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Involvement of Endothelin-1 in Habitual Exercise-Induced Increase in Arterial Compliance

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Abstract

Aim—Habitual aerobic exercise results in a significant increase in central arterial compliance. Endothelin-1 (ET-1) is a potent endothelium-derived vasoconstrictor peptide and could play a role in mediating the habitual aerobic exercise-induced increase in central arterial compliance. The aim of the present study was to examine whether ET-1 involves in the mechanisms underlying the increase in central arterial compliance to aerobic exercise training.

Methods—Seven apparently healthy middle-aged and older (60±3 yr) adults underwent systemic endothelin-A/B ($ET_{A/B}$)-receptor blockade (500 mg of Tracleer) before and after 12 weeks of aerobic exercise training (70±1% of maximal heart rate, 44±2 min/day, 4.4±0.1 days/week).

Results—Basal carotid arterial compliance (via simultaneous B-mode ultrasound and arterial applanation tonometry on the common carotid artery) increased significantly after exercise training. Resting plasma ET-1 concentration decreased significantly after the exercise training. Before the exercise intervention, carotid arterial compliance increased significantly with the administration of $ET_{A/B}$-receptor blockade. After the training, however, increases in carotid arterial compliance previously observed with the $ET_{A/B}$-receptor blockade before the training were abolished.

Conclusions—Regular aerobic exercise training enhances central arterial compliance in middle-aged and older humans. The increase in arterial compliance was associated with the corresponding reduction in plasma ET-1 concentration as well as the elimination of ET-1 mediated vascular tone. These results suggest that reductions in ET-1 may be an important mechanism underlying the beneficial effect of exercise training on central artery compliance.

Keywords

endothelium; exercise training; elasticity

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CONFLICT OF INTEREST

We have no financial, consultant, institutional and other relationships that might lead to bias or a conflict of interest.

INTRODUCTION

As illustrated by the William Osler's axiom that “man is as old as his arteries” (Osler 1892), a hallmark feature of cardiovascular aging is the stiffening of large elastic arteries (Lakatta & Levy 2003). Arterial stiffening impairs the artery's ability to buffer and cushion the pulsation of blood pressure and flow and contributes to a variety of diseases (hypertension, coronary ischemia, etc.) that are common to the elderly (Blacher *et al.* 1999, Laurent *et al.* 2001). Aerobic exercise training has emerged as one of the most effective means to improve the elastic property of arteries (Cameron & Dart 1994, Tanaka *et al.* 2000, Kakiyama *et al.* 2005). However, the physiological mechanisms underlying the destiffening effects of aerobic exercise training remain unclear.

Chronic increases in basal vascular tone have been implicated in the pathogenesis of a age-associated vascular disease, including arterial stiffening (Tanaka & Safar 2005). The age-related elevation in vascular tone is mediated not only by chronically elevated sympathetic vasoconstrictor tone but also by the endothelial function (Dobrin & Rovick 1969). In addition to relaxing factors such as NO, the vascular endothlium also synthesizes and releases vasoconstricting factors, including endothelin-1 (ET-1) (Yanagisawa *et al.* 1988). ET-1 is the most potent vasoconstrictor peptide secreted by vascular endothelial cells (Yanagisawa *et al.* 1988). Aging is associated with the increases in both plasma ET-1 concentrations (Maeda *et al.* 2003) and ET-1 mediated vasoconstrictor (Van Guilder *et al.* 2007) even in healthy subjects. Moreover, synthesis and release of ET-1 peptide is elevated in cultured endothelial cells extracted from the aorta of older adults compared with cells from younger adults (Kumazaki *et al.* 1994).

Considering our previous findings that plasma ET-1 concentration decreases with aerobic exercise training (Maeda *et al.* 2001, 2003), it is reasonable to hypothesize that endogeneous ET-1 may be involved in the mechanisms underlying the increase in central arterial compliance to aerobic exercise training. However, the direct evidence to support such hypothesis was lacking. Accordingly, the present investigation was undertaken to determine the effects of acute endothelin-A/B ($ET_{A/B}$)-receptor blockade on arterial compliance before and after aerobic exercise training in healthy middle-aged and older humans.

METHODS

Subjects

Seven sedentary but apparently healthy middle-aged and older adults (60±3 yr, 2 men and 5 postmenopausal women) were studied. Candidates who were current smokers or smoked in the past 2 yr, who took medications (including hormone replacement therapy), or who had significant intima-media thickening (>1.0 mm), plaque formation, and/or other characteristics of atherosclerosis (e.g., ankle-brachial index <0.9) were excluded. None of the subjects had engaged in regular physical activity (>2/week) in the past 1 yr, which was verified through the questionnaire. All subjects had no apparent cardiovascular disease as assessed by medical history and physical examination. This study was reviewed and approved by the Institutional Review Board at the University of Tsukuba. All potential risks and procedures of the study were explained to the subjects, and they gave their written informed consent to participate in the study.

Experimental Design

All measurements were performed after an abstinence of caffeine and an overnight fast. Subjects were studied under supine resting conditions in a quiet, temperature-controlled room (24-26°C). All the post-training measurements were performed at least 48 h after the last exercise bout to avoid the acute (i.e., residual) effect of exercise on major dependent

variables. After the subject had 15 min of supine rest, baseline measurements were made. After this, a bolus (500 mg) of $ET_{A/B}$-receptor blockade (Tracleer, Actelion Japan, Tokyo, Japan) was administered orally. The measurements were performed 60 min and 120 min after the $ET_{A/B}$-receptor blockade. The particular dose of 500 mg of Tracleer was chosen based on the comprehensive pharmacological analyses conducted by Weber *et al.* (1996) who examined the dose-response issue of an acute administration of $ET_{A/B}$-receptor antagonist in healthy human subject. Although plasma concentrations of the antagonist increased as oral dose was increased from 3 mg to 2,400 mg, there were no significant differences in the magnitude of blood pressure reduction induced by different doses of Bosentan (approximately 5 mmHg). Additionally, in a study involving chronic treatment of bosentan, i.e., Tracleer, a significant reduction in blood pressure was achieved with a daily dose of ≥500 mg in patients with mild-to-moderate essential hypertension (Krum *et al.* 1998).

Carotid Artery Compliance

The combination of ultrasound imaging of the common carotid artery with simultaneous applanation tonometry of the contralateral carotid artery was performed to obtain carotid artery compliance as previously described (Tanaka *et al.* 2000, Miyachi *et al.* 2004). A longitudinal image of the carotid artery was measured with a duplex ultrasound machine (180II, SonoSite, Bothell, WA) equipped with a high-resolution multi-frequency linear-array transducer (axial resolution of 0.06 mm). These images were recorded on a digital videotape for later off-line analysis. Arterial diameter was determined by a perpendicular measurement from the media/advantitia interface of the near wall to the lumen/intima interface of the far wall of the vessel. Three measurements of arterial lumen diameter were taken per frame and averaged. Data reported are the time averages of ≥10 measurements for all variables. Carotid arterial pressure waveforms were obtained with arterial applanation tonometory incorporating an array of 15 micropiezoresistive transducers (formPWV/ABI, Colin Medical Technology, Komaki, Japan) (Cortez-Cooper *et al.* 2003) and calibrated by equating the carotid mean arterial and diastolic blood pressure to the brachial values (Armentano *et al.* 1995). Arterial compliance was calculated using the equations: $[(D_1\text{-}D_0)/D_0]/[2*(P_1\text{-}P_0)*\pi*D_0]$ where D_1 and D_0 are the maximal and minimum arterial diameters and P_1 and P_0 are the highest and lowest blood pressures (Tanaka *et al.* 2000, Miyachi *et al.* 2004). At each time point, averages of 10 cardiac cycles were analyzed. In order to exclude inter-investigator variability, one investigator, who was blinded to the time points, analyzed all ultrasound images and blood pressure waveform. The day-to-day CVs for carotid artery diameter, pulse pressure, and arterial compliance were 2±1, 7±3, and 5±2%, respectively.

Arterial Blood Pressure and Ankle-Brachial Index

Brachial and ankle arterial blood pressure and ankle-brachial index were also measured with the automated device (formPWV/ABI, Colin Medical Technology) (Cortez-Cooper *et al.* 2003). An automatic oscillometric blood pressure device was used to eliminate potential investigator bias associated with the auscultation.

Body Fatness

Percent body fat was determined by bioelectric impedance (HBF-357, Omron Healthcare, Tokyo, Japan) as previously described (Miyachi *et al.* 2004).

Blood Samples

A blood sample was collected from the antecubital vein using venipuncture after an overnight fast. Plasma concentrations of glucose, lipids, and lipoproteins were determined by use of the standard enzymatic technique as previously described (Tanaka *et al.* 1998).

Plasma ET-1 concentration was determined by using a sandwich-EIA Kit (Immuno-Biological Laboratories, Fujioka, Japan) as previously described (Maeda *et al.* 2001, 2003). Plasma samples from each subject before and after the training intervention were analyzed in the same assay run.

Aerobic Capacity

All subjects underwent an incremental cycle exercise test (after 2 min at 20 W, with 15 W increases every 1 min) until they reached 85% of the age-predicted maximal heart rate (208-age*0.7) (Tanaka *et al.* 2001). Heart rate (via ECG) was measured throughout the protocol. Work rate corresponding to 85% of the age-predicted maximal heart rate ($PWC_{85\%}$) was used as a measure of aerobic capacity. $PWC_{85\%}$ has been shown to correlate well with directly measured maximal oxygen consumption (Miyashita *et al.* 1985).

Aerobic Exercise Training Intervention

Subjects underwent aerobic exercise training 4-5 days per week (walk/jog, 2 supervised and additional home-based trainings) for 12 wk. The prescribed duration and intensity of the training were 30-45 min/day and 65-75% of their individual maximum heart rate. Adherence to the exercise prescription was documented through the use of Polar heart rate monitors and physical activity logs. The actual mean heart rate during the exercise training was 70±1% of their individual maximal heart rate, and the actual frequency and duration of the exercise training were 4.4±0.1 days/wk and 44±2 min/day, respectively.

Statistical Analyses

Student's *t*-test for paired values was used to compare dependent variables before and after exercise training. ANOVA and MANOVA with repeated measures were used to determine the effects of exercise training intervention and systemic $ET_{A/B}$-receptor blockade on carotid arterial compliance and other hemodynamic variables. ANCOVA was performed to compare responses of arterial compliance to systemic $ET_{A/B}$-receptor blockade before and after exercise intervention after taking account into the influence of corresponding changes in mean arterial pressure as a covariate. All data are reported as mean±SEM. Statistical significance was set a priori at $P<0.05$.

RESULTS

There were no significant changes in body mass, adiposity, and plasma concentrations of cholesterol and glucose with the exercise training intervention (Table 1). $PWC_{85\%}$, a measure of aerobic capacity, increased significantly after the exercise training intervention. Carotid diastolic diameter at rest was not affected by the exercise training intervention. Brachial and carotid systolic blood pressure and carotid pulse pressure at rest decreased significantly after exercise training, whereas brachial diastolic blood pressure, and heart rate at rest did not change (Table 2). The resting plasma concentration of ET-1 significantly decreased after exercise training (Fig. 1).

There were no significant changes in heart rate and brachial pulse pressure with $ET_{A/B}$-receptor blockade before and after the exercise training (Table 2). Brachial systolic and diastolic blood pressures, carotid systolic blood pressure, and carotid pulse pressure significantly decreased with the administration of $ET_{A/B}$-receptor antagonist both before and after the exercise training, but the magnitude of these changes were not different before and after the exercise training.

Basal (resting) carotid arterial compliance increased significantly after exercise training (Table 2). Before the exercise intervention, carotid arterial compliance increased

significantly with $ET_{A/B}$-receptor blockade (+23.6±3.8% and +17.3±6.2%; 60 min and 120 min after the $ET_{A/B}$-receptor blockade, respectively; Fig. 2). After the exercise intervention, however, carotid arterial compliance did not change significantly after the administration of $ET_{A/B}$-receptor antagonist (+0.4±5.9% and −2.5±3.6%; 60 min and 120 min after the $ET_{A/B}$-receptor blockade, respectively; Fig. 2). Responses of carotid arterial compliance to the $ET_{A/B}$-receptor blockade were significantly greater before than after the exercise intervention. These differential responses in arterial compliance before and after exercise training remained statistically significant ($P<0.05$) even after the influence of corresponding changes in mean arterial pressure was accounted for using ANCOVA. Additionally, changes in arterial compliance were not significantly related to the corresponding changes in mean arterial blood pressure.

DISCUSSION

Using the pharmacological approach, we determined whether ET-1 was involved in the physiological mechanism underlying the influence of regular aerobic exercise on central arterial compliance. We found that regular aerobic exercise training increased central arterial compliance in middle-aged and older adults. The improvement in arterial compliance was associated with decreased plasma ET-1 concentration. Additionally, increases in central artery compliance observed with the $ET_{A/B}$-receptor blockade before the exercise intervention were abolished after the exercise training. These results suggest that endogenous ET-1 plays a role, at least in part, in the mechanism underlying the habitual exercise-induced increase in central arterial compliance.

It is well established that increased vascular tone of vascular smooth muscle cells decrease arterial compliance. Numerous local and neurohumoral factors could influence the vasoconstrictor tone exerted by its smooth muscle cells. Among them, as the most potent vasoconstrictor peptide released by the endothelial cells (Yanagisawa *et al.* 1988, Rubanyi & Polokoff 1994), ET-1 has been implicated in the pathogenesis of arterial stiffening (McEniery *et al.* 2003, Vuurmans *et al.* 2003). McEniery *et al.* (2003) reported that the administration of ET-1 increases arterial pulse wave velocity (PWV), a traditional index of regional arterial stiffness, and treatment with ET receptor antagonist reduces PWV. In the present study, we demonstrated that directly-measured central arterial compliance increased with $ET_{A/B}$-receptor blockade before the exercise training intervention. Taken together, these results indicate that endogenously-generated ET-1 contributes to the regulation of arterial stiffness and arterial compliance in humans.

After 3 months of regular aerobic exercise, we observed a significant decline in plasma ET-1 concentration in middle-aged and older humans. This is consistent with our previous exercise training studies in young adults (Maeda *et al.* 2001). However, plasma ET-1 concentration may not provide a good measure of ET-1 activity in the tissue. For example, in deoxycorticosterone acetate-salt hypertensive rats, the tissue ET-1 concentration in the blood vessels is higher than that in normotensive rats without a change in plasma ET-1 levels (Lariviere *et al.* 1993). Moreover, in rats with cardiac hypertrophy induced by aortic banding, tissue ET-1 concentration in the heart is higher than that in control sham-operated rats without a change in plasma ET-1 levels (Yorikane *et al.* 1993). Therefore, the present investigation using the pharmacological blockade of ET receptors was needed to determine the involvement of ET-1 in modifying central arterial compliance.

We found that before the exercise training intervention, arterial compliance increased significantly with the administration of $ET_{A/B}$-receptor blockade. After the exercise training, however, such increases in arterial compliance were abolished as there was no statistically significant increase in carotid artery compliance with the ET receptor blockade. These

results indicate that chronic restraint placed on large elastic arteries by ET-1 was reduced with aerobic exercise training, resulting in improved arterial compliance.

There are several limitations of this study that should be emphasized. First, no test was conducted to confirm completeness of $ET_{A/B}$-receptor blockade. Second, in order to target the compliance of "central (cardiothoracic)" arteries, where cardiac ejection is effectively buffered, systemic, rather than local, administration of drug was used in this study. Third, the present study only deals with the effects of ET-1. It is likely that other vasodilators could produce a reduction in arterial compliance after exercise training. Indeed, using the gene microarray analyses of rat aorta, we demonstrated that prostaglandin EP2 receptor (PGE-EP2R), prostaglandin EP4 receptor (PGE-EP4R), C-type natriuretic peptide (CNP), and endothelial nitric oxide synthase (eNOS) genes were differentially expressed after a period of aerobic exercise training (Maeda *et al*. 2005). Fourth, a lack of appropriate control condition (e.g., sedentary control group and control infusion) and a small sample size are clearly limitations of this study.

In conclusion, the present study has demonstrated that regular aerobic exercise increased central arterial compliance in middle-aged and older adults. The improvements in arterial compliance were associated with a reduction in plasma ET-1 concentration. Moreover, the increase in central arterial compliance observed with the ET-receptor blockade before the exercise intervention was eliminated after the exercise training intervention. These results indicate that endogenous ET-1 participates in the mechanism underlying the beneficial influence of regular aerobic exercise on central arterial compliance.

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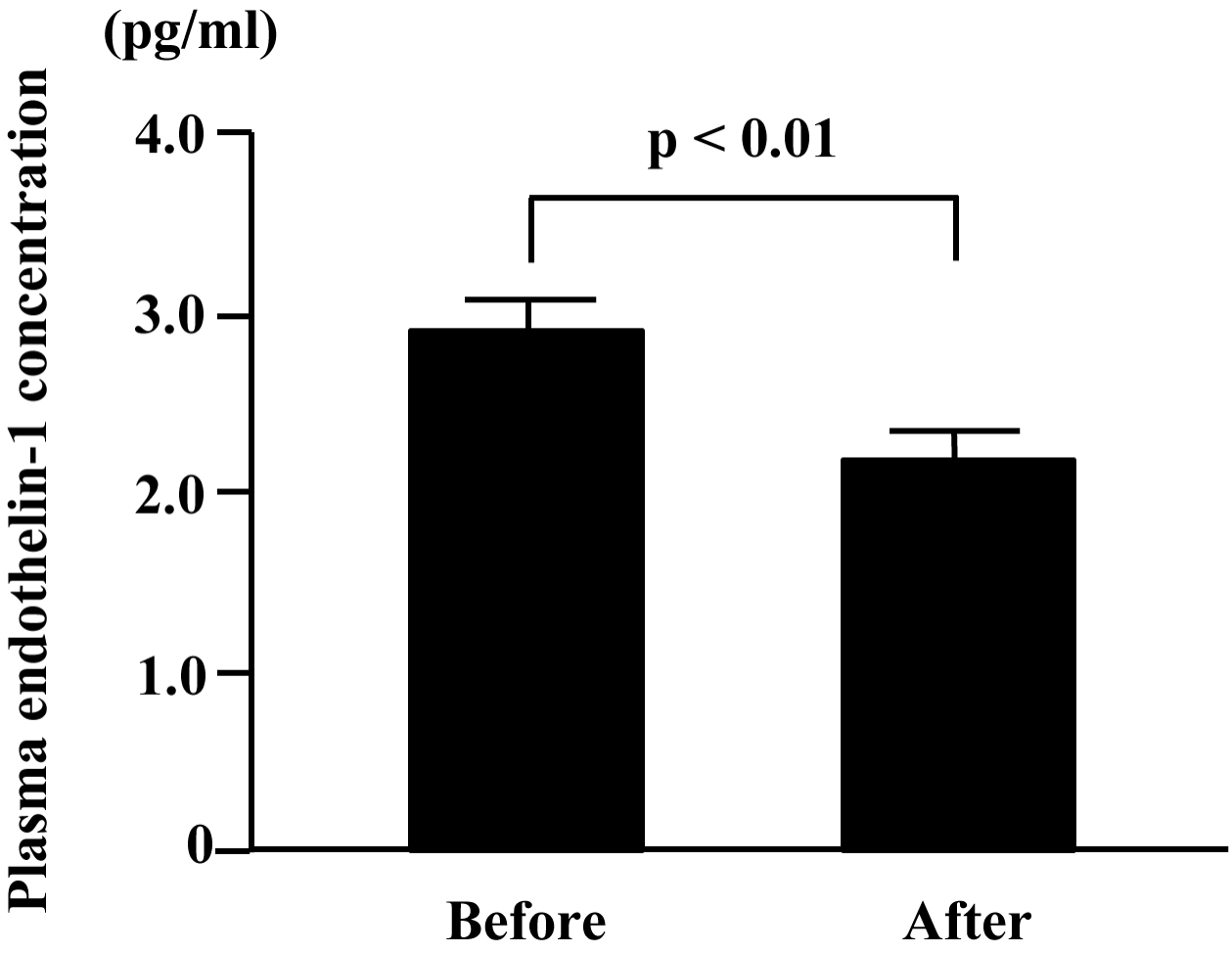

Figure 1.
Venous plasma concentration of endothelin-1 before and after 3 mo of regular aerobic exercise training in healthy middle-aged and older adults. Data are mean±SEM.

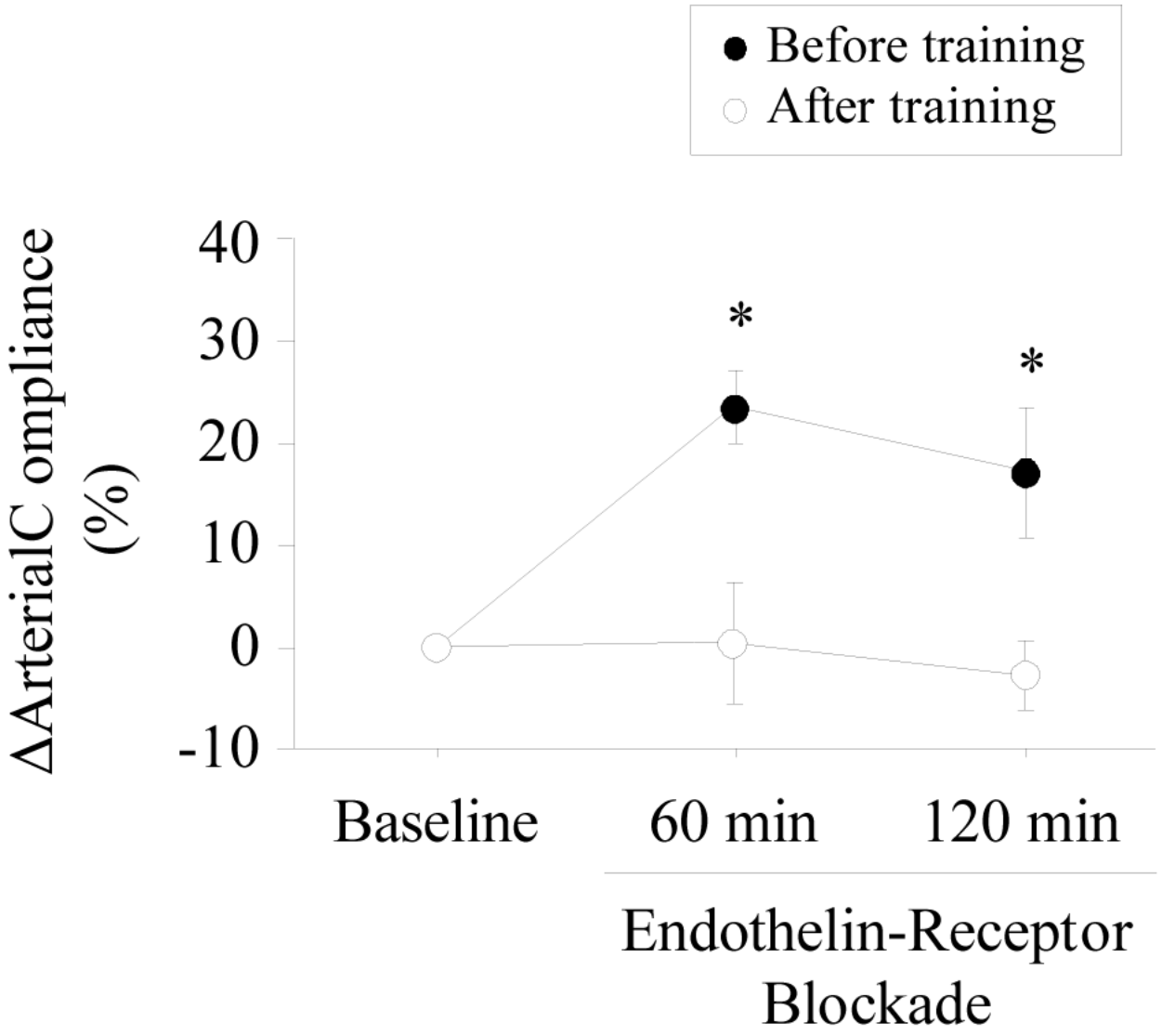

Figure 2.
Changes in carotid artery compliance before and after $ET_{A/B}$-receptor blockade. Data are mean±SEM. *P<0.05 vs. after exercise training.

TABLE 1

Selected Subject Characteristics

	Before Training	After Training
Age, years	60 ± 3	…
Height, cm	161 ± 2	…
Body mass, kg	60 ± 4	60 ± 4
Body mass index, kg/m^2	22.9 ± 1.2	23.1 ± 1.2
Body fat, %	28 ± 2	28 ± 2
Total cholesterol, mmol/L	5.8 ± 0.3	5.4 ± 0.2
HDL-cholesterol, mmol/L	1.6 ± 0.1	1.6 ± 0.2
LDL-cholesterol, mmol/L	3.6 ± 0.2	3.2 ± 0.2
Triglyceride, mmol/L	1.3 ± 0.3	1.3 ± 0.3
Blood glucose, mmol/L	5.2 ± 0.1	5.4 ± 0.2
Carotid diastolic diameter, mm	5.9 ± 0.2	6.0 ± 0.3
Ankle-brachial index	1.18 ± 0.03	1.18 ± 0.03
$PWC_{85\%}$, watt	104 ± 11	114 ± 11 *

Data are mean±SEM.

$PWC_{85\%}$=Physical work capacity corresponding to 85% of the age-predicted maximal heart rate.

* P<0.05 vs. before training.

TABLE 2

Hemodynamic changes in response to endothelin receptor blockade

			Endothelin-Receptor Blockade	
		Baseline	**60 min**	**120 min**
Heart rate, beat/min	Before	61 ± 4	60 ± 4	61 ± 4
	After	59 ± 5	58 ± 4	59 ± 5
Brachial SBP, mmHg	Before	130 ± 8	119 ± 8 †	118 ± 6 †
	After	124 ± 6 *	121 ± 5	115 ± 6 †
Brachial DBP, mmHg	Before	77 ± 4	71 ± 4 †	69 ± 4 †
	After	74 ± 4	71 ± 4 †	67 ± 4 †
Brachial MAP, mmHg	Before	98 ± 6	88 ± 5 †	87 ± 5 †
	After	94 ± 5	90 ± 4	89 ± 5
Brachial PP, mmHg	Before	54 ± 5	48 ± 4	48 ± 4
	After	50 ± 4	50 ± 2	48 ± 3
Carotid SBP, mmHg	Before	119 ± 8	108 ± 7 †	108 ± 6 †
	After	114 ± 6 *	110 ± 5	105 ± 6 †
Carotid PP, mmHg	Before	43 ± 5	37 ± 4 †	38 ± 4 †
	After	39 ± 4 *	39 ± 3	38 ± 4 †
Carotid arterial compliance, $mm^2/mmHg$	Before	0.072 ± 0.006	0.089 ± 0.008 †	0.084 ± 0.007 †
	After	0.080 ± 0.008 *	0.080 ± 0.009	0.077 ± 0.006

Data are mean±SEM. SBP, systolib blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure.

* P<0.05 vs before training.

† P<0.05 vs. baseline.