openheart

Young endurance training starting age in non-elite athletes is associated with higher proximal aortic distensibility

Christoph P Ryffel,[1] Prisca Eser ,[1] Thimo Marcin,[1] Dario Herrsche,[1,2] Nicolas Brugger,[1] Lukas D Trachsel,[1] Matthias Wilhelm [1]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/openhrt-2021-001771).

To cite: Ryffel CP, Eser P, Marcin T, *et al*. Young endurance training starting age in non-elite athletes is associated with higher proximal aortic distensibility. *Open Heart* 2022;**9**:e001771. doi:10.1136/openhrt-2021-001771

CPR and PE contributed equally.

Received 1 July 2021
Accepted 9 January 2022

[1]Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[2]Exercise Physiology Lab, Institute of Human Movement Sciences and Sport, ETH Zurich, Zurich, Switzerland

Correspondence to
MD Matthias Wilhelm; matthias.wilhelm@insel.ch

ABSTRACT

Objective Decreased proximal aortic distensibility (AD) is known to significantly predict all-cause mortality and cardiovascular events among individuals without overt cardiovascular disease. This cross-sectional study investigated the association of endurance training (ET) parameters, namely, ET starting age, ET years and yearly ET volume with AD in non-elite endurance athletes.

Methods Healthy, normotensive, male Caucasian participants of a 10-mile race were assessed with a 2D echocardiogram and comprehensive interview. Ascending aortic diameters were measured simultaneously with pulse pressure. Aortic strain, AD and aortic stiffness index were calculated. Predictors of AD were investigated among training parameters by linear regression models corrected for age, resting heart rate, stroke volume index and mean blood pressure.

Results Ninety-two of 121 athletes (aged 42±8 years) had sufficient echocardiogram quality and were used for analysis. ET starting age (range 6–52 years) and years of ET (range 2–46 years) were highly collinear and used in two separate models for AD. Significant factors for AD were ET starting age, 10-mile race time and resting heart rate in model I, and age, years of ET, 10-mile race time and heart rate in model II (all $p<0.01$).

Conclusions In our cohort of healthy, non-elite, middle-aged runners, AD was significantly higher in athletes with younger ET starting age or more years of ET (in the model adjusted for confounders). In the model with years of ET, age had a negative contribution to AD, suggesting that with older age, the benefit of more years of ET on AD decreased. Future studies assessing the effect of exercise training on arterial properties should include training starting age.

Key questions

What is already known about this subject?

► Endurance-trained athletes are known to have higher aortic distensibility (AD) compared with healthy sedentary people. Low AD is a known predictor for mortality.

What does this study add?

► AD was found to be higher in recreational athletes starting their endurance training at a younger age. The beneficial effect of number of ET years decreased with increasing age.

How might this impact on clinical practice?

► When assessing the effects of exercise training on the cardiovascular system, besides training volume and intensity, training starting age should be considered. Starting endurance training at a younger rather than an older age may be associated with more beneficial adaptations to the cardiovascular system.

INTRODUCTION

Decreased proximal aortic distensibility (AD) has been found to significantly predict all-cause mortality and cardiovascular events among individuals without overt cardiovascular disease.[1] Proximal aortic AD has been suggested to be favourably affected by endurance training (ET) based on higher AD in endurance-trained athletes compared with healthy sedentary controls.[2]

The former study was based on elite athletes in whom ET was systematically started at a young age, as advancing to an elite level is no longer possible after adolescence/young adulthood. The only study to date that assessed ET start in young versus old athletes was the study by Bhuva and colleagues who measured AD before and after a 6-month ET for a first-time marathon participation.[3] They found that AD of the proximal aorta increased in the older and younger athletes (although non-significantly in the younger).[4] Whether AD in older people who take up ET increases beyond the small amount found in the initial 6 months of training as shown by Bhuva and colleagues when ET is sustained over many years is presently unknown. It seems plausible that the beneficial stimulus of ET may have a different effect on a young elastic ascending aorta compared with an older stiffer ascending aorta whose arrangement of elastin is disorganised and disrupted by collagen.[5 6]

We, therefore, hypothesised that ET starting age has an important impact on the elastic properties of the proximal aorta. The objective of this study was to investigate the association of arterial distensibility (AD) with ET training parameters, namely, ET starting age, years of ET and yearly ET volume in non-elite endurance athletes.

METHODS

Participants and protocol

Male non-elite runners of a popular 10-mile race in Switzerland were recruited for a cross-sectional prospective study on endurance exercise and cardiac remodelling in healthy athletes as previously described.[7 8] Runners aged 30 years and older, with and without a history of former long-distance runs, were included between 2010 and 2015. Exclusion criteria were a history of cardiovascular disease, medication intake or cardiovascular risk factors, in particular arterial hypertension, defined as an office blood pressure (BP) ≥140/90 mm Hg (measured two times at the right arm by mercury manometer).[9] Between June and December 2015, athletes were interviewed by comprehensive phone interview on their sports history in detail with history of every sports discipline they took part in, grouped into endurance and resistance type of sports based on the Mitchell classification[10] as previously described.[11] The questionnaire that was filled in during the interviews is provided in online supplemental 1. The calculation of average training hours was determined by the athletes' estimation and/or exercise diary, and average volume of training per week of concerned sports disciplines was calculated on a year-by-year basis. Average volume of competitions per year (in hours) as well as longer training interruptions were also recorded and accounted for in the calculations. For this study, only data for ET (including running, orienteering, cross-country skiing, swimming, rowing, cycling and triathlon) were considered. ET starting age was defined as the age when athletes performed at least 2 hours of ET per week. ET years was defined as years during which at least 2 hours of ET per week were performed, so that training interruptions were excluded. Yearly ET was calculated by dividing the total cumulative ET hours by ET years. All athletes provided written informed consent and the study, which complied with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the local ethics committee. There was no patient and public involvement for the study design as the study was conducted during a time where this was not usually done.

Transthoracic echocardiography

Standard two-dimensional transthoracic echocardiography was performed within 3 months prior to the race on a Phillips iE33 System (X5-1 transducer, Phillips Medical Systems, Zurich, Switzerland). Standard parameters of left ventricle (LV) function and morphology, including LV end-systolic and end-diastolic internal diameters and biplan volumes as well as end-diastolic wall thickness, were measured as previously described.[11] Stroke volume was indexed for body surface area (SVi).

Aortic systolic diameter (SD) and diastolic diameter (DD) were measured inner edge to inner edge in parasternal long-axis view at the maximal diameter of the proximal ascending aorta. DD was obtained at the peak of the R wave, while the SD was measured as the maximal diameter during systole. The relative diameter/area change (aortic strain) was expressed as $(SD^2\text{-}DD^2)/DD^2$. AD, the relative diameter/area change for a pressure increment, was calculated using the simultaneously measured brachial pulse pressure (PP) derived from systolic and diastolic BP, using the formula: $AD=(SD^2\text{-}DD^2)/(DD^2\times PP)$.[12–15] BP was measured in a quiet room after 5 min in supine position shortly before the transthoracic echocardiography. BP was measured once in both arms to detect possible differences with an oscillometric device (Dinamap XL; Criticon, Tampa, Florida). We chose the arm with the higher value as the measuring arm. Then, BP was measured two additional times at the chosen arm and the mean of these measurements used for data analysis. For comparison with other studies, AD was presented as 10^{-3} mm Hg^{-1}, and 10^{-6} $dyne^{-1}cm^{-2}$. To account for potential non-linear BP dependence, the aortic stiffness index was calculated as $(\ln(\text{systolic BP}/\text{diastolic BP}))/((SD^2\text{-}DD^2)/DD^2)$.[15]

The measurements of SD and DD were performed on anonymised data by a single experienced observer (CPR) blinded to athlete's LV parameters and ET data. In case of insufficient quality of the images, the athlete was excluded from the analysis. Resting heart rate was derived from the ECG on the echocardiographic loops.

Anthropometric measurements were taken by a wall-mounted stadiometer and a digital weighing scale immediately before the echocardiography.

Data analysis

The data were analysed with R (V.3.5.1, R Core Team, 2017). The normality of quantitative variables was inspected visually and the homogeneity of variances tested by Levene's test. Normally distributed data were presented as mean±SD, and non-normally distributed variables as median and interquartile range (Q1, Q3).

We performed multivariate robust linear regression models for the dependent variable AD using lmRob from the package robust V.0.5. The following independent variables were included: age, resting heart rate, SVi, mean arterial BP (diastolic BP +PP/3), ET starting age, hours of ET per year, total ET years and 10 mile race time. Independent parameters of the models were centred and standardised. Variance inflation factor (VIFs) and model assumptions of the resulting model were calculated and checked visually. For the independent parameters of the models, alpha was set at 0.05.

Athletes were divided by median ET starting age to form two equally sized groups, namely, those with a young ET starting age (<25 years) and old ET starting age (≥25 years). These groups were compared for the

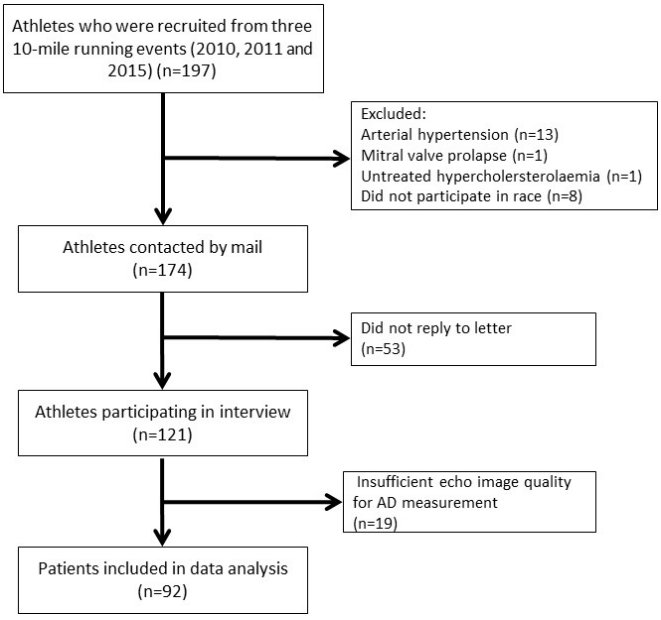

Figure 1 Study flow. AD, aortic distensibility.

relevant anthropometric, haemodynamic, echocardiographic and training history parameters as listed above and tested with independent t tests or Mann Whitney-U tests, as appropriate.

RESULTS

Study subjects

A total of 174 male runners were contacted by mail. The interview on sports history lasting approximately 45 min could be performed with 121 athletes, of whom 98 completed the interview by phone and 23 chose to complete a questionnaire by postal mail. Of these, 92 athletes aged 42±8 years (mean±SD) had sufficient echocardiogram quality of the ascending aorta to be used for analysis (figure 1). Among these, there was no missing data. There were no significant differences with regards to anthropometric and echocardiographic data between the 92 included and 82 excluded athletes, as is seen in online supplemental table 1. A broad spectrum of endurance athletes was included, ranging from leisure-time runners with a first participation in a 10-mile race up to semiprofessional long-distance runners with more than 15 000 cumulative lifetime ET hours (median 3744, Q1 2002, Q3 8502). Anthropometric, haemodynamic, echocardiographic and training history data are shown in table 1. For purely illustrative purposes of assessed parameters with regards to age at ET starts, we have split the total group into two equally sized subgroups according to age at ET starts. This resulted in two subgroups of athletes who started ET young (<25 years) versus those starting at an older age (≥25 years). Means of key parameters for young and old starters are also shown in figure 2.

Determinants of AD

AD had to be log transformed to fulfil model assumptions. There were high VIFs for ET starting age, years of ET and age (>1400). Therefore, two models were performed, one omitting years of ET (model 1) and one omitting ET starting age (model 2).[16] This resulted in two models where all VIFs were below 3.7. 10-mile race time was the variable with the highest VIF (3.6 in both models). When 10-mile race time was excluded from the models, the same factors remained significant and all VIFs were below 2.4. The robust linear regression models are presented in table 2, both explaining 32% of total variance in log AD with the following significant parameters: ET starting age, 10-mile race time and resting heart rate (model 1) and ET years, age, resting heart rate and 10-mile race time (model 2). ET starting age was inversely related to AD, meaning that an earlier ET starting age was associated with higher AD (model 1), while the association with ET years and AD was positive (model 2). Heart rate was inversely related to AD in both models, meaning that a lower HR was associated with more favourable AD. Surprisingly, 10-mile race time was a positive factor in both models, meaning that with all other factors constant, a slower race time was associated with higher AD. However, the univariate Spearman correlation coefficient between AD and 10-mile race time was negative, although not statistically significant (online supplemental table 2). To illustrate the associations between AD and the independent variables with the highest beta coefficients in the models, we have provided raw data of ET starting age and ET years versus AD in figure 3A,B. Spearman correlation coefficients between AD, age and variables of training history are shown in online supplemental table 2.

DISCUSSION

In this study assessing morphology and function of the proximal aorta of a mixed athletic population ranging from recreational to semiprofessional endurance athletes, we found an association between AD and either ET starting age or years of ET. Years of ET predicted AD equally well, however, in this case, age was a negative predictor, meaning that for a given ET duration, AD was higher in athletes who started at a younger age. ET starting age, on the other hand, was associated with AD independently of age, and age was not related directly to AD (online supplemental table 1). Additionally, resting heart rate was found to be an independent predictor for AD in both models. To the best of our knowledge, this is the first study showing an association between ET starting age and AD.

AD and ET

Previous cross-sectional studies showed that endurance-trained athletes have higher AD than sedentary individuals.[2 17 18] In our cohort of middle-aged, non-elite, male endurance athletes, we found that young ET starters with higher cumulative lifetime ET hours and more ET years had higher AD, however, yearly ET hours were not significantly related to AD (table 2). This is consistent with our hypothesis that age at ET start may

Table 1 Anthropometric, haemodynamic, echocardiographic and sports history parameters in our athletes split into two equally sized groups according to young (<25 years) and older (≥25 years) endurance training starting age

Variable	Young starters (n=46)	Old starters (n=46)	P value
Athlete characteristics			
Age (years)	39.6±7.4	44.3±7.4	0.003
BMI (kg/m^2)	22.4±1.6	23.3±1.5	0.005
BSA (m^2)	1.9±0.1	1.9±0.1	0.929
Resting heart rate (bpm)	56.6±10.9	62.0±9.0	0.012
Systolic BP at rest (mm Hg)	120.0±9.4	123.2±8.5	0.095
Diastolic BP at rest (mm Hg)	73.8±6.2	77.9±6.4	0.002
Pulse pressure	46.3±8.4	45.3±7.1	0.537
Echocardiography			
Diastolic diameter of AA (mm)	26.7±2.8	27.0±3.3	0.577
Systolic diameter of AA (mm)	29.3±2.7	28.7±3.2	0.322
Difference in AA diameter (mm)	2.6±1.4	1.7±1.1	0.000
Aortic strain (%)	19.6 (12.6, 30.0)	10.9 (7.0, 17.4)	0.007
Aortic distensibility (10^{-3} mm Hg^{-1})	4.2 (2.8, 6.1)	2.8 (1.5, 3.8)	0.004
Aortic distensibility (10^{-6} dyne^{-1} cm^{-2})	3.2 (2.1, 4.6)	2.1 (1.1, 2.9)	0.004
Beta stiffness index	2.6 (1.7, 3.6)	3.8 (2.7, 6.9)	0.061
LA volume/BSA (mL/m^2)	31.9±6.4	31.4±6.6	0.695
LV mass/BSA (g/m^2)	106.5±17.9	103.2±19.5	0.401
LV concentricity (g/m$^{L2/3}$)	8.1±1.2	8.8±1.7	0.014
LV EDV/BSA (mL/m^2)	67.5±13.4	55.7±7.9	0.000
LV ejection fraction (%)	63.2±5.3	64.7±5.2	0.166
LV stroke volume/BSA (mL/m^2)	42.6±8.9	36.1±6.2	0.000
E peak (cm/s)	76.8±17.0	72.8±14.8	0.231
E' mean (cm/s)	12.8±2.1	12.2±1.9	0.180
E peak/E mean	6.1±1.3	6.0±1.1	0.813
E/A	1.8±0.5	1.5±0.3	0.000
Sports history parameters			
ET starting age (years)	16 (13, 20)	31 (30, 36)	0.000
ET duration (years)	25 (18, 29)	10 (6, 16)	0.000
Cumulative lifetime ET (h)	7449 (3731, 10504)	2184 (1164, 3861)	0.000
ET per year (h)	311 (191, 484)	208 (154, 346)	0.029
Resistance training per year (h)	0 (0, 26)	0 (0, 0)	0.441
10 mile race time (min)	62 (58, 68)*	73 (69, 81)	0.000

Shown are mean±SD or median (Q1, Q3), and p values for independent t-tests or Mann-Whitney U tests as appropriate.
*Data available only in 45 athletes.
AA, ascending aorta; BMI, body mass index; BP, blood pressure; BSA, body surface area; EDV, end-diastolic volume; ET, endurance training; LA, left atrium; LV, left ventricle.

play an important role in the ageing process of the aorta. Results from our models indicate that with each year that ET was started earlier, AD improved by 0.04 × 10^{-3} mm Hg^{-1} (results from model without centred and standardised parameters, not shown). A difference of 1 × 10^{-3} mm Hg^{-1} (which would result from a 22-year difference in ET starting age) corresponds to approximately a decade in ageing between age 40 years and 70 years.[4]

The potential role of age at ET start may have been overlooked in previous studies, who based their findings on young elite athletes only, who forcibly all started training at a young age.[2 17 18] Consequently, AD reported in their studies[2 17 18] was higher than in our study probably based on their much younger study populations. However, whether the benefits that an early ET start may convey on AD will persist into older age and reduce the

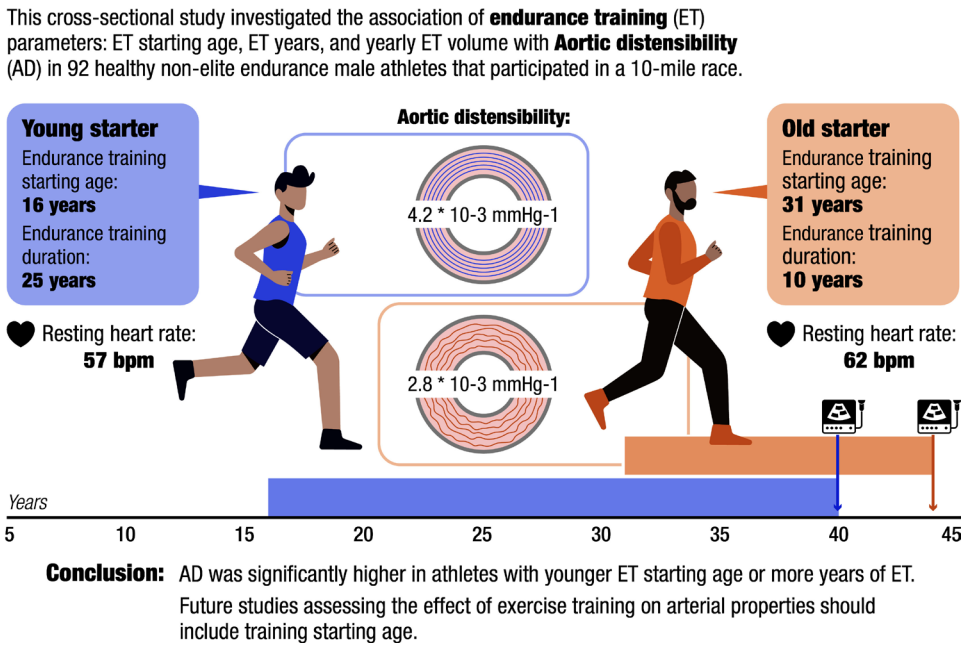

Figure 2 Key parameters of training history and aortic function. Shown are mean or median values from the subgroups (table 1).

burden of cardiovascular disease will need to be assessed in further studies.

AD measured in our young starters was comparable to two healthy non-athletic populations of similar age[4 19] and to a large population of the Oxford Families Blood Pressure Cohort not excluding volunteers with high BP.[20] Bhuva and colleagues assessed the 6-month training effect in first time marathon runners and found comparable improvements in AD with training in older (47±7 years) and younger (30±4 years) athletes, which achieved statistical significance only in the older athletes. However, while their older athletes showed an increase in proximal aortic AD from 5.4×10^{-3} mm Hg^{-1} to 5.9×10^{-3} mm Hg^{-1}, their young athletes had an increase from 10.3×10^{-3} mm Hg^{-1} to 10.6×10^{-3} mm Hg^{-1} and were, therefore, likely to have reached a 'ceiling' level of AD, where a further increase could hardly be expected, as already their baseline level was above values found in 30–39 year olds and even 20–29 year old healthy population.[4] Improvements in AD were greater at the proximal descending and distal descending aorta with higher abundance of trainable smooth muscle cells than the proximal ascending aorta, where elasticity is provided by non-renewable elastin.[3 6] Bhuva and colleagues found higher proximal ascending AD values before and after training in their older athletes compared with AD in our old starters (mean age of their old athletes was 3 years older than our old starters), however, they used central rather than brachial BP for calculation of AD, and they only included athletes with a training history of <100 hours of running training per year. In contrast, even our old starters had a median cumulative ET hours of nearly 2200 hours and had run many

Table 2 Robust (multivariate) linear regression models for log of AD (both explaining 32% of total variance) including 91 athletes (one athlete had missing data for 10 mile race time)

	Model 1		Model 2	
Parameters in standardised units	**Standardised beta coefficient (95% CI)**	**P value**	**Standardised beta coefficient (95% CI)**	**P value**
Age	0.031 (−0.212 to 0.274)	0.800	−0.286 (−0.468 to −0.093)	0.004
Endurance training starting age	−0.400 (−0.608 to −0.192)	0.000		
Total years of endurance training			0.382 (0.183 to 0.581)	0.000
10 mile race time	0.253 (0.030 to 0.475)	0.027	0.251 (0.029 to 0.472)	0.027
Yearly endurance training volume	0.112 (−0.053 to 0.278)	0.181	0.114 (−0.053 to 0.280)	0.178
Resting heart rate	−0.261 (−0.472 to −0.050)	0.016	−0.261 (−0.472 to −0.050)	0.016
Stroke volume index	−0.018 (−0.220 to 0.119)	0.843	−0.019 (−0.203 to 0.164)	0.833
Mean blood pressure	0.048 (−0.201 to 0.165)	0.450	0.050 (−0.076 to 0.175)	0.436

AD, aortic distensibility.

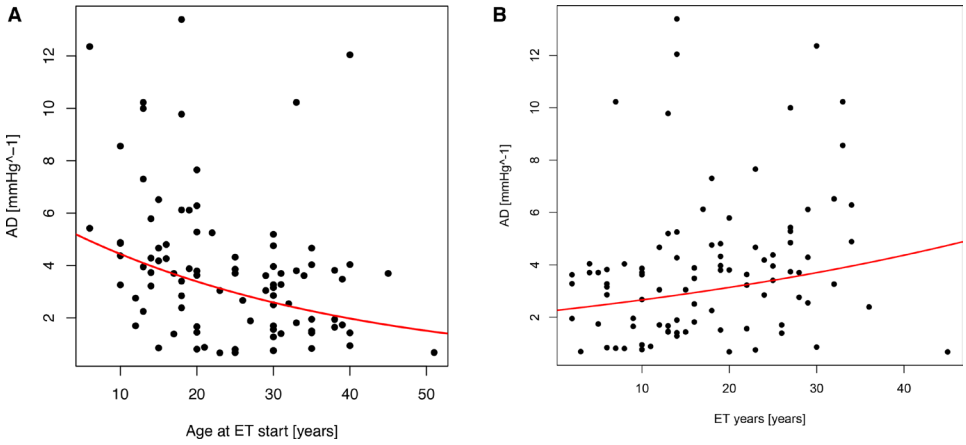

Figure 3 Relationship of age at ET start (A) and ET years (B) with AD. The regression line is for the linear regression of log(AD) with age at ET start (r^2=0.13, p=0.0003, figure 1A) and with ET years (r^2=0.04, p=0.043, figure 1B). AD rather than log(AD) is shown for easier readability. AD, aortic distensibility; ET, endurance training.

races previously. Our data are consistent with the finding by Bhuva and colleagues that slower running times were associated with greater benefits to AD, namely, 10-mile race time was positively associated with AD. Furthermore, both studies highlight the importance of taking into account the starting age of endurance athletes.

Age and AD

In our study, AD was not associated with age neither in the univariate correlation (online supplemental table 1) nor in the model with ET starting age. This is in contrast to findings presented by D'Andrea and colleagues[2] as well as Bhuva and colleagues,[3] however, we only included athletes older than 30 years, while the minimum age in D'Andrea was 18 years and in Bhuva 21 years. AD has been shown to decrease most steeply in young people between age 20 and 50 and remains stable thereafter.[4] Age was a significant factor in the model with ET years because it corrected the effect of ET years on AD.

Besides training history, resting heart rate was a significant inverse predictor for AD. The chronotropic adaptation to ET is resting bradycardia, partly caused by an increased LV stroke volume, but mainly by electrical remodelling of the sinus node.[21 22] A lower resting heart rate has been suggested to impose a lesser mechanical wear[23–25] due to hundreds of millions fewer cumulative heart beats over a life time (26 m vs 31 m heart beats per year at a resting HR of 50 bpm vs 60 bpm, respectively). The wear and tear by heart cycles have been confirmed in clinical studies, where high resting heart rate has been found associated with higher arterial stiffness.[26–28] In a study on 102 elderly healthy volunteers with various sport histories from sedentary to Master athletes, resting heart rate was 10 bpm lower in Master athletes compared with sedentary people, central pulse wave velocity was 26%[29] and LV stiffness 41% lower in Master athletes compared with sedentary controls.[30] In a community-based longitudinal observational study, Ohyama and colleagues found an association between baseline resting heart rate and the decrease AD over 10 years of follow-up.[31]

Limitations

The main limitation was that ET starting age and ET training years were highly collinear and, therefore, their association with AD could not be discriminated. However, age corrected the effect of ET years on AD in that the same number of ET years at a higher age was associated with a lesser AD. The same number of ET years at a higher age corresponded to a higher age at ET start. ET starting age was associated with AD independently of age, namely, it accounted for ET years corrected by age. Furthermore, training hours were based on estimation and/or exercise diary and were, therefore, prone to recall and social desirability bias. Furthermore, we had no information on ET intensity. However, the main objective of our study was to assess age at start of ET, which we expected to be less confounded by recall and social desirability bias than training volume or intensity. The echocardiographic data were reviewed by only one cardiologist. Also, we measured brachial rather than central BP for the calculation of AD and aortic stiffness. Peripheral BP measurements may overestimate systolic and PP in young persons[32] and consequently underestimate their AD. Finally, the cross-sectional design of the study allowed the detection of associations only, rather than cause and effect relationships. However, a longitudinal (randomised) design allocating people to a training group starting ET during adolescence or at an advance age would hardly be feasible.

CONCLUSIONS

In our cohort of non-elite, middle-aged runners, athletes starting at a younger age or having more ET years had a higher proximal AD. Importance of ET starting age may have gone undetected in studies with professional athletes as they show little heterogeneity with regards to starting age.

Consideration of ET starting age should permit to better understand the beneficial morphological and functional adaptations of the ascending aorta linked to ET and the

favourable effects ET introduction during adolescence may have on cardiovascular health in the elderly.

Acknowledgements The authors gratefully acknowledge the athletes' participation in this study. We would like to thank Susana Pérez for the creation of figure 2.

Contributors CPR, PE, LDT and MW contributed to the planning, CPR, PE, TM, DH, NB, LDT and MW contributed to the conduct, and CPR, PE, TM and MW contributed to the reporting of the work described in the article, CPR, PE and MW are responsible for the overall content as guarantors.

Funding This study received funding from an internal grant of the Inselspital.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by Ethics committee of the canton of Berne, Switzerland, Number 029/10. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data are available upon request from the corresponding author.

ORCID iDs
Prisca Eser http://orcid.org/0000-0001-9734-0682
Matthias Wilhelm http://orcid.org/0000-0003-4541-3995

REFERENCES

1 Redheuil A, Wu CO, Kachenoura N, *et al*. Proximal aortic distensibility is an independent predictor of all-cause mortality and incident CV events: the MESA study. *J Am Coll Cardiol* 2014;64:2619–29.
2 D'Andrea A, Cocchia R, Riegler L, *et al*. Aortic stiffness and distensibility in top-level athletes. *J Am Soc Echocardiogr* 2012;25:561–7.
3 Bhuva AN, D'Silva A, Torlasco C, *et al*. Training for a first-time marathon reverses age-related aortic stiffening. *J Am Coll Cardiol* 2020;75:60–71.
4 Redheuil A, Yu W-C, Wu CO, *et al*. Reduced ascending aortic strain and distensibility: earliest manifestations of vascular aging in humans. *Hypertension* 2010;55:319–26.
5 Taghizadeh H, Tafazzoli-Shadpour M. Characterization of mechanical properties of lamellar structure of the aortic wall: effect of aging. *J Mech Behav Biomed Mater* 2017;65:20–8.
6 Tsamis A, Krawiec JT, Vorp DA. Elastin and collagen fibre microstructure of the human aorta in ageing and disease: a review. *J R Soc Interface* 2013;10:20121004.
7 Wilhelm M, Roten L, Tanner H, *et al*. Atrial remodeling, autonomic tone, and lifetime training hours in nonelite athletes. *Am J Cardiol* 2011;108:580–5.
8 Brugger N, Krause R, Carlen F, *et al*. Effect of lifetime endurance training on left atrial mechanical function and on the risk of atrial fibrillation. *Int J Cardiol* 2014;170:419–25.
9 Mancia G, Fagard R, Narkiewicz K, *et al*. 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of hypertension (ESH) and of the European Society of cardiology (ESC). *Eur Heart J* 2013;34:2159–219.
10 Mitchell JH, Haskell W, Snell P, *et al*. Task force 8: classification of sports. *J Am Coll Cardiol* 2005;45:1364–7.
11 Ryffel CP, Eser P, Trachsel LD, *et al*. Age at start of endurance training is associated with patterns of left ventricular hypertrophy in middle-aged runners. *Int J Cardiol* 2018;267:133–8.
12 Laurent S, Cockcroft J, Van Bortel L, *et al*. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006;27:2588–605.
13 Laurent S, Marais L, Boutouyrie P. The noninvasive assessment of vascular aging. *Can J Cardiol* 2016;32:669–79.
14 Kawasaki T, Sasayama S, Yagi S, *et al*. Non-invasive assessment of the age related changes in stiffness of major branches of the human arteries. *Cardiovasc Res* 1987;21:678–87.
15 O'Rourke MF, Staessen JA, Vlachopoulos C, *et al*. Clinical applications of arterial stiffness; definitions and reference values. *Am J Hypertens* 2002;15:426–44.
16 O'brien RM. A caution regarding rules of thumb for variance inflation factors. *Qual Quant* 2007;41:673–90.
17 Erol MK, Yilmaz M, Oztasyonar Y, *et al*. Aortic distensibility is increasing in elite athletes. *Am J Cardiol* 2002;89:1002–4.
18 Kasikcioglu E, Kayserilioglu A, Oflaz H, *et al*. Aortic distensibility and left ventricular diastolic functions in endurance athletes. *Int J Sports Med* 2005;26:165–70.
19 Rose J-L, Lalande A, Bouchot O, *et al*. Influence of age and sex on aortic distensibility assessed by MRI in healthy subjects. *Magn Reson Imaging* 2010;28:255–63.
20 Nethononda RM, Lewandowski AJ, Stewart R, *et al*. Gender specific patterns of age-related decline in aortic stiffness: a cardiovascular magnetic resonance study including normal ranges. *J Cardiovasc Magn Reson* 2015;17:20.
21 D'Souza A, Pearman CM, Wang Y, *et al*. Targeting miR-423-5p reverses exercise training-induced HCN4 channel remodeling and sinus bradycardia. *Circ Res* 2017;121:1058–68.
22 D'Souza A, Bucchi A, Johnsen AB, *et al*. Exercise training reduces resting heart rate via downregulation of the funny channel HCN4. *Nat Commun* 2014;5:3775.
23 Avolio A, Jones D, Tafazzoli-Shadpour M. Quantification of alterations in structure and function of elastin in the arterial media. *Hypertension* 1998;32:170–5.
24 Thorin-Trescases N, Thorin E. Lifelong cyclic mechanical strain promotes large elastic artery stiffening: increased pulse pressure and old age-related organ failure. *Can J Cardiol* 2016;32:624–33.
25 O'Rourke MF. Arterial aging: pathophysiological principles. *Vasc Med* 2007;12:329–41.
26 Whelton SP, Blankstein R, Al-Mallah MH, *et al*. Association of resting heart rate with carotid and aortic arterial stiffness: multi-ethnic study of atherosclerosis. *Hypertension* 2013;62:477–84.
27 Papaioannou TG, Oikonomou E, Lazaros G, *et al*. The influence of resting heart rate on pulse wave velocity measurement is mediated by blood pressure and depends on aortic stiffness levels: insights from the Corinthia study. *Physiol Meas* 2019;40:055005.
28 Sa Cunha R, Pannier B, Benetos A, *et al*. Association between high heart rate and high arterial rigidity in normotensive and hypertensive subjects. *J Hypertens* 1997;15:1423–30.
29 Shibata S, Fujimoto N, Hastings JL, *et al*. The effect of lifelong exercise frequency on arterial stiffness. *J Physiol* 2018;596:2783–95.
30 Bhella PS, Hastings JL, Fujimoto N, *et al*. Impact of lifelong exercise "dose" on left ventricular compliance and distensibility. *J Am Coll Cardiol* 2014;64:1257–66.
31 Ohyama Y, Teixido-Tura G, Ambale-Venkatesh B, *et al*. Ten-Year longitudinal change in aortic stiffness assessed by cardiac MRI in the second half of the human lifespan: the multi-ethnic study of atherosclerosis. *Eur Heart J Cardiovasc Imaging* 2016;17:1044–53.
32 Avolio AP, Van Bortel LM, Boutouyrie P, *et al*. Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. *Hypertension* 2009;54:375–83.