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Effect of Stimulating the Auricular Branch of the Vagus Nerve on the Heart Rate in Patients with Severe Chronic Heart Failure

S. A. Afanasiev, E. N. Pavlyukova, M. A. Kuzmichkina, Y. D. Anfinogenova, and R. S. Karpov

Institute of Cardiology, Tomsk, Russia

e-mail: Tursky@cardio-tomsk.ru

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Abstract—A study was made to evaluate the prospects of improving the cardiac function by electrical stimulation of the auricular branch of the vagus nerve in patients with severe chronic heart failure (CHF). Sympathetic hyperactivity and the cardiac function were evaluated by 24-hour ECG monitoring, echocardiography, and a 6-min walk test. At the time of enrollment into the study, patients had a heart rate (HR) of more than 60 bpm, a left ventricular (LV) ejection fraction (EF) of less than 40%, and CHF NYHA functional class (FC) III or IV even with well tolerated medications. Control-group patients (n = 7) did not show significant changes in the functional state of the heart after sham treatment. In the test group (n = 44), a significant increase in LV EF and a decrease in end-systolic volume were induced by electrical pulse stimulation of the auricular branch. A decrease in HR was documented in 34 patients; CHF FC decreased by one or two grades in 40 patients. The changes were assumed to reflect new balance achieved in the autonomic regulation of the heart to contribute to sustaining competence of the myocardium. Electrical pulse stimulation of the auricular branch of the vagus nerve was concluded to provide a safe and efficacious addition to drug therapy in patients with severe CHF.

Keywords: chronic heart failure, coronary heart disease, hyperactivation of sympathetic nervous system, electrical stimulation of vagus nerve, heart rate

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INTRODUCTION

The autonomic nervous system exerts a substantial effect on the cardiovascular system [1, 2]. Risk of many chronic cardiovascular pathology increases in persistent autonomic disorders, and, in turn, chronic pathologies aggravate imbalance in the autonomic regulation of the heart [3–8]. Metabolic, structural, and functional rearrangements consequently arise in the myocardium in chronic pathologies, affecting the cell adrenoreceptor system, and hyperactivation of the sympathetic nervous system becomes stable via changes at the level of its central structures [9–11].

The auricular branch of the vagus nerve with its sensory fibers starting from the inner surface of the auricle is an anatomic structure belonging to parasympathetic afferents of the autonomic nervous system [12, 13]. Electrical pulse stimulation of the auricular branch has previously been observed to exert a favorable effect in patients with cardiovascular disorders [14–16].

In this work, we evaluated the possibility of correcting the functional changes in the heart in patients with severe chronic heart failure (CHF) via non-drug stimulation of the auricular branch of the vagus nerve.

METHODS

A total of 51 patients aged 50–68 years with CHF of an ischemic origin were included in the study. According to the New York Heart Association (*NYHA*) classification, the patients were in functional class (FC) III or IV. CHF was clinically stable for at least 30 days prior to enrollment in all patients. A heart rate (HR) was more than 60 bpm, and the left ventricular (LV) ejection fraction (EF) was less than 40%. The patients had no signs of intra- and interventricular LV asynchrony and heart valve disease. The patients received optimal drug therapy for their CHF without any changes in medications from 30 days prior to the study through the end of follow-up. Medications included angiotensin I-converting enzyme inhibitors, β blockers, diuretics, nitrates, and cardiac glycosides.

The study was a comparative, single-blind study in design. Patients enrolled in the study were randomized to a test (44 patients) and control (7 patients) groups, which were comparable in clinical characteristics.

The test-group patients received a course of electrical pulse stimulation of the auricular branch of the vagus nerve. Bipolar stimulation with low-frequency (3-Hz) pulses was performed using electrodes attached on both sides to the inner surface of the

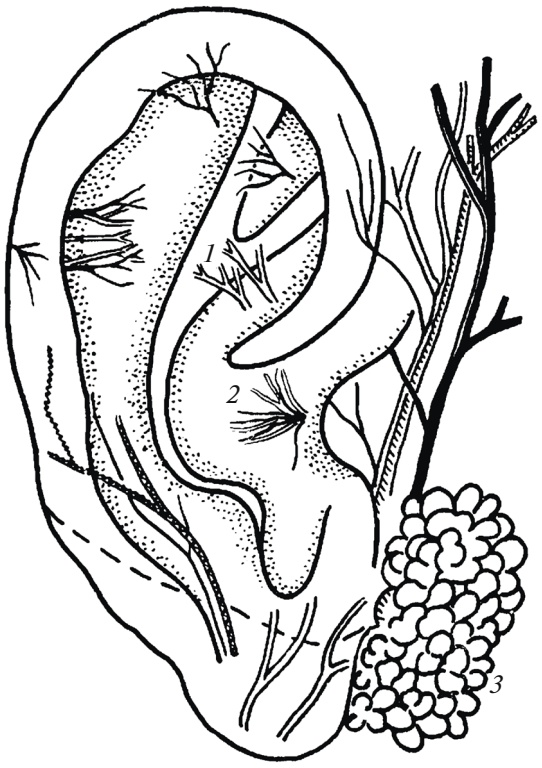

Fig. 1. Location of afferent endings of cranial nerves on the human ear surface [12]: *1*, facial nerve; *2*, auricular branch of the vagus nerve; *3*, parotid salivary gland.

auricular base (Fig. 1), where sensory endings of the auricular branch start [12, 13]. The electrical stimulation course was carried out for 15 days an included once-daily sessions as follows: session 1, 1 min at 0.05 mA; sessions 2 and 3, 5 min at 0.05 mA; sessions 4 and 5, 10 min at 0.08 mA; sessions 6 and 7, 15 min at 0.1 mA; sessions 7–9, 20 min at 0.12 mA; and sessions 10–15, 30 min at 0.15 mA. In the control-group patients, electrodes were placed to the same auricular regions, but electrical pulses were not applied [14–16].

The set of clinical instrumental tests included a 6-min walk test [17, 18], ECG, 24-h Holter ECG monitoring, and echocardiography. All tests were performed prior to and 1 day after the electrical stimulation course or sham treatment.

The average HR was automatically determined from the 24-h ECG monitoring data [4, 5, 19–23]. A decrease in HR was defined as a decrease in 24-h HR average by at least 5 bpm.

Table 1. Patient distribution through CHF FCs in the test group

Patient condition	Functional class			
	I	II	III	IV
Baseline	–	–	42	2
After stimulation	–	38	6	–

Two-dimensional echocardiography was performed and two- and four-chamber views were analyzed using a *Vivid* 7 *Dimension* ultrasound system (*GE Healthcare*). The end-diastolic volume (EDV), end-systolic volume (ESV, Simpson's method), and LV EF were estimated.

The study followed the guidelines of the World Medical Association Declaration of Helsinki. The study protocol and informed consent document were approved by the Biomedical Ethics Committee at the Institute of Cardiology (Tomsk). All patients enrolled in the study voluntarily gave their written informed consent.

The hypothesis of a Gaussian distribution was rejected in testing by the Lilliefors and Shapiro–Wilk modifications of the Kolmogorov–Smirnov test, and we consequently used the Mann–Whitney (U) and Wilcoxon tests. The critical significance level $p = 0.05$ was assumed in all statistical tests. Results were presented as $M \pm SD$, where M is the mean and SD is the mean-square deviation, with the median (Me) and lower and upper quartiles.

RESULTS AND DISCUSSION

Patients of the control group did not show any changes in clinical condition during the study. In contrast, the clinical condition improved, as was seen from a decrease in shortness of breath and fatigue, in the test-group patients after a course of electrical pulse stimulation. The FC improved by at least one grade in 40 patients and remained unchanged only in 4 (9%) patients (Table 1).

The test group was divided into a subgroup of patients with a baseline HR lower than 80 bpm (32 patients) and a subgroup of those with a baseline HR higher than 80 bpm (12 patients) according to 24-h ECG monitoring data. After a course of electrical pulse stimulation, a decrease in HR was observed in 26 patients in the subgroup with a baseline HR lower than 80 bpm (Fig. 2). Eight patients displayed a decrease in HR after a course of electrical stimulation in the subgroup with a baseline HR higher than 80 bpm. A comparison showed that electrical pulse stimulation was less effective in decreasing the HR in patients whose HRs were higher than 80 bpm at the baseline.

A significant increase in LV EF and a decrease in ESV were observed in the test-group patients with baseline HRs lower than 80 bpm after course of electrical pulse stimulation. The effect was independent of whether the HR decreased in response to electrical stimulation. A significant decrease in EDV was additionally observed in patients with an unchanged HR (Table 2). Similar statistically significant changes in LV EF and ESV were observed in 8 out of 12 patients

whose HRs were higher than 80 bpm at the baseline and decreased after electrical pulse stimulation (Table 3). LV EF, EDV, and ESV did not significantly change after electrical pulse stimulation in the patients of this subgroup.

In the control group, LV EF, ESV, and EDV did not significantly change after sham treatment. The LV EF, EDV, and ESV of these patients were, respectively, 28.50 ± 8.32%, 185.93 ± 50.61 mL, and 135.23 ± 45.00 mL at the baseline and 31.60 ± 8.92%, 192.83 ± 64.82 mL, and 134.00 ± 54.91 mL at the end of the study.

Hyperactivation of the sympathetic nervous system is through to be an important element in the pathogenesis of CHF [3, 6–8]. Suppressing this hyperactivation is one of the goals when treating CHF patients [3, 4, 24]. To achieve this goal, we used a course of electrical pulse stimulation of sensory endings of the auricular branch of the vagus nerve in addition to standard drug therapy, which failed to exert a substantial effect. The CHF FC improved by at least one grade in 40 out of 44 patients after electrical pulse stimulation. Improving the functional state of the heart is an important aim of treating patients with severe CHF (FC III or IV). A significant increase in LV EF was observed in 80% of the test-group patients by the end of our study. Favorable changes in EF were accompanied by a decrease in LV systolic dysfunction. Our findings agree with published data from other studies [25–27]. Stimulation of the vagus nerve has been observed to improve quality of life and the LV function in CHF patients. It should be noted that special stimulators have been implanted to increase parasympathetic activity by stimulating efferent fibers of the vagus nerve in those studies. In our work, the effect on the vagus nerve was mediated by a natural reflex arch known for the human body. The reflex arch includes the afferent auricular branch with its surface sensory endings, central *n. vagus* nuclei, and efferent *n. vagus* fibers traveling to the heart [12, 13]. Our approach obviates invasive interventions and prevents adverse reactions to the stimulation procedure. The involvement of the *n. vagus* nuclei in transmitting stimulatory pulses makes it possible to assume that balance of sympathetic and parasympathetic components changes and is stabilized at the central level of the autonomic nervous system.

We think that the improvement in CHF FC and the echocardiographic findings reflect new balance achieved between sympathetic and parasympathetic innervation of the heart. However, this does not mean that an inverse remodeling of the heart was achieved during the treatment. Lack of consistent changes in intracardiac hemodynamics supports this idea. For instance, an increase in LV EF was accompanied by a significant decrease in ESV in all cases, while a decrease in EDV was observed only in the patients who had a HR < 80 bpm and did not display a decrease

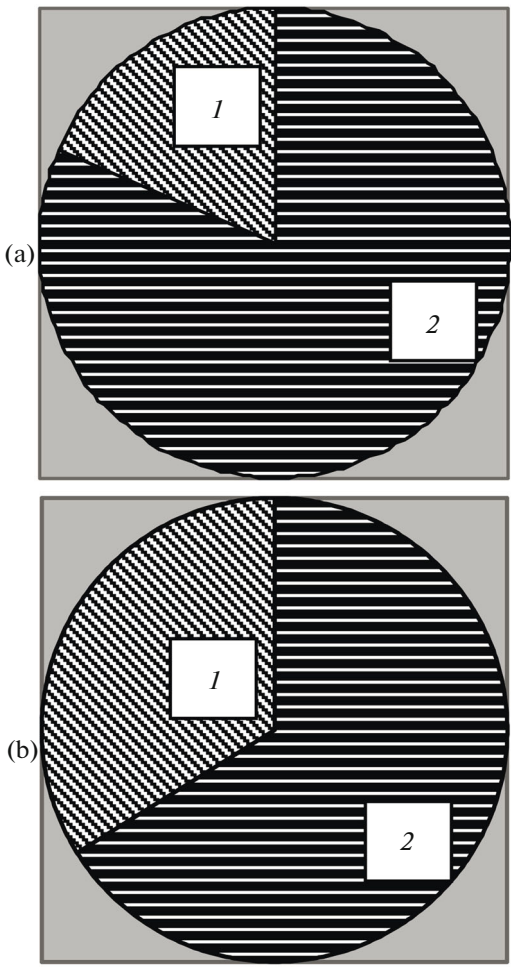

Fig. 2. Proportion of patients differing in HR response to a course of electrical pulse stimulation in the test group. The patients had (a) 60 < HR < 80 bpm or (b) HR > 80 bpm at the baseline. The HR (*1*) remained much the same or (*2*) changed.

in HR (Tables 2, 3). The result probably indicates that the parameters in question are not related directly or, on the other hand, that our samples differ in representation.

Changes in HR are though to provide the most apparent and clinically significant indicator of the state of the autonomic nervous system [20–22]. A decrease in HR was observed in the majority of our patients after a course of electrical pulse stimulation. The effect was greater in patients with HRs lower than 80 bpm at the baseline possibly because they might have milder imbalance of autonomic innervation and milder suppression of its parasympathetic component. The result is in line with our previous findings [14–16] and agrees well with the data that electrical stimulation of the vagus nerve prevents recurrent angina attacks [28].

A decrease in HR was not observed in the control patients, who received sham treatment in our study.

Table 2. LV EF, EDV, and ESV as dependent on the HR change after a course of electrical pulse stimulation in test-group patients with 60 < baseline HR < 80 bpm

Patients		Parameter					
		LV EF, %		EDV, mL		ESV, mL	
		A	B	A	B	A	B
With a decrease in HR (n= 26)	$M \pm SD$	30.45 ± 11.31	40.67 ± 10.21*	214.18 ± 80.98	192.75 ± 53.06	150.14 ± 46.25	115.56 ± 42.57*
	Me	28.00	42.50	197.00	200.00	150.14	113.00
	Lower–upper quartile	24.00–37.00	34.00–49.88	160.00–278.00	149.00–242.00	104.00–178.00	73.00–154.00
Without a decrease in HR (n= 6)	$M \pm SD$	30.68 ± 5.69	38.66 ± 12.57*	269.36 ± 59.03	208.88 ± 43.79*	184.55 ± 38.67	140.95 ± 36.52*
	Me	30.00	38.00	276.00	227.00	188.10	147.00
	Lower–upper quartile	27.50–34.35	29.00–48.00	209.00–338.00	194.00–243.00	140.00–209.00	121.00–156.00

Here and in Table 3: LV EF, left ventricular ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume; A, baseline values; B, values after a course of electrical pulse stimulation. (*) A difference from the baseline was significant at $p < 0.05$.

Table 3. LV EF, EDV, and ESV as dependent on the HR change after a course of electrical pulse stimulation in test-group patients with baseline HR > 80 bpm

Patients		Parameter					
		LV EF, %		EDV, mL		ESV, mL	
		A	B	A	B	A	B
With a decrease in HR (n= 8)	$M \pm SD$	26.66 ± 7.91	30.64 ± 9.79*	261.31 ± 77.42	224.14 ± 68.80	192.01 ± 63.16	159.70 ± 67.16*
	Me	24.54	32.25	279.50	206.50	206.50	140.00
	Lower–upper quartile	22.50–30.50	19.10–41.00	183.00–308.00	166.00–282.00	126.10–248.00	96.00–211.00
Without a decrease in HR (n= 4)	$M \pm SD$	23.20 ± 6.90	25.50 ± 14.43	253.73 ± 72.56	238.27 ± 13.85	190.50 ± 41.60	173.38 ± 34.64
	Me	21.50	36.50	230.50	176.00	191.00	113.00
	Lower–upper quartile	17.41–29.00	24.00–49.00	206.00–300.00	164.00–188.00	162.00–219.00	83.00–143.00

However, the HR decreased in the test-group patients after a course of electrical pulse stimulation, while their baseline medications remain unchanged. We think that the decrease in HR reflects changes in autonomic regulation of the heart. The changes consist in an increasing contribution of the parasympathetic component and help to improve the functional competence of the myocardium.

CONCLUSIONS

Thus, our analysis of the results demonstrates that a course of electrical pulse stimulation of the auricular branch of the vagus nerve according to the protocol described is safe and acceptable in patients with severe CHF who continues receiving optimal drug therapy. The treatment helps to normalize the autonomic regulation of the heart, the effect being reflected in a decrease of HR and an improved functional competence of the heart in patients with severe CHF of an ischemic origin.

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