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2009 Physiol. Meas. 30 707

(http://iopscience.iop.org/0967-3334/30/7/013)

IOP Publishing Physiological Measurement

Physiol. Meas. **30** (2009) 707–717 doi:10.1088/0967-3334/30/7/013

Analysis of blood pressure dynamics in male and female rats using the continuous wavelet transform

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Received 26 March 2009, accepted for publication 22 May 2009
Published 12 June 2009
Online at stacks.iop.org/PM/30/707

Abstract

We study gender-related particularities in cardiovascular responses to stress and nitric oxide (NO) deficiency in rats using HR, mean arterial pressure (MAP) and a proposed wavelet-based approach. Blood pressure dynamics is analyzed: (1) under control conditions, (2) during immobilization stress and recovery and (3) during nitric oxide blockade by N^G-nitro-L-arginine-methyl ester (L-NAME). We show that cardiovascular sensitivity to stress and NO deficiency depends upon gender. Actually, in females the chronotropic effect of stress is more pronounced, while the pressor effect is weakened compared with males. We conclude that females demonstrate more favorable patterns of cardiovascular responses to stress and more effective NO control of cardiovascular activity than males.

Keywords: rhythmic dynamics, wavelet analysis, blood pressure

1. Introduction

Cardiovascular diseases are the leading cause of morbidity, disability and death in industrial countries (Stoney *et al* 1987). The clinical and experimental studies have established the role of female gender as a protective factor in the development of various cardiovascular diseases (e.g., Recelhoff 2001). Although the mechanisms underlying this 'cardioprotection' of females are not fully elucidated, the cardiovascular stress reactivity and vascular production of nitric oxide has been shown to have a potential role in both humans and rats. According to several studies (Matthews and Stoney 1988, Anishchenko *et al* 2007), increased predisposition of males to hypertension is associated with their heightened cardiovascular stress reactivity. Recently, we found that stress was followed by an increase in blood NO concentration in male and female rats (Semyachkina-Glushkovskaya *et al* 2006). After renovascular hypertension modeling the

0967-3334/09/070707+11$30.00 Printed in the UK

blood pressure was higher and the decrease in NO concentration was more pronounced in males than in females. It is interesting to note that levels of NO in healthy and hypertensive females at rest and during stress were higher than in males (Semyachkina-Glushkovskaya *et al* 2006). These specific features probably contribute to higher resistance of the cardiovascular system in females to pathological changes. In order to better understand the phenomenon of sex differences in cardiovascular stress resistance, considerable attention has been given to intersex comparison of cardiovascular activity under challenging conditions. For this purpose, commonly used hemodynamic parameters (heart rate (HR), blood pressure (BP)) and different data processing tools (complexity measures, spectral analysis, etc) can be applied.

Blood pressure dynamics in rats involves a number of physiological control mechanisms including neural, hormonal and local vascular control (Persson 1996, Kitney and Rompelman 1980) that lead to the occurrence of oscillatory behavior in clearly different frequency ranges including very slow oscillations (with the frequency $f < 0.25$ Hz), low-frequency (LF) range (0.25–0.75 Hz) and high-frequency (HF) range (0.75–3.0 Hz). A physiological interpretation of the corresponding areas is described, e.g., in Stauss (2007a, 2007b), and Stefanovska and Bračič (1999). Multimode dynamics with several coexisting rhythmic components creates difficulties when performing physiological interpretation of complexity measures computed from experimental data (BP, beat-to-beat intervals, etc). Such measures represent numerical quantities that provide us with information about some ‘global’ dynamics of the cardiovascular system and related mechanisms. It is not obvious how we can associate these quantities with separate processes taking place in the cardiovascular dynamics.

Aiming to establish a clearer relation between changes of complexity measures and physiological mechanisms responsible for such changes we propose here a wavelet-based approach to characterize the complexity. Within this approach we study evolutionary dynamics of individual rhythmic contributions using the wavelet-transform and we associate complexity measures with individual processes in the blood pressure dynamics. The choice of wavelets as the preferred analysis technique is associated with two main reasons. The first reason is the possibility to easily estimate instantaneous frequencies of rhythmic components associated with the LF- and the HF-dynamics. As a result, it becomes possible to study evolutionary dynamics of oscillatory behavior in these frequency areas separately. The second reason is the nonstationarity of the recorded time series that typically has different origins. On the one hand, it represents some reflection of adaptation processes in the BP-dynamics (i.e., external conditions). On the other hand, there may be differences in the nonstationarity between normal and pathological states (Wolf *et al* 1978) and, therefore, this nonstationarity has a relation with internal properties of organisms. Besides a slow trend that can be easily filtered out from experimental data (this procedure is typically performed for quite short recordings when too slow contributions cannot be studied), nonstationary oscillations can occur in the higher frequency areas (LF- and HF-dynamics). Such nonstationarity obviously has an influence on the estimated characteristics.

Using the proposed approach we study the gender-related particularities in cardiovascular responses to stress and NO deficiency in rats. We show that female rats demonstrate more favorable pattern of cardiovascular responses to stress and more effectively NO control of cardiovascular activity than males.

2. Experiments

Experiments were performed in mongrel normotensive rats of both sexes, weighing from 200 to 250 g. Male and female rats were housed in a temperature-controlled room (22–24 °C) with lights on from 08.00–20.00 daily. Food and water were given *ad libitum*. No attempt to study each female rat at the same point of the estrous cycle is made. All procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

The day before the experiment, rats were instrumented with polyethylene catheters for monitoring mean arterial pressure (MAP) and heart rate (HR). For implantation of catheters, rats were anesthetized with ketamine (40 mg kg^{-1}, ip) supplemented with xylazine (5 mg kg^{-1}, ip). Polyethylene catheter (PE-50 with a PE-10 tip, Scientific Commodities Inc., Lake Havasu City, AZ) was inserted into the left common carotid artery. In addition, the left femoral vein was catheterized with PE-50 tubing fused PE-10 for drug infusion. The free ends of all catheters were routed subcutaneously to exit through the dorsal surface of the neck. The tubing was filled with heparinized saline (75 U ml^{-1}) and plugged with stainless steel wire. After surgical procedures the rats were isolated in restraining cages and were fasted overnight. The amount of water was not limited. The body temperature was controlled before the experiment (digital thermometer, DT-634, Company Ltd, Japan).

HR and MAP were recorded in the home cages of conscious, unrestrained rats. Blood pressure signals were acquired on PowerLab system which is an integrated system of hardware and software designed to record, display and analyze experimental data. Data were collected with the sampling rate of 200 Hz. The rats were attached to an overhead-tethered catheter connected to the pressure transducer (PowerLab, ADInstruments, Australia) and allowed to stabilize for 40 min before the start of the each experiment. After the system reached a steady state the control values of MAP and HR were recorded during 30 min.

After base-line measurement, HR and MAP were recorded continuously during 15 min immobilization stress and 60 min recovery. This protocol was administered to a group of male ($n = 8$) and female ($n = 8$) rats. Changes in hemodynamic responses to inhibition of NO synthesis were evaluated by intravenous administration of N^G-nitro-L-arginine methyl ester (L-NAME, Sigma Chemical Co). HR and MAP were recorded continuously during 120 min after L-NAME injection. This protocol was administered to a group of male ($n = 9$) and female ($n = 14$) rats.

Results were reported as mean ± standard error of the mean (SEM). The changes in MAP and HR were expressed as percentage changes from control values. The differences from the initial level in the same group were evaluated by Wilcoxon test. Inter-group differences were evaluated using Mann–Whitney test and ANOVA-2 (post hoc analysis with Duncan's rank test). Significance levels were set at $p < 0.05$ for all analyses.

Before studying the BP-dynamics in different states, some data preprocessing was realized. Only clear fragments of experimental recordings were selected at each stage of experiments, i.e. time series without artifacts. Using these parts of recordings we performed a transition from original BP-data (figure 1(a)) to time intervals between the local maxima of BP signal (figure 1(b)). Such time intervals contain the most important information about the dynamics of the cardiovascular system in analogy with the RR-intervals of an electrocardiogram. Aiming to increase the precision of maxima identification, a cubic spline interpolation of BP-data is included. The extracted sequences of time intervals are further analyzed using wavelets. In order to do this, we performed a transition to time series of averaged instantaneous frequencies according to the approach proposed in Janson *et al* (1998).

3. Methods

The attractiveness of a particular technique for data processing often depends on its generality, i.e. on the lack of restrictions on signal properties. The wavelet analysis is one of the most

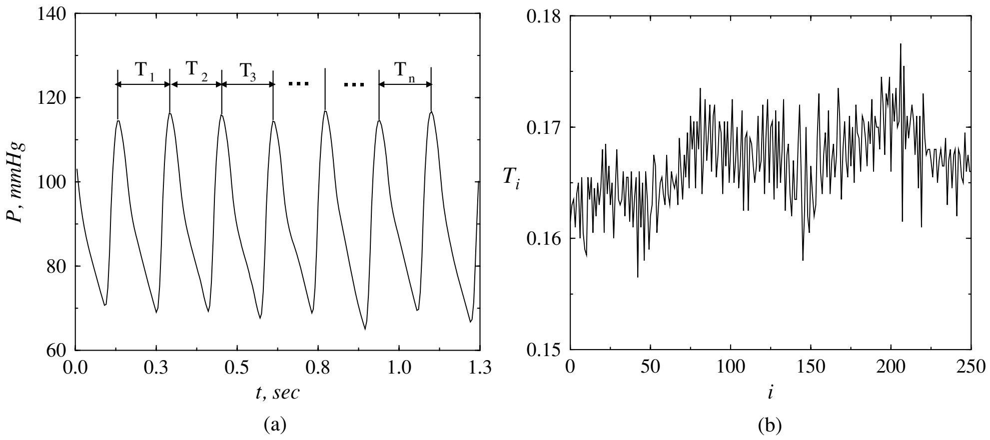

Figure 1. Blood pressure signal of a rat (a) and the sequence of time intervals between the local maxima (b).

universal techniques that can cope with the nonstationarity of time series. The continuous wavelet transform of a signal $x(t)$ involves its projection onto a set of soliton-like functions that can be obtained by means of dilations and translations of the so-called mother wavelet (Daubechies 1992, Mallat 1998):

$$W(a,b) = \frac{1}{\sqrt{a}} \int_{-\infty}^{\infty} x(t)\, \psi^*\left(\frac{t-b}{a}\right) \mathrm{d}t. \tag{1}$$

Here, ψ is the wavelet basic function, a and b are the dilation and the translation parameter, respectively, and the asterisk denotes complex conjugation. $W(a,b)$ is referred to as the wavelet-transform coefficient.

The details of the wavelet transform (such as the selection of the function ψ, the range of dilations, etc) depend on a problem being solved. Each function has its own features in the time and frequency domains. That is why the opportunity to reveal specific properties of a given signal occurs. In the spectral analysis of biological time series, the Morlet function is mainly used whose simplified expression can be written as follows:

$$\psi(\tau) = \pi^{-1/4} \exp(-\mathrm{j}\, 2\pi f_0 \tau) \exp\left[-\frac{\tau^2}{2}\right]. \tag{2}$$

The parameter f_0 allows us to search for some compromise between the localization of the function ψ in time and frequency domains. We shall use $f_0 = 1$, in this case there is a simple relation between the timescale a and the frequency of oscillations f, namely $f \simeq 1/a$ (Kaiser 1994).

The result of the transform (1) can be considered as a surface of coefficients $W(a,b)$. Its visualization can be provided in different ways including a simple projection onto the plane (a,b) by analogy with geographic maps, 'local maxima lines' or 'ridges' (Mallat 1998). One often use the energy density of the signal $x(t)$ in the timescale plane $E(a,b) \sim |W(a,b)|^2$ or in the time–frequency plane by transition to the values f instead of a. The latter is probably the most appropriate way to study the dynamics of instantaneous frequencies. Unlike the analytical signal approach (with the Hilbert transform), wavelets provide the opportunity to simultaneously reveal all rhythms being of interest from time series, and they do not have restrictions related to the frequency band of the analyzed process (since the wavelets serve as band-pass filters).

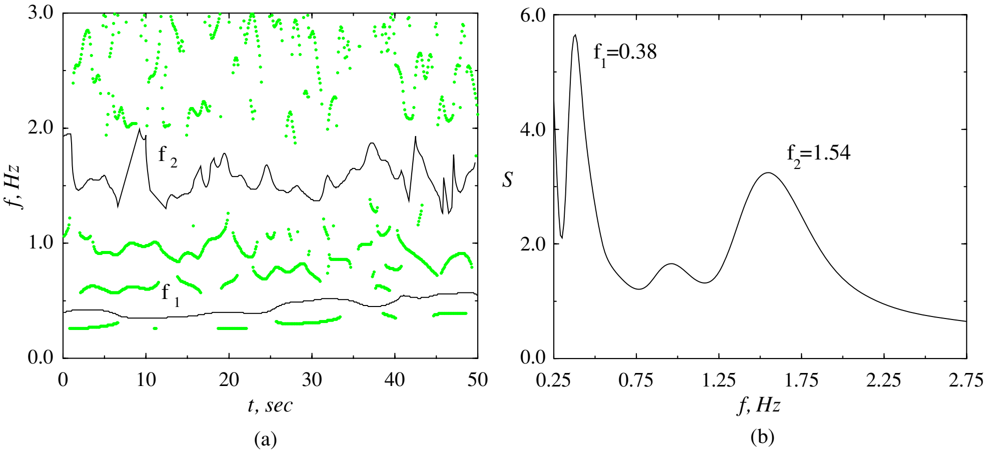

Figure 2. (a) Time–frequency (wavelet) spectrum. The points mark the positions of local peaks. The instantaneous frequencies of characteristic rhythms in the LF- and the HF-ranges are denoted as f_1 and f_2, respectively and (b) scalogram that gives information about the powers of rhythmic components.

Sections of the energy density $E(f, b)$ at each arbitrary chosen time moment $b = t^*$ can be considered as a localized power spectrum of experimental data. It allows us to estimate instantaneous frequencies and amplitudes of rhythmic contributions associated with the selected time moment. By changing the parameter b we shall therefore obtain time series of instantaneous frequencies (so-called ridges) and amplitudes for all rhythms being of physiological interest. Ridges of the wavelet-transform give an opportunity to reveal even quick changes in the rhythmic dynamics. In particular, this is discussed in our previous work (Sosnovtseva *et al* 2007) where a problem of time–frequency resolution of the wavelet transform is discussed and a comparison with another tool for nonstationary data processing is provided.

Figure 2(a) illustrates various rhythms detected in the BP-data presented in figure 1. Two well-distinguished rhythms $f_1(t)$ and $f_2(t)$ in the LF- and HF ranges can be easily revealed. Many points in figure 2(a) are associated with low-amplitude dynamics that can be filtered out if we shall introduce some threshold value for energy. Dominant spectral components can be detected from the averaged power spectrum (figure 2(b)). We clearly see the presence of a peak whose frequency is close to 0.4 Hz (it is probably caused by myogenic dynamics). The second peak with a frequency ≈1.5 Hz corresponds to respiration.

The visual inspection of instantaneous frequencies (figure 2(a)) is not sufficient. In order to describe its nonstationary dynamics, we decided to extract time series of $f_1(t)$ and $f_2(t)$ from the wavelet spectra (figure 2(a)) and then to characterize complexity of these time series using a simple approach: to compute the probability density $p(f)$ and to estimate the Shannon entropy of $p(f)$ as a simple measure that characterize the stability of the instantaneous frequency for each rhythmic component:

$$H_p = -\sum_{k=1}^{N} p_k \log p_k. \tag{3}$$

Here, p_k is the probability of taking the value inside some kth interval of the LF (or the HF) area, N is a number of such intervals (in our study $N = 40$). In fact, H_p characterizes how stable the instantaneous frequency of some rhythm is. It takes the minimal value $H_p = 0$ if the frequency does not show clear changes in time, and the maximal value $H_p = \log N$ for randomly distributed values of the instantaneous frequency (with the same probability).

The choice of Shannon entropy is caused by two main reasons: (1) this measure is simple and (2) it is possible to interpret changes in this measure. Thus, a reduction of Shannon entropy means stabilization of rhythmic activity. Alternatively, other approaches can be applied to characterize the complexity. One of them is considered in the work (Pavlov *et al* 2005) and is based on the multifractal concept. However, physiological interpretation of the results using Shannon entropy is easier.

Our technique assumes a combination of wavelets and another data processing tool, the entropy. Such combined approaches are often quite useful. We could mention, e.g., the problem of image recognition where wavelets are sometimes used together with neural networks or with other techniques (Pavlov *et al* 2007). Methods of data analysis that use both, wavelets and classical tools for data processing, can open new perspectives in the study of biological processes.

4. Results

4.1. Stress-induced changes in the BP-dynamics in male and female rats

The considered immobilization stress caused the significant tachycardia and an increase in MAP in rats of both sexes. The effects of stress on cardiovascular activity were different in females and males. In females, the HR increased more significantly (22−32% versus 13–24%, $p < 0.05$) and recovered more rapidly than in males. The basal values of HR were lower in females versus males (349 ± 4 versus 371 ± 4 beats/min, $p < 0.05$). It is important to note that despite more severe tachycardia under stress in females, the amplitude and duration of MAP elevation were lower than in males (11% versus 18%, $p < 0.05$). There was no significant sex difference in the basal MAP values.

The continuous wavelet-transform analysis allowed us to reveal the corresponding sex differences in cardiovascular stress reactivity and to associate them with the HF-dynamics. So, males typically showed an essentially stronger reaction that can be illustrated using the measure H_p. Probably, the clearest but at the same time typical reactions are given in figure 3.

A male rat (figure 3(a)) shows a change of complexity during stress in the region of HF-dynamics. The entropy H_p estimated for the instantaneous frequency $f_2(t)$ (HF-range) decreases during stress, i.e. some stabilization of the rhythmic dynamics occurs. These findings are in agreement with the results of the previous studies (Semyachkina-Glushkovskaya *et al* 2001, Anishchenko and Semyachkina-Glushkovskaya 2003) where it was established that stress-induced changes in hemodynamic parameters are associated with a reduced complexity of BP signals. The mentioned works did not considered individual physiological control mechanisms. Here we demonstrate that this reduced complexity (rhythms stabilization) is associated only with the HF-range, but not with the LF-dynamics. The oscillations in the low-frequency area (characterized by the instantaneous frequency $f_1(t)$) do not show any clear reaction to the considered type of stress.

However, a female rat (figure 3(b)) does not demonstrate any significant reaction. During all stages of experiments, the complexity measure H_p keeps its value. There is no change of complexity in both, LF- and HF-ranges during stress. As a consequence, no change occurs after the termination of stress (during the recovery process).

Statistics over the groups of rats testifies the observed phenomenon. Thus, in particular, six male rats out of eight demonstrated a reduction of the entropy H_p at stress by more than 4%

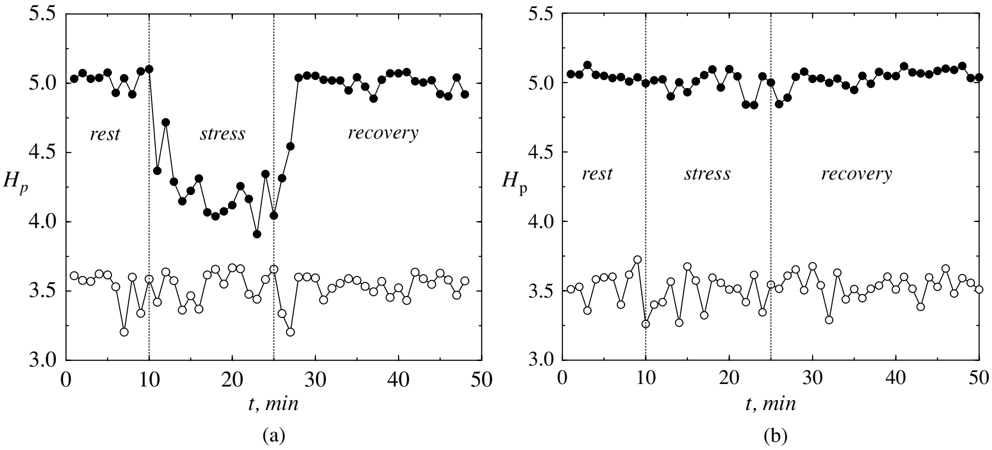

Figure 3. Results of the entropy estimations calculated using equation (3) from time series of instantaneous frequencies for a male (a) and a female (b) rat. Open circles correspond to the estimations performed for the LF-dynamics (using the dependence $f_1(t)$), and filled circles correspond to the case of the HF-dynamics (they are estimated using the dependence $f_2(t)$).

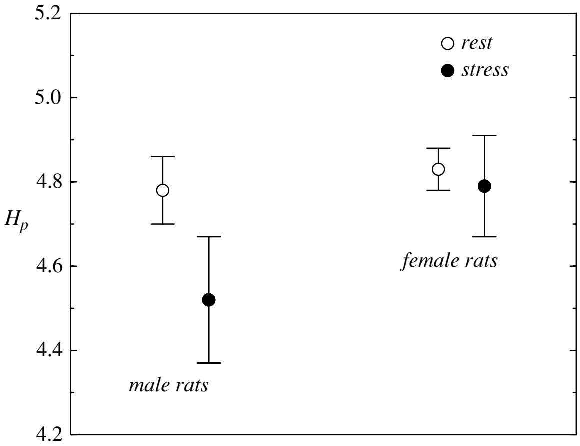

Figure 4. Statistical results over the groups of male and female rats that illustrate distinctions of the stress-induced phenomena (mean ± SD).

as compared to the normal state (for the rhythm $f_2(t)$). But, such a change did not exceeded 4% for seven female rats out of eight. Figure 4 illustrates a statistics over the groups, where the results are given as mean ± SD. Let us note that the corresponding distinctions between two rat strains occur in the HF-range of the power spectrum. They are less expressed in the LF-range.

4.2. Effects of NO blockade on changes in the BP-dynamics in male and female rats

NO blockade with L-NAME caused an increase in MAP with a decrease in HR and these changes depended upon the gender. Female rats in comparison with male ones were more

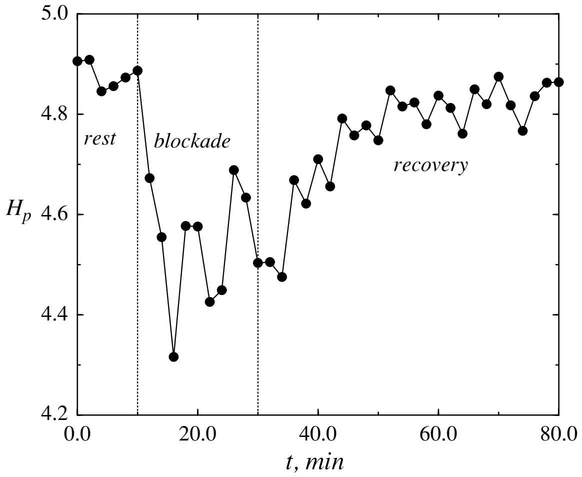

Figure 5. An example showing a reduction of the complexity measure H_p after the blockade of the NO-synthesis and a recovery process.

sensitive to NO deficiency. Actually, L-NAME induced a greater MAP increase with a greater HR decrease in females than in males (25% versus 17%, $p < 0.05$ for MAP; 18% versus 10%, $p < 0.05$ for HR). No statistical differences in baseline MAP and HR values between females and males were observed.

We also found that both male and female rats demonstrated a quite similar reaction, namely, a reduction of the entropy H_p at the blockade of the NO-synthesis. This blockade provided some kind of stabilization of heart rate dynamics associated only with the HF-region of the power spectrum. It is interesting to note that changes in the BP caused by L-NAME can be found in different frequency areas. They are clearly revealed in the HF-dynamics. This phenomenon is in agreement with the work (Sosnovtseva *et al* 2009) where influences of L-NAME on different physiological control mechanisms are observed in renal regulation.

A typical example is given in figure 5. It shows that the value H_p decreased during the blockade. After some time, H_p returned to its original value.

Although such a type of reaction is observed for both male and female rats, some gender differences can still be revealed. There is some opposite situation compared with the stress: female rats showed a stronger change in their cardio-vascular dynamics. This is illustrated in figure 6. Females demonstrated a reduction of H_p by about 4% (in the mean values), while male rats showed a change of the considered complexity measure by about 1%. This illustrates that the considered factors have some gender differences: while stress induces stronger changes in the beat-to-beat dynamics for male rats, the blockade of the NO-synthesis was a more essential factor for female rats.

The proposed approach allows us to easily study a number of important features of physiological adaptation processes. Thus, in particular, it provides a possibility to estimate durations of transient processes in the cardio-vascular dynamics. It should be noted that the duration of transients for the HF-dynamics may not be the same as for the heart rate associated, e.g. with the mean value of beat-to-beat intervals. We did not perform such analysis in this work, since it requires a larger statistics and the increased duration of experimental recordings. Thus, some rats did not restored their normal dynamics even during 1 h after the termination of the effect of the blockade of the NO-synthesis.

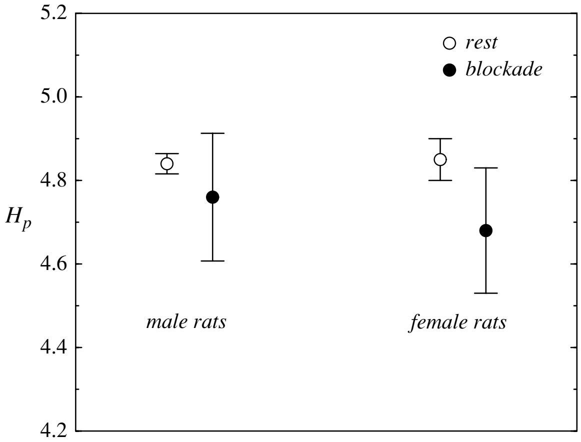

Figure 6. Statistical results over the groups of male and female rats that illustrate distinctions in the reactions to the blockade of the NO-synthesis (mean ± SD).

5. Discussion

We have shown that the proposed approach provides the possibility to reveal gender particularities in cardiovascular sensitivity to stress and pharmacological interventions. In other words, we showed that complexity of BP dynamics depends upon kind of perturbation imposed and gender of rats. Females demonstrated more favorable pattern of cardiovascular responses to stress: in females the chronotropic effects of stress were more pronounced, while the pressor effects were weakened compared with males and hemodynamic parameters in females returned to normal more rapidly than in males. Additionally, males show a stronger change of the complexity measure H_p associated with the HF-dynamics, while females did not show such a clear reaction. Some female rats were even fully insensitive to this stress.

A reduction of Shannon entropy during stress in males means a stabilization of rhythmic dynamics. These findings are in agreement with our previous works (Semyachkina-Glushkovskaya *et al* 2001, Anishchenko and Semyachkina-Glushkovskaya 2003). Here, we found that this stabilization is associated with the HF-range but not with the LF-dynamics. Some authors performed power spectral analysis of BP and pulse interval in conscious unrestrained mice assuming that the HF component of BP is affected by the parasympathetic nervous system activity (Just *et al* 2000). However, parasympathetic influences in modulation of BP and heart rate variability are less clear and significantly differ between authors (Stauss 2007b). Based on the previous studies (Semyachkina-Glushkovskaya *et al* 2001, Anishchenko and Semyachkina-Glushkovskaya 2003) the obtained results allow us to assume that stress-induced changes in the HF-dynamics in males are associated with parasympathetic influences. On the other hand, there are evidences that the HF variability is defined as respiration-related variability (Baudrie *et al* 2007). However, the existence of functional interaction between respiratory and parasympathetic nervous centers is well known. This fact may explain why different authors indicate the same HR-range in one case as respiratory related (Baudrie *et al* 2007), but in other case as the dynamics affected by parasympathetic activity (Just *et al* 2000). Thus, there are difficulties in determination of predominance of parasympathetic or respiratory influences on the HF range especially under challenging experimental conditions.

The phenomenon of rhythm stabilization seems to be the subject of more detailed researches. In particular, the progressive decrease in the complexity of the ECG signal is known before stenocardia attack, myocardial infarction and atrial fibrillation. Thus, based on this fact we conclude that the wavelet-transform analysis in addition to HR and MAP allows us to reveal more favorable patterns of cardiovascular responses to stress in females compared with males.

Since NO plays an important role in the regulation of cardiovascular stress responses and possesses stress-limiting activity (Bondarenko *et al* 2001), we studied the effect of NO blockade on changes in hemodynamic parameters and complexity of BP dynamics in male and female rats. Our results show that female rats in comparison with male ones are more sensitive to NO deficiency: L-NAME increased MAP and decreased HR more effectively in female rats than in male groups. At the same time, male rats show a fairly weak reaction in the HF-range: a reduction of the complexity measure H_p is several times less for males than that for females.

We found that the blockade of NO synthesis was accompanied by the stabilization of heart rate dynamics associated with the HF-range. On the one hand, there is evidence that endothelial-derived NO affected BP variations at very low frequencies and that the LF-dynamics is affected by endothelial-derived NO in rats (Stauss 2007b). On the other hand, it is known that different physiological effects of pharmacological NO blockade depends on the type of NO blockator and its concentration. In our work, we used N^G-nitro-L-arginine-methyl ester that is a non-specific NO blockator (eNOS and nNOS). Furthermore, we used the doze 10 mg kg^{-1} which completely blocks NO production. The given doze has been used also by other researchers with the purpose of full NO blockade (Chen and Hu 1997). Our previous study of renal regulation (Sosnovtseva *et al* 2009) has also demonstrated effects of L-NAME in different frequency areas.

Acknowledgment

This work was partly supported by the Russian Ministry of Education and Sciences grant 2.2.2.2/229.

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