Morning vs Evening Aerobic Training Effects on Blood Pressure in Treated Hypertension

Time of Day of the Exercise in Hypertension

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ABSTRACT

Introduction: The acute blood pressure (BP) decrease is greater after evening than morning exercise, suggesting that evening training may have a greater hypotensive effect. **Objective:** To compare the hypotensive effect of aerobic training performed in the morning versus evening in treated hypertensives. **Methods:** Fifty treated hypertensive men were randomly allocated to 3 groups: morning training (MT); evening training (ET); and control (C). Training groups cycled for 45min at moderate-intensity (progressing from the heart rate of the anaerobic threshold to 10% below the heart rate of the respiratory compensation point), while C stretched for 30 min. Interventions were conducted 3 times/week for 10 weeks. Clinic and ambulatory BP, hemodynamic, and autonomic mechanisms were evaluated before and after the interventions. Clinic assessments were performed in the morning (7-9a.m.) and evening (6-8p.m.). Between-within ANOVAs were used ($P \leq 0.05$). **Results:** Only ET decreased clinic systolic BP differently from C and MT (morning assessment -5±6 mmHg and evening assessment -8±7 mmHg, $P<0.05$). Only ET reduced 24h and asleep diastolic BP differently from C and MT (-3±5 and -3±4 mmHg, respectively, $P<0.05$). Systemic vascular resistance (SVR) decreased from C only in ET ($P=0.03$). Vasomotor sympathetic modulation decreased ($P=0.001$) and baroreflex sensitivity ($P<0.02$) increased from C in both training groups with greater changes in ET than MT. **Conclusions:** In treated hypertensive men, aerobic training performed in the evening decreased clinic and ambulatory BP, due to reductions in SVR and vasomotor sympathetic modulation. Aerobic training conducted at both times of day increases baroreflex sensitivity, but with greater after ET.

Key words: Circadian rhythm, physical activity, hypertension, ambulatory blood pressure, vascular resistance, baroreflex control.

Introduction

Hypertension is estimated to affect 1 billion persons worldwide and is considered one of the most important cardiovascular risk factors, being responsible for 8 million deaths per year, mainly of them due cardiovascular causes, such as stroke, myocardium infarction or sudden death (1). Although anti-hypertensive medications may control blood pressure (BP) (2), low physical activity is an independent risk factor for cardiovascular morbidity and mortality even in treated hypertensives (3). Thus, the increase of physical activity levels, mainly by performing aerobic training, is recommended as a complementary therapy to medication in hypertension (4, 5).

The hypotensive effect of aerobic training has been extensively reported in literature. A classical meta-analysis (6) that included 26 randomized controlled trials with hypertensives concluded that aerobic training decreases systolic BP by -8 (-11 to -6) mmHg and diastolic BP by -5 (-7 to -3) mmHg, with the greater reductions obtained with training sessions conducted 2-3 times per week, lasting 30-45 min and with moderate intensity. However, despite this well-known chronic hypotensive effect (Evidence category A) (7), BP reductions after aerobic training vary across studies, and some factors, such as higher initial BP, moderate to high training intensities, and concomitant diet-induced weight-loss, have been identified as promoters of greater BP decrease (6, 8). Further, up to 25% of hypertensives appear to be non-responders to exercise, and don't demonstrate BP decreases, due to genetic characteristic and/or other unrecognized factors (9). For these reasons, other factors that potentiate the hypotensive effect of aerobic training must be investigated.

Along these lines, the time of day at which aerobic training is performed may influence BP reductions after training. The BP decrease that occurs after a single session of aerobic exercise has been shown to be greater when exercise was performed in the evening than in the morning (10, 11). In addition, acute and chronic hypotensive effects of aerobic exercise are

highly correlated (12, 13), consistent with the concept that the chronic effects of training may result from the sum of its acute effects (12-14). This suggests a novel concept, that aerobic training performed in the evening might potentiate chronic BP reductions. In further support of this concept, the greater BP decrease observed after an acute session of evening aerobic exercise has been attributed to a greater decrease in systemic vascular resistance (SVR) (10), which is also the main mechanism responsible for BP reductions after aerobic training (i.e. a decrease in SVR explains the training-induced decrease in BP) (15).

Despite this background suggesting a better benefit of evening aerobic training for hypertensives, to the best of our knowledge, no previous study has compared the hypotensive effects of aerobic training performed at different times of day. Thus, this study was designed to compare the effects of 10 weeks of aerobic training, performed in the morning versus in the evening, on clinic and ambulatory BPs as well as on hemodynamic and autonomic mechanisms. The hypothesis was that clinic and ambulatory BP would decrease after training performed at both times of day due to a decrease in SVR, but these reductions would be greater after the evening than the morning training.

Methods

Study participants

The subjects were recruited through advertisements at the university campus and social media as well as in hypertension awareness campaigns conducted at different regions of the city of São Paulo, Brazil. To participate, subjects needed to be men, aging between 30 and 65 years, and with resting systolic and diastolic BPs lower than 160 and 105 mmHg, respectively, while receiving anti-hypertensive drugs for at least 4 months. Exclusion criteria included: i) participation in regular exercise more than once a week; ii) presence of secondary hypertension and/or target-organ damage; iii) presence of morningness or eveningness chronotypes (i.e.

scores <42 or >58, respectively, in the Horne and Ostberg's questionnaire) (16); iv) presence of obesity stage 2 or greater (i.e. body mass index - BMI $\geq$ 35 kg/m^2) (17); v) presence of other cardiovascular disease besides hypertension; vi) insulin use; vi) use of medications that directly affect cardiac autonomic modulation assessment, such as beta-blockers and nondihydropyridine calcium channel blockers; vii) presence of any cardiovascular abnormality in resting or exercise electrocardiograms (ECG); and viii) unavailability for participating either in the morning or evening training. In addition, if doses and/or type of anti-hypertensive drugs changed during the study, the subject was excluded.

This study followed the principles in the Declaration of Helsinki, has been approved by the Research Ethical Committee of the School of Physical Education and Sport of the University of São Paulo (nº 966.072), and was registered at the Brazilian Clinical Trials (www.ensaiosclinicos.gov.br - RBR-7q7pz7).

Preliminary exams

Subjects who agreed to participate signed the informed consent and underwent preliminary exams to verify whether they fulfill the study criteria. Medical history was investigated in a detailed interview with a physician. Resting auscultatory BP was measured three times after 5 min of seated rest with a mercury sphygmomanometer (Uniteq, São Paulo, Brazil). This procedure was repeated in two visits, and mean BP of the six measures was calculated (4, 5). Body weight and height were measured (Filizola S.A, Personal, Campo Grande, Brazil), and BMI calculated. Chronotype status was confirmed with the Horne and Ostberg's questionnaire (16). Presence of target-organ damage and possibility of secondary hypertension were assessed through a detailed screening, including blood and urine analyses (5). ECG at rest and during maximal exercise test were analyzed for exclusion of cardiac abnormalities (18).

Study design and experimental protocol

This was a randomized controlled trial designed to compare the effects of morning and evening aerobic training on clinic and ambulatory BP, as the primary outcomes, and on hemodynamic and autonomic mechanisms, as the secondary outcomes. For that the subjects were randomly allocated to one of three groups: morning training (MT: 7-9 a.m.), evening training (ET: 6-8 p.m.) or control group (C). Half of the subjects from the C group were randomly assigned to participate in the control intervention at 7-9 a.m. and the other half at 6-8 p.m. to assure the circadian exposition. These specific time periods were chosen because they overlap the morning increase (7-9.a.m.) and the evening decrease (6-8.p.m.) of BP (19). In addition, acute post-exercise hypotension has been reported to be different between exercises conducted at these specific time periods (10). Thus, these aspects suggest that the times chosen are more likely to reveal any possible effect of time of day on training responses.

Randomization for the groups was conducted by chance, employing a blocking method. Every three subjects who entered the study drew a number from a bag to determine their groups: MT, ET or C. Then, the subject who took the C group did a new raffle to be allocated in either the morning or evening to perform the control intervention. In the next three subjects' randomization block, the subject sorted for the C group performed the control intervention in the other time of day. This process was supervised by a blinded researcher. Interventions in all groups (MT, ET and C) occurred 3 times per week for 10 weeks, and were supervised by a bachelor in physical education. After this period, all subjects were reevaluated (complete flowchart can be seen in supplementary files S1).

Initial and final evaluations were composed by: 1) two maximal cardiopulmonary exercise tests conducted in a random order and separated by at least 3 days: one in the morning (7-9.a.m.) and one in the evening (8-10.p.m.); and 2) two resting cardiovascular evaluations

conducted in the same day, the first in the morning (7-9.a.m.) and the second in the evening (6-8.p.m.), and at least 3 days after the last maximal exercise test. Final evaluations were initiated 3-4 days after the last training session.

Before all evaluations, the subjects were instructed to avoid physical efforts and alcoholic beverages for the previous 24 h, and to take their anti-hypertensive medication as usual. Laboratory temperature was kept between 20-22ºC and the windows were uncovered assuring luminosity as a time-clue for circadian adjustments (20).

For the maximal cardiopulmonary exercise tests, subjects were instructed to have a light meal two hours before. The tests were conducted on a cycle ergometer, initiating with a 3-min warm up at 30 W, followed by 15 W increases every minute until the subjects were unable to maintain 60 rpm. ECG and VO_2 were continuously measured and BP was measured every 2 min.

For the resting cardiovascular assessments, subjects were instructed to arrive at the laboratory after an overnight fast for the evaluation at 7-9a.m., and with at least 4 h fasting for the evaluation at 6-8p.m. Thirty minutes before the assessments, the subjects received a standardized meal (two cereal bars: approximately 148 Kcal, with 84% carbohydrate, 8% protein and 7% fat each; and 50 ml of juice: approximately 27 Kcal with 100% carbohydrate). Then, they rested in the seated position for a total of 40 min. ECG, beat-by-beat BP and breath-by-breath respiratory signals were registered from minutes 10 to 20 for autonomic evaluation. Auscultatory BP, HR, and cardiac output (CO) were measured in triplicate between minutes 20 and 40. In addition, after the evening assessments, an ambulatory BP monitor was positioned on the subjects' non -dominant arm and was removed after 24 hours of recording.

Intervention

The training groups (MT and ET) performed progressive aerobic training only on cycle ergometer (CEFISE, Biotec 2100, Campinas, Brazil). Over the first four weeks of training, exercise duration increased from 30 to 45 min. From the fifth week, intensity increased progressively every two weeks from the HR at the anaerobic threshold to the HR 10% below the respiratory compensation point. This training protocol has shown to decrease BP and improve cardiovascular autonomic regulation in hypertensives (21). Training intensity was set up based on the maximal cardiopulmonary exercise test executed at the same time of day as the training sessions. During the training sessions, HR was continuously monitored (Polar A3tm, Kempele, Finland), and workload was adjusted to achieve the target HR. The subjects from the C group performed stretching exercises for 30 minutes. All subjects were instructed to keep the same routine throughout the study, and not to participate in any other regular exercise program.

Measurements

During the maximal cardiopulmonary exercise tests, ECG was continuously registered (EMG System do Brazil, EMG, 030110/00B, São Paulo, Brazil) and auscultatory BP was measured with a mercury column (Uniteq, São Paulo, Brazil). Oxygen uptake (VO_2) was measured by a metabolic cart (CPX Ultima, Med Graphics, Minnesota, USA), and analyzed in averages of 30s. Anaerobic threshold and respiratory compensation point were determined in accordance with Skinner & McLellan's criteria (22) by two different evaluators, and a third one was consulted to solve discrepancies.

During resting cardiovascular evaluations, the same experienced researcher, who was not blinded to the study group, made all auscultatory BP measurements using a mercury column (Uniteq, São Paulo, Brazil). ECG (EMG System do Brazil, EMG 030110/00B, São Paulo, Brazil) was continuously obtained and HR registered. CO was estimated by the indirect Fick

method of CO_2 rebreathing technique (23) using a metabolic cart (CPX Ultima, Medical Graphics Corporation, Minnesota, USA) as previously reported (10). Stroke volume (SV) and SVR were calculated: SV=CO/HR and SVR=Mean BP/CO. The coefficients of variation of these measures in our laboratory are 8.9% for CO, 12.7% for SVR, and 11.1% for SV. As BP, HR, and CO were assessed in triplicate, the averages of these values were used for analyses.

Cardiovascular autonomic modulation was assessed by the spectral analysis of HR and BP variability. R-R intervals measured by ECG, beat-by-beat BP obtained by photoplethysmography (Finometer, Finapres Medical System, Arnhem, Netherlands), and breath-by-breath respiratory signal assessed by a thoracic piezoelectric belt (UFI, Pneumotrace2, Morro Bay, USA) were continuously registered for 10 min through a data acquisition system (Windaq, Dataq Instruments, Akron, Ohio, USA) with a sampling rate of 500 Hz per channel. These signals were exported to the software for analysis (Heart Scope II, v. 1.3.0.1, A.M.P.S. LLC, New York, USA). HR and BP variability was assessed by autoregressive analysis carried out in stationary segments of 300 beats. Cardiac sympathovagal balance was represented by the ratio between low and high frequency components of the HR variability (LF/HF) and vasomotor sympathetic modulation by the total variance of systolic BP variability (TV_{SBP}). The oscillatory components of the time series were modeled by the Levinson-Durbin recursion and the model order was chosen according to Akaike's criterion (24), as previously described by the Task Force (25). Cardiac spontaneously baroreflex sensitivity (cBRS) was assessed using the sequence technique as previously describe (26).

Ambulatory BP was recorded every 15 min for 24 hours through an oscillometric device (Spacelabs 90207, Spacelabs, Inc., Redmond, Washington, USA). All subjects were instructed to avoid exercise and to keep similar daily routines during both initial and final evaluations. Only records with more than 85% of successful measures were analyzed. Data were averaged across time to provide the following measures: 24-hour (all measurements); awake (all

measurements taken while the subjects reported to be awaked); and asleep (all measurements taken while the subjects reported to be sleeping).

Statistical analysis

Considering a medium effect size (ES) (Cohen's f of 0.30) for clinic systolic BP, a power of 0.80 and an α of 0.05 for a between -within ANOVA with 3 groups, the minimal sample size required for this study was 30 subjects (i.e. 10 per group) (G*Power v. 3.1.9.2, Universität Kiel, Germany). For the other variables, posteriori power analyses were conducted, and a power above 0.80 was also found for almost all analyses (22 analyses); except for asleep and 24h systolic BP (β=0.75 or 0.57, respectively), awake diastolic BP (β =0.65), diastolic BP measured at the morning evaluation (β=0.77), and HR, diastolic BP and TV_{SBP} measured at the evening evaluation (β=0.77, 0.39 and 0.05, respectively).

As this study intended to compare morning and evening training efficacy and not efficiency, only data from the subjects who complete at least 75% of the intervention sessions were analyzed (i.e. non-intention to treat analysis).

The normality of data for each group was checked by Shapiro-Wilk test (IBM SPSS for windows, Illinois, USA). When a normal distribution was not observed, data were natural log-transformed (ln) and normality was achieved. The homogeneity among the groups was tested by Levene's test (IBM SPSS for windows, Illinois, USA).

Data analysis was separately applied for each assessment period (7-9.a.m. and 6-8.pm.). A two-way between-within ANOVA (3 x 2) was employed, considering group (MT, ET, and C) as the between factor and study phase (initial vs. final) as the within factor. Post-hoc comparisons were made using the Newman-Keuls test (Statsoft, Statistic for windows, USA). ANCOVAs analyses considering initial values as covariate were also employed but as results were similar to the ANOVAs, they were not shown. For all analyses, $P \leq 0.05$ was set as

significant and data are shown as mean±standard deviation. As a complementary analysis for clinic BP, the effects sizes (ES) between the groups responses at final evaluation (Final values) were calculated using the Cohen's d, and were classified as small (ES≤0.49), medium (ES 0.50-0.79) or large (ES≥0.80) (27).

RESULTS

A total of 210 subjects were interviewed, and 88 signed the consent to participate and underwent the preliminary exams. Twenty-one did not fulfill the study criteria, and an additional 11 dropped out during the initial evaluation. Therefore, 56 subjects were randomized into the groups (MT=18, ET=18, C=20). During the interventions, 3 subjects from each training groups dropped out. Therefore, 50 subjects (MT=15, ET=15 and C=20) finished the study and had their data analyzed (Complete flowchart in supplementary files – Fig. S1).

Subjects' characteristics

The groups were well matched for age, anthropometrics, rest BP, chronotype, comorbidity, and anti-hypertensive drugs (Table 1). Adherence to training sessions was high and similar among the groups (MT = 95.3±4.3, ET = 96.9±4.4, and C = 95.7±4.2%, p =0.43).

Exercise intensity was similar throughout the MT and ET (first training session - MT = 103.7±5.4 vs. ET = 102.6±4.9 % of HR of anaerobic threshold, P=0.87; and last training session - MT = 90.4±3.3 vs. ET = 89.2±6.2 % of HR of respiratory compensation point, P=0.63). Absolute mean values of HR and workload throughout the training sessions were also similar between MT and ET (MT = 117±9 vs. ET = 124±15 bpm, P=0.20 and MT = 61±15 vs. ET = 57±13 Watts, P=0.32).

Weight did not change in neither group throughout the study (MT = 88.0±12.3 vs. 87.1 ±12.0; ET = 89.1±14.9 vs. 89.4±14.3; and C = 88.2±15.9 vs. 88.4±15.7 kg, P=0.23).

VO_2peak increased significant and similarly after the MT and ET at both, morning and evening tests, and it did not change after the C (morning tests: MT = 21.4±3.2 vs. 23.1±3.4; ET = 21.4±3.4 vs. 23.0±4.6; and C = 21.1±4.3 vs. 21.0±4.0, $ml.kg^{-1}.min^{-1}$, P =0.05; and evening tests: MT = 22.2±3.2 vs. 24.5±3.9; ET 21.0±4.1 vs. 23.3±3.8; C = 21.7±4.3 vs. 21.7±2.9 $ml.kg.min^{-1}$, P =0.03).

Clinic and ambulatory blood pressure

All results of clinic BP are shown in the Figure 1. For the morning evaluation, systolic BP decreased after MT and ET, and did not change after C. Only the decrease after ET was different from C and greater than MT. The ES for ET vs. C was medium (-0.63, CI = -1.03 to +0.07). For the evening evaluation, systolic BP decreased only after the ET, and this decrease was significantly different than MT and C. The ESs for ET vs. C and ET vs. MT were medium (-0.50, CI = -1.17 to +0.19; and -0.61, CI = -1.33 to +0.13, respectively). At both, morning and evening evaluations, diastolic BP decreased only after ET, but these reductions were not different from C. The ESs for ET vs. C at both, morning and evening evaluations were small (-0.36, CI = -1.04 to +0.34 and -0.29, CI = -0.97 to +0.41, respectively).

Ambulatory systolic BP did not change in any of the three groups whether presented as 24-hour, awake or asleep averages. Likewise, awake diastolic BP also did not change. In contrast, 24-hour and asleep diastolic BPs decreased only after ET, and these decreases were significantly different from MT and C (Figure 2).

Hemodynamics and cardiovascular autonomic

All hemodynamic and autonomic variables are presented in the table 2 where significance levels are also shown. For morning evaluations (7-9a.m.), mean BP decreased only after ET, and this reduction was greater than after C and MT. CO did not change in any group,

while SVR decreased after ET and MT, but only the decrease after ET was different from C. SV increased only after ET, and the response was different from after C, while HR decreased similarly after MT and ET, with both being different from after C. LF/HF measured after ET and MT were lower than after C. TV_{SBP} increased after C and decreased only after ET, with responses after MT being different from and C, and responses after ET different from C and MT. cBRS increased after MT and ET, with both increases being different from after C, and the increase after ET greater than MT.

For the evening evaluations (6-8p.m), mean BP decreased only after ET, and this response was different than after C and MT. CO did not change in all groups, while SVR diminished only after ET and this response was different than after C and MT. SV increased only after ET and this response was different than after C, while HR decreased after MT and ET but only HR response after ET was different from after C. LF/HF and TV_{SBP} did not change in any group. cBRS measured after ET was higher than after MT and C.

DISCUSSION

The main findings of the present study were that, in treated hypertensive men, only aerobic training performed in the evening produced clinic and ambulatory hypotensive effects. In addition, this hypotensive effect of evening exercise was accompanied by reductions in SVR and TV_{SBP} and increases in cBRS.

After MT, only systolic BP assessed in the morning evaluation decreased significantly in comparison with the initial values. However, this response was not different from after C, indicating that this decrease in BP cannot be considered as a real hypotensive effect of MT. Additionally, the ES of this comparison was really small (-0.09 vs. C, Figure 1, panel b). Finally, as can be seen in figure 3 (panels a and b), only 53 and 20% of the subjects responded to MT with a decrease in SBP above 4.7 mmHg (i.e. the minimal detectable change calculated

based on resting BP measurements) for morning and evening evaluations, respectively. On the other hand, clinic systolic BP decrease observed after ET in both evaluations, morning and evening, were significantly different from C and also from MT, showing a real hypotensive effect of the ET. In addition, decrease of systolic BP after ET presented medium ES (-0.63 vs. C, Figure 1, panel b), and individual data shown in Figure 3 demonstrate that most of the subjects (60% for evening assessment) decreased systolic BP above the minimal detected change after ET. Interestingly, only ET produced a significant decrease in 24-hour and asleep diastolic BP, and these responses differed from C and MT, also showing a real ambulatory hypotensive effect of ET. Based on these results, the present study showed that only ET decreased clinic and ambulatory BP in treated hypertensive men.

The systolic/diastolic clinic BP decreases observed after ET were -5±6/-3±3 in the morning evaluations and -8±7/-4±3 mmHg in the evening evaluations. In addition, the magnitude of 24-hour and asleep diastolic BP decreases observed in the present study were -3±5 and -3±4 mmHg, respectively. These magnitudes might seem small at first, but they are within those reported in previous meta-analysis for aerobic training in hypertensives [i.e. clinic systolic/diastolic BP decreases of -8 (-11 to -6)/-5 (-7 to -3) mmHg, 24-hour diastolic BP decrease of -3 (-4 to -2) mmHg, and asleep diastolic BP decrease of -2 (-2 to -1) mmHg] (6, 8).

An intriguing result of the present study was the absence of BP reduction after MT. Few studies in literature reported the time of day at which training was conducted. In our literature search, only two studies reported the exact time of day of training, in one of them the subjects trained in the morning (28) and in the other, part of the subjects trained in the morning and the other part in the evening (29). Both studies did not report BP decrease after training, showing previous evidence of the lack of hypotensive effect with training in the morning. The reasons for the absence of hypotensive effect after MT are not clear, but a possible explanation may be the use of anti-hypertensive drugs. Previous study with animals found no additional decrease

in BP when aerobic exercise was combined with anti-hypertensive treatment in comparison with medication treatment alone (30). In addition, the hypotensive effects of training are supposed to be lower when BP levels are lower (6, 8). Anti-hypertensive drugs present their greatest activity until ~3 hours after their ingestion (31). In the present study, all subjects took medications in the morning and only approximately 50% of them also took medications in the evening. Thus, all subjects in the MT went to training sessions under the greatest activity of anti-hypertensives, while only some subjects were under this greatest effect at the ET. Then, it is possible to suppose that the concomitant action of medication might have blunted the hypotensive effect of aerobic training when training sessions were performed in the morning. However, these are only hypotheses that should be tested with an appropriate study design.

The absence of decrease in clinic diastolic BP and in awake BP might also be unexpected. However, the effects of aerobic training on clinic diastolic BP is usually lower when compared to systolic BP since many studies included in meta-analysis have not reported any diastolic hypotensive effect of aerobic training (6, 8). Concerning, awake BP, the same rational regarding the use of anti-hypertensives might be employed since all subjects were under anti-hypertensive effects during the daytime; which might have mitigated the hypotensive effect of both training regimens. Actually, some previous studies with treated hypertensives also did not find reduction in ambulatory BP in treated hypertensives (32).

Regarding hemodynamic and autonomic results, as expected, at both time evaluations (morning and evening), BP reductions induced by evening training were accompanied by a reduction in SVR (15). Among the possible mechanisms for reduced SVR, a reduction in sympathetic activity after aerobic training has been reported (33). In accordance, the current study observed a decrease in vasomotor sympathetic modulation, assessed by TV_{SBP} (34). The new contribution of the present study was to show that these effects, i.e. the decrease of SVR and sympathetic vasomotor modulation as well as the increase of cBRS were more evident

after the aerobic training performed in the evening. It is interesting to note that a previous study reported that autonomic changes precede BP decrease induced by training in hypertensives rats (35), which may explain why MT have not produce a decrease in BP despite its effects on autonomic variables.

As expected, both trainings did not change CO, but decreased HR (15) which was accompanied by a slightly change in LF/HF, especially in morning assessments. Previous studies (36, 37) have also observed HR decrease after training accompanied by small changes in LF/HF, and explanations for not observing greater effects on HR variability is mainly the fact that this assessment reflects cardiac autonomic modulation and not activity (25). In addition, the presence of anti-hypertensive treatment is also a possible explanation since some anti-hypertensives drugs, widely used in the current sample, such as angiotensin receptor type I blockers (47% of the subjects) and angiotensin-converting enzyme inhibitors (40% of the subjects), may have a chronic effect on HR variability (38) that might have masked the effect of training. It is interesting to observe that HR decrease was accompanied by an increase in cBRS, as previously reported (33). However, the novelty of the current study was to show that this effect on cBRS is more evident when training is conducted in the evening than in the morning. In addition, as cBRS was increased while HR decreased in the presence of BP maintenance after MT or decrease after ET, these results suggest that baroreflex set point was changed by training, especially after ET, which should be investigated in the future.

As clinical perspective, the greater hypotensive effect induced by ET may have clinical importance, since a decrease of 3 mmHg in clinic systolic BP has been associated with an 8% lower risk for stroke and 5% for coronary heart disease mortality (39). In addition, ambulatory BP and especially asleep BP are related to end-target damage and cardiovascular risk in hypertension (40). Thus, by decreasing asleep BP, ET may reduce hypertension consequences. Nevertheless, it is also interesting to highlight that cBRS is independently associated with

mortality (41). Thus, as ET and MT increased cBRS, training at both times of day may have benefits on cardiovascular risk. The present results extend previous knowledge by showing that the clinical benefits of aerobic training in treated hypertensive men are especially greater when training is conducted in the evening. Therefore, training at this time of day may be especially recommended for those hypertensives who need a more intensive treatment, such as those with higher cardiovascular risk, resistant hypertension or non-dipper hypertension.

Although the present study has not revealed a significant hypotensive effect of MT, some variables related to BP control (such as HR, LF/HF, $lnVT_{SBP}$ and cBRS) improved in the MT, suggesting that training at this time of day might also bring cardiovascular benefits. In addition, a non-significant decrease in BP in comparison to C was observed suggesting that MT may decrease BP with a greater stimulus. As discussed before, experimental data suggest that autonomic adaptations precede the hypotensive effects of aerobic training (35); thus, a longer period of training may lead to a significant reduction of BP after MT. In addition, a greater weekly frequency and/or a higher intensity or duration may produce a quicker adaptation leading to BP reduction after MT. These hypotheses should be tested in the future.

We acknowledge that we limited our investigation to sedentary middle-aged men, excluded extreme chronotypes and limit training to 10 weeks. Thus, it is necessary caution when generalizing the results to other conditions to life-long exercisers, extreme morningness or eveningness chronotypes, other aged groups or women. There is evidence that BP responses to training (42) vary between genders. As this is the first study investigating time of day influence on BP, only men were studied and future studies should investigate women. Another potential confounder might be the anti-hypertensive medication use since some drugs are more likely to impact on exercise responses than others. Along this line, subjects receiving beta-blocker and non-dihydropyridine calcium channel blockers did not participate in the study due to the direct effect of these drugs on HR variability assessed by spectral analysis. We are unable

to say how subjects using these medications would have responded to either morning or evening training. Evaluators not blinded to interventions may be considered a limitation; however, the same highly experienced evaluator performed all measurements, which minimizes the limitation (43). VO_2 peak was measured with cycle ergometer tests and greater values may be achieved with treadmill tests. However, as training was conducted exclusively with cycling, testing with this ergometer is better to establish exercise intensity and to reveal the effects of training. Despite exercise and diet may change body composition, and consequently, decrease BP, diet was not controlled but the subjects were instructed to keep their eating habits. As their weight did not change, alterations in body composition are unlikely to have impacted the results. Subjects´ physical activity was not monitored, but they were instructed to keep their daily routines throughout the study. Training exclusively in the morning or the evening was applied. As time of day has influenced training responses, future studies should investigate whether these effects are also different with training schedules combining training at different times of day (within the same day or in different days of the week). Finally, power analyses revealed low power (<0.50) for DBP and TV_{SBP} evaluated at evening, increasing the chance of type II error for these variables. However, these variables did not reveal significant differences from C.

In conclusion, in treated hypertensive men, aerobic training performed in the evening decreased clinic and ambulatory BP, due to reductions in vasomotor sympathetic modulation and systemic vascular resistance. In addition, aerobic training conducted at both, morning and evening, increased baroreflex sensitivity with a greater effect after evening training.

Abbreviation list

MT - morning training group

ET - evening training group

C – control group

BP - blood pressure

HR – heart rate

SVR – systemic vascular resistance

CO – cardiac output

SV – stroke volume

LF/HF - low to high frequency ratio of the HR variability

TV_{SBP} - total variance of systolic BP variability

cBRS - cardiac spontaneous baroreflex sensitivity

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Conflicts of interest

There is no conflict of interest, this study had no endorsement by ACSM. All data are original, and none of them were fabricated or manipulated.

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Supplemental Digital Content Requirements

Figure S1. Study flowchart: Enrollment, Randomization, Interventions and Follow-up.

Figures legends

Figure 1. Clinic blood pressure assessed at the initial and the final evaluations in the three groups: aerobic training in the morning (MT = Δ ─), aerobic training in the evening (ET = ▲ ─) and control (C = □ ----): **Morning assessments (7-9a.m) -** Panel a - systolic blood pressure (SBP); b – Effect size and confidence interval between groups of SBP; c - diastolic blood pressure (DBP); d – Effect size and confidence interval between groups of DBP. **Evening assessments (6-8p.m.) -** Panel e - SBP; f – Effect size and confidence interval between groups SBP; g - DBP; h – Effect size and confidence interval between groups of DBP. * different from initial evaluation in the same group (P≤0.05); # different from the C group at the same evaluation (P≤0.05); † different from MT at the same evaluation (P≤0.05).

Figure 2. Ambulatory blood pressure at the Initial and the Final Evaluations in the Three Groups: aerobic training in the morning (MT = Δ ─), aerobic training in the evening (ET = ▲ ─) and control (C = □ ----): Panel a – 24 hour systolic blood pressure (24 h SBP); b - 24 hour diastolic blood pressure (24 h DBP); c – Awake SBP; d – Awake DBP; e – Asleep SBP; and f – Asleep DBP. Data = mean ± standard deviation .* different from initial evaluation in the same group (P≤0.05); # different from the C groupat the same evaluation (P≤0.05); † different from MT at the same evaluation (P≤0.05).

Figure 3. Individual data of clinic systolic blood pressure (SBP) responses in the Morning Training (MT), Evening Training (ET), and Control (C) groups: Dashed line (------) as representative of minimal detectable change of SBP (-4.7 mmHg). Panel a – effect after MT evaluated at 7-9a.m.; b – effect after MT evaluated at 6-8p.m.; c – effect after ET evaluated at 7-9a.m.; d – effect after ET evaluated at 6-8p.m.; e - effect after C evaluated at 7-9a.m.; and f – effect after C evaluated at 6-8p.m.

Table 1. Baseline characteristics of the three groups: aerobic training in the morning (MT), aerobic training in the evening (ET) and control (C).

Variables	MT	ET	C
N	15	15	20
Age (years)	51±8	49±8	50±9
Height (m)	1.72±0.06	1.70±0.10	1.71±0.06
Weight (kg)	87.4±12.1	89.5±14.9	88.2±15.9
Body mass index (kg/m^2)	29.6±3.1	30.7±3.3	29.9±4.3
Chronotype (score)	52±6	56±3	53±4
Hemodynamics			
Resting systolic BP (mmHg)	135±9	132±6	133±12
Resting diastolic BP (mmHg)	92±7	89±5	88±8
Type of anti-hypertensive therapy			
One – no. (%)	11(73)	10(67)	14(70)
Two or more – no. (%)	4(27)	5(33)	6(30)
Anti-hypertensive drugs			
Angiotensin II receptor blockers – no. (%)	8(53)	7(47)	9(45)
Angiotensin-converting enzyme inhibitors – no. (%)	6(40)	7(47)	7(35)
Dihydropyridine calcium channel blockers – no. (%)	4(27)	3(20)	4(20)
Diuretics – no. (%)	4(27)	5(33)	3(15)

Values are mean±standard deviation; body-mass index (the weight in kilograms divided by the square of the height in meters);

Table 2

Table 2. Hemodynamic and cardiovascular autonomic variables evaluated in the morning (7-9.a.m.) and in the evening (6-8.p.m.) at the initial and the final evaluation in the three groups: Aerobic training in the morning (MT); Aerobic training in the evening (ET); and control (C).

		7-9.am.					6-8.p.m.				
	Group	Initial	Final	p (group)	p (phase)	p (interaction)	Initial	Final	p (group)	p (phase)	p (interaction)
MBP (mmHg)	MT	104±8	102±8	0.77	0.008	0.05	104±8	104±7	0.60	0.04	<0.001
	ET	103±7	99±6*#†				107±7	100±9*#†			
	C	102±7	103±6				103±7	104±8			
CO (l/min)	MT	4.4±0.7	4.4±0.6	0.59	0.57	0.79	4.7±1.1	4.8±1.0	0.67	0.57	0.51
	ET	4.6±0.6	4.7±0.5				4.8±1.1	4.9±1.0			
	C	4.6±0.8	4.5±0.8				4.7±0.8	4.6±0.9			
SVR (U)	MT	24±4	22±2*	0.81	0.003	0.03	23±5	23±5	0.45	0.17	0.03
	ET	23±3	21±3*#				23±5	20±4*#†			
	C	23±4	23±4				23±4	24±4			
SV (ml)	MT	62±15	65±12	0.65	0.13	0.04	62±15	65±16	0.57	0.05	0.02
	ET	64±9	68±11*#				63±14	70±18*#			
	C	64±12	62±11				63±12	61±13			
HR (bpm)	MT	74±7	71±7*#	0.18	0.02	0.002	77±7	74±8#	0.59	0.16	0.007
	ET	73±8	69±9*#				76±10	71±9*#			
	C	75±10	77±9				77±8	79±10			
ln LF/HF $_{R-R}$	MT	0.9±1.1	0.7±1.0#	0.58	0.54	0.004	0.7±1.2	0.6±1.2	0.16	0.66	0.36
	ET	0.7±1.1	0.4±1.0#				0.4±1.0	0.0±1.2			
	C	0.7±0.9	1.2±0.9				0.8±1.3	1.0±0.9			
ln TV_{SBP}	MT	3.2±0.8	3.2±0.6#	0.15	0.72	0.001	3.4±0.8	3.2±1.0	0.35	0.73	0.43
	ET	3.0±0.6	2.7±0.6*#†				3.1±0.9	3.1±0.6			
	C	3.1±0.6	3.5±0.7*				3.4±0.6	3.4±0.6			
ln cBRS	MT	1.4±0.5	1.8±0.5*#	0.04	0.03	0.002	1.4±0.6	1.5±0.4	0.18	0.86	0.02
(ms/mmHg)	ET	1.7±0.4	2.1±0.5*#†				1.6±0.7	1.9±0.4#†			
	C	1.6±0.4	1.4±0.5				1.6±0.6	1.4±0.5			

MBP mean blood pressure, CO cardiac output, SVR systemic vascular resistance, SV stroke volume, GR hear rate, TV total variance, LF/HF low to high frequency ratio of RR-interval variability, cBRS cardiac baroreflex sensitivity. Values are mean±standard deviation;

* different from initial evaluation in the same group (P≤0.05); # different from the C group at the same evaluation (P≤0.05); † different from MT at the same evaluation (P≤0.05).

Figure1

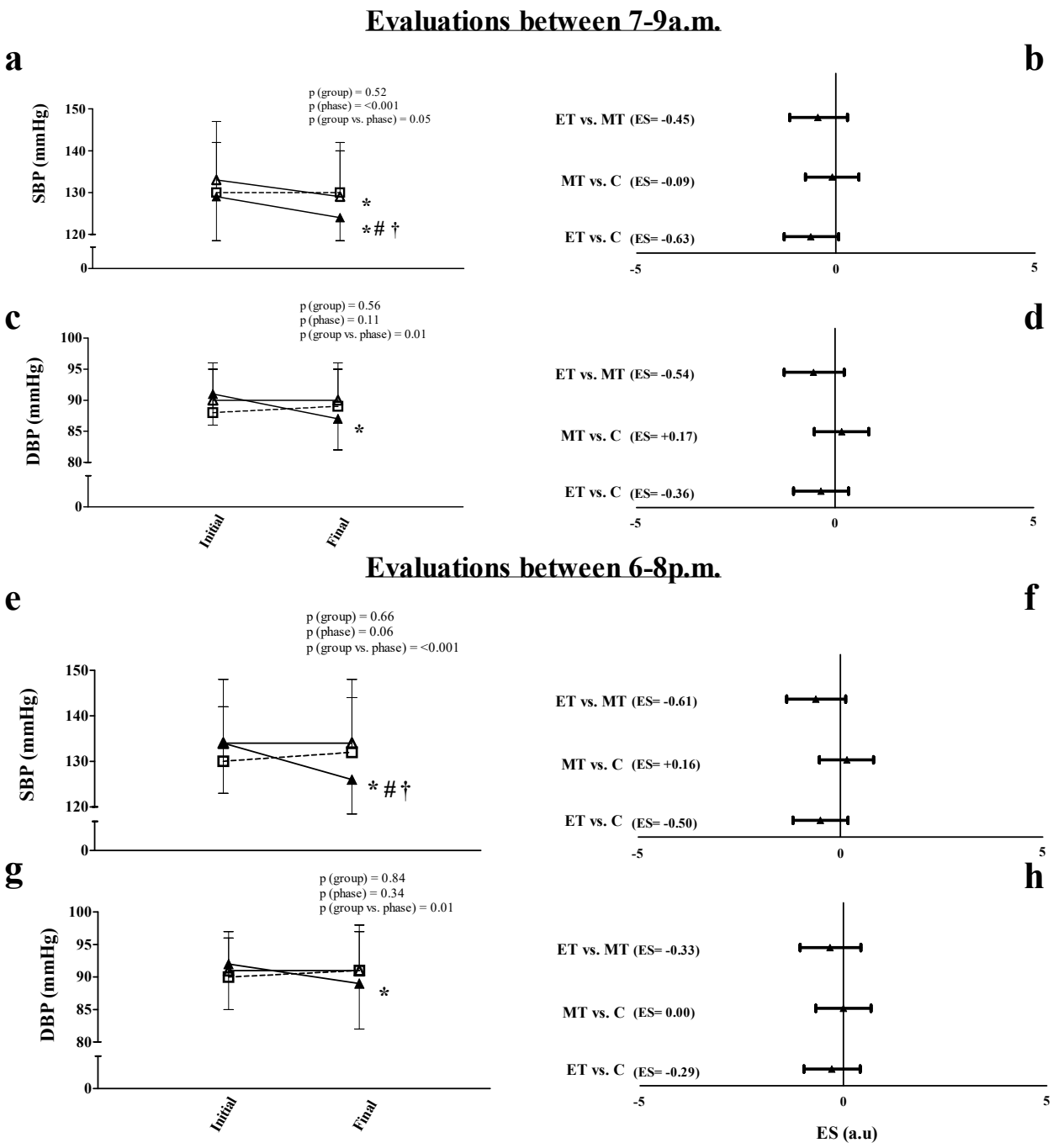

Evaluations between 7-9a.m.
a
b
p (group) = 0.52
p (phase) = <0.001
p (group vs. phase) = 0.05
SBP (mmHg)
150
140
130
120
0
*
*# †
ET vs. MT (ES= -0.45)
MT vs. C (ES= -0.09)
ET vs. C (ES= -0.63)
-5
0
5
c
d
p (group) = 0.56
p (phase) = 0.11
p (group vs. phase) = 0.01
DBP (mmHg)
100
95
90
85
80
0
*
Initial
Final
ET vs. MT (ES= -0.54)
MT vs. C (ES= +0.17)
ET vs. C (ES= -0.36)
-5
0
5
Evaluations between 6-8p.m.
e
f
p (group) = 0.66
p (phase) = 0.06
p (group vs. phase) = <0.001
SBP (mmHg)
150
140
130
120
0
*#†
ET vs. MT (ES= -0.61)
MT vs. C (ES= +0.16)
ET vs. C (ES= -0.50)
-5
0
5
g
h
p (group) = 0.84
p (phase) = 0.34
p (group vs. phase) = 0.01
DBP (mmHg)
100
95
90
85
80
0
*
Initial
Final
ET vs. MT (ES= -0.33)
MT vs. C (ES= 0.00)
ET vs. C (ES= -0.29)
-5
0
5
ES (a.u)

Figure 2

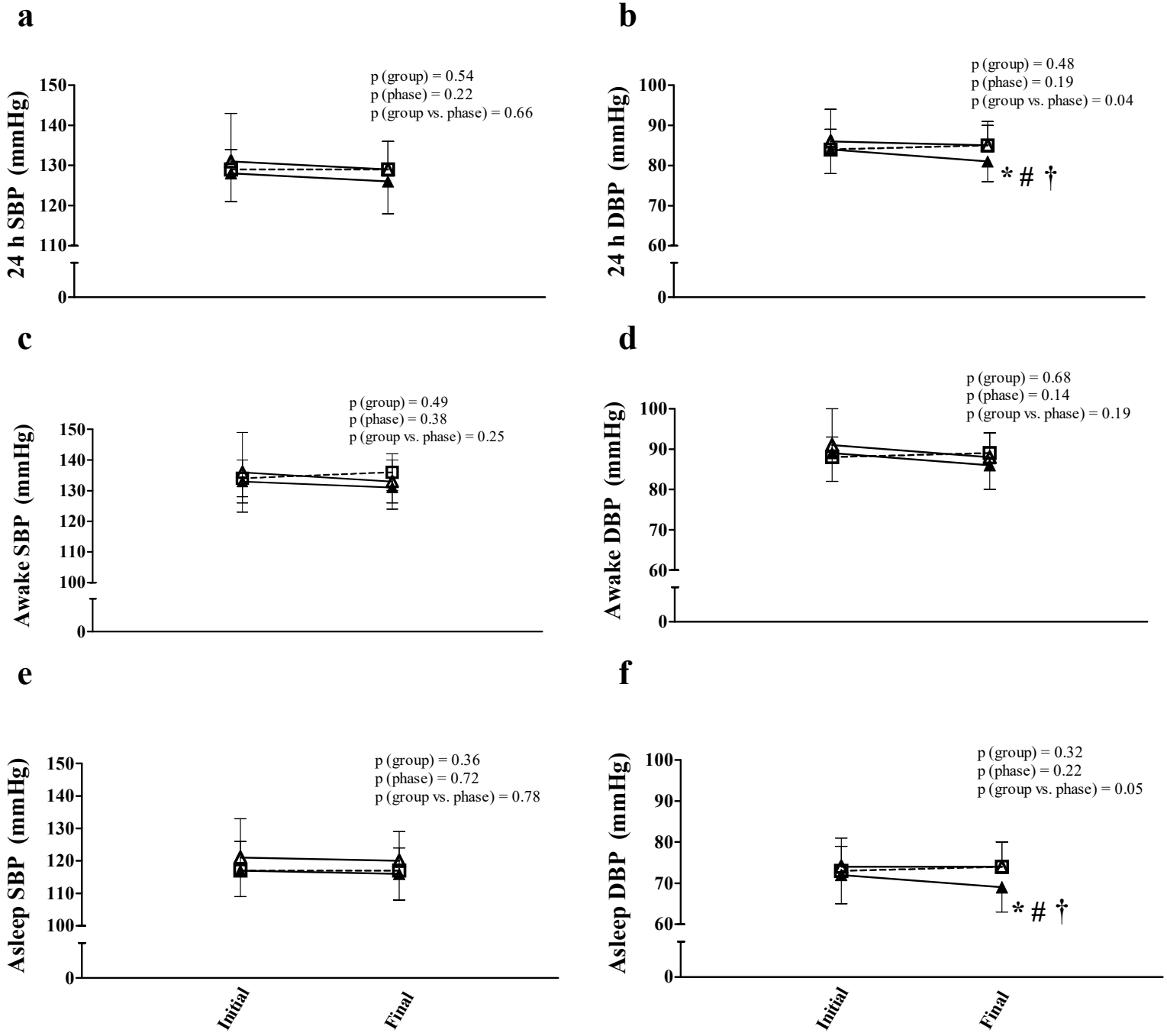
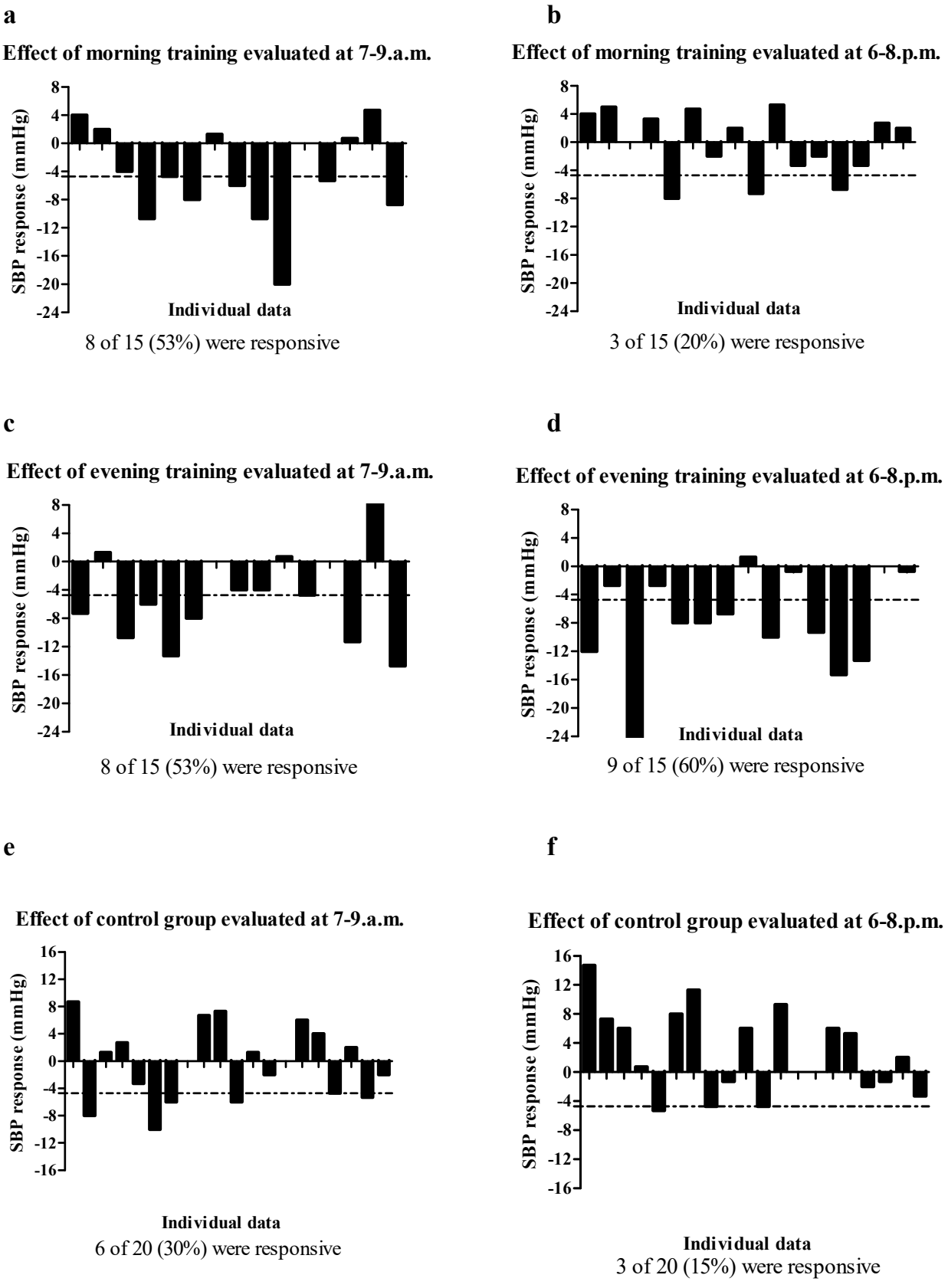

a
24 h SBP (mmHg)
150
140
130
120
110
0
p (group) = 0.54
p (phase) = 0.22
p (group vs. phase) = 0.66
b
24 h DBP (mmHg)
100
90
80
70
60
0
p (group) = 0.48
p (phase) = 0.19
p (group vs. phase) = 0.04
* # †
c
Awake SBP (mmHg)
150
140
130
120
110
100
0
p (group) = 0.49
p (phase) = 0.38
p (group vs. phase) = 0.25
d
Awake DBP (mmHg)
100
90
80
70
60
0
p (group) = 0.68
p (phase) = 0.14
p (group vs. phase) = 0.19
e
Asleep SBP (mmHg)
150
140
130
120
110
100
0
p (group) = 0.36
p (phase) = 0.72
p (group vs. phase) = 0.78
Initial
Final
f
Asleep DBP (mmHg)
100
90
80
70
60
0
p (group) = 0.32
p (phase) = 0.22
p (group vs. phase) = 0.05
* # †
Initial
Final

Figure 3


a
Effect of morning training evaluated at 7-9.a.m.
SBP response (mmHg)
8
4
0
-4
-8
-12
-16
-20
-24
Individual data
8 of 15 (53%) were responsive
b
Effect of morning training evaluated at 6-8.p.m.
SBP response (mmHg)
Individual data
3 of 15 (20%) were responsive
c
Effect of evening training evaluated at 7-9.a.m.
SBP response (mmHg)
Individual data
8 of 15 (53%) were responsive
d
Effect of evening training evaluated at 6-8.p.m.
SBP response (mmHg)
Individual data
9 of 15 (60%) were responsive
e
Effect of control group evaluated at 7-9.a.m.
SBP response (mmHg)
16
12
8
4
0
-4
-8
-12
-16
Individual data
6 of 20 (30%) were responsive
f
Effect of control group evaluated at 6-8.p.m.
SBP response (mmHg)
Individual data
3 of 20 (15%) were responsive