THE EFFECTS OF 4 WEEKS OF AEROBIC EXERCISE ON ARTERIAL STIFFNESS AND THE RENIN-ANGIOTENSIN AND ALDOSTERONE SYSTEM ON STAGE ONE HYPERTENSIVE OBESE INDIVIDUALS

A Thesis
by
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FOREWORD

The research detailed in this thesis will be submitted to *Obesity*, the official journal of the Obesity Society. The thesis has been prepared according to the guidelines set forth by the Graduate School of Appalachian State University.

ACKNOWLEDGMENTS

I would like to thank my mentors, Dr. Scott R. Collier and Dr. Jeffrey T. for their guidance and support in my graduate studies at Appalachian State University. Thesis committee members, Dr. Paul Gaskill and Dr. Gregory Anoufriev, I express my gratitude for your involvement in this project. To my fellow graduate students, I thank you for your friendships over the past two years and look forward to opportunities that may bring us together in the future.

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ABSTRACT

THE EFFECTS OF 4 WEEKS OF AEROBIC TRAINING ON ARTERIAL STIFFNESS AND THE RENIN-ANGIOTENSIN AND ALDOSTERONE SYSTEM ON STAGE ONE HYPERTENSIVE, OBESE INDIVIDUALS. (MAY 2011)

Anne Marie Moody, B.S., High Point University

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Increases in blood pressure (BP) are directly related to increases in body mass, and obesity related hypertension is associated with pronounced activity of the renin-angiotensin-aldosterone system (RAAS) and increased pulse wave velocity (PWV). Moderate intensity aerobic exercise is known to decrease PWV and serves as a valuable option in the treatment of hypertension and obesity. The purpose of this study was to assess RAAS activity and PWV prior to and following 4 weeks of aerobic training program in an unmedicated, pre to stage one hypertensive population. Seven men and three post-menopausal women, (52 ± 3.2 years old) underwent aerobic training [30 minutes of treadmill exercise, 3 days per week at 65% of peak oxygen consumption (VO_2 peak)]. Body mass index (BMI), VO_2 peak, BP, and blood markers were taken at baseline, post 4 week control period and post 4 week training period. There were no significant differences in any descriptive characteristics during the control period; however, there was a significant decrease in plasma aldosterone (ALDO)

(255.4 ± 75 to 215.8 ± 66 pg/ml, $p = 0.001$) and significant decreases in central PWV, (11.2 ± 0.6 vs.9.8 ± 0.8 m/s; $p = 0.04$) pre to post exercise training. These data show that 4 weeks of moderate intensity aerobic training decreases central PWV that may be linked with decreases in ALDO changes in obese, unmedicated hypertensive individuals.

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INTRODUCTION

The link between obesity and hypertension is well established, as hypertension is six times more frequent in obese than in lean individuals (1, 2). It has been shown that obesity related hypertension causes hemodynamic alterations through neurohormonal and structural adaptations, as well as metabolic mechanisms (3). The incidence of obesity and hypertension are escalating in the United States, with a doubling of obese individuals since 1980, increasing the number of obese hypertensives to almost 41% at present (4). Obese hypertensives have been shown to present with higher systemic blood volumes, resulting in greater cardiac output and a concomitant increase in peripheral resistance (3). A significant correlation has been established between the degree of obesity and the rate of pulse wave velocity (PWV; 5, 6). It is well known that an increase in peripheral resistance leads to greater PWV, reflected pulse waves, and increased arterial stiffness, resulting in remodeling of the heart and vascular walls. Obese individuals show an increased level of aortic stiffness, independent of blood pressure (BP) level, ethnicity and age (6). The renin-angiotensin-aldosterone system (RAAS) plays a significant role in BP regulation via changes in plasma renin activity (PRA) and aldosterone (ALDO) which may be over expressed in obese individuals (7). Renin cleaved to angiotensin II (ANG II), a powerful vasoconstrictor, has been shown to be amplified in both obese animals and humans (7). Increases in sympathetic nerve activity and altered intrarenal physical forces in obesity lead to enhanced renin secretion (7). Attenuation of renin through pharmacological blockade or weight loss have been shown to decrease resting BP due to decreases in PRA and ALDO (8).

Moderate intensity, aerobic exercise is prescribed as a cornerstone therapy for the prevention and treatment of obesity and hypertension (9, 10). Previously, our laboratory has shown that moderate intensity, aerobic exercise can decrease both resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) by 4 millimeter of mercury (mmHg) respectively in as little as 4 weeks and confer positive changes in the vasculature and autonomic nervous system (11). Reductions in resting BP as small as 3 mmHg have been shown to reduce the incidence of stroke and mortality by 3 and 7 fold respectively (12).

There is a paucity of literature investigating the effects of exercise on the RAAS and to this author's knowledge, there are no studies using an unmedicated, pre to stage one hypertensive cohort. Therefore, the purpose of this study was to investigate the effect of moderate intensity, aerobic exercise on the RAAS, cardiac autonomic function, and pulse wave transit times in an unmedicated, pre to stage one hypertensive population.

METHODS & PROCEDURES

Subjects

Ten obese, unmedicated, pre to stage one hypertensive individuals (7 males, 3 females) between 40 and 60 years of age were recruited through local community physicians after they had been recently identified with pre (n = 4) or stage one essential hypertension (n = 6). To be included in the study, no subjects had a history of diabetes, coronary heart disease, or kidney disease, all were non-smokers, and none were on any medications, including anti-hypertensives or anti-inflammatants as identified by their physicians and in a health history questionnaire. Due to the confounding influence of estrogen on cardiovascular measures, only postmenopausal women (history of greater than 12 months of amenorrhea) not currently under hormone replacement therapy were recruited. The study was approved by the Institutional Review Board, and all subjects gave written consent.

Experimental Design

Subjects reported to the clinical research unit at the start of testing, at the end of the 4 week control period, and at the end of the aerobic training time period. All blood born markers were assessed at 7:00 a.m. hours following a 12 hour fast, followed by their cardiovascular, and peak oxygen consumption (VO_2 peak) assessment completed within 24 hours.

All subject visits took place at the same time of day to reduce the possibility of diurnal influences on physiological parameters. Pre-testing started with subjects resting quietly in the supine position in a dimly lit room for 15 minutes. Electrocardiogram and beat-to-beat blood pressure recordings were then collected for a period of 10 minutes with metronome-controlled, paced breathing maintained at 12 breaths per minute. Following the second lab visit, each subject underwent a supervised 4 week aerobic training regimen. At the conclusion of 4 weeks of aerobic training, the subjects were asked to report back to the lab within 24 to 48 hours after their last exercise session for post-measurements which repeated all of the control and pre-training measurements.

Anthropometric and Body Composition Assessment

Mass was calculated using a beam scale while stature was measured using a stadiometer and recorded to the nearest 0.5 cm. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Body composition assessment was recorded following a BodPod whole body plethysmography test (BodPod, Life Measurement Inc., Concord, CA).

Maximal Aerobic Capacity

VO_2 peak was assessed using a customized treadmill protocol that has been used in our laboratory. Briefly, participants began walking at an intensity of 3 miles per hour (mph) for a period of 3 minutes. During the test, intensity was first increased by increasing the speed until a comfortable pace was reached, at which point 2.5% grade adjustments every 3 minutes were necessary to reach volitional fatigue. Heart rate was measured and recorded

once per minute during the protocol using a Polar Heart Rate Monitor (Polar Electro Inc., Woodbury, NY). Ratings of perceived exertion (RPE) were also assessed once per stage (13). Expired gases were analyzed using a Quark b^2 breath-by-breath metabolic system (Cosmed, Rome, Italy). Maximal effort was attained when subjects met 3 of the following 4 criteria: (a) no change in HR with a change in workload, (b) a final RPE score of 17 or greater on the Borg scale (scale 6-20), (c) a respiratory exchange ratio (RER) greater than 1.15, and/or (d) a "plateau" (increase of no more than 150 ml) in oxygen uptake with an increase in workload.

Exercise Training

Values attained from the preliminary exercise testing sessions were used to design the aerobic training prescription. Aerobic training consisted of 30 minutes supervised treadmill exercise, 3 days per week at 65% of each individual's VO_2 peak.

Hemodynamic Monitoring

Each subject underwent a BP measurement in compliance with the World Health Organization guidelines prior to the start of each study visit. A manual mercury sphygmomanometer with an appropriately sized cuff was used for 3 measurements which were averaged for later analyses.

For the acquisition of BP during cardiac autonomic modulation testing trials, 3 minute averages of 10 minute epochs were recorded with the subjects in a supine position, attached to a beat-to-beat blood pressure monitoring system via finger plethysmography (Finometer, Finapres Medical Systems, The Netherlands). The Finometer estimates brachial BP using an

integrated brachial BP cuff and reconstructs brachial BP waveforms from finger arterial waveforms by applying an inverse transfer function, a waveform filter, a level correction, and a level calibration(14,15).

Signal acquisition and analysis

As described in prior studies, beat-to-beat HR was recorded using a modified 3 lead configuration (CM5; Biopac Systems, Santa Barbara, CA). The electrocardiogram reading was collected online at a sampling rate of 1000 Hz, in real time, and stored on a computer. All data were stored off-line and used for analysis at a later time. Off-line signal processing was performed at 10 minute epochs. Data were visually inspected for ectopic beats and noise and linearly interpolated to provide a continuous data stream. Heart rate peaks were automatically detected via an established QRS detection algorithm and used to generate an R–R interval time event series (WinCPRS, Turku, Finland). The continuous data stream was re-sampled at 5 Hz and passed through a low-pass impulse response filter with a cutoff frequency of 0.5 Hz (16). Power spectral analysis was performed using a maximum entropy method in order to improve temporal resolution (17). The optimum order of the autoregressive model was determined by Akaike's information criterion. If this method yielded a model order of less than 16, we used 16 to avoid possible shifting of the spectral peaks (18).

The power was calculated by measuring the area under the peak of the power spectra density curve. Three peaks were revealed and their corresponding bandwidths defined as follows: a high frequency (HF) region (0.15–0.40 Hz) caused by arrhythmic respiratory oscillations that is indicative of parasympathetic modulation of the heart; a low frequency

(LF) region (0.04–0.15 Hz) related to baroreflex activity and thermoregulatory components that is mediated by both the sympathetic and parasympathetic arms of the autonomic nervous system; and a very LF component (< 0.04 Hz) resulting from non-harmonic fractal oscillations of unknown origin (19). The very LF component was not used in this study other than in calculation of normalized LF and HF heart rate variability. The power spectra were calculated in both absolute and normalized units in order to represent the relative value of each power component as a proportion of the total power (TP). TP was taken as an index of overall variability (19) and was used as a global marker of vagal modulation (20). The ratio of LF to HF power was used as an indicator of sympathovagal balance (21). All data acquisition and post-acquisition analyses were carried out in accordance with standards put forth by the Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology (19).

PRA, ANG II, and ALDO

Blood markers were measured at 7:00 a.m. following a 12 hour fast. Briefly, blood was collected in ice-cold vacutainer tubes containing 5 mM EDTA for 17 beta-estradiol (E2), 25 mM EDTA for plasma renin activity (PRA), and angiotensin II (ANG II) or 14.3 USP units/ml of heparin for aldosterone (ALDO). PRA is defined as the rate of angiotensin I (ANG I) generation from endogenous substrate. The limit of detection of these assays (in pg/ml) is: PRA, 25; ANG II, 2; and ALDO, 25.

Treatment of the data

Data were analyzed by SPSS version 17 (Chicago, IL). All data were analyzed using a 1 x 3 ANOVA with repeated measures and a Bonferroni post-hoc test was performed for pairwise comparisons. If significant interactions were detected, a one-way ANOVA was conducted to determine where significant changes in dependent variables lied. Significance was set at an alpha < 0.05 and all data are reported as mean ± SEM unless otherwise stated. Normal distribution of the data was assessed with a Shapiro-Wilk test. Data that were not normally distributed were then log transformed (natural log transformation) prior to statistical analyses.

RESULTS

Subjects

There were no significant changes in any subject characteristics from pre to post training (Table 1). There were no significant changes in any descriptive characteristics following the 4 week control period (Table 2).

Hemodynamic variables

SBP and DBP showed a 4 and 5 mm Hg reduction from baseline to post-training, respectively (Table 2).

Blood Panel

No significant changes were observed in any blood variables following the control and training periods (Table 3).

RAAS

No significant changes were observed in PRA ($p = 0.081$) or ANG II (p = no significant differences) from baseline to post-training. There were significant decreases observed in plasma ALDO ($p = 0.001$) from baseline (255.43 ± 75.6) to post-training (215.79 ± 66.1). Results for RAAS variables are displayed in Figures 1, 2, and 3.

PWV

Central PWV (Figure 4) showed a significant decrease ($p = 0.04$) from baseline (11.2 ± 0.6 m/s) to post-training (9.8 ± 0.8 m/s) within subjects.

Table 1. Subject Characteristics (*n* = 10)

Variable	Baseline	Pre-Training	Post-Training
Age (y)	54.1 ± 2.8	-	-
Height (m)	1.62 ± 0.08	-	-
Weight (kg)	73.0 ± 3.0	73.0 ± 5.0	72.5 ± 3.0
BMI (kg/m^2)	33.5 ± 1.4	33.5 ± 1.4	33.5 ± 1.4

Values are mean ± SE for *n* = 10. Baseline values taken at initial lab visit. Pre-training values taken at second lab visit, following a 4 week control period. Post-training values taken within 24 hours after the final exercise session.

Y, years; m, meters; kg, kilograms; BMI, body mass index; kg/m^2, kilograms per meters squared

Table 2. Descriptive Characteristics

Variable	Baseline	Pre-Training	Post-Training
VO_2 (ml/kg/min)	32.4 ± 2.4	-	-
PWV (m/s)	11.2 ± 0.6	11.6 ± 0.4	9.8 ± 0.8*
PRA (pg/ml)	0.979 ± 0.16	0.845 ± 0.11	0.592 ± 0.10
ANG II (pg/ml)	934.25 ± 189.90	932.75 ± 177.22	930.84 ± 107.16
ALDO (pg/ml)	255.43 ± 75.6	252.14 ± 63.1	215.79 ± 66.1*
SBP (mmHg)	140	140	136*
DBP (mmHg)	90	89	85*

Values reported as mean ± SE for $n = 10$.
*Denotes significance at $p < 0.05$.

VO_2, maximal oxygen intake; PWV, pulse wave velocity; PRA, plasma renin activity; ANG II, angiotensin II; ALDO, aldosterone; SBP, systolic blood pressure; DBP, diastolic blood pressure; ml/kg/min, milliliters per kilogram per minute; m/s, meters per second; pg/ml, picograms per milliliters; mmHg, millimeters of mercury .

Table 3. Blood Panel.

Variable	Control	Pre-Training	Post-Training
Sodium	141.4 ± 1.26	141.5 ± 0.85	142.1 ± 1.37
Potassium	4.0 ± 0.13	4.1 ± 0.12	4.2 ± 0.15
Chloride	103.7 ± 1.42	104.6. ± 1.65	104.9 ± 1.97
Carbon Dioxide	26.7 ± 2.36	26.9 ± 1.85	26.2 ± 2.39
Aniongap	10.4 ± 1.96	10.0 ± 1.05	10.7 ± 1.95
Serum Calcium	9.1 ± 0.29	9.1± 0.32	9.2 ± 0.36
Blood Urea Nitrogen	16.2 ± 2.15	16.3 ± 2.63	15.8 ± 2.44
Creatinine	0.86 ± 0.12	0.88 ± 0.09	0.86 ± 0.12
Free Calcium	293.2 ± 2.82	294.3 ± 1.64	295.0 ± 3.33
Glucose	82.4 ± 7.71	83.3 ± 6.57	85.3 ± 10.27
Hemoglobin	15.1 ± 0.55	16.4 ± 1.2	14.2 ± 1.4
Hematocrit	43 ± 0.8	44 ± 1.1	42 ± 2.2

Values expressed as mean ± SE in milligrams per deciliter (mg/dl) for $n = 10$.

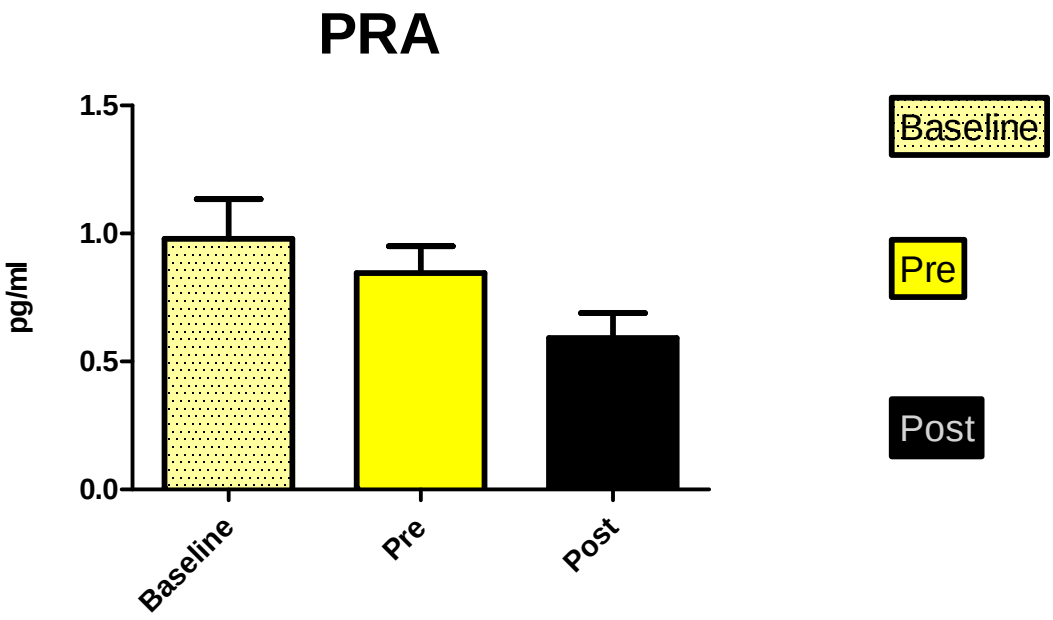

Figure 1. Changes in plasma renin activity (PRA) from baseline to post 4 weeks of exercise training. Data are presented as mean ± SE in picograms per milliliter (pg/ml). Significance set at $p < 0.05$. No significant differences (NSD) are indicated between any measures.

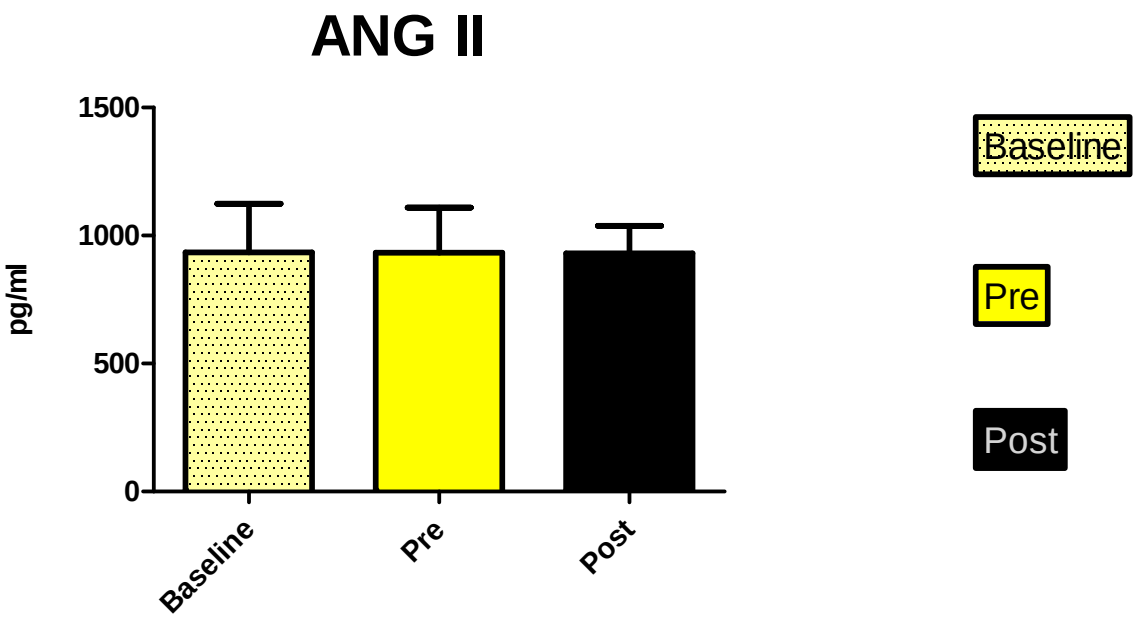

Figure 2. Changes in angiotensin II (ANG II) from baseline to post 4 weeks of exercise training. Data are presented as mean ± SE in picograms per milliliter (pg/ml). Significance set at $p < 0.05$. No significant differences (NSD) are indicated between any measures.

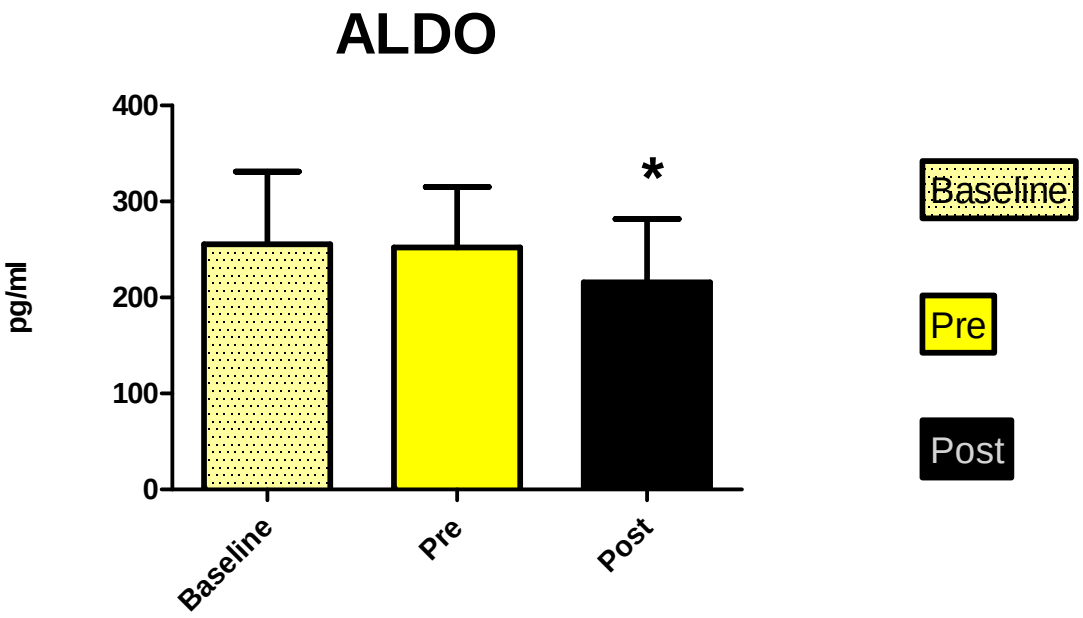

Figure 3. Changes in plasma aldosterone (ALDO) from baseline to post 4 weeks of exercise training. Data are presented as mean ± SE in picograms per milliliter (pg/ml). Significance set at $p < 0.05$. No significant differences (NSD) are indicated from baseline to pre-training (following 4 week control period). Significance (*) is indicated from baseline to post 4 week training ($p = 0.001$).

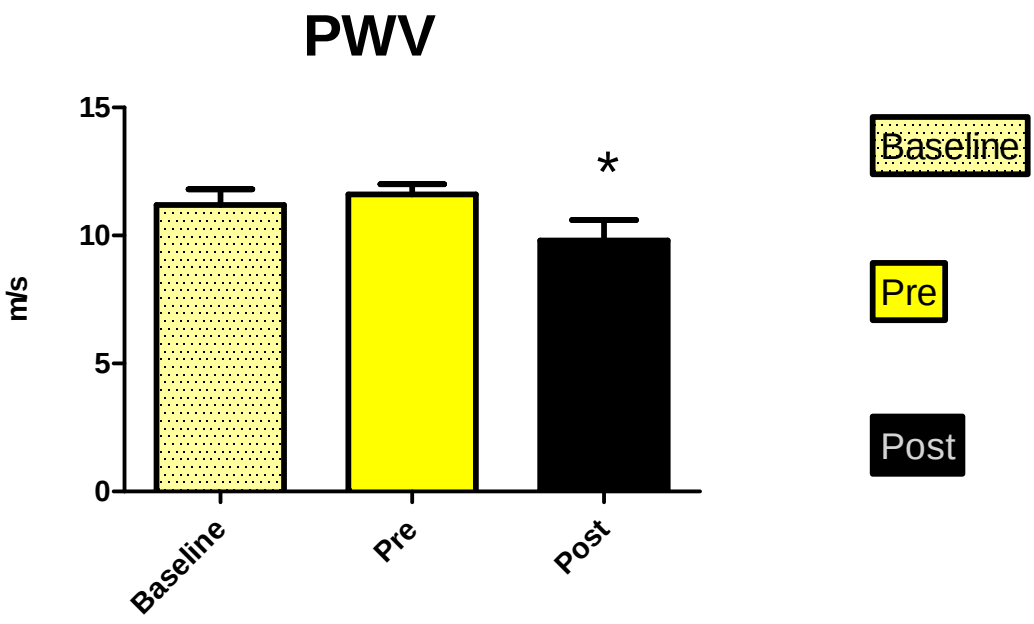

Figure 4. Changes in pulse wave velocity (PWV) from baseline to post 4 weeks of exercise training. Data are presented as mean ± SE in meters per second (pg/ml). Significance set at $p < 0.05$. No significant differences (NSD) are indicated from baseline to pre-training (following 4 week control period). Significance (*) is indicated from baseline to post 4 week training ($p = 0.04$).

DISCUSSION

The major finding of this study was the significant decline in post-training ALDO independent of decreases in body composition, which until now has not been demonstrated in this population. This finding has been supported in the animal literature, yet human studies have shown mixed results. Aerobic exercise is known to improve vascular health primarily through suppression of neurohumoral vasoconstrictors, sympathetic tone, and signaling of nitric oxide release (22). The RAAS is a central mediator on the cardiovascular influence of these components.

Exercise and Hypertension

Aerobic exercise has been shown to reduce BP and markers of arterial stiffness, even without changes in aerobic fitness or body composition (23). Declines in elevated BP with aerobic training occur after a mere 1-4 weeks of moderate intensity exercise (11, 24), and this data is further supported in the present study. Literature addressing RAAS reductions in an unmedicated hypertensive group following aerobic training is relatively absent. In a human model, 6 months of aerobic training lowered plasma ALDO in pre-hypertensive and hypertensive subjects, some previously treated pharmacologically (25). These results were, however, associated with a loss of intra-abdominal fat and without changes in BP. Kohno and colleagues reported that individuals with hypertension and elevated baseline PRA showed the greatest decreases in BP after 3 weeks of moderate intensity training (26), and other studies have produced similar results (27).

PWV

It is known that a relationship exists between plasma ALDO concentrations and arterial PWV in a hypertensive population, likely a result of localized mineralcorticoid receptor activity within the endothelium (28, 29). It is further known that carotid-femoral PWV measurement is most directly linked to assessment of cardiovascular morbidity and mortality risks (22, 30). Park et al. showed significant association with serum ALDO and central PWV, but not in peripheral measurements (31), which may indicate ALDO as more influential in the central vasculature. In the Framington Heart Study, Lieb and colleagues repeated these findings correlating ALDO-to-renin ratio with multiple vascular measures, to include carotid-femoral PWV (32).

ALDO blockade is a common intervention in the treatment of hypertension and arterial stiffness. Matsui et al. showed reductions in central PWV after 12 weeks of hydrochlorothiazide therapy ($p = 0.004$; 28). The influence of aerobic exercise on this relationship has been scarcely researched, and even less is available in an unmedicated group. As previously stated, obese individuals present with aortic stiffness, which was demonstrated in the respective cohort (baseline PWV = 11.2 ± 0.6 m/s). Central PWV measurements revealed an overall reduction (12.5%) in transit time following 4 weeks of aerobic training (post PWV = 9.8 ± 0.8 m/s). Previous studies have indicated factors associated with weight loss as mediation for improved vascular smooth muscle tone and artery compliance (33, 34). The present study is the first to match such findings in an obese, hypertensive group with associated decreases in ALDO concentration, following aerobic exercise training and without weight loss.

The Influence of Aerobic Exercise on RAAS

Independent of body weight factors, the relationship between obesity and hypertension is not fully understood, and current research offers only speculation. Until now, the availability of literature with analysis of ALDO concentrations in human hypertensive models is scarce and clinical studies concerning RAAS components on autonomic control are few. Sarzani and colleagues, along with similar studies, acknowledge the dysregulation of RAAS coupled with an inhibited cardiac function as having a major role in obesity-complicated hypertension (7, 35). Our lab has previously shown small improvements in PRA and ANG II following a moderate aerobic exercise program, which was repeated in the present study. Not previously shown in an unmedicated hypertensive pool is the resultant data for ALDO concentrations, demonstrating an average 40 point dip from baseline to post 4 week training in participants.

PRA

It is well known that accumulated adipose tissue relative to obesity contributes to over expression of the RAAS and the up regulation of PRA. Our study revealed decreases in PRA, although not significant, across the group following the training period with matched drops in arterial pressures. This finding is likely consistent with the small sample size and correlated power. Martinelli and colleagues recently found no changes in PRA in overweight hypertensives, despite reductions in BP and PWV, and they theorized insufficient weight loss as the likely rationale (36). Previous studies produced similar findings, further indicating a negative correlation between decreases in BP and PRA (37, 38) .

Comparable to the present study, ten weeks of aerobic exercise lowered plasma catecholamines, PRA, and arterial BP in an untreated hypertensive group. SBP changes were significantly matched with changes in PRA ($p = 0.005$), but not with an average 1.3% drop in body fat ($p = 0.02$; 39). Decrease in PRA among participants was concluded as a primary cause for lowered SBP.

In a paired study, Higashi and colleagues further evaluated training effects in untreated hypertension. PRA and BP were evaluated after a 12 week training program (5 days per week, 30 minutes at 50% VO_2 max). SBP and DBP changes were reported as significant ($p < 0.05$), while PRA showed insignificant reductions ($p > 0.05$; 40, 41).

ANG-II

Along with PRA, our study reported modest declines in ANG II. It has been suspected that adipocyte markers, specifically elevated plasma leptin hormone, contribute to angiotensinogen (AGT) levels in an obese population. Studies have argued the influence of genetic factors on plasma AGT and angiotensin converting enzyme (ACE) activity against environmental factors (poor diet, sedentary lifestyle). The linkage of ANG II cleaving, obesity, and hypertension remains inconclusive and studies have produced conflicted results. Most recently, an association was seen in ACE genotype, and thus ANG-II, with influence on hypertension but not obesity factors (42). This thought is most in line with our findings, as body composition remained unchanged. Sex differences have been established with the recent identification of a sex chromosome effect on BP and increases in mean arterial pressure following 2 weeks of ANG II infusion in mice (43). It is known that chronic ANG-II signaling from large RAAS activity and hypertension compromises endothelial health and

can be pharmacologically moderated via ACE inhibitor therapy. With respect to ANG II, exercise as therapy is mostly explained by alterations in nitric oxide availability (44).

ALDO

The substantial declines seen with ALDO in the present study are considered the most significant finding. ALDO concentrations, along with renin activity and ANG II, have been reported higher in obese subjects when compared to a leaner population (45, 46). The influence of ALDO has been suspected as influential in autonomic control as part of the biological pathway of RAAS, but has remained relatively uncertain. Apart from our study, ALDO has not been evaluated in an unmedicated hypertensive cohort.

Previous studies that have found reductions in ALDO following exercise are few and have not produced correlations with matched BP decline. Jones and colleagues confirmed 6 months of aerobic exercise as necessary to moderately lower plasma ALDO in medicated and unmedicated cohorts with no changes in BP (25). The dramatic changes in ALDO seen within 4 weeks in our study, along with improved BP and PWV, are novel to the hormonal influence on vagal function. The effects of exercise intervention on lowering blood pressure and PWV have been shown in normotensive and hypertensive groups, independent of RAAS activity and primarily linked to weight loss (47, 48). Based on the present study, we speculate ALDO as the mechanism for observed BP and PWV changes. Pulse pressure measures in the assessment of vascular stiffness have been well established in both obese and non-obese groups. Wildman et al. found a positive correlation between excess body weight and degrees of aortic stiffness (48). This dysfunction of the vascular system has been theorized to predispose obese persons to accelerated aging of the vasculature and chronic

hypertensive conditions. Since changes in body composition did not persuade the present study, the BP and PWV measures of our subjects from baseline to post training appear dependent of improved ALDO activity as a function of moderate intensity exercise.

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VITA

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