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Carotid extra-media thickness increases with age, but is not related to arterial stiffness in adults

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Abstract *Background:* Assessment of carotid artery perivascular adipose tissue through carotid artery extra-media thickness (EMT) ultrasonography has emerged as a novel assessment technique that might contribute unique information to comprehensive evaluations of arterial health. Currently, there is a lack of research examining relationships between EMT and existing measures of arterial health in adults. We investigated the relationships between EMT and established measures of arterial health, including aortic pulse wave velocity (aPWV), carotid distensibility, and intima-media thickness (IMT) in adults.
Methods: Using a cross-sectional, observational design, we assessed resting aPWV, carotid distensibility, IMT and EMT in 81 participants who were categorized as younger healthy adults (YHA; n = 51; 25 ± 6 years), older healthy adults (OHA; n = 15; 70 ± 5 years) or older adults with coronary artery disease (CAD; n = 15; 68 ± 9 years).
Results: EMT, IMT, and aPWV were higher while carotid distensibility was lower in OHA and CAD versus YHA ($P < 0.05$). EMT was correlated with age ($r = 0.48$; $P < 0.01$), aPWV ($r = 0.43$; $P < 0.01$), IMT ($r = 0.41$; $P = 0.01$), and distensibility ($r = -0.37$; $P < 0.01$). Despite significant correlations, EMT was not an independent predictor of any of the traditional measures of arterial health included in this study.
Conclusions: The novel finding of this study is that while EMT is elevated in older versus younger adults, in agreement with established indicators of arterial health, it is not a predictive factor in these existing measures. EMT may, however, still have clinical utility as a target for comprehensive monitoring of interventions specifically designed to impact arterial structure and function.

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Introduction

Cardiovascular disease, and more specifically, atherosclerosis and hypertension, dominate other pathologies as major contributors to death and disability, with a projected number one ranking for mortality by 2020.[1] Hence, the study and analysis of the human cardiovascular system is vital to identify strategies to ameliorate this increasing burden. Many previous studies examining the development and progression of arterial dysfunction have focused on the quantification of the thickness of the inner layers of the common carotid artery wall, termed the carotid artery intima-media thickness (IMT),[2] and have highlighted the predictive capacity of subclinical IMT thickening in individuals at risk for future cardiovascular events.[3]

While the carotid inner wall layers have been extensively examined, the assessment of the outer adventitia layer and the surrounding adipose tissue has been neglected. Preliminary studies suggest that the adventitial layer may be involved in the early pathogenesis of atherosclerosis and other arterial pathologies.[4,5] Changes in the adventitial layer may occur before measurable pathological development in the intimal and medial layers,[6–9] thereby leading to the development of subclinical manifestation of cardiovascular disease such as the stiffening of the central elastic arteries. However, as the border between the adventitia and surrounding tissues is indiscernible with standard imaging modalities, there are currently no techniques available to quantify the thickness of the adventitia alone. Alternatively, measurement of carotid artery extra-media thickness (EMT), which encompasses the thickness of the adventitial layer, as well as the perivascular adipose tissue and venous wall, may be useful in assessment of the early pathogenesis of atherosclerosis.[10] EMT has been shown to have an independent relationship with traditional cardiovascular risk factors such as age and blood pressure, and has been proposed to mostly reflect adventitial thickness in older adults.[11] Furthermore, EMT may be more feasible to assess in routine clinical examination as it only requires ultrasound imaging in the area of the carotid artery rather than the more complex assessments currently available for arterial stiffness.

Previous research indicates that aging and the presence of coronary artery disease (CAD) are negatively associated with measures of arterial health such as aortic pulse wave velocity (aPWV), carotid distensibility and IMT.[12–14] While the link between EMT and subclinical vascular health, as indicated by the association between EMT and distensibility, has been demonstrated in children[15] and young adults,[16] these relationships have not been examined in adults. Therefore, the current study examines the relationships between EMT and traditional measures of arterial health, notably, aPWV, carotid distensibility, and IMT. We aimed to examine these relationships in both younger healthy adults, older healthy adults, and older adults with CAD. We hypothesized that older adults with CAD will have thicker EMT versus older healthy adults, with both older groups having thicker EMT than younger adults. We also hypothesized that EMT will be an independent predictor of aPWV, carotid distensibility, and IMT.

Methods

Participants and ethical approval

Eighty-one participants were recruited to take part in this cross-sectional observational study. The three populations included: younger healthy adults (YHA; n = 51; 25 ± 6 years), older healthy adults (OHA; n = 15; 70 ± 5 years) and older adults with coronary artery disease (CAD; n = 15; 68 ± 9 years). The inclusion and exclusion criteria for our CAD participants follow the guidelines from the New York Heart Association.[17] All participants gave verbal and written consent prior to participation in the study. The study protocols were approved by the Hamilton Integrated Research Ethics Board and conform to the *Declaration of Helsinki* concerning the use of human subjects as research participants.

Study design

Participants were invited for a single visit to the Vascular Dynamics Laboratory in the Department of Kinesiology at McMaster University, Canada. After anthropometric measures were taken, participants were asked to rest in the supine position in a quiet, temperature-controlled room for 10 min. Following this rest period, four brachial artery blood pressure measurements were taken using an automated oscillometric blood pressure unit (Dinamap Pro 100, Critikon LCC, Tampa, Fla, USA). The first blood pressure measurement was discarded,[18] and the average of the last three measurements was recorded. Continuous measurements of single-lead ECG and reconstructed brachial artery blood pressure waveforms from finger cuff plethysmography (Finometer MIDI, Finapres Medical Systems BV, Amsterdam, The Netherlands) were obtained simultaneously using a data acquisition system (Powerlab model ML795; ADInstruments, Colorado Springs, CO, USA), with a corresponding software program (Labchart 7; ADInstruments Inc., Colorado Springs, CO, USA).

Pulse wave velocity

The measurement of aortic stiffness was obtained through the measurement of carotid to femoral PWV, according to the latest standard guidelines.[19] The equation for aPWV is as follows:

$$aPWV = \frac{direct\ distance\ (m) \times 0.8}{pulse\ transit\ time\ (s)}$$

The time difference between the arrival of arterial pressure waveforms from the right carotid and right femoral arteries was denoted as the pulse transit time and measured using simultaneous applanation tonometry (model SPT-301; Millar Instruments, Houston, TX, USA). The tonometry signals were continuously processed with a band pass filter (5–30 Hz) to identify the foot of the waveforms.[20] The distance between pulse measurement sites was estimated using a direct surface measurement with a non-elastic tape measure. Two sets of 10 waveforms were