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# Exercise and arterial adaptation in humans: uncoupling localized and systemic effects

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**Rowley NJ, Dawson EA, Birk GK, Cable NT, George K, Whyte G, Thijssen DH, Green DJ.** Exercise and arterial adaptation in humans: uncoupling localized and systemic effects. *J Appl Physiol* 110: 1190–1195, 2011. First published February 24, 2011; doi:10.1152/jappphysiol.01371.2010.—Previous studies have established effects of exercise training on arterial wall thickness, remodeling, and function in humans, but the extent to which these changes are locally or systemically mediated is unclear. We examined the brachial arteries of the dominant (D) and nondominant (ND) upper limbs of elite racquet sportsmen and compared them to those of matched healthy inactive controls. Carotid and superficial femoral artery responses were also assessed in both groups. High-resolution duplex ultrasound was used to examine resting diameter, wall thickness, peak diameter, and blood flow. We found larger resting arterial diameter in the preferred arm of the athletes ( $4.9 \pm 0.5$  mm) relative to their nonpreferred arm ( $4.3 \pm 0.4$  mm,  $P < 0.05$ ) and both arms of control subjects (D:  $4.1 \pm 0.4$  mm; ND:  $4.0 \pm 0.4$ ,  $P < 0.05$ ). Similar limb-specific differences were also evident in brachial artery dilator capacity ( $5.5 \pm 0.5$  vs.  $4.8 \pm 0.4$ ,  $4.8 \pm 0.6$ , and  $4.8 \pm 0.6$  mm, respectively;  $P < 0.05$ ) following glyceryl trinitrate administration and peak blood flow ( $1,118 \pm 326$  vs.  $732 \pm 320$ ,  $737 \pm 219$ , and  $698 \pm 174$  ml/min, respectively;  $P < 0.05$ ) following ischemic handgrip exercise. In contrast, athletes demonstrated consistently lower wall thickness in carotid ( $509 \pm 55$   $\mu$ m), brachial (D:  $239 \pm 100$   $\mu$ m; ND:  $234 \pm 133$   $\mu$ m), and femoral (D:  $479 \pm 38$   $\mu$ m; ND:  $479 \pm 42$   $\mu$ m) arteries compared with control subjects (carotid:  $618 \pm 74$   $\mu$ m; brachial D:  $516 \pm 100$   $\mu$ m; ND:  $539 \pm 129$   $\mu$ m; femoral D:  $634 \pm 155$   $\mu$ m; ND:  $589 \pm 112$   $\mu$ m; all  $P < 0.05$  vs. athletes), with no differences between the limbs of either group. These data suggest that localized effects of exercise are evident in the remodeling of arterial size, whereas arterial wall thickness appears to be affected by systemic factors.

nitric oxide; blood flow; wall thickness; intima-medial thickness

EXERCISE TRAINING IS ASSOCIATED with changes in the cross-sectional size of conduit and resistance arteries in humans (14, 44), especially when the training stimulus involves large muscle group dynamic exercise (3, 20, 24, 25, 45). However, training of small muscle groups is also associated with localized adaptation (12, 28, 42, 46), indicating that central or reflex mechanisms may not be obligatory. Indeed, recent studies suggest that localized episodic increases in shear stress, associated with repeated exercise bouts, may be an important stimulus to induce arterial adaptation (17, 46). However, exercise also involves changes in circulating factors, inflamma-

tion, and oxidative stress, as well as central hemodynamics, in particular, changes in blood and pulse pressure (10, 11, 41). Central or systemic reflex adaptations, which modulate vascular tone, may also occur following exercise training (7, 15, 29, 31).

Previous studies have examined the impact of localized vascular adaptations in response to exercise by comparing dominant vs. nondominant arms (13, 36) or the impact of unilateral exercise regimes (1, 12, 28, 37). However, to our knowledge, no previous study has examined the relative impacts of localized vs. systemic factors on arterial wall thickness and remodeling of diameter in response to chronic exercise training in humans. This is due, in part, to the difficulty in differentiating between the localized and systemic impacts of repeated exercise. In the present experiment, we measured wall thickness and artery diameters in the dominant and nondominant arms, and lower limbs, of elite level racquet sportsmen and healthy age-matched control subjects. Our rationale was that, if training has systemic, but not localized, effects on conduit arteries, then we would observe no difference between the preferred and nonpreferred upper limbs of elite racquet sportsmen, but differences between the athletes and relatively inactive matched controls. Conversely, if localized effects on the vasculature were apparent, then differences between the upper limbs should be evident in the racquet sportsmen, but not between limbs in the controls. We hypothesize that the localized effect of training in the dominant limb of elite squash players would be associated with greater vascular adaptation in the dominant arm.

## METHODS

### Subjects

Thirteen (inter)national level male squash players from the United Kingdom, who had trained at elite levels for an average of  $13 \pm 5$  yr (range 8–23 yr), and 16 healthy recreationally active age-matched controls were included in this study. The elite athletes played  $\geq 2$  yr at the (inter)national level and trained for  $>22$  h/wk, with 80% being sport specific, including game play, unilateral racket handling, and shadowing skills. Control subjects participated in exercise training  $<3$  h/wk at a recreational level. All participants were free from known cardiovascular disease, diabetes, insulin resistance, hypercholesterolemia, and hypertension. Subjects who smoked or those on medications of any type were excluded from the study. The study procedures were approved by the Ethics Committee of Liverpool John Moores University. Written, informed consent was gained from all participants before the experimental procedures.

### Experimental Design

Participants reported to our laboratory on one occasion after fasting for 6 h, abstaining from alcohol and beverages containing caffeine

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(e.g., coffee, tea, energy drinks) for 12 h and refraining from any intense maximal training sessions 24 h before testing. After familiarization and administration of a training history questionnaire, subjects rested for at least 20 min in the supine position. Baseline ultrasound scans of the carotid, brachial, and superficial femoral artery were then collected for assessment of wall thickness using high-resolution ultrasound (below). Following a >20-min baseline rest period, we examined brachial artery peak blood flow (BF) responses after 5 min of ischemic exercise (iEx), described in detail elsewhere (32). Bilateral brachial endothelium-independent vasodilation was then measured after sublingual administration of a nitric oxide donor, glyceryl trinitrate (GTN). Anthropometric data were assessed using limb volumes, girths, and a dual energy x-ray absorptiometry scan.

#### Experimental Measurements

**Conduit artery wall thickness.** Participants rested in the supine position for at least 20 min. Heart rate and mean arterial pressure were determined twice using an automated sphygmomanometer (Dinamap; GE Pro 300V2, Tampa, FL). Three standardized probe angles (posterior, lateral, and anterolateral) were used to determine resting wall thickness and the diameter of the right carotid artery using a 10-MHz multifrequency linear array probe attached to a high-resolution ultrasound machine (T3000, Terason, Burlington, MA). The sonographer obtained a longitudinal B-mode image of the carotid artery 2 cm proximal to the carotid bifurcation. Recording was performed over a 10-s period. Settings were adjusted to focus on the far wall of the arterial lumen interface and the media adventitia. Wall thickness data were then collected from the brachial and superficial femoral arteries on the dominant and nondominant side using the same procedures as described above. For practical reasons, two planes of assessment were used for the peripheral arteries.

**Hyperemic response to iEx.** After recording of baseline brachial artery diameter and velocity for 1 min, cuffs were positioned proximally around the upper arms, above the imaged artery, and inflated to >200 mmHg for 5 min. During the middle 3 min, rhythmic ischemic handgrip exercise was performed using a 3-kg weight at 30 contractions/min. Diameter and velocity recordings resumed 30 s before cuff deflation and continued for 3 min thereafter. The peak hyperemic forearm BF response to this stimulus in humans provides a valid and accepted index of resistance artery size or remodeling (32), which has been used extensively in the past 2 decades in previous human investigations (36, 39).

**Conduit artery dilator capacity.** Brachial artery peak dilation was examined using a single, sublingual administration of GTN. After a 1-min assessment of the baseline brachial artery diameter and velocity, sublingual administration of GTN (400 µg) was followed by a 10-min recording of both brachial arteries simultaneously using identical ultrasound machines and settings (32).

**Body composition and limb circumferences and volume.** A dual-energy X-ray absorptiometry scanner (Hologic QDR Series Discovery A, Bedford, MA) was used to determine whole body and limb-specific adipose and lean tissue mass in each subject. Limb circumferences were also measured at the maximum girths of the upper arm and forearm on both arms and on the lower legs. In addition, water submersion using a cylindrical container was used to assess lower limb and forearm volumes.

#### Data Analysis

**Artery edge detection, wall tracking, and wall thickness.** Posttest analysis of brachial and superficial femoral artery diameter and velocity was performed using custom-designed, edge-detection and wall-tracking software, which is largely independent of investigator bias (33, 50). Settings were recorded and, where possible, maintained across subjects to establish consistency (34). The software is written in the icon-based graphical programming language (LabVIEW 7.0) and uses an IMAQ vision tool kit for image handling and analysis

routines, with arterial analysis using edge-detection methods. Analysis of carotid, brachial, and superficial femoral artery wall thickness was also performed using a DICOM-based software package, which has proven to be observer independent and has been validated against phantoms (33, 34). Arterial responses to ischemia and GTN were calculated based on standardized algorithms applied to data that had undergone automated edge detection and wall tracking (2, 33, 34), in accordance with recent guidelines (43). Peak BF (ml/min) in response to the iEx stimulus, calculated from simultaneously acquired (at 20 Hz) diameter (cross-sectional area) and velocity data, was identified as the highest mean BF across a 10-s period during the first 30 s after cuff deflation. Peak diameter was identified by the maximal response to GTN (32).

#### Statistics

Statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL) software. All data are reported as means ( $\pm$ SD), unless stated otherwise, while statistical significance was assumed at  $P < 0.05$ . We used a two-way ANOVA to examine differences between groups ("group": squash vs. controls), between sides ("side": dominant vs. nondominant), and whether there was an interaction between both variables ("group  $\times$  side"). When a significant interaction was observed, post hoc Student's paired  $t$ -tests were used to examine differences. Assuming 80% power, an  $\alpha$  of 0.05, and a group size of at least 12 subjects, we were powered to detect a 2.0% difference in the peak dilator response between groups (50). Regarding the wall thickness, we were able to detect a 65-µm difference within subjects and a 95-µm difference between groups (33). Our power was logically higher to detect differences between the limbs in the athletes, given the diminished variability associated with such within-subject comparisons.

## RESULTS

The elite athletes exhibited lower systolic blood pressure and heart rate and were taller, but were otherwise well matched for anthropometric and body composition features (Table 1).

#### Dominant vs. Nondominant Limb Comparisons Within Elite Squash Players and Matched Controls

Squash players and controls possessed significantly higher limb volume, limb circumference, muscle and fat mass in the dominant, compared with nondominant, arm (Table 2). The difference in limb volume and lean fat mass between the dominant and nondominant arms was significantly larger in squash players compared with controls (limb  $\times$  group interaction,  $P < 0.01$ , Table 2).

Table 1. Subject anthropometric characteristics of elite squash players and age-matched control subjects

	Squash	Controls	$t$ -Test
Age, yr	22 $\pm$ 3	22 $\pm$ 2	NS
Systolic blood pressure, mmHg	122 $\pm$ 11	131 $\pm$ 12	$P < 0.05$
Diastolic blood pressure, mmHg	69 $\pm$ 5	68 $\pm$ 5	NS
Height, cm	182 $\pm$ 5	176 $\pm$ 6	$P < 0.01$
Weight, kg	76 $\pm$ 16	76 $\pm$ 8	NS
Body mass index, kg/m <sup>2</sup>	23.5 $\pm$ 1.8	24.9 $\pm$ 4.9	NS
Total body fat, %	12.9 $\pm$ 2.6	16.4 $\pm$ 8.6	NS
Total lean mass, kg	65 $\pm$ 6	61 $\pm$ 6	NS
Heart rate, beats/min	50 $\pm$ 11	63 $\pm$ 10	$P < 0.01$

Values are means  $\pm$  SD;  $n = 13$  squash players and  $n = 16$  control subjects. The  $t$ -test refers to an unpaired  $t$ -test between squash players and controls. NS, nonsignificant.

Table 2. Anthropometric characteristics of the upper limbs of elite squash players and matched control subjects

	Squash		Controls	
	Dominant	Nondominant	Dominant	Nondominant
Fat mass, g	591 ± 110	537 ± 117*	597 ± 262	608 ± 278
Lean mass, g	3,791 ± 318	3,258 ± 355*	3,666 ± 286	3,380 ± 265*
Circumference, cm	29.7 ± 2.2	28.0 ± 1.6*	31.5 ± 4.1	31.3 ± 3.9†
Volume, ml	1,400 ± 141	1,200 ± 169*	1,418 ± 238	1,335 ± 238*

Values are means ± SD;  $n = 13$  squash players and  $n = 16$  control subjects. \*Significantly different between dominant and nondominant upper limb. †Significantly different from squash at  $P < 0.05$ . The difference in limb volume and lean fat mass between the dominant and nondominant arms was significantly larger in squash players compared with controls (limb × group interaction:  $P < 0.01$ ).

**Baseline arterial diameter and wall thickness.** In squash players, brachial artery diameter was significantly larger in the dominant compared with the nondominant arm (Fig. 1, Table 3). No differences were found in wall thickness between upper limbs (Fig. 2, Table 3). In the lower limbs, a slightly, but significantly, larger diameter was evident in the superficial femoral artery of the nondominant leg. Wall thickness was not different between the lower limbs in these athletes (Table 3). No differences in brachial or superficial femoral artery diameter, wall thickness, or wall-to-lumen ratio were found between limbs in the controls (Table 3).

**Peak hyperemic responses to iEx.** Squash players demonstrated a significantly larger brachial artery peak BF in the brachial artery on the dominant side (Table 3). Peak BF was not different between the upper limbs of the control subjects.

**Conduit artery dilator capacity responses.** Brachial artery diameter was significantly larger in the brachial artery of the dominant vs. the nondominant forearm in squash players following administration of GTN. No differences between limbs were evident in controls (Table 3, Fig. 2C).

#### Comparisons Between Squash Players and Control Subjects

**Baseline arterial diameter and wall thickness.** Squash players possessed significantly greater arterial diameters in the brachial and superficial femoral arteries (Table 3). Wall thickness of all arteries was significantly lower in all arteries compared with controls. Consequently, wall-to-lumen ratio of the carotid, brachial, and superficial femoral arteries was significantly lower in squash players than controls (Table 3).

**Peak hyperemic responses to iEx.** Peak brachial BF was significantly higher in the dominant arm of squash players than their nondominant arm or in either limb of the controls (Table 3).

**Conduit artery dilator capacity responses.** Brachial artery peak dilation in the dominant forearm in squash players was significantly higher compared with that in the controls (Table 3, Fig. 2C), but no difference was seen between nondominant limb arteries.

#### DISCUSSION

The major novel findings of this study pertain to the impact of local vs. systemic effects of exercise on conduit artery wall thickness in humans. We observed consistently lower wall thickness measures across carotid, brachial, and femoral arteries in the athletes vs. control subjects. However, brachial artery wall thickness did not differ between the preferred and non-preferred upper limbs of the squash players. These data suggest, in contrast to the remodeling of lumen diameter data discussed below, that training affects artery wall thickness via a systemic rather than a localized mechanism.

Recent studies suggest that training does not typically impact on carotid artery thickness (30, 40), whereas it may influence femoral (5), brachial, and popliteal artery thickness (16, 26, 49). These studies have not been performed in athletes, and the observation that all arteries, including the carotid, were affected in our study may reflect the prolonged intensive nature of the training stimulus in our subjects. The impact of training on wall thickness has potentially important ramifications. From a physiological perspective, it is tempting to speculate that changes in wall thickness and lumen diameter may reflect adaptations consistent with the law of LaPlace, around normalization of wall stress, but this requires further empirical evidence.

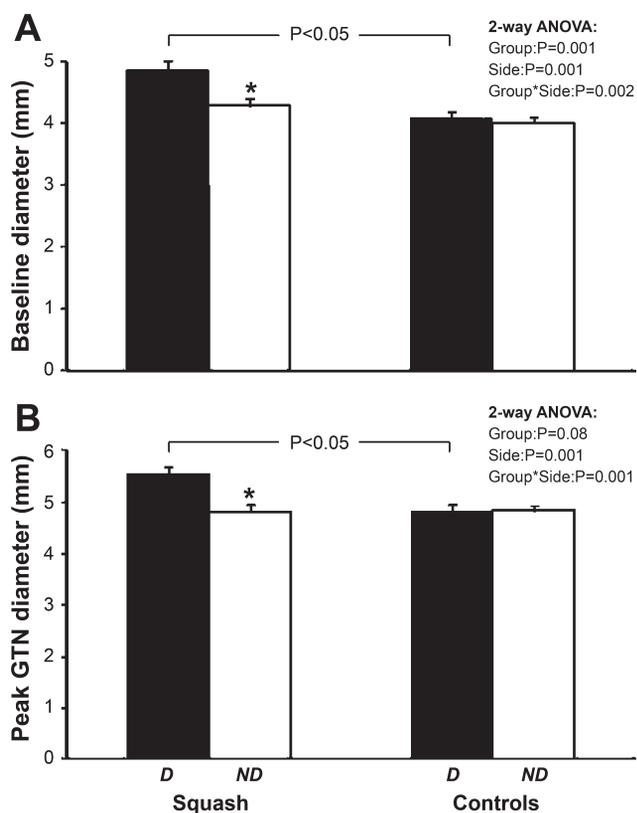


Fig. 1. Brachial artery (BA) baseline (A) and peak diameter (B) in the dominant (D) and nondominant (ND) side in squash players ( $n = 13$ ) and controls ( $n = 16$ ). Values are means ± SE. \*Significantly different from the D side at  $P < 0.05$ .  $P$  value refers to a post hoc unpaired  $t$ -test between squash players and controls. Results from the two-way ANOVA are presented. GTN, glyceryl trinitrate.

Table 3. Brachial, superficial femoral, and carotid artery characteristics in the dominant and nondominant limbs of elite squash players and healthy matched control subjects

	Squash		Controls	
	Dominant	Nondominant	Dominant	Nondominant
<b>Brachial artery</b>				
Diameter, mm	4.9 ± 0.5	4.3 ± 0.4*	4.1 ± 0.4†	4.0 ± 0.4†
Wall thickness, μm	239 ± 100	234 ± 133	516 ± 100†	539 ± 129†
Wall-to-lumen ratio	0.05 ± 0.02	0.06 ± 0.03	0.12 ± 0.03†	0.13 ± 0.03†
Peak blood flow, ml/min	1,118 ± 326	732 ± 320*	737 ± 219†	698 ± 174
Peak diameter, mm	5.5 ± 0.5	4.8 ± 0.4*	4.8 ± 0.6†	4.8 ± 0.6
<b>Superficial femoral artery</b>				
Diameter, mm	7.1 ± 0.7	7.3 ± 0.7*	6.5 ± 0.7†	6.4 ± 0.6†
Wall thickness, μm	479 ± 38	479 ± 42	634 ± 155†	589 ± 112†
Wall-to-lumen ratio	0.07 ± 0.01	0.07 ± 0.01	0.10 ± 0.02†	0.09 ± 0.02†
<b>Carotid artery</b>				
Diameter, mm	6.7 ± 0.5		6.4 ± 0.6	
Wall thickness, μm	509 ± 55		618 ± 74†	
Wall-to-lumen ratio	0.08 ± 0.01		0.10 ± 0.02†	

Values are means ± SD;  $n = 13$  squash players and  $n = 16$  control subjects. \*Significantly different from dominant at  $P < 0.05$ . †Significantly different from squash at  $P < 0.05$ . Peak blood flows were determined from the ischemic handgrip exercise test, according to previous descriptions (32). Peak diameters were determined from the glyceryl trinitrate test, as per Ref. 18.

We observed larger resting brachial arterial diameter in the preferred limb, compared with nonpreferred limb, of squash players. These differences were not evident in the matched control subjects. This suggests a localized impact on structural

arterial enlargement. However, resting arterial diameter can be impacted by sympathetic tone, circulating hormones, and local paracrine effects and may be limited as an index of vascular structure. Our laboratory has previously demonstrated that responses to GTN induce near maximal dilation (32), which is less affected by such influences. Indeed, Haskell et al. (18) established that responses to GTN reveal differences in arterial caliber and dilator capacity between athletes and controls that are not always evident under resting conditions. Our observation, that the absolute brachial artery diameter following GTN administration in the dominant limb of squash players was significantly enlarged compared with the contralateral limb, and also both limbs of the controls, is novel, reinforces the baseline conduit diameter data and gives us confidence to conclude that training-induced arterial enlargement was evident as a result of a localized effect. This localized impact on arterial remodeling is also apparent in the downstream resistance vessels, as the peak reactive hyperemic BF response to iEx, an index of resistance vessel structural remodeling (32, 36) that is not related to sympathetic tone (36, 37, 39) or capillarization (4, 19, 27, 38), was also larger in the preferred forearm of squash players vs. their nonpreferred forearm or either arm of the controls.

The observation that exercise training is associated with conduit and resistance artery enlargement is not new, and data pertaining to this has recently been reviewed (15, 44). Regarding local vs. systemic effects in resistance arteries, we and others have previously reported evidence for such arterial remodeling in the preferred limbs of tennis players (13, 36). However, this is the first study, to our knowledge, that has observed differences between the impact of training on wall thickness vs. arterial lumen remodeling. Clinically, Folkow et al. (6) pointed out in the 1960's that changes in wall-to-lumen ratio of peripheral arteries have implications for vascular hyperresponsiveness and "essential" hypertension. In addition, there is an established prognostic relationship between carotid wall thickness and the presence of subclinical atherosclerotic disease and future cardiovascular events (23). Our data suggest that exercise may have physiological and systemic effects on

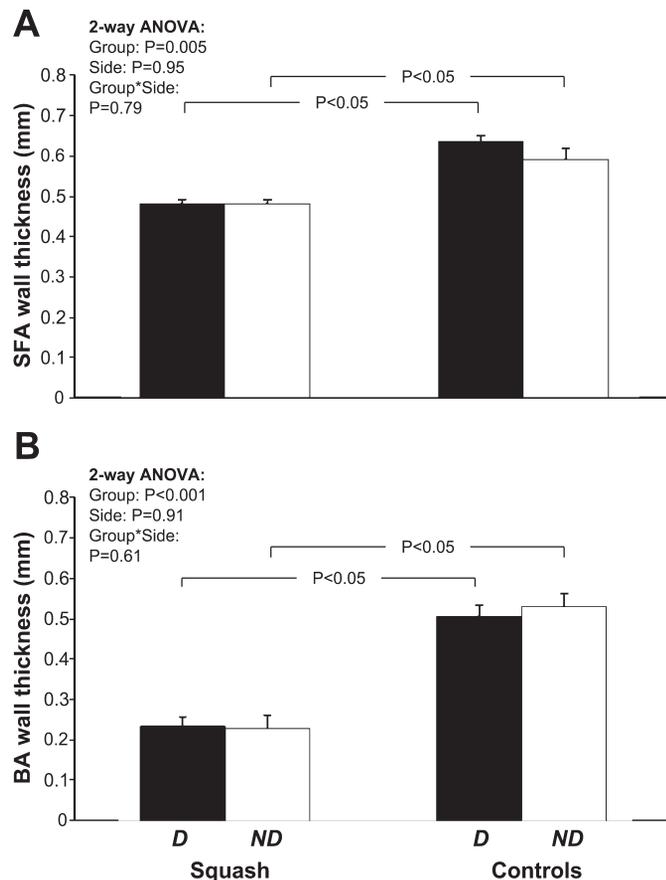


Fig. 2. Superficial femoral artery (SFA; A) and BA (B) wall thickness in the D and ND side in squash players ( $n = 13$ ) and controls ( $n = 16$ ). Values are means ± SE.  $P$  value refers to a post hoc unpaired  $t$ -test between squash players and controls. Results from the two-way ANOVA are presented.

artery wall thickness and wall-to-lumen ratio that have potential clinical implications.

There are several possible mechanisms responsible for local and systemic effects on the vasculature in humans. The impact of exercise-mediated shear stress on vascular function (17, 46) and structure (21, 47, 48) is well established (8). Systemic effects may be mediated by circulating factors, inflammatory or oxidative stress changes, or other as yet unknown factors. It is also conceivable that exercise-related arterial or transmural pressure changes may be one factor that contributes to systemic arterial adaptation (22). Future studies, which specifically manipulate these factors, including arterial pressure (10, 11) and localized shear stress (46), should address specific mechanisms associated with local and systemic adaptations to exercise training in humans.

It is important to state, as a caveat, that we cannot discount the possibility of changes in the nonpreferred upper limb of athletes in terms of both local and systemic responses to whole body exercise. Indeed several studies have established the role of leg exercise in upper limb shear responses (9, 11, 35, 41). However, our findings suggest that any such changes must be threshold dependent in terms of inducing arterial diameter remodeling. Finally, we also cannot discount the possibility that other vasodilator stimuli, such as ischemic handgrip performed against higher loading, might have revealed quantitatively different results between limbs and subjects in this study.

In summary, we have provided evidence for systemic effects of exercise training or physical conditioning on arterial wall thickness in humans, while impacts of exercise on conduit and resistance artery cross-sectional size appear to be dictated more by localized effects. Future studies should focus on the relative impact of different hemodynamic variables on arterial adaptation in humans.

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#### DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

#### REFERENCES

- Alomari MA, Welsch MA, Prisby RD, Lee CM, Wood RH. Modification of forearm vascular function following short-term handgrip exercise training. *Int J Sports Med* 22: 361–365, 2001.
- Black MA, Cable NT, Thijssen DH, Green DJ. Importance of measuring the time course of flow-mediated dilatation in humans. *Hypertension* 51: 203–210, 2008.
- Black MA, Green DJ, Cable NT. Exercise training prevents age-related decline in nitric oxide (NO)-mediated vasodilator function in human microvessels. *J Physiol* 586: 3511–3524, 2008.
- Brown MD, Cotter MA, Hudlika O, Vrbova G. The effect of different patterns of muscle activity on capillary density, mechanical properties, and structure of slow and fast rabbit muscles. *Pflügers Arch* 361: 241–250, 1976.
- Dinno FA, Tanaka H, Monahan KD, Clevenger CM, Eskurza I, DeSouza CA, Seals DR. Regular endurance exercise induces expansive arterial remodeling in the trained limbs of healthy men. *J Physiol* 534: 287–295, 2001.
- Folkow B, Grimby G, Thulesius O. Adaptive structural changes in the vascular walls in hypertension and their relation to the control of peripheral resistance. *Acta Physiol Scand* 44: 255, 1958.
- Fraga R, Franco FG, Roveda F, de Matos LNJ, Braga AM, Rondon MU, Rotta DR, Brum PC, Barretto ACP, Middlekauff HR, Negrao CE. Exercise training reduces sympathetic nerve activity in heart failure patients treated with carvedilol. *Eur J Heart Fail* 9: 630–636, 2007.
- Gielen S, Schuler G, Adams V. Cardiovascular effects of exercise training: molecular mechanisms. *Circulation* 122: 1221–1238, 2010.
- Green D. Point: Flow-mediated dilation does reflect nitric oxide-mediated endothelial function. *J Appl Physiol* 99: 1233–1234; discussion 1237–1238, 2005.
- Green D, Cheatham C, Henderson C, Weerasooriya R, O'Driscoll G. Effect of cardiac pacing on forearm vascular responses and nitric oxide function. *Am J Physiol Heart Circ Physiol* 283: H1354–H1360, 2002.
- Green D, Cheatham C, Mavaddat L, Watts K, Best M, Taylor R, O'Driscoll G. Effect of lower limb exercise on forearm vascular function: contribution of nitric oxide. *Am J Physiol Heart Circ Physiol* 283: H899–H907, 2002.
- Green DJ, Cable NT, Fox C, Rankin JM, Taylor RR. Modification of forearm resistance vessels by exercise training in young men. *J Appl Physiol* 77: 1829–1833, 1994.
- Green DJ, Fowler DT, O'Driscoll JG, Blanksby BA, Taylor RR. Endothelium-derived nitric oxide activity in forearm vessels of tennis players. *J Appl Physiol* 81: 943–948, 1996.
- Green DJ, Maiorana AJ, O'Driscoll G, Taylor R. Topical Review: Effects of exercise training on vascular endothelial nitric oxide function in humans. *J Physiol* 561: 1–25, 2004.
- Green DJ, Spence A, Halliwill JR, Cable NT, Thijssen DHJ. Exercise and vascular adaptation in asymptomatic humans. *Exp Physiol* 96: 57–70, 2011.
- Green DJ, Swart A, Exterkate A, Naylor LH, Black MA, Cable NT, Thijssen DHJ. Impact of age, sex and exercise on brachial and popliteal artery remodelling in humans. *Atherosclerosis* 210: 525–530, 2010.
- Hambrecht R, Adams V, Erbs S, Linke a Krankel N, Shu Y, Baithier Y, Geilen S, Thiele H, Gummert JF, Mohr FW, Schuler G. Regular physical activity improves endothelial function in patients with coronary artery disease by increasing phosphorylation of endothelial nitric oxide synthase. *Circulation* 107: 3152–3158, 2003.
- Haskell WL, Sims C, Myll J, Bortz WM, St Goar FG, Alderman EL. Coronary artery size and dilating capacity in ultradistance runners. *Circulation* 87: 1076–1082, 1993.
- Hudlika O, Brown MD, Cotter MA, Vrbova G. The effect of long term stimulation of fast twitch muscles on their blood flow, metabolism and ability to withstand fatigue. *Pflügers Arch* 369: 141–149, 1977.
- Huonker M, Schmid A, Schmid-Truckass A, Grathwohl D, Keul J. Size and blood flow of central and peripheral arteries in highly trained able-bodied and disabled athletes. *J Appl Physiol* 95: 685–691, 2003.
- Langille BL, O'Donnell F. Reductions in arterial diameter produced by chronic decreases in blood flow are endothelium-dependent. *Nature* 231: 405–407, 1986.
- Laughlin MH, Newcomer SC, Bender SB. Importance of hemodynamic forces as signals for exercise-induced changes in endothelial cell phenotype. *J Appl Physiol* 104: 588–600, 2008.
- Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation* 115: 459–467, 2007.
- Maiorana A, O'Driscoll G, Cheatham C, Dembo L, Stanton K, Goodman C, Taylor RR, Green DJ. The effect of combined aerobic and resistance exercise training on vascular function in type 2 diabetes. *J Am Coll Cardiol* 38: 860–866, 2001.
- Maiorana A, O'Driscoll G, Dembo L, Cheatham C, Goodman C, Taylor R, Green DJ. Effect of aerobic and resistance exercise training on vascular function in heart failure. *Am J Physiol Heart Circ Physiol* 279: H1999–H2005, 2000.
- Maiorana AJ, Naylor LH, Exterkate A, Swart A, Thijssen DHJ, O'Driscoll G, Green DJ. The impact of exercise training on conduit artery wall thickness and remodelling in chronic heart failure patients. *Hypertension* 57: 56–62, 2011.
- Maxwell LC, White TP, Faulkner JA. Oxidative capacity, blood flow, and capillarity of skeletal muscles. *J Appl Physiol* 49: 627–633, 1980.
- McGowan CL, Levy AS, McCartney N, MacDonald MJ. Isometric handgrip training does not improve flow-mediated dilation in subjects with normal blood pressure. *Clin Sci (Lond)* 112: 403–409, 2007.
- Monahan KD, Dinno FA, Tanaka H, Clevenger CM, DeSouza CA, Seals DR. Regular aerobic exercise modulates age-associated declines in

- cardiovascular baroreflex sensitivity in healthy men. *J Physiol* 529: 263–271, 2000.
30. **Moreau KL, Silver AE, Dinenna FA, Seals DR.** Habitual aerobic exercise is associated with smaller femoral artery intima-media thickness with age in healthy men and women. *Eur J Cardiovasc Prev Rehabil* 13: 805–811, 2006.
  31. **Mueller PJ.** Physical (in)activity-dependent alterations at the rostral ventrolateral medulla: influence on sympathetic nervous system regulation. *Am J Physiol Regul Integr Comp Physiol* 298: R1468–R1474, 2010.
  32. **Naylor LH, Weisbrod CJ, O'Driscoll G, Green DJ.** Measuring peripheral resistance and conduit arterial structure in humans using Doppler ultrasound. *J Appl Physiol* 98: 2311–2315, 2005.
  33. **Potter K, Green DJ, Reed CJ, Woodman RJ, Watts GF, McQuillan BM, Burke V, Hankey GJ, Arnolda LF.** Carotid intima-medial thickness measured on multiple ultrasound frames: evaluation of a DICOM-based software system. *Cardiovasc Ultrasound* 5: 29, 2007.
  34. **Potter K, Reed CJ, Green DJ, Hankey GJ, Arnolda LF.** Ultrasound settings significantly alter arterial lumen and wall thickness measurements. *Cardiovasc Ultrasound* 6: 6, 2008.
  35. **Simmons GH, Padilla J, Young CN, Wong BJ, Lang JA, Davis MJ, Laughlin MH, Fadel PJ.** Increased brachial artery retrograde shear rate at exercise onset is abolished during prolonged cycling: role of thermoregulatory vasodilation. *J Appl Physiol* 110: 389–397, 2011.
  36. **Sinoway LI, Musch TI, Minotti JR, Zelis R.** Enhanced maximal metabolic vasodilatation in the dominant forearms of tennis players. *J Appl Physiol* 61: 673–678, 1986.
  37. **Sinoway LI, Shenberger J, Wilson J, McLaughlin D, Musch T, Zelis R.** A 30-day forearm work protocol increases maximal forearm blood flow. *J Appl Physiol* 62: 1063–1067, 1987.
  38. **Snell PG, Martin WH, Buckley JC, Bloomqvist CG.** Maximal vascular leg conductance in trained and untrained men. *J Appl Physiol* 62: 606–610, 1987.
  39. **Takeshita A, Mark AL.** Decreased vasodilator capacity of forearm resistance vessels in borderline hypertension. *Hypertension* 2: 610–616, 1980.
  40. **Tanaka T, Seals DR, Monahan KD, Clevenger CM, DeSouza CA, Dinenna FA.** Regular aerobic exercise and the age-related increase in carotid artery intima-medial thickness in healthy men. *J Appl Physiol* 92: 1458–1464, 2002.
  41. **Thijssen DH, Dawson EA, Black MA, Hopman MT, Cable NT, Green DJ.** Brachial artery blood flow responses to different modalities of lower limb exercise. *Med Sci Sports Exerc* 41: 1072–1079, 2009.
  42. **Thijssen DH, Heesterbeek P, van Kuppevelt DJ, Duysens J, Hopman MT.** Local vascular adaptations after hybrid training in spinal cord-injured subjects. *Med Sci Sports Exerc* 37: 1112–1118, 2005.
  43. **Thijssen DHJ, Black MA, Pyke K, Padilla J, Atkinson GA, Harris RA, Parker B, Widlansky ME, Tschakovsky ME, Green DJ.** Assessment of flow mediated dilation in humans: a methodological and physiological guideline. *Am J Physiol Heart Circ Physiol* 300: H2–H12, 2011.
  44. **Thijssen DHJ, Maiorana AJ, O'Driscoll G, Cable NT, Hopman MTE, Green DJ.** Impact of inactivity and exercise on the vasculature in humans. *Eur J Appl Physiol* 108: 845–875, 2010.
  45. **Tinken TM, Thijssen DHJ, Black MA, Cable NT, Green DJ.** Conduit artery functional adaptation is reversible and precedes structural changes to exercise training in humans. *J Physiol* 586: 5003–5012, 2008.
  46. **Tinken TM, Thijssen DHJ, Hopkins ND, Dawson EA, Cable NT, Green DJ.** Shear stress mediates vascular adaptations to exercise training in humans. *Hypertension* 55: 312–318, 2010.
  47. **Tronc F, Wassef M, Esposito B, Henrion D, Glagov S, Tedgui A.** Role of NO in flow-induced remodeling of rabbit common carotid artery. *Arterioscler Thromb Vasc Biol* 16: 1256–1262, 1996.
  48. **Tuttle JL, Nachreiner RD, Bhuller AS, Condict KW, Connors BA, Herring BP, Dalsing MC, Unthank JL.** Shear level influences artery remodelling, wall dimension, cell density and eNOS expression. *Am J Physiol Heart Circ Physiol* 281: H1380–H1389, 2001.
  49. **van Duijnhoven NTL, Green DJ, Felsenberg D, Belavý DL, Hopman MTE, Thijssen DHJ.** Impact of bed rest on conduit artery intima-media thickness: effect of exercise countermeasures. *Hypertension* 56: 240–246, 2010.
  50. **Woodman RJ, Playford DA, Watts GF, Cheetham C, Reed C, Taylor RR, Puddey IB, Beilin LJ, Burke V, Mori TA, Green D.** Improved analysis of brachial artery ultrasound using a novel edge-detection software system. *J Appl Physiol* 91: 929–937, 2001.