Journal of the American College of Cardiology
© 2007 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 49, No. 9, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2006.10.058

Arterial Reactivity in Lower Extremities Is Progressively Reduced as Cardiovascular Risk Factors Increase

Comparison With Upper Extremities Using Magnetic Resonance Imaging

Harry A. Silber, MD, PHD,* Joao A. C. Lima, MD, FACC,*† David A. Bluemke, MD, PHD,† Brad C. Astor, PHD,‡ Sandeep N. Gupta, PHD,§ Thomas K. Foo, PHD,§ Pamela Ouyang, MD, FACC*

Baltimore, Maryland; and Milwaukee, Wisconsin

Objectives Our goal was to investigate whether the association between established cardiovascular risk factors and arterial reactivity differs between the lower and upper extremities.

Background Resistance artery reactivity in the arm is associated with cardiovascular risk factors, coronary disease, and events. However, the relationship of lower versus upper extremity vasoreactivity to increasing cardiovascular risk factors has not been determined.

Methods We studied 82 subjects in 3 groups: 33 young healthy (YH) (21 to 41 years), 30 older healthy (OH) (>50 years), and 19 older type 2 diabetic subjects (OD). We directly measured systolic shear rate, flow, and radius in brachial and femoral arteries at rest and during post-occlusion hyperemia using magnetic resonance imaging.

Results Brachial and femoral systolic shear rate, flow, and radius were similar among the groups at rest. Brachial hyperemic shear rate and hyperemic flow normalized as a function of baseline radius were not statistically different when YH were compared with OH and OH with OD. In contrast, femoral hyperemic shear rate and hyperemic flow normalized to baseline radius were lower in OH than YH (680 ± 236 s^{-1} vs. 843 ± 157 s^{-1}, $p = 0.001$, and 0.84 ± 0.25 $mm^{1.27}/s$ vs. 1.01 ± 0.16 $mm^{1.27}/s$, $p = 0.001$) and lower in OD than OH (549 ± 183 s^{-1}, $p = 0.02$, and 0.74 ± 0.19 $mm^{1.27}/s$, $p = 0.046$).

Conclusions Persons with increasing cardiovascular risk factor burden had progressively reduced arterial reactivity in lower but not upper extremities. This may help to explain why atherosclerosis usually develops more severely in legs than in arms, and suggests that legs may be more sensitive than arms for assessing early global atherosclerotic risk. (J Am Coll Cardiol 2007;49:939–45) © 2007 by the American College of Cardiology Foundation

Improved methods are needed for predicting atherosclerosis development and cardiac events. Peripheral arterial reactivity noninvasively tests for nitric oxide-dependent endothelial dysfunction, a key early event in atherosclerosis development (1). Although the upper extremity is conveniently available for testing arterial reactivity, there is evidence to suggest that the lower extremity may be a more sensitive site for assessing global cardiovascular risk. Atherosclerosis usually involves the lower extremities more severely than the upper extremities (2), and endothelial function is more impaired in the lower than upper extremity in persons with coronary artery disease (3). This suggests that endothelial function may be impaired earlier or more severely in lower extremities than upper extremities in persons with cardiovascular risk factors but without clinical coronary disease.

Certain tests of arterial reactivity are only partially dependent on nitric oxide, but this does not limit their ability to identify groups at risk. The stimulus for flow-mediated dilation (FMD) is post-occlusion hyperemic shear stress, which is hyperemic shear rate times viscosity (4–7). Hyperemic shear rate and flow are partially dependent on endothelial nitric oxide release from resistance arteries (8–10). However, the hyperemic response is also dependent on other molecular mechanisms, including prostaglandins

From the *Department of Medicine, Division of Cardiology, and the †Department of Radiology, Johns Hopkins University School of Medicine, Baltimore, Maryland; ‡Johns Hopkins University School of Public Health, Baltimore, Maryland; and §General Electric Healthcare Technologies, Milwaukee, Wisconsin. This study was supported by an NHLBI grant (K23 HL04477). Drs. Gupta and Foo were employed by General Electric during this study. Michael O'Rourke, MD, DSc, FACC, served as guest editor for this article.

Manuscript received July 17, 2006; revised manuscript received October 20, 2006, accepted October 27, 2006.

JACC Vol. 49, No. 9, 2007
March 6, 2007:939–45

Abbreviations and Acronyms

FMD = flow-mediated dilation

HDL = high-density lipoprotein

HypQ = hyperemic flow

MRI = magnetic resonance imaging

and adenosine (11). Although hyperemic flow (HypQ) is only partially regulated by endothelially released nitric oxide, reduced hyperemia is associated with cardiac risk factors, coronary artery disease, and cardiac events (8,12–17). This may be partly because other properties that are associated with cardiovascular risk factors, including increased central arterial stiffness, increased local arterial stiffness, and increased sympathetic nervous system activity, are also associated with reduced hyperemic shear or flow (18–20). Indeed, a large study showed that the association between impaired FMD and cardiovascular risk factors was attributable to a reduced hyperemic shear stimulus for FMD (13).

Relatively greater reductions in lower compared with upper extremity HypQ have been demonstrated in subjects with hypercholesterolemia and in subjects with peripheral arterial disease (21,22). However, regional differences in hyperemic shear rate have not been studied in persons with risk factors.

We previously reported a method of directly measuring hyperemic systolic shear rate and hyperemic systolic flow in the brachial and femoral arteries from velocity-encoded images obtained using magnetic resonance imaging (MRI) (23). The purpose of this study was to determine if there are differences in lower versus upper extremity hyperemic shear rate or flow responses with increasing cardiovascular risk factors.

Methods

Study participants. Eighty-two subjects from 3 groups were studied: 1) 33 healthy young adults, ages 21 to 41 years (16 men, 17 women), with no cardiovascular risk factors of hypertension, diabetes, hyperlipidemia, smoking, obesity, or cardiac disease in a first-degree relative; 2) 30 older healthy subjects, ages 50 to 74 years (14 men, 16 women), with no other cardiovascular risk factors; and 3) 19 older subjects with type 2 diabetes, ages 51 to 69 years (14 men, 5 women). Subjects had no acute illness or documented symptoms of intermittent claudication, and were not on nitrate medicine. The study protocol was approved by the Institutional Review Board at the Johns Hopkins School of Medicine. All subjects gave written informed consent.

Study protocol. Subjects abstained from eating or drinking except water for at least 6 h before the study. All scans were performed in the morning. Baseline blood pressure was recorded in the right arm. Phase-contrast MRI was performed as described previously (23), using a 1.5-T scanner (CV/i, General Electric Healthcare Technologies, Milwaukee, Wisconsin) equipped with cardiac gradient coils (40 mT/m, 120 T/m/s). Electrocardiographic leads were placed on the thorax. To image the brachial artery, a 3-inch receiver coil was placed medial to the upper arm. An inflatable cuff was placed on the forearm, extending to just above the elbow. To image the femoral artery, a 4-element phased array receiver coil was placed anterior and posterior to the upper thigh. An inflatable cuff was placed on the lower thigh. The cuff was inflated at least 30 mm Hg above the subject's measured systolic blood pressure for 5 min, then released. For each artery, phase-contrast images using the same fixed cross-sectional axial prescription were obtained before and immediately after cuff release. Serum values of glucose, hematocrit, and fasting lipid panel were obtained in all groups, and hemoglobin A1C in groups 2 and 3, after the scanning portion of the study.

Imaging protocol. Coronal and axial scout images were obtained to locate the brachial artery, to locate the superficial femoral artery at 3 to 5 cm distal to the bifurcation of the common femoral artery, and to verify that the arteries were parallel to the magnet bore. Phase-contrast scans were gated to the electrocardiogram signal. A single imaging plane perpendicular to the artery of interest was prescribed. The imaging parameters were: matrix size 256 × 128, field-of-view 8 × 8 cm for the brachial artery and 10 × 10 cm for the femoral artery, slice thickness 3 mm, flip angle 25°, bandwidth 31.2 kHz, repetition time 11.43 ms, echo time 5.25 ms, 8 views per segment, first-order flow compensation, no phase-wrap, and no magnitude weighting. Settings of 16 signal averages (NEX) were used at baseline, and 2 NEX after cuff release. During peak hyperemia, 10 views per segment were used if necessary to obtain a scan time of 35 s or less. The velocity encoding gradient was 50 to 70 cm/s during baseline and 120 to 150 cm/s during peak hyperemia. Resulting temporal resolution was about 90 to 180 ms. Each scan provided 5 to 9 magnitude (anatomic) and phase (velocity) images of the arterial cross section during the cardiac cycle.

Data analysis. Image data was imported via Scion Image (Scion Corporation, Frederick, Maryland) into a spreadsheet-based (Excel, Microsoft Corporation, Mountain View, California) program created in our laboratory. The program employs a user-independent algorithm to measure arterial radius, blood flow, and shear rate from the phase images. The algorithm located the precise center of the arterial cross section as where the velocity datapoints in a radial plot were optimally correlated. An approach simplified from Oyre et al. (24) was used to calculate shear rate and radius. The cardiac phase containing peak flow was used. A 1-mm wide segment of velocity datapoints in the radial plot near the lumen wall was fit by least-squares method to a parabola, with the assumption that blood flow velocity at the lumen wall is zero. The outer edge of the segment was defined where a smoothed average of the velocity profile decreased to 20% of the peak velocity in the cross section. Systolic shear rate was calculated as the slope of the best-fit parabola where the parabola equaled zero. The distance from this point to the center was defined as the radius of the artery. Systolic flow was calculated by summing the velocity pixels within the radius of the artery. This approach provided sub-pixel precision in determining shear rate and radius.