The Influence of Central Arterial Compliance on Cerebrovascular Hemodynamics: Insights from Endurance Training Intervention

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Running title: Central arterial compliance and cerebral hemodynamics

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Normally, central elastic arteries (e.g. aorta and common carotid artery) effectively buffer cardiac pulsation-induced flow/pressure fluctuations. With advancing age, arterial stiffening deteriorates this function and produces the greater cerebral hemodynamic pulsatility which impacts vulnerable brain tissue. It is well known that the buffering function of the central artery is improved by regular aerobic exercise, but the influence of endurance training on the pulsatile component of cerebral hemodynamics remains poorly understood. To characterize the functional role of the central artery at the heart-brain hemodynamic connection comprehensively, we assessed relations among the endurance training-induced changes in the left ventricle (LV), carotid arterial compliance, and cerebral hemodynamics. Thirteen collegiate tennis players (20±1 yr) underwent a 16-week endurance training intervention designed for improving cardiovascular function. Expectedly, maximal oxygen uptake (VO$_{2peak}$), LV ejection velocity (via Doppler ultrasound), and the maximal rate of pressure increase of estimated aortic pressure waveform (via general transfer function) improved after the training intervention, whereas middle cerebral arterial (MCA) hemodynamics (via transcranial Doppler), such as mean and pulsatile flow velocity, remained unchanged. Carotid arterial compliance (via ultrasound and applanation tonometry) increased after the training intervention and a larger increase in carotid arterial compliance was significantly associated with the greater attenuations of pulsatile MCA velocity ($r=-0.621$) normalized by mean MCA velocity. These results suggest that the training-induced improvement of carotid artery Windkessel function might offset the expected increase in pulsatile component of cerebral perfusion induced by the enhanced LV systolic function.

**Key words:** Cerebral hemodynamics, central arterial compliance, left ventricular contractility, endurance training, pulsatile component.
INTRODUCTION

Cardiac pulsation generates intermittent blood flow and blood pressure pulsatility which could be mechanical forces to high flow and low resistance end-organs, such as the brain and kidneys. The pulsatile components of the end-organs are determined by arterial pressure and cerebrovascular resistance. Normally, these pulsatile forces are dampened by Windkessel function of central elastic arteries (e.g., aorta and carotid artery) effectively (18, 20). The impairment of this function by age- or disease-related central arterial stiffening (19, 30) leads to an increased risk of cerebral microvascular diseases (e.g., White-matter hyperintensities, Lacunar stroke) (8, 11, 30), presumably due to repeated mechanical pulsatile force (9, 16, 20, 33).

On the other hand, endurance training is associated with larger stroke volume and higher left ventricular (LV) systolic performance (6, 21). It is plausible that these cardiovascular adaptations relating to greater blood flow ejection may produce profound mechanical force at the brain. Nevertheless, to the best of our knowledge, there is little evidence indicating pathophysiological adverse effects of endurance exercise on cerebrovascular systems. Although the influence of regular aerobic exercise on pulsatile component of cerebral hemodynamics remains poorly understood, this phenomenon may be explained by the improved Windkessel function of central artery with endurance training.

The primary objective of this study was to determine the functional role of central artery at the heart-brain hemodynamic connection comprehensively. To characterize the role of central artery effectively, we applied a well-organized endurance training program including high-intensity interval training on moderately-trained collegiate tennis players and assessed their LV function, central arterial compliance, and cerebral hemodynamics. The working hypothesis of this study was that the endurance training-induced improvement of Windkessel function offset the expected increase in pulsatile cerebral blood flow (CBF)
velocity induced by the enhanced LV systolic function.

METHODS

Subjects. A total of sixteen collegiate tennis players (8 male and 8 female) participated in this interventional study. All subjects regularly engaged in specific training for tennis but had never experienced high-intensity running training (i.e., sprint interval training). All subjects were healthy, normotensive (<140/90 mmHg), nonobese (BMI<25 kg/m²), nonsmokers, free of medication, and overt chronic heart and lung diseases as assessed by medical history. None of the subjects were taking cardiovascular-acting medication. All subjects participated in mandatory tennis practices (5 days/wk, 3hrs). On average, they had been practicing tennis for 9±2 yrs. This study was reviewed and approved by the Institutional Review Board (University of Tsukuba: 25-105). Additionally, all procedures conform to the ethical guidelines of Helsinki Declaration. Informed written consent was obtained from all subjects prior to participation.

Experimental protocol. All subjects participated in a 16-week endurance training intervention designed for improving cardiorespiratory capacity. Experimental measures including echocardiography, carotid arterial echography, cerebral arterial hemodynamics, body composition, and aerobic capacity were taken before and after the intervention (within a week). In female participants, pre- and post-training measurements were scheduled to be performed at the same period of menstrual cycle by medical survey. All measurements were conducted in an environmentally controlled laboratory with a quiet, air-conditioned room (24-25 °C). Subjects abstained from caffeinated beverages, alcohol, and vigorous exercise for ≥24 hours before the study.

Upon arrival, subjects underwent body composition assessment, which was followed by supine rest more than 30 minutes and cardiovascular and cerebrovascular data
acquisition. Cardiovascular and cerebrovascular measurements were acquired in supine position. An incremental cycling test for aerobic capacity evaluation was performed after the cardiovascular and cerebrovascular measurements on the same day (before the training intervention) or the day after.

**Body composition:** Bioimpedance method (Body composition analyzer BC-118E, TANITA, Tokyo, Japan) was used to determine body composition. Specifically, body mass, percentage of body fat, lean mass, and muscle mass.

**Cardiovascular measurements:** Echocardiographic examinations were performed in the left lateral decubitus position using a ProSound F75™ system (Hitachi-Aloka Co., Tokyo, Japan) equipped with a multifrequency probe (2.5-MHz transducer). The end-diastolic interventricular septum and LV posterior wall thicknesses and LV end-diastolic and end-systolic dimensions were measured on M-mode images in the parasternal view. LV ejection fraction and LV fractional shortening were calculated by Teichholz's method (31). LV ejection velocity was obtained from the Doppler velocity time integral (VTI) via apical three chamber view. Stroke volume was computed from multiplying the VTI by diameter LV outflow tract via parasternal long axis view, as previously reported (13).

For evaluation of LV contractility, the duration of the LV ejection time (ET) and the pre-ejection period (PEP) was automatically measured from simultaneous recordings of an electrocardiogram (ECG), phonocardiogram (PCG), and applanation tonometrically carotid arterial pressure waveforms via an automated polygraph apparatus (form PWV/ABI, Omron-Colin, Kyoto, Japan) with arterial applanation tonometry incorporating an array of 15 micropiezoresistive transducers (CAP-350, Omron-Colin, Kyoto, Japan). The following phases of the cardiac cycle were measured (Figure 1): (i) the total electro-mechanical systolic interval (QS2) was measured from the onset of the QRS complex to the second heart sound; (ii) the LVET was measured from the beginning upstroke to the trough of the dicrotic notch
of the carotid arterial pressure waveforms. Then, (iii) PEP was calculated by subtracting LVET from the QS2 interval (32). Furthermore, the maximal rate of aortic pressure increase during the systolic upstroke (dP/dtMAX) was computed from the proximal aortic blood pressure synthesized from applanation tonometrically carotid arterial pressure waveforms via SphygmoCor device (Atcor Medical, Sydney, Australia) (22). Heart rate was computed from ECG.

**Carotid arterial properties:** For measurement of carotid arterial compliance, an index of Windkesel function of central conduit artery, common carotid artery echography and applanation tonometrically-pressure recording were simultaneously performed. Briefly, the B-mode longitudinal ultrasound images of the left common carotid were recorded via an ultrasound device with a high-resolution (10 MHz) linear transducer (CX50 xMATRIX; Philips Ultrasound., Bothell, WA). Arterial diameter was analyzed offline by using automatic edge-detection software (Vascular Tool 5, Medical Imaging Applications., IA, USA). The diameters were measured from the intima of the far wall to the media-adventitia of the near wall at 1 to 2 cm proximal to the bifurcation of the left common carotid artery. Carotid arterial pressure was calibrated by equating the carotid mean arterial and diastolic blood pressure to the brachial mean arterial and diastolic blood pressure. Brachial blood pressure was measured by oscillometric method using the automated polygraph apparatus (form PWV/ABI, Omron-Colin, Kyoto, Japan). The carotid arterial compliance and β-stiffness index were calculated by use of the equations:

\[
\text{Arterial compliance} = \frac{[(D_1 - D_0)/D_0]/[2(P_1 - P_0)] \times \pi \times (D_0)^2}{(\ln[P_1/P_0]/(\ln[D_1 - D_0]/D_0)}
\]

where \(D_1\) and \(D_0\) are the maximal and minimum diameters and \(P_1\) and \(P_0\) are the highest and lowest arterial pulse pressure (26, 28).

**Cerebral vascular hemodynamics:** CBF velocity was continuously measured at least five
minutes at middle cerebral artery over the temporal window ipsilateral using 2-MHz transcranial Doppler (TCD) probe (EZ Dop; DWL, Sipplingen, Germany.) To ensure the TCD recoding position was the same in each subject before and after the exercise intervention, we recorded the depth, gain, and bony landmarks at pre-measurements and used exactly the same set up for post TCD measurement, as previously recommended (2). During data collection, subjects were instructed to breathe normally. End-tidal CO$_2$ was monitored by a metabolic cart equipped with a respiratory gas analyzing system (AE280S; Minato Medical Science, Tokyo, Japan). Doppler signal was stored at 200 Hz with an acquisition system (PowerLab 8/30, ADInstruments, Colorado Springs, CO, USA) interfaced with a personal computer equipped with data acquisition software (LabChart 7.1, ADInstruments, Colorado Springs, CO, USA). Beat-to-beat time average velocity (e.g., mean velocity), systolic CBF velocity, diastolic velocity, and pulsatile (=systolic – diastolic) velocity were obtained from 1 minute stable phase by offline analysis, and the averaged values of each parameter were reported. Normalized values of systolic, diastolic, and pulsatile velocity for mean (i.e., time-averaged) velocity (%) were also obtained (%systolic CBF velocity, %diastolic CBF velocity, and %pulsatile CBF velocity, respectively) as previously reported (29). Cerebrovascular resistance index was calculated as a ratio of mean carotid arterial pressure to mean CBF velocity.

**Aerobic capacity:** Peak oxygen uptake (VO$_{\text{2peak}}$) was determined during incremental cycling to exhaustion (a 3-min at 20 W for warm-up, with a 20-W increase every minute for male, with a 10-W increase every minutes for female) using the respiratory gas analyzing system (AE280S; Minato Medical Science, Tokyo, Japan). Criteria for exercise termination was i) >90 % of maximal age-predicted heart rate, ii) >1.05 of respiratory exchange ratio, iii) >17 of leg fatigue in ratings of perceived exertion (Borg scale).

**Exercise intervention.** All subjects attended three 60-90 minute exercise training-sessions
per week for a period of 16 weeks. All training sessions were done before the mandatory
2-hour tennis practice. A strength and conditioning specialist closely supervised all exercise
sessions to ensure compliance with the prescribed exercise program. The 16-week training
program was flowed by a periodised progressive design consisting of three training phased
(Figure 2) (24). The first training phase was the “general preparatory phase” (1-4 weeks)
consisting of slow, long distance running (8-10km) with moderate intensity (i.e. jogging and
stretching to condition the body for activity). Total training volume was gradually and
progressively increased during this phase. The “specific phase” (5-10 weeks) was second.
Running intensity was increased and it included elements of lower body strength training and
short interval training (e.g., sprint and plyometric exercises). In the final “competition phase”
(11-16 week), intensity was gradually increased and training time was decreased, but total
volume was maintained. Somewhat one week before the tennis tournament, training volume
reduced to prepare. A loading structure was 2 sessions in a week were hard day and one
session in a week was easy day. During each training session, intensities were individualized
by prescribing grading paces based on VO2peak values. Subjects wore heart rate monitors (T31
coded™ transmitter, Polar, Finland) during all distance running and interval training sessions
to enable individual exercise training intensity. During long distance running and interval
training, target heart rate was aimed at 60-75% and 90% heart rate reserved. Regular
stretching and core strengthening exercise were included in the sessions to minimize injury
risk. Before the intervention, all subjects were given a lecture regarding nutritional intake for
athletes by a registered dietitian, even though diet was not examined in our study. However,
we did closely monitor and orally check their body weight, athletic performance, morning
heart rate, and sleep quality to prevent overtraining syndrome.

Statistics. Students’ paired t-test was performed to determine the impact of 16-week
endurance training intervention on variables of interest. Simple correlation analysis was
applied to determine the relations among variables of interest. All data are reported as mean ± SD. All comparisons were based on a 95% confidence limit with \( P<0.05 \) considered statistically significant.

**Results**

Three subjects withdrew from the training program due to a college-required internship. Results are therefore based on the remaining 13 subjects (7 male and 6 female) who completed the 16-week training program. Selected subjects’ characteristics before and after endurance training intervention are shown in Table 1. Following the 16-week endurance training program, total body fat was significantly decreased \( (P<0.01) \) and total lean mass and muscle mass were significantly increased \( (P<0.001) \) without changing of body mass. VO\(_{2}\)peak was significantly increased \( (P<0.01) \) and heart rate tended to decrease \( (P=0.07) \). There were no significant structural changes in LV; however, PEP was significantly increased \( (P<0.05) \) without change in LVET. Peak LV ejection velocity and dP/dt\(_{\text{MAX}}\) were significantly increased \( (P<0.05, \text{Figure 3}) \) and stroke volume tended to be increased \( (P=0.08, \text{Table 2}) \). As shown in table 2, systolic, diastolic, pulsatile, and mean CBF velocity were not changed with the training intervention. Also, the absolute values normalized by mean CBF velocity also remained unchanged (Figure 4).

Following the training intervention, CBF hemodynamics did not change significantly (Table 2 and Figure 4), but carotid arterial compliance increased \( (P<0.01, \text{Figure 5}) \) and beta-stiffness index decreased \( (P<0.01, \text{Figure 5}) \) presumably due to the increase in arterial distension \( (P<0.01, \text{Table 2}) \). Interestingly, the change in carotid arterial compliance was negatively correlated with individual change in normalized systolic \( (r=0.594, P<0.05; \text{Figure 6A}) \) and pulsatile CBF velocity \( (r=-0.610, P<0.05; \text{Figure 6B}) \) but not with the absolute values. Furthermore, the change in \( \beta \)-stiffness index significantly correlated with
Discussion

The salient findings of the present study were as follows. LV systolic performance at rest was improved following the 16-week endurance training. Nevertheless, either systolic or pulsatile CBF velocity (e.g., pulsatile component of cerebral perfusion) was not changed. Carotid arterial compliance was increased after the training intervention and such changes in carotid arterial compliance were negatively associated with the corresponding changes of systolic and pulsatile CBF velocities. These results suggest that the training-induced improvement of carotid artery Windkessel function might offset the expected increase in pulsatile component of cerebral perfusion induced by the enhanced LV systolic function. To our knowledge, this is the first study to demonstrate that the influence of central arterial compliance on the cerebrovascular hemodynamics discerned from endurance training intervention, especially pulsatile component.

The central conduit arterial wall repeatedly expands and recoils against the intermittent flow generated by cardiac pulsation, and which is changed into the continuous low-pulsatile flow and transmitted to the periphery (16, 20). The reduction of this function would be critical for high-flow, low-impedance end-organ such as the brain. Indeed, previous studies demonstrated the adverse impact of central arterial stiffening with advancing age on cerebrovascular hemodynamics including the increased pulsatility (30). To expand this notion, we attempted to manipulate not only central arterial compliance but also LV ejection by the endurance training program. We chose regularly-trained healthy young adults as promising individuals who could complete the high-intensity endurance exercise training program. Of
note, with the endurance training we provided, a previously trained tennis player could achieve the amelioration of LV systolic performance reflected by the significant increase in peak LV blood flow velocity and \( dP/dt_{\text{MAX}} \). Although evidence of exercise training-related morphological LV adaptations have been appreciated, less is known regarding the occurrence of changes in LV performance as a consequence of athletic conditioning. To date, a recent study firstly demonstrated the superior LV systolic performance in elite athletes compared to sedentary peers (6). Thus, this is the first interventional study demonstrating that exercise training elicited the improvement of LV systolic performance.

Interestingly, despite the enhanced LV systolic function, there was a lack of change in pulsatile CBF velocity following the training. These results suggest that the proximal aorta and carotid artery might dampen the enhanced pulsatile flow generated from LV effectively. We emphasized that carotid arterial compliance not only increased with the training intervention but also correlated negatively with the corresponding changes in cerebral pulsatile hemodynamics. In turn, individuals who had the greater increase in arterial compliance exhibited the more effective Windkessel function (i.e., buffering pulsatile flow).

Cerebrovascular perfusion evaluated by mean CBF velocity is the other important aspect of cerebrovascular health. Previous cross-sectional studies indicated age-related reduction in middle cerebral artery (MCA) mean blood flow velocity (1, 3). Such lower cerebrovascular perfusion would be risk for stroke (15) and Alzheimer's disease and dementia (7). Ainslie et al. (1) demonstrated the possible preventive effect of endurance exercise: well-trained men who were engaging in vigorous aerobic-endurance exercise more than 2 years exhibited higher mean MCA blood flow velocity (vs. sedentary peers) throughout the wide age range (18-79 years). On the other hand, Murrell et al. (17) indicated that such favorable effect of endurance training on cerebral perfusion at rest could not be confirmed clearly in previously inactive volunteers following the 12-week moderate-intensity
endurance training intervention though aerobic capacity and cerebrovascular reactivity to 
CO₂ were improved. Similar to this report, in the present study, MCA mean velocity was 
unchanged by the training intervention. The inconsistency with the cross-sectional study by 
Ainslie et al. (1) might be attributed to the difference in training duration. Further study using 
long-term observation should be warranted to clarify the effect of regular endurance training 
on cerebrovascular perfusion.

We can only speculate possible mechanisms by which arterial compliance is 
enhanced after endurance training. Arterial compliance primarily is determined by the 
intrinsic elastic properties of the arterial wall (i.e., composition of elastin and collagen) and 
the vasoconstrictor tone exerted by its smooth muscle cells. Several previous studies, by use 
of 3-4 months aerobic exercise training intervention, suggest the contribution of latter factor 
such as the recovered endothelial function (14, 27) and sympathetic nervous activity (25) as 
possible mechanisms responsible for the exercise training-related amelioration of central 
arterial compliance in middle-aged and elderly adults. However, since young, healthy 
individuals would have normal endothelial function and sympathetic nervous activity, the 
underlying mechanisms might differ from those of older population. On the other hand, a 
previous study reported that pharmacological inhibition of cross-links in collagen and elastin 
is associated with reduced stiffness of the aorta in young rats (5). It should be examined 
whether the increases in pulse pressure and mechanical distension during the exercise bout 
stretches collagen fibers and modifies their cross-linking, thereby increasing arterial 
compliance, even for several months.

There are several experimental considerations. First, the present study did not 
include the sedentary control group. Additionally, nutritional intake of the subjects was not 
controlled. Therefore, it is uncertain whether the improved Windkessel function of the carotid 
artery was attributed to exercise training per se. Second, heart rate and stroke volume did not
alter significantly \((P=0.07 \text{ and } P=0.08, \text{ respectively})\) following the endurance training. This might be due to subject selection (i.e., regularly-trained healthy young adults) as well as small sample size. Third, in female subjects, we did not measure biochemical parameters (i.e., estradiol) which might influence arterial elasticity, although we confirmed pre- and post-training measurements were performed at the same period of menstrual cycle in each individual by the questionnaire (i.e., the commencement of menstrual cycle). Even with these limitations we are confident that results of the present study support our hypothesized concept of “LV-central conduit artery functional coupling” in young, apparently healthy adults. To gain generalizability of our finding, further interventional studies are needed on a large sample size and other populations (i.e., previously sedentary peers, middle-aged and elderly individuals, patients with cardiovascular and/or cerebrovascular diseases).

**Perspectives**

Cerebrovascular disease is not only a leading cause of mortality but also the major determinant of disability and cognitive function (23). Particularly, the reduced compliance in the central arteries has been hypothesized to be a predominant cause of augmented mechanical forces (i.e., pulsatile blood flow) which impacts microvascular damage at high blood flow, low resistive organs (19, 20). Indeed, the higher arterial stiffness (e.g., deteriorated central arterial compliance) might result in white-matter hyperintensity (30) and Lacunar stroke (10). On the other hand, moderate to high levels of cardiorespiratory fitness are associated with a markedly lower risk of stroke mortality (12) and improved cognition (4). These favorable effects may be attributed to the ameliorated central arterial compliance by regular physical activity (26, 28). In this context, we believe that our finding the contribution of the interaction between LV contractility and arterial compliance to modulation of cerebral hemodynamics could expand the notion of the underlying mechanisms and effective
prevention of cerebrovascular disease. It should be examined in high-risk populations
whether the ameliorated central arterial compliance by regular exercise can modify
cerebrovascular disease risk.

CONFLICT OF INTEREST
None.

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Table 1. Selected subjects’ characteristics before and after 16-week training intervention.

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
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<tbody>
<tr>
<td><strong>Physical characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>58.8 ± 8.3</td>
<td>58.9 ± 8.2</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>20.6 ± 1.9</td>
<td>20.7 ± 1.8</td>
</tr>
<tr>
<td>Total body fat, %</td>
<td>21 ± 6</td>
<td>20 ± 6**</td>
</tr>
<tr>
<td>Total lean mass, kg</td>
<td>46.5 ± 8.4</td>
<td>47.4 ± 8.2**</td>
</tr>
<tr>
<td>Muscle mass, kg</td>
<td>43.9 ± 8</td>
<td>44.8 ± 8*</td>
</tr>
<tr>
<td><strong>Aerobic capacity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO₂peak, ml/min</td>
<td>2726 ± 594</td>
<td>2831 ± 613**</td>
</tr>
<tr>
<td>VO₂peak, ml/min/kg</td>
<td>46.1 ± 5.4</td>
<td>47.8 ± 5.3**</td>
</tr>
<tr>
<td><strong>LV characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-ejection period, ms</td>
<td>97 ± 11</td>
<td>102 ± 13*</td>
</tr>
<tr>
<td>LV ejection time, ms</td>
<td>308 ± 18</td>
<td>310 ± 20</td>
</tr>
<tr>
<td>LV End-diastolic diameter, mm</td>
<td>49 ± 4</td>
<td>49 ± 3</td>
</tr>
<tr>
<td>LV End-systolic diameter, mm</td>
<td>32 ± 3</td>
<td>32 ± 2</td>
</tr>
<tr>
<td>LV Fractional shortening, %</td>
<td>35 ± 3</td>
<td>35 ± 1</td>
</tr>
<tr>
<td>LV Ejection fraction, %</td>
<td>64 ± 4</td>
<td>64 ± 2</td>
</tr>
<tr>
<td><strong>Systemic hemodynamics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, beat/min</td>
<td>54 ± 6</td>
<td>51 ± 6</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>79 ± 3</td>
<td>78 ± 4</td>
</tr>
<tr>
<td>Brachial systolic BP, mmHg</td>
<td>112 ± 6</td>
<td>110 ± 7</td>
</tr>
<tr>
<td>Brachial diastolic BP, mmHg</td>
<td>62 ± 4</td>
<td>62 ± 5</td>
</tr>
<tr>
<td>Brachial pulse pressure, mmHg</td>
<td>50 ± 7</td>
<td>49 ± 8</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>69 ± 14</td>
<td>73 ± 20</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>3.7 ± 0.9</td>
<td>3.7 ± 1.1</td>
</tr>
</tbody>
</table>

Value are means ± SD. *P < 0.05, **P < 0.01 vs before intervention. VO₂peak, oxygen consumption; LV, left ventricle; BP, blood pressure.
Table 2. Carotid arterial and cerebrovascular parameters before and after the intervention.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before</th>
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<tr>
<td><strong>Carotid arterial properties</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic diameter, mm</td>
<td>6.86 ± 0.48</td>
<td>6.97 ± 0.47</td>
</tr>
<tr>
<td>Diastolic diameter, mm</td>
<td>6.13 ± 0.44</td>
<td>6.08 ± 0.41</td>
</tr>
<tr>
<td>Distension, mm</td>
<td>0.74 ± 0.13</td>
<td>0.89 ± 0.21*</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>104 ± 7</td>
<td>106 ± 9</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>42 ± 7</td>
<td>44 ± 10</td>
</tr>
<tr>
<td><strong>Cerebrovascular parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean velocity, cm/s</td>
<td>64 ± 20</td>
<td>64 ± 22</td>
</tr>
<tr>
<td>Systolic velocity, cm/s</td>
<td>100 ± 29</td>
<td>100 ± 32</td>
</tr>
<tr>
<td>Diastolic velocity, cm/s</td>
<td>45 ± 14</td>
<td>44 ± 15</td>
</tr>
<tr>
<td>Pulsatile velocity, cm/s</td>
<td>55 ± 16</td>
<td>55 ± 18</td>
</tr>
<tr>
<td>Cerebrovascular resistance index, mmHg/cm per second</td>
<td>1.34 ± 0.45</td>
<td>1.40 ± 0.59</td>
</tr>
<tr>
<td>P&lt;sub&gt;ETCO2&lt;/sub&gt;, mmHg</td>
<td>40.4 ± 2.6</td>
<td>40.3 ± 2.6</td>
</tr>
</tbody>
</table>

Value are means ± SD. *P < 0.01 vs before intervention. P<sub>ETCO2</sub>, partial pressure of end-tidal carbon dioxide.
Figure legend:

Figure 1. Simultaneous recoding of the electrocardiogram, phonocardiogram, and carotid arterial pressure waveform in a subject. QS; the total electro-mechanical systolic interval, LVET; left ventricular ejection time, PEP; pre-ejection period.

Figure 2: Concept of periodization training. Change in training time and exercise training intensity in each phase and endurance training menu.

Figure 3: Changes in peak left ventricular (LV) ejection velocity and the maximal rate of pressure increase (dP/dt_{MAX}) with the endurance training intervention. Thin lines indicate individual changes.

Figure 4: Changes in cerebral blood flow (CBF) velocity with the endurance training intervention. Data are values normalized by mean CBF velocity.

Figure 5: Changes in carotid arterial compliance and β-stiffness index with the endurance training intervention. Thin lines indicate individual changes.

Figure 6: Association between change in carotid arterial compliance and change in normalized (A) systolic and (B) pulsatile cerebral blood flow (CBF) velocity, and (C) between change in beta-stiffness index and change in normalized diastolic CBF velocity. Each velocity was normalized by time-average (mean) CBF velocity.
Figure 1

- Electrocardiogram
- Phonocardiogram
- Carotid arterial pressure

PEP = QS₂ - LVET
<table>
<thead>
<tr>
<th>Phase</th>
<th>General Preparatory (1-4 week)</th>
<th>Specific (5-10 week)</th>
<th>Competition (11-16 week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endurance Training Menu</td>
<td>Long distance running (8-10 Km)</td>
<td>Running &amp; interval training</td>
<td>Interval training</td>
</tr>
</tbody>
</table>

Figure 2
Figure 3

- Peak LV ejection velocity (cm/s)
  - Before: 80 to 180 cm/s
  - After: 80 to 180 cm/s
  - **P < 0.05**

- dP/dt MAX (mmHg/sec)
  - Before: 100 to 500 mmHg/sec
  - After: 100 to 500 mmHg/sec
  - **P < 0.05**
Figure 4

- Normalized systolic CBF velocity (%)
- Normalized pulsatile CBF velocity (%)
- Normalized diastolic CBF velocity (%)

Before vs. After comparisons.
Figure 5

Carotid arterial compliance (mm²/mmHg)

Beta stiffness index

Before After

$P < 0.01$
Figure 6

(A) Change in normalized systolic CBF velocity (%)

(B) Change in normalized pulsatile CBF velocity (%)

(C) Change in beta stiffness index

Change in carotid arterial compliance (mm²/mmHg)

Change in beta stiffness index

r = -0.594
P < 0.05

r = -0.610
P < 0.05

r = -0.596
P < 0.05