ABSTRACT

Schuster-Decker, R. N. The acute effects of dynamic exercise and nutritional supplementation on blood pressure in hypertensive patients. MS in Adult Fitness/Cardiac Rehabilitation, May 2001, 42pp. (C. Foster)

Hypertension is a modifiable risk factor for coronary heart disease. This study evaluated the reduction in blood pressure (BP) in response to sub-maximal cycling and nutritional supplementation with the active ingredient L-arginine, both independently and in combination. Subjects (N = 9) were clinically stable with a clinical diagnosis of hypertension. Each completed 4 randomly ordered 120 min trials. BP was obtained at 0, 30, 60, 90, and 120 minutes of each trial. Trial 1 consisted of placebo and repeated blood pressure measurements during rest. Trial 2 was identical to trial 1, except with active agent supplementation. Trial 3 consisted of placebo and a 25 min exercise session. Trial 4 was identical to trial 3, except with active agent supplementation. Repeated measures ANOVA was used to examine the changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP) from rest to 90 min and 120 min. Post hoc tests showed a significant ($p \leq 0.05$) reduction in SBP at 90 and 120 min for trials 2, 3, and 4. DBP was significant at 90 min and 120 min only in trial 4. MBP was significant at 90 min in trials 2, 3, and 4, and at 120 min in trial 4 only. Analysis of BP during exercise in trials 3 and 4 revealed no significant difference. We conclude that exercise, as well as supplementation with L-arginine, can lower BP in mildly hypertensive individuals. Further, the effects of exercise and supplementation are shown to be additive.

THE ACUTE EFFECTS OF DYNAMIC EXERCISE AND NUTRITIONAL SUPPLEMENTATION ON BLOOD PRESSURE IN HYPERTENSIVE PATIENTS

A MANUSCRIPT STYLE THESIS PRESENTED

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THESIS FINAL ORAL DEFENSE FORM

Candidate: Rachel N. Schuster-Decker

We recommend acceptance of this thesis in partial fulfillment of this candidate's requirements for the degree:

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The candidate has successfully completed the thesis final oral defense.

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This thesis is approved by the College of Health, Physical Education, Recreation, and Teacher Education.

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"I can do all things through Christ who strengthens me". Phil. 4:13

Thank you to my parents for your love and support, and all the things you have taught me. Without you, I would not be where I am today. I will always be grateful.

To my husband, Brent, thank you for always having confidence in me. You are a constant source of encouragement, patience, and love.

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INTRODUCTION

Cardiovascular disease is the number one cause of death of Americans. It is responsible for an estimated one-half of all deaths in the United States each year (1). The American College of Sports Medicine (2) lists seven risk factors for cardiovascular disease. Of these seven risk factors, four may often be controlled through lifestyle modification (3). Hypertension, or high blood pressure, is one of these modifiable risk factors. One in four Americans is hypertensive (1). Clinicians have studied the effects of exercise on hypertension for many years. Many studies have focused on whether hypertensive patients have a greater arterial blood pressure response to exercise, and on the use of regular exercise as a nonpharmacologic treatment to lowering arterial blood pressure at rest and during daily activities.

In recent years, researchers have become interested in the reduction of arterial blood pressure after a single session of exercise (4). This effect is known as post-exercise hypotension (PEH). Numerous authors (4-12) have suggested that dynamic exercise results in PEH. Post-exercise hypotension is most likely attributed to a reduction in systemic vascular resistance, which is probably secondary to nitric oxide mediated vasodilation (13).

As a parallel issue, there has been a recent surge in interest in the supplemental use of various antioxidant vitamins, and the amino acid L-arginine, as part of the management of atherosclerotic diseases (13). L-arginine is an amino acid that acts as the precursor to nitric oxide (NO) (14), which is regarded as one of the most potent

vasodilators (15). The 1998 Nobel Prize in Medicine was awarded to Robert F. Furchgott, Louis J. Ignarro, and Ferid Murad for their discoveries concerning NO as a signaling molecule in the cardiovascular system (13). Nitric oxide improves blood flow by regulating vascular smooth muscle relaxation, and it inhibits platelet adhesion (16). The NO system plays an important role in the dilation of arteries, with failures of NO synthesis partially accounting for the increased vascular resistance that is observed in hypertension (15). Antioxidants, such as vitamins C and E, and 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 enhancing either the release or action of NO, the purpose of the present study was to investigate the acute changes in blood pressure of hypertensive individuals, in response to exercise and nutritional supplementation, both independently and in combination. This study evaluated systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP).

METHODS

Subjects

The subjects for this study were nine volunteers (3 female, 6 male) who are participants in the La Crosse Exercise and Health Program at the University of Wisconsin–La Crosse. Each participant was clinically stable and had a clinical diagnosis of hypertension. Subjects were instructed to take all medications as usual. Seven of the subjects were taking angiotensin conversion enzyme (ACE) inhibitors, four were taking

calcium channel blockers, seven of the patients were on diuretics, and six of the subjects were taking beta blockers.

Table 1. Characteristics of the Study Population (N = 9)

Characteristic	Value
Age (years)	62 ± 5
Weight (kg)	89 ± 7
Body surface area (kg/m^2)	29.5 ± 1.5
Average resting SBP (mmHg ± st. dev.)	139 ± 1
Average resting DBP (mmHg ± st. dev.)	77 ± 1
Average resting MBP (mmHg ± st. dev.)	97.5 ± .5

Prior to the study all subjects provided informed consent (see Appendix A). The study was approved by the University of Wisconsin-La Crosse Institutional Review Board for the protection of human subjects. The physician of each participant was informed of their participation in the study.

Each subject was asked to schedule four appointments. All of these appointments were 120 minutes in duration. Participants were scheduled at the same time of day for each appointment. Subjects were asked not to consume any food or drink for two hours prior to each testing session, and to refrain from alcohol intake for 24 hours prior to each testing session. None of the subjects studied were active tobacco users.

Protocol

All studies were conducted in the Human Performance Laboratory at the University of Wisconsin-La Crosse. The researcher measured all blood pressures by

ausculatory method with the same sphygmomanometer. Each subject completed four randomly ordered trials. All trials were 120 minutes in duration. In each trial, a resting BP was obtained following five minutes of seated rest after the subject arrived. 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 after the initial blood pressure measurement. Consumption of the bar required five minutes or less. Subsequent resting BP values were obtained at 30, 60, 90, and 120 minutes of each trial. All BP's at 0, 30, 60, 90 and 120 minutes were measured in the seated position. Subjects were allowed to read leisure materials during the study.

The active supplement that was given to each patient was the Heart Bar®, a registered trademark of Cooke Pharma. The Heart Bar® has been approved by the Food and Drug Administration as a medical food. This means that the bar is available without a prescription, but recommended for use under the supervision of a physician. The active ingredient in the Heart Bar® is 3 grams of the amino acid L-arginine. The heart bar also contains 250 mg of vitamin C and 200 IU of vitamin E. Vitamins C and E have been shown to have effects on NO. According to Cooke Pharma (18), the absorption time for L-arginine following the consumption of the Heart Bar® is one to two hours. The placebo bar used in this study was provided by Cooke Pharma. It was identical to the Heart Bar®, except ingredients shown to have an effect on NO (including L-arginine, vitamin C, and vitamin E) were removed.

Trial one measured baseline BP over a two hour period. This trial served as the control for the study. 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 two consisted of active agent nutritional supplementation. The initial 0 value BP 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 three consisted of placebo and exercise. After the initial BP was obtained, the subject consumed a placebo bar. Resting BP was measured again at 30 minutes. Immediately after this BP was obtained, the subject cycled on a stationary bike. Exercise intensity was consistent with contemporary principles of exercise according to the American College of Sports Medicine (2): 60-80% of maximal heart rate. Exercise workload was recorded for each subject. Exercise duration was 25 minutes. During exercise, BP was measured at 10, 20, and 25 minutes. At the conclusion of the 25-minute exercise session, a 5-minute cool down was allowed. After cool down, resting seated BP was measured. This BP served as the measurement at 60 minutes of the trial. Additional resting BPs were taken again at 90 and 120 minutes.

Trial four consisted of a combination of active nutritional supplementation plus exercise. Immediately after the initial BP was obtained, the subject consumed a Heart Bar®. The subject then cycled on a stationary bike for 25 minutes with the same workload as in trial three. After the 25-minute exercise session, a 5-minute cool down was allowed. After cool down, resting seated BP was measured. This BP served as the measurement at 60 minutes of the trial. Additional resting BPs were recorded at 90 and

120 minutes.

Statistical Treatment

Repeated measures ANOVA was used to examine the changes in SBP, DBP, and MBP from rest to 90 minutes (30 minutes post exercise) and 120 minutes (60 minutes post exercise). Tukey's post-hoc tests were used to detect differences between means. Alpha was set at .05 to achieve statistical significance.

RESULTS

SBP did not change significantly under the control condition (placebo + rest) at the 90 or 120 minute time points of the study (Figure 1). For all three interventions (Heart Bar® + rest, placebo + exercise, Heart Bar® + exercise) there was a significant decrease in SBP that persisted at the 90 and 120 minute time points.

DBP did not change significantly in the placebo plus rest, Heart Bar® plus rest, or placebo plus exercise trials at 90 or 120 minutes (Figure 2). However, DBP did decrease significantly at both 90 and 120 minutes in the combined intervention of Heart Bar® plus exercise.

MBP was significantly decreased at the 90 minute time point for all conditions (Heart Bar® + rest, placebo + exercise, Heart Bar® + exercise) compared to the placebo plus rest trial (Figure 3). The only significant decrease in MBP that persisted at the 120 minute time point was in the combination intervention condition (Heart Bar® + exercise).

Analysis of SBP, DBP, and MBP during exercise showed no significant difference between active nutritional supplement and placebo (Figures 4, 5, 6).

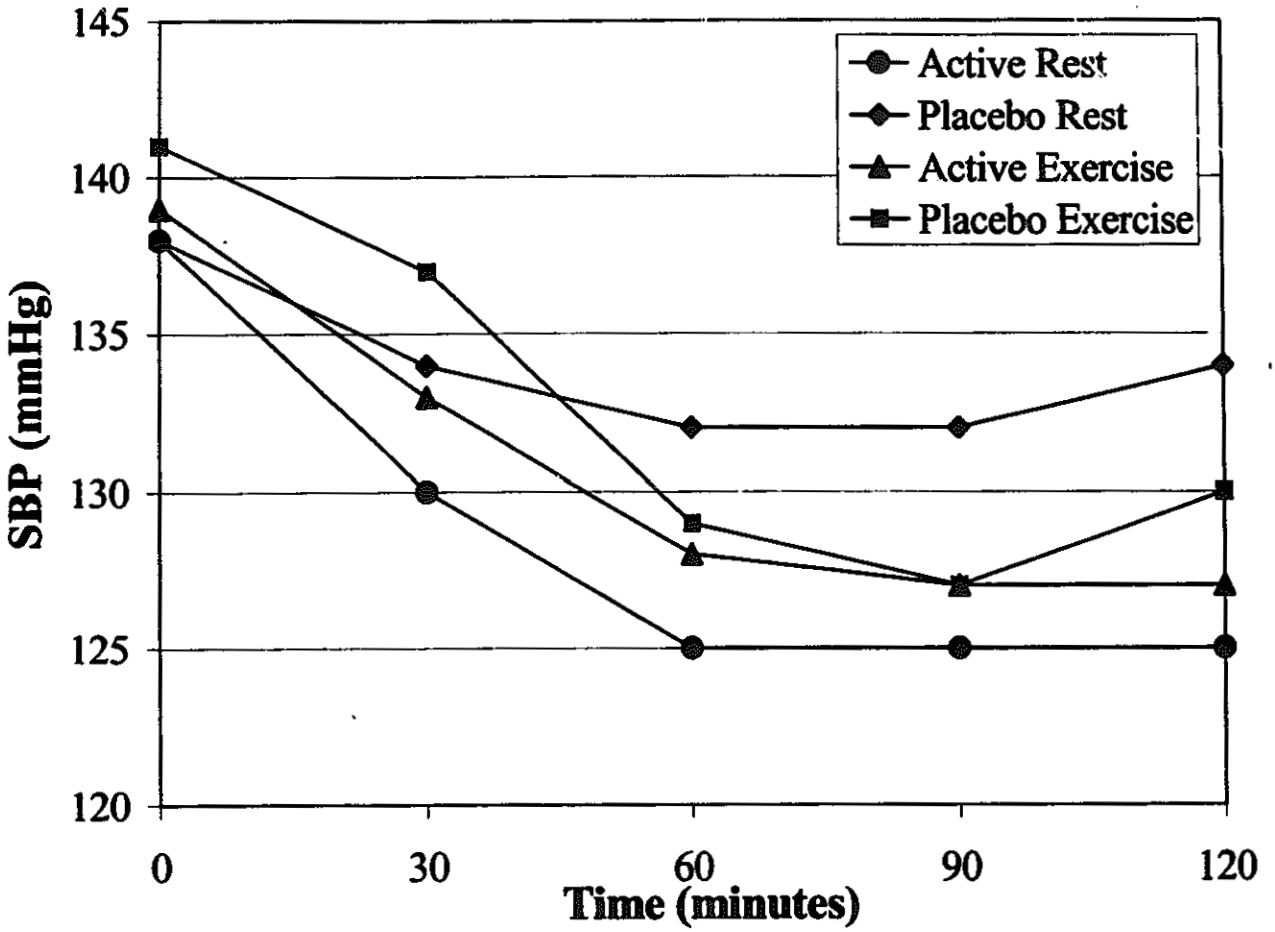

Figure 1. Time versus SBP response across trials.

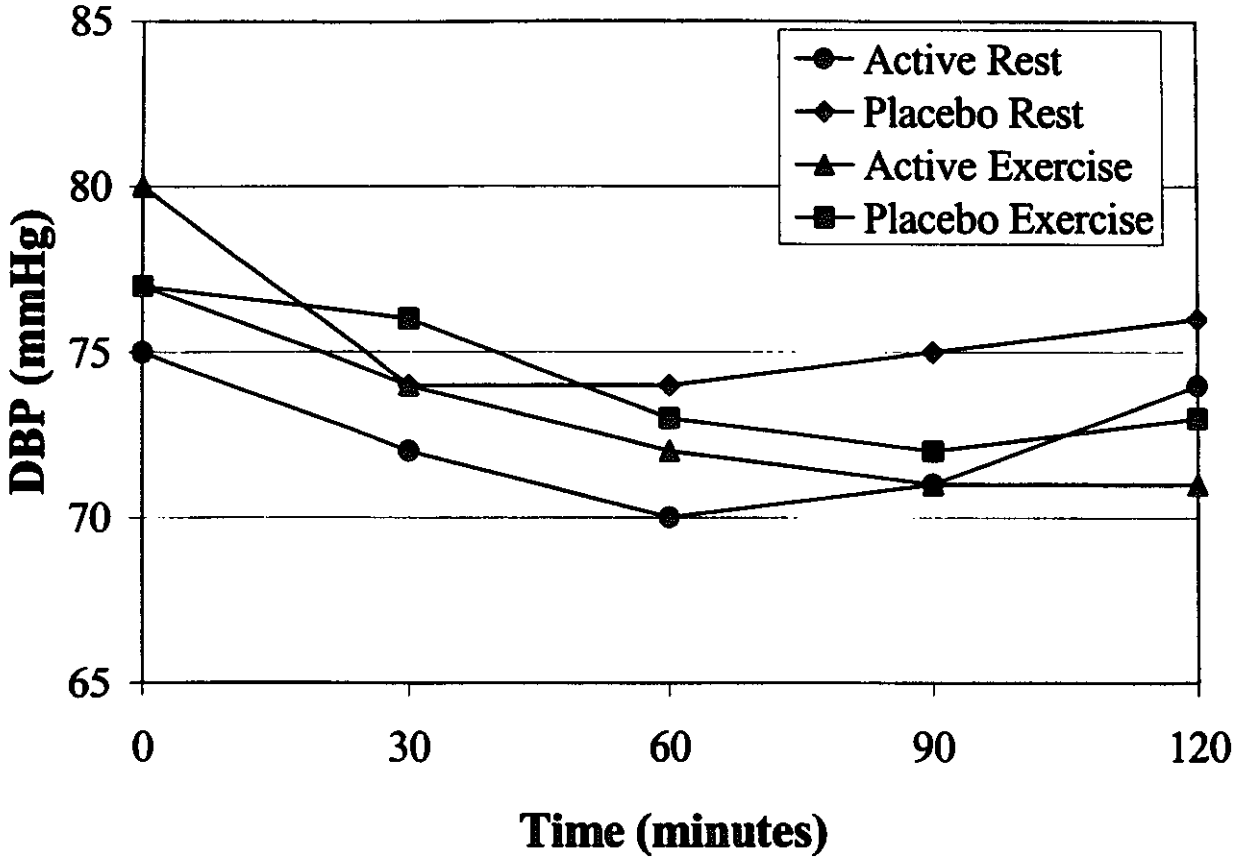

Figure 2. Time versus DBP response across trials.

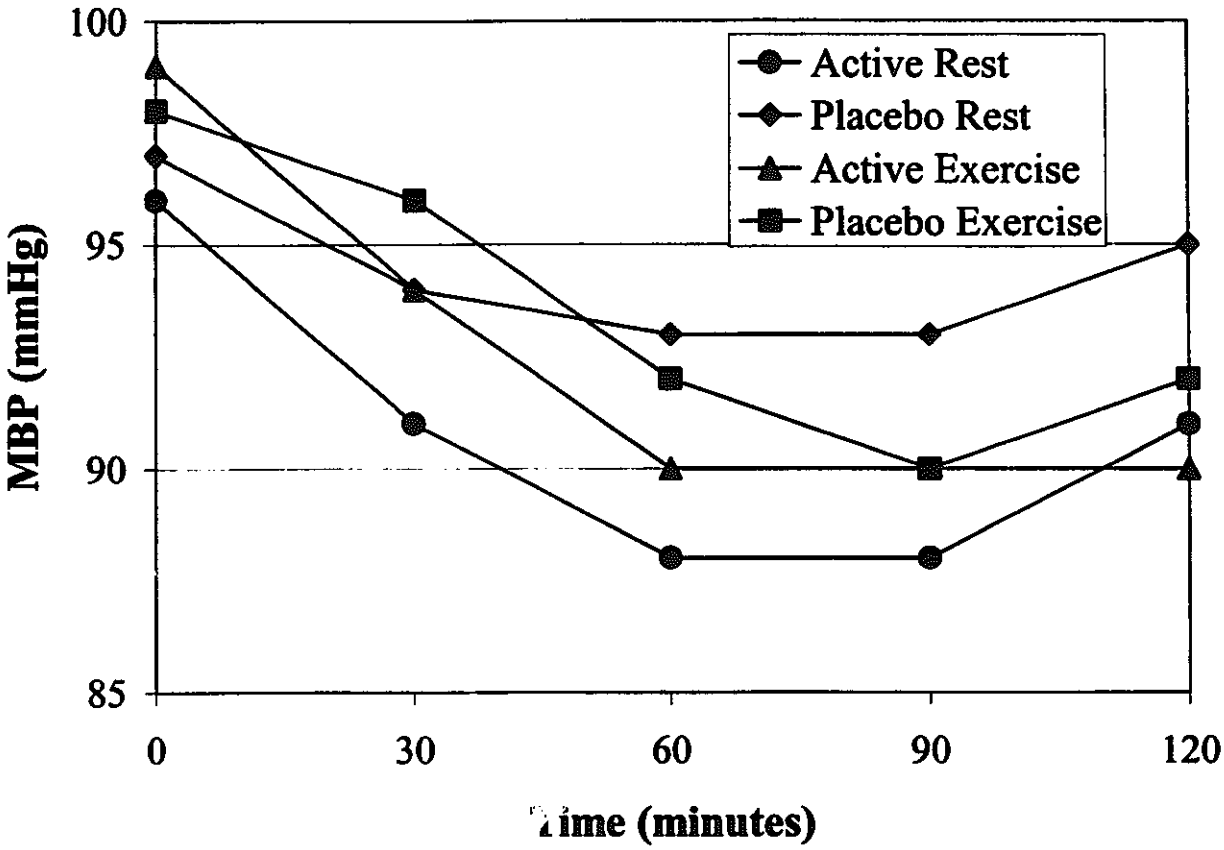

Figure 3. Time versus MBP response across trials.

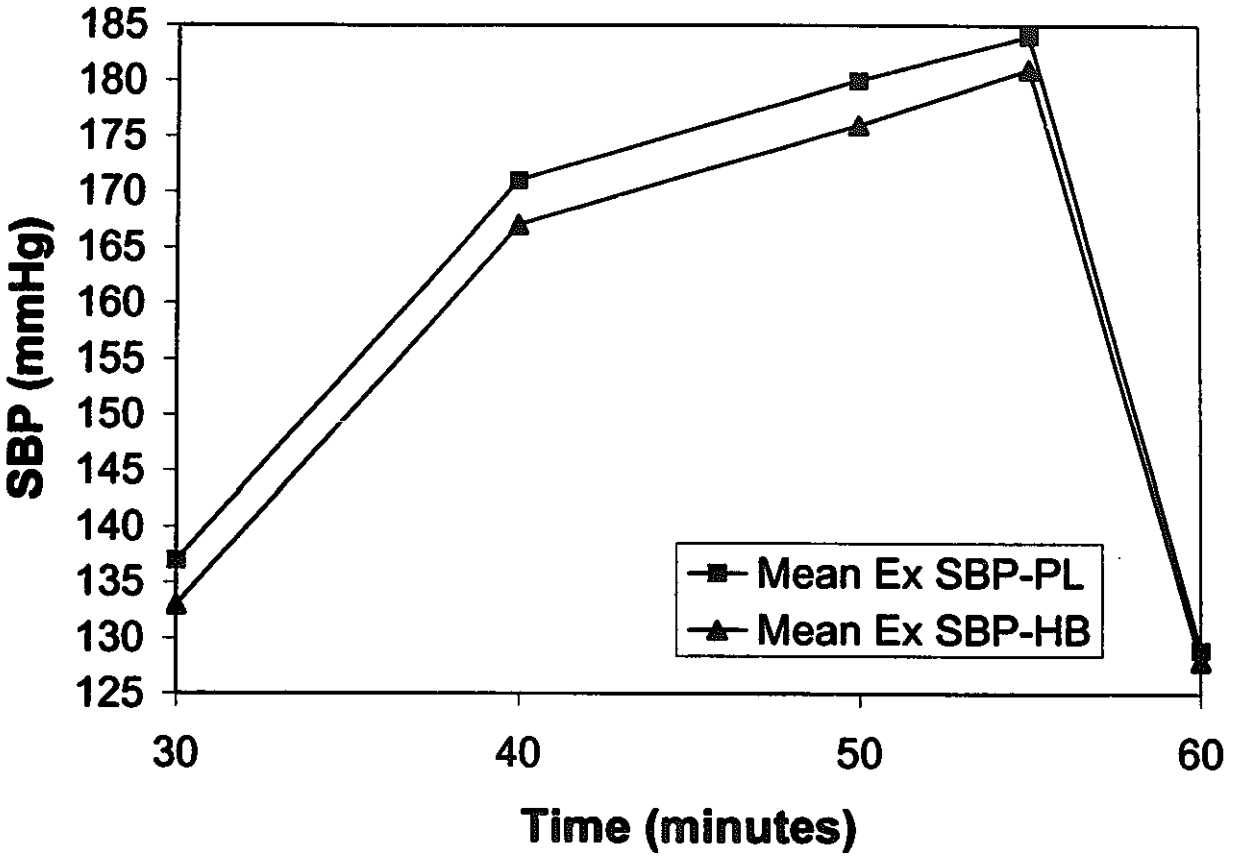

Figure 4. Time versus SBP response immediately before, during, and after exercise.

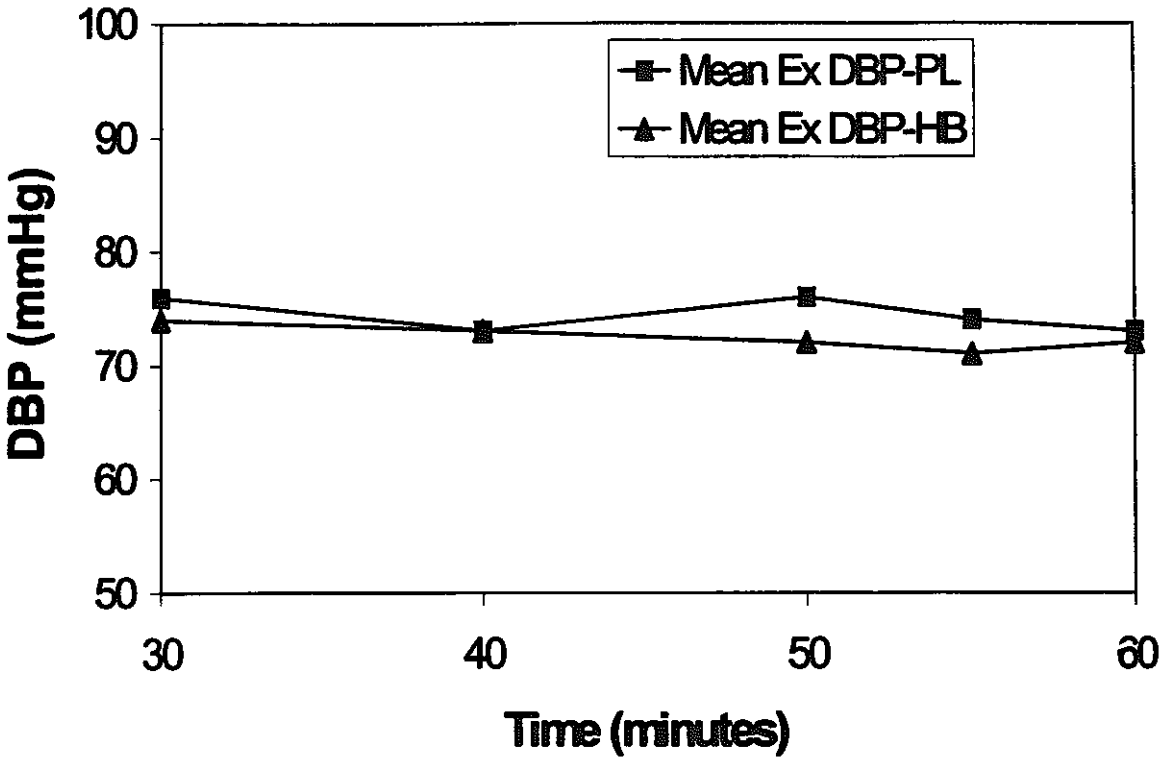

Figure 5. Time versus DBP response immediately before, during, and after exercise.

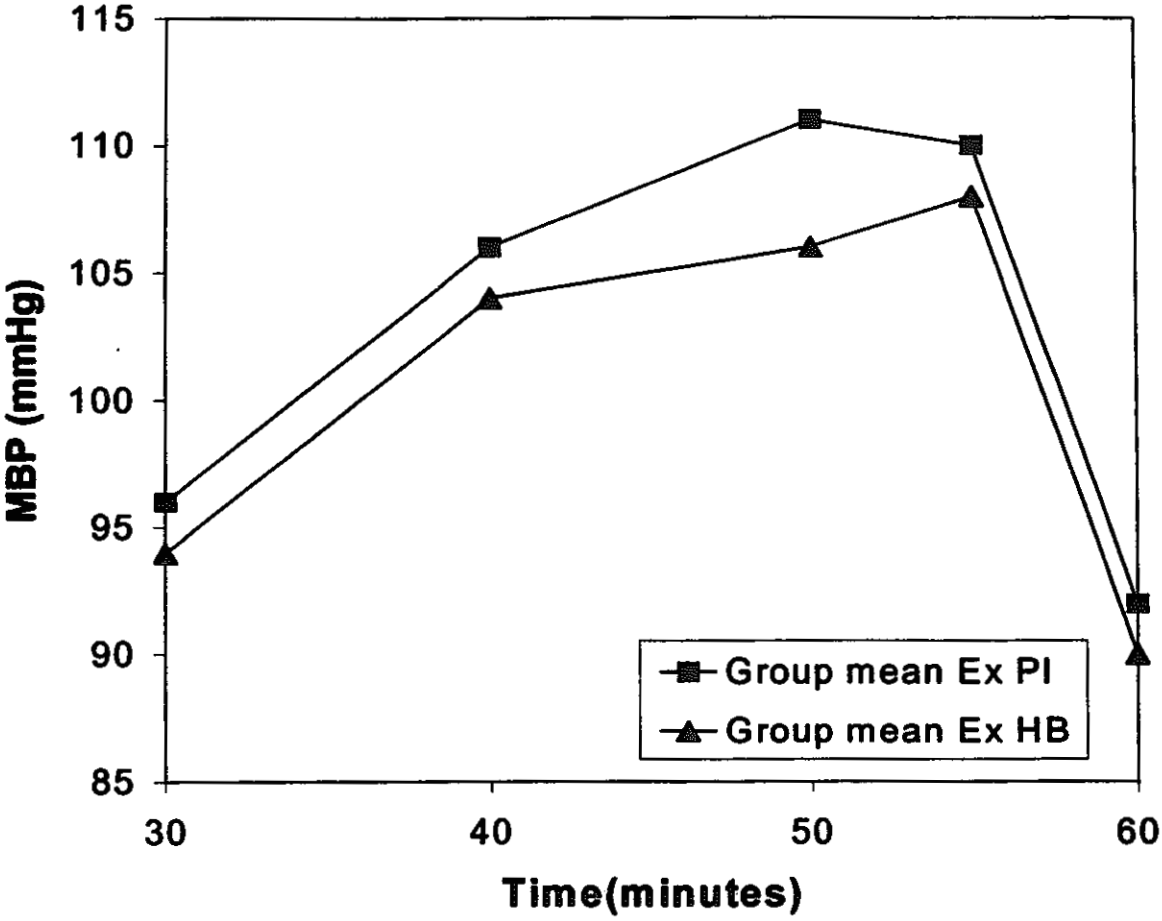

Figure 6. Time versus MBP response immediately before, during, and after exercise.

DISCUSSION

Post-exercise BP was significantly lower than pre-exercise BP in subjects after a single session of submaximal aerobic exercise. Results showed a reduction in SBP at the 90 and 120 minute time points (30 and 60 minutes post-exercise). MBP was reduced at the 90 minute time point (30 minutes post-exercise). This reduction is consistent with the PEH that has been observed in patients with borderline hypertension in previous research (4-12).

The results of this study are similar to the PEH observed in 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 post exercise, and for DBP at 30 minutes post-exercise by Kaufman et al. (5).

While this study evaluated the acute effects of exercise on BP, several other studies suggest that PEH can be sustained for longer periods of time. Bennett et al. (9) found PEH to be sustained for 90 minutes, Cleroux et al. (11) for 2 hours, and Hannum & Kasch (10) for 3 hours after exercise. In two additional studies, PEH was sustained for much longer periods of time. Pescatello et al. (6) observed that PEH lasted 8.7 hours. A later study by Pescatello et al. (7) found PEH to last for seven hours. Results from such studies suggest that the effects of PEH may not be only acute, but a more sustained phenomenon.

In contrast to these studies of PEH, Gilders et al. (19) 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. Results revealed that

exercise conditioning did not change ambulatory or casual BP. However, in this study all blood pressures were taken by ambulatory BP monitors that were worn by the subjects only on days when they did not exercise. Therefore, by monitoring subjects only on their non-exercise days, the effects of PEH were not recorded in this study. This may account for differences in BP response from the present study. The reduction of BP after a single exercise session observed in this study provides supporting evidence that exercise can be an effective therapy for individuals with hypertension.

In this study, L-arginine supplementation produced a significant reduction in SBP at the 90 and 120 minute time points in the rest and exercise trials. MBP in the Heart Bar® plus rest condition showed a significant decrease in BP at 90 minutes, while the Heart Bar® plus exercise condition showed a significant decrease lasting through the 120 minute time point. These results are consistent with the knowledge that L-arginine acts as the precursor to NO (14), which is one of the body's most potent vasodilators (15).

Several studies (14, 20-22) have shown hypertensive individuals to have a defect in the endothelium-regulated vascular relaxation system. A study by Panza, Casino, Badar, & Quyyumi (23) indicated 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. However, in the present study, reduction in SBP and MBP in the Heart Bar plus rest trial was not observed in the placebo plus rest trial. Given that cardiac output basically remains constant at rest, there must be a reduction in systemic vascular resistance in order to account for the reduction in SBP and MBP. These data are suggestive that L-arginine supplementation may have an effect on vasodilation in mildly/borderline hypertensive

individuals. Furthermore, if L-arginine supplementation has a vasodilator effect on hypertensive vessels, it is suggestive that hypertension may be, in part, a dietary deficiency disease.

Another possible explanation for the decrease in SBP and MBP in the present study may be that the subjects remained on all medications as usual, and that these medications may have helped to preserve or repair endothelial function. This is a theory that has been studied by several researchers. While some research has indicated that medications such as ACE inhibitors and calcium channel blockers may reduce endothelial dysfunction in hypertension (24-26), other studies have shown the medications to be ineffective (27-29). Clearly, continued research is needed to fully understand the role of medications and endothelial-derived vascular relaxation in subjects with hypertension.

The results of the present study reveal a significant reduction in DBP at the 90 and 120 minute time points that was present only in the combined intervention of the Heart Bar® plus exercise trial. Further, while there was a significant reduction in MBP for the Heart Bar® plus rest, placebo plus exercise, and Heart Bar® plus exercise trials, only the combination of Heart Bar® plus exercise produced a significant reduction that extended to the 120 minute time point of the trial. These results show the combination of Heart Bar® supplementation and exercise to have an additive effect on the reduction of BP. In a study of patients with chronic heart failure (30), a L-arginine supplementation group, as well as an exercise training group, showed a significant increase in vasodilative response to ACh. Consistent with the results of the present study, the group with the

combination of L-arginine supplementation and exercise training showed a significantly greater vasodilative response to ACh. These results are consistent with the theory that the effects of L-arginine and exercise may be additive.

The dosage and duration of use of L-arginine may be two factors that would affect the results of BP studies. The present study evaluated the acute effects of supplementation. Additional research is needed to evaluate the effects of long-term L-arginine supplementation on BP in hypertensives. Further research is also needed to evaluate the dosage of L-arginine that may be needed to produce the greatest benefit. In this study, the Heart Bar® was only used once as an acute supplementation. Recommendations of Cooke Pharma (18), makers of the Heart Bar®, are to consume 2 bars per day for 2 weeks in order to produce results. After the initial 2 week period, 1 bar per day may be sufficient to maintain a benefit.

In this study, nutritional supplementation with L-arginine, as well as aerobic exercise, produced a decrease in SBP, DBP, and MBP. Further, the combination of active supplementation and exercise produced an additive effect on DBP and MBP, suggesting an additive effect on the endothelium-derived NO system. Endothelium regulates vascular tone by influencing the contractility of smooth muscle, which is important in the control of blood pressure. Treatment of endothelial dysfunction in patients has the potential to improve outcomes in patients with hypertension. Therefore, continued research on the effects of nutritional supplementation and exercise in hypertension is needed.

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APPENDIX A

INFORMED CONSENT

INFORMED CONSENT

EFFECTS OF DYNAMIC EXERCISE AND NUTRITIONAL SUPPLEMENTATION ON BLOOD PRESSURE IN HYPERTENSIVE PATIENTS

I, _____, consent to participate in a study that evaluates the acute effects of exercise and nutritional supplementation on blood pressure. During each trial I will have my blood pressure taken numerous times. During two of the trials I will exercise on an exercise cycle for 25 minutes at about the same intensity that I would normally use during my exercise program. During two of the trials, I will consume a food bar that may be either a special nutritional supplement thought to lower blood pressure, or a placebo.

All testing sessions will be conducted at either Gundersen-Lutheran Medical Center, Franciscan-Skemp Medical Center in La Crosse, or the University of Wisconsin-La Crosse. These sessions will take place in coordination with scheduled exercise sessions and classes or by individual appointment. Testing will be conducted by Rachel Schuster, a graduate student in the Adult Fitness/Cardiac Rehabilitation Master Program under the supervision of Dr. Carl Foster.

I have been informed that I may see a temporary reduction in blood pressure as part of this study. I have been informed that my participation in this study is completely voluntary, and that I have the right to discontinue participation at any time without penalty.

I have been informed that every effort will be made to minimize risk by the availability of emergency trained staff and emergency equipment. However, I have been informed that therapeutic exercise has a certain risk of complication above baseline (e.g. heart attack, etc.) that amounts to about one episode for every 30,000 hours of exercise. It is theoretically possible that the combination of nutritional supplement and exercise may produce hypotension (light-headedness).

I have been informed that all my results will be explained to me. I have also been informed that the results will be confidential and only group data will be used in any final report. No individual data will be identified.

I will inform my physician of my participation in the study prior to my active involvement. I have read the above statements and have been informed of what is expected from me. Any questions that may have occurred to me have been

answered to my satisfaction. If I have any additional questions at any time of the study I may contact Rachel Schuster at 788-2814. I may also contact the faculty research advisor for this study, Dr. Carl Foster at 785-8687. Questions regarding the protection of human subjects may be addressed to Dr. Garth Tymeson, UW-La Crosse, chair of the IRB for the protection of human subjects, (608) 785-8155.

SIGNATURE OF SUBJECT _____ DATE _____

SIGNATURE OF RESEARCHER_____ DATE _____

APPENDIX B

LITERATURE REVIEW

REVIEW OF LITERATURE

Measurement of Blood Pressure

Blood pressure (BP) is defined as "the force exerted by the blood against any unit area of the vessel wall" (1). BP is most commonly measured in millimeters of mercury (mmHg), and expressed as a ratio. The first number refers to the systolic pressure, or the pressure in the arteries during ventricular systole, the second number refers to diastolic pressure, or the pressure in the arteries when the heart relaxes. Normally, the systolic pressure is 140 mmHg or less, and the diastolic pressure is 90 mmHg or less. When a blood pressure is consistently higher than this, there is an increased risk for heart attack or stroke. More than 50 million Americans fall into this category (2).

A recommended method for determining blood pressure is by auscultation using a mercury sphygmomanometer (3). A blood pressure cuff, containing a rubber bladder that encircles at least two-thirds of the arm, is placed around the bare upper arm. A stethoscope is placed over the antecubital space. The blood pressure cuff is inflated above the arterial systolic pressure. This pressure is usually around 200 mmHg, or enough to allow for the closing of the brachial artery. No sounds are heard through the stethoscope at this time. The cuff pressure is released very slowly to allow blood to begin to flow through the artery. When the cuff pressure falls below systolic pressure, tapping sounds are heard. These sounds are referred to as the Korotkoff sounds. As the pressure is slowly released from the cuff, the Korotkoff sounds change in sound and finally disappear when the cuff pressure falls slightly below the diastolic pressure. The

sphygmomanometer reading at the first sound is the systolic pressure, and the reading at the absence of sound is the diastolic pressure (1,3). Because of the factors that influence blood pressure, readings should be averaged over two or more visits (4).

Factors Affecting Blood Pressure

Blood pressure values will change from measurement to measurement in both normotensive and hypertensive individuals (4). Variations result from age, sex, activity level, environmental temperature, body weight, food and alcohol consumption, body position, and various medications (4).

Age and Sex

The average blood pressure of an 18-year-old person is 120/80 mmHg. This increases over time. At age 60 the average systolic pressure is 140 mmHg. Women who are premenopausal have systolic pressures approximately 5 mm Hg lower than men of the same age. However, after menopause women have slightly higher systolic blood pressures than men (4).

Activity and Exercise

Everyday activities will increase blood pressure. Examples of activities include walking up a flight of stairs or reaching above the head to retrieve an item from a shelf. Systolic blood pressure will increase linearly with heart rate and may reach 200 mmHg or higher with heavy exercise. Diastolic pressure will remain constant or decrease slightly during exercise. Blood pressure will usually normalize within five minutes after moderate activity. Therefore, it is necessary to wait for at least five minutes in order to obtain an accurate measurement (3,4).

Environment

Environmental temperature will affect systolic pressure. Heat has a vasodilator effect on the body. Cold conditions have a vasoconstriction effect on the blood vessels. For example, a hot shower will lower blood pressure, and cold showers can vasoconstrict vessels increasing blood pressure. It is necessary to wait 30 minutes after a temperature change in order to obtain an accurate blood pressure reading (4).

Obesity

According to the U.S. Department of Health and Human Services (3), "obesity is an important coexisting and compounding problem to hypertensive disease." The pathophysiology of hypertension and obesity include expanded blood volume, increased dietary sodium intake, elevated cardiac output, and increased adrenergenic tone. With increased body weight, there is a general decrease in vascular tone over time. Increased body weight also adds extra stress on joints, contributes to injury, and limits physical activity.

Food and Caffeine Consumption

Systolic pressure increases about 7 mmHg after eating. Blood pressure rises by 5 to 15 mmHg within 15 minutes of the intake of caffeine. It is recommended to wait two hours after eating or consuming caffeine to obtain a blood pressure reading (4).

Alcohol and Tobacco

Alcohol increases heart rate and cardiac output and causes blood vessels to constrict to compensate for vasodilation in the extremities. This leads to an increase in blood pressure. Tobacco increases blood pressure by causing vasospasm of arterial walls

and increasing the release of catecholamines. Blood pressure measurements should not be taken for a half-hour after tobacco use (4).

Stress

Psychological stress, such as pain, fear, or excitement will raise blood pressure. These emotions cause an increase in the sympathetic nervous system stimulation in the brain. It is important to record blood pressure after the subject is relaxed (4).

Medication

The majority of cardiac patients are taking medication that alters blood pressure (5). Pharmacological therapy decreases cardiovascular mortality and progression to more serious levels of hypertension, and strokes (3). Some medications that reduce blood pressure are adrenergic inhibitors, diuretics, vasodilators, ACE inhibitors, and calcium channel blockers (3).

Body Position

Lastly, body position will also influence blood pressure. Pressure may vary up to 15 mm Hg between supine, sitting, and standing blood pressures. A five-minute period is recommended between recordings if a postural change is made (4).

It is necessary to be familiar will all of the above conditions that can affect blood pressure in order to obtain correct readings.

Exercise and Blood Pressure

There have been many studies (6-10, 12-17) that have documented the effects of exercise on blood pressure (BP). Several studies contain conflicting evidence on the antihypertensive effect of dynamic exercise. However, despite this conflicting evidence,

aerobic exercise is frequently recommended by physicians and allied health professionals for the treatment of hypertension (11). In addition to exercise, diet modification and drugs are used to treat hypertension (7).

A study by Tipton (12) evaluated the effects of exercise conditioning on BP. This study found reductions in BP of 5-25 mmHg. Tipton (12) concluded that there was "sufficient justification" for exercise conditioning to be used as a treatment for hypertension. Results of this study also suggested that borderline and mildly hypertensive individuals may gain the most benefits from exercise conditioning.

In contrast to the study by Tipton (12), a study by Gilders, Voner, & Dudley (13) found no change in BP with exercise conditioning. They studied 21 male and female borderline hypertensive subjects for BP changes during a control period, a conditioning period, and a deconditioning period. BP was evaluated with the use of an ambulatory monitor. No significant changes were found in the subjects in any of the study periods.

In recent years, clinical scientists and physiologists have become interested in the reduction of arterial blood pressure after a single session of exercise. This effect has been termed post-exercise hypotension (PEH). Kenney and Seals (7) report that PEH has been observed in young and middle aged normotensive humans, patients with borderline hypertension, and patients with established hypertension of various ages.

Kaufman, Hughson, & Schaman (6) evaluated the effect of exercise on recovery BP in normotensive and hypertensive subjects. Results of this study (6) found lower SBP and DBP "in the recovery period after dynamic exercise than in pre-exercise conditions". There was a significant decrease of 5-10 mmHg in SBP, and a 2-4 mmHg decrease in

DBP. There was no significant difference in the pattern of BP decrease between normotensive and hypertensive subjects. Furthermore, Kaufman et al. (6) reported that the SBP remained significantly reduced at 60 minutes post-exercise, while DBP had returned to pre-exercise levels. In a similar study Bennett, Wilcox, & MacDonald (14) found that BP was depressed for at least 90 minutes after exercise.

Research by Hannum & Katch (15) studied the changes in resting BP after 40 minutes of exercise. Ten normotensive and 13 hypertensive subjects were evaluated for 2 hours after exercise. Both groups had post-exercise reductions in SBP when compared to their pre-exercise BP. The hypertensive group showed a greater decrease in BP than the normotensive group.

It has been reported (16) that following moderate cycling activity, the hypotensive response in subjects with mild to moderate hypertension averages -11 mmHg for the systolic, and –4 mmHg for diastolic arterial blood pressure. Cleroux et al. (16) also observed that the reduction in blood pressure was maintained during the period two and three hours after exercise. Mean arterial blood pressure has been reported to be reduced an average of 8 mmHg for at least four hours after submaximal cycling exercise in borderline hypertensive individuals (17). Pescatello et al. (8) reported that systolic arterial blood pressure was reduced an average of 6 mmHg over 8.7 hours, and diastolic arterial blood pressure was reduced an average of 9 mmHg over 12.7 hours after submaximal exercise in mildly hypertensive men. The effect of dynamic exercise on the recovery BP in normotensive subjects was less clear. In the study by Pescatello et al. (8), mean arterial pressure after exercise was similar to resting values in the normotensive

group. A possible explanation for the different BP responses after exercise is that absolute changes in recovery BP are less in normotensive subjects than those in hypertensive subjects (8). Additional research of PEH by Pescatello et al. (9) is consistent with previous results. Following a 40-minute exercise session, a decrease in SBP, DBP, and mean arterial blood pressure was present in mildly hypertensive women for up to seven hours. PEH was not observed in the normotensive subjects of this study (9).

An additional study (10) reported the results of PEH. Hypertensive subjects and normotensive subjects experienced a reduction in blood pressure at 30 minutes after a graded exercise test. Despite the striking BP reductions at 30 minutes after exercise, BP measurements recorded at the subjects' homes were not significantly different on exercise and control days in the hypertensive or normotensive groups. Therefore, it was concluded that a single bout of exercise lowers BP for a brief (one hour) period, but this hypotensive response is not sustained (10).

An important issue is whether PEH is simply an interesting short-term phenomenon, or if it might be an important factor in the blood pressure lowering effect of chronic exercise (7). Kenney and Seals (7) state that in order to contribute to the sustained lowering of arterial blood pressure that is observed with regular exercise, PEH must be sustained at an adequate level for an adequate period of time throughout the day. If this can be established, a single session of exercise might be an important component in the control of hypertension.

Nutritional Supplementation

There has been a recent surge in interest in the supplemental use of L-arginine as part of the management of atherosclerotic diseases (18). L-arginine is a naturally occurring amino acid. The increased interest in L-arginine is due to the recent understanding of the contribution of the nitric oxide pathway, in which L-arginine is a key component, in cardiovascular health and disease (18). L-arginine is an amino acid that acts as the precursor to nitric oxide (NO) (19). Nitric oxide is one of the body's most potent vasodilators (20). It is now understood that the vascular system actively regulates blood flow (21).

The 1998 Nobel Prize in Medicine was awarded to Robert F. Furchgott, Louis J. Igano, and Ferid Murad for their discoveries concerning NO as a signaling molecule in the cardiovascular system (18). Nitric oxide protects the heart, stimulates the brain, and kills bacteria (22). Nitric oxide is a gas that transmits signals in an organism. Signal transmission by a gas that is produced by one cell, penetrates through membranes and regulates the function of another cell, represents a new principle for signaling in biological systems. Nitric oxide improves blood flow by regulating vascular smooth muscle relaxation, and inhibiting platelet adhesion and smooth muscle proliferation (22). It was also found that NO acts as a signal molecule in the nervous system, a weapon against infections, and as a regulator of blood pressure and blood flow (22).

The research by Furchgott, Ignarro, and Murad states that when NO is produced by the innermost cell layer of the arteries, the endothelium, it rapidly spreads through the cell membrane to the underlying muscle cells (22). Their contraction is turned off by

NO, resulting in dilation of the arteries. In this way, NO controls the blood pressure and its distribution. It also prevents the formation of blood clots (22).

The importance of the endothelium in regulating the activity of vascular smooth muscle, and thereby regulating vascular tone, was first suggested by the studies of Furchgott and Zawadzki (23). The body contains acetylcholine (ACh) which is an agent that causes an endothelium-mediated vasodilator response. Furchgott and Zawadzki (23) first demonstrated that intact endothelium is necessary for ACh-induced vasodilation. When the endothelium is damaged or removed, the relaxing effect of ACh is lost.

Endothelial dysfunction contributes to the underlying disease process of a number of conditions, including essential hypertension (19). Endothelium-derived relaxing factor (EDRF), known now as NO, is recognized as an important part of endothelium-dependent vascular relaxation (19). "A defect in the endothelium-derived NO system is known to cause abnormal response to ACh in hypertensive vessels, and to partially account for the increased vascular resistance that is observed in hypertension (20)."

Prior to 1996, there was confusion concerning the relationship between EDRF and NO. The 1996 Albert Lasker Medical Research Award was awarded to Robert F. Furchgott. Furchgott established the EDRF, whether as NO or as a related characteristic of NO, has a major role in the regulation of vascular tone, blood flow, and blood pressure (20). It was Furchgott and colleagues' later work with NO that led to their award of the 1998 Nobel Prize in Medicine. Essential hypertension is characterized by impaired endothelium-dependent vasodilation (24). In humans, although not universally

demonstrated, endothelium-dependent vasodilation to acetylecholine is lowered in essential hypertensive patients when compared with normotensive control subjects (25). Taddei et al. (24) reported that offspring of essential hypertensive patients are characterized by a reduced response to ACh linked to a defect in the nitric oxide pathway. This information suggests that an impairment in nitric oxide production precedes the onset of essential hypertension (24).

A study from the University of Leipzig, Germany Heart Center (26) examined the effects of exercise training and oral L-arginine supplementation. The background of this study states that endothelial dysfunction in patients with chronic heart failure can be corrected by L-arginine supplementation and regular exercise. The study examined patients with severe chronic heart failure over a four week period. Patients were randomized into four groups: 1) control, 2) L-arginine supplementation, 3) forearm exercise training, 4) and L-arginine supplementation plus forearm exercise training. Results of this study by Hambrecht and colleagues (26) showed no change in the response of radial artery diameter to ACh in the control group. The L-arginine supplementation group showed a significant increase in vasodilative response to ACh. The exercise training group showed an increase in internal diameter change as well. The combination of L-arginine and exercise training group significantly enhanced the vasodilative response to ACh. The results of this study suggest that supplemental L-arginine improves endothelium-dependent vasodilation, most likely increased by the endothelial release of NO. Exercise training appeared to have the same effect. The

results of this study (26) suggest that the effects of L-arginine supplementation and exercise training on endothelium-dependent vasodilation seem to be additive.

In addition to L-arginine, vitamin C and vitamin E are interventions that may reduce cardiovascular risk through an effect on endothelial function (21). A randomized, placebo-controlled trial showed that vitamin E, a lipid-soluble antioxidant dramatically reduces non-fatal myocardial infarction in subjects who were diagnosed with coronary artery disease (27). Stephens et al. (27) found a 77% reduction in nonfatal myocardial infarction over 3 years, offering strong secondary prevention evidence for vitamin E.

In two large prospective observational studies that involved more than 120,000 people, the men and women who consumed more than 200 IU of vitamin E daily were noted to have an approximately 40% decrease in coronary artery disease events (28, 29). The beneficial effects of vitamin E were dose dependent throughout the reported intake ranges (28). For optimal antioxidant protection, at least 100 to 200 IU/day of vitamin E is necessary, an amount that is unattainable with diet alone; therefore, supplementation is needed (30). Of note, previous studies with vitamin E supplements have shown no evidence of significant toxicity in doses ranging from 400 to 1,200 IU/day (30).

The water soluble antioxidant vitamin C (ascorbic acid) has been shown to improve brachial artery endothelial vasomotor function in patients with coronary artery disease (31). Levine and coworkers (31) reported that oral administration of vitamin C (2g) increased brachial artery flow-mediated vasoactivity after 2 hours from 2% $\pm$ 1% to 10% $\pm$ 2% in patients with coronary artery disease preselected for impaired endothelial function. Significantly less was observed in those subjects with normal endothelial

function (31). The results of a study by Horning and associates (32) extend previous findings reporting beneficial effects of acute administration of vitamin C on endothelium-mediated vascular relaxation in patients with coronary artery disease. This study also indicated that the beneficial effect of vitamin C is related to the increased availability of NO (32).

Chronic smoking is associated with endothelial dysfunction, an early stage of atherosclerosis (33). Heitzer and associates (33) investigated the effects of the antioxidant vitamin C on endothelium-dependent responses in chronic smokers. The results of this study (33) indicated that acute administration of vitamin C markedly improved endothelium-mediated vasodilation, and therefore demonstrating that such treatment almost completely reverses endothelial dysfunction in chronic smokers.

Exercise and EDRF

A recent study (34) evaluated the effects of exercise training on coronary endothelial function in patients with coronary artery disease (CAD). Individuals with hypertension were excluded from this study. After 4 weeks of exercise training, the response of coronary artery constriction to ACh was reduced by 54%. This study (34) concluded that exercise training improves endothelium-dependent vasodilation in both coronary vessels and resistance vessels in patients with CAD.

Hypertension and EDRF

Based on the knowledge that endothelium regulates vascular tone by influencing the contractile activity of vascular smooth muscle, Panza et al. (25) conducted a study to determine if patients with hypertension have an abnormal response of endothelium-

dependent vascular relaxation. Such as abnormality might cause or contribute to the hypertensive process. They studied the response of forearm arterial vessels to ACh in hypertensive individuals and in a control group. The increase in blood flow and reduction in vascular resistance with ACh were significantly reduced in hypertensive patients when compared with the control group (25). These results are consistent with the concept that there is a defect of endothelium-regulated vascular relaxation in subjects with hypertension. However, Panza et al. (25) states that based on these findings, they are unable to determine "whether the dysfunction that was found is primary or secondary to the hypertensive process. Thus the endothelial abnormality found in hypertensive patients may be a consequence and not a cause of the elevated blood pressure" (25). "While the exact nature of the NO system defect in hypertension is still to be clarified, the effects of endothelial dysfunction probably contribute to the cardiovascular complications associated with elevated blood pressure" (25).

While an impaired vasodilator response to ACh indicates endothelial dysfunction, it does not tell the nature of the dysfunction. It has been hypothesized that defects in the synthesis and/or release of NO may have an important role in the endothelial dysfunction of hypertensive vessels (19). Studies (35, 36) have indicated that much less NO is produced and/or released by hypertensive vessels. An additional study (37) provided research that indicates that the defect in the endothelium-derived NO system in hypertensive vessels is most likely not due to a decrease in the availability of L-arginine.

Medication and Endothelial Dysfunction

It is believed that antihypertensive treatment may normalize or at least improve endothelial dysfunction (19). Two studies in hypertensive rats (38, 39) have recorded that treatment with an angiotensin-converting enzyme (ACE) inhibitor or a calcium-channelblocker improved endothelial dysfunction in resistance vessels. These studies suggest that antihypertensive treatment may have a beneficial effect on endothelial function. However, studies in humans are not as clear. Three different studies (40-42) evaluating the effects of ACE inhibitors on endothelial function have found negative results. In contrast, a study by Hirooka et al. (43) showed improvement in endothelial function with ACE inhibitors. However, this study was an acute study (measurements were taken only 1 hour after oral ACE inhibitor administration) rather than a long-term study.

The recently published *Trial on Reversing Endothelial Dysfunction* (TREND) study assessed responses to endothelium-dependent and endothelium-independent vasodilators in the coronary circulation of patients with CAD (44). In this trial, only normotensive or controlled hypertensives were allowed as subjects. After 6 months of ACE inhibitor treatment, the vascular response to ACh in large coronary arteries was significantly improved when compared with placebo. Panza (19) notes that it is important to emphasize that a history of hypertension did not predict an improvement in endothelial function. This would suggest that the effect of the vessels was independent of the ACE inhibitor therapy. Panza (19) speculates that long-term ACE inhibitor therapy may result in a reduction of CAD in hypertensive patients by virtue of its positive effect

on endothelial function. Certainly, there is a need for further investigation of the effects of ACE therapy on endothelial function.

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