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ORIGINAL ARTICLE

Age-related decline in mitral peak diastolic velocities is unaffected in well-trained runners

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Abstract

Objectives. We examined whether diastolic left ventricular function in young and senior lifelong endurance runners was significantly different from that in sedentary age-matched controls, and whether lifelong endurance running appears to modify the age-related decline in diastolic left ventricular function. *Design.* The study comprised 17 senior athletes (age: 59–75 years, running distance: 30–70 km/week), 10 young athletes (age: 20–36 years, matched for running distance), and 11 senior and 12 young weight-matched sedentary controls. Peak early (E) and late (A) mitral inflow and early (e') and late (a') diastolic and systolic (s') annular longitudinal tissue Doppler velocities were measured by echocardiography during four stages (rest, supine bike exercise at 30% and 60% of maximal workload, and recovery). *Results.* The athletes had marked cardiac remodeling, while overall differences in mitral inflow and annular tissue Doppler velocities during rest and exercise were more associated with age than with training status. The senior participants had lower E/A at rest, overall lower E, e' and s', and greater E/e' compared to the young participants (all values of $P < 0.05$). The athletes had greater E/A ($P = 0.004$), but tissue Doppler velocities were not different from those of the controls. *Conclusions.* Lifelong endurance running was not found to be associated with major attenuation of the age-related decline in diastolic function at rest or during exercise.

Key words: *diastole, exercise, left ventricle, stress echocardiography, systole, running, tissue Doppler velocities*

Introduction

The effects of aging on the human heart include a decline in diastolic function, which is characterized by reduced peak early mitral inflow velocity (E) and peak early mitral annular tissue Doppler (TD) velocity (e'), with a compensatory increase in late (atrial phase) peak inflow velocity (A) and peak TD velocity (a') (1).

The decline in cardiac function with advancing age is typically seen in parallel to reduced physical activity, and it has been proposed that lifelong exercise training might attenuate the effects of aging on the heart (2,3). A cross-sectional study of master athletes has indicated that regular endurance training

may partly offset the age-related increase in LV stiffness (4), and some exercise training intervention studies have shown improved diastolic function in terms of LV peak diastolic filling rate, increased resting E/A, and increased E and e' at rest and during exercise (5–9).

The aim of this study was to examine whether lifelong training in endurance running can counteract the age-related decline in cardiac diastolic function assessed during rest and supine exercise. We hypothesized that lifelong endurance running in the young would result in [1] greater peak early mitral inflow velocity (E) at rest and during exercise, [2] greater peak early mitral annular TD velocities

(e') at rest and during exercise, and [3] larger ratio between resting peak early and atrial phase mitral inflow velocities (E/A), and that this pattern of the "athlete´s heart filling" would still be discernible in elderly athletes in spite of the expected age-related decline in diastolic LV function.

Materials and methods

Study design and participants

Fifty healthy males participated, and the group comprised 17 senior athletes (endurance runners); 10 young athletes (endurance runners matched for current running distance); and 11 senior and 12 young sedentary controls, matched with no difference in age, height and weight (Table I). Overall, the trained participants were well-trained endurance middle-distance runners and marathon runners, as illustrated by the VO_2peak (Table II) (10). The running was largely of moderate to high intensity, performed 4–6 days/week. Senior athletes had been training regularly for a median of 27 years (range 15–45) with a mean weekly running distance of 49 km (SD 12), whereas the young athletes had been training for the last 6 (4–10) years with a weekly running distance of 43 (17) km ($P = 0.29$ for weekly running distance); the running distances during the last week before the study were 43 (5) and 48 (7) km respectively (between the groups, $P = 0.61$). To ensure that the effect of exercise training was uniform, only runners were recruited as athletes and the participants had no physically demanding occupation, thus their physical activity level was primarily governed by their leisure activities. The untrained subjects had been sedentary for at least 5 years.

Fifty-one males were recruited through advertising. To minimize the possible effects of parameters other than running and age, the exclusion criteria for this investigation were obesity (body mass index [BMI] > 28 kg·m^{-2}), use of medication, smoking, or diabetes. An oral glucose tolerance test was performed to determine prediabetes. Data on anthropometry and peak oxygen consumption (VO_2peak) have previously been published (11), an additional two senior athletes who had impaired glucose tolerance but normal mean glucose levels (HbA1c) were included, whereas one senior sedentary participant was excluded because of significant aortic regurgitation.

The study was in compliance with the Declaration of Helsinki and was approved by the Scientific Ethics Committee of the Capital Region of Denmark (ref. 25543). Informed written consent was given by all participants.

Cardiopulmonary exercise test

To ensure training status and provide data on maximal workload for calculation of workload applied during echocardiography, VO_2peak was measured during an incremental exhaustive protocol on an electronically braked upright ergometer bike (Monark 839 Ergomedic, ProTerapi, Brøndby, Denmark) as previously described (11). The protocol started at 50 W (senior sedentary group) or 75 W (all other groups), with a 25 W increase in load every minute until volitional exhaustion, which was reached at a point between 4 and 12 min for all subjects. VO_2, CO_2 excretion, respiratory exchange ratio (RER), heart rate (HR), minute ventilation (VE), and cadence in revolutions per minute (RPM) were continuously recorded. All subjects reached RER values above 1.09 (range 1.09–1.34). The VO_2peak was determined as the highest value reached during a 15-sec period and reported as absolute values (mL·min^{-1}) relative to body weight (mL·kg^{-1}·min^{-1}). Table II shows the results of the cardiopulmonary exercise test (CPET) together with resting blood pressure and HR.

Table I. Anthropometric characteristics of participants.

| | Young | | Senior | | |
	Sedentary ($n = 12$)	Athlete ($n = 10$)	Sedentary ($n = 11$)	Athlete ($n = 17$)	P-value[§]
Age [years], median (range)	23 (21–31)	26 (20–36)	66 (60–73)	63 (59–75)	0.274/0.246[†]
Height [cm]	178 (6)	179 (4)	175 (4)	176 (4)	0.154
Weight [kg]	70.3 (8.1)	72.8 (5.6)	75.1 (4.4)	71.1 (5.9)	0.243
BMI [kg·m^{-2}]	22.2 (1.7)[#]	22.7 (1.8)	24.6 (1.6)	23.1 (1.6)	0.009

BMI, body mass index. Values are mean (SD) unless stated otherwise.
[§]P for one-way ANOVA.
[†]P for young sedentary *vs* young athlete and senior sedentary *vs* senior athlete (Wilcoxon signed rank tests).
[#]Young sedentary *vs* senior sedentary, $P = 0.002$ (Holm-corrected).

Table II. VO$_2$peak, maximal workload, resting blood pressure, and heart rate.

	Young		Senior		*P*-value	
	Sedentary ($n = 12$)	Athlete ($n = 10$)	Sedentary ($n = 11$)	Athlete ($n = 17$)	Age	Athlete
VO$_2$peak [mL·min^{-1}]	3131 (452)	4341 (243)	2237 (345)	3323 (458)	<0.001	<0.001
VO$_2$peak [mL·kg^{-1}·min^{-1}]	44.6 (4.3)	59.8 (3.5)	29.6 (3.1)	46.9 (7.0)	<0.001	<0.001
Peak workload [W], (median, range)	275 (200;325)	350 (350;375)	175 (150;225)	275 (200;325)	<0.001	<0.001
Resting systolic blood pressure [mmHg]	120 (16)	120 (7)	127 (10)	138 (18)	0.003	0.159
Resting diastolic blood pressure [mmHg]	65 (10)	62 (6)	78 (5)	76 (14)	<0.001	0.321
Resting HR [min^{-1}]	64 (6)	51 (9)	63 (7)	54 (8)	0.615	<0.001

HR, heart rate. Values are mean (SD) unless stated otherwise. *P*-values of two-way ANOVA. No significant age*athlete interactions.

Echocardiography

Transthoracic echocardiography was performed using a Philips iE33 (Philips Medical Systems, Andover, MA, USA) with a standard S5-1 probe. Loops of three to six cycles were stored for post hoc analysis by an expert cardiologist blinded for age and training status of the participants. Left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) dimensions, posterior wall thickness (PWT), and septum wall thickness (SWT) in end-diastole were measured from the parasternal long-axis view (PLAX). Relative wall thickness (RWT) was calculated as $2 \cdot PWT \cdot LVEDD^{-1}$. The LV ejection fraction (LVEF) was estimated by the biplane method of disks (modified Simpson's rule). Mean LV wall thickness (LVWT) was calculated as mean of PWT and SWT, left ventricular mass (LVM) was calculated as $0.8 \cdot (1.04 \cdot (LVEDD + PWT + SWT)^3 - (LVEDD)^3) + 0.6$ g, left atrium volume (LAV) was estimated from the apical 4-chamber view, and indexed (LVWTI, LVMI and LAVI) for body surface area (BSA) calculated using the Du Bois formula $(0.007184 \cdot [weight\,in\,kg]^{0.425} \cdot [height\,in\,cm^{0.725}]\,m^{-2})$, and in addition, LVM was allometrically adjusted as $LVM \cdot height^{-2.7}$. LVEDD (LVEDDI) and LVESD (LVESDI) were also indexed for BSA. LV mitral inflow pattern with peak early (E) and atrial-phase (A) diastolic inflow velocities were measured by pulsed wave Doppler (PW) in apical 4-chamber view, and the ratio of these (E/A) was calculated. PW tissue Doppler (TD) was used to measure peak early (e') and atrial-phase (a') diastolic and systolic (s') LV longitudinal velocities in the septal, lateral, anterolateral, and inferior positions of the mitral annulus from apical 4-chamber and 2-chamber views, and the averages of these values were used.

We have previously estimated the inter-rater variability in our laboratory to be between 4% and 8% for E and e', and between 16% and 26% for A during rest, exercise, and recovery (12). The agreement was similar between the different conditions and similar to those reported by others (13).

Supine bicycle echocardiography

Participants exercised on a supine ergometer bike (Lode, Groningen, Netherlands) with a back angle support of approximately 20° and left lateral tilt between approximately 20° and 30° while performing 55–65 RPM at 30% and 60% of the maximum workload performed during the CPET. Two minutes into each stage of the examination, measures of LV inflow and mitral annulus TD were obtained as described above. Measures were repeated after 2 min of passive recovery to ensure return to baseline and to strengthen the statistical analyses, by including 4 measurements per parameter for each individual. Blood pressure was measured using an oscillometric blood pressure monitor at the end of each stage. The stages lasted between 4 and 8 min, depending on image acquisition. Increase in HR will eventually (typically when HR exceeds 100–120 beats per minute) cause merging of E with A, and e' with a'. In case of fully merged curves, the velocity was classified as E and e' respectively.

Data analysis

The characteristics based on which participants were selected, that is, height, weight, and age, were analyzed using one-way analysis of variance (ANOVA). If significant differences were present, the Holm multiple comparison post hoc test was used to correct for multiple testing when comparing group differences within the senior (senior sedentary *vs* senior athletes) and the young (young sedentary *vs* young athletes) groups, as well as group differences within the trained (young athletes *vs* senior athletes) and the untrained (young sedentary *vs* senior sedentary) groups. Two-way ANOVA was used to test independent and interacting effects of age and training status

on resting HR and blood pressure, peak exercise variables, and resting echocardiographic measures. Significant interactions were explored by the Holm multiple post hoc comparison test, as stated above. Additionally, multiple linear regressions of resting Doppler and TD parameters as outcomes of age and training status as categorical covariates and resting HR as a continuous covariate were performed.

Mixed-model repeated measures of ANOVA were used to test for effects of age, training status (athlete), stage (rest, 30%, 60% and recovery), and interactions between these for each outcome assessed during exercise echocardiography. The mixed-model ensures that individuals with missing data are not excluded from the statistical model. The likelihood ratio test of nested models (models including and excluding the term to be tested) was used to test interaction terms and stage. In case of a significant interaction term, the Wald test with Holm correction for multiple comparisons was used to test the significance of each level of the interaction term. Non-significant interactions were excluded while the main effects remained in the models. Due to the non-normally distributed residuals, LAVI and E/e' were tested after logarithmic transformation. Pearson correlation coefficients (r) of VO_2peak with LVEDDI, LVEF, Doppler, and TD measures were estimated. Further, stepwise multiple linear regression of VO_2peak on LVEDDI, LVEF, Doppler, and TD measures were performed using both backward elimination and forward selection. Backward elimination included covariates that were significantly correlated with VO_2peak, the covariate with the greatest P-value was eliminated in each step, and only significant covariates remained in the final model. Forward selection included the covariate with the most significant correlation to VO_2peak, and in each step, the covariate that correlated most significantly

with the residuals of the model was included, and the process was terminated when no covariates correlated with the residuals.

Results are given as mean (SD) in text and tables, and as mean (SEM) in figures, unless stated otherwise. For brevity, only P-values less than 0.1 are given in the text and figures. A value of $P < 0.05$ was considered statistically significant. All statistical analysis was conducted using STATA 11.2 (StataCorp, College Station, TX, USA).

Results

Mitral inflow and TD parameters

Overall, the echocardiographic parameters of mitral peak inflow velocities and annular TD velocities during rest and exercise were more influenced by age than by training status (Table III, Figure 1). Athletes had higher E than the sedentary participants at rest, though the difference was small compared to the overall effect of age ($P < 0.001$, Figure 1A). Full merging of E and A occurred in 16 (14 young and 2 senior) and 24 (18 young and 6 senior) participants at exercise levels of 30% and 60%, respectively, leaving only 8 and 4 young participants without full merging of E and A at 30% and 60%, respectively. If fully merged E waves were excluded, the athletes were found to have significantly greater E than the sedentary participants at all stages ($P = 0.012$). The effect, however, was minor compared to the effect of age, and the athlete effect on resting E was eliminated if correction for resting HR was performed.

Athletes had higher E/A than the sedentary participants at rest, but the difference was small compared to the impact of age, and the athlete effect was eliminated by adding resting HR to the model (Table III). Due to the merging of the E and A waves

Table III. Resting mitral inflow and mitral annular tissue Doppler velocities.

	Young		Senior		P-value				
					Two-way ANOVA		Multiple linear regression		
	Sedentary	Athlete	Sedentary	Athlete	Age	Athlete	Age	Athlete	Resting HR
	($n = 12$)	($n = 10$)	($n = 11$)	($n = 17$)					
E [cm·s^{-1}]	81 (18)	93 (12)	56 (8)	63 (15)	<0.001	0.024	<0.001	0.207	0.239
A [cm·s^{-1}]	46 (9)	48 (4)	63 (12)	59 (15)	<0.001	0.581	<0.001	0.308	0.008
E/A	1.7 (0.4)	2.0 (0.3)	0.9 (0.2)	1.1 (0.3)	<0.001	0.018	<0.001	0.861	<0.001
e' [cm·s^{-1}]	13.4 (2.0)	13.8 (1.7)	7.8 (1.7)	8.3 (2.5)	<0.001	0.387	<0.001	0.528	0.884
E/e'	6.1 (1.4)	6.9 (1.4)	7.5 (1.4)	8.1 (2.8)	0.014	0.235	0.014	0.502	0.575
a' [cm·s^{-1}]	7.1 (2.1)	6.8 (2.1)	11.2 (1.0)	10.1 (1.4)	<0.001	0.150	<0.001	0.881	0.013
s' [cm·s^{-1}]	9.7 (1.4)	9.5 (1.2)	9.4 (1.2)	8.2 (1.5)	0.040	0.051	0.027	0.582	0.042

Values are mean (SD). No significant age*training interactions. A, atrial-phase mitral inflow velocity; a', atrial-phase mitral annular tissue Doppler velocity; E, early mitral inflow velocity; e', early mitral annular tissue Doppler velocity; E/A, ratio of early and atrial-phase mitral inflow velocities; E/e', ratio of early mitral inflow and early mitral annular tissue Doppler velocities; s', systolic mitral annular tissue Doppler velocity.
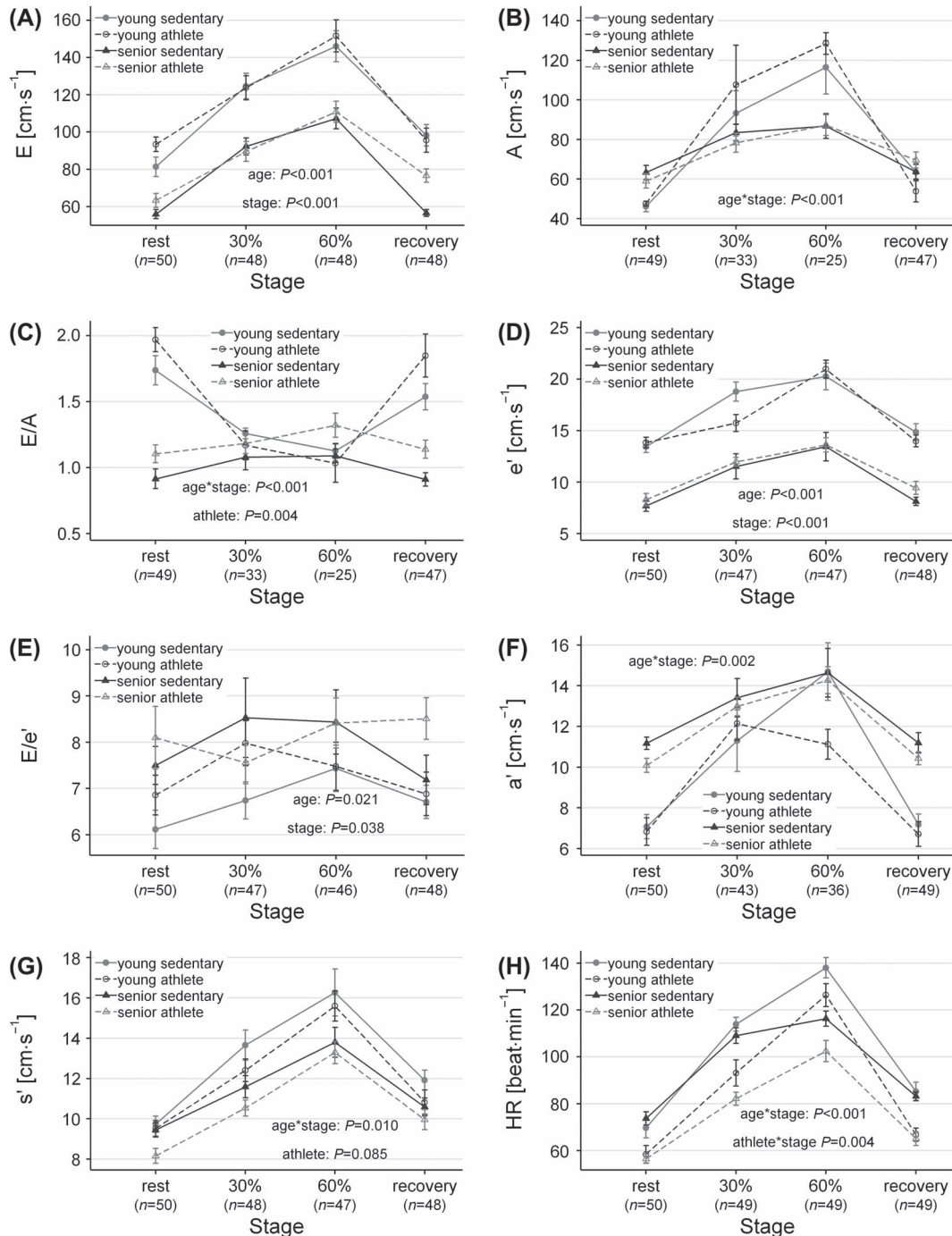
Figure 1. (A–H) Mitral inflow, tissue Doppler velocities, and heart rate during supine exercise echocardiography. Values are mean (SEM). *P*-values < 0.1 of mixed model repeated measures ANOVA are given. A, atrial-phase mitral inflow velocity; a', atrial-phase mitral annular tissue Doppler velocity; E, early mitral inflow velocity; e', early mitral annular tissue Doppler velocity; E/A, ratio of early and atrial-phase mitral inflow velocities; E/e', ratio of early mitral inflow and early mitral annular tissue Doppler velocities; HR, heart rate; s', systolic mitral annular tissue Doppler velocity.

and the resulting small number of young participants with measurable E/A during exercise, the power for detection of differences within the young participants (including age*athlete interaction) in the mixed-model was limited with regard to E/A. Though the E/A of the sedentary young does not seem different

from that of the young athletes during exercise in Figure 1C, there were no significant age*athlete or athlete*stage interactions, and E/A was overall higher in the athletes compared to the sedentary participants. The value of e' was significantly lower for the senior participants (*P* < 0.001), and increased

generally during exercise ($P < 0.001$), with no influence of training status. These results were not altered by the exclusion of fully merged e' (Figure 1D).

The ratio of E/e' was generally higher for the senior participants ($P = 0.021$), and increased slightly but significantly for the total study population from rest to exercise at 60% (rest *vs* 60%: $P = 0.001$, Holm-corrected) (Figure 1E). When fully merged waves were excluded, the age effect was still significant ($P = 0.004$), whereas the increase in E/e' from rest to exercise was no longer significant.

All Doppler velocities rapidly returned toward resting values in the recovery phase.

Matching exercise intensity by relative workload led to greater increase in HR of the young (age*stage $P < 0.001$) and greater increase in HR of the sedentary group, compared to the athletes during each stage of the exercise echocardiography (athlete*stage $P = 0.004$) (Figure 1H).

Echocardiographic dimensions

LV volumes, diameters, and mass, both absolute and adjusted for BSA, were larger in the athletes, with no difference in LVEF (Table IV). LV diameters and mass were also greater in senior participants, without significant differences in LV volumes, regardless of

indexation to BSA and allometric adjustment of LVM to height[2,7]. Consequently, RWT and mass/volume ratio only increased with age. As expected, LAV increased with age, but more so with training status. The effect of age was not modified by training status, and there were no significant age*athlete interactions for echocardiographic dimensions.

The VO_2peak was significantly correlated with several Doppler and TD measures (Table V). Stepwise multiple linear regression yielded the same model when backward elimination and forward selection were applied (Table VI).

Discussion

The main finding of the current study is that only age has a major impact on mitral peak inflow and TD velocities, whereas both age and training status have a compelling impact on exercise capacity and cardiac dimensions. We found minor differences between sedentary participants and athletes in terms of E, E/A and s' during rest, but age-related decline in LV-diastolic function did not appear to be counteracted by training status, nor did exercise stress echocardiography reveal improved adaptation to exercise in the older athletes with regard to these parameters.

Table IV. Echocardiographic dimensions.

	Young		Senior		P-value	
	Sedentary (n = 12)	Athlete (n = 10)	Sedentary (n = 11)	Athlete (n = 17)	Age	Athlete
LVEF [%]	59 (2)	58 (4)	59 (3)	60 (4)	0.732	0.391
LVEDV [mL]	93 (23)	134 (27)	89 (18)	122 (15)	0.183	<0.001
LVEDVI [mL·m^{-2}]	50 (13)	70 (14)	47 (9.2)	66 (8.6)	0.228	<0.001
LVESV [mL]	38 (9.7)	56 (14)	37 (8.5)	49 (9.0)	0.151	<0.001
LVESVI [mL·m^{-2}]	20 (5.2)	29 (6.9)	19 (4.4)	26 (5.0)	0.186	<0.001
LVEDD [mm]	48 (5)	54 (4)	45 (2)	50 (4)	0.004	<0.001
LVEDDI [mm·m^{-2}]	2.6 (0.3)	2.8 (0.2)	2.3 (0.1)	2.7 (0.2)	0.018	<0.001
LVESD [mm]	32 (5)	35 (4)	29 (2)	32 (4)	0.004	0.019
LVESDI [mm·m^{-2}]	1.7 (0.2)	1.9 (0.2)	1.5 (0.1)	1.7 (0.2)	0.010	0.028
LVWT [mm]	7.7 (1.4)	8.2 (1.2)	8.9 (0.9)	10.1 (1.3)	<0.001	0.019
LVWTI [mm·m^{-2}]	4.1 (0.8)	4.3 (0.5)	4.7 (0.5)	5.4 (0.7)	<0.001	0.018
RWT	0.32 (0.09)	0.29 (0.05)	0.38 (0.04)	0.37 (0.06)	0.001	0.310
LVM [g]	122 (30)	159 (29)	129 (20)	188 (39)	0.042	<0.001
LVMI [g·m^{-2}]	65 (16)	83 (12)	68 (11)	101 (20)	0.025	<0.001
LVM·height$^{-2.7}$ [g·m$^{-2.7}$]	26 (6.7)	33 (5.3)	29 (5.1)	41 (8.9)	0.009	<0.001
LVM/LVEDV [g·mL^{-1}]	1.38 (0.44)	1.21 (0.27)	1.49 (0.34)	1.55 (0.34)	0.038	0.695
LAV [mL]	32 (9)	49 (11)	39 (17)	63 (18)	0.021	<0.001
LAVI [mL·m^{-2}]	17 (5)	26 (6)	21 (9)	34 (10)	0.035	<0.001

Values are mean (SD). *P*-values of two-way ANOVA. No significant age*training interactions.
LAV(I), left atrial volume (indexed for body surface area); LVEDD(I), left ventricular end-diastolic dimension (indexed for body surface area); LVEF, left ventricular ejection fraction; LVEDV(I), left ventricular end-diastolic volume (indexed for body surface area); LVESD(I), left ventricular end-systolic dimension (indexed for body surface area); LVESV(I), left ventricular end-systolic volume (indexed for body surface area); LVM(I), left ventricular mass (indexed for body surface area); LVM·height$^{-2.7}$, left ventricular mass allometrically adjusted for height; LVWT(I), left ventricular wall thickness (indexed for body surface area); RWT, relative wall thickness.

Table V. Correlations between VO_2peak [$mL \cdot kg^{-1} \cdot min^{-1}$] and selected echocardiographic parameters.

	R	P-value
E_{rest}	0.57	< 0.001
A_{rest}	-0.47	< 0.001
E/A_{rest}	0.66	< 0.001
e'_{rest}	0.57	< 0.001
a'_{rest}	-0.54	< 0.001
$E_{30\%}$	0.32	0.028
$e'_{30\%}$	0.30	0.040
$E_{60\%}$	0.44	0.002
$e'_{60\%}$	0.42	0.004
$s'_{60\%}$	0.33	0.023
$E_{recovery}$	0.60	< 0.001
$E/A_{recovery}$	0.62	< 0.001
$e'_{recovery}$	0.53	< 0.001
$a'_{recovery}$	-0.48	< 0.001
LVEDVI	0.49	< 0.001

A, atrial-phase mitral inflow velocity; a', atrial-phase mitral annular tissue Doppler velocity; E, early mitral inflow velocity; e', early mitral annular tissue Doppler velocity; E/A, ratio of early and atrial-phase mitral inflow velocities; LVEDVI, left ventricular end-diastolic volume indexed for body surface area; r, Pearson correlation coefficient; s', systolic mitral annular tissue Doppler velocity.
Only parameters for which $P \leq 0.1$ are listed. Subscripts refer to stage of exercise echocardiography.

Age-related changes in cardiac function

Importantly, the effects of age were not found to be different between the athletes and the sedentary participants.

The results of the present study support conclusions of previous larger studies that resting LV diastolic (E, E/A, e' and E/e') and systolic function (measured as s') decline with age (1). The effects of age and endurance training on mitral inflow peak velocities and mitral annular TD velocities during exercise have recently been examined in cross-sectional studies by Donal et al. (13), Molmen et al. (6), and Carrick-Ranson et al. (14). They matched exercise intensity in different ways—absolute HR and relative HR (percentage of maximum HR), respectively. Both mitral peak inflow and TD velocities might correlate with HR; in spite of this, the overall conclusions are in line with the present study.

Table VI. Multiple linear regression with VO_2peak as outcome.

	SC	P-value
E/A_{rest}	0.56	< 0.001
$s'_{60\%}$	0.27	0.009
LVEDVI	0.53	< 0.001

$R^2 = 0.64$. Subscripts refer to stage of exercise echocardiography. E/A, ratio of early and atrial-phase mitral inflow velocities; s', systolic mitral annular tissue Doppler velocity; SC, Standardized coefficient.

Consistently, we, Donal et al. (13), and Carrick-Ranson et al. (14) find that the ratio of E/A decreases during exercise in the young, reaching values comparable to those of the older participants who have merely unchanged E/A during exercise. This should be seen in context of the difficulties in interpretation of the A-wave during exercise in the present study, particularly in the young, because of higher HR. The A-wave amplitude may be regarded as artificially elevated during tachycardia, when partial merging with the E-wave is present (15). Thus, the increased A-wave may be interpreted as an "actual" and smaller A-wave amplitude riding on the residual contribution from the E-wave (15). This would cause us to overestimate the increase in A-wave amplitude in the presence of partially merged E- and A-waves, and overestimate the E-wave amplitude in the presence of fully merged waves. In the study by Carrick-Ranson et al. (14), merging occurred predominantly in the senior participants at the highest workload. Thus, in spite of these challenging technical issues regarding the effects of HR and wave fusion, it seems consistent that young adults have less contribution to LV-filling from atrial systole at rest, with a relatively greater exercise-induced increase of LV-filling during atrial systole, compared to the elderly.

The value of e' was lower both at rest and during exercise in the senior participants in the current study and in the studies by Donal et al. (13) and Carrick-Ranson et al. (14). The higher E/e' during both rest and exercise in the older participants, indicative of higher filling pressures, was in line with a similar, albeit non-significant trend found by Carrick-Ranson et al. (14). Though E/e' can be used even in case of complete merging of E and A (16), it should be noted that E/e' does not reliably track changes in ventricular filling pressures during cardiac loading and unloading in healthy individuals (17).

Effect of training status on resting cardiac function

As hypothesized, both young and senior athletes had greater resting E (8%) and E/A (7%), although the athlete effect was modest in comparison to the 30% higher resting E and 44% higher resting E/A of the young compared to the senior participants. This is in line with most of the previous studies that either found no difference or only modestly higher E and E/A among athletes (6,13,14,18–23). Experiments with increased HR by means of atrial pacing or exercise find A and E/A, and to a lesser extent E, to be affected by HR in young healthy subjects (15,24). The athlete effect was eliminated by correction for resting HR. Conclusions should, however, be drawn

with caution, because athlete status and resting HR are closely related and HR as a continuous variable holds greater statistical power. Further, resting HR had significant effect on A but not on E. We found no effect of training status on A, and as such, our findings for E and E/A are probably not solely due to the lower HR of the athletes. Nor were there indications of differences in relaxation (e') or filling pressures (E/e'). Thus, probable causes of higher E/A are also greater suction by the larger ventricles, greater LV compliance, and greater preload in athletes (4,14,19,25).

We did not find the hypothesized impact of training status on e', which is in accordance with some of the previous studies (13,14,21), whereas studies by Nottin et al. (22) and Molmen et al. (6), which did not include young athletes, reported higher e' of senior athletes compared to sedentary seniors.

It cannot be excluded that the differences in findings could relate to intensity of the training. Generally, improvement in VO$_2$peak is directly related to the "dose" of exercise, that is, intensity (how hard), duration (how long), and frequency (how often) of training. The intensity of the exercise seems to have a pivotal role in the training effects including VO$_2$peak (26). Some intervention studies in heart failure and arterial hypertension indicate that intensive interval training could have greater effect on diastolic parameters than moderate continuous exercise (27,28). However, none of the cross-sectional studies directly report the exact intensity of the exercise training that also will vary over season and years.

Our overall findings in runners are not different from those of the previous studies which also included athletes from sports that imply static components or upper body work (6,13,14,19–22,29). Though long-term longitudinal studies are lacking, it seems from the consistency of findings that long-term endurance training, compared to aging, does not have a marked impact on resting velocities of mitral peak inflow velocities or diastolic and systolic annular TD (6,13,14,19–22,29).

Effect of training status on cardiac function during exercise

Training status did not impact E and e' during exercise as hypothesized, though there was a minor effect on E when fully merged waves were excluded. E/A was higher in the athletes compared to the sedentary participants, both during rest and during exercise. This is in agreement with previous cross-sectional studies (6,13,14), although Donal et al. (13) report that E/A was only higher for young athletes. This

difference might be explained by the senior athletes of Donal et al. (13) having trained for less than 10 years, in contrast to our senior athletes who had been training consistently for up to 45 years.

Stepwise regression showed supplemental predictive power of LV volume, and diastolic and systolic functional measures on VO$_2$peak.

Importantly, the remodeling of the athletes' heart was distinctly different from that of disease-related remodeling, for example, as in hypertrophic cardiomyopathy. The proportions between the cardiac wall and chamber dimension were preserved in the athletes, and systolic and diastolic TD velocities increased appropriately during exercise and returned rapidly toward resting values in recovery.

Limitations

Longitudinal LV velocities do not fully describe the movements involved in LV contraction and recoil. Differences between aging with and without endurance training might exist in the twist movement, as indicated by a recent study showing shorter time from mitral valve opening to peak E and peak untwisting velocity, for endurance-trained compared to untrained middle-aged men at HR-matched exercise (30).

The supine exercise was unusual for the participants, whereas they were all familiar with upright cycling. We applied a workload in the supine position equal to 60% of the maximal workload obtained in the upright position, which corresponds to a considerably greater percentage of the maximal supine workload; however, it does not correspond to exercise at maximal HR. Further, the relative work load of the supine exercise was derived from the maximal work load of the upright CPET, and we cannot exclude that the transfer from upright to supine could have a differential effect depending on age and training status.

Based on interviews and exercise capacity, we assumed that running was largely of moderate to high intensity. However, intensity was not directly measured in the present study.

The selection of senior participants with a sedentary lifestyle but without overt lifestyle-related disease, that is, diabetes or CVD, could lead to selection bias and thus underestimation of the effect of exercise training.

Clearly, the study is cross-sectional, allowing no conclusions of causality. Further, cross-sectional studies are likely to overlook minor improvements in TD velocities at rest and during exercise, which has been attained with well-controlled exercise intervention in young and senior individuals (6–9).

Perspectives

We found that despite marked cardiac remodeling, life-long endurance running was not associated with major attenuation of the age-related decline in diastolic function. The improvements in diastolic function attained in some interventional studies with exercise training for up to 1 year are minor compared to the apparently inherent effect of age found in the cross-sectional studies.

The effect of endurance training on exercise capacity and LV dimensions is well known. The greater LV chamber dimension of endurance athletes implies greater stroke volume and lower resting HR, and thereby greater HR reserve, all of which together contribute to greater functional reserve, maximal cardiac output and VO$_2$peak of exercise-trained individuals.

In conclusion, young and elderly well-trained endurance runners had only moderately higher resting E and E/A, with little or no further adaptations during exercise. Conversely, the effects of age were marked, both during rest and exercise.

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