EFFECTS OF EXERCISE INDUCED BRACHIAL AND CAROTID ARTERY VASCULAR RESPONSES IN NORMAL SUBJECTS

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ABSTRACT

Background: Brachial artery reactivity in response to ischemia hyperemia reflects endothelial health. Responses of brachial artery and carotid artery to a physiologic stimulus of exercise may be a novel method to assess vascular health.

Purpose: To compare brachial artery (BA) endothelium-dependent vasodilation to exercise induced vasodilation and to evaluate carotid artery (CA) responses to exercise in normal subjects.

Methods: We evaluated BA vasodilation in response to arm ischemia induced by blood pressure cuff as well as supine bicycle exercise stress induced BA and CA responses in 13 healthy volunteers aged 30±8 years.

Results: There was a 10%+4% BA vasodilation in response to ischemia. This was associated with a decrease in forearm resistance and an increase in forearm blood flow. Exercise produced 6±6% and 8±5% vasodilation of BA and CA respectively. No significant change in brachial artery blood flow measured by PW Doppler (98±55 to 78±38 ml/min, baseline vs. peak p=0.06, delta=-12±29%) or in CA blood flow (472±125 to 496±237 ml/min, baseline vs. peak p=0.7, delta=-6±21%) occurred.

Conclusion: Supine bicycle exercise produces BA and CA vasodilation, Assessment of BA and CA reactivity by ultrasound is a novel method for assessing vascular endothelial function.

Key Words: brachial artery, carotid artery, ultrasound, exercise, blood flow.

INTRODUCTION

Nitric oxide (NO) release from arterial endothelium causes vasodilation in response to physical stress1, mental stress2, and acetylcholine3 in healthy subjects. Aging4, hypercholesterolemia5, hypertension6, smoking7, diabetes mellitus8, and hyperhomocystenemia9 are associated with an impaired endothelium dependent vasodilation. Brachial artery reactivity (BART) in response to ischemia induced shear stress assesses endothelial function by measuring arterial dilation10, and is abnormal in patients with coronary artery disease11,12 and its risk factors.4,5,6,7,8,9,11,12 This test also assesses forearm arteriolar resistance and blood flow reserve by measuring Doppler velocity shifts before and during hyperemia. BA responses to rhythmic hand grip exercise has been evaluated13,14. Ultrasound evaluation of shear induced vasodilation in response to exercise has not been used in the forearm or cerebral vascular beds. Cerebrovascular endothelial derived NO mediates local increase in cerebral blood flow during increase in cerebral metabolism in health9,15 and disease16. Carotid artery (CA) increasing wall thickness (IMT) is a marker of atherosclerosis17 and correlates with coronary risk factors.20,21 Hypertension is associated with accelerated atherosclerosis and increased CA IMT as well as reduced endothelium-dependent vasodilation.

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in peripheral arteries. Since common CA supplies 80% blood flow to internal CA and only 20% to external CA, and since it is an ideal site to measure atherosclerotic burden via IMT, it may be ideally suited to investigate the effect of atherosclerosis on cerebrovascular blood flow reserve and CA endothelium dependent responses. To investigate the normal responses to a physiologic stimulus such as exercise that is likely to produce increased local shear stress within CA, on CA and BA arteries, we examined the effects supine bicycle exercise on brachial artery (BA) and CA. We hypothesized that BA and CA will demonstrate vasodilation in healthy subjects and that this vasodilation is measurable by ultrasound. Since the conventional ischemia induced BART technique cannot be applied to the cerebral circulation, CA reactivity in response to exercise may be a useful adjunctive tool for assessment of cerebrovascular endothelial function in health and disease.

METHODS

Thirteen healthy subjects participated in BA and CA reactivity during exercise. We performed BA reactivity to compare CA responses against this previously validated technique that measures endothelial function as well as to compare our lab results on BART with the published results. All studies were performed in the morning hours (between 8 and 11 AM) after an overnight fast. Informed consent was obtained and the protocol was approved by the Institutional Review Board for Human Subjects.

Study Recruitment and Eligibility

Subjects older than 18 years, right-handed, normotensive in normal sinus rhythm and able to give informed consent were included. Subjects with history of hypercholesterolemia (total cholesterol >240 and/or LDL cholesterol ≥160 mg/dl), coronary artery disease, congestive heart failure, cerebrovascular disease, diabetes mellitus, smoking during the previous 1 year, know systemic disease or malignancy, plaque in the common CA or its branches or IMT > 1.4 mm in the common CA, use of hormone replacement therapy or oral contraceptives within the last 3 months were excluded. Vitamin C, vitamin E, folic acid were withheld for 24 hours prior to the study participation.

Study Protocol

Demographic information was obtained prior to a 15-minute rest period in a quiet room. Arm blood pressure was measured by an automated machine. Heart rate was measured by ECG leads placed on the chest wall and displayed on the ultrasound system.

Ultrasound Studies. Ultrasound studies were performed using ATL 3000 ultrasound systems equipped with a linear array 5-12 MHz variable frequency scan head. The depth of field, gain, transmit focus and resolution mode settings were adjusted in each patient to give the image of maximum clarity with clear definition of intima and kept constant throughout the study. BA imaging was performed approximately 1-2 inches above medial antecubital fossa. CA imaging was performed to obtain a straight 5-7 cm segment of the CA below the carotid bulb. Ultrasound probe position was marked on the skin with a marker and position as well as baseline orientation of the probe was mimicked during peak hyperemia for BA and exercise for BA and CA. All procedures were recorded on videotape and select loops were digitized. DICOM images for PW Doppler measurements and cine loop recording for BA and CA diameter were stored in the hard as well as in magneto-optical discs.

Ultrasound Measurements. BA and CA diameter was measured at the onset of QRS complex from the cine loop recording as an average of 10 measurements from 2 separate digitized images, as the line identifying the media-adventitia interface in the near to the far wall using calipers in the ultrasound system. CA diameter measurements were made over 3 cm of a straight segment below the CA bulb. PW Doppler measurements included: velocity time integral (VTI), peak systolic (PSV), end diastolic velocity (EDV), pulsatility index (PI = (PSV-EDV)/VTI, resistive index (RI=PSV-EDV)/PSV) and blood flow (ml/min=3.14x (r)^2 x VTI x 60). All PW Doppler data was acquired using a 60° angle.

Five averaged Doppler measurements over atleast 10 cardiac and 2 respiratory cycles were measured.
Quantification was performed on the ATL 3000 ultrasound system.

**Protocol 1: Exercise stress.** Before the start of exercise, standard BART with hyperemic response to ischemia by blood pressure cuff was performed in the left arm. This was followed by ultrasound examination of right CA and right BA before and during peak exercise.

**a) Brachial Artery Reactivity (BART)**

This was performed using standard methods as described by Stradler et al. Briefly left BA diameter and flow were measured before and 60 and 90 seconds after cuff deflation that was placed around the proximal arm above the elbow and inflated to 50 mm Hg above systolic BP pressure for 5 minutes. We observed maximum hyperemia 1.5 minutes after cuff release, hence data for 1.5 minute post cuff deflation is shown. After 15 minutes of rest, 0.4 mg sublingual nitroglycerin (NTG) was given and BA and CA measurements repeated after 5 minutes.

**b) Exercise Test**

We performed baseline ultrasound examination of the right BA and right CA. Subjects then performed maximum tolerated bicycle ergometry exercise in a supine echo bed (Echo™ Bed, Americian Echo, USA). Heart rate was monitored continuously throughout the study and BP was measured at every minute. Exercise data was obtained at peak exercise and within 60 seconds post exercise by repeat ultrasound examination of the CA and BA.

**Statistical Analysis.** Continuous variables are presented as mean ± standard deviation, and categorical variables as counts and percentages. Differences between baseline and post-hyperemia and peak exercise stress variables within each group were compared by Student’s paired t-test. A p value of <0.05 was considered statistically significant.

**Inter-and Intra-observer Variability.** All measurements were made in a blinded fashion. At the onset of our studies, we first tested 3 different methods for measurement of BA diameter: 1) averaged diameter of 10 measurements by caliper, 2) determination of area by manual trace and 3) determination of area by point-by-point method – all 3 available on the ultrasound system. Inter-observer variability was tested in 33 randomly sets of digitized images for baseline, peak hyperemia and NTG images for BART under the same conditions. For CA diameter, 29 randomly selected peak exercise images were measured by the same observer twice and by 2 observers 1 week apart. The intra and inter-observer variability was expressed as a percent error for each measurement and were determined as the difference between the 2 observations divided by the mean value of the two observations (x1-x2/(x1+x2)/2*100). Inter-observer variability was 3.4±4% (0.06±0.21 mm), 3.6±4.2% (0.14±0.2 mm) and 2.3±4% (0.09±0.17 mm) for BA diameter measurements by caliper, area by manual trace and by point-by-point methods respectively. We chose to use caliper method of measurement, because of it ease and because of no significant differences from other relatively more cumbersome methods. Intra-observer variability (for combined 66 measurements by observer 1 and 2 was 1.0±2% (0.02±0.02 mm) for measurements for BA. Interobserver variability for CA diameter was 1.1±1.2% (0.01±0.01 mm). These intra-observer and inter-observer variability are comparable to results published earlier.10,24,25

**RESULTS**

**Brachial Artery Reactivity (BART):**

We studied 13 healthy volunteers, mean age 30±8 years, which included 4 females for both standard BART and BA and CA reactivity exercise protocols. Results are summarized in Table 1 and Figure 1 is a representative example. There was a 10%±4% BA vasodilation in response to ischemia induced

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<th>Table-1: Brachial Artery Reactivity Test (BART) in Healthy Volunteer Subjects (n=13)</th>
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<td>Diam (cm)</td>
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<td>Flow (ml/min)</td>
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Values are mean±SD, n=13, *p<0.05 vs. baseline. There was a 9.8±4% increase in brachial artery diameter in response to hyperemia. Flow = 3.14 x 60 x (radius)² x VTI. RI (resistive index) = PSV – EDV/PSV & PI (pulsatility index) = PSV – EDV/VTI. denote resistance to blood flow, VTI = velocity time integral, PSV = Peak systolic velocity.
hyperemia. This was associated with a decrease in resistance (PI and RI) and an increase in VTI. Volume flow increased by 800%±540%.

Carotid Artery Reactivity:
Carotid Artery Reactivity to Exercise.
Results of exercise study are shown in Table 2. Subjects attained 75%±7% of maximum age predicted heart rate and hence our results represent

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<th>Table-2 : Effects of Exercise on Brachial and Carotid Artery Responses in Healthy Subjects (n=13)</th>
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<td><strong>Brachial Artery</strong></td>
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Values are mean±SD, n=13, *p<0.03 vs. baseline, ‘p<0.0001 vs. brachial artery. Flow = 3.14x60x(radius)^2xVTI. PSV=peak systolic velocity, EDV=end-diastolic velocity, Diam=diameter, VTI= velocity times integral, RI=resistive index, PI=pulsatility index.
the results of moderate exercise. Figure 2 is a representative case example from an exercise study. Systolic BP pressure increased from 120±9 to 168±27 mm Hg, (p<0.001 vs. baseline), diastolic BP from 76±10 to 81±15 mm Hg, (p=NS), mean BP from 91±9 to 110±117 mm Hg, p<0.001 vs baseline) and heart rate from 62±12 to 140±10 bpm, p<0.001 vs. baseline. Exercise produced 8±5% vasodilation of CA and 6±6% vasodilation of BA. There was a trend towards a decrease in BA (p=0.060) and no significant change in CA flow. Correlation between the change in the product of heart rate and systolic BP during exercise and change in CA and BA diameter was 0.59 (p=0.03) and 0.53 (p=0.05) respectively.

**Vascular Reactivity to Nitroglycerin:**

NTG responses were assessed in 8 normal subjects. NTG administration increased the BA diameter from 0.39±0.05 cm to 0.43±0.06 cm (p<0.01) at 5 minutes, representing a 13±5% vasodilation from baseline. Increase in CA diameter in response to NTG was 5±3% (0.67±0.03 to 0.70±0.04 cm, p<0.01). NTG decreased mean BP by 3±4%.

**DISCUSSION**

The main findings of our study are that in healthy subjects supine bicycle exercise produced CA and BA vasodilation proportional to the hemodynamic effects of exercise, a net increase in resistance in both forearm and cerebral circulation, and no significant no significant change in the BA and CA blood flow. Similar to physical exercise, NTG also produced BA and CA vasodilation. These differences in blood flow reserve and vasodilation in normal subjects as measured from the CA and BA are similar, albeit
smaller, to the differences observed using BART in subjects with HTN and other risk factors for coronary artery disease \cite{6,11,16} and in coronary arteries in response to exercise. \cite{27,28,29}

Exercise leads to forearm vasodilation, which is blocked by NO inhibitor N-monomethyl-L-arginine (L-NMMA), suggesting it is nitric oxide mediated. The effects of exercise that we observed on BA are consistent with those of other investigators \cite{16,17} which showed BA vasodilation with physical stress. Previous work suggests that moderate upright exercise induces an increase in cerebral blood flow as measured from CA Doppler velocity, whereas a decrease in CA flow velocities were observed as the work increased beyond moderate levels. \cite{30} This increased resistance and decrease blood flow that we observed in the BA and CA and others \cite{31,32} observed in the CA likely reflects intense cerebrovascular and peripheral autoregulation and vasoconstriction and is partly secondary to catecholamine release, \cite{31} thus altering the balance between adrenergic vasoconstriction and endothelial NO-induced vasodilation during exercise. \cite{27,33}

Earlier venous plethysmographic studies suggest that mental stress produces vasodilation of forearm vasculature and that this vasodilation is NO mediated \cite{2} and not catecholamine mediated. \cite{34} Unlike exercise responses and similar to BART responses to ischemia-hyperemia in the forearm, mental stress-induced forearm responses included vasodilation of BA, a decrease in resistance, and a net increase in blood flow. Thus mental stress induced BA responses appear to be predominantly NO mediated and may provide better assessment of endothelial function, than exercise-induced responses.

Use of physical stress to assess CA and BA endothelial function is a novel non-invasive technique of assessment of vascular endothelial function. Inappropriate vasoconstriction, or lack of dilation in BA and CA in response to exercise may suggest endothelial dysfunction and needs to be further studied in subjects with risk factors for or those with established coronary, peripheral and cerebrovascular disease.

**Limitations**

These are preliminary findings in a small group of subjects. We did not perform continuous imaging of the CA and BA during exercise. This was due to motion artifact during exercise. The exercise protocol exercised leg muscles, hence evaluation of femoral arteries may have provided a better assessment of physiologic effects of exercise. The purpose of our exercise protocol was however to see if a stimulus, i.e. increased shear stress from increased heart rate and blood pressure will cause local vasodilation. In addition, imaging femoral arteries is not feasible on the supine bicycle during exercise. Finally we did not evaluate the effects of nitric oxide antagonists on BA and CA responses to evaluate the exact role of NO in causing BA and CA vasodilation.

**REFERENCES**


