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Original Research

Serum Tumor Necrosis Factor-alpha associates with Myocardial Oxygen Demand and Exercise Tolerance in Postmenopausal Women

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ABSTRACT

International Journal of Exercise Science 11(2): 42-54, 2018. The functional implications of serum tumor necrosis factor-alpha (TNF-α), a marker of oxidative stress, on hemodynamic parameters at rest and during physical exertion are unclear. The aims of this investigation were to examine the independent associations of TNF-α on myocardial oxygen demand at rest and during submaximal exercise, while also evaluating the association of TNF-α on exercise tolerance. Forty, postmenopausal women, provided blood samples and completed a modified-Balke protocol to measure maximal oxygen uptake (VO_{2max}). Large artery compliance was measured by pulse contour analyses while rate-pressure product (RPP), an index of myocardial oxygen demand, was measured at rest and during two submaximal workloads (i.e., ≈55% and ≈75% VO_{2max}). RPP was calculated by dividing the product of heart rate and systolic blood pressure (via auscultation) by 100. Exercise tolerance corresponded with the cessation of the graded exercise test. During higher-intensity exertion, ≈75% VO_{2max}, multiple linear regression revealed a positive association (r = 0.43; p = 0.015) between TNF-α and RPP while adjusting for maximal heart rate, VO_{2max}, large artery compliance, and percent body fat. Path analyses revealed a significant indirect effect of large artery compliance on exercise tolerance through TNF-α, β = 0.13, CI [0.03, 0.35], indicating greater levels of TNF-α associated with poorer exercise tolerance. These data suggest TNF-α independently associates with myocardial oxygen demand during physical exertion, thus highlighting the utility of higher-intensity efforts to expose important phenomena not apparent at rest. TNF-α also appears to be indirectly associated with the link between large artery compliance and exercise tolerance.

KEY WORDS: Aging, atherosclerosis, cytokines, inflammation, vasodilation

INTRODUCTION

While cardiovascular disease (CVD) mortality has declined over recent decades, it remains a major public health concern. Age-related vascular dysfunction, especially arterial stiffening, is a known precursor that contributes to the development of clinically relevant CVD (30). Recent work has indicated that women have an elevated risk for arterial stiffening through the

menopausal transition, presumably due to estrogen deficiency (10). Compared to men, premenopausal women tend to have a lower incidence of CVD mortality, however, this disparity is largely reduced with advancing age and following menopause (19). In fact, data from the National Health and Nutrition Examination Survey has showed that women 65 years of age and older have the highest prevalence of hypertension (20). Certainly, as the number of older adults continues to grow, with an expected 2-fold increase by 2030 (13), further inquiry concerning the factors involved in the initiation and progression of CVD are warranted.

Whereas the underlying etiology of CVD is often varied, oxidative stress has previously been linked to arterial stiffening in postmenopausal women (18). Convincing evidence has emerged from both animal (4) and human (17) models implicating tumor necrosis factor-alpha (TNF-α) as the principal pro-inflammatory cytokine contributing to vascular dysfunction. More specifically, research by Arenas and colleagues (1) has shown that TNF-α upregulates oxidative stress via increased production of reactive oxygen species, which in turn, may reduce vasodilatory potential. Although strenuous exercise is known to dramatically increase the release of TNF-α (23), the functional implications of circulating TNF-α on hemodynamic parameters at rest and during physical exertion are unclear. Indeed, investigating the independent associations of resting (i.e., pre-exercise) TNF-α and cardiovascular responses are of clinical relevance, especially among older adults where increased adiposity-induced inflammation and comorbid conditions are prevalent.

Due to inherent methodological constraints concerning the direct measurement of myocardial oxygen utilization, rate-pressure product (RPP) (i.e., the product of heart rate and systolic blood pressure), offers an index of myocardial oxygen demand and insight regarding coronary heart disease severity (7, 11). Since heart rate and systolic blood pressure rise in accordance with exercise intensity, RPP would be expected to follow a similar pattern. However, within the context of oxidative stress-mediated arterial stiffening, undue strain may be placed on the myocardium owing to an increased afterload (i.e., systemic vascular resistance). Hence increased systemic oxidative stress, as evidenced by resting serum TNF-α, may adversely affect arterial compliance and ultimately restrict exercise tolerance. Examining circulating TNF-α may offer prognostic value among those who may be at risk for occult cardiovascular disease (28).

Therefore, the present investigation sought to examine the independent associations of TNF-α on resting and submaximal myocardial oxygen demand (via RPP), and also, evaluate the association of TNF-α on exercise tolerance among postmenopausal women. Because physical exertion incites a greater systemic perturbation over resting conditions, we hypothesized the following: 1) TNF-α would be independently associated with RPP during submaximal exercise but not at rest; and 2) TNF-α would be independently associated with the link between large artery compliance and exercise tolerance.

METHODS

Participants

As shown in table 1, 40 postmenopausal women without a history of CVD volunteered for the present cross-sectional investigation. Inclusion criteria were as follows: nonsmoker, systolic blood pressure less than 140 mm Hg, diastolic blood pressure less than 90 mm Hg, normal electrocardiogram (ECG) at rest and during exercise, non-diabetic, and not using any medication known to affect heart rate, blood pressure, glucose and/or lipid metabolism. Participants were excluded from the study if they exhibited any abnormal ECG responses (e.g., dysrhythmia, ST depression). Study procedures were approved by the Institutional Review Board at the University of Alabama at Birmingham and conformed to the guidelines established in the Declaration of Helsinki. Prior to enrollment, all participants provided written informed consent. After a preliminary health screen, eligible participants were invited to return for further examination of body composition, blood profile analyses, vascular function, and cardiorespiratory fitness.

Table 1. Descriptive characteristics (n = 40).

Variables	Mean ± SD
Age (y)	65 ± 3
Height (m)	1.65 ± 0.04
Weight (kg)	73.2 ± 10.2
Body Mass Index (kg/m^2)	26.8 ± 3.8
Body Fat (%)	42.2 ± 5.7
Triglycerides (mg/dL)	109 ± 47
Total Cholestrol (mg/dL)	216 ± 39
High-Density Lipoprotein (mg/dL)	64 ± 19
Low-Density Lipoprotein (mg/dL)	130 ± 30
TC/HDL-c ratio	3.5 ± 1.0
LDL-c/HDL-c ratio	2.2 ± 0.8
Tumor Necrosis Factor-alpha (pg/mL)	6.8 ± 2.0
Maximal Oxygen Uptake (mL/kg/min)	23.0 ± 4.3
Resting Heart Rate (bpm)	64 ± 7
Resting Systolic Blood Pressure (mm Hg)	130 ± 14
Resting Diastolic Blood Pressure (mm Hg)	71 ± 8
Large Artery Compliance (mL/mm Hg•10)	12.1 ± 3.3
Systemic Vascular Resistance (dyne/s/cm^{-5})	1622 ± 285
Exercise Tolerance (minutes:seconds)	12:30 ± 2:50

TC, total cholestrol; LDL-c, low-density lipoprotein cholestrol; HDL-c, high-density lipoprotein cholesterol.

Protocol

Body Composition: Dual-energy X-ray absorptiometry (iDXA, GE-Lunar, Madison, WI) was used to measure total and regional body composition (i.e., fat mass and fat-free mass). Consistent with standard practices, participants wore light clothing and rested in the supine position during analyses. All scans were evaluated with ADULT software, LUNAR-DPX-L version 1.33 (GE Medical Systems Lunar).

Blood Profiles: Whole blood samples were collected via venipuncture following an overnight fast and after having refrained from any strenuous exercise/physical activity for at least 48 hours. Blood lipids including triglycerides, total cholesterol (TC), low-density (LDL) and high-density (HDL) lipoproteins were measured using the Ektachem DT60 II system (Kodak Ltd., Hemel Hempstead, U.K.). Sera was centrifuged and stored at -80 °C until batch analyses were

performed. Resting TNF-α was measured in duplicate by high-sensitivity ELISA kit (Quantikine HSTA00C, R&D Systems, Minneapolis, MN) wherein inter-assay and intra-assay coefficient of variations were 11.3% and 6.9%, respectively.

Vascular Assessment: Arterial measurements were performed in the morning hours (before 0900 hours) by trained research personnel under standardized conditions (i.e., overnight fast). Participants refrained from alcohol and caffeine consumption at least 12 hours before assessments. Prior to data recording, participants rested in the seated position for 5-10 minutes, after which, large artery compliance and systemic vascular resistance were measured by pulse contour analyses (HDI/Pulse Wave CR-2000, Hypertension Diagnostics, Eagan, MN). Briefly, an adult-sized blood pressure cuff was positioned around the non-dominant arm while a stabilizer was fastened to the contra-lateral wrist thereby limiting movement and enhancing measurement reproducibility. After palpating the pulse, a solid-state transducer was placed over the radial artery and adjusted to achieve the highest signal strength. A 30-second analog tracing of the radial waveform was digitized at 200 samples per second. According to manufacturer details, a beat-marking algorithm is used to determine the beginning of systole, peak systole, onset of diastole, and end-diastole during the 30-second recording. Large artery compliance and systemic vascular resistance are measured via computer-based analyses of diastolic waveform decay and a modified Windkessel model (3). All assessments were performed in triplicate and averaged for analyses.

Cardiorespiratory Fitness Testing: Participants performed a physician-supervised graded exercise test in accordance with the modified-Balke protocol for measurement of maximal oxygen uptake (VO_{2max} in $mL \cdot kg^{-1} \cdot min^{-1}$). Testing began with participants walking 2.0 mph (0.89 m/s) at 0% grade for 2 minutes on a treadmill (Quinton Q-Stress TM55, Bothell, WA). Grade was then increased 3.5% every 2 minutes until the 12th minute, at which point, grade was decreased to 12% and speed was increased to 3.0 mph (1.34 m/s). Subsequently, grade increased 2.5% each minute until volitional exhaustion. Oxygen uptake and carbon dioxide production were measured continuously via open-circuit spirometry (MAX II Metabolic Cart, AEI Technologies, Pittsburgh, PA). Heart rate was monitored by 12-lead ECG while blood pressure was (Omron, model HEM-780, Bannock, IL) measured at 2 minute intervals. Attainment of VO_{2max}, defined as the highest 20-second average value was confirmed by: 1) VO_2 plateau; 2) heart rate within 10 beats of age-predicted maximum; 3) respiratory exchange ratio ≥ 1.10. Note that all participants included in these analyses reached at least two of the aforementioned criteria. Exercise tolerance corresponded to the time (minutes: seconds) taken to reach volitional exhaustion. Myocardial oxygen demand was calculated from heart rate and systolic blood pressure at rest under orthostasis (i.e., standing) and during two submaximal workloads. For workloads 1 and 2, mean cohort data equated to ≈55% VO_{2max} [≈3.5 metabolic equivalents (METs)] and ≈75% VO_{2max} (≈5.0 METs) at 2.0 mph at 3.5% grade and 2.0 mph at 10.5% grade, respectively.

Statistical Analysis

Participant descriptive characteristics are reported as means and standard deviations. The Shapiro-Wilk test was used to confirm normal distributions. Two-tailed, bivariate correlation

analyses were used to examine the associations among TNF-α, triglycerides, vascular measures, indices of myocardial oxygen demand (i.e., RPP) and exercise tolerance. Multiple linear regression was used to assess the independent associations of maximal heart rate, maximal oxygen uptake, large artery compliance, TNF-α, and body fat percent on RPP at rest (standing) and during two submaximal workloads and also on exercise tolerance. It should be noted that inclusion of the adjusting variables were selected based on their plausible physiologic link to RPP. Collinearity of diagnostics for all variables were within acceptable limits and variable inflation factors for each model were less than 1.61. A path-analytic approach was used to determine the direct and indirect association of large artery compliance on exercise tolerance through TNF-α. To overcome the limitations of our small sample size, the PROCESS macro for SPSS was selected (9). In short, the bootstrapping procedure is accomplished by taking a large number of samples from the original dataset through random sampling with replacement. This permits an empirically derived sampling distribution concerning the indirect effect in which the upper and lower bounds of the 95% confidence interval (CI) match the 2.5% and 97.5% points of the sampling distribution. It should be noted that when CIs do not contain zero, statistical significance is supported. Data were analyzed with SPSS (version 23; IBM Corporation, NY). P-values ≤ 0.05 were considered statistically significant for all analyses.

RESULTS

Descriptive characteristics are shown in Table 1. Mean cohort data revealed participants had slightly elevated systolic blood pressures (prehypertensive category, 120-139 mm Hg) while diastolic values were within a normal range (< 80 mm Hg). In agreement with BMI classifications, participants tended to be overweight (25.0-29.9 kg/m^2) and also had borderline high TC (> 200 mg/dL). Still, favorable atherogenic indices were found, as both TC/HDL-C (< 4.0) and LDL-C/HLD-C (< 2.5) ratios were below the cut-offs for increased CVD risk and within the target range clarified by Millan et al. (16). Seated, resting heart rate was within the 25th and 75th percentile of normative values for women (22). VO_{2max} was 23.0 ± 4.3 mL·kg^{-1}·min^{-1} or approximately 53% greater than the minimum peak VO_2 (15 mL·kg^{-1}·min^{-1}) needed for functional independence in older women (27).

Predictably, bivariate analyses revealed a significant inverse association between large artery compliance and systemic vascular resistance, indicating greater compliance equated to less resistance. A negative association was found between TNF-α and large artery compliance (Table 2; r = -0.34, p = 0.03). As shown in Figure 1, increased oxidative stress (indexed via serum TNF-α) related to poorer arterial compliance. Additionally, large artery compliance was negatively associated with standing and exercise-related indices of myocardial oxygen demand (RPP workload 1 and 2). Figure 2 shows a positive association between TNF-α and RPP during workload 2 (≈75% VO_{2max} or ≈5.0 METs) (r = 0.32; p = 0.04) but not workload 1, indicating higher levels of TNF-α associated with greater myocardial oxygen demand. Of interest, TNF-α and exercise tolerance were inversely associated (r = -0.38; p = 0.014), which in part, suggests increased oxidative stress is linked to poorer exercise tolerance.

Table 2. Correlation matrix (n = 40).

Variables	LAC	SVR	Triglycerides	TNF-α	RPP *Standing*	RPP *Workload 1*	RPP *Workload 2*	Exercise Tolerance
LAC	--	--	--	--	--	--	--	--
SVR	-0.34†	--	--	--	--	--	--	--
Triglycerides	-0.21	-0.02	--	--	--	--	--	--
TNF-α	-0.34†	-0.32†	0.28	--	--	--	--	--
RPP *Standing*	-0.48‡	-0.39†	0.10	0.18	--	--	--	--
RPP *Workload 1*	-0.47‡	-0.50‡	0.29	0.29	0.76‡	--	--	--
RPP *Workload 2*	-0.37†	-0.33†	0.30	0.32†	0.53‡	0.59‡	--	--
Exercise Tolerance	0.06	-0.11	-0.27	-0.38†	-0.06	-0.05	-0.37†	--

LAC, large artery compliance (mL/ mm Hg·10); SVR, systemic vascular resistance (dyne/s/cm^{-5}); Triglycerides (mg/dL); TNF-α, tumor necrosis factor-alpha (pg/mL); RPP, myocardial oxygen demand as indexed by rate-pressure product [(heart rate·systolic blood pressure)/100] at rest (standing) and during 2 submaximal workloads. Treadmill settings corresponded to walking 2.0 mph at 3.5% grade (≈3.5 METs) and 2.0 mph at 10.5% grade (≈5.0 METs) for workload 1 and workload 2, respectively. †Significance at $p \leq 0.05$; ‡Significance at $p \leq 0.01$.

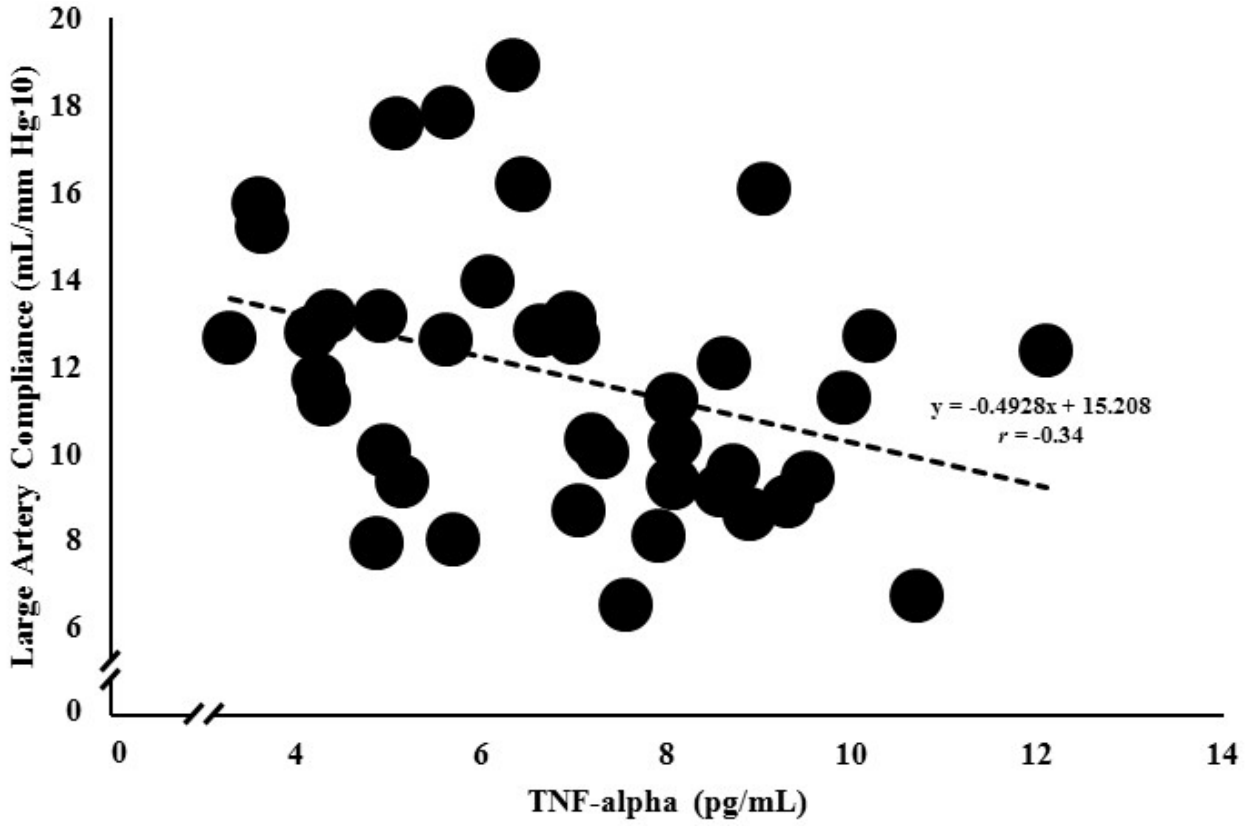

Figure 1. Unadjusted scatterplot of large artery compliance and tumor necrosis factor-alpha (TNF-α) (N = 40).

To examine the hypothesized relationships, multiple linear regression was used to test the independent effects of TNF-α on standing and exercise-related indices of myocardial oxygen demand (i.e., RPP) while adjusting for maximal heart rate, maximal oxygen uptake, large

artery compliance, and body fat percent. Large artery compliance was independently associated with standing RPP (shown in Table 3). Upon physical exertion, both maximal heart rate and large artery compliance were independently associated with RPP during workload 1 (≈55% VO_{2max} or ≈3.5 METs). As exercise intensity increased, maximal heart rate and TNF-α were independently associated with RPP during workload 2 (≈75% VO_{2max} or ≈5.0 METs).

Table 3. Regression models (n = 40).

	Model R	R^2	Slope	Standardized β	Partial r	p-value
Model 1: *RPP Standing*	0.58	0.33	49.5			
Maximal Heart Rate			0.4	0.25	0.27	0.14
Maximal Oxygen Uptake			0.5	0.10	0.10	0.60
Large Artery Compliance			-2.4	-0.36	-0.38†	*0.034*
TNF-α			2.0	0.19	0.21	0.26
Body Fat%			0.2	0.06	0.06	0.74
Model 2: *RPP Workload 1*	0.64	0.41	73.1			
Maximal Heart Rate			0.9	0.39	0.42†	*0.017*
Maximal Oxygen Uptake			0.1	0.02	0.02	0.94
Large Artery Compliance			-3.7	-0.38	-0.42†	*0.018*
TNF-α			3.3	0.21	0.24	0.18
Body Fat%			-0.6	-0.10	-0.11	0.54
Model 3: *RPP Workload 2*	0.76	0.57	-38.2			
Maximal Heart Rate			2.0	0.59	0.63†	*<0.001*
Maximal Oxygen Uptake			-2.3	-0.20	-0.23	0.20
Large Artery Compliance			-3.3	-0.22	-0.29	0.10
TNF-α			8.2	0.34	0.43†	*0.015*
Body Fat%			0.2	0.02	0.03	0.88

RPP, rate-pressure product, calculated by dividing the product of heart rate and systolic blood pressure by 100 at rest (standing) and during two submaximal workloads. Treadmill workloads corresponded to walking 2.0 mph at 3.5% grade (≈3.5 METs) and 2.0 mph at 10.5% grade (≈5.0 METs) for workload 1 and workload 2, respectively. Maximal heart rate (bpm); Maximal oxygen uptake (mL/kg/min); Large artery compliance (mL/mm Hg·10); TNF-α, tumor necrosis factor-alpha (pg/mL). †Significance at $p \leq 0.05$.

Utilizing the PROCESS macro (9), the direct and indirect effects of large artery compliance on exercise tolerance were examined through TNF-α. Large artery compliance was negatively associated with TNF-α, β = -0.23, 95% CI [-0.43, -0.04]. Additionally, TNF-α was negatively associated with exercise tolerance, β = -0.55, 95% CI [-0.98, -0.12] such that increased TNF-α contributed to poorer endurance independent of large artery compliance. Finally, a significant indirect effect of large artery compliance on exercise tolerance was observed through TNF-α, β = 0.13, 95% CI [0.03, 0.35]. These results suggest, in part, that greater arterial compliance and lower TNF-α support better exercise tolerance. Note the CIs from the c-prime (c′) pathway did not include zero, thus supporting statistical significance (Figure 3).

DISCUSSION

Since TNF-α is thought to be the principal pro-inflammatory marker contributing to arterial stiffening (17), we examined the functional implications of resting serum TNF-α on hemodynamic responses at rest and during varying degrees of physical exertion among postmenopausal women. Consistent with our hypotheses, the current investigation shows that

under conditions of heightened physiological strain, approximating ≈75% VO_{2max}, TNF-α independently associates with myocardial oxygen demand. Simply put, higher levels of TNF-α (at rest) are associated with greater myocardial oxygen needs (during higher-intensity exertion), possibly due to increased systemic vascular resistance. Further examination via path-analyses revealed that TNF-α is indirectly associated with the link between large artery compliance and exercise tolerance, such that lower compliance and increased TNF-α associated with poorer endurance.

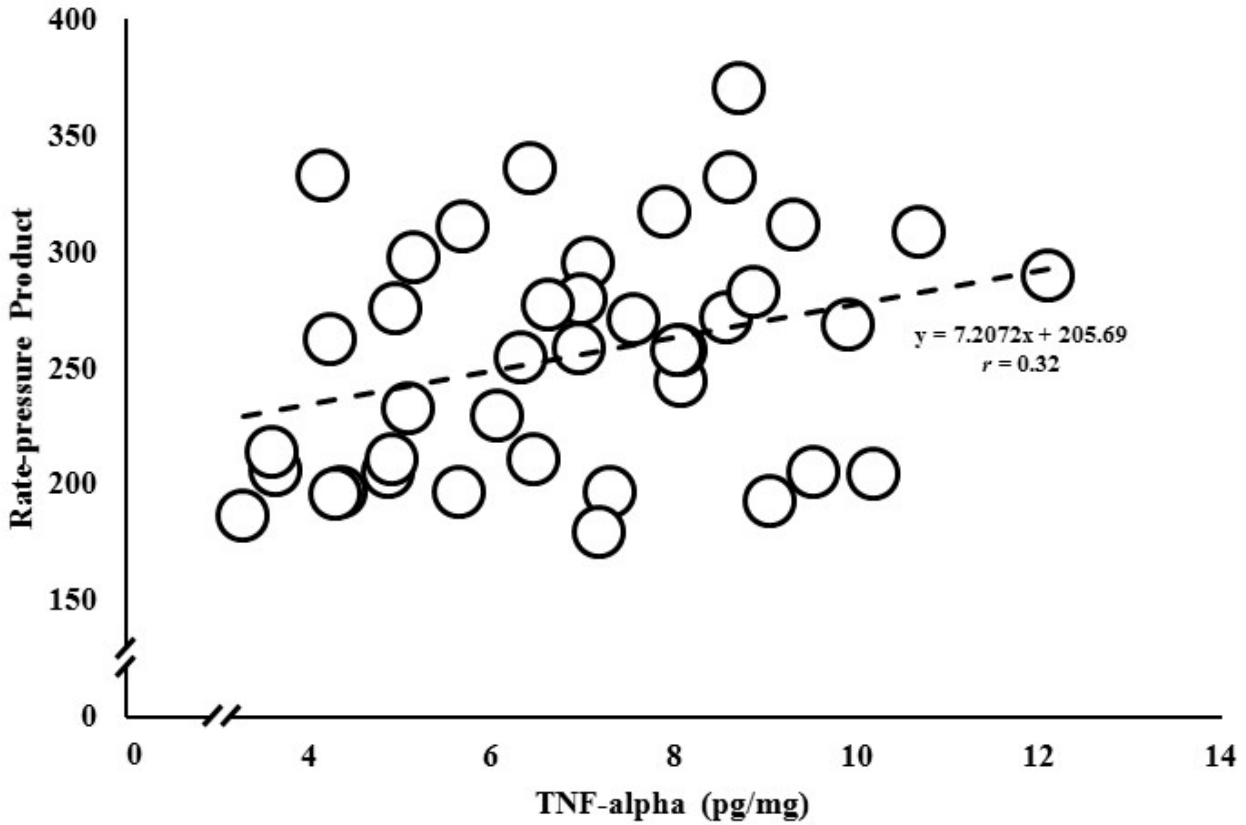

Figure 2. Unadjusted scatterplot of tumor necrosis factor-alpha (TNF-α) and myocardial oxygen demand, as indexed by rate-pressure product [heart rate•systolic blood pressure/100] during submaximal treadmill walking (≈75% VO2max or ≈5.0 METS) (n = 40).

Systolic hypertension is one of the most notable age-related cardiovascular pathologies (8). After age 50, pulse pressure rises from the divergence in systolic and diastolic blood pressures (5). Despite the relative health of our study cohort, 29 of 40 (73%) participants had resting systolic blood pressures greater than 120 mm HG. Structural changes to the vascular wall, including increased collagen deposition and reduced elastin density, are thought to contribute to arterial stiffening (6). Given that mean blood pressure is the product of cardiac output and systemic vascular resistance, failure to appropriately dampen pulsatile oscillations along the arterial network places undue strain on the myocardium for a given workload. In the present study, we have shown that poorer arterial compliance increases the metabolic demands of the myocardium as evidenced by the inverse associations between large artery compliance and RPP at rest and during submaximal exercise. Indeed the age-related expansion in pulse

pressure appears to be a consequence of arterial stiffening and thus is a recognized risk factor for future cardiac events (21).

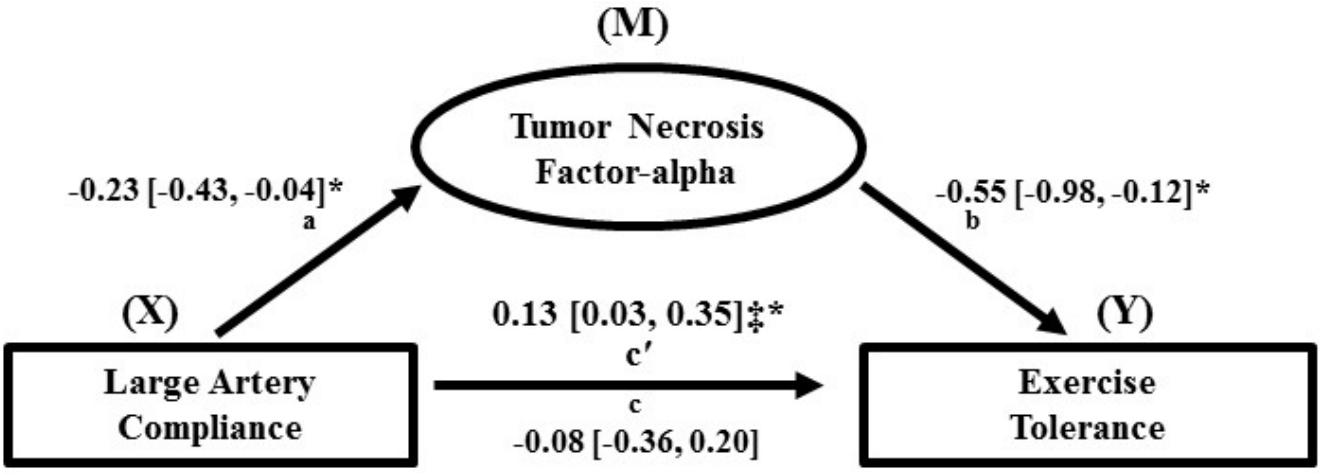

Figure 3. Path coefficients for simple mediation analysis of tumor necrosis factor-alpha. Note a significant indirect effect of large artery compliance on exercise tolerance through TNF-α, β=0.13, CI [0.03, 0.35]. Significant mediation supported as the confidence interval of c′ pathway (indirect effect) does not contain zero. X, independent variable; M, mediator; Y, outcome. *p-value ≤ 0.05. (n=40).

It is well-established that superior cardiorespiratory fitness is associated with lower RPP at rest and during varying intensities of physical exertion. Since physical activity and cardiorespiratory fitness decline with advancing age, the ability to perform everyday tasks can become progressively more difficult. Our group recently found, albeit in premenopausal women, an inverse association between heart rate during a standardized walking task (3.0 mph at 0% grade) and non-exercise activity thermogenesis (NEAT) (12). Since increased NEAT seems to offer resistance to weight gain (14, 25, 29), exercise-related efforts optimizing ease of walking (i.e., lower heart rate) may be a critical component needed to preserve cardiovascular and metabolic health among aging adults (24). In the present work, large artery compliance was associated with myocardial oxygen demand at rest and during moderate-intensity (≈55% VO_{2max}) exercise. However, as intensity reached ≈75% VO_{2max}, maximal heart rate and TNF-α were independently predictive of myocardial oxygen demand. Naturally, higher heart rates necessitate greater myocardial oxygen needs. Nevertheless, TNF-α accounted for nearly 19% of the variation in myocardial workload. Path-analyses also revealed that TNF-α mediates the relationship between large artery compliance and exercise tolerance. Of interest, TNF-α was not associated with myocardial oxygen demand at rest or during exercise at ≈55% VO_{2max}. Possibly, a notable degree of inflammation/oxidative stress may be obligatory before myocardial workload is affected, as vascular compliance may have had ample reserve to dampen pulsatile oscillations at rest and during low levels of physical exertion. Given the relative health of our study cohort, this may partly explain why TNF-α is not a significant factor in regression models 1 and 2. These observations highlight the utility of higher-intensity physical exertion to expose important phenomena not apparent at rest. Moreover, these data

support the integrative link between exercise capacity and cardiovascular health, both of which, are critical for long-term survival (2).

A complex dynamic exists between vascular function and exercise capacity. Though many inflammatory markers are derived from the liver, TNF-α is a pleiotropic cytokine produced by a variety of cells including macrophages and endothelial cells. In the present work, we can only speculate about the mechanisms wherein TNF-α modulates large artery compliance and exercise tolerance. Previously, Yoshizumi and colleagues (31) showed that TNF-α interferes with normal vasodilation due to the inactivation of endothelial nitric oxide synthase. TNF-α has also been shown to induce oxidative stress at the endothelium which effectively reduces nitric oxide bioavailability (1). Though speculative, our results appear to support the opinion that elevated serum TNF-α may contribute to poorer exercise tolerance, due in part, to an adverse influence on endothelial vasodilation and possible disruption in optimal oxygen and carbon dioxide kinetics during higher-intensity physical exertion.

Several limitations are present in this cross-sectional investigation. Inherent with the research design, we recognize the inability to establish causality or direction of the observed outcomes. The findings in the present work are correlative in nature and should be considered hypothesis-generating. Additionally, it should be noted that the participant sample in the current work consisted of postmenopausal women with no previous history of CVD. Therefore, extrapolation of these findings to other demographics must be performed with caution. Large artery compliance and systemic vascular resistance were measured by pulse contour analyses from the radial pulse, and may not necessarily reflect global vascular health. However, research by McVeigh and colleagues (15) have shown that non-invasive assessment by pulse contour analyses are sensitive to the age-related changes in vascular compliance, independent of blood pressure. Strengths include breath-by-breath analyses of maximal oxygen uptake, evaluation of serum blood markers, and estimation of body composition by DXA. Lastly, data were collected in the fasted state and at the same time of day to account for variation in circadian rhythm.

In conclusion, the primary results of this investigation demonstrate that under conditions of heightened physiological strain, approximating ≈75% VO_{2max}, resting serum TNF-α independently associates with myocardial workload. Additionally, TNF-α appears to indirectly associate with the link between large artery compliance and exercise tolerance, thus indicating reduced compliance and increased TNF-α appear to contribute to poorer endurance in postmenopausal women. Given that increased inflammatory cytokines are thought to be a consequence of aging, the present work highlights how TNF-α can potentially exert deleterious effects on hemodynamic responses during strenuous physical exertion. Nevertheless, long-term adherence to a physically active lifestyle can moderate CVD risk/progression with advancing age (26). Future studies should explore potential differential blood pressure-related responses to standardized exercise tasks among older adults and consider the influence of exercise training on myocardial oxygen demand and activity-related energy expenditure.

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