazuju sniženu, ali prisutnu funkciju n. simpatikusa predmnijevajući da su aferentne i eferentne sveze simpatičkog autonomnog sustava u izoliranom segmentu ostale funkcijski neoštećene, iako bez kontrole viših centara kod akutne traume vratne kralježnice.

Ključne riječi: *Vratna kralježnica – ozljede; Kralježnična moždina, ozljede; Autonomni živčani sustav – patofiziologija; Srčani ritam – fiziologija; Simpatovagalna ravnoteža*