PHYSIOLOGY

Role of Sympathetic and Parasympathetic Nervous Systems in Heart Rate Regulation in Cats

N. N. Alipov, O. V. Sergeeva, T. E. Kuznetsova, N. A. Bobrova, and N. Z. Abdulkerimova

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 140, No. 11, pp. 484-489, November, 2005
Original article submitted September 30, 2004

The effects of atropine and β-adrenoceptor blockers on mean HR, wave structure of the cardiac rhythm, and chronotropic reaction to noise stress were examined in cats. Atropine (0.5 mg/kg) increased the mean HR and significantly decreased the spectrum power of HF, LF, and VLF oscillations. The decrease in HF power was most pronounced, which enhanced LF/HF ratio. Propranolol (0.5 mg/kg) decreased the mean HR and slightly increased the power of HF, LF, and VLF oscillations. Atenolol (2 mg/kg) exerted similar but more pronounced effects. β-Adrenoceptor blockers increased HF power to a greater extent than LF and VLF power, which led to a decrease in LF/HF ratio. Atropine markedly decreased the chronotropic reaction to stress. β-Adrenoceptor blockers produced no effect on the amplitude of this reaction, but accelerated restoration of initial HR. It is established that the changes in power spectrum of HR and the phase reflex reactions in cats are mediated by parasympathetic influences; the sympathetic system is involved only in the control of mean HR, probably in response to the level of animal activity. The changes in LF/HF ratio during blockade of sympathetic and parasympathetic systems are caused by opposite influences of these systems on HF oscillations, but not by hypothetic "sympathetic" and "parasympathetic" nature of LF and HF oscillations of the heart rhythm.

Key Words: *heart; nervous regulation; heart rate variability*

Usually, two types of cardiotropic nervous influences are distinquished: tonic and phasic. The tonic influences control mean HR, while phasic ones modulate the short-term changes in HR in response to emotional and physical stress and to stimulation of various reflexogenic areas. However, the cardiac rhythm is not stable. Its variations can be characterized by oscillations at various frequencies, so it is possible to consider three components of nervous cardiotropic regulation: tonic, phasic, and wavelike. In the last decade, spectral analysis of spontaneous oscillations in the heart rhythm became one of the most popular avenues of cardiology. However, none of three branches of nervous regulation of HR (most of all, sympathetic and parasympathetic ones) were studied comprehensively. There is no consensus on the role of both systems in the origin of slow oscillations of the cardiac rhythm [2,6,10,11]. In this field, the experimental studies on animals are far behind the clinical observations. Specifically, pharmacological analysis of HR variations was rarely carried out on animals. There are

Department of Normal Physiology, Russian State Medical University, Moscow. ***Address for correspondence:*** alipov@practica.ru. N. N. Alipov

0007-4888/05/1405-0477

few studies on dogs [9], rabbits [7,12], and rats [4], but we found no related data on cats.

Our aim was to study the role of sympathetic and parasympathetic systems in the regulation of mean HR, spectrum power of HR oscillations, and the phasic reactions of HR in cats. As a rule, the sympathetic and parasympathetic influences are considered as adrenergic and cholinergic, respectively. This opinion is widely accepted, but it is not proved, because there are ample data on the existence of catecholaminergic cells in the heart that are innervated by the vagal fibers. Since there are no data on the role of these cells in the wave structure of cardiac rhythm, we adhered to the above traditional postulate.

MATERIALS AND METHODS

The experiments (n=59) were carried out on 17 mature cats of both sexes. The animals were placed in a screened case, where it could freely change the posture. Two rubber strips with four steel electrodes were attached to the thorax. ECG in three standard leads or three amplified leads was recorded from the extremities. To eliminate drift of the isoline, the first derivative of ECG was also recorded. The signals were fed to the ECG module of a P4Ch-02 polygraph, then to an amplifier of a 12-bit digitizer, and finally to a PC. In all channels, the sampling rate was 1 kHz, the recording time being 2 min. The noise stimulus (metal plate crash) was used as a short-term stress, which induced pronounced vocalization and motor response of the animals. Subcutaneous atropine sulfate (0.5 and 1.0 mg/kg) and intramuscular β-adrenoceptor blockers propranolol (Obsidan, 0.5 mg/kg) or atenolol (2 mg/kg) were used to block parasympathetic and sympathetic influences, respectively.

The initial ECG was recorded for 1 h with 10-min intervals (in some experiments, the record time was prolonged to 4 h to assess adaptation of the animals to the experimental conditions). After stabilization of cardiac rhythm under resting conditions, the test agent was injected, and ECG was recorded with 10-min intervals during the following 1 h. Only one drug was used in each experiment. The noise stress was induced immediately before and 50 min after the injection. The intervals between the experiments in one animal were not shorter than 3 days needed for complete elimination of the drugs [3,5].

The data were processed using Statistica software. Significance and correlation were assessed by Student test and Pierson coefficient, respectively. Spectral analysis was performed by FFT method with preliminary subtraction of the mean, elimination of the trend, and employing Hemming window (5 points wide). The power spectrum was subdivided into high-frequency (HF), low-frequency (LF), and very-low-frequency (VLF) ranges. HF range corresponded to 0.22-1.20 Hz, which was the range of respiratory rhythm observed in our experiments (QRS amplitude recordings [2] completely coincided with the pneumograms documented in some experiments). The frequency ranges of LF and VLF were 0.04-0.22 and less than 0.04 Hz, respectively [8]. In each frequency domain, the power of oscillations was calculated and termed conventionally as HF, LF, and VLF. The power percentages in comparison with the total spectrum power and the LF/HF ratio were also calculated.

RESULTS

The initial parameters of the heart rhythm (mean *RR* interval, σ, HF, LF, and VLF) were characterized by pronounced individual variations (Table 1, Fig. 1, *a*, *b*), although some regularities could be revealed. The most stable and powerful spectrum component was HF (respiratory) rhythm observed in all animals. By contrast, LF and VLF components were less regular and stable. Probably, in addition to nervous influences, sporadic changes in the heart rate during swallowing [2], vocalization, motor and other reactions of the wakeful animal contribute to these two low-frequency components.

TABLE 1. Initial Parameters of Cardiac Rhythm (n=167)

Parameter	M	Min	Max	SD	m
RR	397.6	236.5	652.0	79.3	6.07
s	34.8	8.0	127.3	22.7	1.74
VLF, %	13.0	2.7	40.7	7.2	0.55
LF, %	28.7	11.0	48.2	8.2	0.63
HF, %	58.3	29.8	83.7	12.4	0.96

Note. VLF, LF, and LF are given in percent of total spectrum power. M, SD, and m denote the mean, standard deviation, and standard error of mean, respectively.

There was a significant correlation between mean *RR* value and spectral structure of cardiac rhythm: the correlation coefficients between *RR* and σ, *RR* and VLF, *RR* and LF, *RR* and HF were 0.61, 0.31, 0.46, and 0.55, respectively. Thus, the lower HR, the greater were spontaneous oscillations of HR, especially in HF range (Fig. 1, *a*, *b*), and the larger was their contribution into the total spectrum power.

Atropine increased HR and markedly decreased σ, HF, LF, VLF (Table 2, Fig. 1, *a*, *c*). In these experiments, HF decreased most pronouncedly resulting in relative growth of LF and VLF spectrum power and elevation of LF/HF ratio. In contrast, propranolol decreased HR and induced a small elevation of σ, HF, and VLF, while increment of LF was insignificant (Table 2, Fig. 1, *b*, *d*). HF power increased most pronouncedly, which elevated its relative contributed into the total spectrum and somewhat decreased LF/HF ratio.

Stress presented before injection of the test drugs produced drastic shortening of *RR* intervals followed by their slow recovery (Fig. 2). Atropine efficiently inhibited this drop, while propranolol produced no significant effect. However, propranolol accelerated restoration of the initial rhythm, which was assessed by percentage of restoration of RR initial value in 30 sec after stress stimulation.

To exclude the influence of such factors as insufficient blockade of β-adrenoceptors or side effects of propranolol (its central and quinidine-like effects), we studied the effects of atenolol in a dose of 2 mg/kg. This drug does not cross the blood-brain barrier and exerts no quinidine-like effects. Moreover, it is more resistant to presystemic elimi-

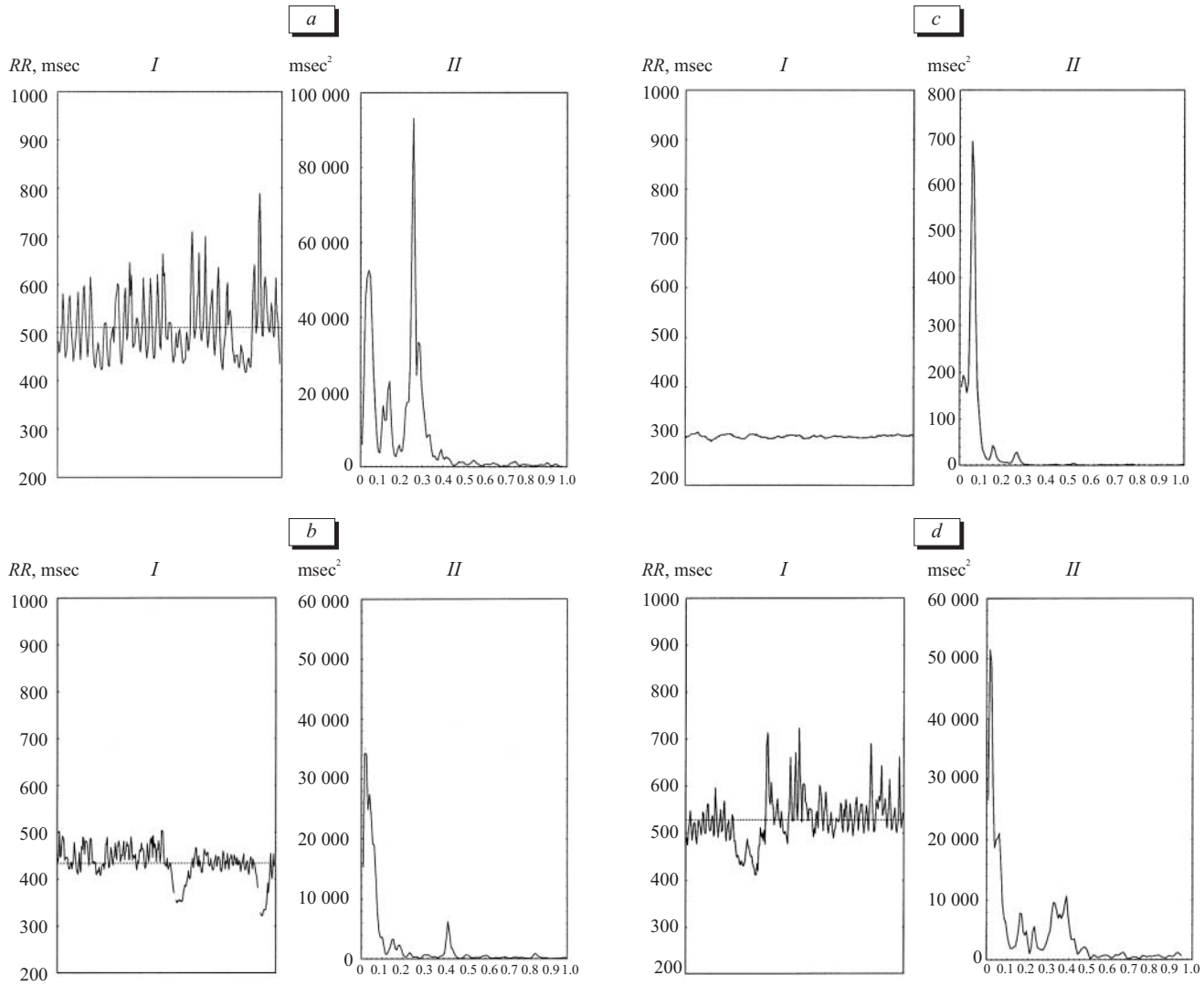

Fig. 1. Effects of atropine and propranolol on cardiac intervalogramms (I) and spectrum power of the heart rate oscillations (II). *a*, *b*) initial plots; *c*) atropine; *d*) propranolol. The dash line in (*I*) shows the mean value. Ordinate and abscissa in (*II*) are spectrum power (msec²/Hz) and frequency (Hz).

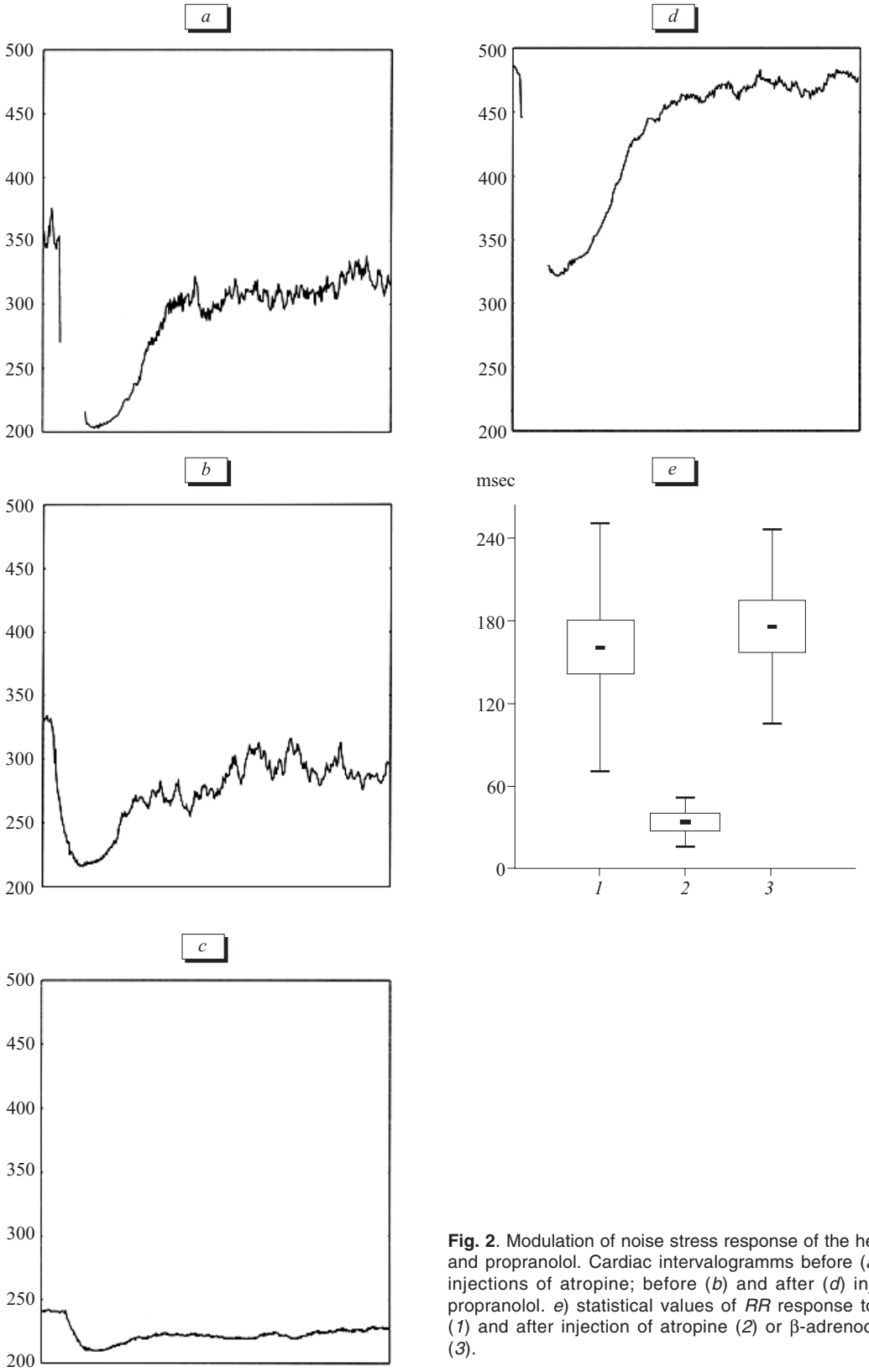

Fig. 2. Modulation of noise stress response of the heart by atropine and propranolol. Cardiac intervalogramms before (*a*) and after (*c*) injections of atropine; before (*b*) and after (*d*) injections of the propranolol. *e*) statistical values of *RR* response to stress before (*1*) and after injection of atropine (*2*) or β-adrenoceptor blockers (*3*).

nation, which explains its higher serum concentration [5]. The effects of atenolol on cardiac rhythm parameters were more pronounced that those of propranolol (Table 2). Atenolol produced a more pronounced decrease in HR and greater increase of σ, HF, LF, and VLF. HF power increased to the

TABLE 2. Effect of Atropine, Propranolol, and Atenolol on the Parameters of Cardiac Rhythm

Drug	RR	σ	VLF	LF	HF	LF/HF
Atropine	71.8±11.3	14.0±10.0	21.2±13.9	9.6±5.6	6.4±8.4	217.3±162.5
Propranolol	120.0±13.8	115.5±35.3	106.2±28.0	100.2±21.3	117.4±37.6	96.9±24.4
Atenolol	133.5±24.7	136.7±83.3	130.4±96.6	133.0±81.7	172.7±97.2	77.3±14.8

Note. The data are percents of background value ±SD

greatest degree (by 72.7% baseline value). The LF/HF ratio decreased respectively. Similarly to propranolol, atenolol did not moderate the response of the heart to stress and accelerated restoration of HR after stress stimulation: in 70.6% cases, the restoration of *RR*-interval was greater with β-adrenoceptor blockers than without them (Fig. 2, *b*, *d*).

Thus, cat heart is under both intensive parasympathetic tonic cardiotropic influences (attested by pronounced elevation of mean HR by atropine) and markedly expressed sympathetic tonic influences on the heart as indicated by significant decrease of HR by propranolol and by even a greater depression of HR by atenolol. In cats, spontaneous oscillations of the heart rate at all frequencies are mostly (if not exclusively) caused by parasympathetic influences: both total dispersion and the power components HF, LF, and VLF are severely suppressed by atropine, although these parameters do not decrease and even somewhat increase after injection of β-adrenoceptor blockers. The LF/HF ratio is widely used as the index of sympathetic/parasympathetic balance. It is considered that this ratio increases (decreases) during enhancement of sympathetic (parasympathetic) influences. This view explains slow and respiratory oscillations by their sympathetic and parasympathetic origin, respectively [6,10]. In our experiments, blockade of parasympathetic influences with atropine increased LF/HF ratio, while inhibition of sympathetic control with β-adrenoceptor blockers decreased it (Table 2). However, these changes did not result from unilateral pharmacological effect on nominator or denominator by any drug. Indeed, atropine decreased and β-adrenoceptor blockers increased all spectrum components, although HF-component was affected most pronouncedly. Thus, LF/HF ratio reflected the sympathetic/parasympathetic balance, but only under the specific experimental paradigm when both subdivisions of the autonomic nervous system exerted predominant and opposite effects on the respiratory waves. Similar effects were reported for humans [1,10,11]. The mechanism of the increase of HF spectrum components under the effect of β-adrenoceptor blockers is not clear. We believe that in cats it is not mediated directly by central influences, which was reported elsewhere [1], because atenolol does not enter CNS, although the indirect (reflex) influences in response to hemodynamic changes induced by β-adrenoceptor blockers are possible. The reaction to severe stress is also mediated by parasympathetic system. This is also true for other phasic changes in the HR: sporadic changes of cardiac rhythm during swallowing, vocalization, motor and other reactions affect the low-frequency spectral components of HR, while atropine (but not β-adrenoceptor blockers) eliminates these components, which therefore should be parasympathetic. At the same time, duration of the reaction to stress stimulation (manifested as residual enhancement of HR) probably depends on sympathetic influences: rapid short-term drop of parasympathetic tone can be replaced by a delayed long-term enhancement of sympathetic one.

Thus, parasympathetic system in cats can play a role of "system of reactions", while the sympathetic system — "system of states". According to this view, the sympathetic influences can be involved only in the formation of the mean HR, while the parasympathetic influences induce phasic and spectral changes against this background.

REFERENCES

1. V. M. Khayutin, M. S. Bekbosynova, E. V. Lukoshkova, and S. P. Golitsyn, *Kardiologiya*, **1**, 22-30 (1998).
2. V. M. Khayutin and E. V. Lukoshkova, *Ros. Fiziol. Zh.*, **85**, No. 7, 893-909 (1999).
3. J. H. Brown and P. Taylor, in: *Goodman and Gilman's The Pharmacological Basics of Theraupeutics, 10th ed.*, New York (2001), pp. 155-173.
4. C. Cerutti, M. P. Gustin, C. Z. Paultre, *et al.*, *Am. J. Physiol.*, **261**, H1292-H1299 (1991).
5. B. B. Hoffman, in: *Goodman and Gilman's The Pharmacological Basics of Theraupeutics, 10th ed.*, New York (2001), pp. 215-268.
6. A. Malliani, F. Lombardi, and M. Pagani, *Br. Heart J.*, **71**, 1-2 (1994).
7. V. Moguilevski, J. Oliver, B. P. McGrath, *Clin. Exp. Pharmacol. Physiol.*, **22**, Nos. 6-7, 475-477 (1995).
8. H. Nagai, T. Suzuki, N. Katsumata, *et al.*, *Masui*, **48**, No. 12, 1294-1301 (1999).
9. O. Rimoldi, S. Pierini, A. Ferrari, *et al.*, *Am. J. Physiol.*, **258**, No. 4, Pt. 2, H967-H976 (1990).

10. Task force report of European society of cardiology and the North American society of pacing and electrophysiology, *Circulation*, **96**, 1043-1065 (1996).
11. J. A. Taylor, D. L. Carr, C. W. Myers, and D. L. Eckberg, *Ibid.*, **98**, 547-555 (1998).
12. U. Zwiener, D. Hoyer, R. Bauer, *et al.*, *Pneumologie*, **51**, Suppl. 2, 415-422 (1997).