Original Article

Endothelial function and arterial stiffness in young adults with histories of chronic resistance activity

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ABSTRACT

Endothelial dysfunction and arterial stiffness indicate vessel damage and are detectable before overt cardiovascular disease. Chronic cardiorespiratory endurance activity improves arterial endothelial function and stiffness. The influence of chronic resistance activity on these variables is less definitive and thus deserves attention. The primary aim of this investigation was to determine if endothelial dysfunction and arterial stiffness were present in apparently healthy young adults who chronically engage in resistance activity with minimal cardiorespiratory endurance activity. Investigators measured endothelial function as LnRHI and arterial stiffness as AI@75 using the EndoPAT-2000. Investigators measured upper-body muscular strength using a standardized one-repetition maximum (1-RM) bench press. The LnRHI and AI@75 between males and females were compared via an independent-samples *t*-test and Mann-Whitney *U* test, respectively. Correlations between 1-RM, bench press to body weight ratio, LnRHI, and AI@75 were evaluated via Pearson's correlation. Males' LnRHI was abnormal according to manufacturer standards and lower than females' (p = .005), but AI@75 was normal and similar for both sexes (p = .22). The 1-RM and bench press to body weight ratio correlated negatively with LnRHI (p = .03 and p = .01, respectively). The bench press to body weight ratio correlated negatively with AI@75 (p = .03), and percentage body fat correlated positively with the AI@75 (p = .003). Young adult males with considerable upper-body muscular strength due to chronic resistance activity, who complete minimal cardiorespiratory endurance activity, appear to have detectable signs of early endothelial dysfunction.
Keywords: Sports medicine; Muscular strength; Resistance adaptations; Blood vessels.

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INTRODUCTION

Cardiovascular disease (CVD), the progressive stiffening and narrowing of arteries, is the leading preventable cause of death worldwide (*The Top 10 Causes of Death*, n.d.). Stiffening and narrowing occur secondary to endothelial dysfunction, which impairs vasomotor function and promotes hypertension and fatty plaque deposition (Libby et al., 2002; Sandoo et al., 2010; van Hinsbergh, 2012; Widlansky et al., 2003; Zhao et al., 2015). Endothelial dysfunction correlates with many CVD risk factors and is predictive of cardiac events in individuals with the disease (Della Rocca & Pepine, 2010; Gokce et al., 2003; Gokce, Keaney, et al., 2002; Rossi et al., 2008; Widlansky et al., 2003). Therefore, cardiovascular health depends on a normally functioning endothelium.

Prospective studies aiming to treat the endothelium have often measured its function as flow-mediated dilation (FMD), a valid measure of NO bioavailability and thus endothelial function (Sandoo et al., 2010). Chronic cardiorespiratory endurance activity alone or in combination with resistance activity has consistently improved FMD in various demographics (Clarkson et al., 1999; Gokce, Vita, et al., 2002; Green et al., 2004). The effects of near-exclusively engaging in chronic resistance activity (i.e. minimal cardiorespiratory endurance activity) have received less attention and are inconclusive. Studies implementing chronic resistance activity (machines and/or free weights) describe contrasting effects on FMD (Rakobowchuk et al., 2005; Spence et al., 2013). In young men, Rakobowchuk et al. (2005) reported brachial artery FMD to be unchanged after 12 weeks, while Spence et al. (2013) reported brachial artery FMD to be increased after 24 weeks. Collectively, these data demonstrate that study length and exercise modality may elicit divergent adaptations in endothelial function and arterial structure.

A 2020 systematic review highlighted the continued lack of clarity about how resistance activity affects the vasculature (specifically arterial stiffness). The authors identified several variables that plausibly modulate vascular adaptations to resistance activity (e.g. intensity, muscles trained, continuous vs. periodic exercise, eccentric vs. concentric contractions) (García-Mateo et al., 2020). Notably, the authors concluded that chronic upper-body training at a vigorous intensity may increase arterial stiffness (García-Mateo et al., 2020). Because resistance activity is a popular chronic exercise modality, this potential maladaptive response deserves attention.

There are several techniques for measuring vascular function, and they vary by factors such as cost, ease of use, and training required. In recent years, Itamar Medical Ltd. developed the EndoPAT-2000, a device that assesses endothelial function and arterial stiffness via peripheral arterial tonometry (PAT). Compared to FMD, PAT is cheaper, requires less training, and utilizes a largely automated procedure to detect two important markers of vascular function—reactive hyperemia index (RHI; endothelial function) and augmentation index (AI; arterial stiffness) (Axtell et al., 2010; *Itamar Medical*, 2020). The RHI negatively correlates with body mass index (BMI), blood lipids, diabetes, and smoking (Hamburg et al., 2008); is dampened in people with CVD (Bonetti et al., 2004); and is predictive of cardiac events and all-cause mortality (Rubinshtein et al., 2010; Xu et al., 2014). The AI has been shown to be elevated in people with erectile dysfunction (Aversa et al., 2011), renal impairment (Moerland et al., 2012), and type 2 diabetes (Moerland et al., 2012). The major theme illustrated by these works is that PAT detects endothelial dysfunction and arterial stiffness in individuals at risk of or diagnosed with CVD (Bonetti et al., 2003, 2004; Hamburg et al., 2008; Kuvin et al., 2003; Moerland et al., 2012; Rubinshtein et al., 2010; Xu et al., 2014).

Studies of how physical activity influences the RHI and AI are limited to older adults. One retrospective study showed a greater RHI but similar AI among veteran European football players over 65 years of age when

compared to inactive controls (Schmidt et al., 2015). A separate prospective study with older adults over 50 years of age showed a greater prevalence of endothelial dysfunction in a low-to-moderately active group compared to a highly active group (Kwaśniewska et al., 2016). Individuals with histories of physical activity in general, and specifically cardiorespiratory endurance exercise, appear to have greater endothelial function according to PAT (Kwaśniewska et al., 2016; Schmidt et al., 2015). To the author's knowledge, the endothelial function of individuals with histories of resistance activity has not yet been elucidated or described.

The authors pursued this study with the understanding that chronic resistance activity is a potent stimulator of increases in lean body mass, muscular strength, and muscular endurance (Egan & Zierath, 2013). Though these adaptations are often the key motivators for engagement, resistance activity can improve insulin sensitivity and reduce inflammatory markers and CVD risk (Egan & Zierath, 2013). Therefore, a reasonable hypothesis would be that chronic resistance activity can promote healthier, responsive blood vessels. We are unaware of any published data on the RHI and AI in apparently healthy young adults engaged in chronic resistance activity with minimal cardiorespiratory endurance activity. Knowing there are potentially divergent vascular adaptions to structured exercise (Egan & Zierath, 2013), particularly resistance activity (García-Mateo et al., 2020), eligibility for the present study was limited to participants with highly developed muscular strength in the upper-body.

MATERIAL AND METHODS

Participants

The Human Subjects Committee of the University of Central Missouri's Institutional Review Board approved this investigation, which consisted of a sample of apparently healthy young adults, aged 20-29 years. All participants completed the revised American College of Sports Medicine (ACSM) preparticipation screening algorithm for general, nonclinical populations (American College of Sports Medicine, 2017). Participants also self-reported a history of resistance activity of at least three times per week for three months with minimal cardiorespiratory endurance activity. Lastly, they were required to affirm a self-belief that they were near the appropriate, sex-specific 90th percentile for upper-body strength. Participants were excluded if they reported suspicion of pregnancy, were pregnant, or if the ACSM algorithm recommended follow-up with a medical professional before exercise. Eligible participants completed an approved informed consent form and were subsequently enrolled.

Procedures and Measures

1st Session

Before the first session, participants were instructed to arrive in comfortable and athletic clothing, having fasted for four hours and forgone consuming alcohol, tobacco, vitamins, caffeine, and any other ergogenic aids within eight hours of their session. Upon arrival, investigators acquired demographic and anthropometric (height and body mass) data. Segmental and overall body composition data were assessed via dual-energy X-ray absorptiometry (GE Healthcare Lunar Prodigy Advance, Chicago, IL). Relevant values are reported in Table 1.

Investigators measured the natural log formation of the RHI (LnRHI), and the AI standardized to 75 heartbeats per minute (AI@75) via the EndoPAT-2000 (Itamar Medical Ltd, Caesarea, Israel). Procedures of this investigation matched the guidelines issued by the manufacturer (*Itamar Medical*, 2020) and published research (Axtell et al., 2010; Moerland et al., 2012). Participants rested in a near-supine position on a patient table in a quiet, dimmed, and temperature-controlled room for 20 minutes before resting blood pressure and subsequent EndoPAT testing (Table 1). The primary investigator recorded and entered resting blood

pressure into the EndoPAT-2000 software. Endothelial function and arterial stiffness data were then collected during three periods: five minutes of baseline, five minutes of occlusion of the brachial artery, and five minutes immediately post-occlusion. Pressure applied to the artery during occlusion was between 60 mm Hg above participants' respective resting systolic blood pressure and 300 mm Hg, maximally. The cuff was fully deflated during the pre- and post-occlusion periods.

2nd Session
The second session occurred a minimum of 24 hours and a maximum of 96 hours after the first. Before their arrival, participants were instructed to wear comfortable and athletic clothing and to fast from solid foods for three hours and liquid energy sources for two hours. Additionally, participants were directed to forgo consuming alcohol, tobacco, vitamins, caffeine, and any other ergogenic aids within eight hours of their session and to have avoided strenuous physical exertion within 12 hours. A 3-5 minute self-selected and dynamic warm-up was completed by each participant before testing. Participants then completed a maximum of four, one-repetition maximum (1-RM) bench press attempts (American College of Sports Medicine, 2017). Standardized, three-minute rest periods and uniform encouragement were provided to all participants. After completion of the 1-RM protocol and with sufficient rest, handgrip strength was measured via a Jamar dynamometer (Jamar TEC, Clifton, NJ). Alternating between hands, attempts were made until investigators observed a plateau or decrease in performance. The rest between attempts was approximately 60 seconds. Participants completed a self-selected cool-down.

Maintenance of Internal Controls
All participants verbally confirmed adherence to pre-testing procedures. All EndoPAT-2000 tests occurred in the same room with dim lighting. Investigators ensured participants kept their legs uncrossed and encouraged them to keep their bodies at ease to prevent hemodynamic disturbances. The primary investigator was the only individual who collected resting blood pressure, with measurements taken in duplicate and 30 s apart. The stopwatch function of the EndoPAT-2000 software was used and verified via a separate stopwatch to time the five-minute baseline, occlusion, and post-occlusion periods.

Internal controls were also maintained during the assessment of upper-body and forearm muscular strength. The primary investigator guided each respective participant's 1-RM bench press and handgrip protocols per ACSM guidelines (American College of Sports Medicine, 2017). Strength testing occurred in the same temperature- and humidity-controlled performance laboratory, and investigators weighed the barbell, weight plates, and weight clips using a Befour digital scale (Befour®, Saukville, WI) to verify the final successful 1-RM total weight lifted.

Analysis
Investigators completed all statistical analyses using IBM SPSS Statistics 24 (SPSS, Chicago, IL). An *a priori* alpha level was set to $\alpha = .05$. The Shapiro-Wilk test and Levene's test were utilized to evaluate normality and equal variances, respectively. The LnRHI and AI@75 data were checked for outliers using the following equation: [(Quartile 3 - Quartile 1) * g) + Q3], where g was a constant equal to 2.2 (Hoaglin & Iglewicz, 1987). An independent-samples *t*-test determined whether the difference in mean LnRHI between males and females was significant. Cohen's *d* was calculated to determine the effect size of between-sex differences in the LnRHI. Interpretation of the effect sizes followed convention: small (0.2), medium (0.5) and large (0.8) (Cohen, 1988).

A Mann-Whitney U test determined whether the difference in median AI@75 between males and females was significant. The equation $r = Z / n^{1/2}$ was calculated to determine effect size for between-sex differences

in the AI@75. Bivariate correlations (Pearson's *r*) were conducted to evaluate the correlations between upper-body muscular strength (absolute and relative), body mass, BMI, and percentage body fat (PBF) and both the LnRHI and AI@75.

RESULTS

Upper-body Relative and Forearm Absolute Muscular Strength
Participants' self-reported engagement in chronic resistance activity was validated by two metrics: upper-body relative and forearm absolute muscular strength, which are reported in Table 1. Suggestive of chronic training, males' (mean = 1.47) and females' (mean = 0.85) respective mean bench press to body weight ratios exceeded the respective 85th percentiles, which were 1.37 and 0.83 (American College of Sports Medicine, 2017). Males' (mean = 126.88 kg) and females' (mean = 72.20 kg) respective grip strengths exceeded the respective normative rankings of "*Excellent,*" which were ≥ 115 kg and ≥ 70 kg (American College of Sports Medicine, 2017).

Table 1. Subjects' demographic, anthropometric, body composition, and upper-body and forearm muscular strength characteristics with baseline values before EndoPAT-2000 testing.

Variables	Total Sample (*n* = 13; M ± SD)	Males (*n* = 8; M ± SD)	Females (*n* = 5; M ± SD)	*p*-value
Demographic and Anthropometric				
Age (yr.)	24.1 ± 2.5	23.8 ± 2.2	24.6 ± 3.1	.724
Height (cm)	174.4 ± 9.6	180.3 ± 7.6	164.9 ± 4.0	.002
Body mass (kg)	88.4 ± 21.5	100.8 ± 18.1	68.5 ± 4.2	.003
BMI (kg/m^2)	28.6 ± 4.6	30.8 ± 4.5	25.2 ± 1.4	.009
Body Composition				
PBF (%)	24.5 ± 6.0	21.9 ± 5.8	28.6 ± 4.0	.045
Upper-Body and Forearm Muscular Strength				
1-RM barbell bench press (kg)	112.6 ± 51.4	146.6 ± 31.7	58.3 ± 13.5	< .001
Bench press to body weight ratio	1.23 ± 0.4	1.47 ± 0.3	0.85 ± 0.2	.001
Hand-grip dynamometer, summation of best attempt with each hand (kg)	105.8 ± 35.3	126.9 ± 28.1	72.2 ± 7.7	.001
Baseline Values for EndoPat-2000 Testing				
Room temperature (°C)	22.2 ± 0.4	22.2 ± 0.4	22.1 ± 0.5	.724
Time in supine position before testing (min)	22.2 ± 1.7	21.8 ± 1.4	23.0 ± 2.1	.222
Resting heart rate (bpm)	65.5 ± 11.1	66.4 ± 12.9	64.0 ± 8.6	.724
Resting systolic blood pressure (mm Hg)	117.1 ± 11.0	119.8 ± 9.9	112.8 ± 12.4	.287
Resting diastolic blood pressure (mm Hg)	72.3 ± 9.8	75.8 ± 10.3	66.8 ± 6.1	.110

Yr. = years; cm = centimetres; kg = kilograms; BMI = Body Mass Index; m = meters; PBF = percentage body fat; 1-RM = one-repetition maximum; °C = degrees Celsius; min = minutes; bpm = beats per minute; mm Hg = millimetres of mercury.

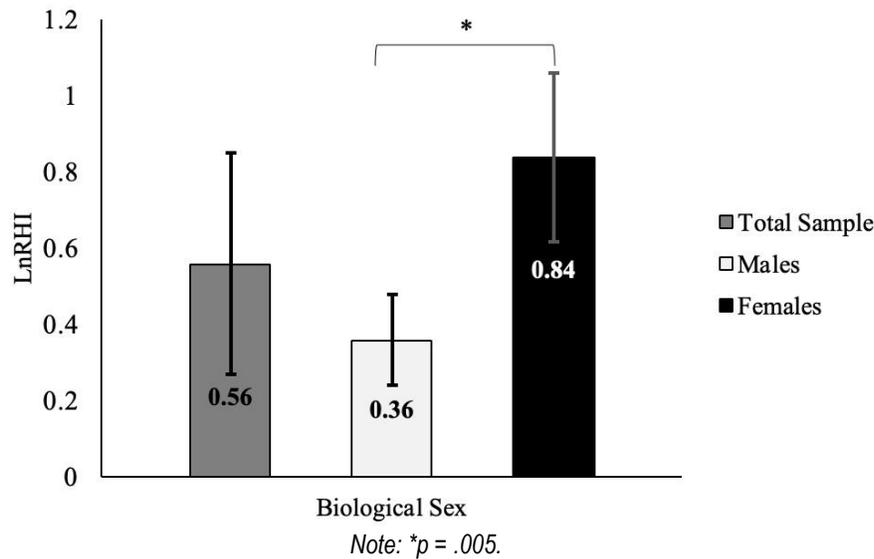***Between-Sex Differences in the LnRHI and AI@75***

Figure 1. Display of the mean ± SD of LnRHI for males (n = 7), females (n = 5), and the total sample.

One male was removed as an outlier before the between-sex comparison of the LnRHI, which consequently left 7 males and 5 females for the analysis. Equal variances were not assumed (p = .043). The LnRHI was significantly lower in males than in females; $t(5.739)$ = -4.462, p = .005, d = -2.61 (Figure 1). The AI@75 was not significantly different between males (n = 8; Mdn = -29.00%) and females (n = 5; Mdn = -13.00%); U = 11.50, p = .22, d = -0.35.
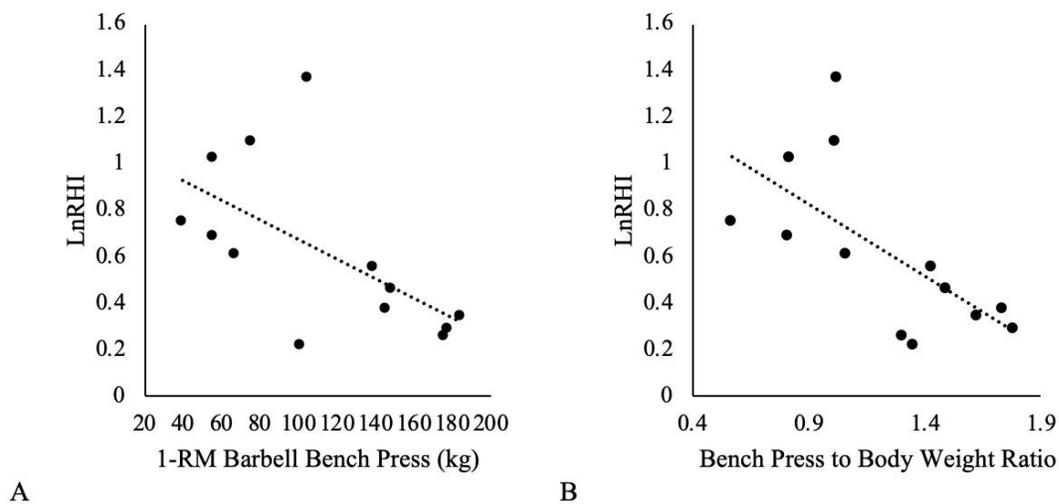
Correlations between Upper-Body Muscular Strength and LnRHI and AI@75

A   B

Figure 2. Scatterplots of the significant, moderate, and negative correlations (n = 13) between 1-RM barbell bench press and LnRHI (A) and LnRHI and bench press to body weight ratio (B). The dotted lines are trend lines. Kg = kilograms.

There were significant, moderate, and negative correlations (*n* = 13) between 1-RM and LnRHI (*r* = -.60, *p* = .03, Figure 2A) and between bench press to body weight ratio and LnRHI (*r* = -.66, *p* = .01, Figure 2B). There was not a significant correlation (*n* = 13) between 1-RM and AI@75 (*r* = -.35, *p* = .25). There was a significant, moderate, and negative correlation between bench press to bodyweight ratio and AI@75 (*r* = -.59, *p* = .03, Figure 3A).

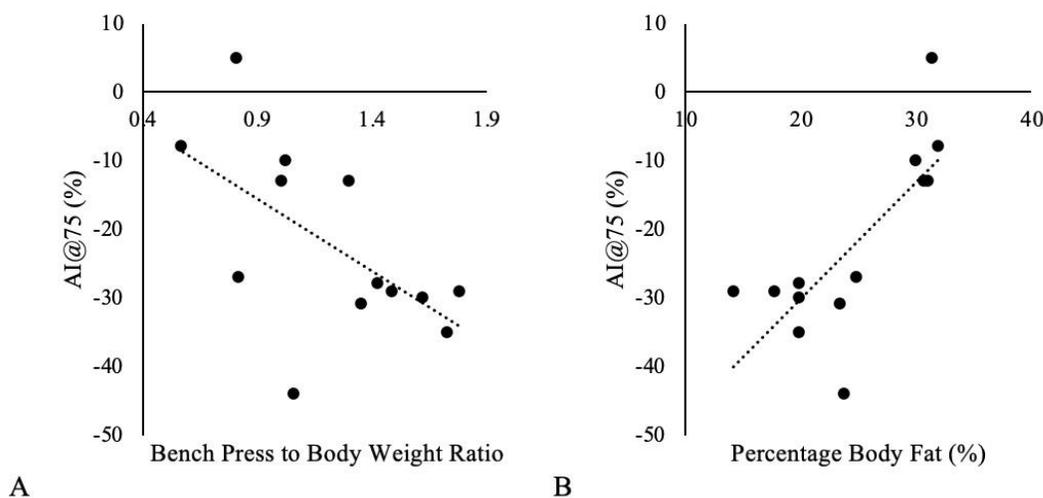***Correlations between Body Mass, Body Mass Index, and Percentage Body Fat and LnRHI and AI@75***

Figure 3. Scatterplots of the significant, moderate, and negative correlations (*n* = 13) between bench press to body weight ratio and AI@75 (A) and the significant, strong, and positive correlation (*n* = 13) between percentage body fat and AI@75 (B). The dotted lines are the trend lines.

There were no significant correlations (*n* = 13) between body mass and LnRHI (*r* = -.33, *p* = .27), BMI and LnRHI (*r* = -.46, *p* = .12), or PBF and the LnRHI (*r* = .52, *p* = .07). There were no significant correlations (*n* = 13) between body mass and AI@75 (*r* = .03, *p* = .93) or between BMI and AI@75 (*r* = -.03, *p* = .93). There was a significant, strong, and positive correlation between PBF and AI@75 (*r* = .76, *p* = .003, Figure 3B).

DISCUSSION

Elucidating the effects of chronic resistance activity is important, given that it is a prevalent type of exercise and vascular adaptations differ according to the exercise chosen (e.g. intensity, muscles trained, continuous vs. periodic exercise, eccentric vs. concentric contractions) (Egan & Zierath, 2013; García-Mateo et al., 2020). Though such data on endothelial function are lacking, short programs of resistance activity (4-12 weeks) have mostly improved arterial stiffness in healthy adults, except for when the activity was intense and focused on the upper-body (García-Mateo et al., 2020). To our knowledge, no published study has reported data on the endothelial function and arterial stiffness of young adults with long histories of intense training in resistance activity but minimal engagement in cardiorespiratory endurance activity. Thus, the authors of the present study used the EndoPAT-2000 to measure the LnRHI (endothelial function) and AI@75 (arterial stiffness) of apparently healthy young adults who reported that they near-exclusively engaged in chronic resistance activity.

Our prominent finding was endothelial dysfunction in our male participants, whose LnRHI is classified as abnormal according to EndoPAT-2000 product information (*Itamar Medical*, 2020). The manufacturer

delineates an LnRHI > 0.51 as normal and ≤ 0.51 as abnormal (*Itamar Medical*, 2020). Males' mean LnRHI was 0.36 ± 0.12, which is greater than one standard deviation below the cut-off value for normal endothelial function. In considering the males, only one of the seven exceeded an LnRHI of 0.51 (LnRHI = 0.56). The abnormally low endothelial response among the males was unexpected, given their young age, active lifestyle, and lack of apparent symptoms of cardiovascular, renal, or metabolic disease. Compared to the males, our female participants' LnRHI was normal (0.84 ± 0.22) and significantly higher despite also having histories of chronic resistance activity and a similar age, systolic blood pressure, and diastolic blood pressure (Table 1).

While both the males and females were demonstrably strong, males were exceedingly so in both absolute and relative units (Table 1). Females' mean 1-RM bench press and bench press to body weight ratio were 58.3 ± 13.5 kg and 0.85 ± 0.2, respectively. In comparison, the males lifted 146.6 ± 31.7 kg for a ratio of 1.47 ± 0.3. This striking difference in strength may explain the males' endothelial dysfunction. Both absolute and relative upper-body muscular strength correlated negatively and moderately with LnRHI. In both Figures 2A and 2B, males disproportionately represent the data points in the bottom-right, whereas females represent the data points in the top-left. It is possible that increases in muscular strength, secondary to chronic, intense resistance activity, are accompanied by vascular adaptations that reduce endothelial responsiveness (i.e. magnitude of LnRHI). We could not locate LnRHI data in a similar sample to corroborate or contradict our finding. Interestingly, a recent large-scale observational study observed a direct U-shaped association between self-reported weekly frequency and duration of resistance activity and CVD morbidity, adverse events, and all-cause mortality (Liu et al., 2019). Completing resistance activity 1-3 times weekly for 1-59 minutes conferred a 40-70% reduction in risk of total CVD events, but ≥ four times or 60 minutes weekly provided no benefit (Liu et al., 2019). While our cross-sectional pilot study does not prove that chronic resistance activity and/or muscular strength mediates endothelial dysfunction, our data do suggest a link, and may be the first to do so; our finding warrants further investigations.

Our secondary finding concerns our participants arterial stiffness. The overall AI@75 was similar and normal in males and females (normal range: -30% to -10%) (Moerland et al., 2012). Of our 13 participants, 11 had a normal AI@75 (Moerland et al., 2012). The remaining two out of 13 participants had an AI@75 between -10% and +10%, indicating increased arterial stiffness (Moerland et al., 2012). Correlational analyses identified a negative, moderate correlation between the bench press to body weight ratio and AI@75 but not the 1-RM and AI@75. Because a lower AI@75 (including negative values) indicates a higher degree of arterial elasticity (*Itamar Medical*, 2020), our data show that our participants with the greatest relative strength tended to have the greatest arterial elasticity (bottom-right of Figure 3A). As with our analyses for LnRHI data, we could not AI@75 find data for comparison. Nonetheless, our finding is noteworthy, as it seems to defy the conclusion of a 2020 systematic review that 4-12 weeks of vigorous upper-body resistance activity may increase arterial stiffness (García-Mateo et al., 2020). Our male participants' histories of such training are evidenced by their mean 1-RM bench approximating 150 kg and 1.5x their body mass. One difference between our sample and the samples in the review (García-Mateo et al., 2020) is that our participants reported years of training, a period many times longer than 12 weeks. Long-term studies implementing vigorous upper-body resistance activity will be required to elucidate its impact on arterial stiffness.

Our tertiary finding was that PBF correlated strongly and positively with AI@75. In other words, participants with the highest PBFs tended to have the stiffest arteries (top-right of Figure 3B). There does not appear to be data linking a higher PBF to stiffer arteries in apparently healthy young adults who regularly complete resistance activity in the literature. Even so, the clinical relevance of this relationship is dubious, given that 11 participants had a normal AI@75. Regarding the other variables, PBF did not significantly correlate with

LnRHI, and there were not any significant correlations among body mass, LnRHI, and AI@75 or BMI, LnRHI, and AI@75. These tertiary analyses were largely exploratory and did not support definitive conclusions about the relationship between PBF and arterial stiffness in our sample. Studies that investigate multivariate associations will be needed to determine the relationships between anthropometrics, body composition, muscular strength, endothelial dysfunction, and arterial stiffness in young adults with histories of chronic resistance activity.

Three key strengths of the present study are worth mentioning. First, we conducted the EndoPAT-2000 procedure in a manner consistent with manufacturer guidelines (*Itamar Medical*, 2020) and published literature (Axtell et al., 2010; Moerland et al., 2012). Second, we maintained a well-controlled testing environment and had all participants complete the same standardized supine rest before testing. Third, only the primary investigator measured participants' blood pressure and conducted the EndoPAT-2000 procedure, thus preventing measurement error that could have been introduced by multiple investigators recording the same variables. Two limitations of the present study should also be noted. We asked our participants if they completed chronic resistance activity, but we did not specify the type of resistance activity or quantify exercise duration, frequency, or intensity. Measuring these variables will be necessary to better understand the relationships between different types of resistance activity, endothelial function, and arterial stiffness. Additionally, we asked our participants to control their diets for only 24 hours preceding the EndoPAT-2000 testing. It is possible that the males and females in our study followed different chronic dietary patterns that influenced their endothelial function and arterial stiffness. To confirm this, investigators will need to assess dietary intake.

CONCLUSIONS

The main purpose of the present study was to determine if endothelial dysfunction and arterial stiffness were present in apparently healthy young adults who chronically engage in resistance activity with minimal cardiorespiratory endurance activity. While the LnRHI of females was normal, males had significantly lower values that were abnormal. AI@75 was normal in both males and females and did not differ between the two sexes. Among all the participants, both absolute and relative strength correlated negatively and moderately with LnRHI. We are careful to provide our data and findings without contending that chronic resistance activity causes endothelial dysfunction. We do highlight the interesting findings related to muscular strength to assert the need for additional investigations to determine if our findings are reproducible in similar samples of young adults engaging in chronic resistance activity. Continued research in this area is important, as it appears that the young adult males in this sample, particularly those toward the upper range of muscular strength, appear to have detectable signs of early endothelial dysfunction.

AUTHOR CONTRIBUTIONS

SUPPORTING AGENCIES

DISCLOSURE STATEMENT

ETHICS STATEMENT

The authors confirm that the procedure was undertaken in accordance with the Declaration of Helsinki. All experimental procedures complied with the current local, state, and federal laws of the United States of America.

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