The Journal of Clinical Hypertension

WILEY

ORIGINAL ARTICLE OPEN ACCESS

Association Between Antioxidant Capacity and Vascular Hemodynamics in Premenopausal Women Following Exercise Training

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Received: 7 November 2024 | **Revised:** 25 March 2025 | **Accepted:** 29 March 2025

Funding: This work was supported by the NIH grants R01AG027084-01, R01 AG27084-S, R01DK049779, P30 DK56336, P60 DK079626, UL 1RR025777.

Keywords: aerobic exercise training | antioxidant capacity | antioxidant enzymes | arterial elasticity | blood pressure | free radicals | healthy subjects | oxidative stress | redox imbalance

ABSTRACT

Oxidative stress plays a role in vascular dysfunction and cardiometabolic health. The purpose of this study was to assess the effects of aerobic exercise training on antioxidant capacity (ferric reducing ability of plasma/FRAP) and hemodynamic measures: systolic blood pressure (ΔSBP), diastolic blood pressure (ΔDBP), mean arterial blood pressure (ΔMAP), large arterial elasticity index (ΔLAEI), and small arterial elasticity index (ΔSAEI) in a cohort of healthy women. This was a secondary data analysis of a study designed to evaluate cardiometabolic outcomes. Participants performed supervised aerobic exercise 3 times/week on a stationary cycle ergometer. FRAP and hemodynamic measures were measured baseline and post-training. The analysis included 15 African American and 14 Caucasian women aged 32.2 ± 5.5 years. No significant changes were observed for FRAP or hemodynamic measures. However, significant negative correlations between ΔFRAP and ΔSBP, ΔDBP, and MAP, as well as a positive correlation with ΔSAEI and ΔLAEI were observed. ΔSBP, ΔDBP, and ΔMAP were each modeled with three multiple regression models: (1) ΔFRAP, ΔSAEI, and ΔLAEI as independent variables. All models had significant R^2. ΔFRAP was significantly related to ΔDBP and ΔMAP after adjusting for ΔSAEI and ΔLAEI (partial R −0.38 and −0.32 respectively). ΔSAEI was independently related to ΔSBP (partial −0.32) and ΔMAP (partial −0.34). ΔLAEI was independently related to ΔSBP (partial −0.36) and ΔMAP (partial −0.40). ΔFRAP is significantly associated with lowered blood pressure and elevated arterial elasticity. While multiple regression analysis suggests that at least some of the lowered blood pressure is achieved through processes associated with increased arterial elasticity.

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; FRAP, ferric reducing ability of plasma; LAEI, large artery elasticity index; LAE, large artery elasticity; LDL, low-density lipoprotein; NO, nitric oxide; OS, oxidative stress; RNS, reactive nitrogen species; ROS, reactive oxygen species; SAEI, small artery elasticity index; SAE, small artery elasticity; SBP, systolic blood pressure.

Trial Registration: ClinicalTrials.gov identifier: NCT01879891

1 | Background

Exercise training is well known to improve blood pressure. However, there are often other factors that are known to impact blood pressure, such as arterial elasticity, endothelial dysfunction, oxidative stress, and inflammation, already present before elevated blood pressure is detected. The loss of arterial elasticity, leading to increased vascular resistance, presents an increased risk for adverse cardiometabolic events. Damage to the vessel wall induced by free radicals and vascular inflammation may contribute to mechanisms that impair arterial elasticity [1]. Under non-pathophysiological conditions, free-radicals, including reactive oxygen species (ROS) and reactive nitrogen species (RNS), are formed as byproduct of normal aerobic metabolism, and serve as signaling molecules playing an important role in the control and maintenance of various cellular functions. Under these conditions free radicals are neutralized in vivo by endogenous and exogenous antioxidant defenses. However, when free radicals are produced in excess of antioxidant defenses, oxidative stress/damage occurs leading to structural and functional damage, impairing processes related to cell signaling, energy metabolism, and inflammatory response [2, 3]. Over time, these processes can contribute to the manifestation and progression of several cardiometabolic conditions including hypertension.

The majority of studies assessing the relationship between markers of oxidative stress, arterial elasticity and exercise have been conducted in animal models [4]. Exercise training in spontaneously hypertensive rats improved endothelial function and vascular stiffness possibly due to a concomitant decrease in oxidative stress and increased NO bioavailability [5]. Additionally, moderate-intensity continuous training (MICT) increased total antioxidant capacity assessed via the ferric reducing ability of plasma (FRAP) in epididymal adipose tissue of Zucker rats [6]. However, studies in humans have yet to convincingly demonstrate an association between oxidative stress and arterial stiffness [7]. Endothelial adaptation, mediated by increased vascular NO production and/or decrease in NO scavenging by ROS, is thought to be one of the underlying exercise-related mechanisms conferring antihypertensive effects [8, 9].

ROS generated by contracting muscles during exercise, although essential for normal muscle force production; may lead to oxidative damage-induced muscle soreness and fatigue [10, 11]. However, regular exercise training seems to prevent the negative effects of ROS via increased expression and activity of antioxidant enzymes [10, 12]. Upregulation of endogenous antioxidant defenses leads to greater resistance to exercise-induced oxidative stress, in turn counteracting the damaging effects of oxidative stress [13–15]. Exercise-induced increase in blood flow and laminar shear stress stimulates an antioxidant cascade at the level of the vascular endothelium. While there are multiple proposed pathways involved, research has shown that factor erythroid 2-related factor 2 (Nrf2) pathway maybe an important mechanism in oxidative stress mediated exercise benefits [13, 16].

Effects of various types of exercise on oxidative stress has been studied in animal models and in humans; predominantly following acute exercise bouts under various environmental conditions [17–20]. However, there is limited information on the effects of chronic aerobic training in healthy population in the state of energy balance. Therefore, the aim of this study was to investigate the effects of chronic aerobic exercise training on changes in antioxidant capacity and vascular hemodynamic responses in healthy volunteers under energy balanced conditions. We hypothesize that antioxidant capacity will be associated with changes in hemodynamic responses following supervised exercise training.

2 | Methods

2.1 | Participants

This is a secondary analysis of a study that was designed to evaluate insulin sensitivity, resting energy expenditure, and blood pressure following a bout of moderate-intensity or high-intensity exercise as compared with no exercise (no exercise for 72 h before evaluation) [21, 22]. Female participants between 20 and 40 years of age participated in the original study. Participants had normal menstrual cycles, were not taking oral contraceptives or any medications known to influence glucose and/or lipid metabolism. Additional inclusion criteria included: (1) normotensive, (2) nonsmoker, (3) sedentary as defined by participating in any exercise-related activities less than once per week, and (4) normoglycemic as evaluated by postprandial glucose response to a 75-g oral glucose tolerance test. All participants provided written informed consent prior to the study participation. Study procedures were approved by the Institutional Review Board at the University of Alabama at Birmingham [23].

2.2 | Study Design

There were 49 participants enrolled in the original study designed to assess the effects of aerobic exercise training on cardiometabolic health outcomes when controlling for energy balance., For this secondary study, we included 29 participants who had data available for both ferric reducing ability of plasma (FRAP) and vascular hemodynamic outcomes, including blood pressure (systolic and diastolic) and arterial elasticity (small and large).

The original study included a baseline evaluation and 16 weeks of exercise training with three post training evaluations: (1) no exercise within 72 h, (2) following a moderate-intensity bout of exercise, and (3) following a high intensity exercise bout. The post-training evaluations were done at 8, 12, and 16 weeks training and were randomly assigned to the three post training evaluations. No difference in any study variable was observed between the 8, 12, and 16 week time points were observed. Only the baseline and post-training evaluation (corresponding to the no acute exercise session, i.e., trained state) were used for data analysis in this study.

2.3 | Supervised Aerobic Exercise Training

Following baseline testing, all participants began an aerobic exercise protocol for the duration of the 16-week study. Continuous exercise on a cycle ergometer was performed 3 days per week, beginning with 3–5 min warm up, and stretching at each session.

During week 1, continuous exercise was maintained for 20 min at ≈67% of maximum heart rate. Over the first 4 weeks exercise, intensity and duration increased so that by the beginning of the 5th week, exercise was maintained for 40 min at ≈80% maximum heart rate until the end of the study. Participants cooled down for 3–5 min, following cessation of exercise [21].

2.4 | Peak Oxygen Uptake VO_2peak

Following the submaximal task, participants completed a graded cycle ergometer test to measure peak oxygen uptake (VO_2peak) as determined by the highest oxygen uptake reached in the final stage of exercise. Starting at 70 W, every 2 min, power was raised 20 W until participants reached volitional exhaustion. Sixty revolutions-per-minute cycle cadence was maintained throughout the test. Oxygen uptake, ventilation, and respiratory exchange ratio were determined by indirect calorimetry using a MAX-II metabolic cart (Physio-Dyne Instrument Company, Quogue, NY). Heart rate was continuously monitored by Polar Vantage XL heart rate monitors (Polar Beat, Port Washington, NY). Although we do not claim a true maximum oxygen uptake since tests were done on a cycle ergometer rather than a treadmill, criteria for achieving a true maximum were heart rate within 10 beats of estimated maximum, RER of at least 1.1, and plateauing of VO_2. All subjects reached at least one criterion, and all but three subjects reached at least two criteria at each of the four test time points.

2.5 | Body Composition

Fat and lean mass were determined by dual-energy X-ray absorptiometry (iDXA, GELunar, Madison, Wisconsin) both at baseline and post training. Scans were analyzed by the same investigator with ADULT software, Lunar-DPX-Version1.33 (GE Medical Systems Lunar).

2.6 | Room Calorimetry and Energy Balance

Participants spent 23 h in a whole-room respiration calorimeter for measurement of total energy expenditure and resting energy expenditure before and after the exercise training period, participants were provided with food and refrained from the exercise for 72 h before testing [23].

2.7 | Blood Pressure and Arterial Elasticity Evaluation

Hemodynamic and arterial elasticity variables including systolic blood pressure (SBP), diastolic blood pressure (DBP), large artery elasticity (LAE), and small artery elasticity (SAE) were measured as reported previously [24].

2.8 | The Ferric Reducing Ability of Plasma (FRAP)

Total plasma antioxidant potential was determined by the Ferric Reducing Ability of Plasma (FRAP) assay according to the methodology of Benzie and Strain [25]. Working FRAP solution was placed in a water bath and warmed to 37°C. Then, 10 μL of blank, samples, and ascorbate STDs were transferred by micropipette into designated well of 96-well plate. Three hundred microliter of FRAP reagent was then added to all wells containing blank, samples, and standards. Ninety-six-well plate was then incubated for 4 min at 37°C before being read at 593 nm in a spectrophotometer (Molecular Devices–SpectraMax M3. Softmax Pro Version 6.3). Samples and standards were analyzed in triplicate, and FRAP values were expressed as vitamin C equivalents as determined by linear regression from a vitamin C curve (0–1000 μmol).

2.9 | Statistical Analysis

All data were analyzed using IBM SPSS version 27. Descriptive statistics were computed at baseline and trained (post-training) state. All continuous variables were reported as mean and standard deviation (SD). Paired samples *t*-test was used to compare values at baseline and trained state. Relationship between change in FRAP (independent variable of interest) and change in vascular hemodynamic (outcome) measures at baseline versus trained state was assessed using Pearson's correlation (r) with coefficient of determination (r^2). Linear regression (univariate and multiple), and scatterplots was used to evaluate the effects of FRAP and SAEI on SBP and DBP. A priori evidence indicated the relationships between ΔFRAP, ΔSAEI, ΔLAEL, ΔSBP, ΔDBP, and ΔMAP would be unidirectional. Therefore, one-tailed tests of significance were used in correlations between these variables. For all analyses, statistical significance was set at 0.05.

3 | Results

A total of 29 participants (14 Caucasian and 15 African American) who had both, baseline and post training FRAP, SBP, DBP, LAEI and SAEI values measured, were included for data analysis in this study. The mean age of the participants at baseline was 32.19 (SD = 5.51) yrs.

Table 1 illustrates baseline, post-training characteristics, change between baseline and trained state (i.e., delta, Δ) and results of paired *t*-tests. No significant differences were observed between baseline and post training values for any of the variables except peak VO_2, which increased.

Table 2 contains correlations between variables of interest. Significant negative correlations between ΔFRAP and ΔSBP, ΔDBP, and MAP, as well a positive correlation between ΔFRAP and ΔSAEI were observed. ΔSAEI was negatively related to all three blood pressure measures, while ΔLAEI was negatively related to ΔSBP and ΔMAP.

ΔSBP, Δ DBP, and ΔMAP were each modeled with multiple regression models: (1) ΔFRAP, ΔSAEI, and ΔLAEI as independent variables (Tables 3A, 3B, 3C). All three models had significant R^2. ΔFRAP was significantly related to ΔDBP, and ΔMAP after adjusting for ΔSAEI and ΔLAEI (partial $R = -0.38$ and -0.32, respectively). ΔSAEI was independently related to ΔSBP (partial R = -0.32) and ΔMAP (partial R = -0.34). ΔLAEI

TABLE 1 | Baseline, post training, comparison of characteristics of study participants and paired *t* test results.

Characteristic	Baseline mean (SD)	Trained state or post-training mean (SD)	Delta (Δ) or (*d*)[a] mean (SD)	*p* value
Age (years)	32.8 (5.6)			
Body weight (kg)	75.5 (14.7)	75.4 (15.0)	−0.1	0.81
BMI	27.1 (5.1)	27.1 (5.1)	0	0.98
% fat	38.0 (7.3)	37.5 (6.9)	−0.5	0.15
Fat mass (kg)	28.3 (9.8)	28.0 (9.6)	−0.3	0.44
Fat-free mass (kg)	44.8 6.1	45.0 5.9	0.2	0.21
Glucose (mg/dL)	88.6 8.5	87.3 7.3	−1.3	0.31
VO_2peak (mL/kg/min)	25.3 (6.5)	26.7 (6.5)	1.4	<0.01
FRAP (μmol)	429.34 (74.29)	414.02 (84.64)	−15.32	0.12
SBP (mm Hg)	116.39 (11.42)	118.08 (12.26)	1.69	0.32
DBP (mm Hg)	69.30 (7.95)	70.29 (9.68)	0.99	0.46
LAEI (mL per mmHg × 10)	16.81 (4.81)	15.71 (4.70)	−1.10	0.36
SAEI (mL per mmHg × 100)	7.45 (2.32)	7.18 (2.32)	−0.27	0.55

Abbreviations: DBP, diastolic blood pressure; LAEI, large artery elasticity index; SAEI, small artery elasticity index; SBP, systolic blood pressure.
[a]Change measured at baseline and post-training. Baseline values subtracted from those at the trained state.

TABLE 2 | Correlation for changes (Δ) in FRAP and vascular hemodynamic (outcome) measures.

	ΔDBP	ΔMAP	ΔLARTEL	ΔSARTEL	ΔFRAP
ΔSBP	0.61**	0.83**	−0.30	−0.42*	−0.35*
ΔDBP		0.77**	−0.08	−0.38*	−0.48**
ΔMAP			−0.33*	−0.42*	−0.33*
ΔLARTEL				0.01	−0.33*
ΔSARTEL					0.38**

Abbreviations: ΔSBP, change in systolic blood pressure; ΔDBP, change in diastolic blood pressure, ΔMAP, change in mean arterial blood pressure; ΔLAEI, change in Large artery elasticity index; ΔSAEI, small artery elasticity index; ΔSBP, systolic blood pressure; ΔFRAP, antioxidant system marker.
*Significant at 0.05 level (2-tailed).
**Significant at 0.01 level (2-tailed).

was independently related to ΔSBP (partial $R = -0.36$) and ΔMAP (partial $R = -0.40$).

Scatterplots showing association between ΔFRAP versus change in individual outcome measures (ΔSBP, ΔDBP, ΔLAEI, and ΔSAEI) are presented in Figure 1. Individual systolic and diastolic blood pressure response are shown in Figure 2.

4 | Discussion

There is a well-reported relationship between oxidative stress and endothelial dysfunction associated with many forms of cardiovascular diseases. Stemming from this is the growing understanding of how exercise training improves antioxidant defenses, in turn mitigating the negative effects of oxidative stress on endothelial health [26]. The purpose of this study was to examine the association between changes in antioxidant capacity and vascular hemodynamic measures following supervised aerobic exercise training, in healthy volunteers. We hypothesized that changes in antioxidant capacity are associated with changes in hemodynamic responses following aerobic exercise training. Supporting this hypothesis, we found significant negative associations between ΔFRAP and change in blood pressure as well as a positive association between ΔFRAP and ΔSAEI. This result suggests exercise related increases in plasma antioxidant capacity may increase small artery elasticity and decrease blood pressure, even in normotensive women.

TABLE 3A | Model for estimation of changes (Δ) in systolic blood pressure.

	Model R	R^2	Slope	Standardized β	Partial *r*	*p* value
Intercept	0.57	0.32	0.18	—		0.02
ΔFRAP	—	—	−0.04	−0.25	−0.27	0.08
ΔSAEI	—	—	−1.21	−0.32	−0.34	0.04
ΔLAEI			−0.46	−0.32	−0.36	0.03

TABLE 3B | Model for estimation of changes (Δ) in diastolic blood pressure.

	Model R	R^2	Slope	Standardized β	Partial *r*	*p* value
Intercept	0.56	0.32	0.26	—		0.02
ΔFRAP	—	—	−0.05	−0.37	−0.38	0.02
ΔSAEI	—	—	−0.70	−0.24	−0.25	0.10
ΔLAEI			0.24	0.21	0.24	0.11

TABLE 3C | Model for estimation of changes (Δ) in mean arterial blood pressure.

	Model R	R^2	Slope	Standardized β	Partial *r*	*p* value
Intercept	0.60	0.36	1.06	—		0.01
ΔFRAP	—	—	−0.05	−0.29	−0.32	0.05
ΔSAEI	—	—	−1.04	−0.31	−0.34	0.04
ΔLAEI			−0.45	−0.35	−0.40	0.02

4.1 | Blood Pressure

Previous work examining the effect of aerobic exercise on blood pressure have reported reductions in both SBP and DBP, highlighting the importance of exercise for reduction of cardiovascular risk [27]. Further, in a meta-analysis by Halbert et al., reduction in blood pressure following aerobic exercise was shown to be independent of intensity and frequency of exercise sessions [28] and is considered to be an effective intervention in the prevention and treatment of cardiovascular diseases via reduction in oxidative stress [29]. Although significant changes in post-training blood pressure were not recorded in our group of normotensive participants, our findings build upon the above, demonstrating a significant negative association between ΔFRAP and Δ blood pressure.

4.2 | Arterial Elasticity

Limited and varied information is available on how duration of aerobic exercise impacts arterial elasticity and cardiovascular hemodynamics. Varying the length of moderate intensity aerobic exercise bouts not only affected arterial elasticity responses, but also demonstrated independent responses of large and small artery elasticity [30]. Moderate-intensity exercise transiently increased small arterial compliance but did not elicit more sustained increases in either large or small arterial compliance [31]. In contrast, another study observed no significant alterations in arterial stiffness after a bout of acute moderate intensity aerobic exercise, despite, increased endogenous antioxidants [32]. In the present study, in the multiple regression model we observed that ΔFRAP, ΔSAEI, and ΔLAEI were all significantly related to ΔMAP, while ΔFRAP was related to ΔSAEI. Taken together these results suggests that increased antioxidant capacity may obtain its effects on blood pressure both through modifications of arterial elasticity and through other unknown mechanisms.

Aerobic exercise is known to improve blood pressure, especially in those with hypertension [33]. The subjects in our study were normotensive; decreases in blood pressure would be expected to be relatively small. Although all subjects self-reported to be inactive, based on baseline bike ergometer peak VO_2 means and standard deviations it is probable that at least some the subjects were moderately fit. Considering that the training program was tailored for physically unfit women, it is possible the training stimulus may have been too low to achieve decreases in blood pressure in at least some of these normotensive women [21].

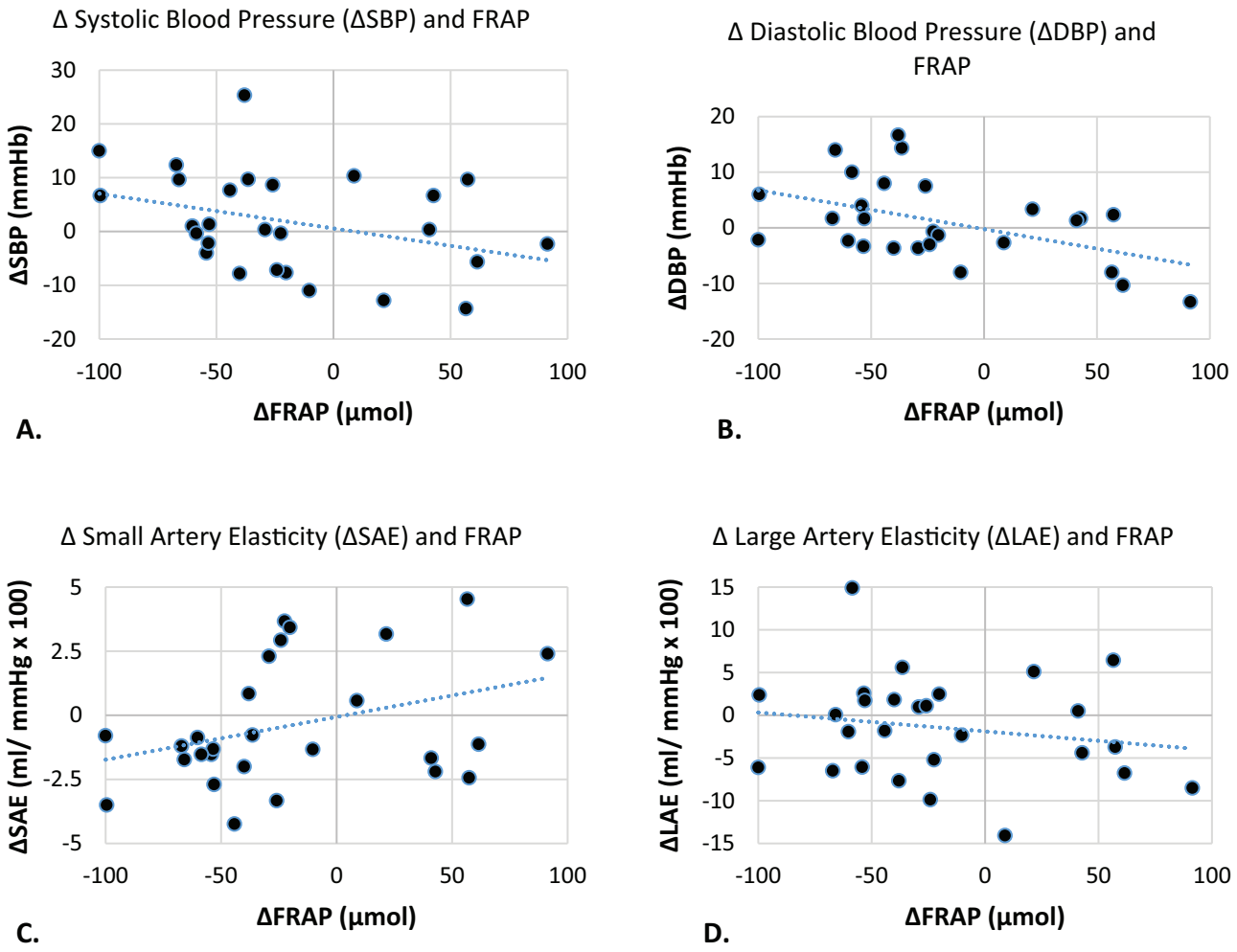

FIGURE 1 | (A) Correlations between change in FRAP and SBP ($r = 0.35$, $p < 0.05$). (B) Correlations between ΔFRAP and ΔDBP ($r = -0.48$, $p < 0.01$). (C) Correlations between ΔFRAP and ΔSAEI ($r = 0.38$, $p < 0.01$). (D) Correlations between ΔFRAP and ΔLAEI (-0.08, $p = 0.67$).

4.3 | Antioxidant Profile

Exercise training, both aerobic and anaerobic, reported improved redox balance [34]. The glutathione (GSH) antioxidant system may play a role in promoting general adaptation to oxidative stress [35]. We anticipated seeing an improved antioxidant profile after exercise training. However, we did not find significant differences between baseline and post training FRAP. One possibility for this unexplained finding may be due to the time-course of FRAP increase following a bout of exercise. It is possible increases in FRAP may be transient after a bout of exercise. Increased FRAP reported previously was measured shortly after performance of maximal exercise [19, 36]. In our study, after 12 weeks of aerobic training, subjects refrained from the exercise for 72 h before testing. Another factor that might be influencing ΔFRAP is the intensity/volume of training. It is possible that the training stimulus was too mild for some of the subjects to increase FRAP, especially 72 h after the last bout of exercise. Thus, as we have previously shown with insulin sensitivity [37], it may be necessary to repeat intense exercise frequently to maintain exercise induced hemodynamic improvements.

Overall strengths of this study include: (1) strict inclusion requirements; (2) the use of whole room indirect calorimetry to control for energy balance prior to assessments; and (3) the use of state-of-the-art methods to assess body composition, hemodynamic measures, and antioxidant capacity. This study provides clinical significance for better understanding the role of the changes in antioxidant capacity with changes in blood pressure and arterial elasticity. The study is limited in that most women enrolled in the study were normotensive and we therefore did not see significant changes in the hemodynamic or antioxidant capacity following exercise training. This may be different when assessed in a cohort of women with hypertension. However, the observation that these variables are associated with one another warrants further investigation and may provide insight for health professionals to identify early risk factors when monitoring hypertension.

5 | Conclusions

Changes in plasma antioxidant capacity as measured by FRAP showed a negative association with changes in blood pressure and positive association with change in small artery elasticity following supervised aerobic exercise training. Multiple regression analysis suggests that increased FRAP following exercise training may induce lower blood pressure both independently and through increased arterial elasticity.

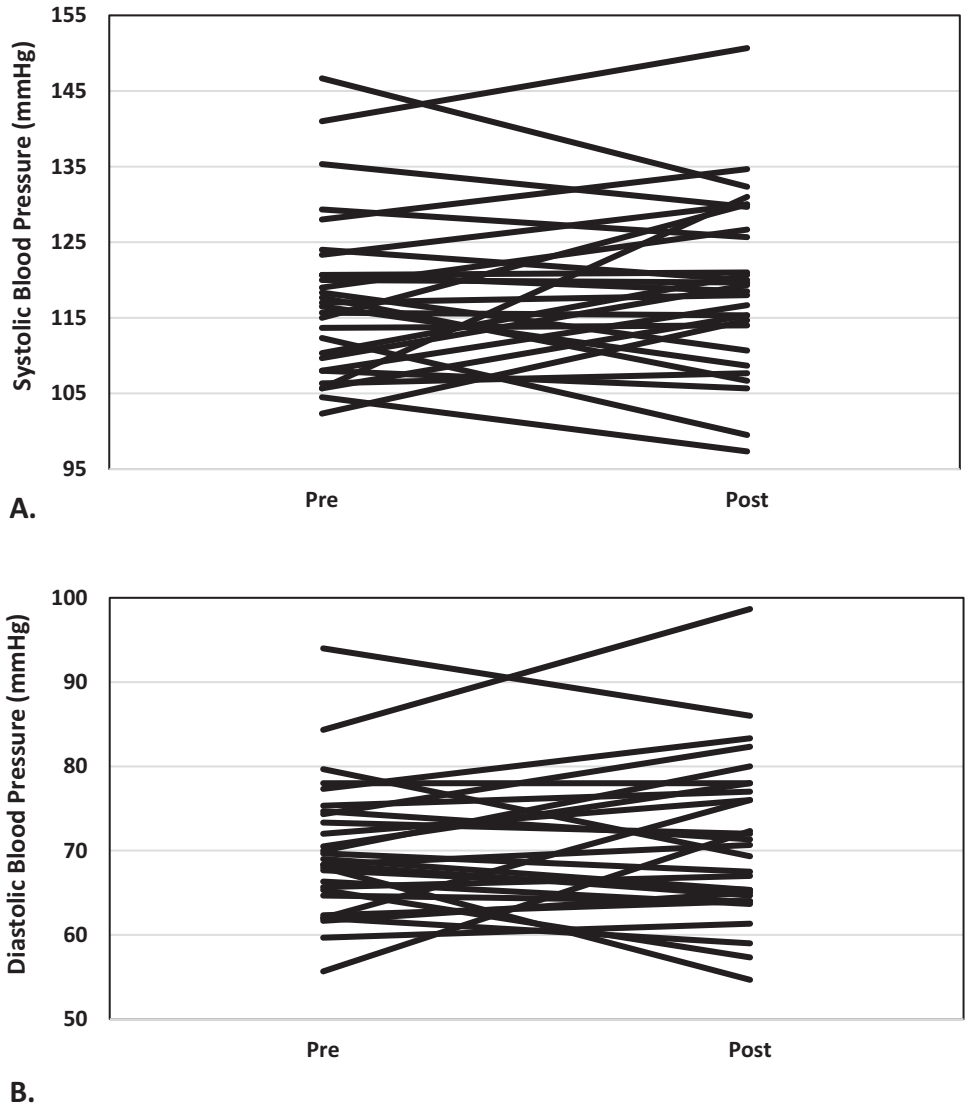

FIGURE 2 | Individual systolic and diastolic blood pressure responses.

Author Contributions

G.H., G.F., and D.M. had full access to all data used for data analysis in this study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: G.F., G.H., and D.M. Analysis and interpretation of data: All authors. Drafting of the manuscript: A.T., C.B. and G.F. Critical revision the manuscript for intellectual content: All authors. Read and approved the final manuscript: All authors.

Acknowledgments

We thank Bob Petri and David Bryan for assistance in data collection.

Ethics Statement

The original study and the secondary database analysis used in this paper was approved by the Institutional Review Board for Human Use at the University of Alabama at Birmingham.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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