Vascular Adaptation to Indoor Cycling Exercise in Premenopausal Women

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Introduction

Regular physical exercise as well as high aerobic capacity reduces cardiovascular risk beyond the level explained by modification of traditional risk factors [23, 47]. The cardiovascular system adapts to repeated aerobic exercise in many ways, and studies comparing endurance athletes with sedentary controls, show besides cardiac enlargement [19] also increased dimension of large veins [20] and arteries that supply muscles at work [34]. Moreover, cross-sectional studies have showed either unaltered [36], thinner [33], or thicker intima media complex in large arteries [1] of athletes compared to untrained controls. Despite these divergent findings, a theory that exercise systemically reshape the arterial wall has been proposed based on results from small studies [33, 41]. The few previous longitudinal studies evaluating the response to 2-6 months of aerobic exercise training have found either altered arterial distensibility and/or geometry [15, 31], or no measurable response [12, 40]. This probably reflects that the vascular adaptation to exercise training is multifactorial, and that factors including selection criteria, exercise mode and accumulated exercise volume influence the response. In addition, the impact of sex-hormones on the cardiovascular system is gender-specific [13], and prolonged exercise may promote divergent neuroendocrine and metabolic effects in men and women [11]. Higher late systolic pressure amplification is found in central arteries of girls compared to boys, while higher age-related decline in carotid wall distensibility has been reported in women [2, 45]. Since most previous exercise intervention studies have recruited only men or present compiled data from men and women [7], knowledge of the vascular adaptation to training in women is limited. The primary aim of the current study was to evaluate the vascular adaptation to indoor cycling in healthy, pre-menopausal women. We hypothesized that arterial adaptation occurs in regions with high blood flow during exercise, and that this association is positively associated to a change in exercise capacity.

Materials and methods

Subjects

By advertisement, 53 non-smoking female Caucasian volunteers (21-45 years, mainly students and hospital employees) were recruited. They were all presumably healthy without any history of cardiovascular disease or diabetes. Pregnancy, use of blood pressure lowering drugs and inability to perform a maximal exercise excluded them from participation. Subjects were characterized as being either sedentary or recreationally active, i.e. performing physical activity at low intensity in their daily life and/or had exercised occasionally in the past. Subjects were assigned to either an indoor cycling exercise group (ICE) or a time control group (CON) instructed to maintain their regular sedentary lifestyle.

Between baseline and follow-up, four subjects in ICE group discontinued exercise training, whereas seven in CON group declined follow-up examinations. Thus, the final study population consisted of 21 subjects in each group. All subjects gave their written informed consent to participation. The present study that meets the ethical standards in sport and exercise research [17], was approved by the regional ethical review board in Linköping, Sweden.

Exercise training regimen

To assure a high generalizability and feasibility, subjects in the ICE group were instructed to join indoor cycling classes at a local gym, aiming to complete three sessions per week over twelve weeks. Each exercise session lasted for 45-60 minutes, cadence and resistance were continuously adjusted by each subject with motivation and instructions from an indoor cycling instructor. Subjects were encouraged to reach a sense of high effort during their work out session. Further details on training regimen are found in the electronic supplement file.

Study protocol

At baseline and at the three months follow-up, each subject visited the clinic twice within one week, where one single operator performed all examinations. Prior to their visits, subjects were requested to avoid caffeinated drinks for three hours, alcohol and heavy exercise for 12 hours.

First visit: A venous blood sample was drawn after an over-night fast. After a light low-fat breakfast, subjects rested in the supine position for ten minutes (room temperature 22-24ºC). First, upper arm and ankle systolic blood pressure (SBP) were determined bilaterally by detecting the return of the pulsatile blood flow during cuff deflation with the aid of a Doppler device, and capillary plasma glucose concentration was determined. Second, arterial wall tracking of 1) mid infra-renal abdominal aorta (AA); 2) right distal common carotid artery (CCA), 1-2 cm proximal from carotid bifurcation and; 3) left distal brachial artery (BA), 0-5 cm proximal from antecubital crease, were performed. Brachial blood pressure and heart rate (HR) were measured before and after each set of diameter distension waveforms. Third, the pressure wave configuration of the left radial artery and the right CCA was recorded non-invasively with the aid of applanation tonometry for 10 seconds. Finally, B-mode ultrasound images from the same arterial sites as during the wall tracking procedure were saved. For statistical analysis, the average values from three saved registrations or imageswere used. The Doppler blood pressure measurements as well as the venous blood sample can be regarded as screening tests to ensure normality in all volunteers.

Figure 1 present an overview over the vascular examinations.

Second visit: Subjects underwent echocardiographic evaluation (data previously reported [21]) followed by an incremental exercise test.

Laboratory measurement

Standard analysis included glycated haemoglobin A1c (HbA1c) and fasting plasma glucose (FPG).The HPLC method was used to determine HbA1c, here presented according to the IFCC standard.

Exercise test

Maximal work capacity was determined on an electronically braked cycle ergometer (RE830, Rodby Electronic, Södertälje, Sweden), connected to an exercise ECG system (Marquette CASE 8000, GE Medical Systems, Milwaukee, WI, USA). The incremental work test commenced at an initial work load of 80 W and was increased thereafter by 10 W/min until volitional fatigue, interrupted by a five minutes steady state plateau at 120 W where the subject also rated their perceived exertion [8]. Heart rate was continuously monitored from a 12-lead ECG. Systolic upper arm cuff pressure was measured by detecting the radial artery pulse with Doppler (Parks model 812, Parks Medical Electronics inc, Aloha, OR, USA) during cuff deflation in sitting position on the bicycle before exercise and during 120 W exercise.

Further information of the vascular methods is available as electronic supplement material, see method and figure file.

Statistical analysis

Data is presented as mean ± standard error unless otherwise noted. Δ denotes the change between the two visits. Paired t-tests were used for pre- to post intervention comparison, while Student's t-tests were used for between group comparisons. The chi-square test was used for the evaluation of categorical data. Pearson's correlation coefficient or univariate regression analysis was used for determining associations between continuous variables. Correlation analysis was performed between change in parameters of fitness (peak workload and submaximal heart rate at 120 W) and change in selected vascular parameters. . $P<0.05$ was considered statistically significant. SPSS version 22 (IBM Software, Armonk, NY, USA) was used for statistical analysis.

Results

Baseline characteristics of subjects are presented in table 1. The 21 subjects in ICE group completed from 22 to 45 (median 32) indoor cycling sessions over the three months. The systolic ankle to brachial pressure index (ABI) was > 1.0, HbA1c < 42 mmol/mol and FPG < 6.1 mmol/L in all subjects at baseline.

Blood pressure and heart rate at rest

Neither brachial nor estimated central pulse pressure changed following the exercise intervention (table 2), while heart rate at rest dropped markedly from 63±1 to 55±1 min^{-1} ($p<0.001$).

Exercise test data

Maximal work capacity improved from 197±7 to 229±7 W ($p<0.001$) in ICE group, whereas no significant change was found in CON (figure 2). After intervention, HR during exercise at 120 W decreased in ICE (154±3 to 139±2, $p<0.001$), whereas no change in the systolic BP at 120 W was seen (174±4 vs 172±4 mmHg). In ICE group, the median rating of perceived exertion at 120 W dropped from 14 to 12 ($p<0.01$), while unchanged at 14 in CON. In the CON group, HR and systolic BP at rest and during 120 W exercise were unchanged.

Arterial geometry

AA, CCA and BA dimensions are presented in table 3. At baseline, there was no difference between groups in lumen diameter (LD), imtima media thickness (IMT) or their ratio at any measurement site. Both AA LD ($p<0.01$) and BA LD ($p<0.05$) increased in the ICE group, whereas no significant changes were found in the CON group. IMT remained unaltered at all sites in the two groups. The diameter of the tubular ascending aorta was higher at follow-up in the ICE group (26.8±0.7 vs 27.8±0.7 mm, $p<0.01$) while unchanged in the CON group (28.1±0.9 vs 27.4±0.9 mm, NS). The aortic root dimension measured at sinuses of Valsalva did not change significantly in either group from baseline to follow-up (ICE: 28.9±0.5 vs 29.0±0.5 mm; CON: 28.8±0.5 vs 29.2±0.6 mm).

Arterial wall properties

Data from pulse wave analysis is presented in table 2. After adjustment for heart rate, no change in recorded radial or estimated central aortic pulse pressure augmentation index was seen.

In CCA, the distensibility coefficient (DC) changed from 45±3 to 53±4 kPa^{-3} in ICE group ($p<0.05$), whereas similar DC were found in AA and BA before and after intervention, and at all sites in CON (figure 3).

Correlations

A positive correlation was found between absolute change in peak workload and absolute change in diameter of the ascending aorta ($r=0.42$, $p<0.01$) in ICE, and after compiling all subjects ($r=0.47$, $p<0.01$). Furthermore, an absolute change in HR@120W was oppositely correlated with change in diameter of the aortic root ($r=0.32$, $p<0.05$) and of the ascending aorta ($r=-0.38$, $p<0.05$). For graphical display of the relation between relative change in peak workload and submaximal heart rate with the change in aortic diameters, see figure 4.

There were no significant correlations between change in peak workload or HR@120W and change in IMT in any vessel. However, a change in AA IMT/LD-ratio was positively and weakly correlated to change in submaximal heart rate ($r=0.34$ for relative change, $r=0.34$ for absolute change, both $p<0.05$).

A change in DC, augmentation index (AI) or AI normalized to a heart rate of 75 min^{-1} was not correlated with change in peak workload or HR@120W. Estimated central pulse pressure was negatively correlated with change in HR@120W (r=-0.40 for relative change and r=-0.38 for absolute change, $p<0.01$ and $p<0.05$ respectively).

Discussion

The main finding of the present study was that regular indoor bicycle exercise for 12 weeks increased the diameter of ascending aorta and the AA LD in premenopausal untrained women. In addition, fitness improved following the intervention, measured as higher exercise capacity and lower heart rate at a submaximal workload, and both measures were correlated to an increase in the diameter of the tubular ascending aorta.

To achieve a high generalizability, we choose a realistic setting with regular indoor cycling classes at a local gym. Despite the maintained popularity of indoor cycling during the last decade, the physiological evaluation has mainly been limited to documented performance during individual sessions, confirming that most individuals during classes occasionally reaches their VO2 max [4, 9].

In the current study, the diameter of ascending as well as abdominal aorta increased following training, while the diameter of sinuses of Valsalva was unaltered. Interestingly, we have previously demonstrated reduced diameter of tubular ascending aorta, but not the aortic root, in young adults following fetal intra-uterine growth restriction and reduced fetal aortic blood flow [5]. While the size of the aortic root has been extensively studied in different categories of athletes, comprehensively summarized in a meta-analysis by Iskandar et al. (2013), the effect of endurance exercise on other aortic segments is far less studied. Neither Houker et al. (2003) nor Peterson et al. (2006) found increased local aortic diameter in road cyclists or rowers, while

Miyachi et al. (1998) observed larger luminal size of abdominal aorta in young healthy males after only two month of ambitious bicycle training. Besides the conduit function, the ascending aorta has a cushioning function, ensuring continuous blood perfusion to peripheral organs over the cardiac cycle. During lower extremity endurance exercise, aortic blood flow as well as pulse pressure increases, while the diameter is unaffected or even decreases, resulting in higher mean shear wall stress and lower oscillatory shear stress that differs in magnitude along the aorta [3, 10]. The shear stress stimuli enhance the release of endothelial nitric oxide and other vasodilating factors from the vessel wall leading to outward remodeling [14]. Thus, it seems plausible that the stimulus responsible for the aortic remodeling in the current study is the repeated periods of volume blood flow through aorta to the lower extremity during the indoor cycling sessions. We have previously shown that sympathetic stimulation does not have any significant effect on the aortic diameter, at least not in the abdominal aorta [37]. It is thus probable that the aortic enlargement represents true vascular remodeling. The absent diameter change of the sinuses of Valsalva in comparison to the tubular ascending aorta could be due to characteristic aortic root geometry which create an altered flow pattern. Moreover, the mechanical stress that causes rapidly alternating wall tension during the cardiac cycle is higher for proximal aorta than abdominal aorta [3]. Nevertheless, young elite athletes (predominantly males) have been found to have larger aortic root diameter than sedentary subjects [24], in parallel to enlarged cardiac chambers. It is possible that training stimulus needs to be greater than in the current study to induce aortic root enlargement, or that this adaptation is secondary to left ventricular remodeling in elite athletes.

We found no difference in CCA LD following the intervention, which is in agreement with an interventional study by Spence et al. (2013) and a cross-sectional study with young female athletes [18]. However, larger luminal size has previously been found in the CCA of young male cyclists and swimmers [46]. The reason for these divergent findings is unknown but differences in selection criteria's as well as a gender specific influence from sex-hormones on the cardiovascular system could be potential contributors [13]. In general, athletes in sports with high demands on lower body muscles present larger size of their conduit muscular arteries than sedentary subjects, while these vessels are narrower in subjects with lower body disability [33, 46]. It is well known that whole body athletes like rowers exhibit enlargement of their brachial artery [30], whereas no or minor effects on brachial artery size are seen in exercise intervention studies where subjects perform dynamic lower body work [16, 37]. Whether the minor BA LD increase in the present study reflect structural changes, change in basal vascular tone, or is just a coincident finding, cannot be determined. However, no reduction of basal sympathetic nerve activity has been reported after aerobic exercise intervention [32].

By ageing, IMT increases as an adaptive response to alteration in flow, lumen diameter or wall tension to normalize local tensile stress. It is believed that intima-media thickening up to certain level reflect a non-atherosclerotic remodeling, whereas a thicker carotid artery wall is positively associated with increased cardiovascular risk [43]. Some argue that that exercise training changes the general arterial structure (i.e. IMT), not only in the conduit arteries that supplies the working muscles [34, 41]. It is striking that we found unaltered IMT at all three arterial sites after the three months intervention period despite improved cardiorespiratory fitness, while others show that similar degree of fitness improvement in males is accompanied by reduced IMT. Since arterial luminal distension is accompanied by intima-media compression, the lack of expansive remodeling may contribute to the unaltered IMT. On the other hand, observation of wider brachial artery on the dominant side but thinner intima-media bilaterally in male squash players [34], suggests that arterial enlargement is not crucial for achieving an exercise related reduction of IMT. Other possible explanations for unaltered IMT could be that three months exercise intervention is to short duration to induce changes of IMT in women, or alternatively, women's arteries respond differently to exercise training. We have previously demonstrated that young female endurance athletes have similar CCA geometry as age-matched controls [6]. Since CCA blood flow only increases slightly during intense aerobic exercise [35], and far less than in conduit arteries that supply the working muscles, it is conceivable that minor enhancement of the pressure and shear stress stimuli has not enough impact on the carotid and brachial artery to alter the local wall thickness in young women.

An age-related loss of arterial wall distensibility ("vascular ageing") is seen in central elastic arteries from early age, mainly because of elastin being replaced by stiffer collagen. Low arterial distensibility is independently linked to increased risk for future cardiovascular events [48]. Thus, it is of considerable interest to explore whether exercise alone might explain the association between a high aerobic fitness level and high arterial distensibility that has been found in earlier cross-sectional studies [28, 42]. In our study, carotid artery distensibility increased somewhat after intervention, while the aortic and brachial mechanical properties, as well as the pressure wave configuration were unaltered (figure 3). Since we recruited young women with presumptively healthy distensible arteries it may be argued that higher exercise volume and/or intensity might be needed to induce effects on arterial distensibility. Accordingly, middle aged and elderly women seem to have a better potential to affect their reduced arterial distensibilty by adopting a physical active lifestyle [28, 39]. Whether the vascular response to exercise is of similar magnitude in both young women and men is at present unknown but improved large artery distensibility after short-term endurance training has been reported in young males [25].

Limitations

First, arterial wall properties might fluctuate over the menstrual cycle [29]. Because of logistic reasons we had to examine the women in different phases of the menstrual cycle, although the second test were performed in the same menstrual phase as the first. Second, aerobic capacity is commonly reported as VO_2 max. Although a linear relation between increasing VO_2 demand

and maximal bicycle power output exist, considerable inter-individual variation may occur when the change in peak power output is related to change in peak VO_2 [44]. Third, the saved ultrasonic B-mode images were analysed off-line in a semi-automatic software. A software for automatic LD and IMT edge detection from video sequences could have diminished the influence by the reader. Finally, the cardiovascular adaptation is influenced by the specific exercise modality that generate different blood flow and shear stress patterns in active and inactive vascular beds [26]. Therefore, our findings are valid only for the used protocol and the vascular bed examined.

In conclusion, indoor cycling at a local gym is a feasible mode of exercise for pre-menopausal women that not only lead to improved aerobic capacity, but also to regional vascular adaptation. Interestingly, the changed ascending aortic diameter was positively correlated to the degree of improved cycling capacity after the three months training period.

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Figure legend

Figure 1

The vascular methods and their approximate recording sites For details, see ‘Methods’ and supplementary material.

Figure 2

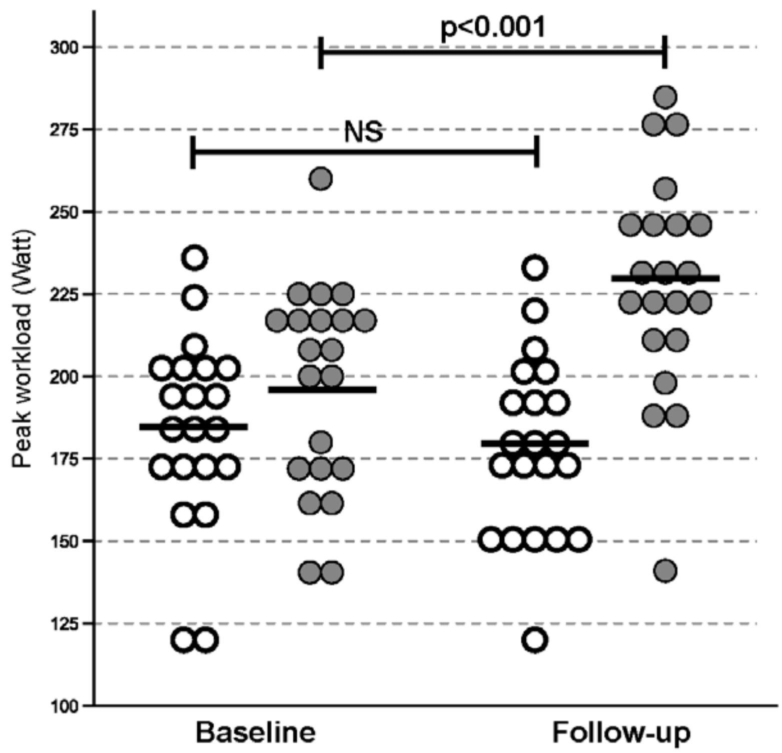
Individual (dots) and mean (horizontal lines) peak workload in each group at baseline and follow-up. Open circles represent controls (CON) and filled circles indoor cycling exercise group (ICE).

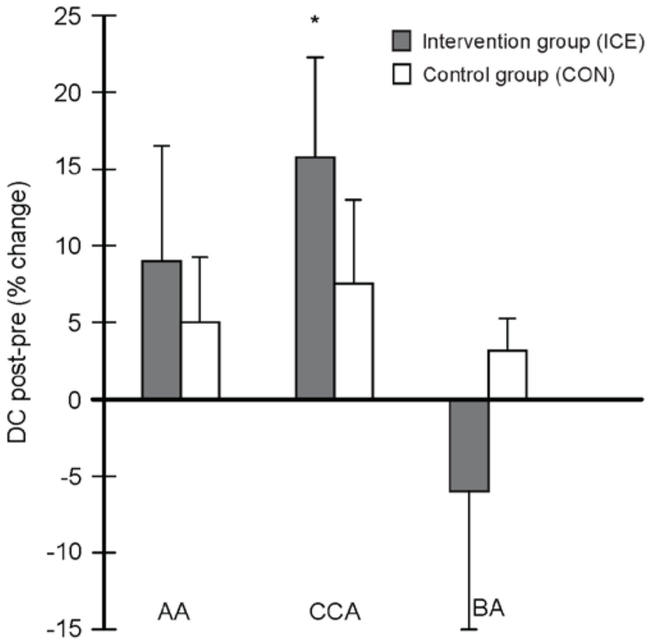
Figure 3

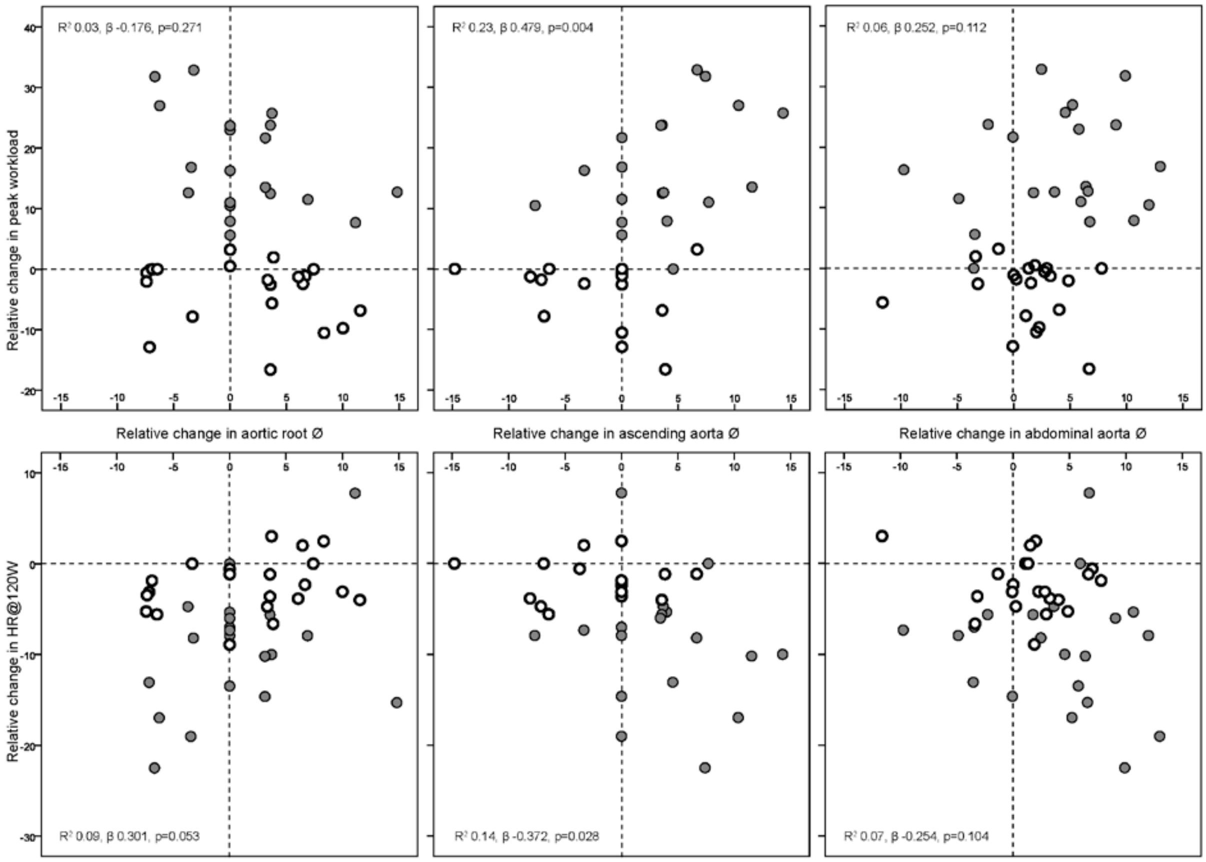
The relative change of the distensibility coefficient (DC) in abdominal aorta (AA), common carotid artery (CCA) and the brachial artery (BA) between baseline and follow-up. Filled grey bars represent exercise group, open bars controls. * $p<0.05$ within the exercise group. comparison.

Figure 4

Graphical display of relation between relative change in two parameters of fitness; peak workload (a-c) and heart rate at 120 Watts (HR@120W, d-f) with relative change in diameter of sinuses of Valsalva (a+d), ascending aorta (b+e) and abdominal aorta (c+f). R^2 and β-values for separate univariate regression models including all subjects. Filled, blue circles represent exercise group and red circles control group.


p<0.001
NS
Peak workload (Watt)
300
275
250
225
200
175
150
125
100
Baseline
Follow-up


Intervention group (ICE)
Control group (CON)
*
DC post-pre (% change)
25
20
15
10
5
0
-5
-10
-15
AA
CCA
BA



R² 0.03, β -0.176, p=0.271
R² 0.23, β 0.479, p=0.004
R² 0.06, β 0.252, p=0.112
Relative change in peak workload
Relative change in aortic root Ø
Relative change in ascending aorta Ø
Relative change in abdominal aorta Ø
Relative change in HR@120W
R² 0.09, β 0.301, p=0.053
R² 0.14, β -0.372, p=0.028
R² 0.07, β -0.254, p=0.104

Electronic Supplementary Material – methods text

Vascular adaptation to indoor cycling exercise in premenopausal women

Exercise training regimen

Subjects in the ICE group were instructed to join indoor cycling classes at a local gym, three sessions per week over twelve weeks. Subjects were encouraged to reach a sense of high effort (rate of perceived exertion 17 on the Borg scale) during their work out session without using heart rate monitors to imitate a realistic scenario. The workout intensity was however checked during one of their first exercise sessions using a heart rate monitor (Polar S610), showing an average heart rate that corresponded to 75-88% of their individual heart rate response (HRR) which was defined as (HRexercise-HRrest) / (HRmax-HRrest), taking HRmax from the baseline ergometer test. At each indoor cycling session, an instructor guided them through a 45-60 minutes program consisting of a warm-up phase followed by more challenging interval phases where resistance and cadence were altered until a period of peak effort was reached, followed by a cool down phase. Each subject self-registered completed exercise sessions in a log book and print-outs of their registered visits at the gym were later collected.

Additional description of the vascular methods

Vascular ultrasound

A digital ultrasound system (HDI 5000, Philips Medical Systems, ATL Ultrasound, Bothell, WA, USA) equipped with an ECG module was used with a phased array (P4-2) transducer for determination of the end-diastolic diameter of the tubular ascending aorta and sinuses of Valsalva, using B-mode guided M-mode measurements in the parasternal view (figure 1A). The intra-observer in-between session coefficient of variation was 1.2% for tubular ascending aortic diameter measurements.

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Linear array broadband transducers were used for scanning the CCA and BA (L12-5), and AA (L9-4). Frozen end-diastolic, magnified B-mode images were saved for later analysis on a PC with software (Artery Measurement System II, Image and Data Analysis, Gothenburg, Sweden) for off-line measurement of lumen diameter (LD) and intima-media thickness (IMT). Calibration and subsequent measurement was performed by manually tracing a cursor along the leading edge of the intima-lumen echo of the near wall, leading edge of the lumen-intima echo and media-adventitia echo of the far wall to obtain mean LD and far wall IMT along a 10 mm long section of the artery (Figure 1C). During analysis, the measurement window was hidden for the operator and values were saved in a text file.

Arterial wall tracking

An ultrasound system (Esaote AU5, Esaote Biomedica, Florence, Italy) equipped with a 7.5 MHz linear array, and a 3.5 MHz curved array transducer was used for real-time imaging of CCA, BA (7.5 MHz) and AA (3.5 MHz). The system was connected to a PC, with the Wall Track System software (WTS2, Pie Medical, Maastricht, The Netherlands). In short, ECG leads were connected to the subject and after visualisation of the artery in a B-mode longitudinal section, the scanner is switched to M-mode, and the M-mode line is positioned perpendicular to the anterior and posterior vessel wall. A window of sufficient width to include the envelope from both anterior and posterior wall is chosen, and the radio frequency signal is transferred to the PC for storage. A sample volume is automatically positioned on the media-adventitia transition of the anterior and posterior wall and track the positions over four seconds, followed by calculation of the diameter distension curve (Figure 2A).

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Blood pressure measurement

A blood pressure cuff of appropriated size was wrapped around the subject's upper arm. The cuff was connected to an oscillometric blood pressure device (Dinamap PRO 200 Monitor, Critikon, Tampa, FL, U.S.A) that automatically calculate systolic, diastolic and mean arterial blood pressure together with heart rate with the aid of an implemented algorithm.

Applanation tonometry

The SphygmoCor system (Model MM3, AtCor Medical, Sydney, Australia) equipped with a Millar pressure tonometer was used to sample pulse waves during ten seconds to a commercially available software for on-line analysis (SphygmoCor version 7.0). The average central pressure waveform was obtained by a transfer function, calculated from the radial artery pressure waveform that was calibrated by taking the brachial systolic and diastolic pressures (Figure 2B). Time to reflection (Tr), augmentation index (AI) and augmentation pressure (Aug) were automatically calculated from the aortic waveform. Each file is given a quality index from 0 to 100 by the software, where the value 100 indicate regular heart rhythm and similar pressure wave configuration for all cardiac cycles. In most saved files, an index > 90 was obtained, while the files with quality index below 75 were rejected. Further prerequisites for accepting a file were; a true arterial pressure wave configuration and reasonable automatic identification of the two peaks, P1 and P2, during systole.

Carotid artery pressure waveform was calibrated by taking mean arterial pressure (MAP) from the integrated radial artery pressure curve in combination with diastolic brachial pressure (DBP).

Calculations and data analysis

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The distensibility coefficient (DC, unit 10^{-3}/kPa) is the relative increase of arterial cross-section area for a given increase in pressure [1].

$$DC = \frac{2D\Delta D + \Delta D^2}{\Delta P D^2}$$

where D is the minimum diastolic diameter in mm, ΔD is pulsatile diameter change, ΔD^2 is the square of the pulsatile diameter change in mm and ΔP is pulse pressure in kPa. The arm pulse pressure (PP) was used as a surrogate measure for local pulse pressure when DC of the AA was calculated, whereas the tonometer derived local PP was used in the calculation of CCA DC. The inter-session coefficients of variation for distensibility coefficients calculated from measurements in the CCA and the BA were 10 % and 14 %, respectively, in a previous methodological evaluation at our laboratory.

The radial augmentation index (RA Al) is defined as the pressure at the second systolic shoulder (P2), divided by pressure at the first peak (P1)

RA AI % = P2/P1 x 100

The aortic augmentation index (AI) is defined as the increase of pressure over the first systolic shoulder (P1) due to wave reflection (Aug), divided by pulse pressure (ΔP).

AI (%) = aug/PP x 100

To account for differences in heart rate, AI@75 is also presented as the AI normalized to a heart rate of 75 min^{-1}.

Reference

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[1] Van der Heijden-Spek JJ, Staessen JA, Fagard RH, Hoeks A, Struijker Boudier H, Van Bortel L. Effect of age on brachial artery wall properties differs from the aorta and is gender dependent. Hypertension 2000; 35: 637-642