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Effect of Physical Activity on Age-Related Changes in Cardiac Function and Performance in Women

Jakovljevic *et al* Aging, Physical Activity and Cardiac Function

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Abstract

Background - Higher levels of physical activity are associated with reduced cardiovascular mortality but its effect on age-related changes in cardiac structure and function is unknown. The present study defines the effect of daily physical activity on age-related changes in cardiac structure, function, metabolism and performance in healthy women.

Methods and Results - Sixty-three healthy women were grouped according to age (Young, 20-30 years, n=21; Middle, 40-50 years, n=22; Older, 65-81 years, n=20) and daily physical activity level (low active <7500 and high active >12500 steps/day). Participants underwent cardiac magnetic resonance imaging including tissue tagging and ^{31}P spectroscopy and exercise testing with non-invasive central hemodynamic measurements. Aging was associated with increased concentric remodelling ($p<0.01$) and left ventricular torsion ($p<0.01$), and a decline in diastolic function ($p<0.01$), cardiac phosphocreatine-to-ATP ratio (PCr/ATP, $p<0.01$), peak exercise cardiac power output ($p<0.01$), and O_2 consumption ($p<0.01$). Older high active women demonstrated a PCr/ATP ratio and relative peak O_2 consumption similar to young low active women, and 23% and 26% higher than older low active women (PCr/ATP, 1.9±0.2 vs. 1.4±0.1, $p<0.05$; O_2 consumption, 24.1±3.8 vs. 17.8±2.0 ml/kg/min, $p<0.01$). In older women physical activity had no effect on eccentricity ratio (0.9±0.2 vs. 0.8±0.1 g/ml, p=0.19), E/A ratio (1.3±0.5 vs. 1.4±0.5, p=0.66), torsion (7.6±1.7 vs. 8.0±2.1 deg, p=0.20), and peak cardiac power output (3.4±0.7 vs. 3.4±0.8 watts, p=0.91).

Conclusion - A higher level of daily physical activity preserves cardiac metabolism and exercise capacity with aging, but has limited effect on age-related changes in concentric remodelling, diastolic function and cardiac performance.

Key words: Cardiac Aging, Physical Activity, Women

Introduction

Chronological age is identified as the major risk factor for cardiovascular morbidity and mortality in the western world with older people significantly more likely to have cardiovascular complications (1,2). In the absence of hypertension or clinically apparent cardiovascular disease, the human heart undergoes structural and functional changes with age that compromise cardiac reserve, lowering the threshold for clinical signs and symptoms (3). Although global systolic function (i.e. ejection fraction) does not appear to change, diastolic function progressively declines with aging (1,4,5). Using the most recent developments in cardiac magnetic resonance imaging with tissue tagging and spectroscopy, several studies have demonstrated age-related changes in intramyocardial strains, longitudinal shortening, systolic torsion and cardiac energetics (6-10).

Much attention has rightly been given to exercise, characterized by structured deliberate activities (such as cycling, running, resistance training), for the prevention and management of cardiovascular diseases (1,3,11). However, it is becoming increasingly clear that everyday physical activity, encompassing activities of daily living such as walking, also plays an important, protective role against cardiovascular disease development and an age-associated decline in physiological and functional capacity (12). Higher levels of physical activity are associated with 30-40% reduced rate of all-cause and cardiovascular mortality in both women and men (13-15). Conversely, the most recent data from the Women's Health Initiative study suggests that low active and sedentary women had 63% greater risk to develop cardiovascular disease than high active women (16).

Although physical activity plays an influential role in cardiovascular health, both physical activity and cardiovascular function decline with age (17-19). Regular exercise training attenuates the age-related changes by improving functional capacity of the cardiovascular system, cardiac function and metabolism (18-23). However, limited evidence is available on

the effect of objectively evaluated daily physical activity (as distinct from exercise training) on the age-related structural and functional changes in the heart, and particularly cardiac performance and metabolism. To date, only one study has reported an association between habitual physical activity, evaluated by a questionnaire, and left ventricular remodelling (23). The lack of data describing the relationship between everyday physical activity, as opposed to structured exercise, and cardiovascular function with increasing age prevents evidence based guidance on whether physical activity could be beneficial in attenuating the age-related decline in cardiovascular function. In light of this, the present study reports cardiac function, performance and aerobic capacity in physically high active and low active young, middle-aged and older women without cardiovascular disease. We hypothesized that a high level of daily physical activity i.e. >12500 steps per day (24), would attenuate age-related changes in cardiac function, performance and aerobic capacity.

Methods

Subjects

Due to a significant difference in age-associated changes in cardiac morphology and function between men and women (5,25-28), we designed the present study to define the effect of daily physical activity on the age-related changes on cardiac function, structure, metabolism and performance in women.

Sixty-three healthy women were recruited from the Newcastle upon Tyne area (United Kingdom) into three groups: young- (ages 20-30 years, n=21), middle- (ages 40-50 years, n=22), and older-age (65-81 years, n=20) women. Subjects were included into the study if their objectively evaluated average daily physical activity level fell into a low active i.e. <7,500 steps/day group or a high active group i.e. >12,500 steps/day, as previously suggested (24). Only subjects with normal glucose tolerance and lipid profile, body mass index <30

kg/m^2; normal resting blood pressure and electrocardiogram and able to undertake a maximal graded cardiopulmonary exercise stress test were included. Subjects were excluded if they: (i) had any prior history of cardiovascular or chronic pulmonary disease, diabetes, or were using medication known to effect cardiovascular function, current or previous smoking or exercise-limiting orthopaedic impairment; (ii) performed regular exercise (≥2 times week) over the previous three years or had been professional or semi-professional athletes; (iii) performed an average daily number of steps between 7,500 and 12,500 steps/day. All subjects signed an informed consent form and the study was approved by the NHS Sunderland Research Ethics Committee.

Physical activity and body composition measurement

Physical activity was assessed objectively using a validated portable multi-sensor array (Sensewear Pro_3, Bodymedia Inc, PA, USA) (29). The monitor was worn for seven days and was only removed for bathing. Self-reported physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) (30). Body composition was measured using air displacement plethysmography (BodPod, Life Measurement Inc., CA, USA) (31).

Exercise testing with non-invasive central heamodynamic measurements

All subjects performed a maximal graded cardiopulmonary exercise test using an electro-magnetically controlled semi-recumbent bicycle ergometer (Corival, Lode, Groningen, Netherlands) with online gas exchange measurements (Metalyzer 3B, Cortex, Leipzig, Germany) and non-invasive central hemodymamics by a bioreactance method (NICOM, Cheetah Medical, Deleware, USA), as previously described (32). Peak oxygen consumption was defined as the average oxygen uptake during the last minute of exercise. The difference in arterial-venous oxygen content (mlO_2/100 mL of blood) was calculated from measured

oxygen consumption and cardiac output at peak exercise. Cardiac power output, a direct measure of cardiac pumping capability (33,34) was calculated as the product of cardiac output and mean arterial blood pressure (26).

Cardiac Magnetic Resonance Examinations

Cine Imaging

A 3T Philips Intera and a 6-channel cardiac coil (both Philips, Best, NL) were used with the subjects in a supine position and ECG gating. Balanced steady-state free precession images were obtained in the short axis view during breath holding, covering the left ventricle (FOV = 350mm, TR/TE = 3.7/1.9ms, turbo factor 17, flip angle 40^{o}, thickness 8mm, 0mm gap, 14 slices, 25 phases, resolution 1.37mm, temporal duration approx. 40ms per phase). Image analysis was performed using the cardiac analysis package of the ViewForum workstation (Philips, Best, NL). Manual tracing of the epicardial and endocardial borders was performed on the short axis slices at end-systole and end-diastole. Details of our algorithm for contour selection and our methods for subsequently calculating left ventricular mass, systolic and diastolic parameters have been described elsewhere (35). The ratio of the left ventricular (LV) mass to the end-diastolic volume was calculated as this parameter is a measure of concentric remodelling.

Cardiac tagging

Tagged short axis images were obtained at the same session. Cardiac tagging works by applying radiofrequency pulses to cancel MR signal from the myocardium in diastole in a rectangular grid pattern and tracking the deformation of these tags through the rest of the cardiac cycle (36). A turbo-field echo sequence with acceleration factor 9 was used

(TR/TE/FA/NEX = 4.9/3.1/10°/1, SENSE factor 2, FOV 350x350mm, voxel size 1.37x 1.37mm, orthogonal CSPAMM grid (36) with tag spacing of 7mm). Short-axis slices of 10mm thickness were prescribed as previously detailed (37). The Cardiac Image Modelling package (University of Auckland) was used to analyse the tagging data by aligning a mesh on the tags between the endo- and epi-cardial contours. Circumferential strain was calculated throughout the cardiac cycle and is quoted for both the whole myocardial wall and the endocardial third of the wall thickness at mid-ventricle. The cardiac torsion was calculated for each cardiac phase as detailed in reference (37). In the healthy heart, torsion occurs such that there is homogeneity of fibre shortening across the myocardial wall (6) and indicates the dominance of epicardial fibres over endocardial fibres as a consequence of greater radius. The relationship between torsion and strain can be approximated by a ratio of the peak torsion and the peak circumferential strain in the endocardial third of the myocardium, the torsion-to-shortening ratio (6,38). This ratio is constant amongst healthy subjects of the same age, and increases with healthy ageing (6,9). Both torsion and torsion-to-shortening ratio are measures of epicardial–endocardial interactions.

Longitudinal shortening was determined from cine-MRI in the 4-chamber view by determining the perpendicular distance from the plane of the mitral valve to the apex in systole and diastole. The myocardial wall thickness at systole and diastole were determined at the same level as the cardiac tagging.

Cardiac spectroscopy

Cardiac high-energy phosphate metabolism was assessed using ^{31}P MRS to record the ratio of myocardial PCr/ATP. Data were collected using the same 3T Intera Achieva scanner (Philips, Best, NL) with a 10cm diameter ^{31}P surface coil (Pulseteq, UK) for transmission/reception of

signal. Full experimental details are provided in the Supplemental Methods available online. Sample spectra using this technique have been previously published (9).

Statistical Analysis

All statistical analysis was carried out using SPSS version 19.0 (SPSS inc. Chicago, Illinois, USA). Prior to statistical analysis, data were checked for univariate and multivariate outliers using standard Z-distribution cut-offs and Mahalanobis distance tests. Normality of distribution was assessed using a Kolmogorov-Smirnov test which indicated that primary outcomes were normally distributed. Two-way analysis of variance (ANOVA) was used to determine the main effects of age and physical activity and the interaction between the age and physical activity on primary outcomes including measures of cardiac structure, function, metabolism and performance. Pearson's coefficient of correlation was used to assess the relationship between variables. As left ventricular structure and function are subject to the influence of body dimensions, the data were scaled to body surface area. Statistical significance was indicated if $p<0.05$. All data are presented as means ±SD unless otherwise indicated.

Results

Subjects characteristics

From 129 women who contacted the research team in order to take part in the study, 63 met the study inclusion criteria: 21 young (10 low, 11 high active; average age 26±3 years), 22 middle-age (10 low, 12 high active; average age 45±3 years), and 20 older (10 low, 10 high active; average age 72±5 years) women. The average physical activity levels for high active

groups were: young 14807±1624, middle-age 15398±1910 and older-age 14442±1524 steps per day. The average physical activity levels for low active groups were: young 6321±985, middle-age 6086±1035, and older-age 5996±1002 steps per day. Only 5 subjects (2 older, 2 middle age and 1 younger) demonstrated sedentary behaviour (<5000 steps per day). The intensity of activity level ranged from low to moderate (up to 6 metabolic equivalent units), and this was expected as no participant was taking part in any regular exercise.

Age was associated with reduced lean body mass ($r=-0.32$, $p=0.04$), and increased blood triglycerides ($r=0.45$, $p<0.01$), total cholesterol ($r=0.62$, $p<0.01$), LDL cholesterol ($r=0.50$, $r<0.01$), and 2-hour glucose ($r=0.49$, $p<0.01$). The effect of age on body composition and blood profile measures is indicated in Supplemental material file (Table 1). At any age, high active women demonstrated lower body weight, body surface area, fat body mass, body mass index, triglycerides, LDL cholesterol, insulin, 2-hour glucose and insulin ($p<0.05$, Table 1).

Cardiac structure

Age was associated with a decrease in end- systolic ($r=-0.36$, $p<0.01$) and -diastolic volumes ($r=-0.27$, $p=0.04$) and an increase in wall thicknesses ($r=0.53$, $p<0.01$) and left ventricular mass to volume ratio (i.e. eccentricity ratio) increased with age ($r=0.36$, $p<0.01$, Figure 1A). No significant correlation was found between age and left ventricular mass index ($p=0.98$). The effect of age on measures of cardiac structure is indicated in the Supplemental material file (Table 2). However, there was a significant effect of physical activity on left ventricular mass index in all age groups with high active subjects demonstrating greater mass index ($p<0.05$, Figure 2A). Physical activity had no effect on eccentricity ratio in any of the age groups (Figure 2B), whereas end-systolic and diastolic volume indices were between 20%

($p<0.05$) and 46% ($p<0.01$) greater in young and middle-age high active than low active women, but not in the older group ($p=0.33$).

Cardiac function and metabolism

In contrast with cardiac systolic function (i.e. stroke volume index, cardiac index, and left ventricular ejection fraction) that were preserved with age, diastolic function (i.e. ratio of early-to-late ventricular filling ratio and early filling percentage) progressively declined with advancing age ($r=-0.72$, Figure 1B and $r=-0.41$, $p<0.01$). The effect of age on measures of systolic and diastolic cardiac function are presented in the Supplemental material file (Table 2). The young and middle-age high active group demonstrated higher stroke volume index than the low active group ($p<0.05$), whereas no effect of physical activity on stroke volume index was observed in older group ($p=0.40$) (Table 2). There was a significant effect of physical activity level on early-to-late ventricular filling ratio in the young and middle-age groups, but not in older women ($p<0.05$, Figure 2C).

Peak left ventricular torsion and torsion-to-shortening ratio significantly increased with advancing age ($p<0.05$) and a significant effect of physical activity was observed in young ($p<0.05$), but not in middle-age and older women respectively (Figure 2D, Table 2). Longitudinal shortening progressively declined with age ($p<0.05$) and was not affected by physical activity in any age group.

Age was significantly associated with cardiac high energy phosphate ($r=-0.27$, $p<0.05$, Figure 1C). The phosphocreatine-to-ATP ratio was significantly reduced in the older- compared to the middle- and young-age groups (young 1.9±0.3, middle 2.1±0.3, and older 1.7±0.2, $p<0.01$), and was significantly affected by physical activity level ($p<0.05$). High active young and older women demonstrated 21% and 23% higher PCr/ATP ratio than low active women

(Figure 3A). Interestingly, high active older women had PCr/ATP ratio similar to that of young but low active women ($p=0.56$). While middle aged women tended to have higher values of PCr/ATP than younger women for matched activity level, this effect did not reach statistical significance.

Cardiac performance

Age was associated with decline in cardiac performance and pumping capability as assessed by peak exercise cardiac power output ($r=-0.37$, $p<0.01$, Figure 1D), maximal flow generating capacity of the heart i.e. cardiac output ($r=-0.48$, $p<0.01$), and oxygen consumption ($r=-0.54$, $p<0.01$). Advanced age was also associated with an increase in maximal pressure generating capacity of the heart i.e. mean arterial blood pressure ($r=0.51$, $p<0.01$) and systematic vascular resistance ($r=0.61$, $p<0.01$). The effect of age on measures of cardiac performance are presented in the Supplemental material file (Table 3). At any age, high active women demonstrated a greater level of relative peak oxygen consumption than low active women ($p<0.01$). Non-significant difference was found in exercise capacity (oxygen consumption/kg and work rate/kg) between older active and young and middle-age low active women (Table 3, Figure 3B). However, physical activity had no effect on peak exercise cardiac power output (Figure 3C) but maximal cardiac index was significantly higher in young and middle-age high active than low active women ($p<0.05$, Figure 3D), due to higher stroke volume. In contrast, there was no effect of physical activity on peak exercise cardiac index ($p=0.40$) and stroke volume index ($p=0.31$) between older high and low active women (Table 3). Advancing age was also associated with a decline in the ability of muscles to extract oxygen, the arterial-venous O_2 difference, and a significant effect of physical activity was found in all three age groups with statistically significant differences ($p<0.05$) ranging between 13% and 19% between high and low active women (Table 3).

Discussion

This is the first study to examine the effect of objectively evaluated daily physical activity on age-related changes in cardiac structure, function, metabolism and performance. The major finding suggests that a high level of daily physical activity preserves cardiac metabolism and exercise capacity with aging, but has a limited effect on age-related changes in cardiac structure, diastolic function, pumping capability, and left ventricular wall motion in women. This finding is important as it demonstrates that increased physical activity in older women has no significant effect on age-related myocardial structural and functional remodelling that increases the risk for cardiovascular morbidity and mortality in older age (3).

With aging there was an increase in mass to volume ratio suggesting concentric remodelling, as previously reported (5). In contrast with men, women preserve their full complement of cardiac myocytes over the lifespan (25). Concentric remodelling in aging heart is related to coupling of ventricular and vascular stiffening process that occurs over a life course (22,39). Decline in diastolic function with aging is reported elsewhere (4,9,22,26,27). This is due to intra-structural and cellular changes including an increase in myocardial collagen deposition, proliferation of the matrix, nonenzymatic cross linking associated with advanced glycation end products rendering collagen molecules stiffer, and calcium activation from the preceding systole (1,3). Furthermore our data show that sensitive measures of the left ventricular wall motion and contraction such as peak torsion and torsion-to-shortening ratio were higher in older women. This indicates a potential subendocardial dysfunction which is further associated with reduction in longitudinal shortening observed with physiological aging and hypertrophic cardiomyopathy (6,7,9).

Previous studies also demonstrated a decline in cardiac high energy phosphate (PCr/ATP ratio) in older individuals (9,10). This may be due to multiple reasons, such as altered creatine content or the activity of creatine kinase which we cannot determine from these data.

However, it may be pertinent that the old low active and high active groups have plasma triglyceride levels that are respectively 62% and 69% greater than those of the young and middle aged groups: previous studies of normotensive subjects with significantly raised triglyceride levels due to obesity (40), Non-Alcoholic Fatty Liver Disease (41) or type 2 diabetes (42) had significantly reduced PCr/ATP ratios compared to their controls groups, including type 2 diabetes controls with lower triglyceride concentrations. Furthermore a significant reduction in plasma triglyceride concentration in obesity due to weight loss was associated with a significant increase in PCr/ATP ratio (43). Under these circumstances fatty acids may be preferentially used over glucose as a cardiac substrate, decreasing metabolic efficiency as more oxygen is needed per ATP molecule generated. Where triglyceride levels were comparable between controls and Non-Alcoholic Fatty Liver Disease no difference in PCr/ATP is found (44). Looking at those subjects with triglyceride above the normal range (>1.7 mmol/L, n=7, all older subjects), the mean PCr/ATP ratio is 1.74 ± 0.16 whereas those in the normal range have mean PCr/ATP ratio 2.12 ± 0.49 ($p=0.015$). Interestingly, the middle aged women had numerically higher but not significant PCr/ATP ratios than younger women, in contrast to our previous data (9). It should be noted that there is a wide variation in this group (though within normative values) and authors suggest that the variance may be due to a combination of population sampling (45) heterogeneous activity levels and triglyceride levels, as opposed to a specific age-related mechanism.

Peak exercise cardiac power output, as a direct measure of overall cardiac function and pumping capability (33) declined with aging because of ~20% reduction in cardiac output. These findings are in agreement with those of Fleg and colleagues (27), but contrary to those of Goldspink et al. (26) who argued that the female heart demonstrates resilience to aging with no reduction in peak exercise cardiac power output. Maximal aerobic capacity was

lower in older women (11,21) due to a decline in both cardiac output and arterial venous oxygen difference.

Although increased activity level was associated with improved cardiovascular risk factors its impact upon cardiac structure and function was not straightforward. First, from the perspective of cardiac structure, while high active young- and middle-age women demonstrate significantly greater left ventricular volumes and mass index, older women had lower end systolic volume and greater left ventricular mass index in comparison with low active older women. Interestingly, physical activity had no significant effect on eccentricity ratio in any age group. One previous study examined the association between intentional exercise of moderate to vigorous intensity and left ventricular remodelling (23). Results revealed that higher physical activity levels were associated with greater left ventricular mass.

Young and middle aged high active women had better diastolic function compared with their low active comparison groups. No significant difference was found in the older age group. Gates *et al.* (22) found that regular aerobic-endurance exercise does not modulate age-associated changes in diastolic function in men. In contrast, Forman and colleagues showed that early to late filing ratio was higher in well trained men and women (46). The present data suggest that diastolic function declines with age irrespective of daily physical activity level, supporting the hypothesis that the impairment of diastolic function is intrinsic to normative aging and may not be reversed with increased physical activity or exercise (47). Torsion-to-shortening ratio was not significantly different between high and low active middle-age and older women. This suggests that physical activity had no effect on age-related changes in subendocardial dysfunction, which is believed to be due to a subendocardial fibrosis associated with aging (6). In contrast older high active women demonstrate a significantly higher level of cardiac high energy phosphate metabolism than low active women. Moreover

PCr/ATP ratio values found in our older low active women were similar to some subjects with dilated cardiomyopathy (8). While low values for PCr/ATP ratios in individuals without heart disease have been recorded before (9,10,45), this study is the first to demonstrate difference due to activity level. Previous reports have shown that men undergoing long lasting endurance training showed a higher level of cardiac metabolism (20) and that gender has no effect on age-related cardiac metabolic change (10). It appears that not only intentional exercise but also a high level of daily physical activity might be considered to be beneficial for cardiac energetics in non-trained individuals.

Finally, from the view of cardiac performance, although young and middle aged high active women demonstrate significantly higher peak exercise cardiac index than low active women, no such effect was observed in older women. Interestingly, peak exercise cardiac power output was not significantly different between the activity groups regardless of age, suggesting that daily physical activity has no effect on age-associated decline in maximal cardiac pumping capability. Aerobic capacity (peak oxygen consumption) and exercise performance (work rate) however, were markedly influenced by daily activity. One of the physiological mechanisms that may explain such a finding is that the anaerobic threshold point occurs significantly earlier in low active than in those highly active women. As the rate of lactate acid production and accumulation exceeds its removal from the muscle, it is likely to cause an onset of fatigue and consequent earlier termination of the exercise test, resulting in a lower exercise performance (work rate) in inactive women. The observed higher fitness level in active women is important as it is associated with better quality of life and functional independence (11,18), making them capable of performing physical tasks that cannot be performed by their sedentary peers.

The present study is not without limitations. Only women were studied due to the significant differences in age-associated changes in cardiac morphology and function between men and

women. It is not known if these results extend to men, to people with cardiac diseases, or people with other comorbidities. All of the women taking part were Caucasian and it is not known whether these results are applicable to subjects from other ethnic backgrounds. The range of PCr/ATP ratios in this cohort was wider than our previously published work (9) but comparable to those from other cohorts acquiring cardiac spectroscopy in healthy controls with this technique (48,49). Although the overall sample size was large for a detailed physiological study, subject numbers were limited when stratified for age and physical activity level. Due to a large number of comparisons made for a relatively modest sample size it is possible that in some cases type I error has been made.

In conclusion, the data reveal that aging is associated with cardiac concentric remodelling, a decline in diastolic function, cardiac metabolism, subendocardial dysfunction and maximal performance. A physically active life style preserves cardiac metabolism and aerobic capacity with aging, but has limited effect on age-related changes in cardiac structure, diastolic function, left ventricular wall motion and pumping capability, particularly in older women.

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Table 1 Anthropometric and blood measures stratified by the age and physical activity

	Low active i.e. <7500 steps/day			High active i.e. >12500 steps/day			Two-way ANOVA (p)		
	Young	**Middle-age**	**Older**	**Young**	**Middle-age**	**Older**	**Age**	**Activity**	**Interaction**
Weight (kg)	73±18	72±10	73±10	60±8*	68±14*	60±8*	0.64	0.02	0.02
Height (cm)	163±7	166±6	160±4	167±6	167±5	157±6	0.33	0.41	0.41
Body mass index (kg/m^2)	27±4	26±4	28±3	21±3*	24±4*	24±3*	0.29	0.02	0.02
Body surface area (m^2)	1.8±0.2	1.8±0.1	1.8±0.1	1.7±0.1*	1.8±0.2*	1.6±0.1*	0.17	0.04	0.04
Fat body mass (%)	41±8	36±6	43±4	25±4*	29±9*	34±9*	0.18	0.03	0.03
Lean body mass (%)	59±8	64±6	57±4	75±12	71±9	66±9	0.10	0.18	0.18
Fat body mass (kg)	31±14	26±8	32±6	15±4*	20±11*	21±6*	0.47	0.01	0.01
Lean body mass (kg)	44±5	46±4	41±5	45±4	48±5	40±4	0.01	0.44	0.44
Waist circumferences (cm)	94±15	95±8	84±11	73±9*	86±14*	83±10	0.33	0.04	0.04
Triglycerides (mmol/L)	0.87±0.43	0.98±0.40	1.41±0.62	0.72±0.22*	0.68±0.47*	1.19±0.80*	0.03	0.01	0.01
Total Cholesterol (mmol/L)	4.4±1.1	4.9±1.1	5.8±0.8	4.4±0.7	4.0±1.9	5.5±0.9	0.01	0.56	0.56
LDL Cholesterol (mmol/L)	2.5±0.9	2.8±0.9	3.4±0.6	2.2±0.6*	2.2±1.1*	2.9±0.7*	0.05	0.02	0.02
HDL Cholesterol (mmol/L)	1.5±0.3	1.7±0.3	1.8±0.4	1.8±0.4*	1.6±0.8	2.0±0.4	0.12	0.04	0.04
Total/HDL Cholesterol ratio	3.0±1.1	3.0±0.6	3.4±0.5	2.4±0.5	2.2±1.2	2.8±±0.8	0.14	0.26	0.26
Insulin (mU/L)	8.5±3.8	4.6±3.9	5.1±3.1	7.8±3.8*	3.3±3.9*	4.6±3.7*	0.03	0.04	0.04
2-hour insulin (mU/L)	42.5±11.9	41.1±10.2	54.7±11.5	18.8±2.5*	30.2±8.6*	40.7±12.9*	0.02	0.01	0.01
Glucose (mmol/L)	5.1±0.3	4.6±0.4	5.3±0.6	5.1±0.6	4.6±0.5	5.2±0.4	0.05	0.24	0.24
2-hour glucose (mmol/L)	5.1±1.1	4.9±0.8	7.2±2.7	4.3±1.1*	4.4±1.0	5.9±1.4*	0.01	0.03	0.03

*p<0.05 high active vs. low active

Table 2 Cardiac morphology, blood pool, energetics, wall motion and diastolic function measures stratified by age and physical activity

	Low active i.e. <7500 steps/day			High active i.e. >12500 steps/day			Two-way ANOVA (p)		
	Young	**Middle-age**	**Older**	**Young**	**Middle-age**	**Older**	**Age**	**Activity**	**Interaction**
Morphology and blood pool:									
End systolic volume index (ml/m^2)	25±12	21±4	21±4	31±7*	36±11*	19±5	0.01	0.02	0.03
End diastolic volume index (ml/m^2)	55±10	59±6	55±7	75±8*	77±12*	58±9	0.05	0.01	0.04
Left ventricular mass index (g/m^2)	41±10	47±6	45±5	53±5*	55±10*	49±7*	0.30	0.02	0.03
Wall thickness diastole (mm)	6±2	7±1	7±1	6±1	7±1	7±1	0.04	0.27	0.11
Wall thickness systole (mm)	9 ±4	11±2	12±1	10±2	10±2	13±2	0.03	0.41	0.24
Cardiac index (l/min/m^2)	1.9±0.7	2.2±0.3	2.1±0.3	2.1±0.4	2.3±0.4	2.3±0.5	0.83	0.37	0.71
Stroke volume index (ml/beat/m^2)	31±12	37±4	35±4	44±5*	51±8*	39±7	0.46	0.04	0.21
Heart Rate (beats/min)	57±21	60±7	58±6	55±11	56±7	60±7	0.70	0.42	0.50
Left ventricular ejection fraction (%)	56±9	64±5	63±5	60±6	58±6	66±6	0.09	0.23	0.23
Wall motion:									
Torsion-to-shortening ratio (rad)	0.44±0.12	0.43±0.11	0.51±0.15	0.47±0.15*	0.46±0.14	0.56±0.11	0.03	0.04	0.05
Peak whole wall circumferential strain (%)	15±3	20±2	19±3	19±2	19±4	20±3	0.61	0.51	0.62
Peak endocardial circumferential strain (%)	18±8	27±3	25±3	26±3*	24±5	27±3	0.05	0.21	0.28
Longitudinal shortening (%)	17±7	14±3	13±4	18±6	14±3	14±5	0.04	0.36	0.36
Diastolic function:									
Early filling percentage (%)	73±27	78±5	61±12	84±10*	81±9	65±9	0.01	0.03	0.05
Early diastolic filling rate (ml/s)	318±166	345±52	243±50	395±89*	369±77	266±109	0.01	0.02	0.04
Late diastolic filling rate (ml/s)	92±47	151±36	205±51	94±30	119±41*	221±44	0.01	0.02	0.05

*p<0.05 high active vs. low active

Table 3 Resting and peak exercise gas exchange, central heamodynamic and ventilatory measures stratified by age and physical activity

	Low active i.e. <7500 steps/day			High active i.e. >12500 steps/day			Two-way ANOVA (p)		
	Young	**Middle-age**	**Older**	**Young**	**Middle-age**	**Older**	**Age**	**Activity**	**Interaction**
Resting:									
Oxygen consumption (ml/kg/min)	3.4±1.1	3.3±0.5	3.4±0.4	4.6±1.1*	4.1±0.9	3.9±0.5	0.23	0.02	0.16
Respiratory exchange ratio	0.87±0.21	0.91±0.08	0.93±0.10	0.94±0.11	0.90±0.06	0.90±0.07	0.61	0.16	0.55
Heart rate (beats/min)	78±10	71±5	70±9	73±12	70±13	71±8	0.19	0.42	0.71
Systolic blood pressure (mmHg)	118±13	131±11	140±12	117±11	127±20	144±14	0.01	0.39	0.29
Diastolic blood pressure (mmHg)	74±7	88±11	83±10	75±8	82±8	87±12	0.03	0.85	0.52
Mean arterial blood pressure (mmHg)	89±9	102±10	102±9	89±8	97±11	106±12	0.04	0.11	0.16
Peak Exercise:									
Oxygen consumption (ml/kg/min)	23.6±2.8	22.2±2.4	17.8±2.0	34.6±3.6*	34.1±7.7*	24.1±3.8*	0.03	0.02	0.04
Oxygen consumption (ml/min)	1695±309	1620±173	1288±136	2046±241*	2244±390*	1451±282*	0.04	0.03	0.05
Arterial-venous oxygen difference (mlO_2)	12±2	12±3	11±2	13±1*	14±3*	12±2*	0.05	0.04	0.06
Respiratory exchange ratio	1.16±0.08	1.24±0.08	1.16±0.06	1.17±0.08	1.17±0.07	1.19±0.12	0.23	0.69	0.34
Heart rate (beats/min)	180±10	167±12	134±14	177±13	172±8	145±11	0.01	0.55	0.16
Stroke volume index (ml/beat/m^2)	47±10	50±11	50±10	56±8*	55±11*	52±2	0.38	0.04	0.24
Systolic blood pressure (mmHg)	168±17	185±19	191±17	170±18	180±25	197±15	0.02	0.89	0.54
Diastolic blood pressure (mmHg)	86±11	95±13	90±13	80±13	88±12	93±8	0.04	0.41	0.24
Mean arterial blood pressure (mmHg)	114±11	125±8	124±11	110±12	119±12	128±8	0.04	0.20	0.31
Cardiac power output (watts)	3.73±0.93	4.00±0.87	3.36±0.77	4.07±0.70	4.25±0.72	3.40±0.68	0.03	0.21	0.18
Systematic vascular resistance (dyne/s/cm^5)	633±104	715±128	840±167	542±101*	604±120*	885±198	0.02	0.04	0.05
Minute ventilation (l/min)	54±10	59±6	43±8	70±12*	77±14*	53±10*	0.02	0.01	0.04
Work rate (watts)	135±14	127±11	88±10	162±17*	179±28*	108±20*	0.04	0.02	0.05
Work rate to body weight ratio (watts/kg)	1.8±0.4	1.8±0.3	1.2±0.2	2.7±0.3*	2.6±0.4*	1.8±0.2*	0.02	0.03	0.04
Anaerobic threshold (ml/kg/min)	13±3	14±2	11±2	21±4*	23±7*	15±3*	0.03	0.04	0.04

*$p<0.05$ high active vs. low active

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Figure 1 Relationship between age and measures of cardiac structure i.e. eccentricity ratio (A), diastolic function i.e. early-to-late diastolic filling rate (B), metabolism i.e. phosphocreatine-to-ATP ratio (C), pumping capability i.e. peak cardiac power output (D).

Figure 2 Cardiac structural and functional measures according to age and physical activity. Left ventricular mass index (A); eccentricity ratio i.e. left ventricular mass to volume ratio (B), early-to-late diastolic filling rate (C), and left ventricular peak torsion (D).

*p<0.05, high vs. low active; †p<0.01 old vs. young and middle age

Figure 3 Measures of cardiac metabolism and performance according to age and physical activity. Cardiac high energy phosphate (A), maximal aerobic capacity (B), peak cardiac pumping capability (C), and peak cardiac index (D).

*p<0.05, high vs. low active; **p<0.01, high vs. low active.

†p<0.01 old vs. young and middle age