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Pro-atherogenic shear rate patterns in the femoral artery of healthy older adults

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In 1954 Rudolf Altschul wrote “One is as old as one’s endothelium;”[1] a visionary statement in a time when the endothelial layer was viewed as a passive sheet of cells lining the vasculature. It is now clear that the endothelium is a dynamic structure, actively involved in numerous arterial functions, from regulation of permeability to modulation of vascular responses to hemodynamic forces. As such, slight disruptions in the physiology of the endothelium can lead to pathophysiological consequences, with endothelial dysfunction considered to be a key initial event for the development of atherosclerosis[2]. In this regard, aging is associated with impairments in endothelial function and an increased prevalence of atherosclerosis[3, 4]. Even in atherosclerotic-free normotensive individuals, endothelial dependent dilation is impaired in older populations[5, 6]. In addition, with age, the endothelium favors constrictive properties[7], expresses pro-inflammatory markers[8], and exhibits enhanced production of reactive oxygen species[9]; factors conducive to the development and progression of atherosclerosis. However, the mechanism(s) contributing to a pro-atherogenic endothelial cell environment with advanced age remain incompletely defined.

Interestingly, atherosclerotic lesions are preferentially located in regions distinguished by oscillatory (bidirectional blood flow) and low mean shear stress; whereas areas exposed to unidirectional and moderate shear are protected[10-12]. In this context, *in vitro* studies using cell culture and isolated perfused arteries have demonstrated that unidirectional high shear stress (within physiological limits) induces expression of anti-atherogenic genes (i.e. eNOS, SOD) and inhibits expression of atherogenic genes (VCAM-1, ICAM-1, E-selectin, MCP-1), while exposure of endothelial cells to periods of disturbed flow (increased oscillatory shear) and/or low mean shear promotes a pro-atherogenic phenotype[13-17]. In

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short, a growing body of evidence indicates that favorable hemodynamic forces are crucial for endothelial regulation and conditions that result in decreased or disturbed shear may precipitate the development of atherosclerosis. Therefore, we sought to characterize vascular shear rate patterns in young and older adults in order to better understand the enhanced susceptibility to atherosclerosis with aging.

Shear rate magnitudes and patterns were examined in the common femoral artery; a vessel highly prone to atherosclerosis[18-20]. Twenty young (24 ± 1 yr; 14 men) and eighteen older (60 ± 1 yr; 12 men) healthy adults volunteered for participation in this study. All subjects were recreationally active, free of known cardiovascular, pulmonary, metabolic, or neurological disease and none were using prescribed or over the counter medications. Fasting blood chemistry screening indicated that triglycerides, cholesterol, lipoproteins, and glucose concentrations in the older subjects were within the normal range for healthy adults. There were no significant age-group differences in resting heart rate, systolic, diastolic or mean arterial blood pressures ($P>0.05$). Experimental procedures were approved by the University of Missouri Health Sciences Institutional Review Board and all subjects provided written informed consent prior to participation

Under supine resting conditions, the common femoral artery was imaged ~2 cm proximal to the bifurcation of the superficial and deep branches using a duplex Doppler ultrasound unit (Logiq 7, GE Medical Systems, Milwaukee, WI) equipped with a linear array transducer operating at a frequency of 10 MHz. Femoral blood velocity was obtained using the same probe in pulsed-wave mode, operating at a linear frequency of 5 Hz and at an insonation angle of 60°. Recordings of femoral artery blood velocity were obtained using a large sample volume to encompass the entire vessel lumen without extending outside of it. Therefore, the measurements of blood velocity represent a mean of the entire cross-sectional area of the vessel. Using femoral artery diameter and velocity, antegrade, retrograde and mean shear rates were calculated. Antegrade shear represents forward flow through the femoral artery, whereas retrograde shear results from a reversal of flow. In addition oscillatory shear, representative of bidirectional flow, was evaluated by calculating the oscillatory shear index: |retrograde shear|/(|retrograde + antegrade shear|).

Femoral artery antegrade shear was lower, whereas retrograde shear was significantly enhanced (i.e. more negative) in the older group; thus both contributing to an overall low mean shear (Figure 1). Moreover, oscillatory shear was 30% greater in the older adults, when compared to the younger subjects, indicating that the femoral artery is exposed to greater bidirectional shear throughout the cardiac cycle. Similar results were found when variables were normalized to lean leg muscle mass obtained from a dual-energy X-ray absorptometry scan (data not shown). Importantly, measurements made on multiple days in a subset of subjects (6 young and 6 older) indicated that these findings are highly reproducibile, with intraclass correlation coefficients of 0.99, 0.98 and 0.98 for mean, antegrade and retrograde shear, respectively. In addition, common femoral artery diameter was similar between the young (0.87 ± 0.03 cm) and older (0.86 ± 0.03 cm) groups.

These findings clearly indicate that shear patterns within the common femoral artery are altered with healthy aging. Given that disturbed shear forces have been proposed to be involved in the pathogenesis of atherosclerosis[13-17], these data lend support to a potential mechanism contributing to atherosclerotic development with aging. Interestingly, recent data in young healthy humans has demonstrated that exposing the brachial artery to an acute period of enhanced retrograde and oscillatory shear negatively impacts flow-mediated dilation[21]. In this regard, even in the absence of overt disease, a chronic decrease in antegrade shear, along with enhanced retrograde and oscillatory shear with age (as shown in

the current findings), may promote a pro-atherogenic environment and place older adults at an increased risk for the development of atherosclerosis.

Considering the potential detrimental impact of age-dependent alterations in vascular shear patterns, an understanding of the possible contributing mechanisms is necessary. In the present study, femoral vascular resistance was higher in the older group ($P<0.05$), with femoral vascular resistance being positively correlated to oscillatory shear in the older ($R^2=0.353$, $P=0.009$), but not younger subjects ($R^2=0.011$, $P=0.661$). As such, any factor that could increase femoral vascular resistance (i.e. increased sympathetic nerve activity, or increased levels of circulating constrictors such as AngII, and ET-1) may contribute to age-related alterations in shear profiles[4]. In addition, age-dependent changes in the structure of the vasculature, such as increased collagen, calcification or decreased elastin content of the arteries, could enhance peripheral vascular resistance and negatively impact shear patterns[4].

Overall, these novel observations demonstrate for the first time that healthy aging is associated with alterations in femoral artery shear patterns. A shift to pro-atherogenic shear patterns was noted, including a decreased overall mean and antegrade shear, and an enhanced retrograde and oscillatory shear. Considering the potential detrimental impact of these hemodynamic patterns, future studies are warranted to determine the underlying mechanisms, as well as potential interventions (e.g. exercise training) that may offset and/or improve shear patterns with aging.

Abbreviations

Ang II	angiotensin II
eNOS	endothelial nitric oxide synthase
ET-1	endothelin 1
ICAM-1	inter-cellular adhesion molecule 1
MCP-1	monocyte chemotactic protein 1
SOD	superoxide dismutase
VCAM-1	vascular cell adhesion molecule 1

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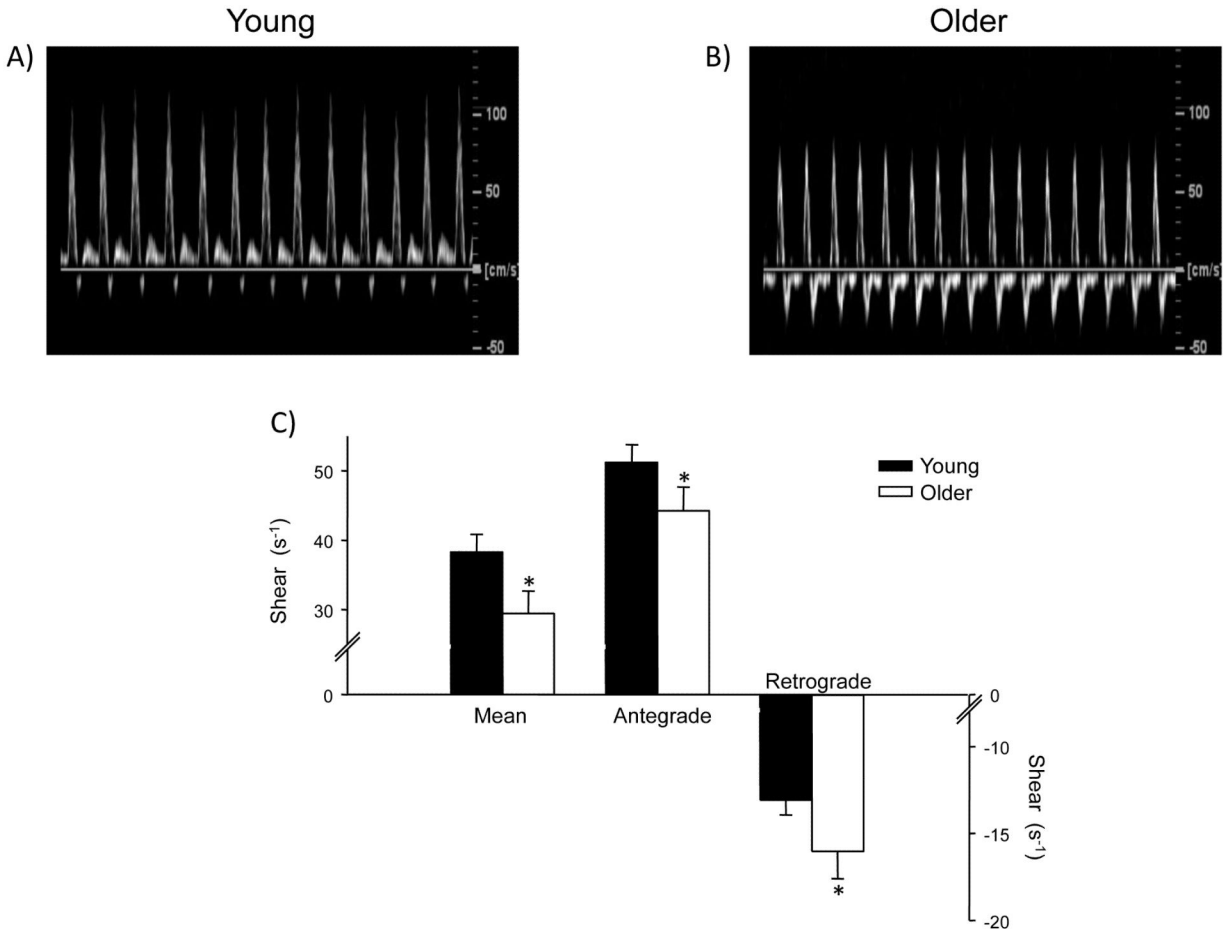

Figure 1.

Original common femoral artery velocity tracings from a young (panel A) and older (panel B) subject. Panel C illustrates the group summary data for mean, antegrade and retrograde shear.