

Acute Effects of Dynamic Exercise and Nutritional Supplementation on Blood Pressure in Mildly Hypertensive Patients

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Abstract

Purpose: Previous studies have demonstrated that both exercise and the consumption of L-arginine can reduce blood pressure, presumably by the common pathway of nitric oxide-mediated vasodilation. This study compared the effects of exercise and L-arginine supplementation and their combination on BP in mildly hypertensive patients.

Method: Nine patients with mild hypertension performed 4 randomly ordered trials consisting of combinations of the consumption of either double-blind administration of a nutritional supplement containing L-arginine, vitamin E, and vitamin C, or an otherwise identical placebo either with or without a 25-min bout of aerobic exercise. BP was measured at baseline and every 30 min for 2 hr. The nutritional supplement was provided following the baseline BP measurement. In exercise trials, 25 min of cycle ergometry were performed following the 30-min BP measurement.

Results: There were no significant BP changes in the placebo + rest condition. For all three interventions (nutritional, exercise, nutritional + exercise) there was a significant ($p < 0.05$) decrease in systolic BP at 90 min (-13, -14, -13 mmHg) and 120 min (-13, -11, -13 mmHg). Diastolic BP decreased significantly at both 90 min and 120 min (-9 mmHg for both) in the combined intervention condition (nutritional + exercise). Mean arterial pressure was decreased at 90 min for all three intervention conditions (-8, -7, -9 mmHg). However, the only significant decrease in mean arterial pressure at 120 min was in the combined intervention condition (-9 mmHg).

Conclusion: On the basis of the outcome data at 120 min, it was concluded that the combination of exercise + nutritional supplementation with L-arginine, vitamin E, and vitamin C produce short-term reductions in BP that are significantly greater than no treatment or either intervention alone.

Key Words: *anti-oxidants, L-arginine, hypertension*

The development of cardiovascular disease is highly related to well-established risk factors, including hypertension, with one in four Americans being hypertensive. Exercise may be a useful tool

in the early detection of hypertension, in that those who are likely to develop fixed hypertension often have hyperdynamic blood pressure responses to exercise even when resting blood pressure is normal (1, 2). Exercise may also be an effective therapeutic strategy for patients with hypertension since both acute and chronic exercise are thought to help control blood pressure (3).

The reduction of arterial blood pressure after a single session of exercise, known as postexercise hypotension (PEH) (4), has been the topic of recent study (4–12) and has been reviewed recently (13). Apparently both aerobic and resistance exercise may induce postexercise reductions in blood pressure that persist for several hours. Although mechanistic studies are lacking, PEH is most likely attributed to a reduction in systemic vascular resistance, which may be secondary to or independent of nitric oxide mediated vasodilation during exercise (13).

Paralleling the observation of PEH, there has been recent interest in the supplemental use of various antioxidant vitamins and the amino acid L-arginine as part of the management of atherosclerotic disease (14). L-arginine, an amino acid that acts as the precursor to nitric oxide (NO) (15), has significant vasodilatory capacity (16). It improves blood flow by regulating vascular smooth muscle relaxation, and additionally by inhibiting platelet adhesion (14). The NO system plays a central role in the regulation of vascular tone, with failures of NO synthesis partially accounting for the increased vascular resistance that is observed in hypertension (14–16). Antioxidants, such as vitamins C and E, as well as the amino acid L-arginine, have been shown to enhance nitric oxide synthesis and improve endothelial vasomotor function (17).

Given that both exercise and dietary supplements may act by a NO-mediated pathway, the question arises as to whether these ac-

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tions are independent and/or potentially additive. Accordingly, the purpose of the present study was to compare the effects of exercise and L-arginine supplementation and their combination on blood pressure in mildly hypertensive individuals.

Methods

The subjects for the study were 9 volunteers (3 F, 6 M) who were participants in a university-based fitness program. Each participant was clinically stable and had a clinical diagnosis of hypertension. Seven were taking angiotensin conversion enzyme (ACE) inhibitors, 4 were taking calcium channel blockers, 7 were taking diuretics, and 6 were taking beta blockers. One subject with a new diagnosis of hypertension was not on medication. None of the subjects had documented coronary artery disease, prior myocardial infarction, symptoms suggesting angina pectoris, or a history of revascularization procedures. The subjects were instructed to take all medications as usual. The mean (\pm SD) resting systolic and diastolic blood pressures were $139 \pm 1 / 77 \pm 1$ mmHg, with a mean arterial pressure of 98 ± 1 mmHg.

Prior to the study, all subjects provided informed consent. The study had been approved by the University of Wisconsin-La Crosse Institutional Review Board. Each subject was studied during four randomly ordered and double-blind (for the nutritional supplement) sessions, performed at least 48 hours apart. Subjects were asked not to consume any food or drink for 2 hours prior to each testing session, and to refrain from alcohol intake for 24 hours prior to each testing session. None of the subjects used tobacco.

During all trials, blood pressure was measured by auscultation following 5 minutes of seated rest after the subject arrived in the laboratory. This initial BP was recorded as the 0-minute value for the trial. In each trial the subject consumed a nutritional supplement bar or a placebo bar immediately after the initial blood pressure measurement. Consumption of the bar required 5 minutes or less. Subsequent resting BP values were obtained at 30, 60, 90, and 120 minutes of each trial with the subject seated.

The active supplement was the medical food, Heart Bar[®], a registered trademark of Cooke Pharma (Belmont, CA). The active ingredient in the Heart Bar[®] is 3 grams of L-arginine, together with 250 mg of vitamin C and 200 IU of vitamin E. The placebo bar used in this study was provided by Cooke Pharma. It was identical to the Heart Bar[®] except that ingredients shown to have an effect on NO (including L-arginine and vitamins C and E) were removed.

During Trial 1, blood pressure was measured over a 2-hour period. This trial served as the control condition. After the 0-minute BP was obtained, the subject consumed a placebo bar. Blood pressure was again measured at 30, 60, 90, and 120 minutes of continuous seated rest.

Trial 2 consisted of active agent nutritional supplementation. The initial 0-value blood pressure was obtained. Immediately following this resting BP, the Heart Bar[®] was consumed. The BP was again measured during continuous seated rest at 30, 60, 90, and 120 minutes of the trial.

Trial 3 consisted of placebo and exercise. After the initial blood pressure was obtained, the subject consumed a placebo bar. Resting BP was measured again at 30 minutes. Immediately after this BP was obtained, the subject exercised on a cycle ergometer for 25 minutes. Exercise intensity was consistent with contemporary principles of exercise prescription and with the subject's usual exercise routine. The mean heart rate during the last 20 minutes of exercise was $73 \pm 5\%$ of each patient's maximal heart rate. During exercise, BP was measured at 10, 20, and 25 minutes. At the conclusion of the 25-min exercise session, a 5-min cooldown was allowed, after which a resting seated BP was measured. This BP served as the 60-min measurement. Additional resting BP was taken again at 90 and 120 minutes.

Trial 4 consisted of a combination of active nutritional supplementation + exercise. Immediately after the initial blood pressure was obtained, the subject consumed a Heart Bar[®]. Following the 30-min BP measurement, the subject exercised on a cycle ergometer for 25 minutes with the same power output as in Trial 3. After the 25-min exercise session, a 5-min cooldown was allowed and then resting seated BP was measured. This BP served as the 60-min measurement. Additional resting BP was recorded at 90 and 120 minutes.

Statistical analysis was performed using repeated-measures ANOVA for changes in SBP, DBP, and MBP from rest to 90 minutes (30 min postexercise) and 120 minutes (60 min postexercise), and for an interaction between nutritional supplementation and exercise. Alpha was set at ≤ 0.05 to achieve statistical significance. Tukey's post hoc tests were used to evaluate pairwise differences when justified by ANOVA.

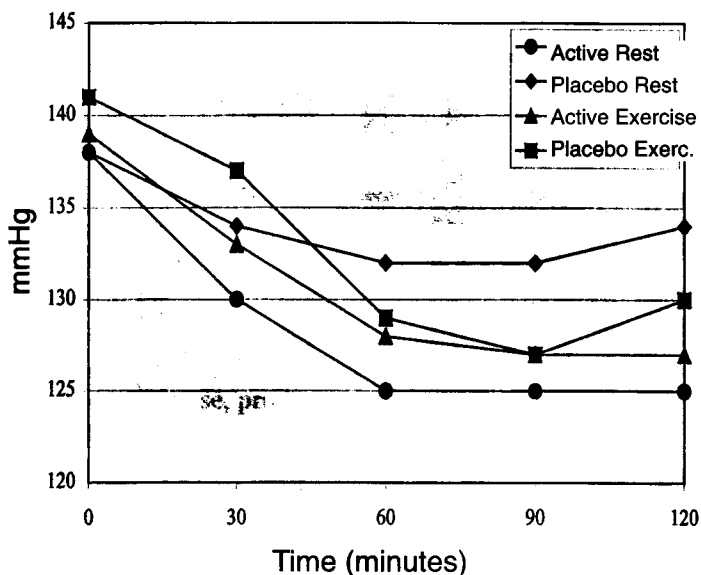
Results

SBP did not change significantly ($p > 0.05$) under the control condition (placebo + rest) at the 90- or 120-min time points of the study. For all three interventions (Heart Bar[®] + rest, placebo + exercise, Heart Bar[®] + exercise) there was a significant decrease in SBP from rest at the 90- and 120-min time points (Figures 1 and 4). There was a statistically significant interaction term in the ANOVA associated with the return toward baseline in the placebo + exercise trial (Figure 1).

DBP did not change significantly from rest in the placebo + rest, Heart Bar[®] + rest, or placebo + exercise trials at 90 or 120 minutes. However, DBP decreased significantly at rest at both 90 and 120 minutes in the combined intervention of Heart Bar[®] + exercise (Figures 2 and 4). There was a statistically significant interaction term in the ANOVA associated with the return toward baseline in the Heart Bar[®] + rest trial (Figure 2).

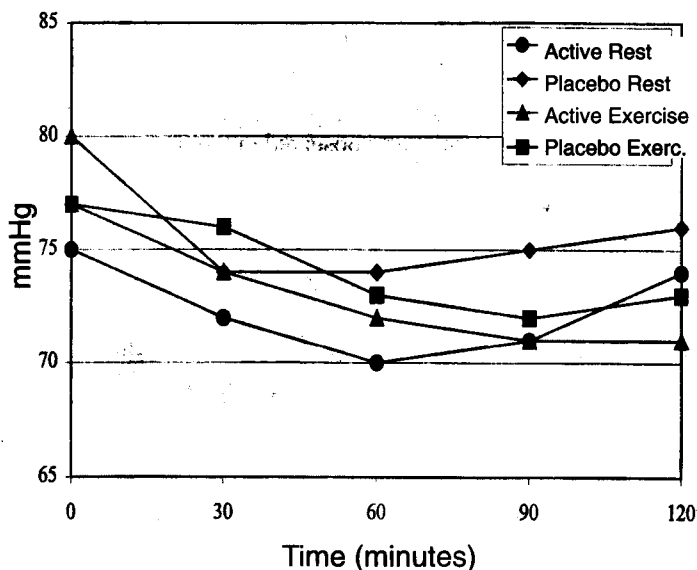
MAP was significantly decreased from rest at the 90-min time point for all intervention conditions (Heart Bar[®] + rest, placebo + exercise, Heart Bar[®] + exercise) compared to the placebo + rest trial, in which MBP was not changed. The only significant decrease in MAP from rest at the 120-min time point was in the combined intervention condition (Heart Bar[®] + exercise) (Figures 3 and 4).

Systolic Blood Pressure



◆ Figure 1 Serial changes in systolic blood pressure in relation to intervention. Note the recovery of SBP toward control values in the placebo + exercise trial.

Diastolic Blood Pressure



◆ Figure 2 Serial changes in diastolic blood pressure in relation to intervention. Note the recovery of DBP toward control values in the active + rest trial.

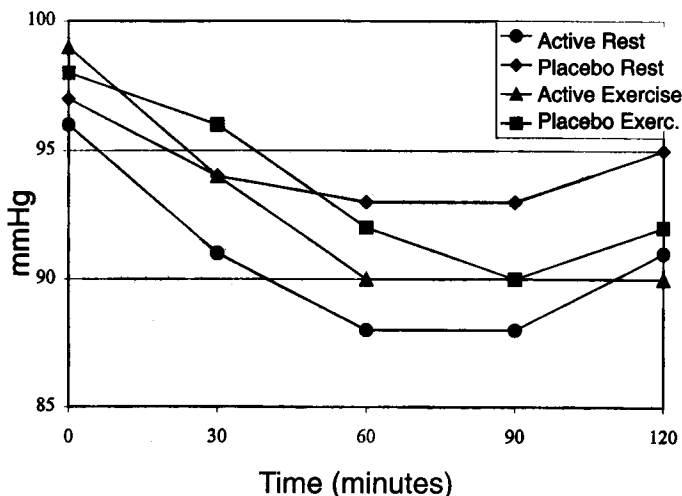
There was a statistically significant interaction term in the ANOVA associated with the return toward baseline in the Heart Bar® + rest and placebo + exercise trials (Figure 3).

Discussion

Submaximal aerobic exercise resulted in a significant reduction in SBP at 90 and 120 minutes (30 and 60 min postexercise). MAP was reduced at 90 minutes (30 min postexercise). This reduction is consistent with the PEH that has been observed in patients with hypertension in previous research (4–12). The amount of reduction in SBP (–11 mmHg), DBP (–4 mmHg), and MAP (–6 mmHg) at 120 minutes postexercise is of sufficient magnitude to be clinically significant. The reductions in BP in this study are of similar magnitude to those observed in both hypertensive and normotensive subjects for a period of 30 minutes after a graded exercise test (8). These findings are also consistent with the PEH observed for SBP at 60 minutes postexercise, and for DBP at 30 minutes postexercise in the study by Kaufman et al. (5). While the present study evaluated the acute effects of exercise on BP, several other studies suggest that PEH can be sustained for longer periods of time, including 90 minutes (9), 2 hours (11), and 3 hours (10) after exercise. In studies by Pescatello et al. (6, 7), PEH was sustained for 7 to 9 hours.

In contrast to these studies of PEH, Gilders et al. (18) evaluated the BP response of borderline hypertensive subjects over an 8-week control period, a 16-week endurance exercise conditioning period, and a 12-week deconditioning period. They demonstrated that exercise conditioning did not change ambulatory BP. How-

Mean Arterial Pressure



◆ Figure 3 Serial changes in mean blood pressure in relation to intervention. Note the recovery MAP toward control values between 90 and 120 minutes in the active-rest and placebo-exercise trials, and the maintenance of a reduced MAP in the active + exercise trial.

ever, in that study all blood pressures were measured on days when the subjects did not exercise, which may explain the lack of observed effects on PEH. Measurement on the day of exercise may account for differences in BP response in the present study.

The reduction in blood pressure after a single exercise session, as observed in our data, provides supporting evidence that exer-

cise can be an effective although short-acting therapy for individuals with hypertension. A recent review of intervention studies suggests that exercise training decreases BP in approximately 75% of hypertensive patients, with mean reductions in systolic and diastolic BP of 11 and 8 mmHg, respectively (3). These are largely comparable to the acute effects observed in the present data.

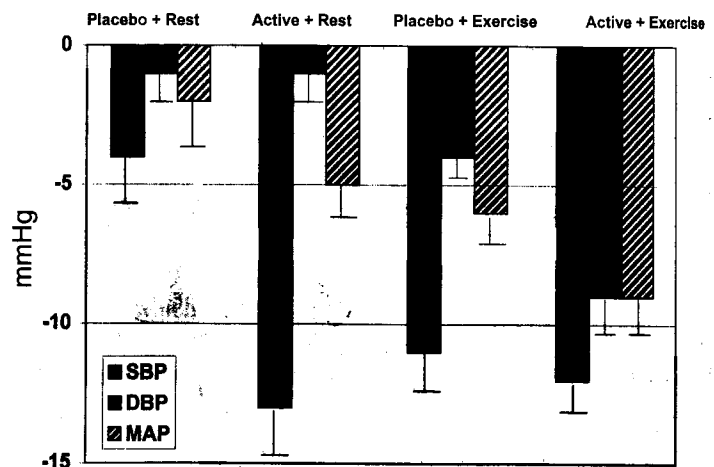
In this study, L-arginine and antioxidant vitamin supplementation resulted in a significant reduction in SBP at the 90- and 120-min time points in both the rest (-13 mmHg for both) and exercise trials (-11 mmHg for both). MAP in the Heart Bar® + rest condition showed a significant decrease in BP at 90 minutes (-8 mmHg), while the Heart Bar® + exercise condition showed a significant decrease at both the 90- and 120-min time points (-9 mmHg for both). These results are consistent with the concept that L-arginine acts as the precursor to NO (15), a potent vaso-dilator (16), while the antioxidants vitamins act to preserv nitric oxide activity.

Several studies (15, 19–21) have shown that hypertensive individuals have a defect in endothelium-regulated vascular relaxation. Panza et al. (22) demonstrated that the defect in the endothelial-derived NO system in hypertensive vessels is most likely *not* due to a decrease in the availability of L-arginine. These data suggest a defect in one or more signal transduction mechanisms from cell surface receptors for acetylcholine and neurokinins, which a combination of L-arginine and cell surface receptor stimulation by acetylcholine cannot overcome. However, stimulation of NO activity by other mechanisms, such as increased blood flow, which has a separate signal transduction mechanism, may bypass the defect in the acetylcholine signal transduction mechanism and could activate the NO pathway. Indeed, the findings by Panza et al. are limited to showing the existence of a defect in the acetylcholine pathway which prevents the activation of the NO pathway, regardless of sufficient L-arginine. There are many mechanisms of dysfunction of the NO pathway in any given vascular disease, however, and hypertension is no exception.

During the active + rest trial we demonstrated a fall in both SBP and DBP. Assuming that the major effect from the supplement comes from the L-arginine, and since there is no obvious stimulus for increased NO activity (neither a bolus of acetylcholine nor an increase in blood flow), it is likely that supplemental L-arginine was overcoming any one of these other deficiencies. Overcoming an elevation in the endogenous inhibitor ADMA (asymmetric dimethylarginine) is one possibility; stabilization of the nitric oxide synthase dimer is another. Supplementation of L-arginine leading to a modest decrease in BP at rest is consistent with several other studies showing a modest effect of L-arginine in various forms of hypertension. Also, the properties of the antioxidants have the effect of preserving NO activity, thereby enhancing any action of increased NO activity.

In the present study, reduction in SBP and MAP in the Heart Bar® + rest trial was not observed in the placebo + rest trial. Assuming that cardiac output basically remains constant at rest, there must have been a reduction in systemic vascular resistance in order to

Changes in BP @ 120 min



◆ Figure 4 Mean (\pm SD) changes in systolic (SBP), diastolic (DBP), and mean (MAP) blood pressure from rest to 120 minutes in relation to intervention. Note that the magnitude of reduction in DBP and MAP is significantly larger in the active + exercise trial.

account for the reduction in SBP and MBP. These data suggest that L-arginine supplementation may have an effect on vasodilation in mildly or borderline hypertensive individuals, although the mechanism of how L-arginine supplementation leads to increased NO production cannot be specifically identified (14).

Another possible explanation for the decrease in SBP and MBP in the present data may be that the subjects remained on medications, and that these medications may have helped to preserve or repair endothelial function, as suggested by others. While some research has indicated that medications such as ACE inhibitors and calcium channel blockers may reduce endothelial dysfunction in hypertension (23–25), other studies have shown medications to be ineffective (26–28). Clearly, continued research is needed in order to fully understand the role of medications and endothelium-dependent vascular relaxation in persons with hypertension.

The results of the present study demonstrate a significant reduction in DBP at 90 and 120 minutes which was only present in the combined intervention of the Heart Bar® + exercise trial. While there was a significant reduction in MAP for the Heart Bar® + rest, placebo + exercise, and Heart Bar® + exercise trials, only the combination of Heart Bar® + exercise produced a significant reduction that extended to the 120-min time point of the trial (Figure 4). These results are consistent with the hypothesis that the combination of Heart Bar® supplementation and exercise have an additive effect on the reduction of BP. In a study of patients with chronic heart failure (29), L-arginine supplementation as well as exercise training resulted in a significant increase of the vasodilatory response to acetylcholine, which is similar to the acute results observed in the present study. These results suggest that the effects of L-arginine and anti-oxidant vitamins and exercise may be additive.

The dosage and duration of L-arginine use may have an effect on blood pressure. The present study evaluated the acute effects of supplementation. Additional research is needed to evaluate the effects of long-term L-arginine supplementation on the acute BP response to exercise in hypertensive patients. Recent studies of L-arginine supplementation in hypertensive patients who are already medically treated have found limited effects of L-arginine on acetylcholine-mediated flow responses (30). Further research is also needed to evaluate the dosage of L-arginine that may be needed to yield the greatest benefit, the interaction with medical therapy and with various dosages of exercise.

In this study, nutritional supplementation with L-arginine, as well as aerobic exercise, produced a decrease in SBP, DBP, and MAP. Further, the combination of active supplementation and exercise produced an additive effect on DBP and MAP, suggesting an additive effect on the endothelium-derived NO system. Treatment of endothelial dysfunction with such simple strategies has the potential to improve outcomes in patients with hypertension.

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