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Cardiac Adaptations to High-Intensity Aerobic Training in Premenopausal and Recent Postmenopausal Women: The Copenhagen Women Study

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Background—We examined the role of menopause on cardiac dimensions and function and assessed the efficacy of exercise training before and after menopause.

Methods and Results—Two groups of healthy premenopausal (n=36, 49.4±0.3 years) and postmenopausal (n=37, 53.5±0.5 years) women with no history of cardiovascular disease and with a mean age difference between groups of only 4 years were studied. Cardiac dimensions and systolic and diastolic function were determined by transthoracic echocardiography with tissue Doppler imaging and 2-dimensional speckle tracking. Measurements were performed at baseline and after a 12-week period of high-intensity aerobic cycle training. LV internal diastolic diameter and LV mass were similar in the 2 groups at baseline and increased by ≈2% to 8% (P=0.04–0.0007) with training in both groups. Left atrial end-diastolic and end-systolic volumes were similar for both groups and increased by 23% to 36% (P=0.0006–0.0001) with training. Systolic function assessed by mean global strain was similar in both groups at baseline and increased by ≈8% (P=0.0004) with training in the postmenopausal group. LV displacement increased by ≈3% (P=0.04) in the premenopausal women only. Diastolic function assessed by E/A ratio was similar at baseline and increased by ≈7% (P=0.01) in the premenopausal group and 11% (P=0.0001) in the postmenopausal group with training.

Conclusions—These results suggest that training-induced cardiac adaptations are preserved in the early postmenopausal phase. Furthermore, the hormonal changes associated with the menopausal transition do not appear to affect cardiac dimensions and function.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT02135575. (***J Am Heart Assoc.*** 2017;6: e005469. DOI: 10.1161/JAHA.117.005469.)

Key Words: E/A ratio • exercise training • menopause • transthoracic echocardiography • women

C ardiovascular disease is the leading cause of death in women globally and constitutes a major socioeconomic burden for society.[1,2] Risk factors for cardiovascular disease include smoking, physical inactivity, age, metabolic syndrome, and loss of estrogen in women.[2] Estrogen has been shown to have a protective effect on the cardiovascular system in women and the risk for cardiovascular events increases markedly after the menopausal transition when substantial hormonal changes occur, including the loss of estrogen production.[3] However, the role of age versus hormonal changes for cardiovascular risk after menopause in women remains debated,[4] in part because of the fact that comparisons of premenopausal and postmenopausal women are often conducted with significant age differences between the groups.[5] We and others have recently provided support for the notion that the menopausal transition per se leads to rapid impairments in vascular function.[6,7] In Nyberg et al,[7] leg vascular function, assessed by infusion of vasoactive compounds, was markedly impaired in recent postmenopausal women compared with age-matched premenopausal women. Although evidence for altered cardiac structure and function exists in older postmenopausal women,[8,9] it is unclear to what extent these alterations are detectable in the first few years after the menopausal transition.

Aerobic exercise training is well known to induce improvements in maximal oxygen uptake (VO$_2$max) in sedentary

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Clinical Perspective

What Is New?

- This study shows that aerobic training improves cardiac structure and function in middle-aged women irrespective of menopausal status.

What Are the Clinical Implications?

- Implementation of aerobic training can be used as a safe prophylactic strategy to oppose deteriorations in cardiac function known to be prevalent in older postmenopausal women.

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individuals.[10,11] This improvement is mainly a consequence of an increase in cardiac dimensions and function[12,13] although an enhanced blood volume may also contribute to improved ventricular filling.[14] Cardiac adaptations in response to aerobic training in sedentary individuals have been documented in a number of studies,[15–17] but adaptations appear to be smaller in premenopausal women than in men.[18–20] Hormonal changes after menopause may further reduce the ability of women to achieve cardiovascular adaptations in response to exercise training[6,21] and it has been proposed that estrogen supplementation is required for vascular adaptations in response to physical activity in postmenopausal women.[22] However, findings in the literature on adaptations to training may also vary as a result of different training regimens, where high-intensity aerobic training may be more effective than low- to moderate-intensity exercise.[23,24] A few studies have examined cardiac function and structure in postmenopausal elite athletes,[25,26] but studies comparing the effect of training on cardiac adaptations in premenopausal versus postmenopausal women are lacking. This knowledge is of clinical importance, in particular for recommendations of hormonal therapy and physical activity in the prevention of cardiovascular disease in middle-aged women.

The method used for determination of cardiac function may be a decisive factor for the ability to detect early changes after menopause and adaptations to exercise. Most studies on cardiac adaptations to physical activity have utilized conventional echocardiographic measures, but development of advanced imaging modalities in recent years with the advent of tissue Doppler imaging (TDI) and 2-dimensional speckle tracking have allowed for more sensitive detection of early subclinical changes in systolic and diastolic function.[27–30] These modalities provide sensitive assessment of subclinical changes in LV contractility and relaxation.[31] Previous studies have found subclinical indications of altered systolic function by TDI in patients with normal ventricular diastolic function and ejection fraction,[32] supporting that these modalities provide

more sensitive measures of early changes. Moreover, cardiac dysfunction determined by TDI has been shown to be an independent predictor of mortality.[33]

The aim of the present study was 2-fold: (1) to compare cardiac dimensions and systolic and diastolic function in premenopausal and early postmenopausal women with a small age difference and (2) to assess the efficacy of 12 weeks of high-intensity aerobic training on cardiac adaptations in premenopausal and recent postmenopausal women. We hypothesized that recent postmenopausal women would have similar cardiac dimensions but impaired systolic and diastolic function compared with premenopausal women and that high-intensity aerobic exercise training would be more effective in inducing cardiac adaptations in premenopausal than postmenopausal women.

Methods

Participants

Participants were recruited from the Copenhagen area through advertisement in local newspapers. Study participants were premenopausal or postmenopausal women with an age range of 45 to 57 years (Table 1). The participants were all informed about potential risks and discomforts associated with the study and written consent was signed before the study experiments.

The study was approved by the ethics committee of Copenhagen and Frederiksberg municipalities Region H (H-1-2012-150) and conducted in accordance with the guidelines of the *Declaration of Helsinki*. All participants signed an informed consent form before participation in the study. The study was registered at ClinicalTrials.gov (NCT02135575).

The premenopausal women were all healthy with regular menstrual cycles. The postmenopausal women were all healthy and had not experienced a menstrual cycle during the previous 12 months but were less than 8 years past their final menstrual period. Menopausal status was verified by measurements of hypothalamic and reproductive hormones from a blood sample (estradiol <0.20 nmol/L and follicle-stimulating hormone: 22–138 IU/L, indicative of postmenopausal status). If the blood samples were indicative of perimenopause hormone levels, the women were excluded. Inclusion criteria were age 45 to 57 years, body mass index <30, and <2 hours of light to moderate physical activity per week of age. Exclusion criteria were smoking, use of hormonal contraceptives, hormone replacement treatment, prescription medicine, hypertension, cardiovascular disease, renal dysfunction, insulin resistance, diabetes mellitus, and hypercholesterolemia.

None of the participants had pathological ECG findings that were incompatible with the exercise intervention on examination. To ensure that all participants were normotensive,

Table 1. General Characteristics

	Premenopausal			Postmenopausal			Group Difference	
	Baseline	12 Weeks	Training Effect	Baseline	12 Weeks	Training Effect	Baseline	12 Weeks
	n=36		P Value	n=37		P Value	P Value	P Value
Anthropometrics								
Age, y	49.4±2.1			53.3±3.0			<0.0001	
Height, m	1.69±0.01			1.67±0.01			0.68	
Weight, kg	67.4±6.9	66.7±6.8	0.03	66.3±8.5	65.8±8.7	0.14	0.54	0.60
Body mass index, kg/m^2	23.9±2.4	23.7±2.3	0.02	23.7±2.4	23.5±2.6	0.17	0.62	0.71
Cardiorespiratory fitness								
Resting heart rate, beats/min	67±8	64±8	0.006	64±7	61±8	<0.0001	0.15	0.07
VO$_2$max, mL/min	2068±295	2283±291	<0.001	2017±217	2204±230	<0.0001	0.40	0.22
Maximum heart rate, beats/min	177±12	175±9	0.03	174±11	172±9	0.27	0.55	0.19
Maximum RER VO$_2$max	1.31±0.10	1.27±0.08	0.02	1.30±0.08	1.29±0.09	0.40	0.61	0.46
Maximum power VO$_2$max, W	194±26	222±26	<0.001	189±21	215±21	<0.0001	0.35	0.25
Systolic BP, mm Hg	111±15	113±15	0.40	113±16	110±13	0.11	0.56	0.38
Diastolic BP, mm Hg	72±11	73±11	0.92	73±10	70±8	0.03	0.68	0.26
Cholesterol								
Total cholesterol, mmol/L	4.90±0.73	4.76±0.63	0.11	5.64±0.72	5.48±0.61	0.03	<0.0001	<0.0001
Training								
Total training sessions	37±6			38±5			0.82	
Time in intervals of HRmax, %								
60% to 85%	58±10			56±10			0.66	
86% to 100%	41±12			41±13			0.97	

BP indicates blood pressure; HRmax, maximum heart rate; RER, respiratory exchange ratio; VO$_2$max, maximal oxygen uptake.
Values are expressed as mean±SD.

blood pressure (BP) was measured 7 consecutive times by an automatic upper-arm BP monitor (M7, OMRON) after at least 15 minutes of rest in the supine position. Heart rate (HR) was measured during the BP monitoring.

The data presented are part of a larger study on the effects of exercise training on women in the menopausal transition funded by the University of Copenhagen Excellence Programme for Interdisciplinary Research and the data presented in Table 1 have previously been published.[7,34]

Study Design

The study was part of a larger study on the effect of menopause and physical activity on cardiovascular and metabolic health. The overall study design was a prospective intervention study with one group of premenopausal and one group of postmenopausal women. The women were selected to be close in age to minimize age as a confounder. All women underwent a 12-week period of high-intensity aerobic training with 3 sessions per week. For the present part of the study, the women underwent echocardiography measurements, a

test for VO$_2$max, and measurements of BP before and after the intervention period.

Exercise Training Intervention

All participants underwent the exercise training intervention. The training was performed on a cycle ergometer (Body Bike). Instructors from the research group supervised 2 training sessions per week and instructors from a local fitness center supervised 1 session. HR was monitored during all training sessions (TEAM2 Wearlink+, Polar). The training sessions were characterized by ≈50 minutes of intermittent high-intensity intervals where the participants reached HRs over 85% of maximum HR (Table 2). For more information and details on the participants' variation in exercise intensities during the training see Nyberg et al[7] and Mandrup et al.[34]

Echocardiography

Transthoracic echocardiography was performed using a GE Vivid 9 ultrasound machine with a 2.5-MHz transducer (GE

Table 2. Echocardiographic measures before and after 12 weeks of high aerobic intensity cycle training

Echocardiographic Variables	Unit	Premenopausal n=36 Baseline	12 Weeks	Training Effect P Value	Postmenopausal n=37 Baseline	12 Weeks	Training Effect P Value	Group Differences Baseline P Value	12 Weeks P Value
LV morphology									
LVIDD	cm	4.5±0.1	4.6±0.1	0.0007	4.5±0.1	4.6±0.1	0.04	0.56	0.94
LVIDS	cm	2.8±0.8	2.7±0.8	0.064	2.9±0.8	2.8±0.8	0.49	0.61	0.15
LVEDV	mL	93.2±2.6	101.7±2.6	0.0006	95.4±2.5	97.6±2.5	0.36	0.36	0.25
LVESV	mL	37.5±1.7	42.0±1.7	0.054	40.3±1.7	41.8±1.7	0.49	0.50	0.93
LV stroke volume	mL	55.6±1.9	59.7±1.9	0.064	55.1±1.9	55.8±1.9	0.76	0.85	0.15
LV mass index	g/m^2	76.9±2.5	82.1±2.5	0.001	81.4±2.4	87.6±2.4	0.001	0.19	0.11
LV mass	g	136±5	145±5	0.001	142±5	152±5	0.002	0.35	0.25
IVSD	cm	0.92±0.2	0.92±0.02	0.91	0.94±0.02	0.97±0.02	0.08	0.42	0.053
IVSS	cm	1.32±0.04	1.37±0.04	0.23	1.35±0.04	1.37±0.04	0.69	0.54	0.96
LVPWd	cm	0.93±0.02	0.926±0.02	0.97	0.94±0.02	0.95±0.02	0.68	0.77	0.55
LVPWs	cm	1.64±0.05	1.80±0.05	0.002	1.74±0.05	1.78±0.05	0.37	0.16	0.81
Systolic function									
EF, biplane	%	59.3±1.3	58.8±1.3	0.79	57.9±1.3	57.5±1.3	0.85	0.45	0.50
GLS	%	−19.8±0.4	−20.2±0.4	0.27	−19.3±0.4	−20.8±0.4	0.0004	0.38	0.25
s′$_{TDI\ color}$, mean	cm/s	6.1±0.2	6.3±0.3	0.41	5.7±0.2	5.8±0.2	0.55	0.10	0.07
Pulsed TDI s′, mean	cm/s	8.3±0.2	8.0±0.2	0.12	7.6±0.2	7.4±0.2	0.39	0.003	0.02
LV displacement	mm	12.4±0.2	12.8±0.2	0.04	11.8±0.2	12.1±0.2	0.16	0.09	0.04
Diastolic function									
Mitral inflow velocity E/A ratio	...	1.29±0.05	1.38±0.05	0.01	1.20±0.04	1.32±0.04	0.0001	0.13	0.40
Mitral deceleration time	ms	207±8	185±8	0.02	190±8	196±8*	0.48	0.11	0.32
E/e′	...	6.5±0.3	7.1±0.3	0.001	7.0±0.3	7.5±0.3	0.02	0.13	0.19
a′$_{TDI\ color}$, mean	cm/s	−6.5±0.2	−6.1±0.2	0.025	−6.4±0.2	−6.5±0.2*	0.49	0.78	0.11
Pulsed TDI a′, mean	cm/s	9.1±0.2	8.9±0.2	0.33	9.2±0.2	9.0±0.2	0.62	0.92	0.69
e′$_{TDI\ color}$, mean	cm/s	−9.0±0.3	−9.2±0.3	0.22	−7.9±0.2	−8.0±0.2	0.53	0.002	0.0004
Pulsed TDI e′, mean	cm/s	11.6±0.3	11.3±0.3	0.18	10.1±0.3	10.1±0.3	0.87	0.0002	0.01
IVRT, mean	ms	86±2	87±2	0.54	96±2	94±2	0.26	0.002	0.03
Mitral valve E velocity	m/s	0.81±0.02	0.87±0.02	0.0002	0.77±0.02	0.82±0.02	0.002	0.20	0.08
Mitral valve A velocity	m/s	0.64±0.02	0.65±0.02	0.54	0.66±0.02	0.64±0.02	0.19	0.46	0.78
Left atrium									
LAEDV	mL	22.9±1.5	28.4±1.5	0.0006	23.5±1.5	31.6±1.5	<0.0001	0.77	0.13
LAEDV index	mL/m^2	12.9±0.8	16.3±0.8	0.0004	13.3±0.8	18.2±0.8	<0.0001	0.73	0.10
LAESV index	mL/m^2	29.4±1.2	36.1±1.2	<0.0001	30.3±1.2	37.8±1.2	<0.0001	0.59	0.31
LAESV	mL	51.9±2.2	63.3±2.2	<0.0001	51.2±2.2	65.6±2.2	<0.0001	0.67	0.45
Right ventricle									
TAPSE	cm	2.59±0.1	2.62±0.1	0.63	2.55±0.1	2.55±0.1	0.99	0.59	0.36
Pulsed TDI s′	cm/s	13.6±0.3	13.9±0.4	0.34	13.4±0.3	13.3±0.3	0.58	0.79	0.22

EF indicates ejection fraction; GLS, global longitudinal strain; IVRT, isovolumic relaxation time; IVSD, left ventricular interventricular septum diastole; IVSS, left ventricular interventricular septum systole; LAEDV, left atrial diastolic volume; LAESV, left atrial systolic volume; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVIDD, left ventricular end-diastolic diameter; LVIDS, left ventricular end-systolic diameter; LVPWd, left ventricular posterior wall thickness diastole; LVPWs, left ventricular posterior wall thickness systole; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue Doppler imaging.
Values are expressed as mean±SEM.
*P<0.05: significant delta change with training between group.

Healthcare). The echocardiographic examinations were performed by 2 investigators but the examination before and after the training intervention were always performed by the same investigator for each participant. During the examination, participants rested in a supine position on their left side in a darkened room. All examinations were analyzed offline in unidentifiable random order, using the Echo Pac software version BT 13.0 (GE Healthcare). To reduce analytical variability, all echocardiographic examinations were analyzed by one of the investigators.

All participants were examined with the same protocol as previously described.[35] In short, cardiac structure was evaluated from parasternal long axis 2-dimensional recordings according to current guidelines.[36] The calculated left ventricular (LV) mass was indexed according to body surface area (m^2=0.20247×height [m]$^{0.725}$×weight [kg]$^{0.425}$, DuBois formula). LV volume and LV ejection fraction (%) were evaluated using Simpson's biplane method. Peak transmitral blood inflow velocity in early (E) and late (A) diastole and the corresponding E/A ratio was measured using pulsed-wave Doppler in the apical 4-chamber view. Peak systolic velocity (s'; cm/s), peak early diastolic velocity (e'; cm/s), and peak late diastolic velocity (a'; cm/s) were measured with pulsed-wave TDI in the 6 LV segments at the level of the mitral annulus. The value of e' represented the average of the segments of early peak diastolic velocities. Color TDI (TDI$_{color}$) at a frame rate >120/s was evaluated at the 6 mitral annular sites and values were averaged. Measurements included peak systolic velocity (s'$_{TDI\ color}$), peak early diastolic velocity (e'$_{TDI\ color}$), and peak late diastolic velocity (a'$_{TDI\ color}$). LV displacement was evaluated using tissue tracking. LV systolic function was evaluated by speckle tracking analysis where a semiautomated function tracks speckles from frame to frame identified within a specified region of interest and reported as the absolute value of global longitudinal strain.

Right ventricular function was evaluated as tricuspid annular plane systolic excursion and pulsed-wave TDI derived peak systolic velocity (s').

Determination of VO$_2$max

VO$_2$max was measured with an Oxycon Pro (Intramedic, Denmark). The protocol was an incremental exercise test on a cycling ergometer (Monark, E9). The participants started with a 10-minute warm-up and thereafter the test was initiated with a start load of 50 W and increased by 25 W/min until volitional fatigue. Criteria for determination of VO$_2$max were: a plateau in VO$_2$, even with increased workload and/or respiratory exchange ratio >1.1 and/or an HR >90% of expected value. Two of 3 criteria had to be attained before the test was approved.

The VO$_2$max tests as well as the echocardiography measurements were conducted in the weeks before the initiation of training and between 2 and 5 days after the training.

HR Monitoring and Compliance of Training

The participants had an individual HR monitor (TEAM2 Wearlink+, Polar) to record HR during the training sessions and ensure the training quality and that intervals reached a target HR >85% of maximum HR. All training sessions were registered throughout the training period.

Statistical Analysis

Our hypotheses could be directly evaluated as differences between groups and within groups in a linear mixed model framework. Fixed-effects factors were "group" (premenopausal, postmenopausal) and "time" (before training, after training). Between-subject variation was modeled using random effects. Model assumptions on homogeneity of variance and normal distribution were confirmed through residual and Q–Q plots. Pairwise differences were performed using post hoc *t* tests (based on the mixed models); no adjustment for multiplicity was applied. Data are reported as mean±SEM. The statistical analysis was executed with R version 3.2.2 (R Core Team, 2015) through the interface RStudio (RStudio Team [2015]. RStudio: Integrated Development for R. RStudio, Inc.) and the extension packages *lme4* and *multcomp*. A significance level of 0.05 was used. Sample size was calculated on the basis of detecting a 10% change in E/A ratio with training, with a power of 0.8 and a significance level of 0.05.

Results

Participant Characteristics

A total of 83 participants (43 premenopausal and 40 postmenopausal) were initially recruited. A CONSORT flow diagram for the participants has been included in Mandrup et al.[34] Ten participants were either excluded or dropped out because of illness (1), during run-in (4), because of insufficient training adherence (2), and because of pregnancy (1). Two premenopausal women were not assessed by echocardiography for logistic reasons. Therefore, a total of 36 premenopausal and 37 postmenopausal women were included in the study. All of the included participants fulfilled the training intervention and participated in the echocardiography examination both before and after the intervention period. The premenopausal women participated on average in 37±6 training sessions (≈93%) and the postmenopausal women in

38±5 training sessions (≈95%). Systolic arterial BP was similar in the 2 groups at baseline and after the training period. In the postmenopausal group, diastolic BP decreased (*P*=0.03) during the training period (by −4.3%) with no change in systolic BP. BP did not change significantly with training in the premenopausal group. It is important to point out that BP data were previously reported on these groups of women and were found to be unaltered with training.[34] The reason for this discrepancy is likely that the number of included participants was lower in the present group and there was a slight difference in statistical approach.

HR at rest was similar in the 2 groups both at baseline and after the training period. There was a decrease (*P*=0.0001) in resting HR after the training period in the postmenopausal group (5.2%), but the change in HR at rest in the premenopausal group did not reach statistical significance. Data on low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides are presented elsewhere.[34]

Cardiac Structure and Function

Intervariability and intravariability of measurements

A sample of 10 participants was reanalyzed for intraobserver and interobserver variability by 2 investigators. The results showed a variation between 0% and 15.2% for the different common variables for interobserver and between 0% and 6.7% for the intraobserver variation.

Cardiac dimensions

Left atrial end-diastolic volume index and left atrial end-systolic volume index were similar in both groups at baseline (Table 2 and Figure 1A). Training increased left atrial end-diastolic volume index by ≈26 (*P*=0.0004) and 36% (*P*<0.0001) and left atrial end-systolic volume index by ≈23 (*P*<0.0001) and 25% (*P*<0.0001)) in the premenopausal and postmenopausal groups, respectively. LV anatomy (determined as LV end-diastolic volume), LV internal diastolic diameter, and LV mass index were similar in the 2 groups at
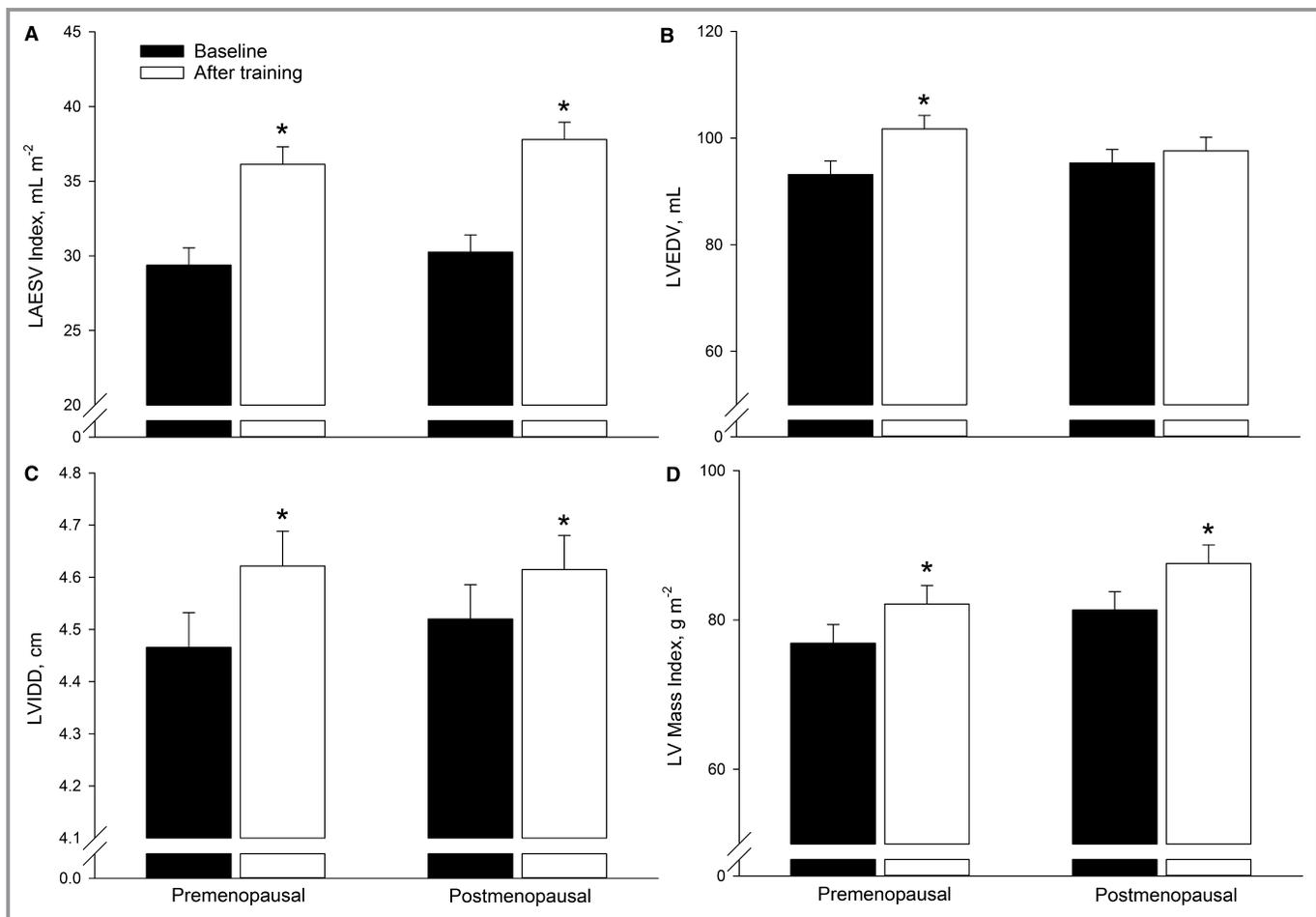
Figure 1. Cardiac structure evaluated as left atrial end-systolic volume (LAESV) index (A), left ventricular (LV) end-diastolic volume (LVEDV, B), LV internal diastolic dimension (LVIDD, C), and LV mass index (D) in premenopausal and postmenopausal women at baseline and after training. **P*<0.05 significantly different from before training.

baseline (Table 2 and Figure 1). Training increased LV end-diastolic volume by ≈9% (P=0.0006) in the premenopausal group (Figure 2B); LV internal diastolic diameter by ≈3 (P=0.0007) and 2% (0.04) in the premenopausal and postmenopausal groups, respectively (Figure 2C); and LV mass index by ≈7 (P=0.001) and 8% (P=0.001) in the premenopausal and postmenopausal groups, respectively (Figure 2D).

Interventricular septum width at diastole and LV posterior wall thickness diastole were similar in both groups at baseline and these variables remained unaltered after the intervention (Table 2).
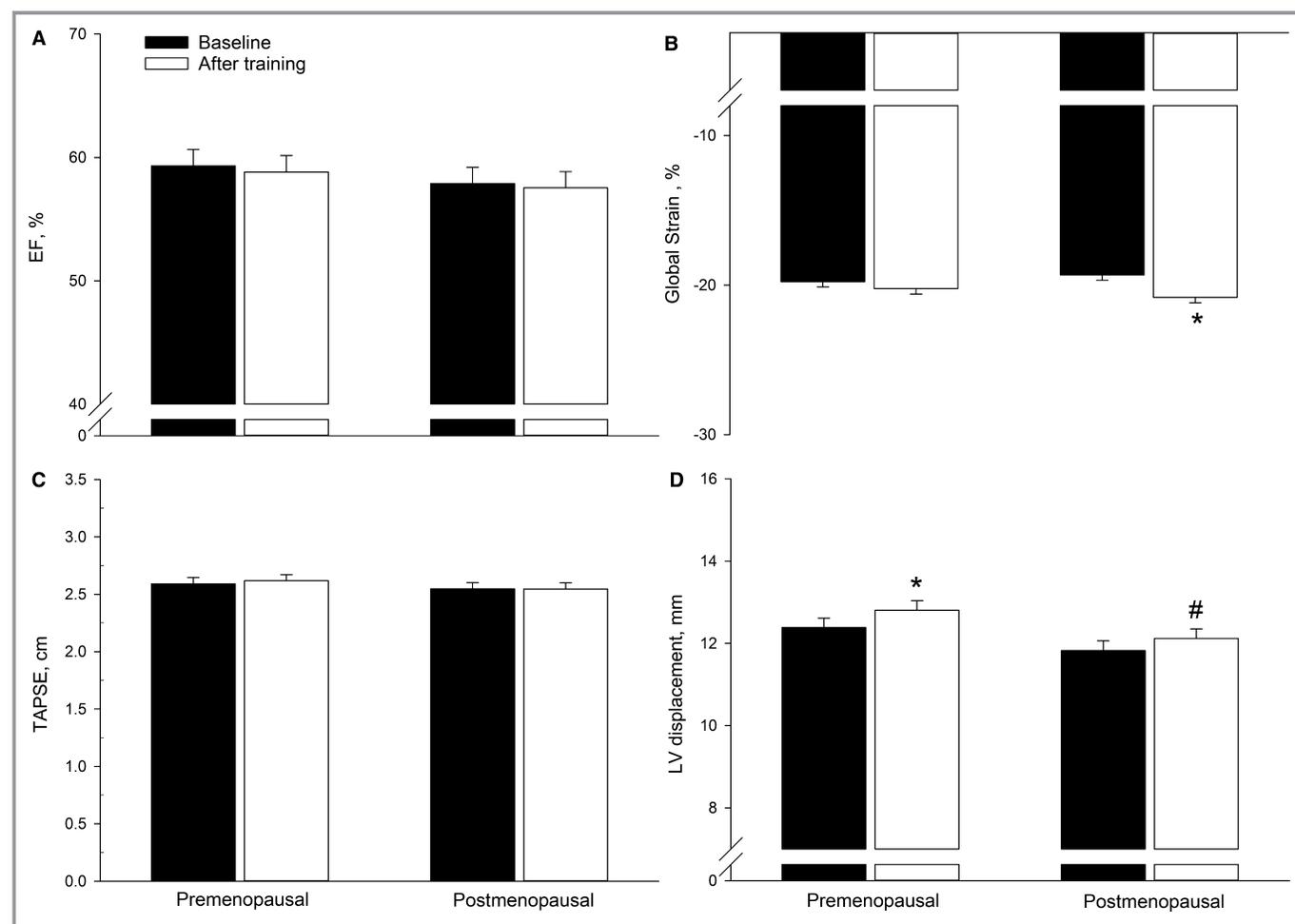
Systolic function

LV ejection fraction was similar in the 2 groups at baseline and was not altered by the training period in either group (Figure 2A). Global longitudinal strain was similar in both groups at baseline and increased (P=0.0004) in the postmenopausal group only (by ≈8%, Figure 2B). LV longitudinal displacement was similar in both groups at baseline (Figure 2D). In the premenopausal group, LV displacement was significantly higher (P=0.04) after the training period (by ≈3%), whereas no change was detected in the postmenopausal group. LV displacement was ≈6% lower (P=0.04) in the postmenopausal compared with the premenopausal group after the training period. Color TDI (s'$_{TDI\ color}$) was similar in both groups at baseline and after the training intervention (Table 2).

Diastolic function

The E/A ratio was similar in both groups at baseline and was higher in ≈7% (P=0.01) and 11% (P=0.0001) in the groups after the training period (Figure 3A). Mitral valve deceleration time was similar in both groups at baseline (Table 2). None of the participants had detectable diastolic dysfunction.

Figure 2. Left ventricular (LV) systolic function evaluated as LV ejection fraction (EF) by Simpson's biplane method (A), 2-dimensional LV longitudinal global strain (global strain, B), right ventricular function by tricuspid annular plane systolic excursion (TAPSE, C), and LV longitudinal displacement by tissue tracking tissue Doppler imaging (D) in premenopausal and postmenopausal women at baseline and after training. *P<0.05 significantly different from before training, #P<0.05 significantly different from premenopausal at that time point.
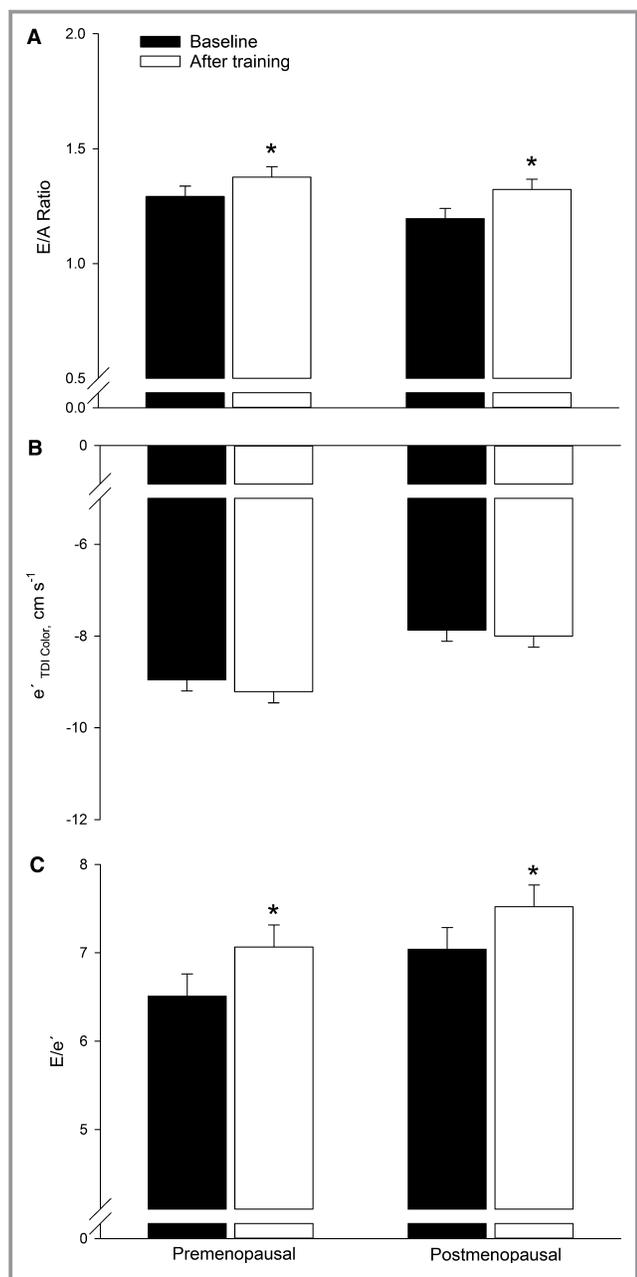
Figure 3. Left ventricular diastolic function evaluated as the ratio between early mitral inflow (E) and late (A) mitral inflow (E/A ratio, A), peak early diastolic velocity (e′, B), and E/e′ (C) in premenopausal and postmenopausal women at baseline and after training. *$P<0.05$ significantly different from before training.

Mitral valve deceleration time was significantly lower ($P=0.02$) in the premenopausal ($\approx11\%$) but not in the postmenopausal group after the training period. The training-induced change in mitral valve deceleration time was different ($P=0.03$) between the 2 groups. The e′ was similar in the 2 groups before training and remained unaltered with training (Figure 3B and 3C). At baseline, isovolumetric relaxation time (IVRT) was $\approx12\%$ lower ($P=0.002$) in the premenopausal compared with the postmenopausal group

(Table 2). The training intervention did not alter IVRT in either group.

Right ventricular function

Tricuspid annular plane systolic excursion (Figure 2C) and right ventricular pulsed-wave TDI s′ was similar in both groups at baseline and remained unaltered with the training intervention.

Discussion

The present study compared cardiac structure and functions in premenopausal and postmenopausal women and assessed the effect of a high-intensity aerobic training period in the 2 groups. Overall, the main findings were that cardiac dimensions and cardiac systolic and diastolic functions were similar in premenopausal and postmenopausal women separated by only 4 years of age. Moreover, a period of high-intensity aerobic training induced adaptations in cardiac dimensions as well as systolic and diastolic function in the 2 groups. These findings indicate that cardiac structure and function are not altered in the early postmenopausal phase and that cardiac adaptations to high-intensity aerobic training are preserved in recent postmenopausal women.

It is well established that estrogen has favorable effects on endothelial and cardiac function[5,37] and loss of estrogen at menopause is associated with an increased risk of cardiovascular disease.[38] In the present study, only minor differences in cardiac dimensions and systolic and diastolic function were detected between the premenopausal and recent postmenopausal women at baseline. This finding was therefore surprising and contrasts our own findings of reduced peripheral vascular function in postmenopausal women, as determined in a subgroup of the same premenopausal and postmenopausal women.[7] The reason for this discrepancy is unclear; however, it could suggest that impairments in vascular function are manifested before changes in cardiac function are detectable. The current study was specifically designed to achieve a small age difference (4 years) between the groups, and therefore cardiac impairments caused by hormonal changes at menopause may not yet have occurred. This possibility is supported by a study showing that approximately half of postmenopausal women at a mean age of 62 years had mild diastolic dysfunction as indicated by E/A ratios ≤1.0, whereas only very few women had E/A ratios <1.0 in the current study. Another possibility is that estrogen loss is more important for vascular function than for cardiac impairments, for which age may be a more influential factor. However, previous studies have shown that estrogen treatment improves diastolic function in postmenopausal women.[39,40] Thus, at least with time, estrogen is likely to also impact cardiac function.

TDI and 2-dimensional speckle tracking used in the examinations of the participants allows for a more sensitive measure of early subclinical changes in systolic and diastolic function. Cardiac dysfunction determined by TDI has been shown to independently predict mortality.[33] Previous studies have reported training-induced adaptations in systolic and diastolic function as assessed by TDI in men[16,35,41] and premenopausal women,[42,43] but no studies have examined training-induced cardiac adaptations in postmenopausal women. We compared a large number of parameters related to cardiac functionality in the contraction phase (systole) and the filling phase of the ventricles (diastole) before and after 12 weeks of high-intensity aerobic training. Within this relatively short time of training we were able to detect changes in a majority of the parameters determined, confirming the sensitivity of TDI for determination of cardiac functionality.

The finding of similar training-induced adaptations in the premenopausal and postmenopausal women rejects the study hypothesis of lesser adaptation in postmenopausal compared to premenopausal women. Our hypothesis was based on previous studies showing that postmenopausal women present lesser adaptations to training with regard to vascular function[21,22] compared with age-matched men, and that improvements in vascular function only occur when combined with estrogen supplementation.[22] However, one explanation for the discrepancy in findings could be differences in age, because the postmenopausal women in the study by Moreau et al[22] and Pierce et al[21] were older than the women in the present study. Numerous studies have shown that inactive aging has a marked influence on cardiac structure and function[44] and it is plausible that the ability to respond to training accordingly is lost with age after menopause.

The magnitude of adaptations to training in the postmenopausal group, both in terms of dimensions and function, is similar to that observed after a period of football training in middle-aged and older men[16,35] and premenopausal women,[43,45] suggesting that high-intensity aerobic training provides an effective means of improving cardiac function in general, including in postmenopausal women. There may, however, be some difference in cardiac adaptation to training between men and women. This was evidenced in a previous study comparing the effect of 1 year of intensive endurance training on cardiac function and dimensions in young men and women. The study showed that the women had similar adaptations in cardiac function to men, whereas adaptations in cardiac dimensions were smaller and plateaued earlier in the women.[20]

Experimental Considerations

Tissue Doppler, atleast for some variables, is thought to be superior for assessing cardiac function compared with conventional echocardiography; however, the method is associated with some potential limitations as the results are sensitive to probe angle and noise interference and are associated with intraobserver and interobserver variability.[46–48] To evaluate the reproducibility and accuracy of the measurements, we therefore assessed intraobserver and interobserver variability and found the variabilities to be within an acceptable range. The women participating in this study were likely more healthy than women in general and not representative of all female populations. The study participants were recruited from greater Copenhagen, which is considered an area with more focus on health than in more rural areas of Denmark, and it seems that Danish women tend to be habitually more physically active than reported in many other Western countries. It is likely that a healthy population such as this has relatively less room for cardiac improvements with training compared with women with metabolic disorders, cardiovascular disease and/or overweight. It would therefore be expected that the adaptations observed herein with exercise training would be similar or even greater in less healthy women. Finally, because of the exploratory nature of the present study, a significance level of 0.05 was used. Hence, it should be acknowledged that this approach implies an increased risk of false-positive findings. Since we only tested recent postmenopausal women and late premenopausal women, we do not know whether late postmenopausal women would adapt just as well to a high-intensity training intervention.

Conclusions

The present study demonstrates that cardiac dimensions and subclinical measures of cardiac function are similar in premenopausal and postmenopausal women with a small age difference. The finding indicates that, despite the known beneficial effects of estrogen on cardiac tissue, loss of estrogen and other hormonal changes at menopause, do not seem to alter cardiac dimensions or functionality in the near term. Moreover, a period of high-intensity aerobic exercise training led to significant and similar adaptations in cardiac dimensions and systolic and diastolic function in premenopausal and postmenopausal women. These findings contrast with the notion that postmenopausal women adapt less well to exercise training and clearly suggest that high-intensity aerobic training is an effective means of attaining beneficial cardiac adaptations in both premenopausal and recent postmenopausal women.

Sources of Funding

Disclosures

None.

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