

Autonomic modulation and chronotropic activity during aerobic exercise in patients using atenolol

Modulação autonômica e atividade cronotrópica durante exercício aeróbico em pacientes que utilizam atenolol

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Abstract

Introduction: The negative chronotropic effect of beta-blockers (BB) can modify itself according to its pharmacokinetics. **Objective:** To investigate the influence of pharmacokinetics of beta-blockers in heart rate (HR) and autonomic activity (AA) in response to the exercise. **Methods:** Three groups of hypertensive patients, users of atenolol (n=9), enalapril, (n=8), and a normotensive control group (n=8), performed two sessions of moderate exercise on a cycloergometer, during 40 minutes, whereby 2 hours (Session I), or 23 hours after drug administration (Session II). Records of electrocardiogram were made before, during and after the exercises. **Results:** The HR was lower in session I comparing with session II of the atenolol group during the exercise. There were no differences in the components of low and high frequency of AA between these sessions. **Conclusions:** These results confirm the negative chronotropic effect of BB. However, the absence of changes in AA suggests that other mechanisms may be contributing to this phenomenon.

Key words: Atenolol; Hypertension; Pharmacokinetics.

Resumo

Introdução: O efeito cronotrópico negativo dos betabloqueadores pode modificar-se de acordo com sua farmacocinética. **Objetivo:** Investigar a influência da farmacocinética dos betabloqueadores na frequência cardíaca (FC) e atividade autonômica (AA) em resposta ao exercício. **Método:** Três grupos de hipertensos, usuários de atenolol, n=9, enalapril, n=8 e um controle normotenso, n=8, realizaram duas sessões de exercício moderado em cicloergômetro, com duração de 40 minutos, sendo 2 horas (sessão I), ou 23 horas após administração do fármaco (sessão II). Registros de eletrocardiograma foram feitos antes, durante e após os exercícios. **Resultados:** A FC, durante o exercício, foi menor na sessão I, quando comparada com a sessão II do grupo atenolol. Não se observou diferenças nos componentes de baixa e alta frequência da AA entre essas sessões. **Conclusão:** Esses resultados confirmam o efeito cronotrópico negativo dos BB. No entanto, a ausência de alterações na AA sugere que outros mecanismos podem estar contribuindo para esse fenômeno.

Descritores: Atenolol; Farmacocinética; Hipertensão.

Introduction

Beta-blockers are widely prescribed for the treatment of cardiovascular diseases¹⁻³. They inhibit β -adrenergic receptors and are classified into three generations according to their selectivity: i) first generation include the non-selective because they block both β_1 and β_2 receptors; ii) second generation have a selective action on β_1 receptors, and iii) third generation are either selective or non-selective and have a vasodilator action⁴.

Atenolol is a second generation beta-blocker which selectively competes with noradrenaline through β_1 receptors leading to a negative chronotropic effect⁵. This can be verified either at rest or during exercise^{1,6-11}. Heart rate (HR) has been widely used for exercise prescription and monitoring, mainly due to its easy applicability and low cost¹². Because there is a reduction in the chronotropic effect during exercise in patients using beta-blockers, HR cannot be adopted for exercise prescription in hypertensives using this medication¹³⁻¹⁵.

Therefore, patients are recommended to perform an ergometric test under the effect of beta-blockers¹⁶. However, since atenolol has a half-life of 4-8 hours and duration of action of 1.8 to 2.2 ml/min.kg^{17,18}, all exercise performed at a different time from the ergometric test might result in different chronotropic responses. This has been confirmed in a previous study of our laboratory¹⁹.

Because this was the first study to demonstrate different HR responses during exercise according to the time of the administration of the beta-blocker, further studies concerning the mechanisms underlying this response need to be conducted. The autonomic modulation on the different heart rate responses during and after plasma half-life should be clarified.

Since beta-blockers act directly on adrenergic receptors, differences in HR can be caused by changes in cardiac autonomic modulation, which regulates heart rate. Thus, further studies should analyze the effects of this medication, not only on HR, but also on its regulative mechanisms – car-

diac autonomic modulation. Hence, the objective of this study was to investigate the autonomic modulation and the chronotropic response during exercise in hypertensive adults using atenolol.

Materials and methods

Subjects

Twenty-five adult women were divided in three groups as follows: 1) atenolol (9 hypertensives, 54.9±5.5 years old, using atenolol, 25 mg/day); 2) enalapril (8 hypertensives, 55.6±5.2 years old, using enalapril, a angiotensin-converting enzyme inhibitor, 5.0 mg/day) and 3) control (8 normotensives, 55.6± 6.1 years old). As inclusion criteria all subjects: a) were engaged in an aerobic exercise program for at least six months, 3-5 times a week; b) had body mass index (BMI) lower than 30.0 kg/m²; c) were free from other chronic diseases; and d) had to take only one dose of the medication per day in the morning. e) women volunteers in the study were postmenopausal.

All subjects showed negative results for myocardial ischemia and arrhythmia on previous ergometric test. Based on the results of the ergometric test, the participants were classified as “weak”, according to the American Heart Association. All volunteers were oriented not to drink alcohol and/or stimulants (tea, coffee, among others) 24 hours before the tests, have a good night's sleep and a light meal at least 2 hours before the test.

This research was performed in accordance with the Helsinki declaration. The research protocols were reviewed and approved by the Human Research Ethics Committee of the Federal University of Paraíba (UFPB-PB), Brazil (process n°. 0420-08).

Study design

All groups performed two exercise sessions on a cycloergometer with a 48-hour interval between them. Session I was performed two hours after the administration of the medication (dur-

ing the plasma half-life period), and session II was performed 23 hours after the administration of the medication (after the plasma half-life period).

These periods were defined considering that the half-life of atenolol is 4 to 8 hours and its maximum plasma concentration is 2 hours¹⁷,¹⁸ according to the information in the bulla of the manufacturer of this drug. All subjects were asked to take the medication at 7 a.m., and initiate the sessions 2 and 23 hours after taking the medication (sessions I and II, respectively). Thus, all participants performed session I at 9 a.m. and session II at 6 a.m. Before, during and after exercise sessions, was made an electrocardiogram to determine the heart rate and autonomic nervous activity by spectral analysis of ECG.

Electrocardiogram

Electrocardiogram (ECG) was obtained by the connection of an electrocardiograph to a signal amplifier (General Purpose Amplifier/Stemtech, Inc., GPA-4, model 2), which converts analog to digital signal. Following, the signal was stored in a computer in the WINDAQ DI200 software (DATAQ Instruments – Akron, Ohio, USA), which performs spectral analyses of the ECG. All data were recorded in a microcomputer with sample frequency of 500 Hz per channel.

ECG was recorded at rest, during exercise, and post-exercise. In order to record ECG at rest, subjects remained in supine position for 10 minutes. After this, signals were obtained in the same period of time. Electrocardiogram during exercise was recorded for 40 minutes, five minutes after the onset of exercise. ECG post-exercise was recorded for 10 minutes, after subjects remained in supine position for 10 minutes.

Respiratory rate

Respiratory rate was obtained with the respiratory belt (pneumographic), which contains bilateral sensors that pick up the sign breathing through the thoracic distensibility, from the respiratory pattern. The sign of breathing was pre-

amplified (General Purpose Amplifier/Stemtech, Inc. GPA-4 model 2), and converted from analog to digital. In real time, the sign of breathing was stored in a computer program through WinDaq DI200, a frequency of 500 Hz. The respiratory rate was recorded at the same moments as the ECG, in order that the interpolation of the series tachogram and respirogram remove undesirable distortions in the spectral analysis.

Assessment of the autonomic control

Windaq PLAYBACK /DATAQ algorithm was used for the spectral analysis of heart rate variability. This program performs the withdrawal of linear tendency and the fast Fourier transform, which was applied in single window, in the sequence of R-R intervals, with the minimum of 256 consecutive beats.

Spectral powers were quantified in the very low-(VLF: < 0.04 Hz), low-(LF: 0.04- 0.15 Hz) and high frequency (HF: 0.15-0.4 Hz) bands. In this study, low frequency (LF) and high frequency (HF) spectral components were used since they best represent sympathetic and vagal components of HR control, respectively. These components were reported in normalized units (LF_{nu} and HF_{nu}), which represent the relative value of each power component in proportion to the total power minus the VLF component. Such components were also expressed as ratio (LF/HF), as markers of the sympathetic-vagal balance^{20, 21}.

Exercise protocol

This study was conducted in an acclimatized room (temperature of around 23 °C and relative humidity of around 54%). Forty-eight hours before experimental sessions, subjects were progressively familiarized with the equipments, research members, environment, evaluation, and tests.

Familiarization included an 8-15 minutes session to determine the load and cadence in the

cycloergometer (ERGOFIT 167 cycles, Germany) in order to reach intensity between 13 and 14 of Borg's perceived exertion scale.

In both experimental sessions, exercise on cycloergometer lasted 40 minutes. Intensity was determined according to the load and cadence obtained in the familiarization session for each subject.

Assessment of blood pressure

A stethoscope and an aneroid sphygmomanometer (Missouri-Brazil), 2.0 mmHg precision were used to measure blood pressure (BP). BP was measured at rest, during exercise and post-exercise. BP at rest was assessed after supine position for 10 minutes. BP during exercise was measured at 20 and 40 minutes. To perform the measurement of 20 minutes, the researchers asked the subjects who did not interrupt the exercise. For the measurement of 40 minutes, the participants were informed that the exercise was over, but kept riding until the arterial pressure measurement was completed. BP post-exercise was measured at 10, 20 and 30 minutes after exercise when subjects remained resting, adopting 30 minutes as reference.

Statistical analysis

Data were presented as mean and standard deviation. Smirnov-kolmogorov test was applied to test normality of the data. Due to this result, analysis of variance (ANOVA) was applied with Tukey's post hoc test in order to identify the differences between groups. Student T test was applied to verify the differences of each group between sessions I and II, adopting reliability level of 95%. GraphPad Instat version 3.0 software was used.

Results

Anthropometric characteristics and HR of the groups are presented in Table 1. Age and BMI were similar between groups ($p>0.05$).

Resting HR of atenolol was significantly lower than enalapril in the exercise session performed during the plasma half-life period (session I) ($p<0.05$). In session II, in which exercise was performed after beta-blockade, resting HR was similar between groups ($p>0.05$).

Table 1: Anthropometric characteristics and heart rate (HR) at rest of the three groups

Characteristics	Atenolol (n = 9)	Enalapril (n = 8)	Control (n = 8)
Age (years)	54.9 ± 5.5	55.6 ± 5.2	55.6 ± 6.1
BMI (kg/m ²)	25.1 ± 3.3	26.4 ± 3.1	25.8 ± 1.9
HR session I (bpm)	60.5 ± 10.1*	71.4 ± 6.0	67.6 ± 8.0
HR session II (bpm)	61.2 ± 10.2	68.5 ± 5.9	64.0 ± 10.7

Values of mean and standard deviation. BMI: body mass index; * difference of atenolol compared with enalapril, $p<0.05$.

The Figure 1 shows that the heart rate during exercise during beta-blockade (session I) was 10.6% lower than after beta-blockade (session II), ($p<0.05$). In both exercise sessions, HR responses were similar between enalapril and control ($p>0.05$). After intra-groups analyses in session I, HR during exercise in atenolol was lower than in enalapril and control ($p<0.01$). There were no differences between groups in session II ($p>0.05$).

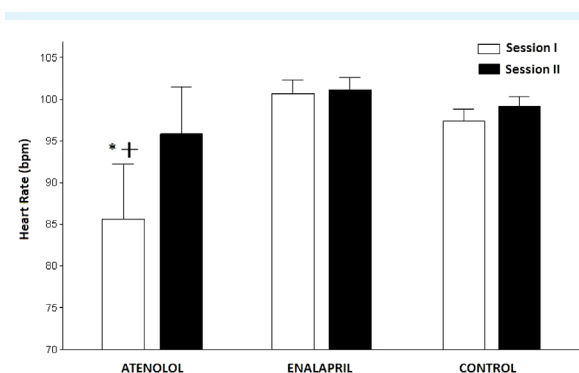


Figure 1: Mean and standard deviation of heart rate during exercise in the three groups

* Difference in atenolol between sessions 1 and 2, $p<0.05$; + difference between atenolol and enalapril and control ($p<0.01$).

The mean and standard deviation of systolic and diastolic blood pressures at rest, during exercise and post-exercise for atenolol, enalapril and control are presented in Figure 2. The three groups presented similar systolic and diastolic blood pressures at rest and during exercise. Moreover, systolic and diastolic blood pressure were similar between sessions I and II in the three groups ($p>0.05$).

Mean and standard deviation of autonomic modulation, including LF and HF, and autonomic balance spectral components for atenolol, enalapril and control at rest are presented in Table 2. There were no significant differences between sessions I and II for any of the three spectral components. In session I, there was a lower resting autonomic balance in atenolol during beta-blockade than in control ($p<0.05$).

Table 2: Normalized low- (LF_{nu}) and high frequency (HF_{nu}), and autonomic balance (LF/HF) spectral components at rest for atenolol, enalapril and control

Sessão I	Atenolol	Enalapril	Controle
LF (nu)	39.0 ± 19.3	59.0 ± 27.1	50.2 ± 24.0
HF (nu)	61.0 ± 18.8	41.0 ± 27.1	49.8 ± 24.0
LF/HF	0.8 ± 0.4*	1.1 ± 0.5	1.4 ± 0.4
Sessão II	Atenolol	Enalapril	Controle
LF (nu)	49.0 ± 22.9	60.5 ± 27.4	34.0 ± 25.4
HF (nu)	49.8 ± 22.0	39.5 ± 27.4	66.0 ± 25.4
LF/HF	1.0 ± 0.6	1.1 ± 0.6	1.2 ± 0.5

* significant difference between atenolol and control, ($p<0.05$)

LF_{nu}, HF_{nu}, and LF/HF spectral components were similar between sessions I and II during exercise ($p>0.05$) (Table 3). Similarly, during the recovery period, there were no intra-groups differences for any spectral components (Table 4).

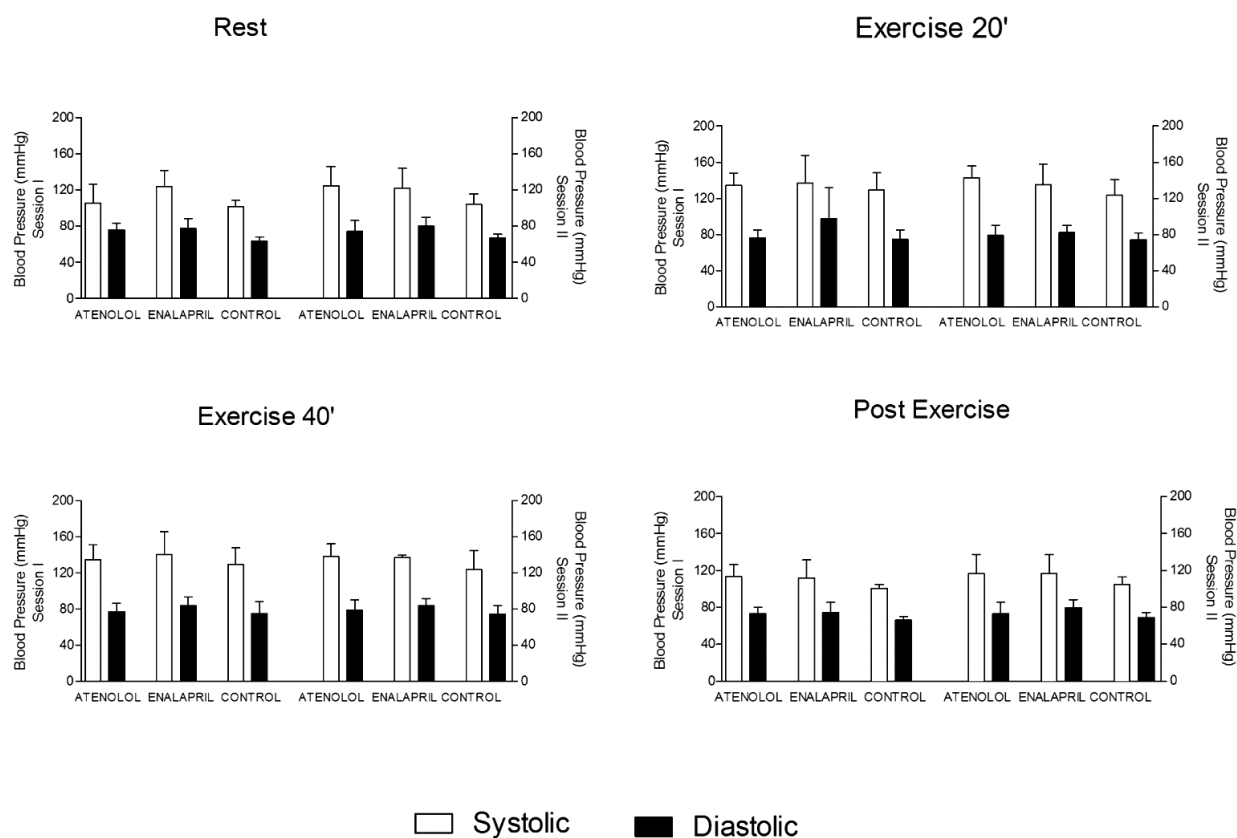


Figure 2: Mean and standard deviation of systolic blood pressure (mmHg) in sessions I and II at rest (panel A), at 20 minutes of exercise (panel B), at 40 minutes of exercise (panel C) and post-exercise (panel D) for atenolol, enalapril and control

Table 3: Normalized low-(LFnu) and high frequency (HFnu), and autonomic balance (LF/HF) spectral components during exercise for atenolol, enalapril and control. values of mean and standard deviation

Sessão I	Atenolol	Enalapril	Control
LF (nu)	48.2 ± 18.4	62.7 ± 17.7	42.2 ± 16.0
HF (nu)	51.7 ± 18.4	37.2 ± 17.7	57.7 ± 16.0
LF/HF	0.9 ± 0.5	0.9 ± 0.4	1.0 ± 0.4
Sessão II	Atenolol	Enalapril	Control
LF (nu)	41.4 ± 18.0	60.5 ± 27.4	41.1 ± 20.2
HF (nu)	58.5 ± 18.0	39.5 ± 27.4	58.8 ± 20.2
LF/HF	1.0 ± 0.4	0.8 ± 0.3	1.1 ± 0.5

Table 4: Normalized low-(LFnu) and high frequency (HFnu), and autonomic balance (LF/HF) spectral components at 20 minutes of recovery for atenolol, enalapril and control. values of mean and standard deviation

Sessão I	Atenolol	Enalapril	Control
LF (nu)	47.8 ± 21.4	58.7 ± 20.7	47.5 ± 30.2
HF (nu)	52.2 ± 21.4	41.2 ± 20.7	52.5 ± 30.2
LF/HF	0.9 ± 0.5	1.2 ± 0.5	0.8 ± 0.3
Sessão II	Atenolol	Enalapril	Control
LF (nu)	46.2 ± 18.0	46.2 ± 23.0	61.1 ± 19.1
HF (nu)	53.8 ± 18.1	53.7 ± 23.0	38.9 ± 19.1
LF/HF	0.7 ± 4.1	0.9 ± 0.5	1.1 ± 0.5

Discussion

The results of this study showed that heart rate chronotropic responses to exercise are lower during plasma half-life of atenolol (session I) compared with exercise performed after atenolol beta-blockade (session II). Concomitant with the reduction of HR, there was a greater vagal activity during atenolol beta-blockade than in control at rest. However, no differences in the autonomic balance were observed in atenolol during and after plasma half-life of atenolol.

Because atenolol is a cardio selective beta-blocker of β_1 receptors, it significantly reduces HR in 20% during exercise⁸. In our study, a 10.6% reduction of HR was found during plasma

half-life of atenolol (session II). These data are in agreement with previous studies of our laboratory, that observed a 10.9% and 10.3% decrease of HR during exercise during atenolol beta-blockade compared with 11 and 23 hours of the administration of atenolol and propranolol, respectively¹⁹. With metoprolol, a second generation beta-blocker, a 5.4 % decrease in HR during an aerobic exercise session was found during beta-blockade²².

In hypertensive patients, the use of atenolol competes with noradrenalin by the β_1 receptors in the cardiac muscle⁵. Thus, the internal environment in the sinoatrial node remains more negative, keeping the sinus rhythm with lack of sympathetic stimulation, leading to a negative chronotropic effect²³. Therefore, even if the central sympathetic stimulus remains high, its effects over the cardiac modulation are minimized. Thus, the autonomic balance obtained by spectral analysis allows the investigation of this effect. In this study, atenolol presented a significantly lower autonomic balance at rest than control, showing a higher parasympathetic activity in hypertensive patients and a higher sympathetic activity in the normotensive adults (control). However, there were no changes in autonomic balance during and after exercise neither between enalapril and control nor between during and after atenolol beta-blockade.

Hence, this work shows the following hypothesis concerning the use of beta-blockers by hypertensive patients engaged in an exercise program: a) the beta-blocker decreases resting HR; b) however, if the exercise is performed after beta-blockade, there is a lower inhibition of the positive chronotropic effect induced by the exercise. Our laboratory is the first to highlight the beta-blocker effect in hypertensive patients engaged in an exercise program; c) although HR during exercise is lower during beta-blockade, the autonomic modulation remains unchanged during exercise performed during and after beta-blockade.

The lower resting HR in subjects using beta-blockers was followed by a predominance

of vagal nervous activity. These results are in agreement with previous studies that showed an association between the use of beta-blockers and the decrease of morbidity and mortality rates. This might be due to an increase of the parasympathetic activity^{24, 25}.

The main finding in the present study is that there are differences in the chronotropic responses during aerobic exercise during and after plasma half-life of atenolol. This is an important issue since several medical societies have recommended that hypertensives using beta-blockers should perform an ergometric test under the effect of this medication to correct the maximal HR for exercise prescription¹⁶. Nevertheless, according to our findings, we can assure that this measure is not completely satisfactory, because the reduction of HR during and after beta-blockade is not the same. Therefore, the time between the administration of the beta-blocker and the exercise needs to be considered when prescribing exercise for hypertensive patients.

Although the increase in the parasympathetic predominance explains the lower resting HR of subjects using beta-blockers, the lower HR during exercise during beta-blockade was not accompanied by changes in cardiac autonomic modulation. It was probably caused because, during exercise, several mechanisms are strongly activated to supply the demands caused by exercise. Thus, this acute exercise demands overtake the effects of atenolol on autonomic modulation. Similarly, the autonomic balance of post-exercise was measured at 20 minutes of recovery. It is probable that, at this time, the acute exercise responses also overtake the autonomic balance induced by the beta-blocker.

Due to the lack of association between the autonomic balance and the lower chronotropic activity during exercise performed during the beta-blockade, further studies should be conducted in order to investigate other possible mechanisms underlying this phenomenon. It is important to note that temperature and humidity, as well as the cadence and load of the

cycloergometer were controlled in this study, eliminating, thus, the influences of these factors in the difference of the heart rate between both sessions. And also, these differences were not caused by hormonal influences, since no differences were found in control and enalapril.

Then, the results in the present study confirm the negative chronotropic effect of beta-blockers in hypertensive women. This effect is attenuated after the plasma half-life period. Therefore, more attention should be taken when prescribing exercise training for hypertensive patients after beta-blockade. Thus, the time interval between beta-blocker administration and exercise should be considered. The analysis of autonomic modulation demonstrates that the continuous use of beta-blockers benefits the cardiac autonomic function in hypertensive patients, protecting them against the development of other pathologies. We conclude, however, that no significant changes were observed in the autonomic modulation between both sessions, which suggests that future research shall to investigate other factors that can contribute to a lower HR in hypertensive patients.

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