

CLINICAL RESEARCH

Drug-Free Correction of the Tone of the Autonomic Nervous System in the Management of Cardiac Arrhythmia in Coronary Artery Disease

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Abstract

Background: The aim of our study was to examine the possibility of ventricular extrasystole (VES) management in CAD (coronary artery disease) patients by attenuating the sympathetic activity with a course of electrical stimulation of the vagus nerve. **Methods:** A decrease in sympathetic tone was achieved via vagus nerve electrical stimulation (VNES). VNES was performed in 48 male CAD patients, mean age 53.5 ± 4.1 years. Antiarrhythmic drug therapy was canceled prior to VNES therapy. The effect of VNES on heart rate variability (HRV) and VES were carefully studied. All the patients received a 24-hour ECG monitoring. HRV was calculated for high frequency (HF) and low frequency (LF) bands and the LF/HF index was determined. **Results:** Immediately following VNES therapy, 30 patients (group 1) reported alleviation of angina signs and the LF/HF index was significantly decreased ($p=0.001$). Eighteen patients (group 2) showed no change either in health or the LF/HF index. According to ECG and echocardiography, the VES number did not significantly change immediately after VNES therapy. One month after the VNES course, group 1 reported further improvement in health; the LF/HF index approached normal values. In group 2, the LF/HF significantly decreased ($p=0.043$). However, in the entire study sample, the VES number significantly decreased overall ($p=0.025$). **Conclusion:** VNES attenuated the cardiac effects of hypersympathicotonia decreased the ischemic impact on the myocardium, alleviated the cardiac angina signs, and beneficially influenced the VES number in CAD patients.

Keywords: coronary artery disease, angina pectoris, electric vagus nerve stimulation, sympathetic nervous system, ECG Holter monitoring.

Abbreviations

EF, ejection fraction; IVS, interventricular septum; LVPW, left ventricle posterior wall; EDV, end diastolic volume; HR, heart rate; VES, total ventricular extrasystole number; MI, myocardial infarction; bpm, beats per minute; VNES, vagus nerve electrical stimulation; LF/HF, low frequency/high frequency.

Introduction

Hyperactivation of the sympathetic nervous system (SNS) is a significant pathophysiological factor determining the chronicity of heart failure of ischemic origin [1-3]. Along with straightforward cardiac ischemia, an increase in the SNS activity is one of the main predictors of cardiac arrhythmias including VES [4-6]. A well-recognized method to detect VES is a 24-hour ECG monitoring (24h-ECG) which enables the evaluation of the status of the autonomic nervous system as well, in patients [1-7].

The evaluation is based on a calculation of the HRV parameters. Activities of the parasympathetic and sympathetic components of autonomic innervation are differentially associated with the high and low frequency HRV components [8-11]. Suppression of the SNS hyperactivity is considered an important component in the treatment of cardiac failure in CAD patients [2, 8, 9, 12]. To achieve this, clinicians use various pharmacological tools ranging from ganglionic blockers and β -adrenoblockers to central α_2 -adrenomimetics [13-17]. Simultaneously, attention is paid to a possibility of drug-free correction of the autonomic nervous system status in patients with heart failure, including those with cardiac rhythm abnormalities [18-20].

The aim of our study was to examine the possibility of ventricular extrasystole (VES) management in CAD patients by attenuating the sympathetic activity with a course of electrical stimulation of the vagus nerve (VNES).

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Methods

Study population

The study included 48 male patients mean age 53.5 ± 4.1 years with CAD associated with angina, functional class II or more. All patients showed no indications for surgical CAD treatment (direct myocardial revascularization) at the time of examination. Fourteen days prior to the examination, antiarrhythmic therapy, including β -adrenoblockers, was canceled for all the patients. The background antianginal therapy remained unchanged, which included the prolonged release of nitrates and calcium antagonists such as amlodipine and nifedipine. The 42 (87.5%) patients included in the study had acute myocardial infarction.

Clinical endpoints

All patients underwent general clinical and instrumental (ECG, echocardiography) examinations as well as 24h-ECG (ECG Holter monitoring) with determination of the following parameters: minimum, maximum, and daily average heart rate (HR); total VES number (number of single, bigeminal, trigeminal, and paired VES). Calculation of the HRV value was done in the HF and LF bands. The LF/HF ratio was determined as an indicator of the presence or absence of autonomic nervous system dysfunction [21, 22]: LF/HF value above 1.5 suggested hyperactivity of the sympathetic component; LF/HF in the range of 1.2 to 1.5 suggested a mixed type of the autonomic nervous system; LF/HF of 1.0 to 1.1 was considered normal; and LF/HF less than 1.0 indicated the pronounced vagotonic type of the autonomic nervous system.

Technique of vagus nerve stimulation

To correct the autonomic nervous status in our patients, indirect electrical stimulation of the nucleus dorsalis nervi vagi in the central nervous system via VNES therapy was performed, similar to our prior work [20]. The stimulation was performed using bipolar pulses of low frequency electrical current flowing through the electrodes located on the internal surfaces of the auricles (Figure 1) in the area of the afferent nerve endings of the r. auricularis n. vagi [23]. The course of the VNES therapy consisted of 10 sessions with a gradual increase in the intensity of the electric current (from 0.05 to 0.15 mA) and the duration of each session (from 5 to 30 min). The patient's condition was



Figure 1.

Topographic location of the afferent nerve endings of cranial nerves on a surface of an auricle. 1: n. facialis; 2: r. auricularis n. vagi; 3: parotid salivary gland.

evaluated before and after each session. Follow-up 24h-ECG monitoring was performed immediately after the VNES course and one month after the treatment.

Statistical analysis of data was done by using the statistics and analytics software package STATISTICA developed by StatSoft Inc., USA (1984–95). Data were analyzed with nonparametric sign test. Data are presented as mean \pm standard

error of the mean. Differences with $p < 0.05$ were regarded as significant.

The study complied with Good Clinical Practice requirements based on the Declaration of Helsinki (1964) amended in 2008. Study protocol and informed consent process were approved by the local Ethics Committee.

Results

Data of initial instrumental examination in CAD patients

Data from the echocardiography and 24h-ECG monitoring studies of the patients at the time of their enrolment in the study are presented in Table 1. In the study sample, the daily average HR varied from 54 to 73 bpm (average 61.71 ± 6.03 bpm). A variation of the daily maximum HR ranged from 96 to 164 bpm. The minimum night HR ranged to a lesser degree, from 40 to 57 (average 46.82 ± 4.42 bpm).

Table 1.

Clinical characteristic of patient groups

Parameters	Patients		
	Group A	Group B	Entire patient sample
EF, %	50 ± 9.92	60 ± 10.45	53.33 ± 4.44
IVS, mm	11 ± 2.75	10 ± 1.14	10.33 ± 0.44
LVPW, mm	10 ± 1.13	9 ± 0.84	9.33 ± 0.44
EDV, mL	155 ± 46.22	205 ± 9.00	175.33 ± 19.78
Average HR, bpm	59.75 ± 4.25	60.87 ± 6.51	61.71 ± 6.03
Minimum HR, bpm	47.50 ± 2.25	46.70 ± 4.49	46.82 ± 4.42
Maximum HR, bpm	128.75 ± 17.36	120.35 ± 18.15	124.88 ± 16.96
VES	2301.5 ± 1405.3	4001.0 ± 2171.41	3559.6 ± 2424.33
LF/HF	2.43 ± 0.78	1.85 ± 0.20	1.92 ± 0.34

The VES number varied from 985 to 18488 (average 3559.59 ± 2424.33) per day including isolated VES from 55 to 9782 (average 2202.71 ± 1177.52) per day; paired VES from 3 to 75 (average 29.71 ± 17.47) as well as episodes of bigeminal and trigeminal VES from 26 to 1544 (324.82 ± 361.55). Autonomic balance, calculated as LF/HF ratio, was 1.92 ± 0.34 ranging from 1.5 to 3.2 suggesting pronounced sympathicotonia in all the patients of the sample studied.

Toward the seventh or eighth session, 30 patients (62.5%) reported a decrease in the intensity and frequency of the angina attacks as well as an improvement in a feeling of general wellbeing, decrease in fatigue during physical exercise, and an improvement in sleep quality. Six patients (12.5%) reported a decrease only in the intensity of the angina attacks; 12 patients (25%) did not notice any change at all in their health condition. This differential response to the treatment persisted until the completion of the VNES course. Based on these results, the patients were assigned into two groups: group A included 30 patients (62.5%) who reported beneficial effects of the VNES course; group B included 18 patients (37.5%) without positive VNES effects.

Clinical results immediately after VNES therapy

Data of the instrumental examinations, performed immediately after the VNES course, did not show any statistically significant changes for the entire patient sample (Table 2). For instance, the average LF/HF index decreased to 1.67 ± 0.42 ($p=0.117$), whereas the daily VES number decreased to an average of 2439.25 ± 1536.08 ($p=0.118$) per day. However, an analysis of the same parameters within groups A and B showed different trends. Originally, group A showed a significantly

Table 2.*The effect of VNES therapy on LF/HF index in patient groups*

Patients	Time of examination		
	Before VNES course	Immediately after VNES course	One month after VNES course
Entire patient sample	1.92 ± 0.34	1.67 ± 0.42	1.51 ± 0.14
Group A	2.43 ± 0.78	1.25 ± 0.25 p = 0.001	1.02 ± 0.03
Group B	1.85 ± 0.20	1.71 ± 0.21	1.56 ± 0.15 p = 0.043

more pronounced disturbance of the autonomic nervous system according to the LF/HF index compared with group B (2.43 ± 0.78 versus 1.85 ± 0.20, respectively). Immediately post VNES therapy, the LF/HF index in group A was 1.25 ± 0.25, which was significantly lower than it was prior to the treatment (p=0.001). The autonomic nervous balance in group B did not significantly change; the LF/HF index was 1.71 ± 0.21 (p=0.536). At the same time, the ECG data and echocardiography in these groups did not show any statistically significant changes in the parameters characterizing the cardiac function, including the VES number.

Clinical results one month after VNES therapy

Data of the follow-up examinations performed one month after the VNES course showed an improvement in the feeling of the wellbeing and health in group A patients; some patients in group B also reported positive dynamics. In more detail, data from the 24h-ECG monitoring showed that the LF/HF ratio approached normal values ranging from 1.0 to 1.1 (average 1.02 ± 0.03). Group B did not show any significant decrease in the sympathetic tone; the LF/HF ratio ranged from 1.3 to 1.7 (average 1.56 ± 0.15; p=0.043).

Evaluation of the VES number showed a decrease in the VES frequency in the patients examined (Table 3). The analysis of the daily VES frequency within the entire sample group of patients revealed a statistically significant decrease in the average total VES number to 1233.48 ± 885.23 per day (p=0.025), ranging from 785 to 6300. The daily VES number in group A decreased by more than 30%. The average VES number of episodes was 1055.72 ± 703.27 per day. The patients in group B did not experience any decrease in the total number of VES.

Table 3.*The effect of VNES therapy on the total daily number of ventricular extrasystoles in patient groups*

Patients	Time of examination		
	Before VNES treatment	Immediately after VNES course	One month after VNES course
Entire patient sample	3559.6 ± 2424.33	2439.25 ± 1536.08 (p = 0.118)	1233.48 ± 885.23 (p = 0.025)
Group A	2301.5 ± 1405.3	1457.3 ± 542.02	1055.72 ± 703.27 (p = 0.036)
Group B	4001.0 ± 2171.41	3421.17 ± 2676.28	3445.74 ± 2568.36

Discussion

Our data suggested that CAD was associated with a disturbance of the autonomic nervous regulation of the heart toward hypersympathicotonia, which could provoke electrophysiological remodeling of the cardiac muscle. In these circumstances, a course of neuronal stimulation by low

frequency electrical current pulses enabled the autonomic nervous regulation of the heart to normalize in CAD patients. The effects of the VNES therapy consisted of an improvement in the clinical condition of CAD patients and a decrease in the total daily VES number. Efficient neuronal stimulation consisted of an application of the electrical pulses to the internal auricular surfaces in the region of the afferent vagus nerve endings [23, 24]. A similar experimental treatment resulted in an antiarrhythmic effect in rats [25]. The mechanistic basis of the VNES treatment can be related to the inhibition of stress-induced noradrenaline release from the sympathetic nerve endings in the myocardium. The high likelihood of this mechanism can be confirmed by the fact that the afferent vagal stimulation leads to a reflex excitation of the efferent vagal activity and to the inhibition of the efferent sympathetic activity [26]. Our data suggested that the antiarrhythmic effect observed post VNES treatment might involve certain delayed mechanisms, such as an attenuation of the ischemia influence on the myocardium. The presence of such an effect was confirmed by the fact that those patients who benefited from VNES therapy reported about a definite decrease in the intensity and frequency of the cardiac angina attacks, alleviation of fatigue during physical exercises, and improvement of sleep quality and general health. This hypothesis was also supported by the fact that the group of patients with pronounced hypersympathicotonia developed a statistically significant decrease in the LF/HF index after VNES therapy. However, we did not observe statistically significant changes in the parameters characterizing cardiac function, including the daily VES number immediately post VNES therapy. Significant changes developed only one month after the completion of the VNES therapy and consisted of a decrease in the total daily VES number in patients who also reported continued improvement in their feelings of wellbeing and general health. Such a delayed result could have developed as a consequence of the changes in the cardiomyocyte metabolism induced by the normalization of the autonomic nervous system regulation and by a decrease in the influence of ischemia on the myocardium. This hypothesis does not contradict our prior data which revealed changes in the myocardium of CAD patients after VNES therapy, including an induction of the ATP and HSP-70 protein synthesis [20].

One of the known possible mechanisms triggering ventricular arrhythmias in chronic CAD patients is a reentry caused by the presence of altered electrophysiological properties in the myocardium, such as an altered structure of the cardiomyocyte plasma membrane and the altered electrical stability of the cardiomyocytes due to neurohumoral factors [27-29]. Thus, the degree of vasoconstriction corresponds to the degree of the increased sympathetic activity. According to the experimental data, the electrical stimulation of the vagus nerve in such a situation enables the prevention of the development of arrhythmia in the ischemic myocardium [31-31]. Some authors report that a similar procedure also enhances prevention against recurrent angina attacks [32].

In conclusion, there is evidence for the pathophysiological rationale of drug-free correction of the autonomic nervous regulation of the heart in CAD patients aimed, among other things, at the prevention of cardiac arrhythmias. The role of the metabolic component in the normalization of the functional status of the heart after a course of auricular vagus nerve stimulation warrants further study.

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