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Impact of age on aortic wave reflection responses to metaboreflex activation and its relationship with leg lean mass in post-menopausal women

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ABSTRACT

Wave reflection (augmentation pressure [AP] and index [AIx]) is greater in older women than men. Resting AP is a better wave reflection index than AIx in older adults. The negative relationship between wave reflection and lean mass (LM) has been inconsistent. We investigated the impact of age and LM on aortic hemodynamic responses to metaboreflex activation in post-menopausal women. Post-menopausal women, younger and older (n = 20 per group) than 60 years, performed 2-min isometric handgrip at 30% of maximal force followed by 3-min post-exercise muscle ischemia (PEMI). We measured carotid–femoral pulse wave velocity (cfPWV) and femoral-ankle PWV (faPWV) at rest, and aortic systolic blood pressure (aSBP), pulse pressure (aPP), AP, AIx, and AIx-adjusted for heart rate (AIx@75) at rest and during PEMI using tonometry. Arm and leg LM were measured by DEXA. Resting cfPWV, aSBP, and aPP were higher, while AIx@75 and leg LM were lower in older than younger women. aSBP and aPP increased similarly during PEMI in both groups. Increases in AP ($P < 0.05$), AIx ($P < 0.05$), and AIx@75 ($P < 0.01$) during PEMI were greater in older than younger women. From these responses, only AP during PEMI was correlated ($P < 0.05$) positively with aSBP and aPP responses, and negatively with leg LM. Resting faPWV, but not cfPWV, was correlated ($P < 0.01$) with AP, aSBP, and aPP during PEMI. Therefore, PEMI induces greater wave reflection responses in older than younger post-menopausal women. Our findings suggest that the increased AP response to PEMI is related to leg arterial stiffness and muscle loss in older women.

1. Introduction

Age-related increases in aortic stiffness (pulse wave velocity, PWV) exceed peripheral PWV after 50 years of age in women and men (Mitchell et al., 2010). However, older women have higher resting wave reflection indices and aortic blood pressure (BP) than men (Namasivayam et al., 2011; Namasivayam et al., 2009; Russo et al., 2012). Interestingly, augmented pressure (AP) progressively increases while augmentation index (AIx) declines beyond age 60 years, especially in women (Fantin et al., 2007; Namasivayam et al., 2009; Torjesen et al., 2014). Therefore, AP has been proposed as the main wave reflection index (Fantin et al., 2007) and contributor to the increase in aortic pulse pressure (PP) with age (Cecelja et al., 2009). The increases in AP and aortic PP (6 and 12 mm Hg per decade) in older women are determined by the vasomotor tone of large muscular arteries independent of aortic PWV (Cecelja et al., 2012). This increased aortic pulsatility and greater left ventricular (LV) afterload may contribute to the increased prevalence of hypertension (Roger et al., 2012) and heart failure in older women (Shim et al., 2011).

Evidence has demonstrated an association between increased AIx and the age-related loss of muscle mass, especially in the legs, known as sarcopenia (Ohara et al., 2014; Snijder et al., 2004). It appears that leg sarcopenia is a more important determinant of AIx than obesity (Snijder et al., 2004). However, older adults with sarcopenic obesity have greater AIx than those with sarcopenia or obesity alone (Ohara et al., 2014), suggesting an additive cardiovascular risk.

Isometric handgrip (IHG) exercise reveals important central hemodynamic characteristics that are not apparent at rest in hypertensive

Abbreviations: AIx, augmentation index; AIx@75, AIx adjusted for heart rate of 75 beats per min; AP, augmentation pressure; ANOVA, analysis of variance; BP, blood pressure; cfPWV, carotid–femoral pulse wave velocity, aortic; DBP, diastolic blood pressure; faPWV, femoral-ankle pulse wave velocity; IHG, isometric handgrip; LV, left ventricular; MAP, mean arterial pressure; MVC, maximal voluntary contraction; PEMI, post-exercise muscle ischemia; PP, pulse pressure; SBP, systolic blood pressure.

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middle-aged adults (Chirinos et al., 2010). Central (aortic and carotid) BP, AIx, and heart rate increase during IHG (Chirinos et al., 2010; Edwards et al., 2008; Figueroa et al., 2010). The exercise pressor response is mediated by neural signals originating from the central command and active muscle metabo- and mechano-receptors (Rondon et al., 2006). The metaboreflex can be isolated following IHG by trapping metabolites in the forearm via circulatory occlusion, a condition known as post-exercise muscle ischemia (PEMI). During PEMI, sympathetic-mediated vasoconstriction (Choi et al., 2012; Roseguini et al., 2007) maintains peripheral and central BP responses elevated while heart rate recovers in healthy young adults (Edwards et al., 2008; Figueroa et al., 2010). Since there is an inverse relationship between heart rate and AIx (Wilkinson et al., 2002), the further increase in AIx during PEMI disappears when AIx is adjusted for a heart rate at 75 beats/min (AIx@75) (Edwards et al., 2008; Figueroa et al., 2010). Recent work has indicated that peripheral BP and sympathetic responses to PEMI are increased by age (Choi et al., 2012) and hypertension (Delaney et al., 2010; Greaney et al., 2014; Sausen et al., 2009). However, peripheral BP is less sensitive than aortic BP and wave reflection indices during IHG and PEMI (Chirinos et al., 2010; Edwards et al., 2008; Figueroa et al., 2010). Evidence has shown that aortic PP is more clinically relevant than brachial PP as it reflects LV afterload (Roman et al., 2007). Moreover, it appears that wave reflection indices are more affected by an increased sympathetic activity than aortic BP in post-menopausal women at rest (Hart et al., 2013). However, previous studies in older adults (Choi et al., 2012; Delaney et al., 2010; Greaney et al., 2014; Roseguini et al., 2007; Sausen et al., 2009) have not assessed aortic BP and wave reflection responses to PEMI, which may reveal differences in aortic hemodynamic characteristics that are not apparent at rest between women older and younger than 60 years of age.

In this study, we tested the hypothesis that PEMI would cause greater increases in wave reflection than aortic BP in older than younger post-menopausal women. Considering the differential age-related changes in resting AP and AIx, we also hypothesized that AP would be the main correlate of aortic BP during PEMI in older women. We examined the relationship between aortic hemodynamic responses to PEMI with resting PWV and lean mass.

2. Methods

2.1. Participants

Women younger ($n = 20$) and older ($n = 20$) than 60 years of age participated in this cross-sectional study. Participants completed a medical history form during the screening. Participants were overweight or obese (body mass index [BMI] > 25 kg/m^2, sedentary (<150 min/week of regular exercise training), post-menopausal (>1 year without menstruation), non-smokers, and with no evidence or diagnosis of cardiovascular diseases other than hypertension. Exclusion criteria included: uncontrolled hypertension (≥160/100 mm Hg), BMI ≥ 40 kg/m^2, evidence of type 2 diabetes, cardiovascular diseases or cancer, and taking hormone replacement therapy. The study protocol was approved by the Florida State University Human Subjects Committee and the participants provided a written informed consent.

2.2. Study design

Participants reported to the cardiovascular laboratory following an overnight fast and refrained from caffeine, alcohol, smoking, and vasoactive medications for 12 h and from moderate-to-vigorous physical activity for 48 h. Cardiovascular parameters were assessed in the supine position after a minimum of 15 min of rest in a dim, quiet temperature-controlled room (23 ± 1 °C).

2.3. Aortic hemodynamics

Brachial systolic BP (SBP) and diastolic BP (DBP) were measured using an oscillometric automated device (Omron HEM-907XL). The average of two measurements was used to calibrate the radial waveforms obtained in duplicate from a 10 s epoch using a high-fidelity tonometer (SPT-301B; Millar Instruments, Houston, TX, USA). Aortic pressure waveforms were derived using a validated transfer function (SphygmoCor, AtCor Medical, Sydney, Australia). AP was calculated as the difference between the second and first systolic peaks. PP was calculated as the difference between SBP and DBP. AIx and AIx@75 were calculated as a percentage of aortic PP (AP/PP × 100). The average of two high quality (operator index ≥ 80) measurements was used in the analysis.

2.4. Arterial stiffness

Resting PWV measurements were obtained using an automatic PWV/ABI device (VP-2000; Omron Healthcare, Vernon Hills, IL.) at rest. Two tonometers over the right carotid and femoral arteries and appropriate-size BP cuffs on both arms (brachial arteries) and ankles (posterior tibial arteries) were used to obtain the carotid–femoral PWV (cfPWV, aortic), femoral-ankle PWV (faPWV, leg), and brachial-ankle PWV (baPWV, systemic). Pulse wave transit time was automatically calculated from the time delay between the pulse wave feet related to the R-wave of the electrocardiogram. The carotid–femoral distance was measured with a non-elastic tape while the femoral-ankle and brachial-ankle distances were automatically calculated according to the participant's height. PWV was calculated as distance/transit time. The average of two measurements was used in the analysis. Heart rate was measured via electrocardiogram.

2.5. Body composition

Body weight and height were measured to the nearest 0.1 kg and 0.01 m using a beam scale and stadiometer (Sunbeam Products Inc, Boca Raton, FL). BMI was computed as weight in kg/height in m^2. Arm and leg lean masses were measured by dual-energy X-ray absorptiometry whole-body scan (GE Lunar DPX-IQ, Madison, WI).

2.6. IHG and PEMI

Participants were familiarized to the maximal and IHG tests in two different occasions during the screening process. Maximal voluntary contraction (MVC) of the dominant hand was the highest of three efforts using a handgrip dynamometer (Lafayette Instrument Co., Lafayette, IN).

On the experimental session, a rapid inflating cuff (E20 Rapid Cuff Inflator, Hokanson, Bellevue, WA, USA) was placed around the upper arm to occlude the forearm circulation. Following resting cardiovascular measurements, a bout of 2-min IHG was performed at 30% of MVC. Participants had visual feedback and received verbal encouragement to maintain the target force throughout the IHG. Ten seconds prior to cessation of IHG, the arm cuff was rapidly inflated to suprasystolic pressure (≥200 mm Hg) for 3 min. Brachial BP and pressure waves were obtained during the last 2 min of PEMI. Measurements were not performed during the exercise since 50 s in the last min of IHG is insufficient time to collect two accurate pressure wave recordings.

2.7. Statistical analysis

Based on previous studies (Choi et al., 2012; Delaney et al., 2010; Greaney et al., 2014), we calculated that at least 18 participants per group would provide an 80% power at α level of 0.05. All variables were normally distributed (Shapiro–Wilk test). Independent-sample *t*-test was used to compare both groups at rest or PEMI. A two-way