Effect of Exercise on Arterial Stiffness: Is There a Ceiling Effect?

David Montero,[1] Andreas Breenfeldt-Andersen,[2,3] Laura Oberholzer,[2] and Thomas Haider[2]

BACKGROUND
Whether arterial stiffness (AS) can be improved by regular exercise in healthy individuals remains equivocal according to cross-sectional and longitudinal studies assessing arterial properties at discrete time points. The purpose of the present study was to pinpoint the time course of training-induced adaptations in central AS.

METHODS
Aorta characteristic impedance (Z_c) and carotid distensibility (CD) were determined with ultrasonography prior to (week 0) and across 8 weeks (weeks 2, 4, and 8) of supervised endurance training (ET) (3 × 60 minutes cycle ergometry sessions per week), in 9 previously untrained healthy normotensive adults (27 ± 4 years) with no history of cardiovascular disease. Exercise capacity was assessed by maximal oxygen consumption (VO_{2max}) elicited by incremental ergometry.

RESULTS
VO_{2max} increased throughout the ET intervention (+12% from week 0 to week 8, $P < 0.001$, P for linear trend <0.001). Systolic blood pressure rose with ET (+7% from week 0 to week 8, $P = 0.019$, P for linear trend <0.001). Aorta Z_c augmented from week 0 to week 8 of ET in all individuals (+38%, $P = 0.003$, P for linear trend = 0.002). CD did not significantly differ among time points ($P = 0.196$) although a linear decreasing trend was detected ($P = 0.016$).

CONCLUSIONS
Central AS augments during a conventional ET intervention that effectively enhances aerobic exercise capacity in young individuals. This suggests that normal, healthy elastic arteries are not amendable to improvement unless impairment is present.

Keywords: aorta characteristic impedance; blood pressure; ceiling effect; common carotid distensibility; hypertension.

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Arterial distensibility, and its opposite arterial stiffness (AS), characterize the capacity of an artery to expand/recoil in response to changes in blood pressure and strongly predict cardiovascular disease and mortality when assessed in central elastic arteries.[1] Accumulating evidence indicates that aortic and carotid distensibility (CD) are generally improved by regular exercise, particularly endurance training (ET), in aged and/or diseased individuals.[2,3] Whether ET can further enhance the distensibility of intact and thoroughly functional (i.e., healthy) large elastic arteries remains uncertain.[3–6] In this regard, a landmark cross-sectional study reported similar CD in young endurance-trained compared with sedentary age-matched individuals,[3] suggesting the presence of a "ceiling" effect. However, few longitudinal studies have described variable central arterial distensile properties following short-term (up to 8-week) ET in healthy young individuals.[4–6] One possible explanation for disparate cross-sectional and longitudinal findings relates to the potential time-dependent adaptation of arterial distensibility to ET, akin to the established oscillating status of vasodilator function during the initial month of ET in humans, whereupon vascular adaptations tend to stabilize after 6 weeks.[7] To our knowledge, the time course of ET-induced phenotypic modifications in arterial distensibility has not yet been addressed. Therefore, we sought to determine AS in aorta and carotid arteries prior to and through 8 weeks (weeks 2, 4, and 8) of a supervised ET intervention, known to elicit extensive central circulatory adaptations, in previously untrained healthy individuals.[8]

METHODS

Study subjects

Nine healthy, previously untrained individuals (5 males, 4 females; age = 26.7 ± 4.4 years; body surface area = 1.8 ± 0.2 m^2) were recruited to participate in the study. All individuals were normotensive, medication free, presented normal electrocardiogram, and no history of cardiovascular disease. The study was approved by the local Ethical Committee (KEK-ZH-Nr. 2015-0453) and conducted in accordance with

Correspondence: David Montero (David.MonteroBarril@usz.ch).

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[1]Department of Cardiology, University Hospital Zurich, Zurich, Switzerland; [2]Zurich Center for Integrative Human Physiology (ZIHP), Institute of Physiology, University of Zurich, Zurich, Switzerland; [3]Department of Nutrition, Exercise and Sports, University of Copenhagen, Copenhagen, Denmark.

the declaration of Helsinki. Prior to the start of the study, informed oral and written consents were obtained from all participants. A parallel investigation from this cohort has been published.[9]

Experimental design

Assessments were performed after fasting overnight in a quiet room with controlled temperature (22–24 °C), prior to (week 0) and across 8 weeks of ET (at weeks 2, 4, and 8). In order to limit the influence of lifestyle confounders, all individuals slept in our laboratory and were monitored from the night before each testing day, which was scheduled at least 48 hours following the last training session to attenuate the acute effects of exercise.

Experimental measures

Arterial stiffness (AS). All measurements commenced after 10 minutes of supine rest and were executed by the same operator at a similar day time (between 6 AM and 7 AM) with the subject placed in the supine position. Characteristic impedance (Z_c), an intrinsic marker of AS, was determined by the ratio of pulse pressure and forward peak blood flow velocity measured at the proximal descending aorta with duplex ultrasonography (Mindray M7, China), conforming to the water hammer equation.[10] This measurement does not exclude the effects of wave reflection, thus it might also comprise AS elements contributing to the augmentation pressure. Aortic reverse peak blood flow velocity/forward peak blood flow velocity ratio (aortic R/F ratio) was also calculated.[11] CD was assessed by means of high-resolution ultrasonography equipped with a 7 MHz linear array probe (Mindray M7) in the right common carotid artery according to established guidelines.[10] CD was determined using the following formula:

$$CD = \left(C_{Sdiam} - C_{Ddiam}\right) / \left(\left(SBP - DBP\right) \times C_{Ddiam}\right)$$

Where C_{Sdiam} and C_{Ddiam} are carotid systolic and diastolic diameters, while SBP and DBP are systolic and diastolic blood pressures, respectively. Heart rate and brachial blood pressure were measured on the left arm with an automated system (Dinamap, GE Medical Systems).

Maximal oxygen consumption (VO2max). Maximal oxygen consumption (VO_{2max}) was determined using cycle ergometry (Monark E839, Sweden) with continuous measurements of VO_2 through an online gas collection system (Innocor M400, Innovision, Denmark). The test started with a warm-up period of 5 minutes at a workload of 50–75 W, followed by 5 minutes at 100–130 W. Thereafter, the workload was increased by 25 W every minute until voluntary exhaustion with a pedal frequency >50 revolutions per minute. The highest 30-second average value was taken as the VO_{2max} provided that standard criteria were fulfilled.[12]

Exercise training

All individuals underwent 24 × 60 minutes supervised cycle ergometry (Monark E839, Sweden) sessions in our laboratory for 8 weeks. Training intensity was similar in relative terms for each individual, gradually increasing along the ET program from 50 to 70% of maximal power output obtained during the incremental exercise test at baseline (week 0), subsequently updated at mid-intervention (week 4).

Statistical analysis

All statistical analyses were performed using IBM SPSS v. 20 (Chicago, IL) software package. One-way repeated measures analysis of variance was used to determine the impact of ET on study variables. The influence of sex was evaluated by 2-way repeated measures analysis of variance. Data are reported as mean ± SD. A 2-tailed P value <0.05 was considered significant.

RESULTS

VO_{2max} increased with ET (+12.3 ± 8.9% from week 0 to week 8, $P < 0.001$, P for linear trend <0.001). Cardiovascular variables are presented in Table 1. Systolic blood pressure (SBP) and pulse pressure augmented from week 0 to week 8 (+7.3 ± 3.9%, $P = 0.019$, P for linear trend <0.001; +26.2 ± 21.3%, $P = 0.005$, P for linear trend = 0.002, respectively). A linear decreasing trend was observed for aortic forward peak blood flow velocity ($P = 0.012$). Figure 1 illustrates the effect of ET on aorta Z_c, which increased from week 0 to week 8 (+38.3 ± 29.4%, $P = 0.003$, P for linear trend = 0.002). Moreover, a linear decreasing trend was noted for CD ($P = 0.016$). Sex did not influence the impact of ET on exercise capacity and hemodynamic variables.

DISCUSSION

The purpose of the present investigation was to determine the impact of ET on AS in central elastic arteries of previously untrained healthy young individuals. To this end, aorta and carotid distensile characteristics were assessed prior to and across 8 weeks of ET. In keeping with the largest (cross-sectional) study in healthy young individuals,[3] neither aorta nor carotid AS were improved by ET, despite substantial increases in aerobic exercise capacity were manifest.

This is the first study to pinpoint the time course of central AS adaptations during an exercise training intervention. The finding of gradual increases in AS in the aorta and carotid arteries contrasts with 2 interventions showing decreased central AS, albeit comparable increases in exercise capacity after similar cycle ergometer ET programs lasting 4 and 8 weeks in healthy young individuals.[4,6] These studies, however, did not report at what time point the postinterventions assessments were performed.[4,6] This involves an important methodological point since the measured impact of ET on AS, particularly by *via* discrete time points, is prone to confounding effects inherent to acute exercise. Indeed, central

Table 1. Cardiovascular variables prior to (week 0) and during 8 weeks of endurance training

	Training period				*P* value	
	Week 0	Week 2	Week 4	Week 8	ANOVA	Linear trend
HR (bpm)	59.50 ± 7.03	59.33 ± 8.86	55.56 ± 8.95	55.89 ± 8.27	0.230	**0.016**
SBP (mm Hg)	109.9 ± 9.8	109.0 ± 11.2	114.1 ± 10.7	117.9 ± 10.7[12]	**0.019**	**<0.001**
DBP (mm Hg)	68.4 ± 5.4	65.3 ± 6.3	66.7 ± 5.5	66.6 ± 6.2	0.366	0.438
PP (mm Hg)	41.5 ± 8.9	43.7 ± 8.1	47.4 ± 6.0	51.3 ± 9.1[12]	**0.005**	**0.002**
Aortic FPV ($cm \cdot s^{-1}$)	119.6 ± 16.9	114.3 ± 14.2	108.1 ± 11.5[1]	107.6 ± 10.5[1]	0.062	**0.012**
Aortic RPV ($cm \cdot s^{-1}$)	49.6 ± 6.4	47.1 ± 6.2	49.0 ± 4.2	49.1 ± 6.8	0.818	0.967
Aortic R/F ratio	42.2 ± 8.5	41.4 ± 4.8	45.8 ± 6.6	46.4 ± 10.2	0.258	0.057
C_{Sdiam} (mm)	6.62 ± 0.30	6.78 ± 0.33[1]	6.67 ± 0.38	6.62 ± 0.28	0.096	0.587
C_{Ddiam} (mm)	6.08 ± 0.27	6.24 ± 0.29	6.16 ± 0.25	6.08 ± 0.31[2]	0.058	0.730
$C_{\Delta diam}$ (mm)	0.543 ± 0.128	0.533 ± 0.187	0.509 ± 0.195	0.538 ± 0.099	0.872	0.706
CD ($10^3 \cdot cm^2 \cdot dyne^{-1}$)	2.235 ± 0.677	2.039 ± 0.937	1.736 ± 0.612[1]	1.767 ± 0.388[1]	0.191	**0.016**

Data are mean ± SD. Superscript numbers (1, 2, 3) correspond to differences ($P < 0.05$) between training periods and respectively refer to 'week 0', 'week 2', and 'week 4'. Significant *P* values ($P < 0.05$) are presented in bold.

Abbreviations: ANOVA, analysis of variance; C_{Ddiam}, carotid diastolic diameter; CD, carotid distensibility; C_{Sdiam}, carotid systolic diameter; $C_{\Delta diam}$, change in carotid diameter; DBP, diastolic blood pressure; FPV, forward peak blood flow velocity; HR, heart rate; PP, pulse pressure; R/F ratio, reverse peak blood flow velocity/forward peak blood flow velocity ratio; RPV, reverse peak blood flow velocity; SBP, systolic blood pressure.

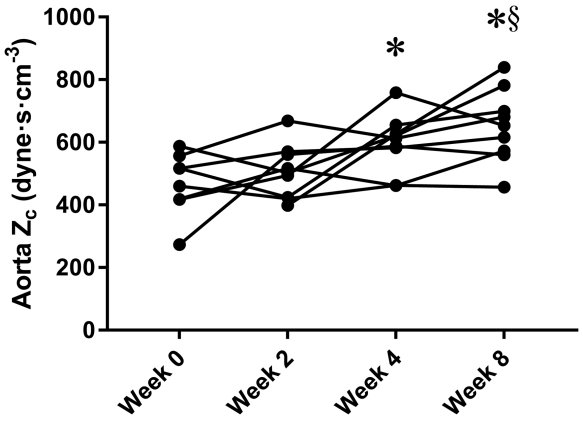

Figure 1. Aorta characteristic impedance (Z_c) prior to (week 0) and during 8 weeks of endurance training. *P* for linear trend = 0.002. *Significantly different ($P < 0.05$) from week 0. §Significantly different ($P < 0.05$) from week 2.

arterial distensibility is transitorily enhanced after a cycling bout in healthy individuals.[13,14] In an effort to limit this and other lifestyle confounding factors, herein the measurements commenced ≥48 hours following the last exercise session and furthermore, all individuals slept in the laboratory the night anterior to each evaluation. Such standardization may have contributed to the relatively uniform individual responses throughout the ET intervention (Figure 1). While further research is needed to comprehensively identify arterial phenotypic modifications with ET, the current study indicates that healthy central elastic arteries are not amendable to ET-induced "de-stiffening" effects.

The question arises as to which mechanism(s) underlie the observed increases in AS. In this regard, arterial lumen dimensions were unaltered (except at week 2) whereas SBP augmented during the 8-week ET intervention (Table 1). In parallel, there was a linear decreasing trend for heart rate, suggesting a concomitant increase in stroke volume, a common early adaptation to ET that was not measured in this study.[8] Whilst speculative, "supra-optimal" remodeling in elastic arteries facilitating the accommodation of enhanced stroke volume may require longer/chronic ET stimuli, as experienced by young endurance athletes exhibiting enlarged central arterial diameters and similar AS and brachial SBP vs. age-matched sedentary individuals.[3] In the absence of arterial lumen enlargement with increased stroke volume, SBP may increase if there is no "room" for AS improvement, concurring with the ultimate structural constraint of arterial distensibility.[15] In addition, lower heart rate may be accompanied by prolonged ventricular ejection time enabling the reflected pulse pressure wave to appear in late systole, thereby increasing SBP.[16] Of note, we measured peripheral (brachial) but not central blood pressure, the former being augmented due to the phenomenon of SBP amplification from central to peripheral arteries.[17] The results of this study could be confounded if ET modifies SBP amplification, which seems unaffected according to cross-sectional comparisons.[18] Finally, the current investigation demonstrates that improvements in central arterial distensibility may not be indispensable for increases in aerobic exercise capacity,[8,19] suggesting that AS does not limit convective oxygen delivery under normal healthy conditions. Nonetheless, given the small number of study subjects, our conclusions should be taken with caution.

CONCLUSION

This study provides evidence that AS in central elastic arteries is not reduced by an otherwise successful ET intervention in healthy young individuals. These findings are consistent with the notion that when arterial distensibility is at optimal levels, as in healthy arteries of young individuals, improvements do not occur possibly due to a ceiling effect.

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DISCLOSURE

The authors declared no conflict of interest.

REFERENCES

1. van Sloten TT, Schram MT, van den Hurk K, Dekker JM, Nijpels G, Henry RM, Stehouwer CD. Local stiffness of the carotid and femoral artery is associated with incident cardiovascular events and all-cause mortality: the Hoorn study. *J Am Coll Cardiol* 2014; 63:1739–1747.
2. Montero D, Vinet A, Roberts CK. Effect of combined aerobic and resistance training versus aerobic training on arterial stiffness. *Int J Cardiol* 2015; 178:69–76.
3. Tanaka H, Dinenno FA, Monahan KD, Clevenger CM, DeSouza CA, Seals DR. Aging, habitual exercise, and dynamic arterial compliance. *Circulation* 2000; 102:1270–1275.
4. Cameron JD, Dart AM. Exercise training increases total systemic arterial compliance in humans. *Am J Physiol* 1994; 266:H693–H701.
5. Currie KD, Thomas SG, Goodman JM. Effects of short-term endurance exercise training on vascular function in young males. *Eur J Appl Physiol* 2009; 107:211–218.
6. Kakiyama T, Sugawara J, Murakami H, Maeda S, Kuno S, Matsuda M. Effects of short-term endurance training on aortic distensibility in young males. *Med Sci Sports Exerc* 2005; 37:267–271.
7. Tinken TM, Thijssen DH, Black MA, Cable NT, Green DJ. Time course of change in vasodilator function and capacity in response to exercise training in humans. *J Physiol* 2008; 586:5003–5012.
8. Montero D, Cathomen A, Jacobs RA, Flück D, de Leur J, Keiser S, Bonne T, Kirk N, Lundby AK, Lundby C. Haematological rather than skeletal muscle adaptations contribute to the increase in peak oxygen uptake induced by moderate endurance training. *J Physiol* 2015; 593:4677–4688.
9. Montero D, Breenfeldt-Andersen A, Oberholzer A, Haider T, Goetze JP, Meinild-Lundby AK, Lundby C. Erythropoiesis with endurance training: dynamics and mechanisms. *Am J Physiol Regul Integr Comp Physiol* 2017; 312:R894–R902.
10. O'Rourke MF, Staessen JA, Vlachopoulos C, Duprez D, Plante GE. Clinical applications of arterial stiffness; definitions and reference values. *Am J Hypertens* 2002; 15:426–444.
11. Hashimoto J, Ito S. Aortic stiffness determines diastolic blood flow reversal in the descending thoracic aorta: potential implication for retrograde embolic stroke in hypertension. *Hypertension* 2013; 62:542–549.
12. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, Forman D, Franklin B, Guazzi M, Gulati M, Keteyian SJ, Lavie CJ, Macko R, Mancini D, Milani RV; American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Interdisciplinary Council on Quality of Care and Outcomes Research. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation* 2010; 122:191–225.
13. Kingwell BA, Berry KL, Cameron JD, Jennings GL, Dart AM. Arterial compliance increases after moderate-intensity cycling. *Am J Physiol* 1997; 273:H2186–H2191.
14. Sugawara J, Komine H, Miyazawa T, Imai T, Ogoh S. Influence of single bout of aerobic exercise on aortic pulse pressure. *Eur J Appl Physiol* 2015; 115:739–746.
15. Sugawara J, Otsuki T, Maeda S, Tanabe T, Kuno S, Ajisaka R, Matsuda M. Effect of arterial lumen enlargement on carotid arterial compliance in normotensive postmenopausal women. *Hypertens Res* 2005; 28:323–329.
16. Albaladejo P, Copie X, Boutouyrie P, Laloux B, Déclère AD, Smulyan H, Bénétos A. Heart rate, arterial stiffness, and wave reflections in paced patients. *Hypertension* 2001; 38:949–952.
17. Herbert A, Cruickshank JK, Laurent S, Boutouyrie P; Reference Values for Arterial Measurements Collaboration. Establishing reference values for central blood pressure and its amplification in a general healthy population and according to cardiovascular risk factors. *Eur Heart J* 2014; 35:3122–3133.
18. Knez WL, Sharman JE, Jenkins DG, Coombes JS. Central hemodynamics in ultra-endurance athletes. *J Sci Med Sport* 2008; 11:390–395.
19. Montero D, Diaz-Cañestro C, Keiser S, Lundby C. Arterial stiffness is strongly and negatively associated with the total volume of red blood cells. *Int J Cardiol* 2016; 221:77–80.