Effects of the Angiotensin II Antagonist, Losartan, on Circulo-respiratory Responses to Submaximal Exercise in Hypertensive Women

by

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Dissertation submitted to the faculty of the

Virginia Polytechnic Institute and State University

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Education Research and Evaluation

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October 30, 1997

Blacksburg, VA

Keywords: Hypertension, Angiotensin II, Losartan, Total peripheral resistance and Exercise

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(ABSTRACT)

The effects of the antihypertensive agent Losartan (Lo), on acute exercise performance was assessed in six sedentary, hypertensive women. The purpose, benefits and potential risks of the study were explained to each subject and their informed consent received. In a double blinded crossover design subjects were randomized to 7 days of (Lo) 50 mg, once every morning or placebo (Pl). Subjects reported to the laboratory for an exercise trial on the 7^{th} treatment day. They received the final treatment dose 2.5 hours before the exercise trial. Blood samples for analysis of plasma renin activity (PRA) and Angiotensin II (Ang II) were obtained 15 min before the exercise trial began. In each trial, the subject rested for 15 min in a seated position on the stationary cycle. Hemodynamic and respiratory measurements were obtained. They began exercise at a workload equivalent to 45% $VO_{2\,pk}$ for 15 min, immediately followed by a progression of 30 Watts min^{-1} until volitional fatigue. Measurements included: blood pressure, heart rate, respiratory gas exchange, cardiac output (Q) and rate of perceived exertion (RPE). Total peripheral resistance index (TPRI), stroke volume index (SVI) and rate pressure product (RPP) were calculated. Compared to the pre-administration conditions, 1 week of Losartan

treatment significantly reduced ($p < .05$) resting MAP, SBP and DBP in these subjects. Losartan treatment did not modify submaximal exercise HR, Q, VO_2 or RPE. The RPP also was not different between the Lo and Pl trials at rest ($p > .05$), but was reduced at peak exercise with Lo treatment ($p < .05$). Losartan significantly reduced calculated TPRI at rest ($p < .05$) in comparison with Pl (12%) but not during steady-state exercise. Circulating plasma levels of Ang II and PRA were significantly higher with Lo ($p < .05$). In conclusion, Losartan, a new antihypertensive medication, reduced BP without altering exercise performance in hypertensive women. Losartan is an appropriate first line antihypertensive agent to use in treatment of hypertensive individuals who wish to participate in a regular exercise program.

ACKNOWLEDGEMENTS

I thank my committee members for the time, direction and expertise they provided throughout my education, especially during these final steps. The members are Drs. Shala Davis, John Lee, Doug Southard and Edwin Wilder. To my advisor and co-chair, Dr. William Herbert, I thank you for being a mentor who provided opportunities, encouragement and direction as I travelled an unknown path. Thank you, Dr. Jimmie Fortune, my co-chair, whose open door policy found me inside on many occasions for assistance in statistics and a friendly chat. A special thank you to Dr. Shala Davis a mentor and friend who spent many early hours in the cardiac program and exercise lab helping me perfect my teaching and research skills.

I would never have made it through this educational adventure without my dear friends Jeff and Pam Ocel. They included me as part of their family. They shared their love, laughter, fun and children. They are a family.

To all the great folks in the cardiac rehab program who made each morning at VT fun, thank you. Of course this would not have been possible without the subjects who gave up early morning hours to help me out. Thanks to Rick Davis who assisted with the data collection.

I especially thank my parents, family and friends who provided constant support and encouragement to help me accomplish my goal. I thank God for giving me strength to endure what seemed like impassable obstacles, to persevere and to achieve the goals I set for myself.

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Chapter I

INTRODUCTION

Hypertension, defined as a systolic blood pressure of 140 mmHg or greater and / or a diastolic blood pressure of 90 mmHg or greater, is the most prevalent of the cardiovascular diseases (American Heart Association, 1993). It is present with increased frequency in patients who have arteriosclerotic and atherosclerotic diseases such as, coronary artery disease (CAD), peripheral vascular disease (PVD), cerebral vascular accidents (CVA) and renovascular diseases (Pickering, 1990; Levy, Wilson, Anderson and Castelli, 1990; Chobanian, 1986). Hypertension presents a major health problem in the United States, as there are over 55 million people with known high blood pressure, nearly half of these are women (Burt, Whelton, Roccella, Brown, Cutler, Higgins, Horan and Labarthe, 1995). Ninety-five percent of all hypertension is classified as primary or essential hypertension, where the pathogenesis is unexplained. The remaining 5% of hypertension, classified as secondary hypertension, is a manifestation of an underlying disease (such as, polycystic kidney or Cushing's syndrome). Although the cause for essential hypertension is unknown, multiple factors, mechanisms and their interactions have been implicated as possible sources in the disease process. These factors include a genetic predisposition, defects in transport of sodium across the cell membrane, overactivity of sympathetic nervous system, circulating insulin, endothelial cell injury and smooth muscle cell hypertrophy (Kaplan, 1992; Thadani, 1996).

The endothelium lining of blood vessel walls have paracrine factors that influence underlying smooth muscle tone and platelet aggregation (Harrison, 1992). Abnormalities in endothelium may influence vascular hypertrophy and local regulation of blood flow. The

endothelial cell can be damaged as a result of increased wall shear stress allowing lipoprotiens to penetrate the lining and promote cell proliferation and adherence (Sprague, Steinbach, Nerem and Schwartz, 1987). The endothial cell may be a primary contributor to or perhaps an underlying cause of hypertension.

Neurohormonal mechanisms involving the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) also have been implicated and extensively studied in efforts to delineate their contributing roles in the development of hypertension. Abnormal functions of the RAAS, specifically angiotensin II (Ang II) contribute directly and indirectly to development of high blood pressure. The direct effects are mediated through the vasoconstriction of vascular resistance vessels and veins. The indirect effects of Ang II result from activation of the sympathetic nervous system, aldosterone synthesis and release and vascular smooth cell hypertrophy. There is strong evidence from research and drug trials with angiotensin-converting enzyme (ACE) inhibitors that Ang II is actively involved in the generation of vascular lesions and stiffening in the arterial wall (Simon, Levenson, Bouthier, Maarek, and Safar, 1985; Asmar, Pannier, Santoni, Laurent, London, Levy, and Safar, 1988; Powell, Clozel, Muller, Kuhn, Hefti, Hosang, and Baumgartner, 1989; Hayoz, Nussberger, Waeber, and Brunner, 1993).

Regardless of the cause(s), hypertension is a chronic disease that can be controlled with proper medical management in the majority of those afflicted. The goal of medical management is to reduce and maintain blood pressure to levels considered desirable for the health of the individual. The American Heart Association (AHA) defines desirable levels as a systolic blood pressure (SBP) below 140 mmHg and a diastolic blood pressure (DBP) below 90 mmHg. A reduction in the diastolic blood pressure of 5-6 mmHg can reduce the incidence of stroke 40%

and the incidence of cardiovascular disease (CVD) by approximately 25% (Poulter, 1991). Hypertension was reclassified in the Fifth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (1993), to stress the increased risk of CVD even with a high normal blood pressure. This reclassification was a culmination of scientific evidence that indicated active detection and management of high blood pressure has contributed to a decline in CVD mortality (American Heart Association, 1993).

The treatment strategy for high blood pressure depends on the severity, evidence of target organ damage and coexisting cardiovascular risk factors. There is little doubt about the benefit of reducing hypertension using pharmacologic or nonpharmacologic therapy. The initial steps in management of high normal, mild and moderate blood pressure involve efforts to change lifestyle behaviors. Recommended lifestyle changes include increasing physical activity and reducing body fat, dietary salt and fat intake and alcohol consumption. Of these lifestyle changes, regular physical activity has emerged as the one change that is physiologically effective and desirable.

Epidemiological studies have made significant contributions to understanding the beneficial effects of physical activity on the reduction of risk factors for heart disease. These studies have presented evidence for a causal role of physical inactivity and the development of hypertension and cardiovascular disease (Blair, Goodyear, Gibbons and Cooper, 1984; Blair, Kohl, Paffenberger, Clark, Cooper and Gibbons, 1989; Blair, Kohl, Barlow and Gibbons, 1991; Paffenberger, et al., 1991). Physically active hypertensive individuals have a lower mortality rate than hypertensives who are not active (Paffenbarger, Jung, Leung and Hyde, 1991; ACSM, 1993; Blair, et al., 1991). The noted improvements in blood pressure with regular physical activity is often accompanied by favorable adapatations of other risk factors. Many investigators have

demonstrated a modest, but statistically significant reduction in blood pressure with regular aerobic exercise (Sannerstedt, Wasir, Henning and Werko, 1973; Cade, Mars, Wagemaker, Zauner, Packer, Privette, Cade, Peterson and Hood-Lewis, 1985; Duncan, Farr, Upton, Hagan, Oglesby and Blair, 1985; Jennings, Nelson, Nestel, Esler, Korner, Burton and Bazelmans, 1986**;** Matsusaki, Ikeda, Tashiro, Koga, Miura, Ideishi, Tanaka, Shindo and Arakawa, 1992).

Lifestyle changes require time. These changes are not easily made and may not provide the necessary reduction in blood pressure. Therefore, adjunct pharmacological therapy may be necessary in some situations, especially if target organ damage is present.

The goals of antihypertensive drug treatment are numerous. First, it is to reduce and then maintain a normal blood pressure. Secondly, it is used to prevent target organ damage, cardiovascular events and premature death (Zanchetti, 1994; JNC V, 1993; WHO/ISH Mild Hypertension Liaison Committee, 1993). The appropriate antihypertensive agent to use as initial monotherapy is individualized, and depends on age, race, economic status and concomitant medical condition(s). One of the challenges of managing hypertension is compliance with drug therapy. Side effects present the greatest influencing factor to compliance. Compliance with pharmacologic therapy can reduce morbidity associated with hypertension. Noncompliance hinders effective treatment and prolongs the time to stabilize blood pressure (Miller, Wikoff, and Hiatt, 1992). Undesireable side effects associated with the medication, the number of doses required each day and the cost will influence patient compliance. The use of an agent with minimal side effects, given as a single daily dose, may be more conducive to compliance.

Physical activity is an important part of the behavioral aspect in managing hypertension. It is important to utilize antihypertensive medications that will not impair the ability to perform

physical activity or have a negative impact on its benefit. Traditional antihypertensive therapy uses diuretics, ß-adrenoceptor antagonists (ß blockers) and angiotensin converting enzyme(ACE) inhibitor medications as the drugs of first choice.

Increasing physical activity while taking diuretics may lead to hypokalemia and enhance their volume depleting action. Ikram, Chan, Espiner and Nicholls, (1980) demonstrated a 5 day regimen of diuretic therapy increased in the plasma levels of angiotensin II and aldosterone in a small group of congestive heart failure patients. Therefore, in an attempt to lower blood pressure with diuretics one could actually trigger the renin-angiotensin-aldosterone system into action. This action is a protective mechanism against volume depletion, and ultimately it can lead to increase blood pressure.

ß blockers have several side effects that may negate its use in hypertensive patients who wish to follow a physically active lifestyle. ß blockers, particularly those of the non-cardioselective type, increase feelings of dizziness, lethargy and fatigue. They also have a negative influence on blood lipid levels. Therefore, they would be contraindicated in hypertensive patients with cholesterol problems and hyperlipidemia.

ACE inhibitors are a common class of drugs used to treat hypertension. ACE inhibitors reduce blood pressure by several mechanisms. The principal action is to block the renin-angiotensin-aldosterone system. ACE inhibitors prevent the conversion of angiotensin I to angiotensin II, a potent vasoconstricting hormone. The resulting action is vasodilation of the systemic arterioles, reducing peripheral resistance and therefore lowering blood pressure. ACE inhibitors also enhance the effects of braykinin and prostaglandins. These autocrine and paracrine agents, are involved in local control of blood vessel vasodilation and inhibition of

platelet aggregation (Tepperman and Tepperman, 1989). A common undesireable adverse side effect of ACE inhibitors is a persistent dry cough necessitating the termination of its use.

Recently, a new agent has been approved for use in the treatment of hypertension. Losartan Potassium (Losartan) is an oral angiotensin II antagonist (Ang IIA). The preliminary advantages Losartan offers over other antihypertensive agents, specifically angiotensin converting enzyme (ACE) inhibitors, is its selectivity and specificity of action (Kang, Landau, Eberhardt, and Frishman, 1994). Losartan prevents the vasopressor effects of circulating angiotensin II at the receptor site and does so without interfering with bradykinin and prostaglandin actions (Christen, Waeber, Nussberger, Porchet, Borland and Lee, 1991; Christen, Waeber, Nussberger, Lee, Timmermans and Brunner, 1991; MacFayden and Reid, 1994; Carr and Prisant, 1996).

Clinical studies have shown ACE inhibition to reduce mortality in patients with heart failure and improve left ventricular function (Cohn, Johnson, Zieche, Cobb and Tristani, 1991). The hemodynamic effects of Losartan studied in congestive heart failure patients demonstrated vasodilator actions and reductions in mean arterial pressure (Dickstein, Gottlieb, Fleck, Kostis, Levine, DeKock and LeJemtel, 1993; Eberhardt, Kevak, Kanf and Frishman, 1993). Losartan may not only reduce and control high blood pressure, but may also provide beneficial results in the treatment of left ventricular hypertrophy (LVH) resulting from the chronic pressure overload of hypertension.

Clinical drug trials indicate that Losartan produces well-tolerated, long lasting benefits in essential hypertensive individuals with single daily doses, ranging from 50 to 100 mg (Burnier, Rutschman, Nussberger, Versaggi, Shahinfar, Waeber and Brunner, 1993; Nelson, Merrill, Sweet,

Bradstreet, Panebianco, Bryny, Herman, Lasseter, Levy, Lewis, McMahon, Reeves, Ruff, Shepherd, Weilder and Irvin, 1991). Tsunoda, Abe, Hagino, Omata, Misawa, Imai and Yoshinaga (1993), demonstrated a reduction in blood pressure and minimal adverse side effects with incremental increasing doses of Losartan in eight male hypertensives. They reported that serum uric acid levels were reduced, which may have significant clinical relevance in hypertensives who also suffer from gout. Losartan may prove beneficial in other RAAS abnormalities. Future research will tell.

Regular physical activity is an appropriate and recommended nonpharmacologic therapy in treatment of hypertension (Fagard, 1991; Fletcher, et al, 1996; ACSM, 1993). Exercising at low to moderate intensity levels (40 -60 % of VO_2 max) can reduce blood pressure as much if not more than exercising at higher intensities (ACSM, 1993). There is limited research published on the hemodynamic alterations of exercise during Losartan therapy. Therefore, it is important to ascertain the physiological effects and subjective effort of physical activity that may be a consequence of Losartan.

Statement of Problem

The medical community and healthcare professionals recommend and support physical activity as an appropriate nonpharmacologic intervention in management of mild to moderate high blood pressure. Concurrent pharmacological therapy may be required depending on coexisting cardiovascular risk factors and medical conditions. Losartan is a new pharmacologic agent used in the treatment of essential hypertension. Its antihypertensive properties are effective over a 24 hour period, following a single daily dose (Goldberg, Dunlay and Sweet, 1995). Current literature indicates that losartan significantly reduces blood pressure in hypertensive individuals

with minimal adverse side effects (Nelson, et al., 1991). Losartan may offer other specific cardiac, renal and vascular protective benefits as well (Brunner, Nussberger, Burnier and Waeber, 1993; Carr and Prisant, 1996). The effects of Losartan on hemodynamic and respiratory parameters during exercise need to be elucidated.

Significance of Study

Since the mid-1980s cardiovascular disease rates in men have steadily decreased. Over the same period, heart disease has replaced breast cancer as the number one cause of death in women (AHA, 1993). There are more than 25 million women in the United States with high blood pressure. Therefore, women represent a clinically relevant group of the population who would receive drug therapy for treatment of hypertension. Many questions exist in the medical community regarding gender differences in disease and treatment responses (Mann, 1995; Gura, 1995). Current research indicates significant gender difference exists in response to medications. These differences may be related to hormonal fluctuations (Jensvold, 1992). The lack of women participating in drug trials provides a significant clinical problem for practitioners who need evidence to support the best approaches to pharmacologic management of their female patients.

Research Hypotheses

H_O: The hemodynamic responses to submaximal exercise in hypertensive women are the same when taking Losartan or a placebo.

H_O: The respiratory responses to submaximal and maximal exercise in hypertensive women are the same when taking Losartan or a placebo.

Basic Assumptions

The following assumptions were made:

1. Three separate blood pressure measurements taken after a seated rest in a quiet laboratory environment were adequate to determine the presence of hypertension.

2. Short-term dosing of Losartan, (eight daily doses) will provide therapeutic levels of the drug.

3. The exercise session conducted 2.5 hours after the last dose provides sufficient time for the drug to be assimilated and mediate a pharmacologic effect .

4. Laboratory training experience and practice trials adequately familiarized the subjects with the cycle ergometer, breathing apparatus and cardiac output rebreathing techniques, so as to minimize habituation effects on their exercise performance.

5. Subjects exerted a maximal effort during determination of maximal oxygen consumption.

Delimitations

The following delimitations are present in this study:

1. The subjects were volunteers who previously had been diagnosed by their physicians as having essential hypertension.

2. Subjects served as their own control within each treatment.

3. Subjects were pre-menopausal females, who were not engaged in a regular exercise program.

Limitations

The following limitations are present in this study:

1. The sample size is small.
2. The subjects were volunteers, thus selected in a non-random fashion.
3. The findings cannot be generalized to the population of individuals with hypertension.
4. The subjects were not identical in the extent or duration of hypertension.

Definitions and symbols

Hypertension (HTN) - chronic elevation of blood pressure; defined in this study as a mean arterial pressure $\geq$ 110 mmHg on three separate days.

Heart Rate (HR) - the number of heart beats per minute ($bt \cdot min^{-1}$).

Systolic blood pressure (SBP) - the maximum pressure in the arterial system, estimated by auscultation of the brachial artery and measured in millimeters of mercury (mmHg).

Diastolic blood pressure (DBP) - the minimum pressure in the arterial system; estimated by auscultation of the brachial artery and measured in millimeters of mercury (mmHg).

Mean arterial pressure (MAP) - the measure of average pressure load imposed on the systemic vasculature; estimated as 1/3 (systolic pressure - diastolic pressure) + diastolic pressure.

Rate-pressure product (RPP) - the product of heart rate and systolic blood pressure; used as a relative index of myocardial oxygen demand.

Stroke Volume (SV) - the calculated volume of blood ejected from the left ventricle with each heart beat.

Stroke Index (SI) - stroke volume divided by body surface area (SV/BSA); a correction for differences in body size ($ml \cdot stroke^{-1} m^{-2}$).

Cardiac Output (Q) - the amount of blood ejected by the left ventricle into the aorta in a minute; the product of heart rate and stroke volume ($L \cdot min^{-1}$).

Cardiac Index (CI) - cardiac output divided by body surface area (Q/BSA); a correction for differences in body size ($L \cdot min^{-1} m^{-2}$).

Total peripheral resistance (TPR) - the resistance of the entire systemic circulation to the flow of blood. Calculated from MAP/Q (mmHg / $L \cdot min^{-1}$).

Total peripheral resistance (TPRI) - mean arterial pressure divided by cardiac index; a correction for differences in body size (mmHg/ $L \cdot min^{-1} \cdot m^{-2}$).

Oxygen consumption (VO_2) - the volume of oxygen utilized by the individual, during any given period of time ($ml \cdot min^{-1}$)

Peak oxygen consumption (VO_{2pk}) - the criterion measure of aerobic capacity; the highest volume of oxygen consumed at peak exercise; normalized for body weight ($ml \cdot kg \cdot min^{-1}$).

Respiratory exchange ratio (RER) - the ratio of carbon dioxide expired to oxygen consumed at the level of the lungs, measured by open circuit spirometry. An RER exceeding 1.1 was used to indicate the subjects gave a maximal effort during VO_{2pk} testing.

Ventilatory equivalent (VE/VO_2) - the ratio of the volume of air ventilated and the amount of oxygen consumed by the tissues. Indicator of breathing economy ($L \cdot min^{-1}$).

<u>Indicators of Perception</u>

Rate of perceived exertion- legs (RPE_L) - an individualš subjective assessment of the effort required for the exercise; specifically how the legs felt.

Rate of perceived exertion- overall (RPE_O) - an individual's subjective assessment of the effort required for the exercise; specifically how the entire body felt.

Indicators of Circulating Hormones

Angiotensin II (Ang II) -an octapeptide formed from the precursor Angiotensin I, by the activity of angiotensin converting enzyme. Ang II is a potent vasopressor hormone and stimulator of aldosterone production and secretion; measured by radioimmune assay.

Plasma Renin Activity (PRA) - Renin, an enzyme that leads to angiotensin I formation. Determination of renin activity, by radioimmune assay measurement of angiotensin II.

Chapter II

REVIEW OF LITERATURE

Development of Hypertension

Hypertension is a medical diagnosis in which blood pressure is chronically elevated above levels considered acceptable or desirable for the health of an individual. Hypertension can be an asymptomatic disease. The disease progression is slow and its presence does not reveal the cause nor maintenance of the higher pressures (Egan & Schmouder, 1988). The hemodynamic pattern of hypertension can vary considerably among the diagnosed hypertensive population. Long term regulation of blood pressure is maintained through changes in extracellular fluid, blood volume, renal mechanisms and microcirculatory structures. Therefore, by the time elevated blood pressure is diagnosed as hypertension, the initiating factors may be lost due to mechanisms that alter cardiac output and / or peripheral resistance (Kaplan, 1992).

The two most important determinants of blood pressure are cardiac output and total peripheral resistance. The persistent elevation in blood pressure develops in response to either an increase cardiac output or a rise in total peripheral resistance.

Julius (1988) described essential hypertension evolving through two different phases: an early phase and an established phase. In the early phase of hypertension the characteristic hemodynamic disturbances include increased heart rate and cardiac output. He attributes this "hyperkinetic" circulation to neurogenic mechanisms. The hemodynamic disturbance in the established phase of hypertension is an increase in total peripheral resistance. Cardiac output and stroke volume remain within normal ranges with the heart rate usually higher than in normal

control subjects. The early phase of hypertension would coincide with functional changes within the circulatory system while the established "chronic" phase relates to the structural adaptations that occur.

Vascular Changes in Hypertension

The cardiovascular system constantly adjusts to various neurohumoral agents, metabolic requirements of local tissue and postural changes via vasocontriction and vasodilatation of vascular beds in order to maintain arterial pressures at levels that ensure optimal blood flow to all vascular beds. The arterial system adjusts to elevated pressure with functional and structural adaptations related to the overload principle (Egan & Schmouder, 1988).

The functional changes are a first line of defense to altered volumes and pressures within the arterial system. Rapid autonomic neural responses and baroreceptor reflexes respond via vasoconstriction or vasodilatation to maintain normal arterial pressure (Strauer, 1987).

The constant overload leads to structural adaptations, hypertrophy of smooth muscle and resetting of the baroreceptor reflex (Zanchetti and Mancia, 1991). Early structural adaptations of smooth muscle cells in the arterial system maintains the wall thickness (w) to lumen radius (r_i) proportional to the presenting pressure (P). Therefore, according to Laplace's law, the tension per unit (T) remains constant. As the smooth muscle cells hypertrophy, there is a concomitant decrease in lumen radius, leading to development of concentric vascular hypertrophy. The luminal reduction is a critical factor in the determination of vascular resistance. Based on Poiseuille's law, minor changes in luminal diameter of a vessel has an exponential effect on blood flow resistance (Jern, 1992). These structural changes correspond to the functional requirements of the vasculature. Once structural adaptations correct for a given pressure or load, they induce

other functional and structural changes, increasing peripheral resistance and ultimately elevating blood pressure. The cycle then continues to repeat. This represents a positive feedback interaction. These changes can occur within a few months in humans. The vessels may become less distensible than those seen in the resistance vessels of normal controls (Folkow, 1988). Therefore, in the established phase of essential hypertension, the cardiac output reverts to normal ranges and total peripheral resistance is elevated compared to age matched controls. When elevated blood pressure is left untreated, the intima of the vessel walls become damaged, and accelerate arterial and atherosclerotic processes (Kaplan, 1992).

Cardiac Structure And Function In Hypertension

Hypertension induces changes in cardiac structure and function. The heart adapts to the physiologic or pathologic hemodynamic loads, pressure or volume imposed upon it. The adaptations can result in either concentric or eccentric hypertrophy of the left ventricle (Jern, 1992). Concentric hypertrophy is characterized by an increased left ventricular mass, increased wall thickness, and decreased left ventricular chamber size. These changes result from chronic exposure to increased afterload. Eccentric hypertrophy develops from a chronic volume overload and increased preload. The left ventricular mass and chamber volume size are increased. The ratio of wall thickness to chamber diameter remains the same (Jern, 1992).

Hypertension and LVH accelerate atherosclerosis in coronary arteries, increases myocardial oxygen demand, and limits the oxygen supply to the myocardium. These conditions increase incidence of cardiac arrhythmia, ischemic episodes, myocardial infarction and sudden death. Hypertension is the major cause of heart failure in the United States (DiPette and Frolich, 1988). Changes in cardiac structure occurs parallel to vascular changes. Therefore, evidence of

left ventricular hypertrophy (LVH) present in electrocardiography and echocardiography studies can provide an indication of the concurrent peripheral changes, which occur with essential hypertension and are not easily assessed (Strauer, 1987). When using echocardiography, the prevalence of LVH in the hypertensive population is estimated to be 20-42% (DiPette and Frolich, 1988; Bahler and Gatzoyis, 1990). Koren, M., Casale, P., Savage, D. and Laragh, J. (1990), followed 250 hypertensives over a 10 year period and noted all-cause mortality and cardiovascular events were higher in hypertensive subjects with concentric hypertrophy.

Exercise Hemodynamics In Hypertension

Julius, (1988), described mild hypertensive subjects as having a "hyperkinetic" circulation. This was characterized by an increased heart rate (HR) and high cardiac output (Q), at rest. While at rest, individuals with essential hypertension have an increased total peripheral resistance (TPR) and a normal or low stroke volume (Lund-Johansen, 1980). Several studies have demonstrated an attenuated response to exercise in hypertensive subjects, leading to a normalization in circulation. During exercise the HR is increased, stroke volume and Q increase subnormal, and there is an attenuation in the reduction in TPR compared to normotensive, age matched controls (Sannerstedt, et al., 1973; Lund-Johansen, 1991).

Sannerstedt, et al., 1973, compared hemodynamics at rest and during exercise in 5 mildly hypertensive men before and after 6 weeks of supervised aerobic training. All subjects were removed from antihypertensive therapy before participating in the study. Hemodynamics measured at rest and during exercise included HR, invasive blood pressure and oxygen consumption (VO_2). The Q was obtained using dye-dilution technique. Peripheral resistance, stroke volume (SV) and arteriovenous oxygen difference were calculated. The HR, MAP and

RPP were reduced at rest and during exercise after the training. After training, Q was lower although not statistically significant. Calculated SV was unchanged therefore the lower Q was attributed to a lower HR. The results of calculated TPR were inconsistent although MAP were reduced. These results parallel results seen in normal controls after participating in a conditioning program.

Fagard, Staessen and Amery (1988), measured hemodynamic responses, invasively, to maximal graded exercise on cycle ergometer in 50 untreated hypertensive men. They found reduced stroke volume, cardiac output and maximal oxygen consumption. When the investigators controlled for age, the reduction of maximal oxygen consumption (16%) was seen in the high resting blood pressure group. The results of this study were consistent with other hemodynamic measurements in hypertensive subjects during exercise (Sannerstedt, et al., 1973; Franciosa, Ragan and Rubenstone, 1976; Lund-Johansen, 1991).

Cross sectional studies comparing subjects of varying ages and stages of hypertension indicate there is a progression from a "hyperkinetic state" early to a normal kinetic state and increased peripheral resistance. These studies could be misinterpreted if independent factors which contribute to altered cardiovascular function, such as age, dietary intake and obesity are not accounted for during analysis. There is a question of whether young individuals with borderline or mild hypertension will develop essential hypertension later in life. These concerns can be address through longitudinal research.

Lund-Johansen, (1991) conducted a 20 year longitudinal study to follow the natural course of change in hemodynamics and cardiac abnormalities that develop in male hypertensive subjects (age 17 - 66) and a group of normal controls. The subjects were divided into 4 groups

according to age (group I 17-29, n=19; group II 30 -39, n=17; group III 40-49, n=25 and group IV 50-66, n=16). The subjects under 50 years of age were hypertensive with a hyperkinetic state and normal peripheral resistance. Initially, all subjects had invasive hemodynamic measurements at rest and during exercise. The young hypertensive subjects had a high Q, normal TPR, HR was 15% higher and VO_2 was also higher at rest than age matched controls. Therefore, the increased blood flow matched the increase oxygen demand of the tissue and there is not a hyperperfusion state. This pattern changed with increasing age, as low Q and high TPR were noted.

During exercise measurements all hypertensive subjects had reduced Q. Blood flow related to VO_2 was also reduced. Since HR increased proportionally to exercise, the lower Q was a result of attenuated SV. TPR did not fall to the same low levels of age matched controls. It was concluded that there is a disturbance in the resistance vessels in all stages of hypertension.

The ten year follow-up, invasively, studied 33 hypertensive subjects all from groups I - groups III. There were only 4 surviving members of group IV at this follow-up. None were studied invasively. All subjects restudied were untreated for hypertension over the previous 10 years. In groups I, the rest data showed little change in MAP and a significant decrease in VO_2. VO_2 was essentially unchanged in Group II at rest. During exercise VO_2 was slightly decreased in both groups, compared to initial data. MAP was significantly increased in both groups during exercise. TPRI was also significantly increased at rest and during exercise in both groups. Cardiac Index (CI) was significantly decreased at rest and during exercise. The reduction is related to a decrease in stroke index (SI). There were no noted differences in HR at rest or during exercise in group I but group II had significant decrease in HR at rest, but not in exercise.

Group III demonstrated significant increase in MAP, increased TPR and decreased Q at rest and during exercise. After 10 years, group IIIs cardiac function was markedly reduced.

At the time of the twenty year follow-up, a total of 50 subjects were restudied invasively (group I=14; group II = 15; and group III = 21). All subjects who were taking antihypertensive medicine (n=21) had treatment discontinued under clinical supervision 2 months before the invasive measures were made. The CI and SI were reduced along the same magnitude as noted at the 10 year follow-up. TPRI was significantly increased in groups I and II. HR was reduced from the previous study only during exercise and TPRI was again markedly increased.

Group III subjects had been treated with antihypertensive therapy over the previous ten years, treatment was stopped for only 2 weeks before invasive measurements. Diastolic blood pressure was significantly reduced at rest and during exercise, MAP was only slightly decreased. Systolic blood pressure was minimally reduced at rest but significantly attenuated at each level of exercise. CI was reduced 31% at rest and 25-40% during exercise. There were significant differences at rest and during exercise SI was reduced, with an significant reduction in HR and TPRI was dramatically increased at rest and during exercise compared to the initial and 10 year studies. Unfortunately, normal controls were not restudied after the 10 year follow-up.

The results of this longitudinal study demonstrate a definite change in the pattern of hypertension, from a high CO, low peripheral resistance, early, to a decreased CO and high resistance in well established hypertension. There were also noted differences in the hemodynamic pattern of hypertension when comparing young hypertensives (group I with the older hypertensives (group IV) where entry level MAP was the same. The older population tended to have higher systolic blood pressures with low CO and a higher TPRI at rest and with

exercise. Lund-Johansen concluded the lower CO is compensated by increased arteriovenous oxygen difference and reduced oxygen reserve in the blood flow.

Renin-Angiotensin System

There are a multitude of factors that stimulate cardiac and vascular hypertrophy and potentially lead to development of essential hypertension. This review will focus on the role of the renin-angiotensin system in the development of essential hypertension.

The renin-angiotensin-aldosterone system (RAS) plays a role in both short term and long term regulation of arterial blood pressure. The primary physiological functions of the RAS are to maintain homeostasis of the body's fluid volume, electrolyte balance and blood pressure. In the short term regulation of arterial pressure, the RAS reacts within minutes to acute loss of blood volume or blood pressure through its vasoconstrictor mechanisms and stimulation of norepinephrine release from sympathetic nerve endings. The RAS long term regulation of body volume and arterial pressure comes via stimulating the release of aldosterone.

The RAS was traditionally thought to act exclusively through the endocrine system, circulating angiotensin II (Ang II). Renin secretion and therefore Ang II formation are controlled by renal arteriolar blood pressure, sodium concentration of tubular fluid and renal sympathetic nerve activity. Renin, an enzyme, secreted from the juxtaglomerular cells of the afferent and efferent arterioles, cleaves angiotensinogen to form angiotensin I (Ang I), a biological inactive substance. Angiotensin converting enzyme (ACE) converts Ang I to Ang II. ACE is the rate-limiting step in Ang I conversion to Ang II, but ACE levels do not vary acutely. Therefore, renin is the major rate-limiting step in determining circulating plasma Ang II levels.

Ang II has affects on multiple organs such as the kidneys, adrenal glands, heart and vascular smooth muscle. Ang II has several sites of action in the kidney. It stimulates juxta-glomerular cells to inhibit renin release, promotes sodium reabsorption in the distal tubules, and vasoconstricts efferent arterioles increasing filtering action. The adrenal response to Ang II is to release catecholamines, stimulate aldosterone and cortisol biosynthesis (Kang, Landau, Eberhardt and Frishman, 1994). Under normal homeostasis the properties of Ang II are to protect the organism from sodium and water deprivation.

Ang II can contribute to hypertension in three different ways: 1.) increase fluid retention, 2.) direct and indirect vasoconstriction of arterioles and veins and 3.) acts as a "trophic" agent in vascular hypertrophy (Fouad-Tarazi, 1994; Stock, Liefeldt, Paul and Ganten, 1995). Ang II's role in fluid retention results from stimulating aldosterone secretion from the adrenal cortex and release of an antidiuretic hormone from the posterior pituitary gland. Both of these hormones increase sodium reabsorption and water retention resulting in expansion of the extracellular fluid volume.

Ang II, a potent vasoconstrictor hormone, has a wide range of effects on many systems in the body. Its vasoconstriction properties act primarily on the arterioles, increasing peripheral resistance and elevating arterial pressure. Ang II has mild constrictor affects on the venous system, increasing blood return to the hear. It and enhancing pump function. Ang II modulates norepinephrine release from sympathetic nerve endings and blocks its re-uptake, thereby contributes indirectly to increased local vascular tone and vasoconstriction (Dzau,1993).

Ang II, an effector peptide, elicits a hypertrophic tissue response, through a complex cell signaling cascade (Tepperman and Tepperman, 1989). Ang II couples to G protein receptors

and activate phospholipase C. This initiates a downstream cascade of enzymatic reactions of second messengers such phosphatidyl inositol (PIP_2) inositol triphosphate (IP_3) and diacylglycerol (DAG). Each of these messengers have distinct responses and act cooperatively to increase intracellular calcium, activate protein kinase C, promote protein and RNA synthesis and enhance gene expression thus leading to cell hypertrophy and alteration of vascular structure (Nishizuka, 1984; Dzau, 1993). The vascular smooth muscle cell is usually quiescent. Increased wall stress as seen in essential hypertension can injure arterial wall. This injury stimulates endogenous growth promoter factors of the smooth muscle cell. Ang II augments mitogenic factors of platelet derived growth factor (PDGF), but also simultaneously activates transforming growth factor beta 1 (TGFB_1) which inhibits hyperplasia and contributes to vascular hypertrophy (Morishita, Gibbons, Ellison, Lee, Zhang, Yu, Kaneda, Ogihara and Dzau, 1994; Dahlof, 1995; Davis, Zhou, Ali, Coffin, Doetschman and Dorn, 1997).

Recent research on RAS has provided significant evidence for the existence of local tissue RAS in organs such as the kidneys, adrenal glands, heart and blood vessels (Campbell, Towrie, Kladis and Valentijin, 1991; Kim, Tokuyama, Hosoi and Yamaoto, 1992). Renin has been found in the walls of the aorta and smooth muscle cells of arteries. Ang II is locally concentrated in the periadventitial fat and media and ACE in vascular endothelial cell in hypertensive rats (Oliver and Sciacca, 1984; Okamura, Miyazaki, Inagemi and Toda,1988). Local vascular RAS may not have all the components generated at the site of action but can still function if regulatory steps take place at the site via paracrine and autocrine action. If all components of the RAS are found in sufficient amounts in the vascular wall, without local renin present, the local system draws plasma renin from the circulation, and subsequently Ang II synthesis will occur (Stock, et al., 1995).

Urata, Kinoshita, Bumpus, Graham and Husian, 1992, provided research to support evidence of partial RAS in the cardiac muscle. They detected the presence of an enzyme, heart chymase, which produces Ang II in the cardiac myocytes. The effect of this Ang II production is thought to contribute to hypertrophic, chronotropic and inotropic actions.

Local RAS exerts long term physiological effects on blood pressure regulation by directly influencing specific receptors in vascular smooth muscle, enhancing the structural and functional changes of the vasculature and cardiac systems. Local production of Ang II acts as a positive feedback mechanism in vasotone. As previously mentioned, it has direct vasoconstricting properties on the vessels. It also stimulates synthesis of prostaglandins, which produce a vasodilatory action of the vessel, balancing Ang IIš own vasoconstricting effects, which maintain homeostasis of blood flow (Dzau, 1993).

Angiotensin II Antagonists

For decades' scientists have studied the complex physiologic mechanisms and their interactions in regulation of blood pressure, and possible contributions to the development of essential hypertension. Understanding the multiple actions of RAS and Ang II in the maintenance of cardiovascular homeostasis and as a contributor to essential hypertension has cumulated in the development of RAS specific pharmacological agents, such as renin inhibitors, angiotensin converting enzyme (ACE) inhibitors and Angiotensin II antagonists (Menard, 1993). These agents block Ang II production and action at different sites of the RAS.

The first Ang II antagonist was introduced in the clinical setting in the early 1970š. Saralasin, an Ang II analog, established the role of blocking Ang II at its receptor as the most

specific and direct approach to inhibit Ang II action, whether it is generated in the systemic circulation or locally in tissue (Brunner, et al, 1993).

Brunner, Gavras, Laragh and Keenan, (1973) conducted the first study to evaluate the efficacy of saralasin in the treatment of human hypertension. Twelve patients with several forms of hypertension were recruited for the saralasin infusion. PRA was determined before and after the infusion in all patients, and classified as normal, low or high based on a renin sodium nonogram. Eight of the patients were classified as "high" PRA prior to treatment, the other 4 were "normal" or "low." The saralasin infusion varied from 2 hours to several days with fixed doses of 1, 5, 10, 50 and 100. The infusion was interrupted for an hour, and restarted to determine a blood pressure rebound effect with cessation of saralasin.

The results of this studied demonstrated a significant decrease in systolic and diastolic blood pressure during the infusion in all patients with high plasma renin levels. Maximal drop in blood pressure was seen with an infusion rate of 10 ug/kg/min with no additional decrease noted with higher infusion rates. There was a significant increase in post infusion PRA in the 10 patients whose values were obtained. In the patients with normal or low PRA, there was no change in blood pressure with saralasin infusion, even though these subjects also had a significant increase in PRA post infusion. This investigation provided clinical evidence that renin/angiotensin is actively involved in hypertension states of individuals with high renin activity. Other encouraging findings from this study were the lack of adverse side effects, renal impairment, drug toxicity or a hypotensive response with the high doses. Saralasin demonstrated the potency, efficacy and specificity of action with Ang II blockade.

The shortcomings of the saralasin were its lack oral bioavailability and intrinsic agonistic action. This prevented its use in long term treatment of hypertension.

At this same time orally active ACE inhibitors were introduced to clinical treatment of hypertension and well received in the medical community. ACE inhibitors are vasodilators with effects in both the arterial and venous systems (Fitzpatrick and Julius, 1985). The therapeutic use of ACE inhibition in the control of hypertension had been shown to reduce blood pressure approximately 10-15 mmHg and reduce total peripheral resistance with no change in heart rate, stroke volume or cardiac output at rest. During exercise these indices were not significantly altered (Omvik and Lund-Johansen, 1990). ACE inhibitors have also been successfully used in treatment of heart failure and post myocardial infarction patients, decreasing mortality in these groups of patients (Consensus Trial Study Group, 1987; The SOLVD Investigators, 1991). The reduced preload and afterload associated with ACE inhibitors improves cardiac function in heart failure patients. These inhibitors have clearly demonstrated the significant role of Ang II in development of hypertension and heart failure. As a result of these large clinical trials, ACE inhibitors have emerged as a standard pharmacological intervention in the treatment of hypertension and heart failure.

The benefits of ACE inhibitors in management of heart failure and hypertension and the promise of Ang II antagonism effectively lowering blood pressure provided stimulus to find an oral Ang II antagonist agent. It was also realized, a more specific antagonist may eliminate the major side effect common to all ACE inhibitors, a dry cough. Pharmaceutical companies synthesized many nonpeptide, Ang II selective antagonists, DuPont Medical was the first company to develop an orally active, potent Ang II antagonist, Losartan (Timmermans, Duncia,

Carini, Chiu, Wong, Wexler and Smith, 1995). Losartan became the proto-type of this new class of agents, as others quickly followed. The pharmacological properties of this orally active Ang II antagonist included a high affinity for Ang II receptors, functional antagonism, lack of Ang II agonistic properties and selectivity. Losartan was selective to Ang II receptor blockade and did not interfere with normal norepinephrine, bradykinin or serotonin activity (Brunner, et al, 1993; Timmermans, et al, 1995).

In Vivo Studies of Ang II Antagonists

In vivo studies of Ang II antagonists have demonstrated selective blockade of Ang II, leading to dose-related antihypertensive effects in several types of experimental models of hypertension. Losartan did not elicit agonist properties (Bovee, Wong, Timmermans and Thoolen, 1991; Camargo, von-Lutterotti, Campbell, Pecker, James, Timmermans and Laragh, 1993; Kanagy and Fink, 1993; Lacour, Roccon, Cazaubon, Segondy and Nisato, 1993; Basso, Kurnjek, Ruiz and Cannata, 1995).

The selective functional antagonism of the Ang II receptors, by Losartan, was demonstrated by Bovee, et al (1991) in spontaneously hypertensive dogs. The study was designed to examine the dose-response effects on renal perfusion, arterial blood pressure and heart rate in genetic modeled essential hypertensive dogs. Seven dogs received incremental doses of placebo and Losartan over a 6 week study. Pressure measurements were recorded via indwelling arterial catheter. Venous blood samples were drawn from an indwelling saphenous vein catheter for plasma renin activity. Renal clearance studies were performed from urine samples obtained from transurethral catheter after administration of drug or placebo. A dose dependent reduction in arterial pressure of 10 - 15 mmHg was seen, with no effect on heart rate. Renovascular resistance

and sodium reabsorption were also dose dependently reduced and renal perfusion was significantly increased. These effects are attributed to the selective antagonism of Ang II receptors in the renal system and peripheral vasculature.

The binding of Ang II to its receptor stimulates a downstream cascade of reactions and events leading to different physiological action depending on the effector tissue activated. The specificity of action the new nonpeptide Ang II antagonist exhibit suggests there are several types of Ang II receptors. In fact, distinct subtypes of Ang II receptors have been characterized by their radioligand binding to saralasin, losartan, or PD 123177, an Ang II antagonist developed by Park-Davis Pharmaceutical (Brunner, et al, 1993; Kang, et al, 1994; Timmermans, et al, 1995). Ang II subtype I receptor response, (AT_1) is inhibited by losartan, Ang II subtype II receptors (AT_2) are inhibited by PD123177, and both types are inhibited by saralasin. Other atypical Ang II receptors have been described in small animals and amphibians, but do not appear to be relevant to functional activity of Ang II (Siegl, 1990).

The AT_1 receptors are responsible for the known functional effects of Ang II, such as vasoconstriction, release of aldosterone, cell proliferation, and renal function. These effects are attenuated with Losartan administration but not with PD123177 (Siegl, 1990). The role of the AT_2 receptors remains under investigation.

The role of Ang II in hemodynamic response to exercise was examined in six mini-swine during treadmill running (Symons and Stebbins, 1996). Cardiac output, peripheral resistance and arterial pressure were invasively measured after doses of saralasin, losartan and normal saline administration during treadmill exercise. Losartan decreased mean arterial pressure and systemic vascular resistance during exercise compared to saralasin and normal saline. Renal blood flow

was also enhanced compared to the other treatment. This study indicated Ang II contributes to the hemodynamic responses seen with exercise, and losartan effectively attenuates these responses.

Clinical Studies with Losartan

The role of Ang II as a potential factor and cause in essential hypertension and vascular cell hypertrophy was defined with Saralasin and the ACE inhibitors. Therefore, the use of the oral Ang II antagonist Losartan, in treatment of hypertension and congestive heart failure appears promising to the medical community. It should have all the benefits of the ACE inhibitors without the adverse side effects. It also may have other potential medical benefits, such as regression of hypertrophy.

Several early preclinical and clinical studies have reported the efficacy, safety and tolerability of Losartan. Christen, Waeber, Nussberger, Lee, Timmermans and Brunner, (1991), studied the dose response effects on the pressor action of exogenous Ang I and II in healthy normotensive males in 2 consecutive studies. The first study examined the blood pressure and heart rate response of a single dose of Losartan or placebo. Losartan was administered in the morning. Predetermined intravenous Ang I bolus challenges, designed to increase systolic blood pressure 25 - 40 mmHg, were administered regularly for up to 33 hours after Losartan administration. This procedure was repeated 4 times increasing the dose of Losartan. Blood pressure measurements were obtained using finger photoplethysmography.

The second protocol examined the effects of predetermined Ang II bolus on blood pressure and heart rate response after 1, 4 and 8 days of varying doses of Losartan or placebo. Ang II challenges were administered 6 and 12 hours after day 1, as well as 24, 30 and 36 hours

after day 8 of dosing. Plasma renin activity (PRA) was determined before and 6 hours after dosing on days 1, 4 and 8.

The results of both studies demonstrated a dose dependent pressor inhibition to exogenous Ang I and II, after of oral administration of Losartan. These effects remained evident 24 hours after Losartan administration. There was also a dose dependent compensatory rise in PRA and circulating Ang II in the second study group, as would be expected with successful blockade of Ang II receptors. There were no significant adverse side effects noted in any of the volunteers in either group The drug was well tolerated as single dose, over a one week administration. These studies demonstrate the long-lasting duration of Ang II receptor blockade in healthy males (Christen, Waeber, Nussberger, Porchet, Borland, Lee, Maggon, Shum, Timmermans and Brunner, 1991).

The hemodynamic and renal response to Losartan were evaluated in pre-clinical studies using healthy volunteers (Burnier, Rutschmann, Nussberger, Versaggi, Shahinfar, Waeber and Brunner, 1993; Doig, MacFadyen, Sweet and Reid, 1995). Burnier et al, (1993) evaluated the effects Losartan in 24 healthy subjects who maintained high sodium and low sodium diets, in a double blind, crossover design study. The two 6 day diets periods were separated by a 5 day washout period. The diets were consumed in a hospital dining area under supervision of a dietitian. In the morning of diet day 6, subjects were water-loaded, and after preliminary preparations to ensure a steady state, the subjects received either 100 mg of Losartan (n =16) or a placebo (n =7).

Renal perfusion and flow, via urinary electrolyte excretion and clearance, blood pressure and heart rate were obtained at 30 minute intervals over 6 hours. Blood samples for PRA and Ang II were obtained at 4 and 6 hours after drug administration.

The results indicate a single dose of Losartan had no significant effect on blood pressure, renal flow or glomerular filtration rate regardless of the sodium content of the diets. As demonstrated in previous studies circulating PRA and Ang II levels were markedly increased at 4 and 6 hours after Losartan, an indication of successful blockade of Ang II receptors (Brunner et al, 1973; Christen, et al, 1991; Bovee, et al, 1991). The baseline activity of RAS was stimulated in the low sodium diets, with higher circulating PRA and plasma Ang II levels compared to the high sodium diet.

Losartan had a profound effect on urinary uric acid excretion with a 300% increase noted after drug administration in both diets. This was associated with a decrease in plasma uric acid. These results are similar to those found in healthy Japanese males (Nakashima, Uematsu, Kosuge and Kanamara, 1991).

Doig et al, (1995), examined the response of a single dose Losartan (100 mg) versus placebo on hemodynamic, renal excretion and hormones in healthy volunteers studied in salt depleted and salt repleted states. The salt depleted states were accomplished using twice a day doses of a diuretic, over a 3 day period. The salt repleted states were accomplished using salt replacement of 100 mmol/day. Drug administration and measurements were obtained on day 4. Each phase of the investigation was conducted over 4 days, with two week periods separating each phase.

Measurements included supine and erect blood pressures and heart rates. Blood samples were collected via intravenous catheter at intervals throughout the study to determine electrolytes and PRA. Urine collection was made immediately before drug or placebo administration and every 2 hours throughout the study day.

The results of this study are similar to those of Burnier et al, (1993). Losartan induced a significant increase in serum PRA in both salt depleted and salt repleted states, with the increase significantly greater during salt depletion. Losartan decreased urine excretion of sodium in the salt depleted state but had no significant effect on urinary volume. There was no effect on urinary volume or sodium excretion in the sodium repleted state. In a salt depleted state, there was a significant decrease in supine and erect blood pressure after losartan versus placebo administration. There were no significant differences noted between supine and erect blood pressure in the salt repleted states after losartan or placebo. Although this study noted an increase in baseline heart rate with losartan administration in the salt depleted state it was not significantly different from placebo

Nakashima, et al, (1991) examined the uricosuric effect of losartan in healthy Japanese volunteers participating in a single dose study and a multiple dose study. The single dose study divided subjects into 4 groups of 6 subjects. Each group was given 25, 50, 100 or 200 mg of Losartan after an overnight fast. Blood samples for uric acid were taken before, 4 hours and 24 hours after drug ingestion. Frequent urine samples were obtained for uric acid excretion. The results demonstrated a dose dependent decrease in serum uric acid concentration with a dose dependent increase urinary uric acid excretion.

The placebo controlled, multiple dose trial, administered 100 mg daily for 7 days to 6 subjects, while 3 subjects received placebo. Blood and urine samples were obtained 4 hours before the first and last doses and also 24 hours after the last dose. Urine sample were obtained at regular daily intervals, throughout the week. The results of this trial also showed a decrease in serum uric acid after 4 hours with a concomitant increase in urinary uric acid excretion. The effect was similar after day 1 and day 7 and similar to the single dose of 100mg. These studies suggest additional clinical benefits of losartan treatment in hypertensive and congestive heart failure patients with gout.

The pre-clinical trials investigating the antihypertensive response of losartan have demonstrated promising results in elucidating the role of Ang II as a contributing factor in essential hypertension. Losartan may have all the benefits of ACE inhibitors with a more favorable side effect profile. Therefore, it important to compare the therapeutic effects of losartan with antihypertensive agents widely accepted and utilized in treatment of hypertension.

Losartan was found to significantly lower casual and 24 hour blood pressure, in essential hypertensive patients (Tsunoda, Abe, Hagino, Omata, Misawa, Imai and Yoshinga, 1993). The patients were treated over a 2 - 4 week period with a daily dose of losartan titrated to achieve a 20mm Hg drop in supine systolic pressure and a 10 mmHg in diastolic pressure. The average losartan dose administered was 59 mg over a three week period. Serum uric acid concentration was significantly lowered with losartan therapy, without disturbance in electrolyte balance.

Ramsey and Yoe, (1995) conducted a comparative study to evaluate the incidence of cough with ACE inhibition, losartan and hydrochlorothiazide (HCTZ). A cohort of one hundred and thirty hypertensive patients with known ACE inhibitor cough were recruited to participate in

the multi-center study. The ACE inhibitor cough was confirmed by lisinopril challenge and placebo rechallenge. Patients were randomized into an eight week, once a day dose, antihypertensive treatment group to receive either losartan 50 mg, lisinopril 20 mg or HCTZ 25mg. Cough, the endpoint of the study, was measured by self reported questionnaire and average visual analogue scale score for treatment. Study phases were terminated with reports of intolerable cough. Blood pressure, heart rate, laboratory results and other adverse side effects were also considered measures.

Cough developed in 72% of lisinopril treated patients whereas losartan and HCTZ patients reported 29 % and 34 % respectively. This represents a significant difference between ACE inhibitors and the other treatments. There was an increase incidence of cough reported in women than men, although both were significantly different in the lisinopril treatment. Due to the shorter duration of lisinopril treatment the other variables were not statistically analyzed. There was a decrease in blood pressure measurements in all treatment groups. Heart rate and body weight did not differ. The results of this study support the suggestions that ACE inhibitor cough is related to bradykinin activity and the specificity of losartan does not interfere with bradykinin activity.

The safety and tolerability of losartan was demonstrated in a pooled analysis of 16 open-label double-blind clinical trials (Goldberg, Dunlay and Sweet, 1995). Approximately 3,800 hypertensive patients were enrolled in the clinical trials comparing drug related side effects between losartan, losartan and a diuretic, ACE inhibitors, calcium channel blockers, *B*-blockers, and placebo. Approximately 2,900 patients received losartan or the losartan diuretic combination. During the 8 - 12 week treatment period drug related adverse events were recorded. Headache

and dizziness were the most frequently reported side effects in patients taking losartan or the losartan and diuretic combination. The incidence of these complaints were comparable to the other antihypertensive agents as well as placebo. The report of dry cough was 3 times higher in patients receiving ACE inhibitors than either group of losartan patients. The patients receiving *B*-blocker therapy reported the highest incidence of dizziness and insomnia. The percentage of patients who discontinued losartan therapy or losartan and diuretic combination were 2.3% and 2.8 % respectfully. This was comparable to patients who discontinued ACE inhibitors and diuretics and less than the patients treated with placebo. Calcium channel blocker and *B*-blocker treated patients had the highest incidence of withdrawals (9.3%) and (8.8%), respectfully.

When reporting the drug related side effects based on demographics, the losartan groups were predominantly Caucasian males who had known hypertension for 10 years. This was comparable to other treated patients. Losartan did not have any influence on glucose, lipid levels or other metabolic factors.

There is clear evidence that losartan is an effective pharmacological agent in the treatment of mild to severe essential hypertension (Tsunoda, et al, 1993; Ramsay and Yeo, 1995; Dunlay, Fitzpatrick, Chrysant, Francischetti, Goldberg and Sweet, 1995; Goldberg, Bradstreet, McWilliams, Tanaka, Lipert, Bjornsson, Waldman, Osborne, Pivadori, Lewis, Blum, Herman, Abraham, Halstenson, Lo, Lu and Spector, 1995). It has an excellent safety profile and is well tolerated in hypertensive patients. The specificity of action permits the use of losartan use in patients with other concomitant medical problems such as renal disease and heart failure (Gansevoort, et al, 1994; Dickstein, et al, 1994; Goldberg, et al, 1995).

The Role of Physical Activity

Physical inactivity increases the incidence of cardiovascular disease, and is considered as great a relative risk for cardiovascular disease as hypercholesterolemia, hypertension and smoking (Nissinen, 1991; Blair and Connelly, 1996; Fletcher, Balady, Blair, Blumenthal, Caspersen, Chaitman, Epstein, Sivarajan-Froelicher, Froelicher, Pina and Pollock, 1996). Physical activity reduces risk of cardiovascular disease as well as modifies the effects of other risk factors such as obesity, hyperlipidemia and diabetes.

Epidemiological studies have made significant contributions to understanding the beneficial effects of physical activity on the reduction of risk factors for heart disease. These studies have presented evidence for a causal role of physical inactivity and development of hypertension and cardiovascular disease (Blair, Goodyear, Gibbons and Cooper, 1984; Blair, Kohl, Paffenberger, Clark, Cooper and Gibbons, 1989; Blair, Kohl, Barlow and Gibbons, 1991; Paffenberger, et al., 1991). The scientific evidence supporting whether exercise alone can achieve and sustain significant reduction in blood pressure remains in question. The literature is mixed with confounding variables closely associated with high blood pressure that are directly influenced by physical activity (JNC V, 1993).

The patterns of physical activity on the development of hypertension was reported by Paffenberger, et al., (1991). Three different groups of alumni, from a larger health study cohort were evaluated for the development of hypertension over a 23 year period. The alumni completed questionnaires regarding health history, lifestyle habits and type and duration of sports or leisure activities in which they regularly participated. The results of the questionnaire, indicated the alumni who did not engage in vigorous activity were at greater risk (35%) of developing

hypertension. Walking (5 - 15 km/wk) did not provide a significant reduction in hypertension incidence. Overall, this longitudinal study found an increased incidence of hypertension in men who did not engage in vigorous sports activities.

Several epidemiological studies investigating the role of physical fitness in development of hypertension and all-cause mortality have been published by Blair and associates, from Institute of Aerobics Research, in Dallas. Blair et al., (1984) published their findings on the influence of fitness levels and development of hypertension in a large normotensive population of men and women. The sedentary and low fit individuals had a 20 - 50 % increased risk of developing hypertension during the follow-up period when compared to their fit, more active peers.

Blair et al., (1989), reported the results of an 8 year follow up study, which investigated the role of fitness level on all cause mortality. Healthy men and women, were assigned a fitness score, determined by exercise treadmill tests. After adjusting for confounding variables, all cause mortality rates were lower in the higher physical fitness quintiles for both men and women than their lower fit counterparts.

Blair et al., (1991) evaluated the role of physical fitness and all cause mortality, in a large cohort of normotensive and hypertensive men over a 15 year period. The fitness levels, determined by graded exercise tests, were then classified into 5 levels. The results of this study found hypertensive and normotensive men, in the lower fitness groups, had higher incidence of death than either of the high fit groups.

Regular physical activity is recommended for prevention of cardiovascular disease (Fagard, 1991; Fletcher, et al, 1996; ACSM, 1993). Low to moderate physical activity is associated with a reduced risk for development of cardiovascular disease. Exercising at low to

moderate intensity levels (40 -60 % of VO_2 max) can reduce blood pressure as much if not more than exercising at higher intensities (Hagberg, Montain, Martin and Ehsani, 1989; ACSM, 1993). Many studies have shown the beneficial effects of exercise as a nonpharmacologic therapy in lowering blood pressure in mild to moderate hypertensive individuals (Sannerstedt, et al., 1973; Duncan, et al,1985; Nelson, et al, 1986; Hagberg, et al.,1989; Franz, 1991; Matsusaki, et al, 1992; Marceau, Kouamé, Lacourcière and Cléroux, 1993; Ried, Dart, Dewar and Jennings, 1994).

The differences in exercise protocols, as well as the divergent hypertensive population, have led to discrepancies in benefits of exercise in hypertensive subjects. The exercise effects on the average reduction in blood pressure have ranged from 4 mmHg to 20 mmHg systolic and 2 to 16 mmHg diastolic pressure. Sannerstedt, et al., (1973) demonstrated a small reduction in MAP (5 mmHg) at rest and during exercise after 6 weeks of training on cycle ergometer in 5 borderline hypertensive men. The authors concluded physical activity would be a beneficial means for normalizing blood pressure in latent hypertensive men.

A 16 week exercise training program in borderline hypertensive men resulted in significant reductions in both systolic and diastolic pressure, ranging from 6.3 to 15.5 mmHg and 6.4 to 8.1, respectfully (Duncan, et al, 1985). Similar results were reported by Matsusaki, et al., (1992) in a low intensity, 10 week exercise program. Nelson, et al., (1986), reported blood pressure reduction of 11/ 9 mmHg (systolic/diastolic) after 4 weeks of exercise performed 3 x/week. The blood pressure was reduced 16/11 mmHg, after 4 weeks of exercising 7 x/week, over the sedentary period in 13 essential hypertensive men. TPRI, MAP and HR was also significantly improved during both exercise periods.

Hypertensive individuals taking pharmacologic therapy also benefit from a regular exercise program. Significant blood pressure reductions were noted after an exercise program designed by Cade and associates, (1984). Their study assessed the effects of a regular conditioning program on blood pressure in 135 hypertensive patients. The exercise program was progressive in nature. The goal was to comfortably walk 2 miles in forty minutes and work up to running 2 miles daily. After 3 months of running, 105 subjects were evaluated. Of the patients who participated, 47 were taking medication to control blood pressure. All subjects experienced a reduction in MAP, except 5 men who had renal problems. Of the 47 patients who were taking medication for BP control, 24 were able to discontinue their medication and maintain normalized pressures with continued exercise. The 23 other patients did not increase or change medication during the study.

Summary

Hypertension presents a major health problem in the United States. It is the most prevalent of the cardiovascular diseases (American Heart Association, 1993). The goal of medical management is to reduce and maintain blood pressure to levels considered desirable for the health of the individual, as well as prevent target organ damage. Physical activity reduces risk of cardiovascular disease as well as modifies the effects of other risk factors such as hypertension, obesity, hyperlipidemia and diabetes. Participating in aerobic exercise at a low to moderate intensity can help control blood pressure (ACSM, 1993).

If pharmacologic therapy is required, the ideal medication should have minimal dose requirements, be tolerable, safe and permit a physically active lifestyle. Losartan is a new agent used to treat hypertension. It has an excellent safety profile and is well tolerated in hypertensive

patients. The specificity of action permits losartan use in patients with concomitant medical problems (Gansevoort, et al, 1994; Dickstein, et al, 1994; Goldberg, et al, 1995).

The present study was designed to assess the efficacy, hemodynamic, respiratory and perceptual responses of acute exercise in hypertensive women taking the anti- hypertensive agent, Losartan. This information will assist in the pharmacological management of hypertension in individuals who wish to incorporate a physical activity program.

Effects of the Angiotensin II Antagonist, Losartan, on Circulo-respiratory Responses to Submaximal Exercise in Hypertensive Women

Running Head: Losartan and Exercise Responses in Hypertension

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Introduction

Hypertension is a major health problem in the United States. It is estimated that 50 million individuals have elevated blood pressure (BP). Ninety-five percent of all hypertension is classified as primary or essential hypertension, where the pathogenesis is unexplained. More than 20% of hypertensives in the US are women [2] and this disease follows age and smoking in importance as a major risk factor for development of cardiovascular disease. [36]

The renin-angiotensin-aldosterone system has been implicated and extensively studied in efforts to delineate its contributing role in the development of hypertension. Angiotensin II (Ang II) contributes directly and indirectly to development of high blood pressure. The direct effects are mediated through promotion of the vasoconstriction of vascular resistance vessels and veins. The indirect effects of Ang II result from activation of the sympathetic nervous system, aldosterone synthesis and release and vascular smooth cell hypertrophy [8, 25, 27].

The goal for medical management of hypertension is to reduce and maintain blood pressure to levels considered desirable for the health of the individual. Adequate management of hypertension will reduce the morbidity and mortality associated with the disease process. The treatment strategy for high blood pressure depends on the severity, evidence of target organ damage and coexisting cardiovascular risk factors.

Regular physical activity has emerged as a primary intervention for lowering BP in mild to moderate hypertension [9]. Although the reported effects are somewhat variable [10,15,18, 38,39], considerable evidence indicates that aerobic exercise training at a moderate intensity (40 - 60% VO_2 max), in most well-controlled non-randomized studies, support the interpretation that

aerobic training decreases blood pressure an average of 6 - 10 mmHg [28, 10,16]. Many studies have shown the beneficial effects of exercise as a nonpharmacologic therapy in lowering blood pressure in mild to moderate hypertensive individuals [4,12,15,16,18,24]. The scientific evidence supporting whether exercise alone can achieve and sustain significant reduction in blood pressure remains in question. The literature is mixed with confounding variables closely associated with high blood pressure that are directly influenced by physical activity [19].

If an antihypertensive agent is needed to control blood pressure it is important to utilize a medication that will not impair the ability to perform physical activity or negate its health benefits. Losartan, a newer angiotensin II antagonist, has proven effective in the treatment of hypertension [3, 5, 13**,** 23, 28]. The safety and tolerability of losartan was demonstrated in a pooled analysis of 16 open-label double-blind clinical trials [14]. The present study was designed to assess the efficacy, hemodynamic, respiratory and perceptual responses of submaximal exercise in hypertensive women who received a short-term administration of this anti- hypertensive agent.

Methods

Subjects

Subject recruitment consisted of 125 women screened via telephone interviews. Of this number, 11 agreed to report to the exercise laboratory for assessment of BP status. Interviews were completed to select those with recent histories of physical inactivity, i.e. did regular physical activity less than two times/wk. Inclusion and exclusion criteria were based on a medical health history, physical examination, blood chemistry analysis, blood lipid profile, and urine pregnancy test. Six pre-menopausal women with known hypertension met this final screening step and were eligible to participate in the study. Each signed an Institutional Review Board approved informed

consent prior to participation in the study. There were four of six subjects taking medication for hypertension. These women had their medications withdrawn under the direction of their physician and remained without prescribed medications for then next 2 wk, i.e. prior to determination of baseline status. All subjects reported to exercise laboratory to determine baseline cardiovascular status over a 2 wk period. Subjects were evaluated three times each week to establish that they satisfied the study inclusion criteria for high blood pressure (SBP > 140 mmHg or DBP > 90 mmHg). The average of three measurements, taken on the last monitoring day, served as the entry level BP. All BP measurements were determined by auscultation in the left arm using a zero mercury sphygmomanometer [30]. One trained technician took all BPs throughout the study.

Insert Table 1. Here

Study design

This was double-blind crossover study design. The order of exposure to the two treatments was randomized . The treatments consisted of subjects receiving a tablet a day of the active drug (losartan 50 mg), or placebo for 7 days with an exercise trial performed on the seventh day. The placebo tablet was a compressible sugar tablet of similar size to that of losartan. After a 7-day washout period the identical protocol was repeated for the remaining treatment. During the trials neither the BP technician nor the subject knew whether treatment was Losartan (LO) or placebo (Pl). All exercise trials were performed in the early morning with the subjects reporting to the lab in a 4 hr post-absorptive state. Upon arrival to the lab, subjects ingested the last treatment dose and were prepared for measurements in the exercise trials. The trial began 2.5

hr after drug ingestion. While in the laboratory, the subjects' resting HR and BP were monitored every 15 min after drug ingestion.

In order to familiarize the subjects to the exercise protocol and measurements, two preliminary trials were performed prior to randomization. Next, each subject underwent a graded exercise test using a cycle ergometer (Monark 818E) to determine the maximal functional capacity. Each exercise test started at 0 Watts with 30 W increases every 2 min. Test termination occurred when the subject was unable to maintain a 60 rpm cadence, reached volitional fatigue or requested to stop. Measurement of oxygen uptake (VO_2), was determined using a computerized metabolic cart (MedGraphics CPX/D, St. Paul, MN). The highest value recorded for VO_2, in the last full minute of exercise, was accepted as peak oxygen consumption (VO_{2pk}). An electrocardiogram (Mortara-XScribe, Milwaukee, WI) was used continuously to monitor HR and the ECG responses. The exercise BP was measured in last 45 s of each stage, using the ausculatory method. Ratings of perceived exertion (RPE), overall (RPE_O) and for the legs (RPE_L) were obtained during the last 15 s of each minute.

Each of the submaximal exercise evaluation trials, performed at the conclusion of 7-day treatment periods consisted of the subject resting for 15 min in a seated posture on the stationary cycle, before hemodynamic and respiratory measurements were made. In these exercise tests, a workload equivalent to 45% of each subjects' $VO_{2\,pk}$ was imposed and continued for 15 min, with hemodynamic, respiratory and perceived exertion measurements being made in the final minutes. Immediately thereafter and without interruption of exercise, the workload was increased in a progressive manner at a rate of 30 Watts min^{-1} and continued until the subject reached volitional fatigue.

Data Collection Procedures

Blood samples were drawn via venipuncture of the antecubital vein, for radioimmunoassay of plasma renin activity [7] and angiotensin II [29] 15 min before each of the two post-treatment exercise trials. The sample for PRA was collected in a chilled tube with Sodium EDTA (1 mg/ml) and for the angiotensin II assay, in a second chilled tube with sodium EDTA (1mg/ml) and Aprotinin (500 $KIU \cdot ml^{-1}$). Samples were processed and stored at - 20°C for batch analysis.

Values for HR, BP and RPE were recorded at minutes 3, 5, 9 and 13 during both the rest and steady-state exercise intervals. Cardiac output (Q) was measured at minutes 6, 10 and 14 during both rest and steady-state exercise, by indirect Fick method, using a CO_2 rebreathing technique [4]. In each case it was verified that this 4 min period between Q measurements was sufficient to allow VCO_2 to be restored to levels noted immediately before the CO_2 re-breathing procedure required in the Q determination. Oxygen consumption was measured with the same apparatus, using breath by breath analysis via metabolic cart (MedGraphics CPX/D, St. Paul, MN).

Statistical analysis was performed with simple paired t-tests and, when appropriate, by repeated measures analysis of variance. A value of $p < 0.05$ was considered statistically significant. Data are reported as mean $\pm$ SEM.

Results

All subjects were medically classified as essential hypertensive. They had sedentary lifestyles as demonstrated by average $VO_{2\,pk}$ of 20.4 $\pm$ 2.2 (mean and SD). There were no observed or reported side effects from any subject during either treatment period. One wk of losartan (50 mg daily) treatment significantly reduced MAP, SBP and DBP from the time of entry

into the study (Table 2). In addition, losartan tended to lower resting MAP ($p = .07$), SBP ($p = .08$) and DBP ($p = .11$) compared to placebo treatment. SBP response was significantly attenuated ($p < .05$) with losartan compared to placebo treatment during steady state exercise and peak exercise (Fig. 1). Compared to placebo, losartan treatment had no effect on HR, SVI or CI (Table 3). The RPP response was not different between the two treatments at rest ($p = .45$), but was significantly lower with losartan during peak exercise ($p < .05$; Table 3). Calculated TPRI at rest was significantly reduced with losartan ($p < .05$) but not significantly different between drug and placebo during steady-state exercise (Fig. 2). Oxygen consumption, ventilatory equivalent, workloads and RPE were not altered with losartan therapy (Table 4). Levels for plasma Ang II (Fig. 3**)** and PRA (Fig. 4) were both significantly elevated after a week of losartan administration, as compared to placebo and the time of study entry. There were no differences in plasma levels of Ang II or PRA between time of entry and placebo treatment level.

Discussion

The effects of antihypertensive medication on physical activity have drawn increased attention recently, as physical activity increasingly is being advocated as effective nonpharmacological treatment for mild to moderate hypertension [11]. Pharmacological therapy may be required in addition to a regular exercise program to facilitate adequate blood pressure control. Exercise and various other acute stresses increase blood pressure as a normal physiological response.

A major concern when selecting appropriate antihypertensive therapy for active individuals is whether blood pressure is adequately controlled during exercise as well as at rest. Ostensibly, the optimal therapeutic drug should counter intrinsic tendencies for higher intravascular pressures

that increase risk of vascular accidents during activity or exacerbate disease development, but yet not blunt the central and peripheral circulatory competence needed to effectively meet exercise demands. The ß-blockers, calcium channel blockers and ACE inhibitors have demonstrated effective BP control during submaximal and maximal exercise [22, 31, 35]. The findings of this investigation extends the available information on the exercise performance and circulatory effects of losartan, in a group of women for whom this particular agent would be clinically indicated.

Losartan has been shown to effectively lower BP in essential hypertensives without altering heart rate or producing untoward side effects [14, 37]. In the early stages of essential hypertension, heart rate, stroke volume and cardiac output under resting conditions usually are increased and total peripheral resistance is not abnormal. Over time, the central hemodynamics change and there is a reduction in heart rate and cardiac output, with an increase in total peripheral resistance [13]. The subjects in the study reported here had an average resting heart rate of 71 ($bt \cdot min^{-1}$), a cardiac output of 5.2 $L \cdot min^{-1}$, a stroke volume of 70 ml/ min and a calculated TPRI of (39 $mmHg \cdot L \cdot min^{-1} \cdot m^2$). The dominating hemodynamic disturbance in the elevated blood pressure of these subjects is the increased total peripheral resistance. Thus, there is some indirect evidence that our subjects, in terms of the disease development continuum, were beyond the early stage of apparent essential hypertension. Consequently, structural changes in the vascular smooth muscle may, in part, have influenced the magnitude and pattern of hemodynamic effects induced by losartan. Somewhat different effects might be found in evaluating subjects at early stages of hypertension.

Even small reductions in DBP (4 - 6 mmHg) and SBP (10 mmHg) can reduce the risk of stroke and cardiovascular events by a third and a sixth, respectfully [2]. The reduction in DBP in

the present study ranged from 4 mmHg (at rest) to 7 mmHg (during peak exercise). This is a favorable reduction after only one week of therapy. Maximal therapeutic effects are noted after six weeks [13]. The TPRI was significantly reduced at rest with losartan therapy. There was a 14% fall in resting TPRI with losartan treatment compared to placebo. It is important to note with this reduced TPRI there was no reflex tachycardia and CI was not affected. These results are similar to calcium antagonists, without the adverse side effects. Nifedipine produced a 22% reduction in TPRI after the initial dose, but also resulted in a reflex tachycardia [21]. This is a common side effect of calcium channel blockers. The decrease in afterload improves cardiac function as demonstrated by an increased cardiac index at rest (Table 4). The acute reduction in TPRI with losartan indicates that Ang II is at least partially responsible for the increased TPR and elevated blood pressure noted in this group of subjects. When Ang II vasoconstriction action on the vascular bed is blocked, the initial decrease in blood pressure is a direct result of reduced vascular resistance [20]. Although the TPRI was significantly higher at rest in the PL treatment the percent fall (29%) was similar to LO treatment during the steady state exercise. The exercise activity provided evidence in this group of "late" essential hypertensive women they have the ability to adequately vasodilate the peripheral vasculature. This demonstrates the hypotensive benefits of exercise on peripheral vascular resistance. This study suggests if these women participate in a low level exercise program regularly they may lower their blood pressure and decrease the need for medication.

Rate pressure product (RPP), an indirect measure of myocardial oxygen consumption and cardiac work, was reduced at peak exercise with losartan verses placebo treatment. This study showed RPP was reduced 12% and 28% from resting to submaximal and peak exercise,

respectfully, during losartan treatment as compared to placebo. Losartan preserved cardiac function during the exercise trial. These results are similar to the reported effects of ACE inhibitors and calcium channel blockers in treatment of hypertension [9, 35]. Cardiac output was not altered in mild hypertensive patients after treatment with captopril [9]. Treatment with the ACE inhibitor, trandolapril did not alter exercise capacity, heart rate, energy metabolism or maximum oxygen consumption in well trained healthy male subjects [31]. The hemodynamic changes noted with ACE inhibition arise primarily from withdrawal of Ang II vasoconstriction in the vascular beds and prolonged presence of bradykinin. Losartan does not interfere with bradykinin activity.

There are a number of drugs commonly used in treatment of hypertension. These include diuretics, ß-blockers, calcium channel blockers and ACE inhibitors. When comparing losartan to other antihypertensive drug therapies, previous studies seem clear in demonstrating that losartan has a more favorable side effect profile [14]. The major drawback of ß-blockers, is the frequently reported increase in feelings of dizziness, fatigue and exercise intolerance. These side effects are especially common in non-selective ß-blockers, like propranolol. Propranolol produced a significant reduction in maximal VO_2 as well as reduced exercise times in uncomplicated hypertensive subjects during cycle exercise [35]. The report of fatigue during exercise with propranolol, may be a result of the altered availability of energy substrates rather than altered hemodynamics during exercise [22].

The subjects in this study were able to maintain exercise tolerance and achieve their maximal oxygen consumption as determined prior to treatments. All subjects were blinded to treatment condition, as the PL tablets were similar in shape and size to LO. Upon completion of

the study they were interviewed to determine if they were aware of treatment. One subject correctly identified the treatment order, but stated it did not influence her perceived effort during the exercise. Overall, subjects perceived efforts to the exercise, RPE_O and RPE_L were the same after LO treatment, as reported after PL treatment. Losartan did not have a negative effect on exercise.

Exercise has been extensively utilized in the evaluation of treatment therapy of hypertension. Resting blood pressure does not predict blood pressure responses to normal daily activities. Maximal graded exercise tests are commonly used to evaluate adequate control of hypertension after initiating drug therapy. Our protocol measured BP responses and calculated TPR, from rest to moderate then peak activity. This method simulates physical stress levels most likely to occur during an average day. It can provide more reliable means to evaluate the efficacy of antihypertensive medications.

Losartan provides an effective long acting reduction in elevated blood pressure with once a day administration. The specificity and selectivity of its action limits unwarranted side effects and does not interfere with exercise performance. The major action of losartan is blocking the vasoconstrictive effects of Ang II in the peripheral vasculature. ACE inhibitors have helped define the role of Ang II in development of heart failure and hypertension. Long term studies are needed to assess the potential benefits losartan offers in regression of cardiac, vascular hypertrophy and renal failure that develops as a result untreated hypertension.

Losartan effectively lowered BP after one week of therapy. The SBP and RPP responses to exercise were attenuated during steady state and peak exercise with losartan. The antihypertensive effects of Losartan appear to act directly on systemic peripheral resistance,

increasing vasodilatation without adversely affecting cardiac output. Losartan did not alter exercise tolerance, perceived exertion or peak exercise performance in this group of hypertensive women. From a clinical standpoint losartan may help delineate the mechanism behind some essential hypertension. It has a good side effect profile and is well tolerated. Losartan appears to be a more favorable antihypertensive agent for active hypertensive patients.

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Table 1. Clinical characteristics of subjects. (n = 6)

	$\bar{X}$	SD
Age (yr)	41.2	5.9
Weight (kg)	77.0	9.5
Height (cm)	160.8	8.2
Body fat (%)	38.0	2.4
SBP (mmHg)	144.0	6.9
DBP (mmHg)	99.0	4.3
MAP (mmHg)	114.0	3.9
HR ($bt \cdot min^{-1}$)	71.0	4.7
VO2 ($ml \cdot kg^{-1} \cdot min^{-1}$)	20.4	2.2

Table 2. Resting blood pressures for study group (n = 6) at entry into protocol and after 7-days administration of drug or placebo

BP (mmHg)	Entry	Placebo	Losartan
SBP	144 ± 2.8*	142 ± 3.2	133 ± 3.7*
DBP	99 ± 4.3*	94 ± 2.6	90 ± 2.9*
MAP	114 + 1.9 †*	110 + 2.6*	105 + 2.7 †

values expressed as means ± SEM (* $p < .05$; †$p = .001$)

Table 3. Circulatory and perceptual responses to exercise after 7 days of placebo and losartan treatment

Rest	Placebo	Losartan
HR (bts·min^{-1})	74 ± 5.6	78 ± 3.7
RPP (HR x SBP$^{10-2}$)	107 ± 8.2	104 ± 5.5
SVI (ml·stroke^{-1} m^{-2})	26 ± 1.5	25 ± 1.9
CI (l·min^{-1} m^{-2})	2.9 ± .15	3.2 ± .24
Steady state exercise		
HR(bts·min^{-1})	107 ± 6.4	107 ± 5.9
RPP (HR x SBP$^{10-2}$)	184 ± 13.2	169 ± 14.2[a]
SVI (ml·stroke^{-1} m^{-2})	25 ± 1.8	25 ± 1.5
CI (l·min^{-1} m^{-2})	4.4 ± 0.3	4.3 ± 0.3
Peak exercise		
HR(bts·min^{-1})	167 ± 4.9	170 ± 4.2
RPP (HR x SBP$^{10-2}$)	346 ± 13.2	311 ± 14.2

values expressed as means.

[a] denotes significant difference between placebo and losartan ($p < .001$)

Table 4. Respiratory and perceptual responses to exercise after 7 days of placebo and losartan treatment.

Rest	Placebo	Losartan
VO_2 ($ml \cdot min^{-1}$)	227 ± 14.3	239 ± 13.4
VE ($l \cdot min^{-1}$)	9.1 ± .35	9.1 ± .45
VE/VO_2	40.8 ± 2.0	38.3 ± 2.3
RER	.86 ± .02	.86 ± .01
Steady State Exercise		
VO_2 ($ml \cdot min^{-1}$)	732 ± 32.2	723 ± 21.4
VE ($l \cdot min^{-1}$)	25 ± 1.1	24 ± 1.4
VE/VO_2	33.9 ± 1.7	33.6 ± 1.9
RER	.92 ± .02	.91 ± .02
RPE_L	8.8 ± 2.2	9.0 ± 2.1
RPE_O	8.8 ± 2.4	8.3 ± 2.3
Peak Exercise		
VO_2 ($ml \cdot min^{-1}$)	1492 ± 91.7	1509 ± 80.9
VE ($l \cdot min^{-1}$)	62 ± 3.4	66 ± 3.9
VE/VO_2	40 ± 2.3	43 ± 3.4
RER	1.2 ± .02	1.2 ± .03
RPE_L	16.7 ± 1.1	15.8 ± 1.2
RPE_O	16.7 ± 1.1	16.0 ± 2.0
Workload(watts)	120 ± 5	120 ± 5

values expressed as means and SEM.
VO_2 -the volume of oxygen utilized by the individual, during any given period of time ($ml \cdot min^{-1}$)
RER-Respiratory exchange ratio - the ratio of carbon dioxide expired to oxygen consumed at the level of the lungs, measured by open circuit spirometry. An RER exceeding 1.1 was used to indicate the subjects gave a maximal effort during VO_{2pk} testing.
VE/VO_2 - the ratio of the volume of air ventilated and the amount of oxygen consumed by the tissues. Indicator of breathing economy ($L \cdot min^{-1}$).
RPE_L - the subjectś subjective assessment of the leg effort required for the exercise.
RPE_O - the subjectś subjective assessment of the overall effort required for the exercise.

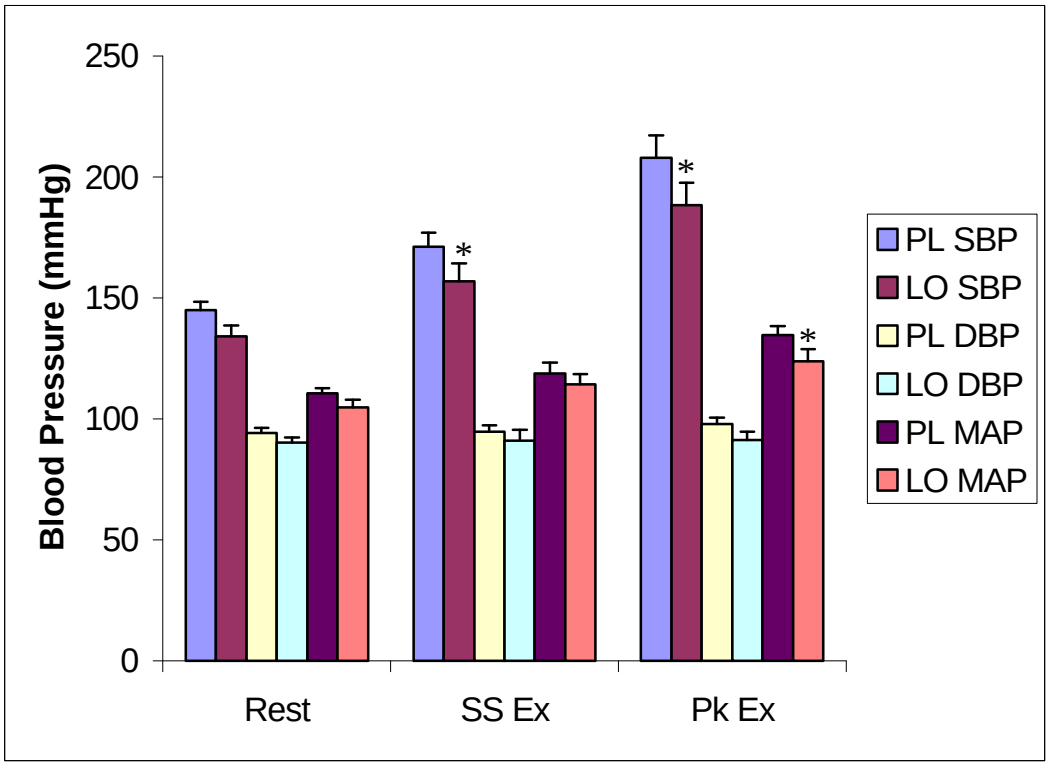

Figure 1. Blood pressure responses at rest and during submaximal steady state and peak exercise after 7 days of treatment with placebo (PL) and losartan (LO) in women (n = 6) with essential hypertension. Values are mean ± SEM (* $p < .05$).

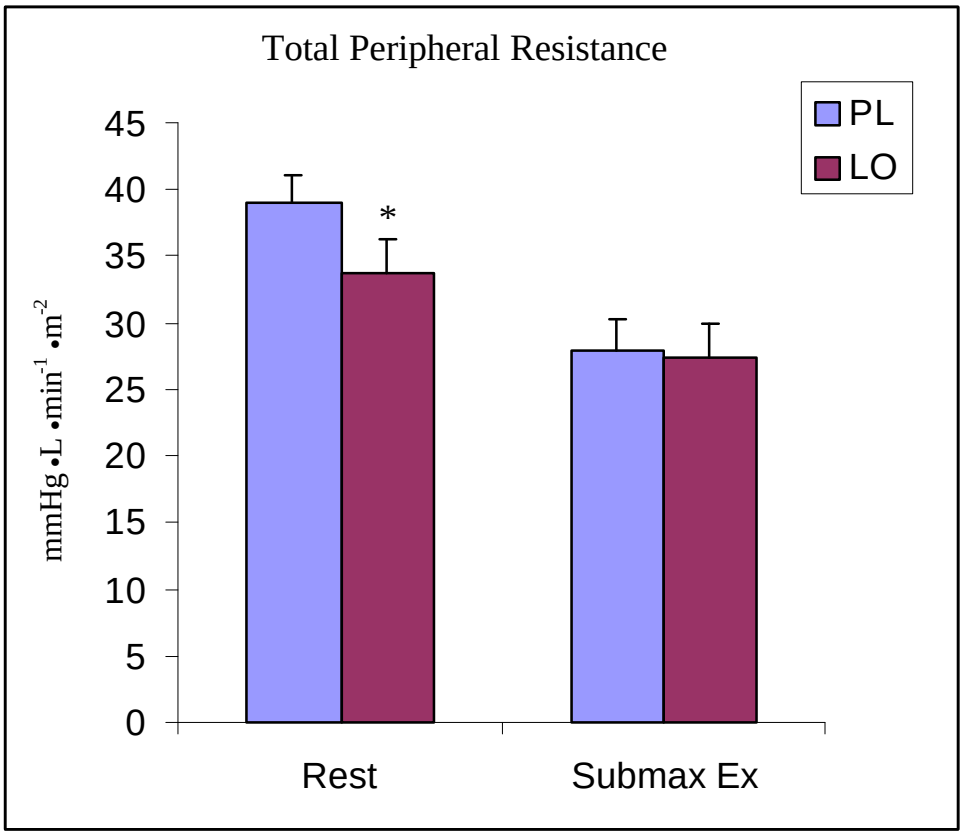

Figure 2. Calculated total peripheral resistance index at rest and during submaximal steady state exercise after 7 days of treatment with placebo (PL) and losartan (LO) in women (n = 6) with essential hypertension. Values are mean ± SEM (* $p < .05$).

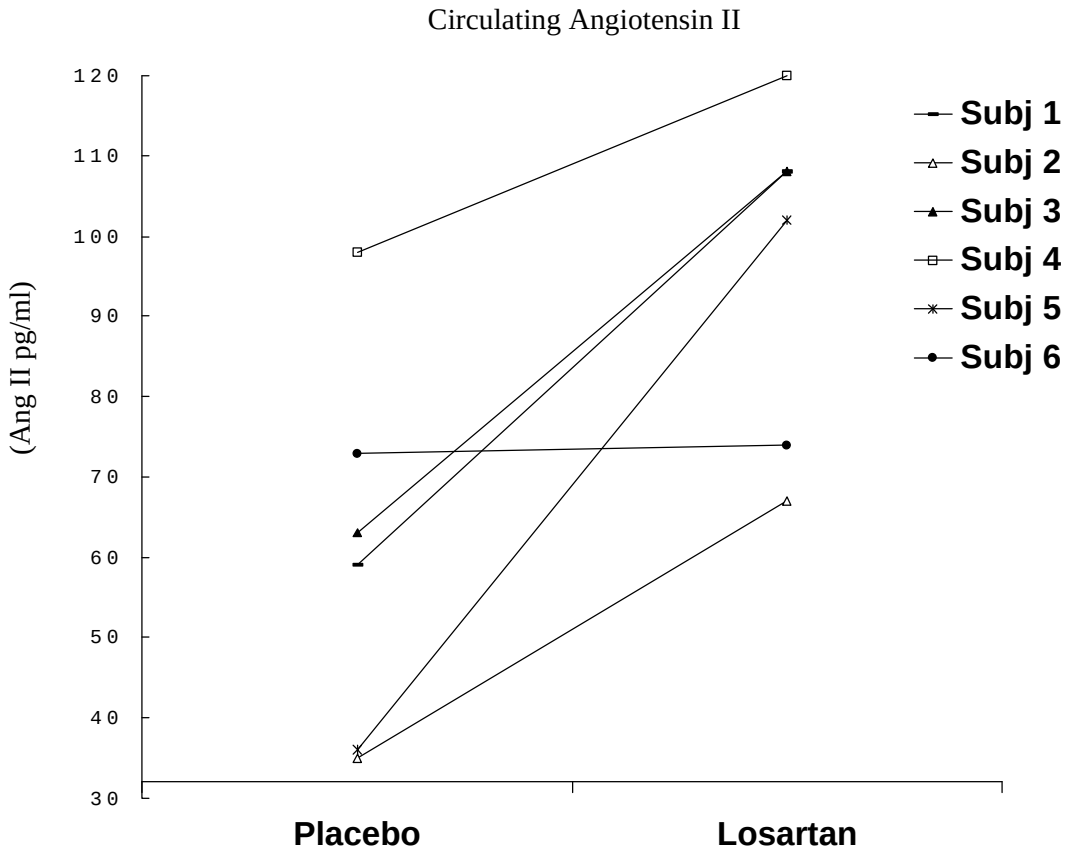

Figure 3. Individual subject responses of circulating Angiotensin II after 7 days of Placebo (PL) and Losartan (LO) treatments. Group mean for PL was significantly different from group mean of LO ($p< 05$).

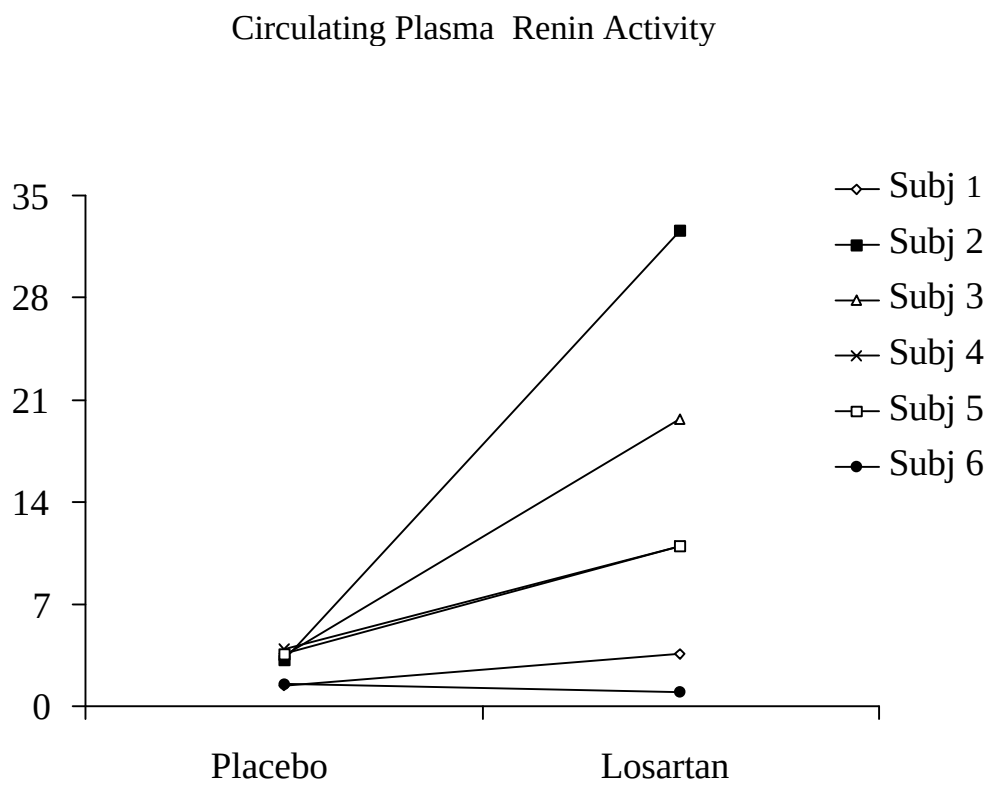

Figure 4. Individual subject responses of circulating plasma renin after 7 days of Placebo (PL) and Losartan (LO) treatments. Group mean for PL was significantly different from group mean of LO ($p < 05$).

Chapter IV

SUMMARY

Hypertension presents a major health problem in the United States, as there are over 55 million people with known high blood pressure, nearly half of these are women (Burt, Wheaten, Rochelle, Brown, Culture, Highness, Horn and Labarthe, 1995). The risk of nonfatal and fatal cardiovascular events increases progressively with high levels of systolic and diastolic BP (JNC V, 1993).

The various mechanisms responsible for development of hypertension are difficult to determine and present a challenge for the medical community to identify and manage. Inappropriate activity of renin-angiotensin system has been extensively studied and considered a major mechanism involved in the development of hypertension. The renin-angiotensin system contributes to hypertension directly or in concert with other mechanisms such as sympathetic nervous system, adrenal glands and vascular endothelial cell dependent vasodilatation. The direct influence of Ang II on hypertension is its vasoconstriction properties. This increases peripheral resistance and increases arterial pressure. Ang II acts as growth promoter in vascular smooth muscle, which leads to cell hypertrophy, increased peripheral resistance and ultimately increased blood pressure.

Losartan, an angiotensin antagonist, is a new pharmacological agent available for the management of hypertension. The mechanism of action of this agent offers specific therapy for treating hypertension resulting from renin angiotensin system overactivity. Losartan specifically blocks Ang II, type 1 receptors. The AT_1 receptors are responsible for the known functional effects of Ang II, such as vasoconstriction, release of aldosterone, cell proliferation and renal

function. The specificity of action also permits the use of losartan when other concurrent conditions are present and various medications are required. Compared to ACE inhibitors, Losartan provides more complete blockade of the renin-angiotensin system and is associated with lower incidence of cough and edema, common side effects of ACE inhibitors.

This study suggests the essential hypertension in this group of premenopause women is, at least, partially related to the pressor action of Ang II. This study demonstrated losartan's ability to inhibit angiotensin II vasoconstriction properties. This is indicated by a reduction in total peripheral resistance after one week of therapy.

The advantage to this response is reduced afterload, decreased mechanical stress of myocardium and ultimately improved cardiac function, with effectively lower BP. In this study losartan significantly lowered resting BP after a week of treatment and the SBP reduction was maintained during exercise. Losartan did not alter exercise tolerance or cause unwarranted side effects in this group of subjects. Future research is required to ascertain effects of Losartan on reduction or prevention of end target organ damage.

Implication for Clinical Applications

Losartan inhibits the effects of Ang II by direct receptor blockade. The use of this drug in hypertension will allow clinicians to identify the contributing role of Ang II in hypertensive patients. After a week of losartan therapy the subjects in this study were able to maintain exercise tolerance, therefore it does not interfere with exercise tolerance.

The specificity of action and tolerability of Losartan makes it a good medication to use in hypertensive patients who wish to be physically active.

Implications for future research

The following studies are suggested based on the findings of this study and other relevant literature:

1. The lack of an age-matched control group in the present study does not permit an evaluation of causal relationship of Angiotensin II and hypertension. Repeat this study with a control group.

2. The ability to generalize this study to all hypertensive patients is limited due to the small sample size and exclusion of hypertensive men. Repeat this type of study with groups of age matched hypertensive men and women. This will allow identification of gender differences.

3. The antihypertensive effect of losartan noted over a 24 hour period is due initially to the parent compound, losartan, and later to the active metabolite, Exp 3174. The initial hypotensive response of losartan is seen between 2- 4 hours after administration. The current study demonstrated significant reduction in BP during this time frame, with minimal effects on exercise response. Performing the exercise trial during the later hypotensive response would provide useful information for exercise effects and protection for hypertensive patients who exercise 6 - 10 hours after taking their medication.

4. Losartan lowers blood pressure after one week of initiating therapy and is maximal by six weeks of therapy. Repeat the exercise trial after 6 weeks of losartan therapy to determine maximal BP protection over several levels of physical activity.

5. Recruit hypertensive subjects who are pharmacologically managed and participate in a regular physical activity program to discern the antihypertensive effects of losartan in active hypertensives and determine if long term exercise performance is altered.

6. Losartan is a antihypertensive agent designed specifically to block Ang II at the receptor site. Blocking Ang II receptors in the vascular smooth muscle, inhibits vasconstriction of the arterioles, enhancing blood flow. Venous occlusion plethysmography is another noninvasive tool for measuring the effects of medications on peripheral blood flow. An interesting research study would be to compare venous occlusive plethysmography determination of peripheral resistance with that calculated by indirect cardiac output after losartan therapy.

Conclusions

This study demonstrated a single daily dose of losartan (50 mg) effectively lowered resting BP without complaints of adverse side effects. Systolic BP response was significantly reduced during submaximal and peak exercise after losartan therapy compared to placebo. Total peripheral resistance was significantly reduced at rest and remained slightly lower with submaximal exercise. Losartan did not alter exercise performance in this group of hypertensive women. Overall, subjects perceived efforts to the exercise, RPE_O and RPE_L were the same after losartan treatment, as reported after placebo treatment. Losartan did not have a negative effect on exercise.

Maximal graded exercise tests are commonly used to evaluate adequate control of hypertension after initiating drug therapy. Our protocol measured BP responses and calculated TPR, from rest to moderate then peak activity, simulates stress levels most likely to occur during an average day. It may provide more reliable means to evaluate the efficacy of antihypertensive medications.

Although there are limited studies to indicate exercise alone can reduce and maintain high blood pressure, the recommendations from JNC V, (1993) are that individuals with uncomplicated

hypertension should participate in a physical activity. Low to moderate physical activity can effectively lower BP reduce cardiovascular events.

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APPENDIX A

Informed Consent

VIRGINIA POLYTECHNIC INSTITUTE AND STATE UNIVERSITY

Informed Consent for Participants of Investigative Projects

Title of Study: Effects of the Angiotensin II Antagonist, Losartan, on Circulo-respiratory, and Perceptual Responses to Exercise in Hypertensive Women

Principal Investigators: Laura L. Craft, RN, MSS, William G. Herbert, Ph.D. and J. Edwin Wilder, MD

Purpose of This Research

I am invited to participate in a study that will determine if the amount of blood pumped from the heart, blood pressure, breathing patterns and perceived work effort during exercise are different in women with high blood pressure while taking Losartan and a placebo. Losartan was recently approved by the FDA. Premenopause women with high blood pressure, will be invited to participate in this study.

Procedures

Prior to being included in the exercise protocol, I will complete a medical/health history, undergo a medical examination including a resting electrocardiogram, blood chemistry analysis, urinalysis, and a urine pregnancy test. These procedures will be performed at no cost to me. If the results of the screening procedures indicate I am an appropriate subject I will report to the Laboratory for Health and Exercise Science (LHES) for the exercise trials. If I am currently taking high blood pressure medication, it will be necessary for me to gradually stop taking my medication at least one week prior to my participation. My physician must agree and provide written consent, for me to be withdrawn from my blood pressure medication. My physician will specify how my medicine will be withdrawn and how I will start taking it again after the study period is over.

I agree to perform a total of 5 exercise trials on a stationary cycle. I will report to the LHES on the mornings of the exercise trials, 2 hours before the exercise is to begin and at least 4 hours after consuming any food. I will refrain from all caffeine, and nicotine products for 12 hours prior to each exercise trial. I will not consume alcoholic beverages during the time I am taking the placebo or Losartan. The first trial, under physician supervision, will be administered to determine the maximum amount of exercise I can perform on the stationary cycle. This will include an increase in workload every 2 minutes, on the cycle until I am unable to continue the work, or maintain the required pedal speed. I will decide when I am unable to continue and the technician will stop the exercise when I so request. The remaining exercise trials (2 baseline trials, placebo, and Losartan conditions) will involve cycling for 15 minutes at a low level (~ 40 - 45% of my maximum effort), then the intensity will increase every 2 minutes until I experience volitional fatigue. Electrodes will be placed on my torso for continuous monitoring of my heart rate and rhythm. A blood pressure cuff will be placed around my left arm and my blood pressure measured every 3 minutes throughout the exercise and during recovery. Exhaled gases will be collected during each test, this will require me to wear a mouthpiece and nose clip throughout the exercise. Each exercise visit will take about 3.0 hours. The first (maximum test), second and third (submaximal) visits will be at least 48 hours apart and then there will be a minimum of 8 days between the remaining two submaximum trials.

Every morning, for one week before trial 4 and one week before trial 5, I will ingest one tablet of placebo or Losartan (50 mg. prescribed by the study physician), randomly assigned to me. On the first and second mornings of each week I will report to the LHES, the nurse will give me the medication to ingest. She will monitor my heart rate and blood pressure and evaluate me

for adverse effects for about 2 hours, after I take the tablet. If there are no adverse effects I will be given the remaining week's dosages (a total of 5). I will take one tablet, at the same time, each morning as instructed by the nurse. If some adverse problem occurs I will remain in the lab until such adverse effects subside and the study physician provides follow-up instructions. If at any time during the study I experience any adverse effects I will contact the study nurse immediately.

Upon arrival to the LHES, on the mornings of trial 4 and trial 5, I will receive the final tablet, approximately 3 hours before the exercise begins. The registered nurse will withdraw 5 ml of blood from a vein in my right arm. The blood will be used to analyze the hormones, Renin and Angiotensin II, at the end of the study.

Risks and Discomforts

Losartan is a new FDA approved drug for use in the treatment of high blood pressure. Taking this drug may involve risks to a nursing infant, embryo or fetus, none of these effects are known at this time. Therefore, if I am pregnant, nursing an infant, or planning to become pregnant, I cannot enter this study. If I am in childbearing years, I must use adequate birth control measures throughout this study. The common side effects associated with losartan include headache, dizziness, and feeling "light-headed". I will be given a checklist of possible side effects with written instructions of what to do and who to contact if I experience severe reactions.

The possible discomforts I may experience in this study include leg fatigue, muscle soreness, a dry mouth (from the mouthpiece), pain, bleeding and local bruising at the site the blood sample was taken. I will be monitored by a registered nurse, with advanced cardiac life support skills, during all exercise trials. There will be certified Exercise Specialists present during

all exercise trials. The LHES has emergency protocols, equipment and staff who are authorized and trained to use such equipment for emergency care. There is a working telephone in the testing area. There is an emergency rescue squad on the campus of Virginia Tech and their average response time to LHES is 4 - 5 minutes.

Benefits of This Research

My participation in this study will provide the investigators with information that will begin to clarify the effects of the new drug, Losartan, in the treatment of hypertension in women who are trying to follow an exercise program. If I choose, I may receive a summary of this research when it is completed. Benefits from the study procedures have not been guaranteed to secure my participation.

Compensation

I understand that no monetary compensation is available to me for my time and effort as a subject in this research. However, I will receive the information from the laboratory tests, medical examination and exercise tests. If I so request the information obtained from this study will be sent to my physician. I am eligible to receive, 2 months of free participation in one of the programs of the Cardiac and Intervention Center at Virginia Tech. In addition, I will receive information regarding my current exercise condition and tolerance and a complimentary plan for developing my physical fitness provided by an ACSM certified Exercise Specialist.

Anonymity and Confidentiality

The results of this study will be kept strictly confidential. At no time will the investigators release the results of the study to anyone other than individuals working on the research project

without my written consent. The information I provide will have my name and identity removed and a subject number will identify me during analyses and any written reports of the research.

Freedom to Withdraw

I am free to withdraw from this study at any time without penalty.

Approval of Research

This research protocol has been approved by both the Institutional Review Board for projects involving human subjects at Virginia Polytechnic Institute and State University and the Department of Human Nutrition and Foods.

Subject's Responsibilities

I know of no reason I cannot participate in this study. I accept that it is my responsibility to:

1. Accurately report medical history
2. Arrive to the testing lab 4 hours after eating for the exercise trials
3. Refrain from caffeine, and nicotine products for 12 hours prior to the exercise trials
4. Refrain from drinking alcoholic beverages while I am taking any of the medication during the study
5. Remain in the testing area 1 hour after the exercise trials
6. Refrain from vigorous physical activity for 12 hours on all testing days.
7. Take the medication as instructed, at the designated time every morning for a total of 7 dosages, prior to trials 4 and 5
8. Report any adverse effects that might occur outside the lab during the period of taking the medication even if I feel it is not related to the medication to Laura Craft, RN (231-8209 /951-7586) who will notify the study physician
9. Immediately notify the investigators if during the study I become pregnant or think I might be pregnant

_____

Signature Date

Subjects' Permission

I have read and understand the informed consent and conditions of this research study. I agree to undergo all screening procedures described above prior to acceptance into the study.

I understand it is my right to withdraw from the study at anytime without penalty and that I can be dropped from the study by the investigators without my consent. I also understand the risks of my participation and the nature of any potential benefits.

I have had the opportunity to ask questions. Any questions that I have asked have been answered to my complete satisfaction. I hereby acknowledge the above and give my voluntary consent for participation in this study.

Questions/Response: _____

_____

_____ _____

Print name Signature Date

_____ _____

Witness Date

Should I have any questions about this research or its conduct, I will contact:

Laura L. Craft, RN Principal Investigator	231-8209	William Herbert, Ph.D. Principal Investigator	231-6565
J. Edwin Wilder, MD Principal Investigator	951-3311	Marilyn Prehm, Ph.D. Human Nutrition & Foods	231-5840
Ernest Stout Chair, IRB Research Division	231-6077		

APPENDIX C

Medical and Health History Questionnaire

VIRGINIA TECH LABORATORY FOR HEALTH AND EXERCISE SCIENCE
MEDICAL and HEALTH HISTORY

Name: _____ Age: _____ Date of Birth: _____

Address: _____

Phone number: Home: _____ Work: _____

Person to contact in case of emergency: _____

Relationship: _____ Phone: _____

Primary Care Physician: _____ Phone: _____

Medical History

Please indicate any current or previous conditions or problems you have experienced or have been told by a physician you have had:

	Yes	No
Heart disease or any heart problems:	_____	_____
Rheumatic fever:	_____	_____
Respiratory disease or breathing problems:	_____	_____
Circulation problems:	_____	_____
Kidney disease or problems:	_____	_____
Urinary problems:	_____	_____
Reproductive problems:	_____	_____
Musculoskeletal problems:	_____	_____
Fainting or Dizziness:	_____	_____
High Cholesterol:	_____	_____
Diabetes:	_____	_____
Thyroid problems:	_____	_____
Allergies:	_____	_____

If "yes" to any of the above please indicate the date, explain and describe:

_____

_____

_____

Please list any hospitalizations/operations/recent illnesses (Type/Date):_____

_____

_____

	Yes	No
Have you ever been diagnosed as having high blood pressure?	_____	_____
Date: _____		
Are you currently being treated for high blood pressure?	_____	_____
If "yes" please explain: _____		
_____		
Do you use birth control?	_____	_____
If "yes" what form of birth control: _____		
Date of last menses: _____		

Please list all medications (prescription and over-the-counter) you are currently taking or have taken in the past week: _____

_____

_____

Health Habits

	Yes	No
Do you add salt to your food?	_____	_____
Are you on any special type of diet?	_____	_____
If "yes" please describe _____		
_____		
Do you drink caffeinated beverages?	_____	_____
How many cups per day? _____		
Do you drink alcoholic beverages?	_____	_____
How many drinks per week? _____		
Do you smoke cigarettes?	_____	_____
Packs per day: _____		

Exercise Habits	Yes	No
Do you engage in regular exercise?	_____	_____

If "yes" please list:

Activity	Frequency (times per week)	Duration (minutes)
_____	_____	_____
_____	_____	_____

Do you ever feel faint, short of breath, or chest discomfort with exertion? _____

If "yes", please explain : _____

_____

Are there any orthopedic limitations you have that may restrict your ability to perform exercise on a stationary cycle? Yes _____ No _____

If "yes" please explain: _____

_____

Family History

Has anyone in your family been diagnosed or treated for any of the following?

	Yes	No	Relationship	Age
Heart attack	_____	_____	_____	_____
Heart disease	_____	_____	_____	_____
High blood pressure	_____	_____	_____	_____
Stroke	_____	_____	_____	_____
Kidney disease	_____	_____	_____	_____
Diabetes	_____	_____	_____	_____

Please sign to indicate the above information is correct:

_____ _____

Print Name Signature Date

APPENDIX C

Data Collection Sheets

Functional Capacity Assessment

Subject ID: _____ Age: _____ Height: _____ cm. Weight: _____kg. Date: ____

Resting: HR: ___ BP: _____ Seat Ht: .

MIN	WATTS	HR	BP	RPE-L	RPE-O
0	0				
1					
2	30				
3					
4	60				
5					
6	90				
7					
8	120				
9					
10	150				
11					
12	180				
13					

Recovery Data

MIN	HR	BP
IPE		
2		
3		
4		
5		
6		

Skin folds	Tricep	Suprailiac	Thigh
Ave:			

% Body Fat: _____

Pre-Exercise Data

Date: _____ Subject #: _____ Wt: _____

Time session began :____ Treatment: T_1 T_2

Initial BP: _____ HR: _____

Time Dosed: _____

30 minute BP: _____ HR: _____

45 minute BP: _____ HR: _____

60 minute BP: _____ HR: _____

75 minute BP: _____ HR: _____

90 minute BP: _____ HR: _____

105 min. BP: _____ HR: _____

120 min BP: _____ HR: _____

Blood drawn: _____

Comments: _____

Exercise Data

Subject #:_____ Weight: _____kg. Height: _____ Seat Ht.: _____ Trial: _____

MIN	HR	BP			
3			$Q1_{(6)}$	$Q2_{(10)}$	$Q3_{(14)}$
5			V_T:		
9			VCO_2:		
13			BagVol:		
15			Q:		

Constant Load: 30 Watts

MIN	HR	BP	RPE-O	RPE-L	
16					$Q4_{(21)}$
17					V_T
18					VCO_2
19					B.Vol
20					Q
21					$Q5_{(25)}$
22					V_T
23					VCO_2
24					B.Vol
25					Q
26					$Q6_{(29)}$
27					V_T
28					VCO_2
29					B.Vol
30 (0)					Q

60 Watts Incremental Starts

MIN	WATTS	HR	BP	RPE-O	RPE-L
31					
32	90				
33					
34	120				
35					
36	150				

Recovery Data

MIN	HR	BP	COMMENTS:
1			
2			
4			
6			

APPENDIX D

Detailed Methodology

Detailed Methodology

Subjects

Six premenopausal women with known hypertension, recruited from Virginia Tech campus employees participated in this study. All subjects reviewed and signed an informed consent prior to participation. The physician for each subject was apprised of the nature of the study and provided written approval for subject participation. Subjects taking medication for hypertension were taken off their medication, under the direction of their physician, at least two weeks prior to the screening process.

Study Plan

Screening.

Subjectš blood pressures were screened over a 10 day period to establish baseline values. Subjects reported to the Laboratory for Health and Exercise Science (LHES) for blood pressure screening. The subjects were placed in a quiet room, seated in a comfortable chair. After a 15 minute quiet period the blood pressure was measured following the recommendations of the American Heart Association (Perloff, Grim, Flack, Frohlich, et al., 1993). The average of the three measurements taken on the last day of screening served as the entry level blood pressure. The subjects met inclusion criteria based on a medical health history, (Appendix B), resting 12-Lead electrocardiogram, blood chemistry analysis, lipid profile and urine pregnancy test.

Determination of Functional Capacity

The morning of the functional capacity test (FCT) the subjects were asked to report to the LHES in a four hour post-absorptive state and to refrain from caffeine, nicotine and alcohol products the preceding 12 hours. Upon arrival each subject was weighed and body fat was

determined using skinfold calipers. She was then prepared for a 12-Lead electrocardiogram (ECG). A blood pressure cuff was applied to the left arm.

Using a cycle ergometer (Monark 818E), the exercise test consisted of graded 30 Watts (W), increases in workload, starting with 0W. Each stage was two min. in duration with the subject receiving considerable verbal encouragement throughout the test. Visual and auditory cues were used to ensure a pedal cadence of 60 rpm. Test termination occurred when the subject was unable to maintain a 60 rpm cadence, reached volitional fatigue or requested to stop.

During the test the subjectś electrocardiogram was monitored continuously (Mortara-XScribe, Milwaukee, WI). A12-Lead ECG strip was recorded during the last 10 s of each stage. Blood pressure (BP) was measured during the last 45 s of each stage using the ausculatory method. Ratings of perceived exertion (RPE), overall (RPE_O) and for the legs (RPE_L) was obtained during the last 15 s of each min.

The subject was fitted with a mouthpiece, disposable pneumotach, and nose clip for continuous breath-by-breath measurement of oxygen uptake (VO_2), carbon dioxide (VCO_2), and ventilation (VE), using a computerized metabolic cart (MedGraphics CPX/D, St. Paul, MN). The VO_2 during the second min. of each stage in this protocol was plotted against the workloads for each stage. This plot was used to establish the workload for the subsequent exercise trials that corresponded to ~ 45% of each subjectś VO_2 peak ($VO_{2\,pk}$).

Preliminary procedures

Prior to the exercise trials each subject reported to the LHES for 2 orientation sessions to become familiar with the testing procedures and breathing apparatus they were to use. They were given a demonstration with verbal instructions. The subject was then positioned on the

cycle ergometer, with the breathing apparatus and nose clip in place. They pedaled to a cadence of 60 rpm with a minimal workload. After cycling 5 minutes, the slide valve on the breathing apparatus was shifted and the subject was instructed to breathe with metronome cadence of 40 breathes per minute for a 20 s period while maintaining her pedal cadence. The orientation sessions lasted until the subjects were proficient with the regulated breathing and cycle cadence simultaneously.

Testing

This was double-blind crossover study design. The order of testing was determined according to random assignment. There was a seven day washout period between treatment 1 and treatment 2. During this period, BP was monitored on 3 different days. Note that neither the BP technician nor the subject knew whether she was receiving the Losartan (Lo) or placebo (Pl) treatment.

On the first and second mornings of each treatment period the subject reported to the LHES between 6 and 8 AM to receive a dose of either Lo or Pl, as randomly assigned. After 15 min. of seated rest, BP was determined. The subject was then given a tablet to ingest. Seated HR and BP was taken every 15 min. over the next 2 hr. If the subject did not experience adverse side effects she was allowed to leave and was instructed to take one tablet, at the same time ($\pm$ 30 min.) each morning over the remainder of the treatment period. Otherwise, she was monitored for an additional period of time.

On the last morning of the treatment period the subject was instructed to report to LHES 30 min. after ingesting the last tablet, in a 4 hr post-absorptive state. Upon arrival the subject was weighed, prepped for 12-Lead ECG and a BP cuff was placed on her left arm. She then sat in a

quiet room and HR and BP was monitored every 15 minutes for 2 hr. prior to the exercise test. A blood sample was drawn from the subjects antecubital vein for assay of plasma renin activity (PRA) and angiotensin II (AII), 15 min. before the beginning of the exercise. PRA was collected in a chilled tube with Sodium EDTA (1 mg/ml) and AII was collected in a chilled tube with sodium EDTA (1 mg/ml) and Aprotinin (500 KIU/ml). Samples were placed in a ice slurry until centrifuged. PRA was centrifuged at 4° C at 1200 x g. for 15 min. AII was centrifuged at 0° C at 1600 x g. for 15 min. All samples were stored frozen at -20°C for batch analysis.

Data Collection

The subject was seated on the cycle ergometer. The BP cuff was applied to the left arm. The subjects electrocardiogram and heart rate were monitored continuously, with a 10 sec. strip. BP and RPE were taken at min 3, 5, 9 and 13 of rest and steady state exercise. The mouthpiece with disposable pneumotach, cardiac output slide valve with rebreathing bag and nose clip were properly positioned. The weight of this breathing apparatus was supported from the ceiling, so as to not hinder the subject. The rebreathing bag was connected to a regulator on a tank of gas containing a mixture of 4% CO_2, 35% O_2 and the balance N_2. Gas analysis VO_2, VCO_2, VE, and RER was measured using 8 breath recursive averaging on the MedGraphics CPX/D metabolic cart.

When steady state was determined using VO_2 values, cardiac output (Q) was measured in triplicate at min 6, 10 and 14 m of rest. This time frame allowed sufficient time between measurements to restore VCO_2 to initial values. After completion of 15 min of rest on the cycle ergometer, the subject was instructed to begin pedaling at 60 rpm. The workload was preset to correspond to 45% of $VO_{2\,pk}$, as determined during the FCT. Once steady state exercise was

achieved Q was measured at min 6, 10 and 14. After the last determination of Q, at min 15, the workload was increased 30 W every 2 min until the subject reached volitional fatigue, $VO_{2\,pk}$, or signaled to stop. During the incremental cycling BP, HR, an ECG strip and RPE were measured during the second min of each stage. The test was terminated and recovery BP and HR were measured until they returned close to resting values.

Cardiac Output

Three determinations of Q were obtained in each the rest and exercise phase of the protocol, using the (automated MedGraphics CPX/D non-invasive cardiac output module) exponential method as described by Defares, (1958). The subjects were breathing room air at a comfortable respiratory rate for the activity. The subjects were in a metabolic steady state as determined by stable VCO_2 values ($\pm$ 25 ml/min). The screen on the metabolic cart was switched from gas exchange data collection to the Q screen. The subject was instructed to raise her finger at the end of a complete exhalation. At that time the slide valve was open to the rebreathing bag. The subject was instructed to breath to a cadence of 40 breaths per min (inhale on 1, exhale on 2) over a 20-30 s. period. She was then instructed to inhale to remove all air from the bag, the slide valve was switched back to room air breathing and the subject resumed a comfortable respiratory rate and the screen on the cart was returned to gas exchange data collection.

Statistical Analysis

Statistical analysis was performed with Student's *t* test and when appropriate by repeated measures analysis of variance. A value of $p < 0.05$ was considered statistically significant. Data are reported as mean $\pm$ SEM.

APPENDIX E

Raw Data

Circulatory Variables

Subject	treatment	cond	Q ($L \cdot min^{-1}$)	Q ($ml \cdot min^{-1}$)	HR ($bt \cdot min^{-1}$)	SV ($ml \cdot$ stroke)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)
1	1	1	4.45	4450	76	59	146	101	115
1	1	2	6.05	6050	115	53	187	100	129
2	1	1	5.70	5700	69	83	159	100	119
2	1	2	7.40	7400	94	79	187	106	133
3	1	1	5.65	5650	99	57	142	92	108
3	1	2	9.05	9050	135	67	172	91	119
4	1	1	4.50	4500	65	69	134	91	104
4	1	2	7.50	7500	101	74	151	90	110
5	1	1	6.35	6350	75	85	147	91	109
5	1	2	9.30	9300	102	91	169	91	117
6	1	1	4.65	4650	60	78	144	91	108
6	1	2	7.90	7900	95	83	164	91	104
1	2	1	5.50	5500	74	74	153	100	117
1	2	2	6.80	6800	110	62	187	102	130
2	2	1	5.45	5450	80	68	133	91	105
2	2	2	7.15	7150	103	69	154	91	112
3	2	1	5.70	5700	95	60	130	96	107
3	2	2	9.15	9150	135	68	163	97	119
4	2	1	5.25	5250	73	72	123	80	94
4	2	2	7.80	7800	102	76	140	81	98
5	2	1	8.45	8450	74	114	139	87	106
5	2	2	9.50	9500	97	98	159	89	112
6	2	1	4.50	4500	70	64	127	87	100
6	2	2	6.30	6300	97	65	139	86	115

Treatment 1 = Placebo, 2 = Losartan; Condition 1 = Rest, 2 = Steady state submaximal exercise

Circulatory Variables

Subject	Tx	cond	RPP	TPR	BSA (m^{-2})	TPRI (mmHg/L·$min^{-1}m^{-2}$)	CI (L·$min^{-1}m^{-2}$)	SVI ml $stroke^{-1}m^{-2}$
1	1	1	109	0.0387	1.76	45.48	2.53	30.06
1	1	2	215	0.0469	1.76	37.53	3.44	33.45
2	1	1	110	0.0479	1.81	37.44	3.15	21.91
2	1	2	176	0.0180	1.81	33.65	4.09	22.99
3	1	1	140	0.0191	1.73	37.79	3.27	30.31
3	1	2	232	0.0131	1.73	32.53	5.23	25.81
4	1	1	86	0.0231	1.63	34.68	2.76	23.54
4	1	2	153	0.0147	1.63	28.2	4.60	21.95
5	1	1	110	0.0172	2.02	33.07	3.14	23.86
5	1	2	172	0.0126	2.02	22.75	4.60	22.15
6	1	1	86	0.0232	1.94	32.66	2.40	25.03
6	1	2	156	0.0132	1.94	22.63	4.07	23.33
1	2	1	113	0.0470	1.76	37.67	3.13	23.68
1	2	2	205	0.0523	1.76	23.91	3.86	28.47
2	2	1	106	0.0193	1.8	29.01	3.03	26.42
2	2	2	159	0.0157	1.8	20.35	3.97	25.93
3	2	1	124	0.0188	1.74	34.67	3.28	29.00
3	2	2	220	0.0130	1.74	25.41	5.26	25.67
4	2	1	90	0.0179	1.62	25.47	3.24	22.53
4	2	2	143	0.0126	1.62	23.93	4.81	21.18
5	2	1	103	0.0125	2.03	45.06	4.16	17.78
5	2	2	154	0.0118	2.03	25.54	4.68	20.73
6	2	1	89	0.0222	1.94	43.11	2.32	30.18
6	2	2	135	0.0183	1.94	35.41	3.25	29.87

Treatment 1 = Placebo, 2 = Losartan; Condition 1 = Rest, 2 = Steady state submaximal exercise

Respiratory Variables

subject	treatment	condition	VO_2 ($ml \cdot kg \cdot min^{-1}$)	VCO_2 ($ml \cdot kg \cdot min^{-1}$)	RER	VE ($L \cdot min^{-1}$)
1	1	1	207.27	190.7	0.92	8.2
1	1	2	644.23	596.29	0.93	22.9
1	1	3	1367	1535.5	1.14	51.7
1	2	1	211.46	173.14	0.83	7.4
1	2	2	701.45	610.06	0.87	22
1	2	3	1447.5	1603.5	1.12	51.4
2	1	1	237.71	197.59	0.83	9.2
2	1	2	646.03	578.64	0.9	22.8
2	1	3	1281	1521.5	1.18	53.7
2	2	1	252.69	219.33	0.88	9.8
2	2	2	678.94	623.34	0.91	23.5
2	2	3	1292	1631.3	1.3	63.1
3	1	1	257.06	232.11	0.9	9.58
3	1	2	760.77	736.79	0.96	24.4
3	1	3	1517.3	1841.5	1.24	64.9
3	2	1	281.83	247.97	0.88	9.7
3	2	2	767.73	738.73	0.96	24.3
3	2	3	1515.5	1831	1.24	62.1
4	1	1	215.99	188.57	0.87	10.26
4	1	2	771.71	730.64	0.94	29.7
4	1	3	1590.5	1789.5	1.14	73.9
4	2	1	233.64	198.89	0.85	10.39
4	2	2	775.79	723.27	0.93	29.9
4	2	3	1569	1809	1.16	79.7
5	1	1	269.71	229.16	0.85	9.57
5	1	2	847.86	723.86	0.85	22.6
5	1	3	1879.8	2212.3	1.21	65.5
5	2	1	262.94	220.03	0.84	8.4
5	2	2	760.77	667.3	0.87	20.1
5	2	3	1859.8	2296.8	1.24	66.5
6	1	1	174.34	139.9	0.79	8.04
6	1	2	719.51	657.26	0.91	25.8
6	1	3	1315.5	1497	1.14	61.4
6	2	1	193.87	167.4	0.86	8.81
6	2	2	651.39	601.41	0.92	25.3
6	2	3	1372	1337	1.19	70.7

Treatment 1 = Placebo, Treatment 2 = Losartan;
Condition 1 = Rest, Condition 2 = Steady state exercise, Condition 3 =Peak exercise

RPE Variables

Subject	treatment	time (min)	RPE-O	RPE-L	Subject	treatment	time	rpe o	rpe l
1	1	2	10	10	4	1	2	7	7
1	2	2	8	8	4	2	2	7	7
1	1	5	10	10	4	1	5	7	7
1	2	5	9	9	4	2	5	7	7
1	1	9	11	11	4	1	9	7	7
1	2	9	9	9	4	2	9	7	7
1	1	13	11	11	4	1	13	7	7
1	2	13	11	11	4	2	13	7	7
1	1	17	12	12	4	1	17	9	9
1	2	17	11	11	4	2	17	8	7
1	1	19	13	13	4	1	19	14	12
1	2	19	13	13	4	2	19	12	12
1	1	21	15	15	4	1	21	17	18
1	2	21	13	14	4	2	21	17	15
2	1	2	7	7	5	1	2	7	7
2	2	2	7	7	5	2	2	7	7
2	1	5	7	7	5	1	5	10	10
2	2	5	7	7	5	2	5	8	8
2	1	9	7	7	5	1	9	12	12
2	2	9	7	7	5	2	9	9	9
2	1	13	8	8	5	1	13	12	12
2	2	13	7	7	5	2	13	7	7
2	1	17	11	11	5	1	17	13	13
2	2	17	9	9	5	2	17	12	12
2	1	19	16	15	5	1	19	14	14
2	2	19	15	15	5	2	19	14	14
2	1	21	19	19	5	1	21	16	16
2	2	21	19	19	5	2	21	15	15
3	1	2	10	10	6	1	2	7	7
3	2	2	10	10	6	2	2	7	7
3	1	5	10	12	6	1	5	7	7
3	2	5	10	11	6	2	5	7	7
3	1	9	12	12	6	1	9	6	6
3	2	9	11	11	6	2	9	7	7
3	1	13	13	13	6	1	13	7	7
3	2	13	13	13	6	2	13	9	9
3	1	17	15	15	6	1	17	9	9
3	2	17	14	14	6	2	17	11	11
3	1	19	16	16	6	1	19	13	13
3	2	19	16	16	6	2	19	13	13
3	1	21	18	18	6	1	21	15	15
3	2	21	17	17	6	2	21	15	17

Treatment 1 = Placebo, Treatment 2 = Losartan;
Time = min of exercise RPE -O = overall ; RPE -L = leg

Hormonal Variables

Plasma Renin Activity

Subject	Condition	Temp	PRA (conc/ml)	Subject	Condition	Temp	PRA (conc/ml)
1	1	37	1.587	4	1	37	2.605
1	1	37	0.47	4	1	37	2.663
1	1	4	0.59	4	1	4	0.661
1	1	4	0.367	4	1	4	0.939
1	2	37	0.927	4	2	37	1.895
1	2	37	0.855	4	2	37	2.265
1	2	4	0.428	4	2	4	0.709
1	2	4	0.439	4	2	4	0.81
1	3	37	2.176	4	3	37	4.429
1	3	37	1.777	4	3	37	6.16
1	3	4	0.71	4	3	4	1.663
1	3	4	0.827	4	3	4	1.58
2	1	37	3.09	5	1	37	3.885
2	1	37	2.934	5	1	37	2.576
2	1	4	1.519	5	1	4	1.48
2	1	4	1.569	5	1	4	1.759
2	2	37	1.358	5	2	37	1.924
2	2	37	2.163	5	2	37	1.991
2	2	4	0.646	5	2	4	0.785
2	2	4	0.755	5	2	4	0.7
2	3	37	11.301	5	3	37	5.003
2	3	37	13.167	5	3	37	2.99
2	3	4	1.831	5	3	4	1.473
2	3	4	0.882	5	3	4	0.433
3	1	37	1.401	6	1	37	0.706
3	1	37	1.329	6	1	37	0.806
3	1	4	0.613	6	1	4	0.644
3	1	4	0.544	6	1	4	0.742
3	2	37	6.066	6	2	37	0.881
3	2	37	8.144	6	2	37	0.714
3	2	4	0.301	6	2	4	0.532
3	2	4	0.767	6	2	4	0.443
3	3	37	1.071	6	3	37	0.95
3	3	37	1.697	6	3	37	*
3	3	4	0.2	6	3	4	0.464
3	3	4	0.205	6	3	4	*

Condition 1 = Study entry, Condition 2 = Placebo, Condition 3 = Losartan

Angiotensin II

Subject	Sample	Treatment	AII(pg/ml)	Subject	Sample	Treatment	AII(pg/ml)
1	1	0	58.432	4	1	0	94.361
1	1	0	56.201	4	1	0	94.087
1	2	1	58.446	4	2	1	96.284
1	2	1	59.927	4	2	1	98.944
1	3	2	127.327	4	3	2	118.782
1	3	2	87.662	4	3	2	120.651
2	1	0	20.808	5	1	0	77.414
2	1	0	18.234	5	1	0	62.623
2	2	1	35.91	5	2	1	33.209
2	2	1	34.425	5	2	1	38.593
2	3	2	66.525	5	3	2	89.106
2	3	2	67.213	5	3	2	114.374
3	1	0	25.802	6	1	0	65.985
3	1	0	32.213	6	1	0	63.205
3	2	2	108.936	6	2	2	78.75
3	2	2	107.148	6	2	2	68.25
3	3	1	66.869	6	3	1	75.575
3	3	1	59.448	6	3	1	71.887

Treatment 1 = Study entry, Treatment 2 = Placebo, Treatment 3 = Losartan

APPENDIX F

Summary Paired t - test

Summary ANOVA Tables

Paired t-test: rest HR

Group	Mean	SD	SEM
placebo	74.000	13.653	5.574
losartan	77.667	9.092	3.712
Difference	-3.667	6.713	2.741

t = -1.338 with 5 degrees of freedom. (P = 0.239)
95 percent confidence interval for difference of means: -10.712 to 3.378

Paired t-test: Rest SBP

Group	Mean	SD	SEM
placebo	145.000	8.142	3.321
losartan	134.167	10.704	4.370
Difference	10.666	11.466	4.681

t = 2.208 with 5 degrees of freedom. (P = 0.07)
95 percent confidence interval for difference of means: -1.699 to 22.366

Paired t-test: Rest DBP

Group	Mean	SD	SEM
placebo	94.333	4.803	1.961
losartan	90.167	7.139	2.915
Difference	4.167	5.419	2.212

t = 1.883 with 5 degrees of freedom. (P = 0.118)
95 percent confidence interval for difference of means: -1.520 to 9.854

Paired t-test: Rest MAP

Group	Mean	SD	SEM
placebo	110.500	5.468	2.232
losartan	104.833	7.679	3.135
Difference	5.667	6.022	2.459

t = 2.305 with 5 degrees of freedom. (P = 0.069)
95 percent confidence interval for difference of means: -0.653 to 11.987

Paired t-test: Rest RPP

Group	Mean	SD	SEM
placebo	106.833	19.964	8.150
losartan	104.167	13.467	5.498
Difference	2.667	7.992	3.263

t = 0.817 with 5 degrees of freedom. (P = 0.451)
95 percent confidence interval for difference of means: -5.720 to 11.053

Paired t-test: Rest CO l/min

Group	Mean	SD	SEM
placebo	5.217	0.791	0.323
losartan	5.808	1.359	0.555
Difference	-0.592	0.901	0.368

t = -1.608 with 5 degrees of freedom. (P = 0.169)
95 percent confidence interval for difference of means: -1.538 to 0.354

Paired t-test: rest SV

Group	Mean	SD	SEM
placebo	71.833	12.073	4.929
losartan	75.333	19.623	8.011
Difference	-3.500	16.920	6.908

t = -0.507 with 5 degrees of freedom. (P = 0.634)
95 percent confidence interval for difference of means: -21.257 to 14.257

Paired t-test: Rest CI

Group	Mean	SD	SEM
placebo	2.875	0.363	0.148
losartan	3.193	0.589	0.241
Difference	-0.318	0.457	0.187

t = -1.707 with 5 degrees of freedom. (P = 0.149)
95 percent confidence interval for difference of means: -0.798 to 0.161

Paired t-test: Rest SVI

Group	Mean	SD	SEM
placebo	25.785	3.552	1.450
losartan	24.932	4.578	1.869
Difference	0.853	4.958	2.024

t = 0.422 with 5 degrees of freedom. (P = 0.691)
95 percent confidence interval for difference of means: -4.350 to 6.056

Paired t-test: Rest TPRI

Group	Mean	SD	SEM
placebo	3895.167	521.284	212.813
losartan	3372.500	623.616	254.590
Difference	522.667	385.094	157.214

t = 3.325 with 5 degrees of freedom. (P = 0.021)
95 percent confidence interval for difference of means: 118.535 to 926.798

Paired t-test: Steady state exercise HR

Group	Mean	SD	SEM
placebo	107.000	15.633	6.382
losartan	107.333	14.376	5.869
Difference	-0.333	5.203	2.124

t = -0.157 with 5 degrees of freedom. (P = 0.881)
95 percent confidence interval for difference of means: -5.793 to 5.126

Paired t-test: Steady state exercise SBP

Group	Mean	SD	SEM
placebo	171.667	13.880	5.667
losartan	157.000	17.675	7.216
Difference	14.667	12.044	4.917

t = 2.983 with 5 degrees of freedom. (P = 0.031)
95 percent confidence interval for difference of means: 2.027 to 27.306

Paired t-test: Steady state exercise DBP

Group	Mean	SD	SEM
placebo	94.833	6.616	2.701
losartan	91.000	7.563	3.088
Difference	3.833	7.574	3.092

t = 1.240 with 5 degrees of freedom. (P = 0.270)
95 percent confidence interval for difference of means: -4.115 to 11.782

Paired t-test: Steady state exercise MAP

Group	Mean	SD	SEM
placebo	118.667	11.003	4.492
losartan	114.333	10.443	4.264
Difference	4.333	11.130	4.544

t = 0.954 with 5 degrees of freedom. (P = 0.384)
95 percent confidence interval for difference of means: -7.346 to 16.013

Paired t-test: Steady state exercise RPP

Group	Mean	SD	SEM
placebo	184.000	32.305	13.188
losartan	169.333	34.795	14.205
Difference	14.667	4.633	1.892

t = 7.754 with 5 degrees of freedom. (P = <0.001)
95 percent confidence interval for difference of means: 9.804 to 19.529

Paired t-test: Steady state exercise CO l/min

Group	Mean	SD	SEM
placebo	7.867	1.192	0.487
losartan	7.783	1.295	0.529
Difference	0.0833	0.810	0.331

t = 0.252 with 5 degrees of freedom. (P = 0.811)
95 percent confidence interval for difference of means: -0.767 to 0.934

Paired t-test: Steady state exercise SV

Group	Mean	SD	SEM
placebo	74.500	13.293	5.427
losartan	73.000	13.115	5.354
Difference	1.500	10.445	4.264

t = 0.352 with 5 degrees of freedom. (P = 0.739)
95 percent confidence interval for difference of means: -9.461 to 12.461

Paired t-test: Steady state exercise CI

Group	Mean	SD	SEM
placebo	4.338	0.612	0.250
losartan	4.305	0.739	0.302
Difference	0.0333	0.426	0.174

t = 0.192 with 5 degrees of freedom. (P = 0.856)
95 percent confidence interval for difference of means: -0.414 to 0.481

Paired t-test: Steady state exercise SVI

Group	Mean	SD	SEM
placebo	24.947	4.389	1.792
losartan	25.308	3.724	1.520
Difference	-0.362	3.951	1.613

t = -0.224 with 5 degrees of freedom. (P = 0.831)
95 percent confidence interval for difference of means: -4.508 to 3.785

Paired t-test: Steady state exercise TPRI

Group	Mean	SD	SEM
placebo	2796.167	582.610	237.849
losartan	2735.667	613.681	250.534
Difference	60.500	539.167	220.114

t = 0.275 with 5 degrees of freedom. (P = 0.794)
95 percent confidence interval for difference of means: -505.321 to 626.321

Paired t-test: Peak exercise HR

Group	Mean	SD	SEM
placebo	166.500	11.996	4.897
losartan	169.667	10.309	4.208
Difference	-3.167	3.656	1.493

t = -2.122 with 5 degrees of freedom. (P = 0.087)
95 percent confidence interval for difference of means: -7.003 to 0.670

Paired t-test: Peak exercise SBP

Group	Mean	SD	SEM
placebo	208.000	22.343	9.121
losartan	188.333	22.748	9.287
Difference	19.667	16.657	6.800

t = 2.892 with 5 degrees of freedom. (P = 0.034)
95 percent confidence interval for difference of means: 2.186 to 37.147

Paired t-test: Peak exercise DBP

Group	Mean	SD	SEM
placebo	98.00	6.693	2.733
losartan	91.67	6.976	2.848
Difference	6.33	9.245	3.774

t = 1.678 with 5 degrees of freedom. (P = 0.154)
95 percent confidence interval for difference of means: -3.369 to 16.035

Paired t-test: Peak exercise MAP

Group	Mean	SD	SEM
placebo	134.667	8.892	3.630
losartan	123.833	12.238	4.996
Difference	10.833	8.954	3.655

t = 2.964 with 5 degrees of freedom. (P = 0.031)
95 percent confidence interval for difference of means: 1.437 to 20.230

Paired t-test: **Peak exercise RPP**

Group	Mean	SD	SEM
placebo	346.167	43.673	17.830
losartan	311.333	45.933	18.752
Difference	34.833	25.980	10.606

t = 3.284 with 5 degrees of freedom. (P = 0.022)
95 percent confidence interval for difference of means: 7.569 to 62.098

Paired t-test: Rest VO_2

Group	Mean	SD	SEM
placebo	227.013	35.003	14.290
losartan	239.405	32.918	13.439
Difference	-12.392	11.601	4.736

t = -2.616 with 5 degrees of freedom. (P = 0.047)
95 percent confidence interval for difference of means: -24.567 to -0.217

Paired t-test: Rest RER

Group	Mean	SD	SEM
placebo	0.860	0.0473	0.0193
losartan	0.857	0.0207	0.0084
Difference	0.0033	0.0572	0.0233

t = 0.143 with 5 degrees of freedom. (P = 0.892)
95 percent confidence interval for difference of means: -0.0566 to 0.0633

Paired t-test: Rest VCO_2

Group	Mean	SD	SEM
placebo	9.142	0.864	0.353
losartan	9.083	1.093	0.446
Difference	0.058	0.771	0.315

t = 0.185 with 5 degrees of freedom. (P = 0.860)
95 percent confidence interval for difference of means: -0.751 to 0.868

Paired t-test: Rest VE

Group	Mean	SD	SEM
placebo	9.142	0.864	0.353
losartan	9.083	1.093	0.446
Difference	0.058	0.771	0.315

t = 0.185 with 5 degrees of freedom. (P = 0.860)
95 percent confidence interval for difference of means: -0.751 to 0.868

Paired t-test: Steady state exercise VO_2

Group	Mean	SD	SEM
placebo	731.685	78.839	32.186
losartan	722.678	52.435	21.407
Difference	9.007	56.852	23.210

t = 0.388 with 5 degrees of freedom. (P = 0.714)
95 percent confidence interval for difference of means: -50.656 to 68.669

Paired t-test: Steady state exercise RER

Group	Mean	SD	SEM
placebo	0.915	0.0383	0.0157
losartan	0.910	0.0352	0.0144
Difference	0.005	0.0288	0.0118

t = 0.425 with 5 degrees of freedom. (P = 0.688)
95 percent confidence interval for difference of means: -0.0252 to 0.0352

Paired t-test: Steady state exercise VE

Group	Mean	SD	SEM
placebo	24.700	2.741	1.119
losartan	24.183	3.342	1.364
Difference	0.517	1.118	0.456

t = 1.132 with 5 degrees of freedom. (P = 0.309)
95 percent confidence interval for difference of means: -0.656 to 1.690

Paired t-test: Steady state exercise VCO_2

Group	Mean	SD	SEM
placebo	670.580	70.681	28.855
losartan	660.685	59.199	24.168
Difference	9.895	39.941	16.306

t = 0.607 with 5 degrees of freedom. (P = 0.570)
95 percent confidence interval for difference of means: -32.021 to 51.811

Paired t-test: Peak exercise VO_2

Group	Mean	SD	SEM
placebo	1491.850	224.512	91.657
losartan	1509.300	198.163	80.900
Difference	-17.450	42.029	17.158

t = -1.017 with 5 degrees of freedom. (P = 0.356)
95 percent confidence interval for difference of means: -61.556 to 26.656

Paired t-test: Peak exercise RER

Group	Mean	SD	SEM
placebo	1.175	0.0428	0.0175
losartan	1.208	0.0646	0.0264
Difference	-0.033	0.0489	0.0199

t = -1.671 with 5 degrees of freedom. (P = 0.156)
95 percent confidence interval for difference of means: -0.0846 to 0.0179

Paired t-test: Peak exercise VE

Group	Mean	SD	SEM
placebo	61.850	8.216	3.354
losartan	65.583	9.442	3.855
Difference	-3.733	5.173	2.112

t = -1.768 with 5 degrees of freedom. (P = 0.137)
95 percent confidence interval for difference of means: -9.162 to 1.695

Paired t-test: Peak exercise VCO_2

Group	Mean	SD	SEM
placebo	1732.883	277.174	113.156
losartan	1751.433	320.980	131.040
Difference	-18.550	97.822	39.936

t = -0.464 with 5 degrees of freedom. (P = 0.662)
95 percent confidence interval for difference of means: -121.208 to 84.108

One Way Repeated Measures ANOVA Angiotensin II

Group	Mean	SD	SEM
Entry	55.767	27.538	11.242
Placebo	60.767	23.661	9.660
Losartan	96.267	21.022	8.582

Source of Variation	DF	SS	MS	F	P
Between Subjects	5	6123.727	1224.745		
Between Treatments	2	5851.000	2925.500	10.928	0.003
Error	10	2676.953	267.695		
Total	17	14651.680			

All Pairwise Multiple Comparison Procedures (Tukey Test):

Comparisons for factor: treatment

Comparison	Diff of Means	p	q	P<0.05
Losartan vs. Entry	40.500	3	6.063	Yes
Losartan vs. Placebo	35.500	3	5.315	Yes
Placebo vs. Entry	5.000	3	0.749	No

One Way Repeated Measures ANOVA for PRA

Group	Mean	SD	SEM
Entry	3.156	2.078	0.848
Placebo	2.860	1.147	0.468
Losartan	13.091	11.597	4.735

Source of Variation	DF	SS	MS	F	P
Between Subjects	5	305.772	61.154		
Between Treatments	2	406.925	203.462	5.153	0.029
Residual	10	394.857	39.486		
Total	17	1107.554			

All Pairwise Multiple Comparison Procedures (Tukey Test):

Comparisons for factor: treatment

Comparison	Diff of Means	p	q	P<0.05
Losartan vs. Placebo	10.231	3	3.988	Yes
Losartan vs. Entry	9.935	3	3.873	No
Entry vs. Placebo	0.296	3	0.116	No

VITA

Laura Lee Craft was born in South Bend, Indiana and raised in New Carlisle, Ohio. She is the second oldest of eight children born to Margaret and Allen Craft. Following in the foot steps of her mother, she became a registered nurse, graduating in May, 1980 from the College of Mount Saint Joseph, Cincinnati, Ohio with a BSN degree. Her nursing career began at Childrens Hospital Medical Center in the newborn intensive care. She was a staff nurse and a member of the Transport team for several years before accepting the NICU Education Coordinator position. After working 5 years at Childrens Laura decided to pursue other professional interests. This decision led her to Mobile, Alabama, were she received a MSS degree in Fitness Management. She returned to Cincinnati and worked as an exercise physiology consultant for AT&T corporate fitness center. An employment opportunity at Scottsdale Community College took her to Phoenix, Arizona. Laura worked as a staff member in the SCC fitness center and as a nurse in cardiac rehabilitation at Humana Hospital, Phoenix. As a result of her professional experiences in Arizona, Laura decided to pursue a doctoral degree in clinical exercise physiology. Therefore, she moved to Virginia, attended Virginia Tech, and received her Ph.D. in 1997.

Currently, she is employed at the University of Cincinnati, in the Division of Cardiology, as the SCOR Research Coordinator. She is a member of a research team working on an NIH heart failure grant and other heart failure studies.

Laura L. Craft