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VASCULAR CHARACTERISTICS IN YOUNG WOMEN – EFFECT OF EXTENSIVE ENDURANCE TRAINING OR A SEDENTARY LIFE-STYLE

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Short title – Vascular function in female athletes

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Abstract

Aim: To explore whether high level endurance training in early age has an influence on the arterial wall properties in young women.

Methods: Forty-seven athletes (ATH) and 52 controls (CTR), all 17 to 25 years of age, were further divided into runners (RUN), whole-body endurance athletes (WBA), sedentary controls (SC) and normally active controls (AC). 2-D ultrasound scanning of the carotid arteries was performed to determine local common carotid artery (CCA) geometry and wall distensibility. Pulse waves were recorded with a tonometer to determine regional pulse wave velocity (PWV) and pulse pressure waveform.

Results: Carotid-radial PWV was lower in WBA than in RUN ($p<0.05$), indicating higher arterial distensibility along the arm. Mean arterial pressure was lower in ATH than CTR, and in RUN than WBA ($p<0.05$). Synthesized aortic augmentation index (AI@75) was lower among ATH than CTR (-12.8±1.6 vs -2.6±1.2%, $P<0.001$), and in WBA than RUN (-16.4±2.5 vs -10.7±2.0%, $P<0.05$), suggesting a diminished return of reflection waves to the aorta during systole. Carotid-femoral PWV and intima-media thickness (IMT), lumen diameter and radial distensibility of the CCA were similar in ATH and CTR.

Conclusion: Elastic artery distensibility and carotid artery IMT are not different in young women with extensive endurance training over several years and in those with sedentary life-style. On the other hand, our data suggest that long-term endurance-training is associated with potentially favourable peripheral artery adaptation, especially in sports where upper body work is added. This adaptation, if persisting later in life, could contribute to lower cardiovascular risk.

Key words: aortic augmentation index; artery; athletes; blood pressure; physical activity; pulse wave velocity; ultrasound

Introduction

There is evidence that atherosclerosis develops early with a slow progression from subclinical coronary atherosclerosis in childhood to cardiovascular disease in adulthood.[1-3] This development of detectable atherosclerosis is likely to start around puberty (age 12-15 years).[4,5] It has been convincingly documented that a high level of regular physical activity is one of the best means to prevent cardiovascular disease with a risk reduction above 50% with a physically active life.[6,7] Recent indirect evidence of the cardioprotective effect of regular physical activity was obtained in the Bolivian Tsimane population, who has the lowest reported levels of coronary artery disease of any population recorded to date.[8] The authors report that Tsimane men and women spend a mean of 6–7 h and 4–6 h per day, respectively, engaging in physical activity.

With this background it is conceivable that, from a strict perspective of cardiovascular disease prevention, physical activity becomes important already in childhood, adolescence and early adulthood. There is increasing evidence in support of this notion, most clearly with respect to coronary heart disease risk factor reduction with increased physical activity in both sexes.[9] It has been shown that carotid intima-media thickness (IMT), a strong indicator of cardiovascular disease,[10] increases in teenagers with a combination of physical inactivity and overweight.[11] Such IMT-increase can be counteracted in both sexes by physical activity of modest intensity.[11] There are reports of the effectiveness of physical training, also in normal-weight young men[12] or in mixed groups of men and women[13] to decrease carotid artery IMT (or aortic IMT[14]). However, few of these reports contain IMT-data for men and women separately. In two such reports, evidence was presented that differences between endurance-trained and less physically active men or boys in femoral artery IMT,[15] and in carotid arterial

stiffness,[16] were not accompanied by similar differences between endurance-trained and untrained women.

Available data thus seem to indicate that the relationship between the individual´s physical activity level and markers of atherosclerosis development may differ between women and men. Carotid IMT may not be expected to be influenced by physical training in normal-weight adolescents of either sex, although a decreased carotid IMT has been found in some studies of exercise-trained men 22-25 years old; an 8-week programme of cycle exercise training,[17] or when comparing cyclists or swimmers with controls.[12] On the other hand, there are documented positive effects of exercise training regarding carotid arterial distensibility (compliance) in young men,[18,19] but not in young women.[20] It has been stated that, due to the inherently high arterial compliance values in women, central arterial compliance may be resistant to increase further with endurance training in young women.[20]

The majority of the hitherto published data on the vascular adaptation to regular exercise training are from studies investigating men only and there are few reports available for women, especially at young age. However, investigations of the effect of intensive training on variables related to arterial stiffness seem especially warranted in women, due to the higher late systolic amplification that is recorded in central arteries of girls compared to boys, explained by earlier pulse wave reflection.[21] The increased pulse wave amplification in women has been speculated to be the source of a slow process that in hypertensive women, at a higher rate than in men, eventually leads to left ventricular hypertrophy and severe heart failure.[21,22] The higher pulse wave reflection in girls than in boys, as determined by the augmentation index (AI), is independent of body height and has been documented in childhood,[21] in teenage years and in adulthood.[23] Some previous reports have given evidence that endurance training diminishes the contribution of wave reflection during systole, [24,25] while this is refuted by other studies.[26,27]

The aim of the present study was to further explore the effect of endurance training on arterial wall properties in young women. Due to the potentially negative health consequences in women of a high central arterial pulse wave reflection during systole, we investigated whether this can be influenced by endurance training. Furthermore, we wanted to study whether elastic artery distensibility and carotid artery intima-media thickness are in fact resistant to change with endurance training in young women. We also evaluated if the vascular adaptation to endurance training is dependent on the mode of exercise, especially with respect to the relative involvement of the upper and lower body. In order to provide additional knowledge on these issues, it was important both to study a relatively large group of women and to ascertain that the exercise stimulus was high.

Results

Subject characteristics and level of physical activity (Table 1).

Table 1 shows baseline characteristics of the athletes (ATH) and controls (CTR), with the subgroups RUNNERS (RUN), WHOLE-BODY ENDURANCE ATHLETES (WBA), SEDENTARY CONTROLS (SC) and NORMALLY ACTIVE CONTROLS (AC). ATH had performed at least six training sessions per week over the last five years (the average was 8.7±0.3 training sessions per week, corresponding to 12.2±0.6 hours of weekly training) and started their dedicated exercise training before they became fifteen years old. All the ATH were competitive but on different levels in their sport. Category 1 (n=25) belonged to the absolutely best in the country in their age-group. Category 2 (n=14) were highly ranked in their sport and competed on the Swedish national level, whereas Category 3 (n=8) had a high

regional ranking. The amount of weekly training was not different between categories (with the exception of category 3 in RUN, who trained on average 7 hours per week). Among the 25 Category 1 athletes, six were medallists in regular World or European championships, 13 were medallists in regular Swedish championships and 2 were Junior World Champions. SC had a low physical activity in their daily life and had never been involved in endurance or strength training in their leisure time or in competitive sports. AC were doing physical activities of low intensity in their daily life and/or had occasionally performed endurance or strength training in the past, but never on a regular basis.

Basic hemodynamic data: Peripheral blood pressure, stroke volume, total peripheral resistance (Table 2).

Systolic blood pressure (SBP) did not differ between ATH and CTR, but was lower in RUN compared to WBA (101±2 mmHg vs 110±2, $P<0.01$). No differences in blood pressure data were detected between SC and AC. DBP was lower in ATH than in CTR, but did not differ between RUN and WBA. Mean arterial pressure (MAP) was lower in both ATH than in CTR (74±1 mmHg vs 77±1, $P<0.05$) and in RUN compared to WBA (72±1 mmHg vs 76±1, $P<0.05$). Resting heart rate was lower in ATH than CTR (55±1 $\cdot$ min^{-1} vs 75±2, $P<0.001$), but not different between RUN and WBA. Resting heart rate was also lower in AC compared to SC (69±2$\cdot$ min^{-1} vs 78±2, $P<0.01$). The markedly lower heart rate at rest in ATH than in CTR was balanced by a higher stroke volume (SV) (ATH 76±2 mL vs CTR 59±1, $P<0.001$). This resulted in similar values for CO (data not shown) and TPR at rest across the groups. No significant differences in SV were detected between RUN and WBA or between AC and SC.

Common carotid artery geometry, distensibility and pressure (Table 2).

As described in detail under Methods, diastolic CCA LD and IMT were analysed with two different software tools, a semi-automatic border detection software (AMS, Method 1) was used on saved images and UAC (Method 2) on cine-loops. Regardless of method, IMT was similar in ATH and CTR. A slightly larger CCA LD was found in ATH than CTR, and in AC than in SC, but only with the AMS method (Table 2, method 1). By indexing CCA LD to body surface area (mm/m^2), the LD-difference with the AMS method disappeared between the groups.

Accordingly, the IMT/LD-ratio was similar in ATH and CTR with the AMS method. The carotid pulse pressure, which is normally correlated to the IMT, did not differ between groups but showed a trend to be higher in SC than in AC. A significantly lower DC in the CCA was found in CTR than in ATH, but the difference disappeared in the ANCOVA analysis after adjustment for MAP as a continuous variable.

Measures of arterial distensibility (Figures 2-3, Tables 2-3).

PWVcf did not differ between the groups. A trend ($P<0.1$) towards lower PWVcf in RUN compared to WBA disappeared when the lower MAP in RUN was taken into consideration in an ANCOVA. For PWVcr, a trend ($P<0.1$) towards lower values in ATH compared to CTR disappeared when the lower MAP in ATH was taken into consideration in an ANCOVA. PWVcr was lower in WBA than in RUN. The difference persisted when the lower MAP and heart rate in RUN were taken into consideration in an ANCOVA. Consequently, the ratio PWVcf/PWVcr was significantly lower in RUN than in WBA (Figure 2, Table 2). There was no difference in PWVcr between AC and SC. The PMAP-adjusted data (PMAP, peripheral

mean arterial pressure) on PWVcf and PWVcr (Supplemental material, Table 4S) yielded within 0.1 m/s identical results as those described above. Therefore, comparing PMAP-adjusted PWVcf and PWVcr yielded the same result as the ANCOVA test, when the groups were compared.

The peripheral augmentation index (RA AI), measured in the radial artery and normalized to a heart rate of 75 (RA AI@75) was not different between ATH and CTR, but tended to be lower in WBA than in RUN (Figure 3). This trend was converted to a robust difference when group differences in MAP and body height were taken into consideration in an ANCOVA. The trend toward higher values in SC compared to AC disappeared when differences in MAP and body height were taken into consideration in an ANCOVA. Similar results were obtained when comparing PMAP-adjusted pulse wave values between the groups (Supplemental material, Table 4S).

The synthetized aortic augmentation index normalized to a heart rate of 75 (AI@75) was significantly lower in ATH than in CTR. Furthermore, AI@75 displayed similar differences between RUN and WBA as did the peripheral augmentation index (lower in WBA, $P<0.05$). Both these differences remained after an ANCOVA controlling for differences in MAP and for differences in both MAP and body height as depicted in Figure 3. For this variable there was also a large difference between AC and SC (lower in AC). This difference remained after the ANCOVA controlling for differences in MAP, but not after an ANCOVA controlling for differences in both MAP and body height. When instead PMAP-adjusted data were used for AI@75 (Supplemental material, Table 4S), the difference between AC and SC became statistically significant ($P<0.05$), whereas the difference between RUN and WBA was just outside statistical significance ($P=0.06$).

In Table 3, PWVcf, PWVcr, PWVcf/PWVcr, RA AI@75 and AI@75 are shown across performance categories of the athletes. The table illustrates that results were similar whether the athletes belonged to the absolutely best in the country in their age-group (Category 1) or had lower rankings (Categories 2 or 3).

Estimated central systolic blood pressure and central pulse pressure was significantly lower in RUN than in WBA, with no significant difference between ATH and CTR. No significant differences in the carotid artery augmentation index, CA AI@75, were detected.

Results from the Cardiopulmonary exercise test (Table 4).

Submaximal exercise (100W)

The mechanical efficiency of exercise, expressed as the oxygen uptake at 100W, did not differ between the groups (Table 4). While HR at 100W was significantly lower in ATH compared to CTR (125±2 vs 165±2 $\cdot$ min^{-1}, P<0.001), oxygen pulse (VO_2/HR), a measure closely related to SV, was higher in ATH than in CTR. The relative difference in oxygen pulse between ATH and CTR (12.5±0.2 vs 9.6±0.2 mL/beat, P<0.001) was similar as that in heart rate, indicating similar CO at 100W. There were no differences in HR or oxygen pulse between WBA and RUN, while AC had lower HR and higher oxygen pulse than SC. As expected, oxygen pulse at 100W was significantly correlated to SV at rest (r=0.63, P<0.001, n=99). Systolic blood pressure was similar between the groups while sitting on the cycle ergometer before the exercise test. At 100 W, SBP did not differ between ATH and CTR or between RUN and WBA. However, the SC had a higher SBP at 100W than the AC.

Maximal exercise

VO_2max obtained during the maximal cycle ergometer test as well as maximal work load were as expected markedly higher in the ATH compared to CTR (39% and 50%, respectively, both P<0.001). A large difference (24% and 34%, respectively, both P<0.001) was also detected between AC and SC (higher in AC). The only difference detected between RUN and WBA was a trend (P<0.08) towards higher VO_2max (expressed in L/min) in the WBA, but this trend was abolished when the weight difference between the groups was considered. VO_2max expressed as $mL \cdot kg^{-1} \cdot min^{-1}$ was for the ATH group 53.6±1.8 (RUN) and 53.9±1.3 (WBA), whereas corresponding values for CTR were 44.2±1.0 (AC) and 37.1±0.9 (SC). For the ATH group, these values are given for the different performance categories in Table 3. For the 39 athletes who represented the top and elite categories in their age group in Sweden (Categories 1 and 2, see Methods), VO_2max values ($mL \cdot kg^{-1} \cdot min^{-1}$) and range in each sport are given in the Supplemental material, Table 3S. These values were within the range of published reference values for members of the Swedish womens´ national teams in the respective sports.[28] Reference data for triathletes and 1500-3000 m runners were obtained from other national teams.[29] In category 1 athletes, only one middle-distance runner and one orienteer had a VO_2max below the range of Swedish national team members. Of the 15 elite athletes (Category 2), five orienteers had a VO_2max below the range of Swedish national team members. It should be pointed out that, due to the low age of the present ATH group, it is likely that several of the present athletes had not yet reached their individual maximal achievable VO_2max level.[30] The maximal heart rate was lower in ATH than in CTR, but similar in RUN vs WBA and in AC vs SC. Oxygen pulse, used as surrogate marker of SV, was 43% (P<0.001) higher in ATH than in CTR (compared to the 29% difference in echocardiographically determined SV at rest and the 30% difference in oxygen pulse at 100W, see above). Similar to the value at 100W, the oxygen pulse at maximal exercise was

significantly correlated to SV at rest (r=0.67, P<0.001, n=99). The correlation coefficient between the oxygen pulse values at 100W and at maximal exercise was r=0.87 (P<0.001, n=99). Systolic blood pressure could for technical reasons not be accurately determined at maximal exercise, but was determined at a HR of 170 (ATH 182±2 mmHg vs CTR 164±2, P<0.001). There were no differences between RUN and WBA or between AC and SC regarding SBP at HR 170/min.

Correlations to measures of arterial distensibility and common carotid artery geometry (Table 5).

In the CTR group, AI@75 was strongly negatively correlated with the body weight-normalized maximal work load reached on the cycle ergometer (r=-0.61, P<0.001). In a multiple stepwise regression model, only the work capacity remained an independent predictor of AI@75 (ß=-0.61, R^2=0.37), whereas PMAP, height and HR were excluded. HR was correlated to the arterial distensibilty in the whole CTR group, but most apparent in the SC cohort. In this group, the correlation coefficient between HR and PWVcf was r=0.61, (p<0.001) and that between HR and CCA DC -0.63 (p<0.001). The expected negative association between blood pressure and arterial wall distensiblity was more clearly seen in the CTR group, where PWVcf was significantly correlated to peripheral pulse pressure (PPP) (r=0.40, p<0.01), with no corresponding association in the ATH. In the SC group, MAP was related to both PWVcf (r=0.60, p<0.001) and CCA DC (r=-0.66, p<0.001). Besides MAP (ß=-0.46, R^2=0.44), was also HR independently related to CCA DC (ß=-0.39, R^2=0.11, p<0.05) in the SC group.

Discussion

The first main finding of the present study was that neither arterial distensibility in the central elastic arteries (PWVcf and CCA DC) nor the carotid IMT was different in young women of similar age, weight, height and waist/hip-ratio, despite large differences in accumulated physical activity and physical training state. The inclusion criteria dictated that ATH had performed at least six training sessions per week over the last five years and had started their dedicated exercise training before they became fifteen years old. This would equal a difference of at least 3000 hrs of sports training compared with the sedentary control group who had never been involved in regular endurance or strength training in their leisure time. The data therefore indicate that, in normal weight women 17-25 years old, neither extensive long-term aerobic training nor a sedentary life-style induces measurable influence on arterial wall properties of central elastic arteries.

The intensity and duration of endurance training performed by ATH was close to maximal for young women and therefore had the potential to induce a high cumulative stimulus on the arterial walls. This criterion is important to fulfil before one can conclude whether high-level endurance training in early age has the ability to significantly alter the arterial wall properties in young women. Twenty-five of the athletes were categorized as top-level athletes, i.e. the absolutely best in the country in their age group (Category 1, see Methods), and had very high aerobic fitness as verified by their determined VO_2max level (see Results). Nevertheless, the comparison between ranking categories of athletes (Table 3) indicates that the national ranking of the athletes had no or only minor importance for the determined pulse

wave and arterial distensibility data. This supports the concept that it is the high amount of training, a characteristic of all athletes of the present study, together with training type that were the determining factors behind the results observed.

The conclusion from the present data that neither extensive endurance training nor a sedentary life-style are accompanied by measurable differences in arterial wall properties of central elastic arteries in young women is in accordance with a previous cross-sectional study on female athletes, in which 7 of the 9 subjects were middle-distance and long-distance runners (21±1 years of age), with a competitive career of 6 years, where no differences in carotid artery compliance or distensibility coefficient were found relative to controls.[20] The present conclusion is also in accordance with a study,[15] where no IMT-changes (femoral aorta) were found in endurance trained women (mean age 30 years), in spite of a significant IMT reduction in endurance-trained men. The present conclusion is in some disagreement with a previous study, involving 16 men and 13 women with an average age of 27 (20-40) years, showing an inverse correlation between VO_2max and carotid IMT and stiffness index.[13] However, it can be speculated that the correlations reported in that study mainly stemmed from the young male participants, where positive effects of exercise training regarding central arterial wall characteristics have been previously documented.[16-19] In the present study neither PWVcf, CCA DC nor carotid intima-media thickness was significantly correlated with VO_2max.

The lack of an obvious association in women between the amount of physical exercise and central arterial compliance, as indicated by the present and previous studies, corroborates the notion that central arterial wall characteristics are more resistant to physical training-induced change in young women than in young men. A plausible explanation to a gender difference in early age is provided in a study by Ahimastos et al.,[31] who found that prepubertal females had

stiffer large arteries and higher pulse pressure than age-matched males, but that females during puberty developed more distensible large arteries. These changes during puberty suggested that large artery stiffness is strongly modulated by both male and female sex steroids. In women, such effects may in some way be related to the effect of estrogen to inhibit sympathetic outflow or via other mechanisms.[32] In the present investigation, the study groups were similar in their use of contraceptives. Even if central arterial wall characteristics seem resistant to change with physical training in young women, it has been clearly documented at older age that endurance training positively influences central arterial compliance both in women and men.[33,34] This effect mainly consists of a reduction in the age-related decline in carotid artery compliance (by 50%).[33]

There is evidence that endurance training involving running in some instances leads to increased arterial stiffening,[35] a finding that has been related to the eccentric contractile component of downhill running.[36] In the present study, the results on central arterial compliance in young women were similar for the runners (RUN) and the whole-body endurance athletes (WBA). Therefore, we have no evidence that running *per se* modulated the arterial distensibility in the studied group of young women. It has been speculated that running with more prolonged bouts of exercise would be necessary for this potential negative vascular effect to be observed.[37]

The second main finding of the present study was that arterial distensibility in the muscular arteries was markedly different between the different study groups according to their type and level of physical activity. Arterial stiffness in the muscular arteries of the upper extremity was measured in the present study as the carotid-radial pulse wave velocity (PWVcr). This value was significantly lower in WBA than in RUN, but not significantly different between ATH and CTR. In addition, the quotient between the central arterial pulse wave velocity

(PWVcf) and PWVcr was significantly higher in WBA than in RUN. By the aid of applanation tonometry, the pulse pressure wave form was traced at different sites in order to calculate augmentation index (AI). From the radial artery wave form, an implemented transfer function synthesized the aortic wave form in order to achieve the aortic augmentation index (AI). AI normalized to a HR of 75, (AI@75) differed between all study groups in a step-wise fashion: SC > AC > RUN > WBA, although the difference between SC and AC did not remain statistically significant after an ANCOVA controlling for differences in both MAP and body height ($P<0.1$). In accordance with the difference detected between ATH and CTR in the present study, a previous report found a significant difference in AI between middle-aged competitive (predominantly male) endurance athletes and recreationally active subjects.[38] When a younger cohort is investigated (<50 years), AI is considered a more sensitive marker of arterial distensibility and function and of arterial aging than central PWV (PWVcf in the present study).[39] Specifically, AI reflects not only the distensibility and size of central arteries, but also that of the peripheral (muscular) arteries via the effect of wave reflection.[39] It is therefore possible that differences in the basal tone of resistance vessels in the upper and lower extremities affect the total amount of wave reflection during late systole, in part explaining the present group differences of aortic AI obtained among ATH and between ATH and CTR. The present data do not provide definite insights into the possible mechanisms that may underlie effects on arterial distensibility of habitual aerobic exercise. Nevertheless, in the CTR group, we found that the aortic AI was strongly (inversely) dependent on the exercise capacity on the cycle ergometer. Together with the lower PWVcr recorded in the WBA group, this indicates that regular muscle activation is an important factor with the potential to influence the distensibility in muscular arteries. There is some support of this notion in a recent study on male and female endurance athletes, aged 18-55 years, where a negative relationship between VO_2max and AI@75% was found for the men

and significantly lower values of AI@75% for women with a VO_2max >45 mL · kg^{-1} · min^{-1}.[24] There is some evidence that endurance training may lower muscle sympathetic nerve traffic,[40] but other data argue against this notion.[41,42] Irrespective of this, it has been shown that aerobic exercise training may modulate sympathetic vasoconstriction in resting skeletal muscle and to enhance functional sympatholysis through a nitric oxide–dependent mechanism.[43,44] That lower muscle sympathetic vasoconstriction could to some extent explain the lower AI in the physically trained groups is however contradicted by the finding that the calculated value of total peripheral resistance (TPR) was not significantly different between any of the groups of the present study (Table 2). Therefore an alternative and more likely explanation of the detected differences in AI with exercise training or sedentary life style, in spite of that indicators of central arterial distensibility were not different, may be changes in endothelial function as a result of the level of exercise-induced increase in shear stress.[45,46] An inverse correlation has been reported between AI and the nitric oxide synthase activity of vascular endothelium.[47,48] The present data indicate that the effect of regular muscle activation to enhance the distensibility in the muscular arteries is strong enough to override the effect of distending pressure, which is normally one of the main determinants of arterial wall mechanics, as also indicated by the correlations in Table 5. One example of this is that the WBA and AC groups had clearly different values of PWVcr although PMAP was identical. Another example is the lower PWVcr in WBA than in RUN, in spite of PMAP being higher in WBA than in RUN.

It has been shown that women have higher central AI than men, irrespective of age.[39,49] The cause of the higher AI in women is not currently known, but it can be speculated that smaller dimensions of large peripheral arteries may be a contributing factor. In middle-aged and older individuals, a high AI is associated with a higher cardiovascular risk and this is especially

true for women.[50] Whether the aortic-brachial PWV ratio, a less blood pressure-dependent measure, may provide additional prognostic value in predicting overall cardiovascular mortality compared to PWVcf alone is debated.[51,52] In response to normal aging, central arteries stiffen much faster than the peripheral arteries.[52] It is likely that the PWV ratio better reflects differences between cohorts in the upper extremity wall behaviour than PWVcr alone, due to it being less pressure dependent. Nevertheless, we can not at this point conclude anything regarding whether differences in AI and PWVcf/PWVcr detected in 17-25 year old women, as in the present study, will have an impact on the incidence of cardiovascular disease later in life.

As mentioned above, a factor that may explain differences in AI is the arterial dimension. In the present study, only the dimension of the common carotid artery (CCA) was studied. Of the two used off-line methods for lumen diameter determination, (Method1 and Method2, see table 2), only method1 showed a slight absolute difference between groups (ATH>CTR; AC>SC), but not after indexing by appropriate dimension, such as body surface area (BSA), body height or the square root of BSA. Previous studies have addressed the impact of regular exercise on CCA LD. Walther et al.[12] found increased CCA LD in young male endurance athletes, whereas differences in physical fitness level had no influence in a mixed group of young men and women.[53] On the other hand, it is firmly established that endurance training in young men results in expansive remodeling with increased lumen diameter of conduit peripheral arteries to the exercised limbs.[54,55] Since common carotid artery blood flow only increases slightly during intense aerobic exercise,[56] and far less than in conduit arteries that supply the working muscles, it is conceivable that neither pressure nor shear stress have enough impact on the carotid wall to induce remodeling in young women. In the present study, PWVcr was lower in WBA than in RUN, which may be an effect of long-term upper

body exercise by WBA, indicating altered arterial wall property and/or geometry along the arm. Conduit artery lumen diameter data in young women in response to exercise training have not previously been reported separately and also in the present study, data on the lumen diameter of conduit peripheral arteries are lacking. Thus it seems likely that differences in arterial dimension may be one factor that explains the differences between groups noted in AI. In a previous study, we found that trained females had larger Inferior Vena Cava dimensions compared to untrained females.[57]

Based on the knowledge that hypertensive middle-aged and aged women have higher risk of developing left ventricular hypertrophy and severe heart failure than men, it has been concluded that preventive strategies directed toward earlier and more aggressive blood pressure control are especially important in women.[22] In the light of this, the present blood pressure data may provide some clues regarding the preventive potential of physical exercise in women. Although systolic blood pressure at rest did not differ between athletes and controls, controls had higher mean arterial pressure. A striking result regarding blood pressure was the markedly higher systolic blood pressure during cycling at 100 W in the sedentary (SC) compared to the normally active controls (AC), despite the same resting systolic blood pressure. This is likely explained by a more pronounced exercise pressor reflex,[58] secondary to the SC group being closer to the anaerobic threshold due to their lower VO_2max. In the present study, based on values determined at rest, HR was inversely correlated to the arterial distensibility in the whole CTR group, and most apparent in the SC cohort. In addition, the expected negative association between blood pressure and arterial wall distensiblity was more clearly seen in the CTR than in the ATH group. Whether a similar difference between ATH and CTR also exists during ambulatory conditions involving physical activity is not known. A decreased distensibility in central and upper body arterial

segments has been documented immediately following acute aerobic exercise, which is likely reflecting changes occurring during exercise that continues into early recovery.[59,60] In view of evidence that the degree of decrease in arterial distensibility with aerobic exercise at a given exercise intensity is higher in sedentary than in well-trained individuals,[61] it is conceivable that the increases in HR and blood pressure that accompanies physical exercise are involved.[62]

The significant differences between the SC and AC groups in VO_2max and oxygen pulse (a measure closely related to SV) suggest that not only high intensity endurance training, but also the amount of everyday physical activities are determinants of an individual´s maximal circulatory and aerobic capacity. The present finding that the difference in oxygen pulse between ATH and CTR was higher at maximal exercise (43%) compared to the difference detected at 100W work load (30%) and to the difference in SV measured at rest (29%) is difficult to interpret. On one side, it has been shown that well-trained individuals, unlike untrained subjects, may display a continuous increase in SV with increased exercise intensity up to maximal work loads.[63,64] On the other side, long-term endurance-trained young athletes may display higher maximal arterio-venous oxygen difference compared with body size-matched healthy control subjects,[65] a difference which would lead to a higher oxygen pulse not related to SV.

Limitations: First, although suitable for exploring associations between variables and investigating between-group differences, the cross-sectional design applied in the current study has inherent limitations in establishing cause-effect relationships. Therefore, it can not be excluded that also other differences between the groups have been present and influenced

the results, even if age, height and BMI were not significantly different between the ATH and CTR groups of the present study. Second, we did not measure PWV specifically in the lower limb and therefore do not know whether differences in lower limb arterial distensibility exist and contribute to the difference between ATH and CTR regarding aortic AI. Third, as discussed above, conduit artery lumen diameter and functional differences in the vascular endothelium, which both could have affected differences in AI, were not determined in the present study.

In conclusion, the present data indicate that elastic artery distensibility and carotid artery IMT in normal weight women, 17-25 years old, are similar in individuals who have performed extensive endurance training over several years and in those with a sedentary life-style. On the other hand, our data suggest that high level of physical activity at young age diminishes the late systolic pressure amplification in aorta, a factor linked to future cardiovascular risk in middle-aged women. This is especially apparent in sports where upper body work is added.

Material and methods

Subjects

Forty-seven female athletes (ATH) in sports with high aerobic requirements and 52 female controls (all 17-25 years) fulfilled the inclusion criteria and were enrolled for the study. All subjects were healthy non-smokers, non-snuff users, had never been pregnant, or shown any sign of cardiovascular disease or diabetes. In order to explore the regional effect of regular

exercise training on both the arm and leg vascular beds, the female athletes were divided into two main groups. One group practised endurance training mainly involving the legs (four middle-distance (800-1500 m) runners, four 1500-3000 m runners and 18 orienteers); referred to as RUNNERS, (RUN, n=26), while the other group was active in sports where also the muscles of the upper extremity are heavily involved (4 biathletes, 5 canoeists, 5 swimmers and 4 triathletes); referred to as WHOLE-BODY ENDURANCE ATHLETES (WBA, n=18). In addition, three of the endurance athletes that we recruited were cyclists. They could neither be classified as RUN nor WBA, but were included in the larger group of ATHLETES (ATH). Control subjects (CTR) were students recruited from Linköping University (n=15) or local high schools (n=37). The control subjects were prior to the experiments subdivided into two groups according to their history of physical exercise, SEDENTARY CONTROLS (SC, n=31), and NORMALLY ACTIVE CONTROLS (AC, n=21). The training volume/level of physical activity of ATH and CTR is given in the Results section. All but 7 ATH and 4 CTR had regular menstruations. 25 ATH and 19 CTR were on contraceptives. All subjects gave their written informed consent to participate in the study that was approved by the Regional Ethical Review Board, Stockholm, Sweden.

Blood pressure and body measurements

Non-invasive upper arm blood pressure was recorded with an oscillometric method (Dinamap PRO 200 Monitor, Critikon, Tampa, FL, USA). A cuff was wrapped around the subject's upper arm and, following automatic cuff inflation and deflation, the systolic, diastolic and mean blood pressures were presented on the monitor based on calculations made by the implemented algorithm. Body weight was measured to the nearest 0.5 kg and height to the nearest 0.5 cm. The circumference of the hip and waist was determined to the nearest 0.5 cm

with a measurement tape placed in the horizontal plane. The waist circumference was determined at the level of the narrowest circumference of the torso between the lowest rib and the iliac crest.[66] This measure was also used in the waist circumference/hip circumference ratio calculation.

Exercise test

A maximal cardiopulmonary exercise test was performed on an electronically braked cycle ergometer (ebike basic, GE Medical Systems, GmbH, Freiburg, Germany), connected to an exercise ECG system (Marquette CASE 8000, GE Medical Systems, Milwaukee, WI, USA). Heart rate (HR) was continuously monitored from a 12-lead ECG, whereas auscultatory blood pressure was measured in supine position at rest. Before and during exercise, the systolic upper arm blood pressure (SBP) was measured in sitting position by Doppler detection at the radial artery flow (Parks model 812, Parks Medical Electronics inc, Aloha, OR, USA) during cuff deflation. During exercise, the subject was wearing a facemask connected to a gas analyser for continuous breath-by-breath analysis of O_2 and CO_2 content in exhaled air (Jaeger Oxycon Pro, Viasys Healthcare, Hoechberg, Germany). 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 100 W. Data on respiratory gases were presented as averages of four (100W work load) or two (higher work loads) consecutive 15-second periods. The peak oxygen uptake (here designated as VO_2max) was defined as the highest mean value taken from two consecutive 15-s periods. Respiratory exchange ratio (RER) was calculated as the net output of carbon dioxide (VCO_2) divided by the simultaneous net uptake of oxygen (VO_2) and oxygen pulse (mL of oxygen consumed per heart beat) as VO_2/HR. The gas analysers were

calibrated against two gas mixtures with known O_2 and CO_2 concentrations prior to each test and the flow meters with an automatically generated constant flow. During exercise, the subject rated the perceived exertion according to the RPE scale.[67]

Vascular ultrasound

A digital ultrasound system (HDI 5000, Philips Medical Systems, ATL Ultrasound, Bothell, WA, USA), equipped with a 38 mm 5–12 MHz linear array transducer (L12–5), was used to scan the carotid artery in the longitudinal direction and oriented horizontally in the image. Prerequisites for the measurements include that the double-line pattern from the boundaries of the lumen-intima and media-adventitia is clearly visible at both the near and the far wall. Standard instrument settings were used but it was desirable to achieve the best possible spatial and temporal quantification. Therefore the area of interest was zoomed using HDZoom, which changes the scan settings so that only the zoomed area is scanned. Furthermore, only one transmit focus was used, and the persistence function was off. These settings allowed a frame rate of 55 Hz, and a spatial quantification of 52 µm in each direction, i.e. a resolution of 19.2 pixels/mm. The data, compressed scan-converted magnitude information, was stored as consecutive frames. The acquisition memory of the ultrasound scanner allowed up to 5.5 seconds of data to be collected. From this 5.5 s cine-loop sequence, intima-media thickness (IMT) and lumen diameter (LD) were measured (method 2, M2, as described below). In addition frozen end-diastolic images were stored for analysis using method 1 (M1, see below). The ultrasound B-mode cineloop was transferred to a PC for post processing and visualized in HDILab (Philips Medical Systems, ATL Ultrasound, Bothell, WA, USA), a software designed for off-line cineloop analysis, where the algorithms for measurement of lumen diameter,[68] diameter change,[69] and IMT,[70] were

implemented. The reader marked the location for automatic calculation of the lumen diameter change within a 2.5 mm wide zone and visualized the outlined traces of the near and far wall by replaying the full cine-loop, before the window showing the diameter distension curve was opened. Successful lumen diameter (LD) wall-tracking was followed by calculation of the far wall IMT. This method (Ultrasound Arterial Characterisation, UAC) is referred to as method 2 (M2) in the results section and in Table 2.

In addition, two consecutive frozen images with special focus on lumen-intima echo and media-adventitia echo of the far arterial wall were saved. Later, the digital B-mode images were transferred to a personal computer, where software for offline measurement of LD and IMT is installed (Artery Measurement System II, AMS2, Image and Data Analysis, Gothenburg, Sweden). Calibration and subsequent measurement were performed by manually tracing a cursor along the leading edge of the intima-lumen echo of the near wall, the leading edge of the lumen-intima echo and the media-adventitia echo of the far wall over a 10 mm long section. During analysis the measurement window was hidden for the reader and values were saved in a text file. This method (Artery Measurement System, AMS) is referred to as method 1 (M1) in the results section and in Table 2.

Cardiac Ultrasound

The echocardiographic examination was carried out with the subjects at rest in the left lateral decubitus position and included registrations and measurements as previously described.[71] At the echocardiographic examination, the left ventricular outflow tract (LVOT) diameter and velocity time integral (VTI) were obtained.[72,73] Heart rate was measured in the same recordings. From these variables, stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) were calculated as described below (see Calculations and data analysis).

Applanation tonometry

The SphygmoCor system (Model MM3, AtCor Medical, Sydney, Australia) equipped with a Millar pressure tonometer was used in order to derive pulse waves, which were transferred on-line to the connected personal computer where software (SphygmoCor version 8.0) was installed. For pulse wave analysis, the central pressure waveform was obtained by a transfer function, calculated from a 10 seconds recording of the radial artery pressure waveform, which was calibrated using the brachial artery systolic- and diastolic pressure. Augmentation index (AI) and augmentation pressure (Aug) was automatically calculated from the aortic waveform as shown in Figure 1. 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). By connecting ECG to the SphygmoCor system, calculation of pulse wave velocity (PWV) was possible. Pulse wave transit time was achieved by recording duration from peak R-wave to intersection tangent of pulse wave arrival to proximal or distal sites during 10 seconds. The pulse travelling distance was estimated by placing a yardstick along the body surface from 1) the suprasternal notch to femoral pulse via umbilicus, and 2) the suprasternal notch to the radial pulse, and subtracting the distance to the carotid recording site to adjust for simultaneous pulse propagation in different directions within the arterial tree. Carotid → femoral PWV (aortic PWV, in the following denoted as PWVcf) and Carotid → radial PWV (arm PWV, in the following denoted as PWVcr) were automatically calculated (distance / time), according to the subtraction method. Heart rate readings were taken from the pulse wave recordings.

Study protocol

All subjects were instructed to abstain from strenuous physical exercise 24 hrs prior to, and from drinking beverages containing alcohol or caffeine 12 hrs before the vascular examination, which took place with the subject in supine position in a silent room with air temperature 22-24˚C. Following ten minutes of rest, bilateral upper arm blood pressure was registered. ECG leads were connected to the subject. A tonometer pencil probe was pressed towards alternately the left femoral and right carotid artery, and later the left radial and right carotid artery, in order to estimate pulse wave velocity and analyse the pressure pulse configuration. The right carotid was scanned and zoomed B-mode images of the distal common carotid artery (1-3 cm proximal from the carotid bifurcation) were recorded for later off-line analysis. Oscillometric left upper arm blood pressure was measured before each new set of pulse wave recordings, and before and after the ultrasound scanning. In a second examination room, body measurements were followed by the exercise test. The cardiac ultrasound examination was either performed as the first test of the day or on a separate occasion. All presented data from the vascular examination, including blood pressure recordings, are mean values obtained from two consecutive registrations. One investigator performed all examinations and measurements. The only exception was cardiac ultrasound which was performed by one of several experienced operators. All cardiac recordings were later checked by one responsible investigator.

Calculations and data analysis

Stroke volume, CO and TPR were calculated from LVOT diameter, LVOT-VTI and HR data obtained at the echocardiographic examination as described above.

$SV\ (mL) = LVOT_{VTI} \cdot LVOT_{AREA}$ (equation 1)

assuming that LVOT is circular in shape.

$CO\ (mL \cdot min^{-1}) = SV \cdot HR$ (equation 2)

TPR was calculated as:

$TPR\ (dyn \cdot s \cdot cm^{-5}) = 80 \cdot MAP/CO$ (equation 3)

Distensibility coefficient (DC) is the relative increase of arterial cross-sectional area for a given increase in pressure.

$$DC\ (10^{-3}/kPa) = \frac{2D\Delta D + \Delta D^2}{\Delta P D^2} \quad \text{(equation 4)}$$

where ΔP is pulse pressure increase in kPa, D is the minimum diastolic diameter in mm, ΔD is pulsatile diameter increase (mm) and ΔD^2 is the square of the pulsatile diameter increase (mm^2). Calibration of the carotid artery pressure wave was done from MAP obtained from the integrated radial artery pressure curve in combination with diastolic brachial pressure (DBP). Calculated carotid pulse pressure was used in the calculation of the common carotid artery DC.

The synthesized 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 (PP), see Figure 1.

AI % = aug/PP x 100 (equation 5)

Aug (mmHg) is achieved by subtracting the first systolic peak (P1) from the second systolic peak (P2), PP (mmHg) is pulse pressure.

The registered local augmentation index in the carotid artery (CA AI) and the radial artery (RA AI or Peripheral AI) are defined as the pulse pressure at the second systolic peak (P2) divided by the pressure at the first systolic peak (P1).

CA AI % or Per AI % = P2/P1 x 100 (equation 6)

When comparing VO_2max data of the present athletes with reference values from womens´ national team members, it was taken into consideration that VO_2max determination during cycle ergometer exercise, as in the present study, yields lower results than VO_2max obtained during treadmill running (inclination ≥3 degrees), as was done when obtaining the reference values.[28] The VO_2max during sitting upright cycle exercise is normally estimated to be 92-96% of VO_2max achieved during uphill treadmill running.[28]

Statistical analysis

Version 10 of the STATISTICA package was used. The Kolmogorov-Smirnov test was used to confirm that data-distribution did not differ from normality. Differences between groups were tested with the Student´s t-test in two consecutive steps, first between ATH and CTR and then between the subgroups within the ATH and CTR groups, respectively (RUN vs WBA and SC vs AC). No *post hoc* test was performed. Correlation or multiple stepwise regressions was used to evaluate the association between continuous data. ANCOVA analyses were used to control for effects of extraneous variables, such as PMAP, HR and Body Height, that might have influenced Pulse wave velocity (PWV) or Augmentation indices. In addition, since blood pressure is one of the main determinants of pulse wave velocity, values of PWV and Augmentation indices were also individually adjusted to PMAP following the formula (shown here for PWVcf only):

adjusted PWVcf = PWVcf + constant * (PMAPindividual – PMAPwhole group)

the constant being the slope of the linear regression line with PMAP as independent and PWV as dependent variable. All values were adjusted to a PMAP of 75.7 mm Hg, which was the mean PMAP of all subjects (=PMAPwhole group in formula). Two different linear regression lines were used (one for ATH and one for CTR, although using one line for the whole group ATH+CTR yielded virtually identical results). The PMAP-adjusted data are presented in the Supplemental material, Table 4S. Values are presented as mean ± SEM except as noted. $P<0.05$ was considered statistically significant.

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Conflict of interest

None of the authors declare any conflict of interest.

References

1. Zhdanov VS, Sternby NH, Drobkova IP, Galakhov IE: Hyperplasia of coronary intima in young males in relation to development of coronary heart disease in adults. *Int J Cardiol* **76:** 57-64, 2000.

2. Martin H, Hu J, Gennser G, Norman M: Impaired endothelial function and increased carotid stiffness in 9-year-old children with low birthweight. *Circulation* **102:** 2739-44, 2000.

3. Berenson GS, Srinivasan SR: Prevention of atherosclerosis in childhood. *Lancet* **354:**1223-4, 1999.

4. Stary HC: Lipid and macrophage accumulations in arteries of children and the development of atherosclerosis. *Am J Clin Nutr* **72:** 1297S-1306S, 2000.

5. Mikola H, Pahkala K, Ronnemaa T, Viikari JS, Niinikoski H, Jokinen E, Salo P, Simell O, Juonala M, Raitakari OT: Distensibility of the aorta and carotid artery and left ventricular mass from childhood to early adulthood. *Hypertension* **65:** 146-52, 2015.

6. Lee DC, Sui X, Artero EG, Lee IM, Church TS, McAuley PA, Stanford FC, Kohl HW 3rd, Blair SN: Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the Aerobics Center Longitudinal Study. *Circulation* **124:** 2483-90, 2011.

7. Lee IM, Paffenbarger RS Jr: Preventing coronary heart disease: the role of physical activity. *Phys Sportsmed* **29:** 37-52, 2001.

8. Kaplan H, Thompson RC, Trumble BC, Wann LS, Allam AH, Beheim B, Frohlich B, Sutherland ML, Sutherland JD, Stieglitz J, Rodriguez DE, Michalik DE, Rowan CJ, Lombardi GP, Bedi R, Garcia AR, *et al.*: Coronary atherosclerosis in indigenous South American Tsimane: a cross-sectional cohort study. *Lancet* **389:** 1730-1739, 2017.

9. Katzmarzyk PT, Malina RM, Bouchard C: Physical activity, physical fitness, and coronary heart disease risk factors in youth: the Quebec Family Study. *Prev Med* **29:** 555-62, 1999.

10. Simons PC, Algra A, Bots ML, Grobbee DE, van der Graaf Y: Common carotid intima-media thickness and arterial stiffness: indicators of cardiovascular risk in high-risk patients. The SMART Study (Second Manifestations of ARTerial disease). *Circulation* **100:** 951-7, 1999.

11. Meyer AA, Kundt G, Lenschow U, Schuff-Werner P, Kienast W: Improvement of early vascular changes and cardiovascular risk factors in obese children after a six-month exercise program. *J Am Coll Cardiol* **48:** 1865-70, 2006.

12. Walther G, Nottin S, Karpoff L, Perez-Martin A, Dauzat M, Obert P: Flow-mediated dilation and exercise-induced hyperaemia in highly trained athletes: comparison of the upper and lower limb vasculature. *Acta Physiol (Oxf)* **193:** 139-50, 2008.

13. Hägg U, Wandt B, Bergström G, Volkmann R, Gan LM: Physical exercise capacity is associated with coronary and peripheral vascular function in healthy young adults. *Am J Physiol Heart Circ Physiol* **289:** H1627-34, 2005.

14. Pahkala K, Laitinen TT, Heinonen OJ, Viikari JS, Ronnemaa T, Niinikoski H, Helajarvi H, Juonala M, Simell O, Raitakari OT: Association of fitness with vascular intima-media thickness and elasticity in adolescence. *Pediatrics* **132:** e77-84, 2013.

15. Moreau KL, Silver AE, Dinenno FA, Seals DR: Habitual aerobic exercise is associated with smaller femoral artery intima-media thickness with age in healthy men and women. *Eur J Cardiovasc Prev Rehabil* **13:** 805-11, 2006

16. Ried-Larsen M, Grontved A, Ostergaard L, Cooper AR, Froberg K, Andersen LB, Moller NC: Associations between bicycling and carotid arterial stiffness in adolescents: The European Youth Hearts Study. *Scand J Med Sci Sports* **25:** 661-9, 2015.

17. Thijssen DH, Dawson EA, van den Munckhof IC, Birk GK, Timothy Cable N, Green DJ: Local and systemic effects of leg cycling training on arterial wall thickness in healthy humans. *Atherosclerosis* **229:** 282-6, 2013.

18. 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* **37:**267-71, 2005.

19. Otsuki T, Maeda S, Iemitsu M, Saito Y, Tanimura Y, Ajisaka R, Miyauchi T: Vascular endothelium-derived factors and arterial stiffness in strength- and endurance-trained men. *Am J Physiol Heart Circ Physiol* **292:** H786-91, 2007.

20. Hayashi K, Sugawara J, Aizawa K, Komine H, Yoshizawa M, Nakamura M, Yokoi T: Arterial elastic property in young endurance and resistance-trained women. *Eur J Appl Physiol* **104:** 763-8, 2008.

21. Ayer JG, Harmer JA, Marks GB, Avolio A, Celermajer DS: Central arterial pulse wave augmentation is greater in girls than boys, independent of height. *J Hypertens* **28:** 306-13, 2010.

22. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK: The progression from hypertension to congestive heart failure. *JAMA* **275:** 1557-62, 1996.

23. Barraclough JY, Garden FL, Toelle B, O´Meagher S, Marks GB, Cowell CT, Celermajer DS, Ayer JG: Sex differences in aortic augmentation index in adolescents. *J Hypertens* **35:** 2016-24, 2017.

24. Denham J, Brown NJ, Tomaszewski M, Williams B, O´Brien BJ, Charchar FJ: Aortic augmentation index in endurance athletes: a role for cardiorespiratory fitness. *Eur J Appl Physiol* **116:**1537-44, 2016.

25. Ashor AW, Lara J, Siervo M, Celis-Morales C, Mathers JC: Effects of exercise modalities on arterial stiffness and wave reflection: A systematic review and meta-analysis of randomized controlled trials. *PLoS One* **9:** e110034, 2014.

26. Laurent P, Marenco P, Castagna O, Smulyan H, Blacher J, Safar ME: Differences in central systolic blood pressure and aortic stiffness between aerobically trained and sedentary individuals. *J Am Soc Hypertens* **5:**85-93, 2011.

27. Montero D, Roche E, Martinez-Rodriguez A: The impact of aerobic exercise training on arterial stiffness in pre- and hypertensive subjects: A systematic review and meta-analysis. *Int J Cardiol* **173:** 361-8, 2014.

28. Åstrand PO, Rodahl K, Dahl HA, Strömme SB: *Textbook of work physiology. Physiological bases of exercise., 4th ed.,* Champaign, IL, Human Kinetics, 2003.

29. Suriano R, Bishop D: Physiological attributes of triathletes. *J Sci Med Sport* **13:** 340-7, 2010.

30. Rusko HK: Development of aerobic power in relation to age and training in cross-country skiers. *Med Sci Sports Exerc* **24:** 1040-7, 1992.

31. Ahimastos AA, Formosa M, Dart AM, Kingwell BA: Gender differences in large artery stiffness pre- and post puberty. *J Clin Endocrinol Metab* **88:** 5375-80, 2003.

32. Ettinger SM, Silber DH, Gray KS, Smith MB, Yang QX, Kunselman AR, Sinoway LI: Effects of the ovarian cycle on sympathetic neural outflow during static exercise. *J Appl Physiol (1985)* **85:** 2075-81, 1998.

33. Tanaka H, Dinenno FA, Monahan KD, Clevenger CM, DeSouza CA, Seals DR: Aging, habitual exercise, and dynamic arterial compliance. *Circulation* **102:** 1270-5, 2000.

34. Matsubara T, Miyaki A, Akazawa N, Choi Y, Ra SG, Tanahashi K, Kumagai H, Oikawa S, Maeda S: Aerobic exercise training increases plasma Klotho levels and reduces arterial stiffness in postmenopausal women. *Am J Physiol Heart Circ Physiol* **306:** H348-55, 2014.

35. Vlachopoulos C, Kardara D, Anastasakis A, Baou K, Terentes-Printzios D, Tousoulis D, Stefanadis C: Arterial stiffness and wave reflections in marathon runners. *Am J Hypertens* **23:** 974-9, 2010.

36. Burr JF, Boulter M, Beck K: Arterial stiffness results from eccentrically biased downhill running exercise. *J Sci Med Sport* **18:** 230-5, 2015.

37. Burr JF, Phillips AA, Drury TC, Ivey AC, Warburton DE: Temporal response of arterial stiffness to ultra-marathon. *Int J Sports Med* **35:** 658-63, 2014.

38. Edwards DG, Lang JT: Augmentation index and systolic load are lower in competitive endurance athletes. *Am J Hypertens* **18:** 679-83, 2005.

39. McEniery CM, Yasmin, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR, Investigators ACCT: Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). *J Am Coll Cardiol* **46:** 1753-60, 2005.

40. Grassi G, Seravalle G, Calhoun DA, Mancia G: Physical training and baroreceptor control of sympathetic nerve activity in humans. *Hypertension* **23:** 294-301, 1994.

41. Svedenhag J, Wallin BG, Sundlöf G, Henriksson J: Skeletal muscle sympathetic activity at rest in trained and untrained subjects. *Acta Physiol Scand* **120:** 499-504, 1984.

42. Seals DR: Sympathetic neural adjustments to stress in physically trained and untrained humans. *Hypertension* **17:** 36-43, 1991.

43. Just TP, Cooper IR, DeLorey DS: Sympathetic Vasoconstriction in Skeletal Muscle: Adaptations to Exercise Training. *Exerc Sport Sci Rev* **44:** 137-43, 2016.

44. Just, TP, DeLorey DS: Exercise training and alpha1-adrenoreceptor-mediated sympathetic vasoconstriction in resting and contracting skeletal muscle. *Physiol Rep* **4:** e12707, 2016.

45. Clarkson P, Montgomery HE, Mullen MJ, Donald AE, Powe AJ, Bull T, Jubb M, World M, Deanfield JE: Exercise training enhances endothelial function in young men. *J Am Coll Cardiol* **33:** 1379-85, 1999.

46. Tinken TM, Thijssen DH, Hopkins N, Dawson EA, Cable NT, Green DJ: Shear stress mediates endothelial adaptations to exercise training in humans. *Hypertension* **55:** 312-8, 2010.

47. Wilkinson IB, Qasem A, McEniery CM, Webb DJ, Avolio AP, Cockcroft JR: Nitric oxide regulates local arterial distensibility in vivo. *Circulation* **105:** 213-7, 2002.

48. Kinlay S, Creager MA, Fukumoto M, Hikita H, Fang JC, Selwyn AP, Ganz P: Endothelium-derived nitric oxide regulates arterial elasticity in human arteries in vivo. *Hypertension* **38:**1049-53, 2001.

49. London GM, Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME: Arterial wave reflections and survival in end-stage renal failure. *Hypertension* **38:** 434-8, 2001.

50. Cadeddu C, Franconi F, Cassisa L, Campesi I, Pepe A, Cugusi L, Maffei S, Gallina S, Sciomer S, Mercuro G, Working Group of Gender Medicine Italian Society: Arterial hypertension in the female world: pathophysiology and therapy. *J Cardiovasc Med (Hagerstown)* **17:** 229-36, 2016.

51. Fortier C, Sidibé A, Desjardins MP, Marquis K, De Serres SA, Mac-Way F, Agharazii M: Aortic-brachial pulse wave velocity ratio. A blood pressure-independent index of vascular aging. *Hypertension* **69:** 96-101, 2017.

52. Niiranen TJ, Kalesan B, Larson MG, Hamburg NM, Benjamin EJ, Mitchell GF, Vasan RS: Aortic-brachial arterial stiffness gradient and cardiovascular risk in the community. The Framingham Heart Study. *Hypertension* **69:** 1022-28, 2017.

53. Gando Y, Yamamoto K, Kawano H, Murakami H, Ohmori Y, Kawakami R, Sanada K, Higuchi M, Tabata I, Miyachi M: Attenuated age-related carotid arterial remodeling in adults with a high level of cardiorespiratory fitness. *J Atheroscler Thromb* **18:** 248-54, 2011.

54. Black JM, Stohr EJ, Shave R, Esformes JI: Influence of exercise training mode on arterial diameter: A systematic review and meta-analysis. *J Sci Med Sport* **19:** 74-80, 2016.

55. Rowley NJ, Dawson EA, Hopman MT, George KP, Whyte GP, Thijssen DH, Green DJ: Conduit diameter and wall remodeling in elite athletes and spinal cord injury. *Med Sci Sports Exerc* **44:** 844-9, 2012.

56. Sato K, Ogoh S, Hirasawa A, Oue A, Sadamoto T: The distribution of blood flow in the carotid and vertebral arteries during dynamic exercise in humans. *J Physiol* **589:** 2847-56, 2011.

57. Hedman K, Nylander E, Henriksson J, Bjarnegård N, Brudin L, Tamas E: Echocardiographic Characterization of the Inferior Vena Cava in Trained and Untrained Females. *Ultrasound Med Biol* **42:** 2794-2802, 2016.

58. Secher NH, Amann M: Human investigations into the exercise pressor reflex. *Exp Physiol* **97:** 59-69, 2012.

59. Rakobowchuk M, Stuckey MI, Millar PJ, Gurr L, MacDonald MJ: Effect of acute sprint interval exercise on central and peripheral artery distensibility in young healthy males. *Eur J Appl Physiol* **105:** 787-95, 2009.

60. Mutter AF, Cooke AB, Saleh O, Gomez YH, Daskalopoulou SS: A systematic review on the effect of acute aerobic exercise on arterial stiffness reveals a differential response in the upper and lower arterial segments. *Hypertens Res* **40:** 146-72, 2017.

61. Liu HB, Yuan WX, Quin KR, Hou J: Acute effects of cycling intervention on carotid arterial hemodynamics: baketball athletes versus sedentary controls. *BioMedical Engineering Online* **14:** Suppl 1, S17, 2015.

62. Quan HL, Blizzard CL, Sharman JE, Magnussen CG, Dwyer T, Raitakari O, Cheung M, Venn AJ: Resting heart rate and the association of physical fitness with carotid artery stiffness. *Amer J Hypertens* **27:** 65-71, 2014.

63. Gledhill N, Cox D, Jamnik R: Endurance athletes' stroke volume does not plateau: major advantage is diastolic function. *Med Sci Sports Exerc* **26:** 1116-21, 1994.

64. Vella CA, Robergs RA: A review of the stroke volume response to upright exercise in healthy subjects. *Br J Sports Med* **39:** 190-5, 2005.

65. Montero D, Diaz-Canestro C, Lundby C: Endurance Training and VO_2max: Role of Maximal Cardiac Output and Oxygen Extraction. *Med Sci Sports Exerc* **47:** 2024-33, 2015.

66. Lohman TG: *Anthropometric standardardization reference manual*, Champaign, IL, Human Kinetics, 1988.

67. Borg G, Ljunggren G, Ceci R: The increase of perceived exertion, aches and pain in the legs, heart rate and blood lactate during exercise on a bicycle ergometer. *Eur J Appl Physiol Occup Physiol* **54:** 343-9, 1985.

68. Cinthio M, Jansson T, Eriksson A, Ahlgren AR, Persson HW, Lindström K: Evaluation of an algorithm for arterial lumen diameter measurements by means of ultrasound. *Med Biol Eng Comput* **48:** 1133-40, 2010a.

69. Cinthio M, Jansson T, Ahlgren AR, Lindström K, Persson HW: A method for arterial diameter change measurements using ultrasonic B-mode data. *Ultrasound Med Biol* **36:** 1504-12, 2010b.

70. Cinthio M, Ahlgren AR, Jansson T, Nilsson T, Lindström K, Persson, HW: An automatic method for measurement of intima-media thickness using B-mode data. In: NOWICKI, A., LITNIEWSKI, J. & KUJAWSKA, T. (Eds.) *Acoustical Imaging.* London, U.K., Springer, 2012.

71. Hedman K, Tamas E, Henriksson J, Bjarnegård N, Brudin L, Nylander E: Female athlete's heart: Systolic and diastolic function related to circulatory dimensions. *Scand J Med Sci Sports* **25:**372-81, 2015.

72. Ihlen H, Amlie JP, Dale J, Forfang K, Nitter-Hauge S, Otterstad JE, Simonsen S, Myhre E: Determination of cardiac output by Doppler echocardiography. *Br Heart J* **51:** 54-60, 1984.

73. Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA: Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr* **15:** 167-84, 2002.

Table 1. Physical characteristics of the female athletes and controls

	Athletes (ATH)			Controls (CTR)			P-value		
	All (n=47)	RUN (n=26)	WBA (n=18)	All (n=52)	SC (n=31)	AC (n=21)	ATH/ CTR	RUN/ WBA	SC/ AC
Age, y	20.3±0.4	20.2±0.4	19.4±0.5	20.4±0.3	19.9±0.5	21.1±0.6	NS	NS	NS
Height, m	1.68±0.01	1.68±0.01	1.68±0.01	1.66±0.01	1.64±0.01	1.68±0.01	NS	NS	<0.01
Weight, kg	61±1.0	58±1.2	64±1.3	57±0.9	56±1.3	59±1.2	<0.05	<0.01	<0.05
BMI, kg/m^2	21.6±0.3	20.5±0.3	22.7±0.4	20.8±0.3	20.7±0.5	21.0±0.4	NS	<0.001	NS
WC (cm)	72±0.6	70±0.7	74±0.9	71±0.8	70±1.2	72±1.4	NS	<0.01	NS
W/H ratio	0.76±0.005	0.75±0.005	0.77±0.007	0.74±0.006	0.74±0.009	0.74±0.008	<0.05	<0.05	NS

Values are mean±SEM. RUN, runners; WBA, whole-body endurance athletes; SC, sedentary controls; AC, normally active controls; WC, waist circumference; W/H, waist to hip ratio.

Table 2. Arterial properties and hemodynamics at rest in female athletes and controls.

	Athletes (ATH)			Controls (CTR)			P-value		
	All (n=47)	RUN (n=26)	WBA (n=18)	All (n=52)	SC (n=31)	AC (n=21)	ATH/ CTR	RUN/ WBA	SC/ AC
PSBP (mmHg)	105±1.5	101±1.7	110±2.3	107±1.2	108±1.7	106±1.7	NS	<0.01	NS
PDBP (mmHg)	58±0.8	57±1.2	59±1.2	61±1.0	62.±1.4	60±1.5	<0.05	NS	NS
PMAP (mmHg)	74±0.9	72±1.2	76±1.4	77±1.1	79±1.6	76±1.4	<0.05	<0.05	NS
PPP (mmHg)	47±1.3	45±1.5	51±2.0	46±0.8	47±0.9	45±1.3	NS	<0.05	NS
CSBP (mmHg)	86±1.1	84±1.4	89±1.7	89±1.1	90±1.6	87±1.5	NS	<0.05	NS
CPP (mmHg)	28±0.7	26±0.9	30±1.0	27±0.5	27±0.6	27±0.8	NS	<0.01	NS
AI (%)	-0.6±1.6	1.3±2.0	-4.0±2.7	-0.3±1.3	0.8±1.8	2.0±1.8	NS	NS	NS
AI@75 (%)	-12.8±1.6	-10.7±2.0	-16.4±2.5	-2.6±3.2	0.0±1.4	-6.4±1.7	<0.001	<0.05	NS

RA AI (%)	49±1.8	51±2.1	45±3.3	43±1.4	43±1.8	42±2.2	<0.05	NS	NS
RA AI@75 (%)	35.6±1.7	38.3±2.0	31.7±3.0	38.5±1.3	40.5±1.6	35.4±2.1	NS	0.05	NS
CA AI@75 (%)	75±1.9	75±2.4	76±3.3	75±1.7	75±2.4	75±2.5	NS	NS	NS
PWVcf (m/s)	5.1±0.1	5.0±0.1	5.3±0.2	5.2±0.1	5.2±0.2	5.2±0.1	NS	NS	NS
PWVcr (m/s)	7.0±0.1	7.2±0.1	6.7±0.2	7.4±0.1	7.2±0.2	7.5±0.2	NS	<0.05	NS
PWVcf / PWVcr	0.73±0.02	0.69±0.01	0.81±0.05	0.73±0.03	0.74±0.04	0.71±0.04	NS	<0.05	NS
CCA LD (mm) *M1*	5.4±0.0	5.5±0.1	5.4±0.1	5.3±0.0	5.1±0.1	5.4±0.1	<0.05	NS	<0.05
CCA LD (mm) *M2*	5.4±0.1	5.4±0.1	5.4±0.1	5.3±0.1	5.2±0.1	5.4±0.1	NS	NS	NS
CCA IMT (mm) *M1*	0.46±0.01	0.46±0.01	0.46±0.01	0.46±0.01	0.46±0.01	0.46±0.01	NS	NS	NS
CCA IMT (mm) *M2*	0.53±0.01	0.54±0.01	0.52±0.01	0.53±0.01	0.53±0.01	0.53±0.01	NS	NS	NS
CCA DC(10^{-3}/kPa)	92±2.3	94±3.6	88±2.9	84±2.5	82±3.3	89±3.5	NS	NS	NS

HR (min^{-1})	55±1.4	54±1.4	57±2.9	75±1.7	78±2.3	69±2.1	<0.001	NS	<0.01
SV (mL/min^{-1})	76±2.0	73±2.5	79±3.3	59±1.1	57±1.5	61±1.4	<0.001	NS	NS
TPR ($dyn{\cdot}s\ {\cdot}cm^{-5}$)	1541±44	1571±57	1526±79	1570±42	1577±57	1558±61	NS	NS	NS

Values are mean±SEM. RUN, runners; WBA, whole-body endurance athletes; SC, sedentary controls; AC, normally active controls; PSBP, peripheral systolic blood pressure; PDBP, peripheral diastolic blood pressure; PMAP, peripheral mean arterial pressure; PPP, peripheral pulse pressure; CSBP, central systolic blood pressure; CPP, central pulse pressure; AI, aortic augmentation index; RA AI, radial artery augmentation index; CA AI, carotid artery augmentation index; @75, AI corrected to heart rate 75 min^{-1}; PWV; pulse wave velocity; cf, carotid-femoral; cr, carotid-radial; CCA, common carotid artery; LD, lumen diameter, *M1,* method 1; IMT, intima media thickness; DC, distensibility coefficient; HR, heart rate; SV, stroke volume; TPR, total peripheral resistance.

Table 3. Pulse wave and aerobic capacity data in subgroups of athletes.

	RUNNERS (n=26)			WHOLE BODY ENDURANCE ATHLETES (n=18)			CYCLISTS (n=3)	
Performance level	1 (n=8)	2 (n=11)	3 (n=7)	1 (n=15)	2 (n=2)	3 (n=1)	1 (n=2)	2 (n=1)
VO_{2max} ($mL \cdot min^{-1} \cdot kg^{-1}$)	54.8±0.9	54.7±2.0	50.3±1.4	53.0±1.5	47	43	57	50
PWVcf (m/s)	4.8±0.2	5.0±0.2	5.1±0.2	5.3±0.3	5.1	5.3	4.9	4.5
PWVcr (m/s)	7.0±0.3	7.2±0.1	7.5±0.3	6.7±0.3	6.8	7.2	7.7	7.0
PWVcf / PWVcr	0.69±0.02	0.70±0.02	0.67±0.02	0.83±0.06	0.66	0.81	0.65	0.64
AI@75 (%)[A]	-10.6±5.4	-11.6±2.4	-9.3±2.5	-16.4±2.9	-18.5	-14.5	-15	-10
RA AI@75 (%)[B]	42.0±3.7	35.9±3.5	37.7±2.9	31.5±6.7	30.4	33.4	31	37

Data are mean±SE or mean. Performance level 1, among the absolutely best Swedish athletes in their sport and age group; Performance level 2, competitive on a high Swedish national level; Performance level 3, competitive on a high Swedish regional level. VO_{2max}, peak oxygen consumption.; PWV, pulse wave velocity; cf, carotid-femoral; cr, carotid-radial; AI@75, aortic augmentation index adjusted to heart rate 75; RA AI@75, radial artery augmentation index adjusted to heart rate 75. [A] Data from 15 Whole body endurance athletes (WBA); [B] Data from 16 WBA.

Table 4. Circulatory and ventilatory parameters during the incremental exercise test.

	Athletes (ATH)			Controls (CTR)			P-value		
	All (n=47)	RUN (n=26)	WBA (n=18)	All (n=52)	SC (n=31)	AC (n=21)	ATH/ CTR	RUN/ WBA	SC/ AC
100 Watt									
HR (min^{-1})	125±2	125±3	128±3	165±2	174±2	153±4	<0.001	NS	<0.001
PSBP (mmHg)	156±2	154±3	159±4	159±2	164±3	152±3	NS	NS	<0.001
RPE	10±0.2	10±0.3	10±0.4	14±0.3	15±0.5	13±0.4	<0.001	NS	<0.01
RER	0.94±0.01	0.93±0.01	0.96±0.01	0.97±0.01	0.99±0.01	0.93±0.01	<0.05	<0.05	<0.001
V_E ($L \cdot min^{-1}$)	35±0.6	35±0.9	36±1.0	43±1.2	47±1.5	39±1.2	<0.001	NS	<0.001
VO_2 ($L \cdot min^{-1}$)	1.54±0.01	1.53±0.01	1.56±0.02	1.56±0.01	1.57±0.02	1.54±0.02	NS	NS	NS
O_2 pulse	12.5±0.2	12.4±0.3	12.3±0.3	9.6±0.2	9.1±0.1	10.2±0.2	<0.001	NS	<0.001

V_E/VCO_2	25.4±0.4	26.0±0.5	24.8±0.7	29.0±0.5	29.9±0.6	27.8±0.7	<0.001	NS	<0.05
Maximal									
HR $_{peak}$ (min^{-1})	189±1	189±2	191±2	195±1	195±2	195±2	<0.05	NS	NS
RER	1.15±0.01	1.15±0.01	1.14±0.01	1.11±0.01	1.10±0.01	1.13±0.01	<0.01	NS	NS
V_E ($L \cdot min^{-1}$)	114±3	110±4	122±5	88±2	81±3	97±2	<0.001	NS	<0.001
VO_2 ($L \cdot min^{-1}$)	3.2±0.05	3.1±0.06	3.3±0.09	2.3±0.05	2.1±0.05	2.6±0.05	<0.001	NS	<0.001
O_2 pulse	16.9±0.3	16.5±0.3	17.2±0.4	11.8±0.3	10.6±0.2	13.5±0.3	<0.001	NS	<0.001
V_E/VCO_2	33.1±0.6	33.2±0.7	34.0±1.1	34.7±0.6	35.5±0.8	33.6±0.8	NS	NS	NS
Work load (W)	259±4	257±5	256±6	173±5	152±5	203±4	<0.001	NS	<0.001

Values are mean±SEM. RUN, runners; WBA, whole-body endurance athletes; SC, sedentary controls; AC, normally active controls; HR, heart rate; PSBP, peripheral systolic blood pressure; RPE, Rate of Perceived Exertion; RER, respiratory exchange ratio VCO_2/VO_2; V_E, pulmonary ventilation; VCO_2, net output of carbon dioxide; VO_2, net uptake of oxygen (oxygen consumption); O_2 pulse, mL oxygen consumption per heartbeat.

Table 5. Pearson's correlation coefficient for selected parameters.

	PWVcf			PWVcr			AI@75		
Variable	All (n=99)	ATH (n=47)	CTR (n=52)	All (n=99)	ATH (n=47)	CTR (n=52)	All (n=99)	ATH (n=47)	CTR (n=52)
BMI	**0.27†**	0.19	**0.40†**	-0.15	-0.07	-0.16	-0.02	-0.16	**0.31***
WC	**0.26***	0.02	**0.44†**	**-0.24***	-0.20	-0.24	-0.02	-0.26	0.25
W/H ratio	0.13	-0.07	**0.33***	**-0.27†**	**-0.29***	-0.22	-0.13	-0.23	0.11
HR	**0.32†**	0.18	**0.48‡**	0.14	-0.05	0.07			
HR_{100w}	0.03	-0.11	-0.06	0.10	-0.13	-0.04	**0.46‡**	0.05	0.27
PMAP	**0.52‡**	**0.40†**	**0.57‡**	**0.28†**	0.17	**0.34***	**0.28†**	0.08	**0.30***
PPP	0.18	0.03	**0.40†**	**-0.23***	-0.16	-0.36	-0.12	-0.28	-0.12
SBP_{100w}	0.11	-0.05	0.24	-0.09	-0.04	-0.19	0.06	-0.08	0.12
PWVcf				-0.04	-0.05	-0.07	0.18	0.22	0.11

PWVcr	-0.03	-0.05	-0.07				0.16	0.27	-0.04
AI@75	0.18	0.22	0.11	0.16	0.27	-0.04			
CCA DC	**-0.42‡**	**-0.39†**	**-0.38†**	**-0.23***	-0.11	-0.25	**-0.36‡**	**-0.31***	**-0.29***
VO_{2max}	0.06	0.17	0.17	-0.06	-0.02	0.17	**-0.45‡**	-0.09	**-0.43†**
$VO_{2max} \cdot kg^{-1}$	-0.08	-0.04	-0.01	-0.04	-0.07	0.12	**-0.51‡**	0.07	**-0.51‡**
$Watt_{max} \cdot kg^{-1}$	-0.12	-0.14	-0.02	-0.02	0.21	0.16	**-0.52‡**	0.12	**-0.61‡**

RUN, runners; WBA, whole-body endurance athletes; SC, sedentary controls; AC, normally active controls; WC, waist circumference; W/H, waist to hip ratio HR, heart rate; PMAP, peripheral mean arterial pressure; PPP, peripheral pulse pressure; SBP, systolic blood pressure; PWV, pulse wave velocity; cf, carotid-femoral; cr, carotid-radial; AI@75, aortic augmentation index adjusted to heart rate 75; CCA DC; common carotid artery distensibility coefficient; VO_{2max}, peak oxygen consumption; $Watt_{max,}$ peak work load on bicycle ergometer. *** p <0.05; †<0.01; ‡<0.001**.

Legends to figures

Figure 1. Schematic illustration of the aortic pulse pressure waveform, from which Augmention index (AI) and Augmentation pressure (Aug) was automatically calculated. Aug (mmHg) is achieved by expressing the height of the second systolic peak (P2) over the first systolic shoulder (P1). 1A. The expected aortic waveform in a middle-age woman. 1B. The typical aortic waveform in a young woman in the present control group (CTR).

Figure 2. Aortic pulse wave velocity (PWVcf) in relation to the arm pulse wave velocity (PWVcr) in the different study groups. PWVcf/PWVcr is a direct measure of the predominantly muscular artery distensibility along the arm in relation to that of the central elastic arteries. PWVcf denotes Carotid → femoral PWV (aortic PWV) and PWVcr denotes Carotid → radial PWV (arm PWV). These were automatically calculated (distance / time), as described in Methods. ATH, athletes (n=47); CTR, controls (n=52); RUN, runners (n=26); WBA, whole-body endurance athletes (n=18); SC, sedentary controls (n=31); AC, normally active controls (n=21). * Significantly different from the group indicated, $P<0.01$.

Figure 3. The peripheral (radial) augmentation index (RA AI%) and the synthesized aortic augmentation index (AI%) in the different study groups. The radial pulse pressure waveform was recorded locally with an applanation tonometer to calculate the peripheral augmentation index (RA AI). Based on the recorded waveform, an implemented transfer function synthesized the aortic pulse pressure waveform in order to achieve AI. AI@75 denotes AI normalized to a HR of 75. For further explanation, see the Legend to Figure 1.

* + significantly different from the group indicated, $P<0.05$ and $P<0.001$, respectively.

Table S1. Pearson's correlation coefficient between selected parameters in the athletes.

		BMI	WC	PMAP	PPP	HR	HR_{100}	SBP_{100}	Watt	PWV_{cf}	PWV_{cr}	$Alx_{@75}$	CCADC	VO_{2max}	SV_{rest}
BMI	*ATH*		**0.76‡**	**0.37***	**0.52‡**	0.06	0.04	**0.34***	**0.33***	0.19	-0.07	-0.16	**-0.30***	**0.50‡**	0.24
	RUN		**0.69‡**	0.27	0.34	**0.44***	0.03	0.19	0.29	0.26	0.20	0.32	-0.38	0.33	-0.19
	WBA		**0.76‡**	0.22	**0.60†**	0.04	-0.19	-0.04	-0.10	0.05	-0.28	-0.32	-0.33	0.32	0.18
WC	*ATH*	**0.76‡**		0.25	**0.49‡**	-0.06	-0.12	**0.30***	**0.34***	0.02	-0.20	-0.26	-0.13	**0.49‡**	0.25
	RUN	**0.69‡**		0.27	0.12	0.03	-0.25	0.14	**0.55†**	0.10	0.06	0.17	0.20	**0.55†**	0.18
	WBA	**0.76‡**		-0.05	**0.59†**	-0.10	-0.03	0.25	0.13	-0.23	-0.11	-0.50	0.44	0.16	0.07
PMAP	*ATH*	**0.37***	0.25		**0.36***	0.28	0.13	**0.40†**	0.22	**0.39†**	0.17	0.08	-0.19	**0.30***	0.24
	RUN	0.27	0.27		0.15	**0.44***	0.06	0.06	0.28	0.36	0.28	0.23	-0.09	0.32	0.15
	WBA	0.22	-0.05		**0.49***	0.10	0.23	**0.74‡**	0.13	0.38	0.32	0.13	-0.30	0.15	0.16
PPP	*ATH*	**0.52‡**	**0.49†**	**0.36***		-0.05	**0.31***	**0.62‡**	0.07	0.03	-0.16	-0.28	-0.26	0.25	0.20
	RUN	0.34	0.12	0.15		-0.16	0.35	**0.59†**	-0.02	0.00	-0.24	0.07	-0.38	-0.06	0.14
	WBA	**0.60†**	**0.59†**	**0.49***		0.21	0.31	**0.60†**	0.24	-0.11	0.20	-0.47	0.30	0.28	0.07
HR	*ATH*	0.06	-0.06	0.28	-0.05		**0.44†**	0.16	-0.16	0.18	0.05		-0.28	-0.10	**-0.37***
	RUN	0.24	0.03	**0.44***	-0.16		0.26	0.06	-0.20	**0.43***	0.27		**-0.47***	-0.13	-0.36
	WBA	0.06	-0.10	0.10	0.21		**0.66†**	0.34	0.01	0.04	-0.18		0.13	0.17	-0.47
HR_{100}	*ATH*	0.04	-0.12	0.13	**0.31***	**0.44†**		**0.37***	**-0.54‡**	-0.11	-0.13	0.05	-0.26	-0.35*	-0.26
	RUN	0.03	-0.25	0.06	0.35	0.26		**0.42***	**-0.70‡**	-0.14	-0.18	0.18	-0.36	**-0.44***	-0.20
	WBA	0.14	-0.03	0.23	0.31	0.32		0.32	-0.20	-0.19	0.16	-0.24	0.01	-0.24	-0.42
SBP_{100}	*ATH*	**0.34***	**0.30***	**0.40†**	**0.62‡**	0.16	**0.37***		-0.01	-0.05	-0.04	-0.09	-0.15	0.04	0.05
	RUN	0.19	0.14	0.06	**0.59†**	0.06	**0.42***		-0.13	-0.15	-0.10	0.10	-0.07	-0.30	0.06
	WBA	0.30	0.25	**0.74‡**	**0.60†**	0.34	0.32		0.06	-0.04	0.22	-0.15	-0.20	0.11	-0.20
Watt	*ATH*	**0.33***	**0.34***	0.22	0.07	-0.16	**-0.54‡**	-0.01		0.02	0.09	-0.13	**0.40†**	**0.78‡**	**0.48†**
	RUN	0.29	**0.55†**	0.28	-0.02	-0.20	-0.01	-0.23		0.29	0.03	-0.10	0.30	**0.75‡**	**0.44***
	WBA	0.30	0.13	0.13	0.24	0.01	-0.20	0.06		-0.10	0.14	-0.02	0.38	**0.87‡**	0.47
PWV_{cf}	*ATH*	0.19	0.02	**0.40†**	0.02	0.18	-0.11	-0.05	0.02		-0.05	0.22	**-0.39†**	0.10	-0.01
	RUN	0.26	0.10	0.36	0.00	**0.43***	-0.14	-0.15	0.29		**0.48***	0.04	-0.36	0.24	-0.25
	WBA	0.05	-0.23	0.38	-0.11	0.04	-0.19	-0.04	-0.10		-0.28	**0.62***	-0.36	-0.01	0.09
PWV_{cr}	*ATH*	-0.07	-0.20	0.17	-0.16	0.05	-0.13	-0.04	-0.02	-0.05		0.27	-0.07	-0.07	0.05
	RUN	0.20	0.06	0.28	-0.15	0.27	-0.18	-0.11	0.03	-0.28		0.29	-0.31	0.16	-0.26
	WBA	0.00	-0.11	0.32	0.20	-0.18	0.16	0.22	0.14	-0.28		0.06	-0.02	-0.01	0.43
$Alx_{@75}$	*ATH*	-0.16	-0.26	0.08	-0.28	0.08	0.05	-0.08	-0.13	0.22	0.27		**-0.31***	-0.18	-0.24
	RUN	0.32	0.17	0.23	0.07	0.10	0.18	0.10	-0.10	0.04	0.29		**-0.54†**	0.03	-0.12
	WBA	-0.32	-0.50	0.13	-0.47	-0.06	-0.24	-0.15	-0.02	**0.62***	0.06		-0.17	0.01	-0.22
CCADC	*ATH*	**-0.30***	-0.13	-0.19	-0.26	-0.28	-0.29	-0.15	**0.40†**	**-0.39†**	-0.07	**-0.31***		0.18	0.14
	RUN	-0.38	0.20	-0.09	-0.38	**-0.47***	-0.26	-0.07	0.30	-0.36	**-0.41***	**-0.54†**		0.29	0.34
	WBA	-0.33	.0.44	-0.30	0.30	0.13	0.01	-0.20	0.38	-0.36	-0.02	-0.17		0.21	-0.02
VO_{2max}	*ATH*	**0.50‡**	**0.49‡**	**0.30***	0.25	-0.10	**-0.35***	0.04	**0.78‡**	0.10	-0.07	-0.18	0.18		**0.33***
	RUN	0.33	**0.55†**	0.32	-0.06	-0.13	**-0.44***	-0.30	**0.75‡**	0.24	0.16	0.03	0.29		0.25
	WBA	0.32	0.16	0.15	0.28	0.17	-0.24	0.11	**0.87‡**	-0.01	-0.01	0.01	0.21		0.17

SV_{rest}	*ATH*	0.24	0.25	0.24	0.20	**-0.37***	-0.26	0.05	**0.48†**	-0.01	0.05	-0.24	0.14	**0.33***
	RUN	-0.19	0.18	0.15	0.14	-0.36	-0.20	0.06	**0.44***	-0.25	-0.26	-0.12	0.34	0.25
	WBA	0.18	0.07	0.16	0.07	-0.47	-0.42	-0.20	0.47	0.09	0.43	-0.22	-0.02	0.17

WC, waist circumference; PMAP, peripheral mean arterial pressure; PPP, peripheral pulse pressure; HR, heart rate; $_{100}$, at 100 watt work load; Watt, peak work load during the exercise test; PWV, pulse wave velocity; cf, from carotid to femoral; cr, from carotid to radial, Alx, aortic augmentation index; CCADC, common carotid artery distensibility coefficient; VO_{2max}, peak oxygen consumption; SV_{rest}, calculated stroke volume during supine rest**. *p < 0.05, † < 0.01, ‡ < 0.001**

Table S2. Pearson's correlation coefficient between selected parameters in the controls.

		BMI	WC	PMAP	PPP	HR	HR_{100}	SBP_{100}	Watt	PWV_{cf}	PWV_{cr}	$Alx_{@75}$	CCADC	VO_{2max}	SV_{rest}
BMI	*CTR*		**0.87‡**	**0.33***	0.22	0.12	-0.23	0.12	0.18	**0.40†**	-0.16	**0.31***	**-0.29***	0.13	0.18
	SC		**0.89‡**	**0.38***	**0.38***	0.18	-0.32	0.35	0.25	**0.47†**	-0.25	0.32	-0.29	0.21	.0.24
	AC		**0.81‡**	0.28	0.00	0.12	-0.16	-0.18	0.07	0.20	0.03	**0.49***	-0.37	-0.06	-0.04
WC	*CTR*	**0.87‡**		0.22	0.08	0.10	-0.27	0.00	0.12	**0.44†**	-0.24	0.25	-0.17	0.06	0.12
	SC	**0.89‡**		0.27	0.30	0.17	**-0.41***	0.22	0.10	**0.49†**	**-0.39***	0.27	-0.20	0.02	0.13
	AC	**0.81‡**		0.18	-0.26	0.06	-0.10	-0.29	0.05	0.30	0.11	0.42	-0.26	-0.03	-0.02
PMAP	*CTR*	**0.33***	0.24		0.25	**0.39†**	0.02	**0.34***	-0.04	**0.57‡**	**0.34***	**0.30***	**-0.58‡**	-0.01	0.02
	SC	**0.38***	0.27		0.32	**0.51†**	0.00	0.13	0.19	**0.60‡**	**0.48†**	0.26	**-0.66‡**	0.22	0.04
	AC	0.28	0.18		0.09	-0.19	-0.30	**0.57†**	0.03	**0.53***	0.16	0.26	-0.37	0.15	0.08
PPP	*CTR*	0.22	0.08	0.25		0.25	0.07	**0.52‡**	0.13	**0.40†**	**-0.36†**	0.17	**-0.31***	0.10	0.16
	SC	**0.38***	0.30	0.32		0.19	-0.33	**0.46***	**0.61‡**	**0.43***	-0.30	0.11	0.13	**0.58†**	0.32
	AC	0.00	-0.26	0.09		0.31	0.28	**0.61†**	-0.07	0.41	**-0.45***	0.16	-0.32	-0.16	-0.01
HR	*CTR*	0.12	0.10	**0.39†**	0.25		**0.41†**	0.22	-0.20	**0.48‡**	0.07		**-0.43†**	-0.17	-0.21
	SC	0.18	0.17	**0.51†**	0.19		0.19	0.07	0.27	**0.61‡**	0.25		**-0.63‡**	0.30	-0.18
	AC	0.12	0.06	-0.18	0.31		0.35	-0.04	-0.29	0.20	-0.18		0.24	-0.21	0.02
HR_{100}	*CTR*	-0.23	-0.27	**0.39†**	0.07			0.23	**-0.72‡**	0.23	-0.04	0.27	-0.06	**-0.66‡**	**-0.34***
	SC	-0.32	**-0.41***	0.00	-0.33	0.19		-0.13	-0.38	-0.04	0.20	-0.02	-0.14	-0.27	-0.28
	AC	-0.16	-0.10	-0.30	0.28	0.35		-0.04	**-0.72‡**	-0.15	-0.10	0.16	0.32	**-0.61†**	-0.28
SBP_{100}	*CTR*	0.12	0.00	**0.34***	**0.52‡**	0.22	0.23		-0.20	0.23	-0.19	0.12	-0.28	-0.15	0.02
	SC	0.35	0.22	0.13	**0.46***	0.19	-0.13		0.36	0.16	-0.21	-0.03	-0.01	0.48	0.14
	AC	-0.18	-0.29	**0.57†**	**0.61†**	-0.04	-0.04		0.06	**0.49***	0.01	-0.04	-0.33	0.05	0.13
Watt	*CTR*	0.18	0.12	-0.04	0.13	-0.20	**-0.72**‡	-0.20		0.17	0.12	**-0.43†**	0.08	**0.94‡**	**0.30***
	SC	0.25	0.10	0.19	**0.61‡**	0.27	**-0.38***	0.36		0.30	-0.04	-0.26	-0.13	**0.95‡**	0.21
	AC	0.07	0.05	0.03	-0.07	-0.29	**-0.72‡**	0.06		0.12	0.10	-0.26	0.08	**0.72‡**	0.20
PWV_{cf}	*CTR*	**0.40†**	**0.44†**	**0.57‡**	**0.40†**	**0.48‡**	-0.06	0.23	0.17		-0.19	0.11	**-0.39†**	0.20	-0.01
	SC	**0.47†**	**0.49†**	**0.60‡**	**0.43***	**0.61‡**	-0.04	0.16	0.30		-0.03	0.13	**-0.50†**	0.28	0.28
	AC	0.20	0.31	**0.53***	0.41	0.20	-0.15	**0.49***	0.12		-0.20	0.09	-0.18	0.28	-0.01
PWV_{cr}	*CTR*	-0.16	-0.24	**0.34***	**-0.36†**	0.07	-0.04	-0.19	0.12	-0.19		-0.04	-0.07	0.12	-0.03
	SC	-0.24	**-0.39***	**0.48†**	-0.30	0.25	0.20	-0.21	-0.04	-0.03		0.07	-0.29	-0.01	-0.01
	AC	0.03	0.11	0.16	**-0.46***	-0.19	-0.10	0.01	0.10	-0.20		-0.09	0.22	0.08	-0.10
$Alx_{@75}$	*CTR*	**0.31***	0.25	**0.30***	0.17		-0.18	0.12	**-0.43†**	0.11	-0.04		**-0.29***	**-0.40†**	0.07
	SC	0.32	0.27	0.26	0.11		-0.02	-0.03	-0.26	0.13	0.07		-0.16	-0.26	0.26
	AC	**0.49***	0.42	0.26	0.16		0.16	-0.11	-0.26	0.09	-0.09		-0.36	-0.16	-0.01
CCADC	*CTR*	**-0.29***	-0.17	**-0.58‡**	0.14	**-0.65‡**	-0.05	0.03	-0.12	**-0.38†**	-0.25	**-0.29***		-0.04	0.23
	SC	-0.29	-0.20	**-0.66‡**	0.13	**-0.63‡**	-0.14	-0.01	-0.15	**-0.50†**	-0.29	-0.16		-0.36	0.29
	AC	-0.37	-0.33	-0.37	0.22	-0.40	0.21	0.13	-0.16	-0.17	0.08	0.12		-0.04	-0.01
VO_{2max}	*CTR*	0.13	0.06	-0.01	0.10	-0.17	**-0.66‡**	-0.15	**0.94‡**	0.20	0.12	**-0.40†**	-0.04		0.27
	SC	0.21	0.02	0.22	**0.58†**	0.30	-0.27	0.48	**0.95‡**	0.28	-0.01	-0.26	-0.36		0.21
	AC	-0.06	-0.03	0.15	-0.16	-0.21	**-0.61†**	0.05	**0.72‡**	0.28	0.08	-0.16	-0.04		0.15

SV_{rest}	*CTR*	0.18	0.12	0.02	0.16	-0.21	**-0.34***	0.02	**0.30***	-0.01	-0.03	0.07	0.23	0.27
	SC	.0.24	0.13	0.04	0.32	-0.18	-0.28	0.14	0.21	0.28	-0.01	0.26	0.29	0.21
	AC	-0.04	-0.02	0.08	-0.01	0.02	-0.28	0.13	0.20	-0.01	-0.10	-0.01	-0.01	0.15

WC, waist circumference; PMAP, peripheral mean arterial pressure; PPP, peripheral pulse pressure; HR, heart rate; $_{100}$, at 100 watt work load; Watt, peak work load during the exercise test; PWV, pulse wave velocity; cf, from carotid to femoral; cr, from carotid to radial, Alx, aortic augmentation index; CCADC, common carotid artery distensibility coefficient; VO_{2max}, peak oxygen consumption; SV_{rest}, calculated stroke volume during supine rest**. *p < 0.05, † < 0.01, ‡ < 0.001**

Table S3. Maximal oxygen uptake at the cycle ergometer test

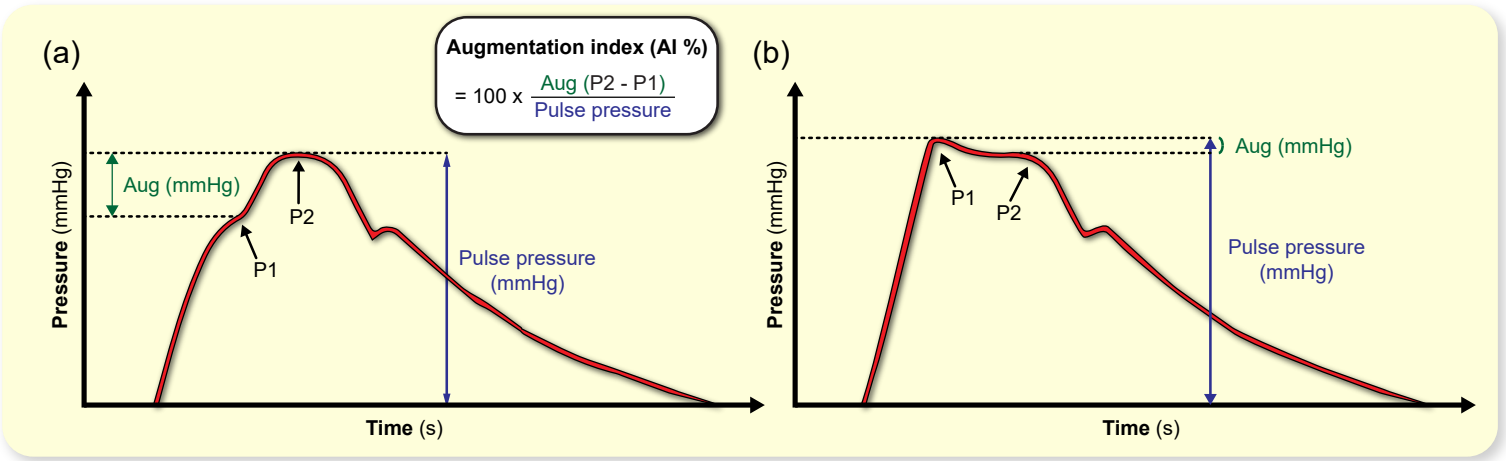
Sport	VO_2max
Runners 800-1500 m	54.4 (49-59)
Runners 1500-3000 m	64.5 (55-70)
Orienteers (top level only)	55.8 (53-58)
Biathletes	50.8 (48-54)
Canoeists	47.4 (42-54)
Swimmers	53.4 (46-60)
Triathletes	58.1 (52-64)
Cyclists	54.5 (50-61)

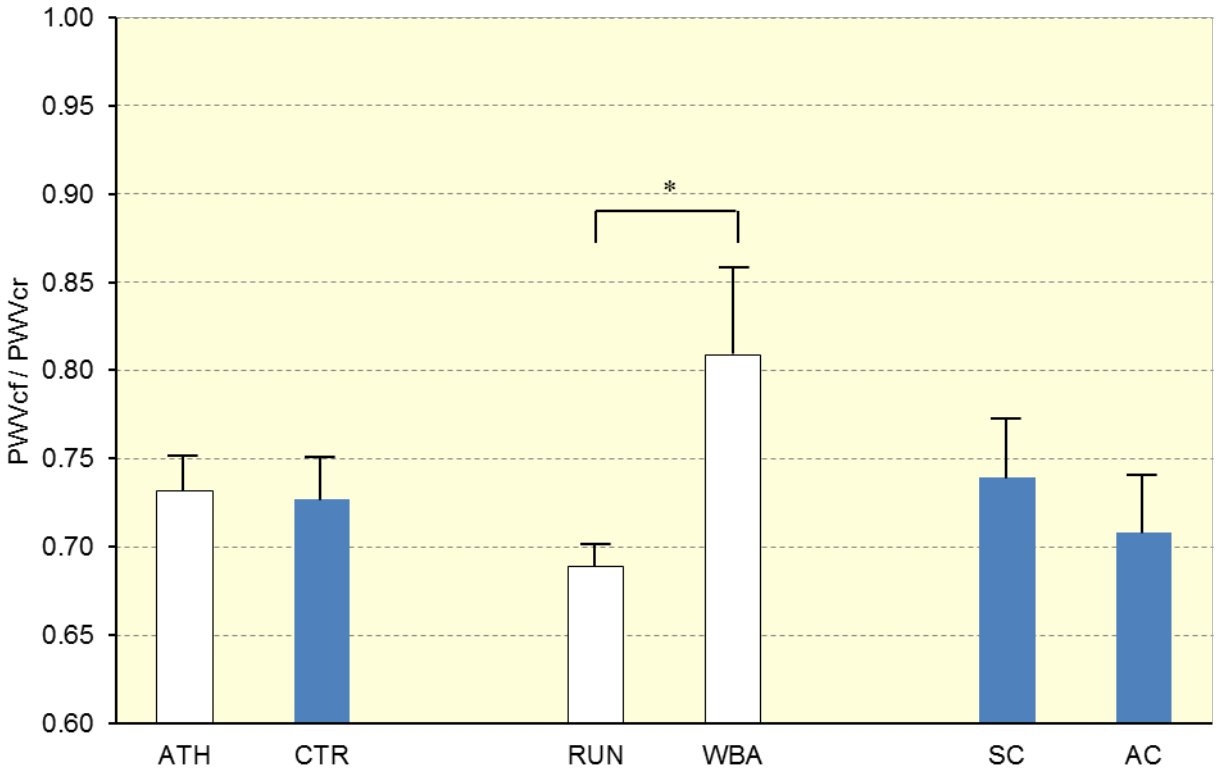
Data from 39 of the 47 female athletes in the present study who represented the Swedish elite. Of the 39 athletes, 25 belonged to the absolutely best in the country in their age-group (top level) and 14 were highly ranked in their sport and competed on the Swedish national level.
Values are mean (range). VO_2 expressed as $mL \cdot kg^{-1} \cdot min^{-1}$

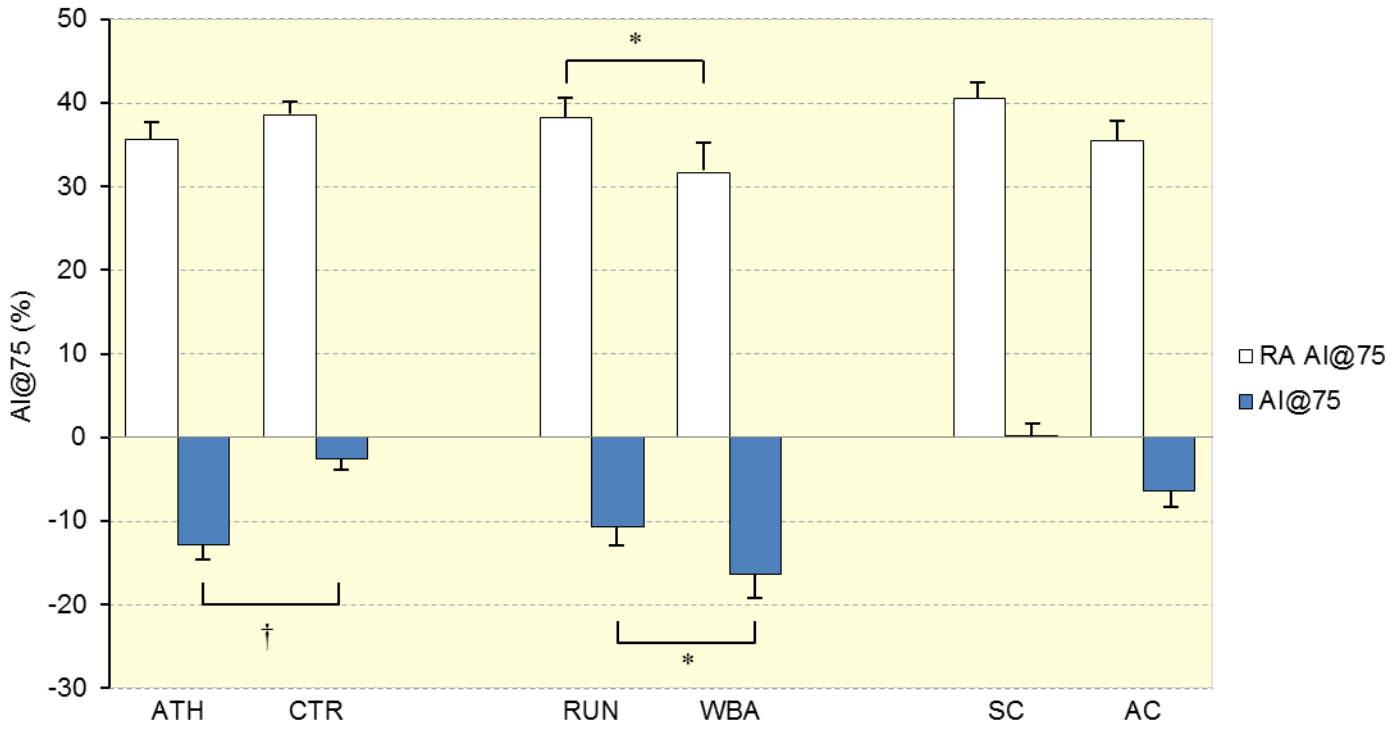
Table S4. Arterial properties and hemodynamics at rest after adjustment to standardized mean arterial pressure (MAP) in female athletes and controls.

	Athletes (ATH)			Controls (CTR)			P-value		
	All (n=47)	RUN (n=26)	WBA (n=18)	All (n=52)	SC (n=31)	AC (n=21)	ATH / CTR	RUN / WBA	SC / AC
PWVcf (m/s)	5.2±0.1 (0.04)	5.1±0.1 (0.04)	5.3±0.2 (0.04)	5.1±0.1 (0.06)	5.1±0.1 (0.06)	5.2±0.1 (0.06)	NS	NS	NS
PWVcr (m/s)	7.1±0.1 (0.02)	7.3±0.1 (0.02)	6.7±0.2 (0.02)	7.3±0.1 (0.04)	7.1±0.2 (0.04)	7.5±0.2 (0.04)	NS	<0.05	NS
RA AI@75 (%)	36.1±1.7 (0.29)	39.3±1.9 (0.29)	31.5±2.9 (0.29)	37.6±1.2 (0.49)	39.1±1.4 (0.49)	35.4±2.0 (0.49)	<NS	<0.05	NS
AI@75 (%)	-12.5±1.6 (0.13)	-10.2±2.0 (0.13)	-16.5±2.5 (0.13)	-3.1±1.1 (0.32)	-0.9±1.4 (0.32)	-6.4±1.7 (0.32)	<0.001	0.06	<0.05

Values are mean±SEM, adjusted to a PMAP of 75.7 mm Hg, which was the mean PMAP of all subjects. Adjustment of each individual value was done using the formula: Adjusted value = Measured value + constant * (PMAP-75.7). The constant is the slope of the regression line for ATH or CTR for the measured variable with PMAP as a predictor and is given in parenthesis under each value in the table. RUN, runners; WBA, whole-body endurance athletes; SC, sedentary controls; AC, normally active controls; PMAP, peripheral mean arterial pressure; RA AI, radial artery augmentation index; AI aortic augmentation index; @75, AI corrected to heart rate 75 min^{-1}; PWV; pulse wave velocity; cf, carotid-femoral; cr, carotid-radial.


(a)
Augmentation index (AI %)
= 100 x Aug (P2 - P1) / Pulse pressure
Aug (mmHg)
P1
P2
Pulse pressure (mmHg)
Pressure (mmHg)
Time (s)
(b)
Aug (mmHg)
P1
P2
Pulse pressure (mmHg)
Pressure (mmHg)
Time (s)


1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
PWVcf / PWVcr
*
ATH
CTR
RUN
WBA
SC
AC


50
40
30
20
10
0
-10
-20
-30
AI@75 (%)
*
†
*
ATH
CTR
RUN
WBA
SC
AC
RA AI@75
AI@75