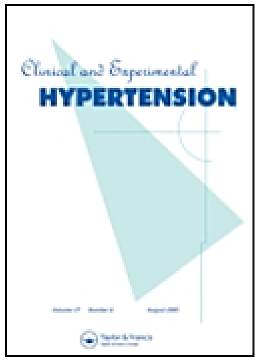

Effects of ACEi and ARB on post-exercise hypotension induced by exercises conducted at different times of day in hypertensive men

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Antihypertensive drug, exercise and time of day

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Background: Post-exercise hypotension (PEH) is greater after evening than morning exercise, but anti-hypertensive drugs may affect the evening potentiation of PEH. Objective: To compare morning and evening PEH in hypertensives receiving angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB). Methods: Hypertensive men receiving ACEi (n=14) or ARB (n=15) underwent, in a random order, two maximal exercise tests (cycle ergometer, 15 watts/min until exhaustion) with one conducted in the morning (7 and 9 a.m.) and the other in the evening (8 and 10 p.m.). Auscultatory blood pressure (BP) was assessed in triplicate before and 30 min after the exercises. Changes in BP (post – pre-exercise) were compared between the groups and the sessions using a 2-way mixed ANOVA and considering $P<0.05$ as significant. Results: In the ARB group, systolic BP decrease was greater after the evening than the morning exercise, while in the ACEi group, it was not different after the exercises conducted at the different times of day. Additionally, after the evening exercise, systolic BP decrease was lower in the ACEi than the ARB group (ARB = -11±8 vs -6±6 and ACEi = -6±7 vs. -8±5 mmHg, evening vs. morning, respectively, P for interaction = 0.014). Conclusions: ACEi, but not ARB use, blunts the greater PEH that occurs after exercise conducted in the evening than in the morning.

Keywords: blood pressure, hypertension, aerobic exercise, circadian rhythm.

Introduction

Hypertension is a multifactorial disease characterized by the maintenance of high blood pressure (BP); which compromises several organs, such as heart, lung, brain and kidney (1, 2), and increases the risk for heart disease and stroke (1, 3, 4). In addition, hypertension is highly prevalent, affecting more than 1 billion people worldwide (1). Thus, interventions for prevention and treatment of hypertension are mandatory.

Among many anti-hypertensive strategies, aerobic exercise has been proven as an efficient non-pharmacological tool (1, 2, 5). Interestingly, the chronic effects of aerobic training can be predicted by the acute decrease observed in BP after the execution of a single session of exercise (6-8), which has been called post-exercise hypotension (PEH). Additionally, PEH per se has been shown to have clinical relevance because it presents a clinically relevant magnitude of blood pressure reduction (9) and lasts for many hours (10), reducing the mean 24-h BP after the exercise (11). Thus, factors that might potentiate or inhibit PEH should be studied.

Previous studies have reported that PEH is potentiated when exercise is conducted in the evening rather than in the morning (9, 12, 13). This greater reduction in BP after evening exercise has been attributed to a greater decrease in systemic vascular resistance (9, 12) due to the maintenance of a greater vasodilation after the exercise conducted at this time of day (9). This response suggests that physiological systems involved in vasoconstriction and vasodilation might be involved in the potentiated PEH after evening exercise.

Increasing evidence suggests the involvement of the renin-angiotensin- system (RAS) on PEH. Along this line, polymorphisms in some components of this system (14) and the use of drugs that act on RAS (15) have been shown to change PEH magnitude. Additionally, a decrease of angiotensin converting enzyme (ACE) activity (16) and an increase of bradykinin and angiotensin 1-7 (16, 17), potent vasodilators (18), have been reported after an exercise bout, suggesting the involvement of these components of RAS on PEH. Since this system present a well-known circadian pattern (19), it is possibly involved in the differences observed after exercises conducted at different times of day with a greater release of bradykinin and angiotensin 1-7 after the evening exercise.

ACE inhibitors (ACEi) and angiotensin type 1 receptor blockers (ARB) are the mostly widely used anti-hypertensive drugs in Brazil (20). However, these drugs have different effects on the RAS and only ACEi chronically increases plasma bradykinin and angiotensin 1-7 levels (18). Thus, it is possible to suppose that the higher levels of these substances induce a sustained and similar vasodilation throughout the day, blunting the greater vasodilation after evening exercise and therefore mitigating the difference in PEH after morning and evening exercises.

Assuming this exploratory hypothesis, this study compared PEH after a single bout of maximal exercise performed in the morning and in the evening in hypertensives receiving ACEi or ARB. The hypothesis is that ACEi, but not ARB, prevents the evening potentiation of PEH.

Methods

This study used a database from a larger clinical trial that evaluated the effects of morning and evening aerobic training in medicated hypertensive men and whose main data was published elsewhere (21). Data analyzed here comprises the maximal tests performed before the training period in the subjects receiving ACEi and ARB. The larger study was approved by the Ethics Committee of the School of Physical Education and Sport of University of São Paulo (966.072) and was registered at the Brazilian Clinical Trials (www.ensaiosclinicos.gov.br - RBR-7q7pz7). All subjects gave written consent before enrollment.

Participants

Twenty-nine hypertensive men (30-65 years old) receiving monotherapy with either ACEi (n=14) or ARB (n=15) were included in the study. Their main characteristics are shown in table 1.

[Table 1 is about here]

Anti-hypertensive treatment was determined by each subject's own physician and had been consistent for at least 4 months preceding the study. Additionally, BP was assessed in two visits, in which auscultatory BP was measured three times after 5 minutes of seated rest, and the subjects were only included in the study if their mean systolic and diastolic BPs were, respectively, below 160 and 105 mmHg (1, 2). In addition, only subjects with neither type of chronotypes (<59 or >41) were included based on the Horne and Ostberg questionnaire (22).

Subjects were excluded if they: i) had a prior medical diagnosis of other cardiovascular disease, any target organ damage, or secondary hypertension, which was checked by the detailed screening procedure of the Hypertension Unit of the General Hospital of the University of São Paulo that follows Brazilian guidelines (2); ii) had obesity level II or greater, which was checked by a body mass index equal to or greater than 35 kg/m (23); iii) practiced regular structured physical exercise more than twice a week, which was checked in an interview; iv) received any drug that directly affects cardiovascular function, except for ACEi or ARB, which was checked by an interview; and v) presented electrocardiographic abnormalities at rest or during exercise, which was checked by the execution of a maximal exercise test (24).

Study design

The study had a crossover random design in which each subject performed both the morning and the evening exercises at different occasions and the order of execution was randomly defined.

The experimental protocol was composed by five visits to the laboratory conducted on different days. The first three visits were used to check compliance to the study criteria (interview, questionnaire application, physician examination, body mass index determination, BP measurements, and Hypertension Unit exams). Then, the subjects who fulfilled all study criteria underwent, in a random order, two exercise sessions with one conducted in the morning (7-9 a.m.) and the other in the evening (8-10 p.m.). An interval of 3-7 days was kept between the sessions. For these sessions, the subjects were instructed to have a light meal 2 hours before, and to avoid alcoholic and caffeinated beverages as well as physical effort for the previous 24 hours. Laboratory temperature was kept between 20 and 22 ºC.

In the experimental session, the exercise consisted of a maximal cardiopulmonary exercise test conducted on a cycle ergometer (Lode Medical Technology, Corival, Groningen, Netherland). For this test, after 3-min of seated rest on the cycle ergometer, the subjects performed a 3-min warm-up at 30 watts and then the workload was increased by 15 watts every minute until the subjects were unable to go on. This exercise phase was followed by a 5-min active recovery at 30 watts. During the exercise, HR was continuously assessed by ECG (Welch Allyn, Cardio Perfect, Batesville, USA), auscultatory BP was measured every 2 min (Unitec, São Paulo, Brazil), and oxygen consumption (VO_2) was assessed by a metabolic cart (Medical Graphics Corporation, CPX Ultima, Minnesota USA).

For the purpose of this study, during the experimental sessions, BP was measured in the pre-exercise period after 10 min of rest, and in the post-exercise period, after 30 min of recovery, which is an adequate period for identifying PEH (25) and has already been employed in other PEH studies (26, 27). In each period, to increase the value accuracy (25), measurements were taken in triplicate with the subjects seated on a comfortable chair, and the mean value was used for analyses. BP was measured on the non-dominant arm, using the auscultatory technique, a mercury column sphygmomanometer (Unitec, São Paulo, Brazil), and accepting phases I and

V of the Korotkoff sounds to respectively determine the systolic and diastolic BP values, mean BP was calculated [mean BP = (systolic BP – diastolic BP)/3 + diastolic BP]. Auscultatory BP measurement has shown good/excellent reliability for PEH evaluation (28). Additionally, to minimize any possible influence of the evaluator (29), all the measurements were done by the same highly trained researcher who was blinded to the type of anti-hypertensive taken by the subjects.

Statistical analysis

As data derived from a larger study, the sample size was calculated a priori for the larger study. Thus, for the present study, a posteriori post-hoc power analysis was performed, and considering an α error of 0.05, the power calculated for systolic BP interaction was 0.72 (G*Power v. 3.1.9.2, Universität Kiel, Germany).

Normality of data was checked by Shapiro-Wilk test (SPSS for windows; IBM, Chicago, IL). For analyses, firstly, PEH occurrence was evaluated using T-tests to compare pre- and post-exercise BP absolute values within each session of each group (SPSS for windows; IBM, Chicago, IL). Afterwards, mixed two-way ANOVAs (Statsoft V.5, Statistic for windows, USA) were employed to compare PEHs (calculated by the difference between post and pre-exercise values in each session) between the groups (ACEi vs ARBs – between main factor) and the times of day (morning vs. evening – within main factor). For all analyses, $P<0.05$ was set as significant. Data are showed as mean±standard deviation.

Results

Peak cardiometabolic responses to exercise were similar between the groups and the exercises conducted in the morning and the evening (Table 2).

[Table 2 is about here]

Regarding the occurrence of PEH, in both groups and sessions, systolic BP decreased significantly from pre to post-exercise (ACEi morning: 128 ± 14 vs. 120 ± 14 mmHg, P<0.001; ACEi evening: 128 ± 11 vs. 122 ± 8 mmHg, P=0.000; ARB morning: 131 ± 10 vs. 124 ± 12 mmHg, P<0.001; and ARB evening: 130 ± 12 vs. 119 ± 13 mmHg, P<0.001). Diastolic BP did not change from pre to post-exercise in either group or session (ACEi morning: 89 ± 10 vs. 89 ± 9 mmHg, P=0.93; ACEi evening: 91 ± 7 vs. 90 ± 6 mmHg, P= 0.74; ARB morning: 88 ± 7 vs. 89 ± 6 mmHg, P=0.24; and ARB evening: 90 ± 8 vs. 89 ± 9 mmHg, P=0.73). Mean BP decreased significantly from pre to post-exercise in the ACEi group after the morning exercise and in the ARB group after the evening exercise (ACEi morning: 102 ± 10 vs. 99 ± 10 mmHg, P=0.012; ACEi evening: 103 ± 7 vs. 101 ± 6 mmHg, P=0.09; ARB morning: 101 ± 8 vs. 101 ± 7 mmHg, P=0.68; and ARB evening: 103 ± 9 vs. 99 ± 10 mmHg, P=0.017).

Concerning comparisons of PEH between the groups and the times of day (Figure 1), in the ARB group, post-exercise systolic and mean BP decreases were significantly greater after the evening than the morning exercise, while in the ACEi group, these decreases were similar after the exercises conducted at both times of day (Systolic BP - ARB = -11±8 vs -6±6 and ACEi = -6±7 vs. -8±5 mmHg, P for interaction = 0.014; and mean BP - ARB = -4±5 vs. -1±5 and ACEi = -2±5 vs. -3±4 mmHg, P for interaction = 0.021). Additionally, after the exercise conducted in the evening, systolic BP decrease observed in the ACEi group was significantly lower than in the ARB group. Diastolic BP behavior after exercise was similar between the groups and the times of day.

[Figure 1 is about here]

Discussion

The main finding of the study was that ACEi, but not ARB, blunted the greater evening PEH, which is consistent with the hypothesis. For clinical practice, these results may suggest that the choice of anti-hypertensive drug therapy, mainly when involving the RAS inhibition, can influence the daily variation of the clinically relevant manifestation of PEH. For the scientific field, the present results raise a possible influence of antihypertensives on PEH circadian variation that needs to be confirmed and expanded by future studies specifically designed for investigating this influence.

The hypertensives included in the study were middle-aged men using antihypertensive drugs that act on RAS and mainly with overweight or obesity; which are common characteristics among the hypertensive population in Brazil (20). Additionally, their VO_2peak values were similar to the ones reported for non-trained hypertensives in studies employing cycle ergometer tests and directly measuring VO_2 (30, 31). Thus, the sample of the study reflects the clinical reality of the non-trained male hypertensive population.

In the present study, a consistent PEH was observed for systolic BP in hypertensives receiving either ACEi or ARB and after exercises conducted in the morning and the evening. In contrast, diastolic BP did not change after the exercise conducted at either time of day or in either group. Nevertheless, the absence of diastolic PEH is commonly reported in literature (25), especially after a maximal exercise protocol and when post-exercise values were compared with pre-exercise values (32), as in the present study. Although maximal effort is not the most commonly used exercise protocol for PEH assessment (25), similarly to the present results, previous studies also reported significant BP decreases after maximal exercise (33-35). Additionally, maximal tests are recommended for pre-training health screening in hypertensives (1, 2, 5), and the systolic PEH induced by this test has been shown to predict the chronic hypotensive effect to chronic exercise training (33). Therefore, the results of this study confirm that a maximal exercise test with triplicate post-exercise BP measurement performed at 30 minutes of recovery can be employed to assess the occurrence of systolic PEH.

In the ARB group, PEH was greater after evening than morning exercise and it was also greater in the ARB than the ACE group after the evening exercise, showing that both, type of anti-hypertensive and time of day interaction may impact PEH. Additionally, it is important to note that the differences in PEH magnitudes between the groups and the times of day cannot be attributed to differences in cardiovascular stress induced during maximal exercise tests since tests duration, peak VO_2, workload, heart rate and BP were similar among the tests conducted in both groups and both times of day. Additionally, no correlation was identified after a complementary analysis (data not shown) between BP response to the tests and HPE induced by them for each exercise session.

It has been demonstrated that regardless of environmental and behavioral changes, the human endogenous circadian system influences systolic BP responses after exercise (36), resulting in a potentiated PEH after evening exercise compared with morning exercise in healthy subjects (12, 13) as well as in pre-hypertensives (9). The current study expands this knowledge to hypertensives receiving ARB, but not ACEi. This result shows that ACEi changes the expected circadian pattern of PEH, interfering with the potentiated systolic BP decrease associated with evening exercise.

The mechanisms responsible for this response were not assessed in the present study. However, as exposed in the introduction, ACEi but not ARB is known to increase plasma levels of bradykinin and angiotensin 1-7 (37). These are potent vasodilatory substances (18) that are released by exercise (16, 17) and are increased after the exercise when PEH was observed in hypertensives (17), suggesting their role in PEH generation. Since RAS presents a circadian pattern (38), a greater release of these substances after evening exercise might explain the greater vasodilation and PEH observed when exercise is conducted at this time of day, while their chronically higher levels induced by ACEi use might blunt this greater evening response. The present study results support this hypothesis, but future studies measuring the components of the RAS system, as well as assessing vasodilation after morning and evening exercise in hypertensives receiving both drugs should be conducted to confirm it. Additionally, other mechanism might be involved, but as an exploratory investigation, this study did not include a "no drug" control group or a group receiving anti-hypertensive drugs that act in other mechanisms despite RAS, which could provide additional insights into the mechanisms.

The present finding may have important scientific and clinical impact. To the best of our knowledge, this is the first study to show that the type of anti-hypertensive drug may differently affect BP response after exercises conducted at different times of day. As PEH after maximal exercise has a strong correlation with the hypotensive chronic effect of aerobic training (33), the present results suggest that, depending on the type of anti-hypertensive therapy, the beneficial effects of chronic exercise training might be different. Along this line, our bigger study demonstrated that 10-weeks of evening but not morning aerobic training reduces clinic and ambulatory BP in hypertensives medicated with different types of drugs (21). Based on the present result, this effect might be blunted in hypertensives receiving only ACEi, and may be different in hypertensives taking other types of medications. This is an important area for future research. Thus, the finding of this exploratory study highlights the need for a new research line about the relationship between type of medication, responses to exercise, and circadian patterns.

Study limitations

The study presents limitations. The dosage, type, and time of taking ACEi and ARB were not controlled in the study because the subjects were taking the medication as prescribed by their own physician. While this issue deserves acknowledgement and some caution in interpret results is warranted, it increases the external validity of the results. The sample was composed only by non-trained men. As PEH and its mechanisms can change between the sexes (7, 39) and training status (38), future studies should focus on women and trained subjects. Additionally, sample size was not previously determined and posteriori power was set as 72%, implying in a type II error of 28%; which reinforces the need of future studies with greater sample sizes. A maximal exercise test and only one time-point post-exercise BP measurement at 30-minutes of recovery were employed. The reasons of using maximal protocol were already discussed, and future studies should use other exercise protocols and follow BP longer (e.g. using ambulatory BP monitoring) to evaluate PEH duration. Finally, auscultatory method was employed to measure BP and although the evaluator was blinded to the antihypertensive use (ACEi or ARB), he cannot be blinded to the time of day (morning vs. evening), which may be considered a limitation that was minimized by the evaluator previous training.

Conclusions

In hypertensive men, ACEi, but not ARB use, blunts the greater PEH that occurs after exercise conducted in the evening than in the morning.

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Disclosure statement

There is no conflict of interest.

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Tables

Table 1. Characteristics of the hypertensives taking angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB).

Variables	**ACEi**	**ARB**	**P**
N	14	15	
Age (years)	50±8 (36 – 60)	49±8 (34 – 61)	0.74
Chronotype (score)	53.1±4.3 (44 – 57)	52.7±4.8 (44 – 58)	0.81
Height (m)	1.70±0.08 (1.55 – 1.80)	1.72±0.06 (1.61 – 1.83)	0.56
Weight (kg)	90.1±14.7 (63.0 – 108.3)	88.2±15.3 (63.0 – 105.0)	0.75
BMI (kg/m^2)	30.9±3.6 (24.7 – 34.8)	29.8±4.1 (21.8 – 34.9)	0.45
Systolic BP (mmHg)	132±11 (115 – 154)	135±12 (117 – 153)	0.54
Diastolic BP (mmHg)	88±6 (75 – 97)	91±7 (72 – 102)	0.26

BMI – body mass index; BP – blood pressure. Data are showed in mean±standard deviation (minimal value – maximal value).

Table 2. Peak responses to maximal exercise performed in the morning and the evening in the hypertensives taking angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB).

Variables	**ACEi**		**ARBs**				
	Morning	**Evening**	**Morning**	**Evening**	**P g**	**P s**	**P g x s**
Peak Workload (watts)	154±18	159±25	168±28	168±32	0.23	0.38	0.39
VO_2 peak ($mL.kg^{-1}.min^{-1}$)	20.2±4.7	21.3±5.1	22.8±3.1	22.9±2.5	0.14	0.18	0.25
Peak Systolic BP (mmHg)	208±24	214±23	209±26	210±29	0.88	0.30	0.45
Peak Diastolic BP (mmHg)	92±17	90±18	88±15	87±17	0.55	0.59	0.83
Peak Heart Rate (bpm)	164±13	163±13	161±12	163±17	0.79	0.90	0.44

VO_2 – oxygen uptake; BP – blood pressure; g – group, s – session, g x s – interaction between groups and sessions Data are shown in mean±standard deviation.

Figure captions

Figure 1. Comparisons of systolic (panel A); diastolic (panel B), and mean (panel C) blood pressure (BP) changes (post-exercise – pre-exercise values) observed after maximal exercise conducted in the morning and in the evening in hypertensive men taking angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). *Significant difference between times of day (Morning vs. Evening) ($P<0.05$). † Significant difference between groups (ACEi vs. ARB) ($P<0.05$). Values are shown as mean±standard deviation.

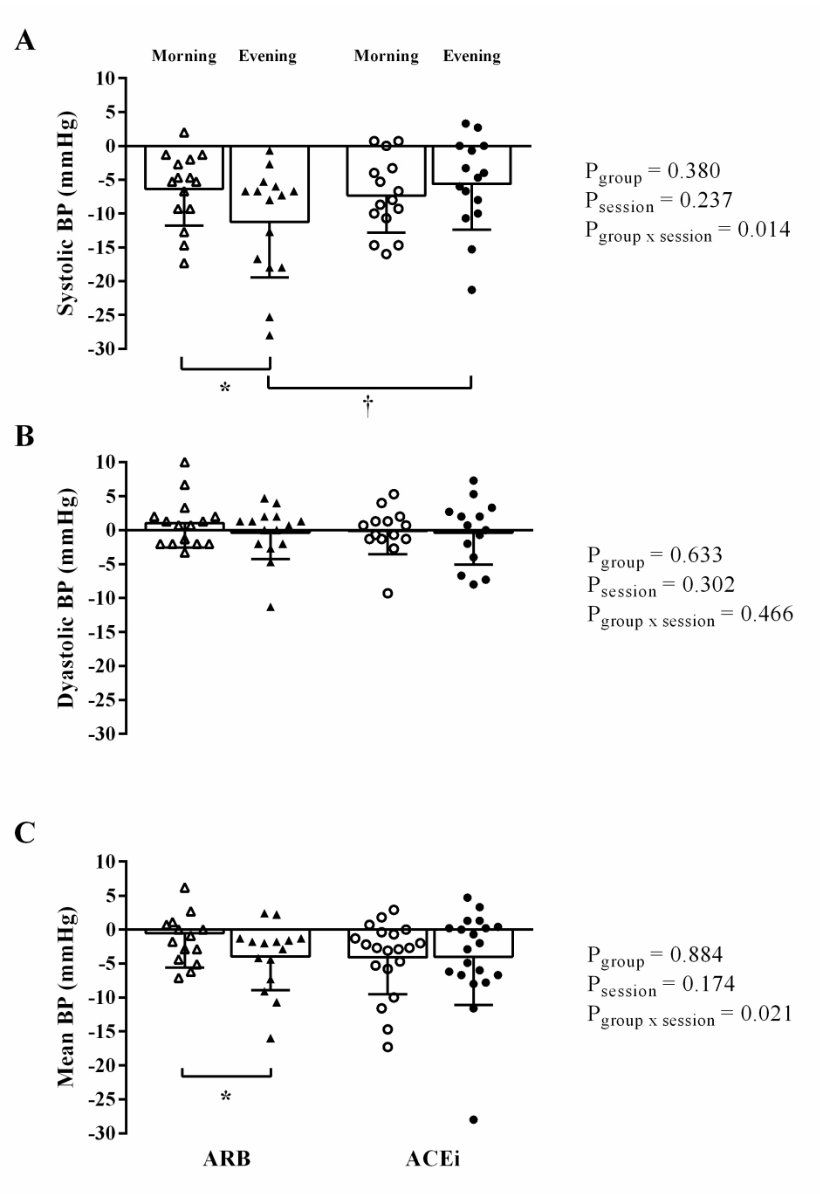

Figure 1

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