Normalized Entropy Applied to the Study of Sex Differences in Cardiovascular Stress-response to Atropine and Propranolol in Rats

OV Glushkovskaya-Semyachkina, TG Anishchenko

Saratov State University, Saratov, Russia

Abstract

The cardiovascular sensitivity in normal and stressed rats to sympathetic and parasympathetic blockades was greater in females than in males when studied using the heart rate, mean arterial pressure and normalized entropy, a new measure of complexity degree of blood pressure signals. It is supported that sympathetic and parasympathetic influences on cardiovascular system are more pronounced in females than in males both under normal and stress conditions. Normalized entropy was demonstrated to be more sensitive marker of gender and individual differences in cardiovascular responses to external and internal perturbations.

1. Introduction

Cardiovascular disease is more prevalent in men than in women [1]. Although the reasons for this phenomenon are not well understood, considerable attention has been given to sex particularities in cardiovascular reactivity and sympathetic and parasympathetic control in cardiovascular stress-responses [2,3]. Although heart rate (HR) and blood pressure (BP) remain the most commonly measures of cardiovascular activity, now it is possible to apply the nonlinear dynamics methods to quantitate the dynamic behaviour demonstrated by cardiovascular system [4]. In our previous experiments [5,6] it has been established the high sensitivity of new criteria of the complexity degree of ECG and BP time series- "normalized entropy" (E/H), which is Shannon entropy related the system energy [7].

The purpose of this study was to investigate the gender particularities in cardiovascular responses to atropine and propranolol in normal and stressed rats using the conventional measures of cardiovascular activity – HR and BP and new measure of complexity degree of BP signals –E/H.

2. Materials and methods

All experiments were performed on male and female mongrel rats weighting from 250 to 300 g. The animals were instrumented with the polyethylene catheters in the carotid artery for direct measuring mean arterial pressure (MAP) in freely moving rats and in jugular vein for drug injections under pentobarbital anesthesia (0.35-0.40 mg/100g, ip). The catheters were tunneled subcutaneously and exteriorized at the back of the neck. The rats were allowed to recover for 24 hours. The E/H computation algorithm was used [8] to quantify changes in the complexity of BP time series in male and female organisms at rest, during stress and drug injections. All procedures were performed in accordance with the Declaration of Geneva (1990) on the International Guiding Principles for Biomedical Research Animals. The study of HR, MAP and E/H was performed: 1) under control condition; 2) during 60 min immobilization stress (IS); 3) 24h later during cholinergic blockade by atropine sulfate (Voroneg, Russia, 0.2 mg/100g, iv) or propranolol (ISIS Pharma GmbH, 08056 Zwikau, 0.1 mg/100g, iv); 4) 24h later during IS against atropine or propranolol injection. Results were presented as means±standard error of the mean (SEM). The changes in MAP, HR and E/H were expressed as percentage changes from control values. The statistical analysis of the data was performed using the Wilcoxon's ranks sums test, Mann-Whitney U test and ANOVA-2 test, followed by the Duncan multiple range test. $P<0.05$ was taken as indicating statistical significance.

3. Results

IS caused the significant tachycardia, which was more pronounced in females compared with males (32% against 24% vs. basal values, $P<0.05$). Between sexes difference was statistically significant ($P<0.05$). Notice, that basal values of HR were lower in females vs. males (359±8 and 405±8 beats/min, respectively; $P<0.05$). The stress-induced changes in MAP were less pronounced and continued compared with HR. Really, maximal increase in MAP was observed only during 5 min of IS and then MAP gradually reached the basal values. Interestingly notice, that despite the more significant HR increase in females vs. males the

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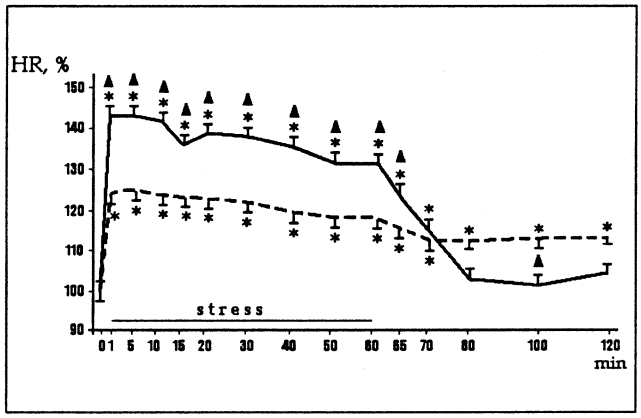
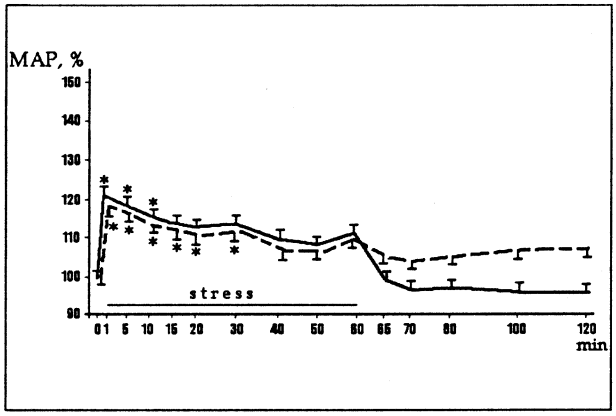
increase in MAP was lower in females than in males (11% against 18% vs. basal values, P<0.05) and the recovery of HR was more rapid in females than in males.

The atropine injection was accompanied by more significant increase in HR in females than in males (29% against 17%, P<0.05 vs. basal values). Between sexes difference was statistically significant (P<0.05). Notice, that basal values of HR were lesser in females vs. males (375±12 and 400±8 beats/min, respectively; P<0.05). The atropine didn't induce any significant changes in MAP in both females and males.



* - p<0,05 vs. basal levels
▲ - p<0,05 vs. males
females
males

Fig.1 The HR response to IS in female and male rats injected by atropine



* - p<0,05 vs. basal levels
females
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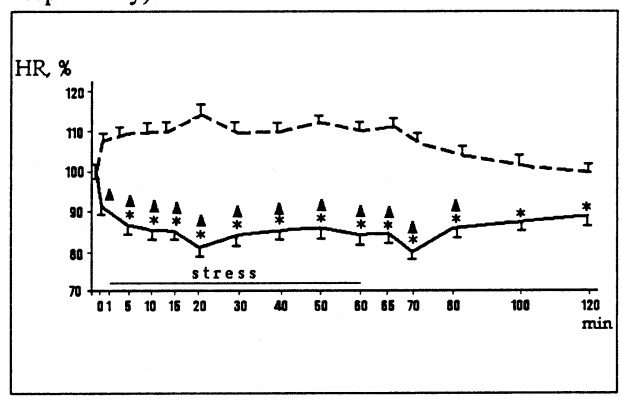
Fig. 2. The MAP response to IS in female and male rats injected by atropine

The stress significantly increased the cardiovascular sensitivity (HR intensity) to atropine in females but not in males. Actually, the stress-induced increase in HR reached 42% (P<0.05) in females and only 25% (P<0.05) in males (Fig.1). Between sexes difference was statistically significant (P<0.05). Notice, that basal values of HR were lower in females than in males (355±5 vs. 409±4 beats/min, respectively; P<0.05). Interestingly, that the intensity of MAP response to IS didn't differ significantly between sexes (Fig. 2) and corresponded to stress levels of MAP during IS.

In all sets of experiments the basal values of MAP didn't differ reliably between females and males.

The propranolol injection caused the decrease in the HR that was pronounced in a greater degree and in the greater number of females vs. males. Actually, HR decreased by 25% (P<0.05) in 67% of females and only by 10% (P<0.05) in 58% of males. Maximal bradicardic effect was observed to 60 min of experiment in both females and males (30% against 15%, P<0.05). Besides, this bradicardic effect of propranolol was accompanied by compensatory hypertension (21% in females and 15% in males, P<0.05). Notice, that basal values of MAP and HR didn't differ reliably between sexes in this experiment.

The IS of rats injected by propranolol was accompanied by bradicardic response in females and small, statistically nonsignificant tachycardic response in males (Fig. 3). Notice, propranolol didn't depress stress-induced elevation in MAP that was similar in males and females. The stress-induced pattern of MAP in rats injected by propranolol was practically the same that is presented in fig.2. So, while HR was significantly modulated by atropine and propranolol the stress-evoked increase in MAP was not changed by these pharmacological agents. The basal values of HR and MAP were higher in females vs. males (406±4 in females and 338±4 in males beats/min; 142±2 in females and 122±3 in males mmHg, P<0.05, respectively).

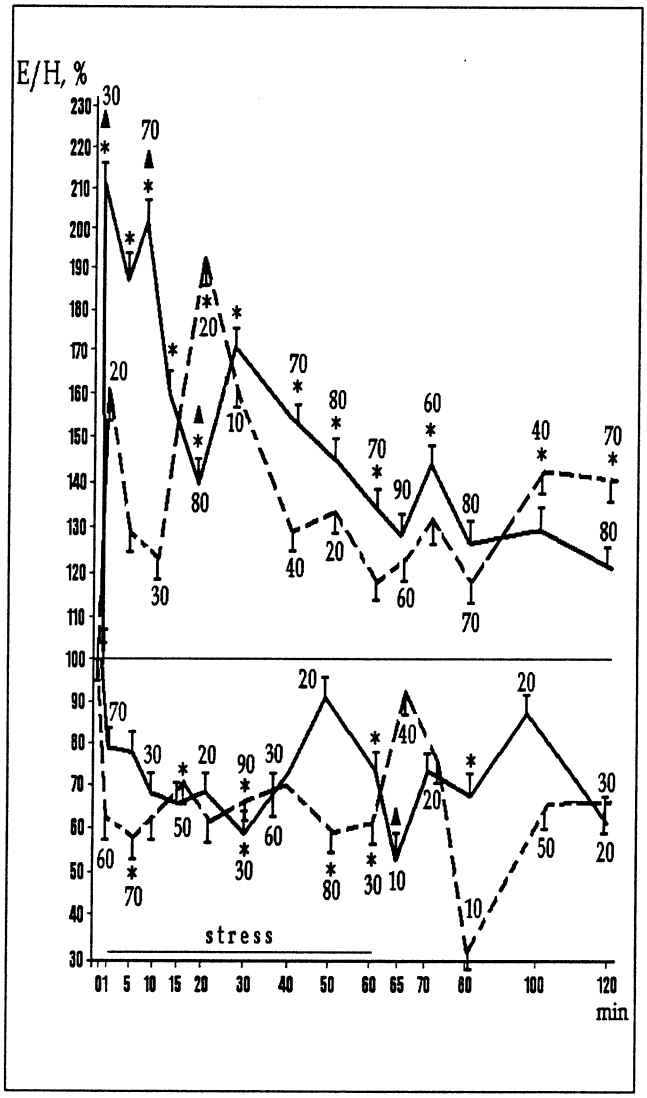


* - p<0,05 vs. basal levels
▲ - p<0,05 vs. males
females
males

Fig. 3. The HR response to IS in female and male rats injected by propranolol

In contrast to HR and BP, that increased or decreased during different perturbations, the E/H increased in one part of rats and decreased in other part of ones in all sets of experiments. These changes of E/H reflected the increase in the complexity degree of BP

signal in one part of rats and decrease of this parameter in other part of ones. The number of rats with elevated E/H increased during recovery period. The amplitude and duration of E/H changes were determined by the nature of perturbation. The changes in complexity degree of BP signal were established to be more pronounced and continued in comparison with HR and MAP.

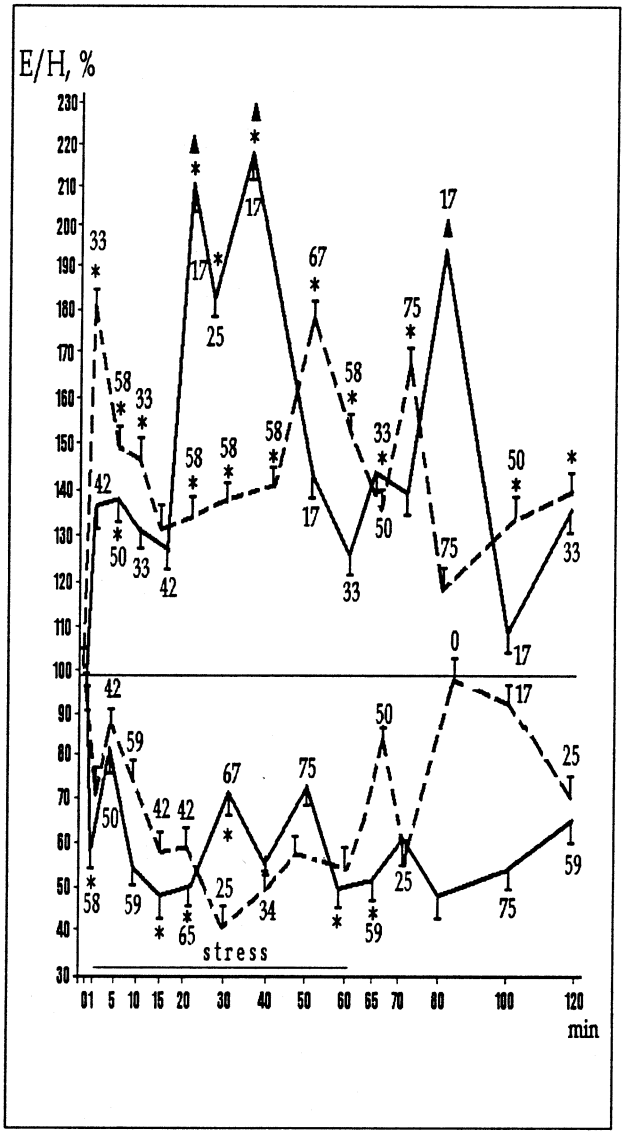


* - p<0,05 vs. basal levels
▲ - p<0,05 vs. males
10 - number of animals in %
—— females
- - - males

Fig. 4. The E/H response to IS in female and male rats injected by atropine

During IS the number of rats with elevated E/H increased in a greater degree and in the greater number of females vs. males. The tachycardic response to atropine that was more pronounced in females was accompanied by significant increase in the number of females with elevated E/H. Under the most strong perturbation (IS+Atropine) the amplitude of E/H increase was nearly 5-fold and 10-fold higher than those for HR and MAP, respectively (Fig.4).

The bradicardic response to propranolol that was more pronounced in females was accompanied by significant increase in the number of females with decreased E/H. So, during the first 30 min after propranolol injection the number of rats with decreased E/H reached 100% in females and 75% in males. Also, during IS against propranolol the number of rats with decreased complexity degree of BP signal was greater in females than in males. As in previous experiments the changes in the E/H were more significant and



* - p<0,05 vs. basal levels
▲ - p<0,05 vs. males
10 - number of animals in %
—— females
- - - males

Fig. 5. The E/H response to IS in female and male rats injected by propranolol

continued than those in HR and MAP. So, during IS against propranolol the amplitude of E/H decrease and especially increase was significantly higher than those in MAP and especially in HR (Fig. 5).

4. Discussion

The cardiovascular responsivity in normal and stressed rats to sympathetic and parasympathetic blockades was greater in females than in males when studied using the HR and E/H, a measure of complexity degree of BP signals. Actually, tachycardic response to IS, atropine and IS+atropine was more significant in females vs. males. At the same time, in these experiments the E/H increased in the greater degree and in the greater number of females than males. On the other hand, bradicardic effect of propranolol being greater in females vs. males was accompanied by significant elevation of the number of rats with decreased complexity degree of BP signal in females but not males. These data suggest that sympathetic and parasympathetic modulations of cardiovascular activity are more pronounced in females than in males both under normal and stress conditions. Similarly to HR and BP, the pattern of E/H changes was determined by the nature of perturbation. But in every experiment the E/H increased in one part of rats and decreased in other part of ones. The changes in the complexity degree of BP signal were always more significant and prolonged in comparison with those in HR and BP. These findings give evidence that the changes in cardiovascular activity induced by internal and external perturbations are far richer than that we can see applying conventional cardiovascular measures.

We believe that stress-induced changes in the complexity degree of BP dynamics may reflect variations in the activity of multiple neural, hormonal, mechanical and local subcellular biochemical cardiovascular control mechanisms as well as changes in their interactions. It has been shown that variations in parasympathetic activity correlate with changes in approximate entropy [9] and two-dimensional entropy changes [10] of ECG dynamics. Our results give evidence that variations in sympathetic and parasympathetic activity are accompanied by changes in the complexity degree of BP dynamics in both normal and stressed rats. So, one may suggest that stress-induced changes in the E/H of BP time series are attributed in part to changes in autonomic cardiac regulation. Our results demonstrated that the study of E/H, a new measure of the complexity degree of BP signal, may be useful for research of mechanisms underlying the gender differences in cardiovascular responses to stress.

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References

[1] Tunstall-Pedoe, H, Morrison C, Woodward M, Fitzpatrick B, Watt G. Sex differences in myocardial infarction and coronary deaths in the Scottish MONICA population of Glasgow 1985 to 1991: presentation, diagnosis, treatment, and 28-day case fatality of 3991 events in men and 1551 events in women. Circulation 1996; 93:1981-1992.

[2] Frankenhaeuser, M., Dunne, E., Lundberg, U. Sex differences in sympathetic-adrenal medullar reactions induced by different stressors. Psychopharmacol 1976; 47: 1-5.

[3] Stoney, C.M., Davis, M.C., Matthews, K.A. Sex differences in physiological responses to stress and coronary heart disease: a causal link? Psychophysiol 1987; 24: 127-131.

[4] Elbert, T., Ray, W.J., Kowalik, Z.J., Skinner, J.E., Graf, K.E., Birbaumer, N. Chaos and Physiology: Deterministic chaos in excitable cell assemblies. Physiol. Rev. 1994; 74: 1-47.

[5] Anishchenko TG, Saparin PI, Igosheva NB, Anishchenko VS. Sex differences in human cardiovascular responses to external excitations. IL Nuovo Cimento 1995; 17:7-8-699-707.

[6] Anishchenko TG, Igosheva NB, Yakusheva TA, Glushkovskaya-Semyachkina OV, Khokhlova ON. Normalized entropy applied to the analysis of interindividual and gender-related differences in the cardiovascular effects of stress. Eur J Appl Physiol 2001;85:3-4-287-299.

[7] Klimontovich JuL. A criterion of relative degree of chaos or order for open systems. Biosystems 1997;42:85-102.

[8] Anishchenko VS, Safonova MA, Saparin PI. Measurement and computer complex for the diagnostics and numerical characterization of complicated regimes of self-oscilations. Sov J Commun Technol Electron 1992;37:82-92.

[9] Ryan SM, Goldberger AL, Pincus SM, Mietus J, Lipsitz LA. Gender and age-related differences in heart rate dynamics: Are women more complex than men? J Am Coll Cardiol 1994;24:1700-7.

[10] Kanters JK, Holstein-Rathlou NH, Agner EE. Two dimensional entropy as a measure of parasympathetic activity. A method of quantifying non-linear patterns of heart rate variability. J Mol Cell Cardiol 1994 (Abstract) 26:CXX.

Address for correspondence.

Glushkovskaya-Semyachkina Oksana
Russia, 410026 Saratov, Astrachanskaya 83, Chair of Physiology of Human beings and Animals
oksana@chaos.ssu.runnet.ru