Evaluation of Autonomic Functions by Heart Rate Variability after Stenting in Patients with Carotid Artery Stenosis

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Objective: Although carotid stenting is an effective treatment for severe carotid stenosis, it has been associated with alterations in autonomic functions during or shortly after the procedure. Heart rate variability (HRV) is an established tool for the assessment of autonomic functions. In this study, our aim was to investigate the relation between the alterations in autonomic functions and HRV by Holter monitoring parameters.

Methods: Patients (19 male, 8 female) that are suitable for carotid artery stenting, without a history of hypertension, diabetes mellitus, severe coronary artery or valvular heart disease, were enrolled to our study. Short-term HRV analysis recordings were obtained at the beginning, and after the procedure. The square root of the mean squared differences of successive NN intervals (RMSSD), total frequency, low frequency (LF), high frequency (HF), normalized units LF (LFnu), normalized units HF (HFnu), LF/HF ratios were analyzed. Results were statistically analysed by using Wilcoxon test.

Results: Total frequency did not show any significant changes after the procedure (1101 ± 829 , 981 ± 855). While RMSSD and HFnu values significantly increased respectively ($23 \pm 12/33 \pm 22$, and $22 \pm 10/35 \pm 10$, $p < 0.05$) after the procedure, HF values increased nonsignificantly after the procedure ($82 \pm 92/92 \pm 108$). LF, LFnu, and LF/HF values were significantly decreased after the procedure. ($228 \pm 166/112 \pm 100$, $70 \pm 15/55 \pm 18$, $4 \pm 2.5/2.1 \pm 2$, respectively, $p < 0.05$)

Conclusions: While RMSSD and HF are used as markers of vagal activity, LF is a marker of sympathetic modulation and LF/HF ratio shows sympathovagal balance. In our study, we showed that carotid artery stenting is associated with increase in parasympathetic activation, and this finding is demonstrated by HRV parameters.

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autonomic functions; carotid artery stenting; heart rate variability

Carotid artery stenting (CAS) has been emerged as an alternative procedure to carotid artery endarterectomy for the treatment of carotid atherosclerotic disease.¹ Hemodynamic fluctuation occurs during CAS due to stretching of the carotid sinus baroreceptors, mainly during balloon dilatation. The impact of this phenomenon on prognosis and outcomes is still controversial.^{2,3}

Heart rate variability (HRV) is known to be a reliable, noninvasive marker of autonomic nervous system activity.⁴ It has been recognized as a prognostic factor for several diseases (myocardial infarction, idiopathic dilated cardiomyopathy, congestive heart failure, and stroke).^{5–8} The purpose of this study was to evaluate the relationship between alterations in autonomic functions after

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CAS procedure and HRV parameters by Holter monitoring.

METHODS

In the period of November 2010 to December 2011, 27 consecutive patients with extracranial internal carotid artery stenosis due to atherosclerosis that are eligible for CAS were included to our study. Internal carotid artery stenosis were associated with diameter reduction, more than 70% in symptomatic patients and 80% in asymptomatic patients, measured per North American Symptomatic Carotid Endarterectomy Trial Collaborators (NASCET) criteria.⁹ Patients with cardiac arrhythmias, pacemakers, history of coronary artery disease, hypertension, diabetes mellitus, or valvular heart disease and treated with medications that may interfere with autonomic activity such as beta blockers were excluded. Written informed consent was obtained from all patients.

All patients received 300 mg of acetyl salicylic acid and 75 mg of clopidogrel daily for at least 3 days before the procedure. CAS was performed through a femoral approach; self-expanding Carotid Wallstent (Boston Scientific, USA) or Protege Rx carotid stent system (EV3), equipped with embolic protection device, Filter EZ (Boston Scientific, USA). Balloon postdilatation was routinely performed once with 4,5–5,0 mm diameter balloon. All patients received an intravenous dose of 1 mg atropine at the time of balloon dilatation. After CAS, vital and neurologic signs of patients were monitored for a minimum of 24 hours.

Short term (5 minutes) HRV recordings were made before and the day after the CAS procedure in the same time period (10 a.m.) in all subjects. Recordings were obtained in a quiet room, ambient temperature was between 22 and 24 °C, in supine position and spontaneous breathing by use of a digital Holter monitor (DMS 300–7, Compact Flash Card Holter Recorder, DMS, Stateline, NV, USA). The data stored were processed by use of the Cardio Scan 12.0 software to assess HRV. All records were visually examined and manually over-read to verify beat classification. Abnormal beats and areas of artifact were automatically and manually identified and excluded. For the frequency domain analysis power spectral analysis based on a Fast Fourier transformation algorithm was used. Total frequency, high frequency (HF;

Table 1. Baseline Characteristics of Study Population

Baseline Characteristics	
Age (years)	66 ± 11
Men/women (person)	19/8
Stenosis degree (%)	84 ± 12
Stenosis side (left/right)	19/8

0.15–0.4 Hz), and low frequency (LF; 0.04–0.15 Hz) components were measured. The ratio LF/HF was calculated as an expression of sympathovagal balance. LF and HF components were also presented in normalized units (nu), obtained as follows: HFnu = (HF square milliseconds/(LF square milliseconds+HF square milliseconds) × 100).⁴ We also measured the root mean square of successive RR interval differences (RMSSD) which is a marker of time domain analysis but suitable for short term analysis.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, Chicago, IL, USA), version 15.0 software for Windows. Friedman and Wilcoxon tests were used for the comparison of variables. Data are presented as mean ± standard deviation. P values <0.05 were regarded as significant.

RESULTS

Table 1 lists the characteristics of the 27 patients with extracranial internal carotid artery stenosis included to our study. All CAS interventions were done successfully without any adverse neurological events. Men/women ratio was 19/8. The mean age was 66 ± 11 years (range 36–80 years). All patients had unilateral stenosis, where the mean degree of stenosis was 84 ± 12%.

Total frequency did not show any significant changes after the procedure. (1st measurement: 1101 ± 829, 2nd measurement: 981 ± 855) Although RMSSD (1st measurement: 23 ± 12, 2nd measurement: 33 ± 22, P < 0.05) and HFnu (1st measurement: 22 ± 10, 2nd measurement: 35 ± 10, P < 0.05) values significantly increased after the procedure, HF values increased nonsignificantly after the procedure (82±92/92±108). LF (1st measurement: 228 ± 166, 2nd measurement: 112 ± 100, P < 0.05), LFnu (1st measurement: 70 ± 15,

Table 2. Comparison of HRV Parameters Prior and After CAS

	1st Measurement	2nd Measurement	P Value
Total frequency	1101 ± 829	981 ± 855	0.673
HF	82 ± 92	92 ± 108	0,782
HFnu	22 ± 10	35 ± 10	< 0,05
LF	228 ± 166	112 ± 100	< 0,05
LFnu	70 ± 15	55 ± 18	< 0,05
LF/HF	4 ± 2.5	2.1 ± 2	< 0,05
RMSSD	23 ± 12	33 ± 22	< 0,05

2nd measurement: 55 ± 18 , $P < 0.05$), and LF/HF (1st measurement: 4 ± 2.5 , 2nd measurement: 2.1 ± 2 , $P < 0.05$) values were decreased significantly after the procedure (Table 2).

DISCUSSION

This study mainly showed that an increase in RMSSD, HF and HFnu parameters, and a decrease in LF, LFnu, LF/HF parameters occurred after the CAS procedure, which may be a reflection of parasympathetic dominance after CAS.

The carotid sinus baroreceptors are the most important regulatory mechanism in control of blood pressure and heart rate. Changes in baroreceptor activity may cause hemodynamic fluctuations, as observed after CAS.¹⁰ The baroreceptors are stretch receptors that are stimulated by distention of the arterial wall due to changes in blood pressure. The carotid sinus baroreceptors, which are innervated by the carotid sinus nerve, provide a continuous information to the central nervous system about the changes in blood pressure. Activation of central nervous system leads to an increase of the discharge of vagal cardioinhibitory neurons and a decrease in the discharge of sympathetic neurons both to the heart and peripheral blood vessels. This results in bradycardia, decreased cardiac contractility and decreased peripheral vascular resistance, and venous return.¹¹

Carotid artery endarterectomy and CAS may have differential effects on sympathovagal balance of the heart. Although a deviation in cardiac autonomic balance toward the sympathetic side occurs after carotid artery endarterectomy, parasympathetic dominance is seen after CAS. The alterations in cardiac autonomic functions after CAS may be related to the changes in baroreceptor

functions. Although compressing the atheromatous plaque into the arterial wall increases tension over the baroreceptors, CAS placement causes a continuous mechanical distension over the carotid bulb. Both situations lead to inhibition of the sympathetic fibers and stimulation of the parasympathetic pathway. The incision of the carotid artery bulb during carotid artery endarterectomy can denervate baroreceptors, leading to an elevation of sympathetic tone.¹²

The HRV analysis is based on assessing the autonomic modulation exerted on the sinus node.¹³ HRV can be assessed in time and in frequency domain analysis. Because short-term heart rate regulation is predominantly directed by sympathetic and parasympathetic activity, examination of heart rate fluctuations provides an observation of the autonomic nervous system. Frequency domain analysis of HRV enables us to calculate the HF and LF power spectrum of fluctuation RR interval.⁴ Although LF fluctuations in heart rate are mediated by both sympathetic and parasympathetic influences, HF fluctuations are merely mediated by parasympathetic system.¹⁴ Some studies indicate LF power, particularly when expressed in normalized units, as a measure of sympathetic modulations.¹⁵ The LF/HF ratio reflects the global sympathovagal balance.¹⁶

According to our results, parasympathetic dominance occurs after CAS procedure. Mangin et al. report the reduction in heart rate due to immediate influence on cardiac autonomic control for CAS procedure.¹⁰ And also, Yakhov et al. showed parasympathetic dominance in comparison of short term (8 and 24 hour postprocedure) effects on cardiac baroreflex, as well as autonomic cardiovascular control in CAS patients, but not in carotid artery endarterectomy patients.¹⁷ On the other hand, Huang et al. suggested reduced baroreceptor function as transient rather than permanent.¹⁸

The first limitation of our study is the small sample size due to necessity to exclude patients with hypertension, diabetes mellitus, severe coronary artery disease or valvular heart disease, and patients on medications interfering with autonomic functions. The second limitation is that due to not having a control group, a comparison between HRV parameters could not be done.

In conclusion, changes in HRV parameters may reveal parasympathetic dominance after CAS procedure. Further studies in larger populations are needed to confirm these findings.

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