Effects of intense aerobic exercise and/or antihypertensive medication in individuals with metabolic syndrome

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Running head: Exercise interactions with antihypertensive medication.

ABSTRACT
We studied the blood pressure lowering effects of a bout of exercise and/or antihypertensive medicine with the goal of studying if exercise could substitute or enhance pharmacologic hypertension treatment. Twenty-three hypertensive metabolic syndrome patients chronically medicated with angiotensin II receptor blocker antihypertensive medication underwent 24-hr monitoring in four separated days in a randomized order; a) after taking their habitual dose of antihypertensive medicine (AHM trial), b) substituting their medicine by placebo medicine (PLAC trial), c) placebo medicine with a morning bout of intense aerobic exercise (PLAC+EXER trial) and d) combining the exercise and antihypertensive medicine (AHM+EXER trial). We found that in trials with AHM subjects had lower plasma aldosterone/renin activity ratio evidencing treatment compliance. Before exercise, the trials with AHM displayed lower systolic (130±16 vs 133±15 mmHg; P=0.018) and mean blood pressures (94±11 vs 96±10 mmHg; P=0.036) than trials with placebo medication. Acutely (i.e., 30 min after treatments) combining AHM+EXER lowered systolic blood pressure (SBP) below the effects of PLAC+EXER (-8.1±1.6 vs -4.9±1.5 mmHg; P=0.015). Twenty-four hour monitoring revealed no differences among trials in body motion. However, PLAC+EXER and AHM lowered SBP below PLAC during the first 10 hours, time at which PLAC+EXER effects faded out (i.e., at 19 PM). Adding exercise to medication (i.e., AHM+EXER) resulted in longer reductions in SBP.
than with exercise alone (PLAC+EXER). In summary, one bout of intense aerobic exercise in the morning cannot substitute the long-lasting effects of antihypertensive medicine in lowering blood pressure, but their combination is superior to exercise alone.

ClinicalTrials.gov Identifier: NCT03019796

Key words: antihypertensive medication; aerobic exercise; metabolic syndrome X; ambulatory blood pressure.

INTRODUCTION

The observation that blood pressure (BP) declines below resting levels after exercise is more than a century old. 1 Exercise, seems to reduce BP in labile 2 and resistant hypertension patients. 3 Although general guidelines are available the precise therapeutic exercise prescription to treat hypertension has not yet developed. This is likely due to uncertainties regarding magnitude/duration of the BP lowering effects of a bout of exercise. Nevertheless, recent studies are helping to define the most efficient exercise intensity and mode to acutely lower BP. Although high intensity exercise results in accumulation of heat and metabolites which could induce vasodilation 4, some studies sustain that exercise intensity does not affect the magnitude of post-exercise blood pressure lowering effect. 5-7 In contrast, others studies show that intense exercise results in larger post-exercise BP reductions than moderate intensity aerobic exercise 8-10 and that the lowering effects last longer. 10-12 Regarding the exercise mode, it seems that a combination of resistance and endurance exercise is also effective on reducing BP 13 although its actions do not last as long as after aerobic exercise in elderly individuals with essential hypertension. 14 Furthermore, some authors are proposing frequent short bouts of exercise during the day instead a single bout of exercise to spread the BP lowering effects 15,16 although the compliance with this exercise regime is unclear.

While more is known about exercise effects on lowering BP, the prevalence of antihypertensive medication use increases 17 with angiotensin II receptor type 1 blockers (ARB) leading the increase. These medicines are prescribed in conjunction with medical advice to reduce salt intake, body weight, quitting smoking, and engagement in regular exercise. 18 However, little is known about the interactions between intense aerobic exercise and ARB antihypertensive medicines. If both therapies have additive effects, exercise could lower the need for medication or even fully substitute it in mild hypertensive individuals, as already suggested. 19 However, continuous 24-hr ambulatory BP (i.e., ABP) analysis was not conducted in this experiment, and it is unclear if the effects of exercise on restraining blood pressure persisted during the night. The information derived from 24-hr tracking of BP is important, because it has been revealed that ABP is a more sensitive risk predictor of coronary events and stroke than occasional office BP measurement. 20

Literature analyzing the combined effects of antihypertensive medication and exercise is scarce and current studies do not provide a full factorial design to analyze the separated and combined effects of exercise and medication. Our objective is, by using that design, to determine if exercise could substitute or enhance pharmacologic hypertension treatment with ARB. The hypothesis is that ARB medicines will act additively with intense exercise resulting in larger and more prolonged BP lowering effects. We chose to study a population of hypertensive metabolic syndrome (MetS) patients because hypertension is their most frequent component 21 and it is strongly associated with the risk of suffering cardiovascular diseases. 22
METHODS

Participants and preliminary testing. Twenty-three subjects (58.5±6.5 years) with a BMI of 31±4.7 kg m\(^{-2}\) and a resting systolic/diastolic BP measured after 48-hr of placebo of 134±15/79±9 mmHg were recruited for this study. Fourteen participants had isolated high systolic BP, 5 isolated high diastolic BP and 4 of them had both pressures in the hypertension range according to metabolic syndrome thresholds (i.e., SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg). All subjects were diagnosed with MetS based on accumulation of 3 or more risk factors, were physically active and medicated with angiotensin II type 1 receptor blockade (ARB) drug during at least 1 year prior to the onset of the study (Table 1 and Table 2). Participants’ ARB prescriptions differed in dosage and active ingredient (Table 2), but ARB’s were the only antihypertensive medications used by participants. Individuals signed a witnessed, informed consent of the protocol approved by the local Hospital’s Ethics Committee in accordance with the declaration of Helsinki. Subjects underwent medical physical examination and completed a maximal cardiopulmonary graded exercise test (GXT) on an electronically braked cycle ergometer (Ergoselect 200, Ergoline, Germany) with ECG monitoring (Quark T12, Cosmed, Italy) to screen for myocardial diseases. The highest heart rate value (HR\(_{\text{peak}}\)) obtained during the GXT was used to set exercise intensity. This is a sub-study part of a larger clinical trial evaluating the effects of 4-month exercise training in hypertensive metabolic syndrome individuals.

Experimental design. Using a repeated-measures crossover, double-blind, placebo randomized design, subjects completed four trials, separated by at least two weeks. Random order sequence was generated using the macro feature of Excel (Microsoft Office) without repetition. Random assignment was set in blocks of six subjects per trial to balance trial order. The team physician performed the randomization and concealed it to the rest of the team until data analysis completion. Upon study enrollment, participants turned in their ARB prescription drugs to the team physician. Masking consisted on embedding participants’ prescription drug into larger capsules. Identical capsules were used for placebo but filled with 50 mg of dextrose. Prescription and placebo capsules were placed into plastic pill bottles wearing an alphanumeric code only known to the physician. Every third day participants turned their research pill bottle to the physician and he returned the container to them, allowing him to provide participants with either placebo or ARB prescription. Participants were instructed not to alter their habitual medicine dosage (number of pills ingested per day) during the whole study. The team physician did not participate in data collection and thus was not able to reveal treatments to the rest of the research team. During the first trial, subjects filled out an activity/diet diary which was replicated for the 24-hr prior and during all trials. Subjects were instructed to refrain from stimulants that could altered their BP (alcohol, tobacco, coffee, tea, or herbal extracts). Main outcomes were 24-hr body motion and BP, measured in four trials, a) after taking their habitual dose of angiotensin II-block antihypertensive medicine (AHM trial), b) substituting their medicine by placebo medicine (PLAC trial), c) placebo medicine with a morning bout of intense aerobic exercise (PLAC+EXER trial) and d) combining the exercise and antihypertensive medicine (AHM+EXER trial). Trials commenced at 8 AM in the same day of the week for each subject. After 20 min of lying in a quiet, temperature-controlled room (22±1 ºC and 25±6% humidity) BP was measured using ambulatory BP device.

Following, in the trials with exercise (PLAC+EXER and AHM+EXER trial) subjects pedaled during 43 min alternating high (90% of HR\(_{\text{peak}}\)) and low intensities (70% HR\(_{\text{peak}}\)) since data supports the effectiveness of this exercise mode to lower BP in the short and long term. In the non-exercise trials (AHM and PLAC trials), subjects remained resting supine during those 43 min. In the placebo trials (PLAC and PLAC+EXER trials) subjects’ prescription was substituted by identical capsules filled with dextrose. Placebo was taken during the 48-hr prior to the trials, because this time exceeds the half-life for the angiotensin II receptor 1 blockade medications in all subjects (Table 2). After exercise (or rest) subjects returned to the gurney and after 20 min of rest, BPs were assessed again.
to measure the acute effects of the treatments. Then, a blood sample was drawn from an arm vein (i.e., 10 cc) and the ABP and body motion devices were affixed to the subject’s non-dominant arm and wrist, respectively.

**Ambulatory BP (ABP).** Three ABP validated devices based on oscillometry with step deflation were used in all trials (Oscar2, Suntech, Morrisville, NC, USA). ABP of adequate cuff size for each participant were placed in the non-dominant arm. After 20 min of undisturbed supine rest on a gurney, brachial blood pressures (systolic and diastolic; SBP and DBP) were measured in triplicate. The first reading was discarded and the mean of the two following readings with a coefficient of variation < 10% were averaged, with additional readings performed if required. Upon leaving the laboratory, the ABP device was programmed to take a measurement every 20 min during daytime (9:30 AM-23:00 PM) and every 60 min at nighttime (23:00 PM-6:00 AM). Subjects were instructed to relax arm and maintain elbow extension during the blood pressure collection and to abstain from vigorous exercise but do not avoid physical activity of their daily routine. ABP data were downloaded (AccuWin Pro v3.4 software) filtered as previously described and averaged hourly. Participants’ data were excluded from analysis if there were more than 20% missing ABP readings in 24 hours, or more than three consecutive hours of missing data. The duration of the BP reduction was determined by plotting the hourly accumulated reductions from PLAC trial and identifying when that line crossed the 95% lower confident limit. The magnitude of BP reduction was calculated averaging BP over the time period determined in each case (daytime, nighttime and 24-hr).

**Blood analysis.** The 10-cc blood sample was separated into two tubes, one containing EDTA and another with a clot activator (Vacutainer®; Becton-Dickinson, USA) to, upon centrifugation, obtain plasma and serum, respectively. Plasma was analyzed for renin activity (radioimmunoassay; SR300, Stratec biomedical, Germany) and serum for aldosterone concentration (chemiluminescence immunoassay; LiaisonXL, DiaSorin, Italy). Aldosterone to renin activity ratio was calculated to gauge subject compliance with the antihypertensive/placebo medicine.

**Body posture and motion measurements.** A wrist-worn activity monitor (Polar Electro, Kempele, Finland) were placed in the non-dominant wrist to measure the time spent in sedentary (sitting and lying-down) and active (standing and walking) modes during each trial.

**Statistical analysis.** Normality was evaluated by the Shapiro-Wilk test. Sample size calculation revealed that 18 subjects per group were sufficient to detect a treatment effect in systolic ABP assuming a power of 0.8 and an α error probability of 0.05. Daytime, nighttime and 24-hr average data for ABP, HR, MAP and body motion, as well as plasma hormone data were analyzed using one-way (treatment) repeated-measures ANOVA. Acute BP effects (baseline vs. 30-min post-treatment) were analyzed using two-way (treatment and time) repeated measures ANOVA. After a significant F test, pairwise differences were identified using post hoc Tukey’s HSD. Data is presented as mean±SD unless otherwise noted. Effect size (ES) is based on the following criteria, ≥0.70 large effect, 0.30-0.69 moderate effect and ≤0.30 or small effect. All analyses were performed with SPSS version 21 (Chicago, IL). Statistical significance level was set at P≤0.05.

**RESULTS**

**Exercise responses.** The bout in the trials involving exercise (i.e., PLAC+EXER and AHM+EXER) was set at identical average workload (88.4 ± 29.6 vs 88.4 ± 29.1 W; P=0.468) eliciting similar exercise heart rates (127 ± 12 vs 126 ± 12 bpm; P=0.128) an oxygen consumption rates (17.6±2.8 vs 17.7±2.7 mL O2/kg/min; P=0.890) which corresponded to 5.1±0.6 METs.

**Acute BP responses.** At baseline, before exercise BP in trials under the effect of ARB medication (AHM and AHM+EXER) were in conjunction lower in systolic (130±16 vs 133±15 mmHg; P=0.021, ES=0.21) and mean BPs (94±11 vs 96±10 mmHg; P=0.032, ES=0.19) than trials with placebo medication (PLAC and PLAC+EXER). Thirty min after treatment, systolic BP was in all trials lower than PLAC (P=0.033, ES=0.50; Figure 2). Mean arterial pressure was lower after AHM (94±13 mmHg, P=0.038, ES=0.30) and AHM+EXER (91±10 mmHg; P=0.005, ES=0.67) in comparison to PLAC (97±10
mmHg). The reductions in systolic BP 30-min after treatments, were significant in the PLAC+EXER (-4.9±1.5 mmHg, P=0.003, ES=0.34) and AHM+EXER (-8.1±1.6 mmHg, P=0.001, ES=0.56) trials. Of note, the reduction in SBP was larger in AHM+EXER than in PLAC+EXER (P=0.049, ES=0.35; Figure 2). However, SBP remained unchanged in the non-exercise trials (PLAC and AHM). Only AHM+EXER reduced DBP (77±9 vs 74±8 mmHg; P=0.029, ES=0.30) and mean arterial pressure (95±10 vs 90±9 mmHg; P=0.001, ES=0.44) in comparison to baseline. Heart rate significantly increased after both exercise trials (82±11 and 81±10 beats·min⁻¹, for AHM+EXER and PLAC+EXER, respectively) compared to resting trials (61±8 and 60±7 beats·min⁻¹, AHM and PLAC, respectively).

**Ambulatory BP responses.** ABP responses are depicted in Figure 3. During daytime (9:30 AM-23 PM), SBP was significantly reduced below PLAC (137±14 mmHg) in PLAC+EXER (132±14 mmHg, P=0.006, ES=0.30), AHM (132±15 mmHg, P=0.020, ES=0.33) and AHM+EXER (130±15 mmHg, P=0.002, ES=0.47). DBP was significantly reduced below PLAC (81±8 mmHg) in PLAC+EXER (79±9 mmHg, P=0.027, ES=0.25), AHM (78±9 mmHg, P=0.004, ES=0.34) and AHM+EXER (78±9 mmHg, P=0.003, ES=0.37). MAP was also significantly reduced below PLAC (99±9 mmHg) during PLAC+EXER (97±10 mmHg, P=0.006, ES=0.30), AHM (96±10 mmHg, P=0.005, ES=0.36) and AHM+EXER (95±10 mmHg, P=0.002, ES=0.45). During nighttime (23 PM-6 AM), SBP was reduced in AHM below PLAC and PLAC+EXER trials (116±13 vs 123±19 and 122±16 mmHg; P=0.007, ES=0.44) without differences in diastolic and mean BPs among trials. When averaging 24-hr ABP data collection, SBP were lower than PLAC in AHM (ES=0.39) and the AHM+EXER (ES=0.40) trials (132±15 vs 126±13 and 126±14 mmHg, respectively; both P=0.005).

**Ambulatory heart rate responses.** During the 12-hr after exercise heart rate was elevated in the PLAC+EXER and AHM+EXER trials in comparison to PLAC (76±10 and 79±10 vs 72±10 bpm; P=0.005) and AHM (72.0±8.9 bpm; P=0.006). However, during nighttime there were no differences between trials.

**Duration and magnitude of the ambulatory systolic BP reductions.** Compared to PLAC, AHM+EXER reduced systolic BP until 4 AM by -6.3±7.3 mmHg (P=0.001, ES=0.42) which was the highest reduction of all trials. PLAC+EXER reduced SBP below PLAC until 19 PM by -4.9±4.7 mmHg (P=0.000, ES=0.37). AHM reduced SBP below PLAC by -5.0±6.4 mmHg (P=0.001, ES=0.35) being the effect enhanced at nighttime. During daytime no differences existed between PLAC+EXER and AHM (-0.5±7.1 mmHg, P=0.735) but starting at 23 PM, the reduction in BP with AHM was higher than PLAC+EXER (-5.3±8.9 mmHg, P=0.009, ES=0.38).

**Antihypertensive medicine uptake compliance.** The angiotensin concentration to renin activity ratio decreased in 96% of the subjects when angiotensin II receptor 1 blockade medicine was taken (AHM and AHM+EXER trials) in comparison to when placebo was provided, evidencing compliance with the experimental treatments (Figure 1).

**Body posture and motion measurements.** For AHM+EXER, PLAC+EXER, AHM and PLAC, subjects spent 77.3, 77.9, 77.3 and 75.6 % of 24-hr standing or walking (active body motion), while 22.7, 22.1, 22.7 and 24.4 % of 24-hr in the sitting or recumbent sedentary mode. There were no significant differences between trials.

**DISCUSSION**

Exercise have been proposed as an alternative therapy to antihypertensive medication in individuals with mild hypertension due to its post-exercise BP lowering effects. However, reports of the magnitude/duration of exercise BP lowering effects in comparison to the effects of antihypertensive medicine in the same subjects, are scarce the literature. To our knowledge, we are first to provide 24-hr ambulatory BP data in primary hypertensive subjects comparing the effects of angiotensin-targeted antihypertensive medicine (AHM) to a bout of intense exercise. Our results suggest that in the mid-term (10-hr after treatment; Figure 4) the effects of exercise are similar to AHM on lowering BP in hypertensive MetS subjects. However, exercise BP lowering effects weaken at night (Figure 4) while medication effects persisted during 24-hr. It has been reported that high
systolic BP during the night, is more strongly associated with cardiovascular mortality and morbidity than daytime values. Thus, our results dispute the notion that morning exercise could substitute AHM to prevent cardiovascular morbidity. Although exercise could be part of the non-pharmacological therapy in people with hypertension, it does not seem to be substitute for careful and closely monitored antihypertensive drug treatment.

Increased activation of the renin-angiotensin-aldosterone system is associated with the development of hypertension. ARB inhibits angiotensin II production, reducing plasma aldosterone concentration which by feedback stimulates renin production. Thus reduced aldosterone/renin ratio was used as a test of drug intake compliance in our subjects when comparing PLAC and AHM trials (Figure 1). In addition, exercise activates renin production, which raises aldosterone concentrations. Plasma renin activity is stimulated at maximum when exercise is combined with ACEI. Figure 1 shows that ARB effects on lowering the aldosterone/renin ratio are independent of the actions of exercise, being a useful index of drug compliance in both situations (rest and exercise).

Combination of exercise and AHM. It is unclear if exercise may interfere or potentiate the actions of antihypertensive medicines in chronically medicated hypertensive individuals. A study reports that high-intensity aerobic exercise aggravates the arterial stiffness of hypertensive subjects that are not medicated. On the other hand, aerobic exercise training is able to reduce BP in subjects with resistant hypertension medicated with three antihypertensive agents. In heart failure patients, the combination of exercise and ACEI had similar effects than doubling the dose of ACEI on improving endothelial function. Our data show that exercise, rather than interfere with antihypertensive medication, it helped in its BP lowering actions. The additive effects on lowering systolic BP appeared soon after exercise was completed (Figure 2) and extended during day-time beyond the effects of exercise alone (Figure 4) to return to the levels of the AHM trial at night.

On the other hand, some authors suggest that antihypertensive medication may potentiate the post-exercise reduction in BP. Following this hypothesis, two studies have investigated the interactions between angiotensin converting enzyme inhibitors (i.e., Captopril and Fosinopril) and exercise. Like ours, those studies used the same group of hypertensive subjects in a crossover placebo-controlled design but subjects underwent only two trials; exercise with placebo medication and exercise with antihypertensive medication. Since the magnitude of BP decline was similarly in both trials, authors conclude than antihypertensive medications do not potentiate the actions of exercise. Those studies did not use 24-hr ABP and only the magnitude but not the duration of the actions was assessed. Furthermore, they could not compare to a control situation where exercise was not performed. In our complete, four trials design we found a reduction in BP from PLAC to the exercise trial (PLAC+EXER) and further reductions when AHM was added to the exercise (AHM+EXER). This pattern, took place in the short-term (Figure 2) and those differences remained in the 24-hr long term (Figure 4).

Mechanisms of action of exercise and AHM. The novel finding of our study is the potentiation of ARB lowering of blood pressure by concomitant aerobic exercise. The fact that exercise lowers BP below the actions of ARB could be interpreted to suggest that exercise and medication acted upon different tissues/mechanisms. The opposite could be argued when observing that a bout of exercise does not lower BP as much in medicated as in non-medicated hypertensive patients. Expectedly, AHM will deflate the exercise-induce BP reductions, suggesting that they act throughout the same mechanism/tissue in which vasodilation was already maximized by AHM. Careful conducted studies from Halliwill and co-workers reveal that post-exercise vasodilation takes place in previously recruited skeletal muscle with no contribution from the splanchnic and renal vascular beds; some contribution from skin vasodilation and negligible contribution from the exercise-induced reductions in plasma volume. The large increase in skeletal muscle blood flow with exercise may allow AHM to reach more muscle, reducing the angiotensin vasoconstriction effects in those previously low perfused tissues. This seems to be the scenario in a study in which the increase in forearm post-exercise conductance, upon lower body
negative pressure challenge, was better maintained when subjects were medicated with ARB.\textsuperscript{43} Thus, it is possible that both AHM and exercise could vasodilate skeletal muscle upon different, additive mechanisms (e.g., histamine vs angiotensin receptors).

Our morning, high intensity interval exercise bout did not extend its BP lowering actions during the night. A recent meta-analysis agrees with our results reporting that aerobic exercise training blood lowering actions, do not extend during the night period in hypertensive or normotensive adults.\textsuperscript{44} It is possible, that the post-exercise blood lowering effect is mediated by reducing sympathetic nerve activity which is naturally lowered during sleep. Heart rate, an indirect index of the sympathetic activation, was similarly low in all trials during the night. In contrast, pharmacokinetic studies demonstrate that ARB medication (Lorsatan, Candesartan, Valsartan and Telmisartan) supplied in doses similar to the ones prescribed to our participants lowers BP during 24-hr\textsuperscript{45} which included the night, which suggests that ARB act beyond the effect of sleep on reducing sympathetic nerve activity. We subjected our hypertensive middle-aged subjects to near the maximal tolerable dose of exercise that could be completed in a bout (43 min) without undue fatigue\textsuperscript{46} and minimal attrition (i.e., 15%\textsuperscript{47}). Even so, this exercise bout was less efficacious than AHM on 24-hr BP control. However, it is a promising hypothesis that spreading the exercise dose during the day could prolong the exercise actions\textsuperscript{15,16} to maybe reach the duration of AHM.

Limitations and conclusions. There are some limitations in our study. In an attempt to perform an ecological study, we did not prescribed the AHM treatment but recruited subjects with a primary care doctor prescription of angiotensin II receptor type 1 blocker medicine. Subjects underwent a medicine washout period of 48-hr which exceeded half-life of all prescriptions (Table 2). The reduction in the aldosterone-to-renin activity ratio in the placebo trials (Figure 1) suggests that medicine effects were at least partially removed. Nevertheless, it is possible that 48-hr medicine withdrawal was insufficient to completely washout the antihypertensive effects of the ARB medication. Thus, we do not discard that some drug effect could still be present accounting for the low BP values shown in the placebo trials (Figure 2) for these hypertensive Mets\textsuperscript{11} individuals. An alternative study design is to initiate borderline hypertensive participants with antihypertensive medication. In this design, since drug is given for research not medical purposes, drug withdrawal could be extended for weeks. Our local ethical committee deemed that to avoid potential adverse cardiovascular events, 48-hr medicine withdrawal was a safe period. On the other hand, the advantage of using subjects own prescribed medications is that we could gauge the real-life substitutive potential of exercise. Another limitation is that the study does not assess the mechanism or locus of the AHM and/or post-exercise induced lowering of BP. The strengths of this study are its cross-over, double-blind randomized order design with a sufficient sample size to appropriately assess the efficacy of exercise and/or AHM on hypertension.

In conclusion, our data suggest that a morning bout of intense-prolonged aerobic exercise lowers BP in primary hypertensive subjects but, is not substitutive of angiotensin II receptor type 1 blocker antihypertensive medication at night, a time related to increased cardiovascular risk. Of novelty, this study reveals that an exercise bout potentiates the BP lowering actions of ARB antihypertensive medication mostly during the awakening hours.

Perspectives
Our data suggest that a morning bout of intense aerobic exercise (i.e., 43 min) lowers blood pressure to the levels elicited by angiotensin receptor blockers (ARB) medicine for 10 hours after exercise. However, the exercise effects weaken at night while ARB medication effects persisted during 24-hr. Elevated blood pressure at night, is strongly associated with cardiovascular mortality and thus morning exercise should not be viewed as substitutive of antihypertensive ARB treatment. Furthermore, combining participant’s habitual ARB dose with morning exercise prolongs the blood pressure lowering effect of exercise. Our data support that both therapies, ARB and exercise, could be used simultaneously without adverse interactions.
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REFERENCES


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**FIGURE CAPTIONS**

**Figure 1.** Individual blood aldosterone concentration to plasma renin activity ratio in the four trials, a) after taking their habitual dose of antihypertensive medicine (AHM trial), b) substituting their medicine by placebo medicine (PLAC trial), c) placebo medicine with a morning bout of intense aerobic exercise (PLAC+EXER trial) and d) combining the exercise and antihypertensive medicine (AHM+EXER trial). Data corresponds to 23 hypertensive metabolic syndrome patients. ‡ AHM+EXER lower than PLAC+EXER, P=0.013; ES=0.81. AHM was not significantly lower than PLAC, P=0.067; ES=0.59.

**Figure 2.** Acute response to the treatments in systolic BP at baseline (Pre) and 30-min after treatments while resting in a gurney (Post). Data are presented as mean±SEM. * Significantly lower than PLAC at that time point. † Significantly lower than PRE for that trial. ‡ Significantly lower than PLAC+EXER at that time point, all P<0.05.

**Figure 3.** Pattern of systolic and diastolic BP during daytime (9:30 AM-23 PM) and nighttime (23 PM-06 AM) for 23 hypertensive metabolic syndrome participants. Data are presented as mean±SEM. * Significantly lower than PLAC. ‡ Significantly lower than PLAC+EXER at those time points, all P<0.05.

**Figure 4.** Hourly accumulated reduction of SBP from PLAC with 95% confidence limits (dotted lines) with departure from the lower limit marked with an arrow indicating time of day at cessation of BP reduction from PLAC in that particular trial.

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Table 1. Anthropometric and metabolic syndrome factors of participants.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.5 ± 6.5</td>
</tr>
<tr>
<td>BMI (kg·m⁻²)</td>
<td>31.2 ± 4.7</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>106 ± 9</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>108 ± 17</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>157 ± 56</td>
</tr>
<tr>
<td>HDL-c (mg/dL)</td>
<td>47 ± 12</td>
</tr>
<tr>
<td>Resting SBP (mmHg)</td>
<td>134 ± 15</td>
</tr>
<tr>
<td>Resting DBP (mmHg)</td>
<td>79 ± 9</td>
</tr>
<tr>
<td>Years under ARB treatment</td>
<td>8.9 ± 5.3</td>
</tr>
</tbody>
</table>

Data are mean ± SD for 23 metabolic syndrome patients (17 men and 6 women). Blood pressures are the average of 3 consecutive measurements in the PLAC trial. ARB; angiotensin II receptor blockade antihypertension medicine.


Table 2. Angiotensin II receptor blockers use and pharmacokinetics data.

<table>
<thead>
<tr>
<th>Subjects (%) sample</th>
<th>Dose (mg/day)</th>
<th>Bio-availability</th>
<th>Half-life (h)</th>
<th>AT₁ affinity (nmol/L)</th>
<th>Tmax (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irbesartan 7 (30.5%)</td>
<td>200±77</td>
<td>70%</td>
<td>11-15</td>
<td>IC₅₀, 1.3</td>
<td>1.5-2.0</td>
</tr>
<tr>
<td>Valsartan 5 (21.7%)</td>
<td>150±50</td>
<td>25%</td>
<td>9</td>
<td>IC₅₀, 2.7</td>
<td>2</td>
</tr>
<tr>
<td>Telmisartan 3 (13%)</td>
<td>60±28</td>
<td>43%</td>
<td>24</td>
<td>Kᵢ, 3.7</td>
<td>0.5-1.0</td>
</tr>
<tr>
<td>Losartan 3 (13%)</td>
<td>50±25</td>
<td>33%</td>
<td>6-9</td>
<td>IC₅₀, 20</td>
<td>3-4</td>
</tr>
<tr>
<td>Candesartan 3 (13%)</td>
<td>12±5</td>
<td>42%</td>
<td>9</td>
<td>Kᵢ, 0.6</td>
<td>3-4</td>
</tr>
<tr>
<td>Olmbersartan 2 (8.7%)</td>
<td>40±20</td>
<td>26%</td>
<td>13</td>
<td>IC₅₀, 33</td>
<td>1-2</td>
</tr>
</tbody>
</table>

IC₅₀ is half maximal inhibitory concentration, Kᵢ inhibition constant (Kᵢ=IC₅₀/(1+[L]/Kᵢ)) where [L] is the concentration of the radioligand and Kᵢ is the dissociation constant. Tmax is the time to peak blood concentration. Pharmacokinetic data from Burnier, M., Circulation 103(6), 2001 and Barreras, A. and Gurk-Turner, C., Proc, 16(1), 2003.
Figure 1

Aldosterone / Plasma Renin activity (a.u.)

PLAC | AHM | PLAC+EXER | AHM+EXER

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Figure 2

SBP prior and after treatments (mmHg)

- PLAC
- AHM
- PLAC+EXER
- AHM+EXER

Pre Post Pre Post Pre Post Pre Post

* *† *‡

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Figure 3

Systolic Blood Pressure (mmHg)

Daytime
- PLAC
- AHM
- PLAC+EXER
- AHM+EXER

Nighttime
- PLAC
- AHM
- PLAC+EXER
- AHM+EXER

Diastolic Blood Pressure (mmHg)

Time of day

9:30, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 0, 1, 2, 3, 4, 5, 6
Figure 4

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