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Research article

Effects of long-term physical activity on cardiac structure and function: A twin study

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Abstract

Previous studies have shown that athletic training or other physical activity causes structural and functional adaptations in the heart, but less is known how long-term physical activity affects heart when genetic liability and childhood environment are taken into account. The aim of this study was to investigate the effects of long-term physical activity vs. inactivity on cardiac structure and function in twin pairs discordant for physical activity for 32 years. Twelve same-sex twin pairs (five monozygotic and seven dizygotic, 50-67 years) were studied as a part of the TWINACTIVE study. Discordance in physical activity was initially determined in 1975 and it remained significant throughout the follow-up. At the end of the follow-up in 2007, resting echocardiographic and electrocardiographic measurements were performed. During the follow-up period, the active co-twins were on average 8.2 (SD 4.0) MET hours/day more active than their inactive co-twins ($p < 0.001$). At the end of the follow-up, resting heart rate was lower in the active than inactive co-twins [59 (SD 5) vs. 68 (SD 10) bpm, p=0.03]. The heart rate-corrected QT interval was similar between the co-twins. Also, there was a tendency for left ventricular mass per body weight to be greater and T wave amplitude in lead II to be higher in the active co-twins (18% and 15%, respectively, p=0.08 for both). Similar trends were found for both monozygotic and dizygotic twin pairs. In conclusion, the main adaptation to long-term physical activity is lowered resting heart rate, even after partially or fully controlling for genetic liability and childhood environment.

Key words: Exercise, echocardiography, electrocardiography, heart rate, controlling for genetic liability, longitudinal study.

Introduction

Cardiovascular diseases are still one of the leading causes of death worldwide, which sets challenges to health care systems and highlights the importance of preventive procedures. Physical activity is a well-documented way to reduce the risk of hypertension (Whelton et al., 2002) and occurrence of coronary heart disease (Batty, 2002). Part of the benefits of physical activity in reducing the risk of cardiovascular diseases may be mediated through its positive effects on cardiac structure and function.

Certain changes in cardiac structure and function, such as pathological left ventricular hypertrophy (LVH) (Vakili et al., 2001), increased resting heart rate (Dyer et al., 1980) and repolarization abnormalities (T wave inversions) (Ristola, 1983; Rose et al., 1978), are associated with increased risk of cardiovascular morbidity and mortality. Numerous case-control studies in athletes have reported that athletic training causes opposite changes in cardiac function, such as a lowered resting heart rate (Bjørnstad et al., 1991; Parker et al., 1978; Sharma et al., 1999; Stolt et al., 1997). Athletic training may also cause repolarization changes (Bjørnstad et al., 1991; Sharma et al., 1999), which can be manifested either by lowered or heightened T wave amplitudes. T wave inversion ≥ 2 mm may be associated with an increased risk for the development of structural cardiac disease, such as hypertrophic cardiomyopathy (Pelliccia et al., 2008), but milder changes do not have any prognostic significance (Pelliccia et al., 2008; Serra-Grima et al., 2000). Structural changes, for example increased left ventricular mass (LVM) and enlarged cavity dimensions (Pluim et al., 2000), are suggested to be of physiological rather than pathological origin, since these changes are not associated with diastolic dysfunction (Pluim et al., 2000) and they are mainly reversible after detraining (Ehsani et al., 1978; Pelliccia et al., 2002). Physiological LVH improves cardiac function by increasing stroke volume and cardiac output, thus enabling better aerobic capacity. Increased aerobic capacity is important not only for the peak performance of top level athletes, but also for the ability to cope with activities of daily living among the general population, in particular among elderly and/or diseased people.

Randomized controlled trials or other longitudinal studies in this area are less numerous, but some relatively short-term exercise intervention studies have been conducted, also in sedentary or other non-athletic people (Adams et al., 1981; Morrison et al., 1986; Schuit et al., 1998). The findings reported after training in these studies have been similar to those of athletic case-control studies. However, less is known about the long-term effects of leisure time physical activity on cardiac structure and function, especially in non-athletic populations. Research in this area is challenging as, on the one hand, it is difficult to carry out long-term randomized controlled exercise trials, while, on the other hand, observational population-

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based follow-ups may include genetic selection bias. The latter may also have caused problems in the interpretation of the results of case-control studies between athletes and sedentary people, since cardiac structure (Sharma et al., 2006) and function (Mutikainen et al., 2009) as well as participation in physical activity (Stubbe et al., 2006) are all moderately to highly affected by genetic factors. This may make it easier for some people to engage in athletic training or other vigorous physical activity, resulting in an apparent but non-causal association of physical activity with cardiac structure and function.

To minimize such issues in the present study, we carried out within-pair analyses of cardiac structure and function in twin pairs identified on the basis of their long-term discordance for physical activity. By studying both monozygotic (MZ) and dizygotic (DZ) twin pairs, we were able to control for childhood environment and partially for genetic liability as MZ co-twins share all and DZ co-twins on average half of their segregating genes. The purpose of this study was to investigate the effects of long-term leisure time physical activity vs. inactivity on cardiac structure and function (in a resting state) in twin pairs who have been discordant for leisure time physical activity habits for 32 years. We also aimed at investigate the effects of long-term physical activity/inactivity on submaximal and peak heart rates during the symptom-limited clinical exercise test. We hypothesized that a physically active lifestyle causes adaptations in the heart, which are in the same direction as those caused by athletic training, even after controlling for genetic liability and childhood environment.

Methods

Participants

The present study is part of the TWINACTIVE study, the aim of which is to investigate the metabolic and cardiovascular consequences of physical activity vs. inactivity using a study design of twin pairs persistently discordant for physical activity. The details on recruitment and physical activity assessment have been described elsewhere (Leskinen et al., 2009) and are briefly summarized here. Sixteen twin pairs (7 MZ and 9 DZ pairs, mean age 60 years) were identified from the nationwide Finnish Twin Cohort (n = 5663 pairs) (Kaprio and Koskenvuo, 2002) on the basis of both leisure time and commuting physical activity data collected at several time points during the follow-up period. The amount of leisure time physical activity was documented using validated methods (Leskinen et al., 2009; Waller et al., 2008). Of the collected data, MET indices (for leisure time physical activity and commuting physical activity separately) were calculated by assigning a multiple of the resting metabolic rate (intensity of activity x duration of one session x monthly frequency). This was expressed as a sum score of MET hours/day (Kujala et al., 1998; Waller et al., 2008).

The identification of twin pairs discordant for leisure time and commuting physical activity (i.e. the same co-twin of each twin pair was more active than his/her co-twin) proceeded as follows. Firstly, the selected twin pairs were discordant for physical activity at the baseline questionnaire assessments in 1975 and 1981 (165 pairs out of 5663 pairs). Secondly, the discordance between the co-twins was found in at least four out of the six assessed time points in the retrospective follow-up interview from 1980 to 2005 (54 pairs out of the 165 pairs). Thirdly, before issuing an invitation to participate in the laboratory study measurements, pairs whose health status/medication (malign cancer, rheumatoid arthritis, Alzheimer´s disease, disability/high age, insufficient collaboration) would severely violate the study aims were excluded (n = 7 pairs) as also were pairs whose physical activity discordance was at the lowest level (21 pairs). Of the remaining 26 pairs, 9 pairs declined to participate and one pair was no longer discordant for physical activity. Therefore, 16 twin pairs were found to be discordant for leisure time and commuting physical activity at the follow-up assessment conducted in 2007 and these pairs underwent the detailed examinations. The zygosity of the participating pairs was determined by the genotyping of ten highly polymorphic genetic markers.

In the present substudy, inclusion of twin pairs was done solely on the basis of leisure time physical activity discordance, since published studies to date have shown that rather vigorous exercise might be needed to achieve changes in the heart's electrical function. Thus, three pairs, who showed the smallest discordance in leisure time physical activity (0.6-3.0 MET $h \cdot day^{-1}$) during the 32-year period, were excluded. In addition, since specific conduction abnormalities make it impossible to interpret resting ECG features in a meaningful way, one pair with right bundle branch block was excluded. After these procedures, the final number of pairs included in the statistical analyses was 5 MZ pairs and 7 DZ pairs (50-67 years, three female pairs and nine male pairs).

During the follow-up period, the average difference in leisure time physical activity between the inactive and active co-twins was 8.2 (SD 4.0) MET $h \cdot day^{-1}$ [1.2 (SD 1.1) vs. 9.4 (SD 3.8) MET $h \cdot day^{-1}$, $p < 0.001$], which is the equivalent of, for example, a 2-hour walk daily. The difference was similar in both the MZ pairs and DZ pairs. The MET value for the inactive co-twins is the equivalent of, for example, 45 min brisk walking two times a week and the MET value for the active co-twins 90 min running four times a week.

The study was conducted according to the guidelines for good clinical and scientific practice laid down by the Declaration of Helsinki. All the participants were informed about the study and they signed a written informed consent prior to any measurements. The study plan was approved by the Ethics Committee of the Central Finland Health Care District.

Echocardiographic measurements

Echocardiographic studies were performed with a Siemens Acuson CV70 instrument using a P4-2 3.6 MHz transducer. All the measurements were performed by the same examiner (MP). Participants were positioned in a 45º left lateral decubitus position and an integrated M-mode and two-dimensional analysis was performed to determine interventricular septal (IVST) and left ventricular (LV) posterior wall thickness (PWT) at the diastole as well as LV end-diastolic (LVEDD) and end-systolic (LVESD) diameters. The two-dimensionally targeted M-

mode recordings were obtained in parasternal long-axis view. IVST, PWT and LVEDD were measured at the peak of the R wave in the electrocardiogram (ECG). LVESD was measured at the narrowest point between the septum and posterior wall. LVM was calculated using the Devereux formula: mass (g) = 0.8 x {1.04 x [(IVST + LVEDD + PWT)^3 – (LVEDD)^3]} + 0.6 (Devereux et al., 1986), where the variables needed are measured in the diastole and expressed as centimeters. To take into account the influence of body size on cardiac dimensions, LVEDD and LVM were adjusted for body surface area (BSA), calculated by the Mosteller formula (Mosteller, 1987): [(height in centimeters x weight in kilograms) / 3600]^{½}. LVM was also adjusted for body height and weight. The ejection fraction (EF, %) was calculated as follows: EF = 100 x [(EDV-ESV)/EDV]. EDV refers to LV end-diastolic volume and ESV to LV end-systolic volume. In the statistical analyses, one participant was excluded owing to a technically poor quality image. In another participant, for the same reason, it was impossible to measure the variables needed for the calculation of LVM, and thus this participant was also excluded from the LVM-related analyses.

Electrocardiographic measurements

Standard 12-lead resting ECG (including heart rate) was recorded in the supine position at 50 mm/s and 10 mm/mV standardization using a GE Medical Systems IT CardioSoft V5.02. The measured variables are presented in the Results section and Table 2. Heart rate-corrected QT interval was calculated by the Bazett's formula (QT/RR$^{1/2}$) (Bazett, 1920). LVH indices were calculated as follows: Sokolow Lyon voltage (SV_1+RV_5) (Sokolow and Lyon, 1949), Cornell voltage (RaVL+SV_3) (Casale et al., 1985) and Cornell product (Cornell voltage x QRS duration) (Molloy et al., 1992). The components of Sokolow Lyon voltage and Cornell voltage as well as T wave amplitudes in leads V_1, V_5 and II were measured manually while the other variables were collected from the automatic listings of the ECG recorder. Both echocardiographic and ECG measurements were carried out blinded to physical activity status, zygosity and co-twin's data.

Clinical exercise test

The symptom-limited maximal clinical exercise test with a cycle ergometer was performed for the assessment of cardiorespiratory fitness after the resting ECG measurement (Leskinen et al., 2009). The testing protocol comprised of 2-minute stages, beginning with a learning stage at 20 W and a warm-up stage at 25 W. Thereafter the increase in workload was 25 W/stage. Heart rate was recorded from the ECG both before the test (sitting on the cycle ergometer) and thereafter at the end of each stage. Peak heart rate was defined as highest heart rate achieved in any stage. VO_{2peak} was estimated from the highest load achieved in the test.

Other measurements

Baseline data and follow-up data concerning smoking habits and work-related physical activity were collected with diary, questionnaire and interview methods as previously described (Kaprio and Koskenvuo, 2002; Kujala et al., 1998; Waller et al., 2008). The follow-up assessment of the presence of chronic diseases and use of medications as well as routine anthropometric and resting blood pressure measurements were carried out in the clinical examination.

Statistical analysis

Pairwise analyses were used to study differences between the co-twins. First, the analyses were carried out for all twin pairs and then for MZ and DZ pairs separately to test whether the trends were similar by zygosity. The normality of the data was analyzed using the Shapiro-Wilk test, and pairwise analyses were carried out as follows: paired samples Student's t-test was used for normally distributed continuous variables, Wilcoxon signed ranks test for non-normally distributed continuous variables and the symmetry test for categorical variables. Significance was set at $p < 0.05$ (two-sided). Data were analyzed using SPSS 14.0 (SPSS Inc., Chicago, IL, USA) and Stata Version 8 (Stata Corp., College Station, TX, USA).

Results

The baseline characteristics in 1975 and follow-up characteristics in 2007 for all 12 twin pairs are shown in Table 1. In addition to leisure time MET index, the only variable statistically significantly different between the inactive and active co-twins was peak oxygen uptake showing that the discordance for physical activity was also reflected in the co-twins' cardiorespiratory fitness levels [28.1 (SD 3.7) vs. 34.4 (SD 4.9) ml·kg^{-1}·min^{-1}, p = 0.003].

At the end of the follow-up, there were significant differences between the inactive and active co-twins in some of the resting echocardiographic and ECG variables (Table 2). Resting heart rate was on average 8.8 bpm (95% CI 1.3 to 16.4) lower in the active than inactive co-twins (p = 0.03). The heart rate-corrected QT interval was similar between the co-twins. In addition, there was a tendency for LVM per body weight to be greater and T wave amplitude in lead II to be higher in the active co-twins (18% and 15%, respectively, p = 0.08 for both). LVEDD, LVEDD/BSA, EF, PR interval, QRS duration, P, QRS and T axes, P duration, T wave amplitudes in leads V_1 and V_5, and LVH indices were not statistically significantly different between the active and inactive co-twins.

Similar trends in the intra-pair differences were found for both the MZ and DZ pairs, except for QRS duration, P axis and T axis (Table 2). Among the MZ pairs, the intra-pair differences in part of the studied variables were larger than those for the whole study group. Of these, LVM per body weight attained statistical significance. The absolute LVM and LVMs corrected for BSA, body height or body weight were 21-22% greater, P axis 20% smaller and T wave amplitude in lead II 17% higher in the active co-twins compared with the inactive co-twins. Resting heart rate was 9.6 bpm (95% CI -4.2 to 23.4) lower in the active co-twins. The results of resting heart rate and LVM per body weight for each MZ pair are presented in Figures 1 and 2.

Heart rates for the inactive and active co-twins before and during clinical exercise tests are shown in Figure

Table 1. Baseline and follow-up characteristics of 12 twin pairs (9 male and 3 female pairs). Data for continuous variables are mean (SD).

Characteristic	Inactive co-twins (n=12)	Active co-twins (n=12)	p value*
Baseline in 1975			
Age (yrs)	27 (range 18-35)		
Height† (m)	1.77 (.09)	1.75 (.11)	.33
Weight (kg)	71.0 (17.8)	66.8 (9.8)	.36
Body mass index† ($kg \cdot m^{-2}$)	22.8 (4.9)	22.1 (2.1)	.57
Leisure time MET index‡ § ($h \cdot day^{-1}$)	.1 (.2)	3.1 (2.4)	.002
Work-related physical activity (n)			.51
Sedentary	3	5	
Standing or walking at work	2	3	
Light manual work	7	4	
Heavy manual work	0	0	
Follow-up in 2007			
Age (yrs)	59 (range 50-67)		
Height (m)	1.75 (.10)	1.73 (.10)	.32
Weight (kg)	82.3 (20.1)	73.0 (12.8)	.09
Body mass index ($kg \cdot m^{-2}$)	26.7 (3.9)	24.2 (2.3)	.08
Body surface area (m^2)	2.0 (.3)	1.9 (.2)	.08
Leisure time MET index‡ ($h \cdot day^{-1}$)	1.2 (1.1)	9.4 (3.8)	< .001
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	28.1 (3.7)	34.4 (4.9)	.003
Systolic blood pressure (mmHg)	145.0 (27.2)	141.6 (19.0)	.66
Diastolic blood pressure (mmHg)	90.3 (14.4)	86.3 (9.7)	.39
Use of beta-blockers (yes; n)	2	1	.32
Smoking status (n)			.39
Current smokers	2	0	
Former smokers	6	6	
Never smoked	4	6	
Work-related physical activity (n)			.26
Sedentary	3	5	
Standing or walking at work	1	2	
Light manual work	4	0	
Heavy manual work	0	1	

* For the difference between the inactive and active co-twins, based on paired samples Student's t-test for normally distributed continuous variables, Wilcoxon signed ranks test for non-normally distributed continuous variables and the Symmetry test for categorical variables. † n = 11. ‡ See the details of definition and calculation in Methods section. § Includes both leisure time physical activity and physical activity to and from work.

3. The heart rate in the sitting position before the test was significantly lower in the active co-twins compared with the inactive co-twins [61.8 (SD 3.8) vs. 74.0 (SD 10.3) bpm, respectively] and it remained significantly lower in the active co-twins at each submaximal stage. However, the peak heart rate achieved during the test (not seen in the figure) was similar between the co-twins [161.7 (SD12.0) bpm in the active vs. 161.8 (SD 16.4) bpm in the inactive, p = 0.99). Similar trends were seen when MZ and DZ pairs were studied separately.

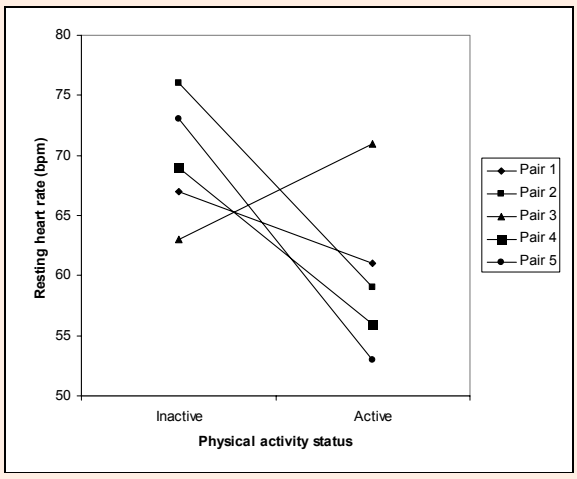

Figure 1. Resting heart rate in monozygotic twin pairs.

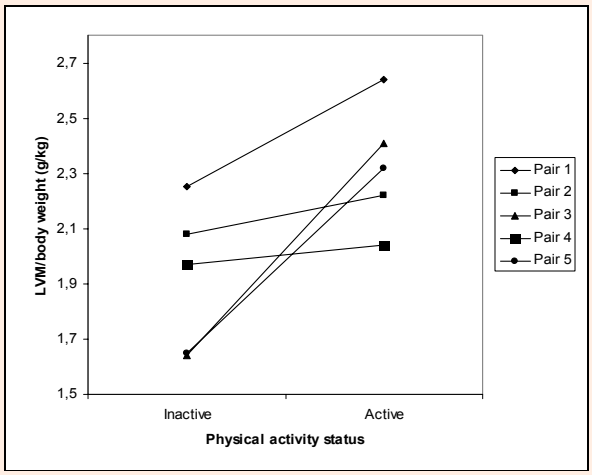

Figure 2. Left ventricular mass (LVM) per body weight in monozygotic twin pairs.

Discussion

Our twin study showed that a persistent physically active lifestyle during a period of over 30 years causes lowering

Table 2. Follow-up results for echocardiographic and electrocardiographic variables in 12 twin pairs, whose within-pair difference in leisure time physical activity is 8.2 (SD 4.0) MET h·day^{-1}.

Characteristic	Inactive co-twins, mean (SD)	Active co-twins, mean (SD)	Mean difference (95% CI)	p value*
All 12 pairs				
LVM† (g)	130.5 (44.5)	147.7 (56.3)	-17.2 (-51.4 to 16.9)	.28
LVM/BSA† (g·m^{-2})	67.1 (19.2)	77.9 (22.4)	-10.8 (-26.3 to 4.8)	.15
LVM/body height† (g·m^{-1})	74.7 (22.7)	84.9 (28.8)	-10.2 (-29.0 to 8.6)	.25
LVM/body weight† (g·kg^{-1})	1.7 (.5)	2.0 (.5)	-.3 (-.7 to .0)	.08
LVEDD‡ (mm)	58.8 (8.2)	59.4 (10.1)	-.6 (-7.9 to 6.7)	.85
LVEDD/BSA‡ (mm·m^{-2})	30.5 (3.0)	31.9 (3.2)	-1.4 (-4.5 to 1.7)	.33
EF‡ (%)	56.8 (9.8)	62.9 (10.4)	-6.1 (-13.5 to 1.3)	.10
Resting heart rate (bpm)	68.0 (10.2)	59.2 (5.1)	8.8 (1.3 to 16.4)	.03
RR interval (ms)	902.3 (134.1)	1011.7 (80.1)	-109.4 (-216.4 to -2.3)	.05
P duration (ms)	91.8 (15.8)	103.8 (12.1)	-12.0 (-27.8 to 3.8)	.12
PR interval (ms)	157.5 (21.9)	166.7 (26.7)	-9.2 (-21.2 to 2.8)	.12
QRS duration (ms)	88.8 (10.5)	89.2 (14.0)	-.4 (-9.5 to 8.8)	.94
QT interval (ms)	400.7 (25.6)	422.0 (18.2)	-21.3 (-39.2 to -3.5)	.02
QTc (ms)	423.8 (25.9)	417.3 (15.8)	6.5 (-9.1 to 21.9)	.38
Sokolow Lyon voltage (mV)	2.7 (.7)	2.9 (.9)	-.2 (-1.0 to .7)	.88
Cornell voltage (mV)	1.2 (.5)	1.5 (.6)	-.3 (-.7 to .2)	.22
Cornell product (mV x ms)	110.5 (42.0)	136.7 (67.7)	-26.2 (-64.8 to 12.6)	.17
P axis (degree)	49.3 (18.3)	45.9 (16.4)	3.4 (-7.0 to 13.8)	.49
QRS axis (degree)	32.0 (20.2)	40.3 (22.9)	-8.3 (-31.7 to 15.0)	.45
T axis (degree)	37.8 (13.6)	39.8 (14.3)	-2.0 (-15.1 to 11.1)	.74
T wave amplitude in lead V_1 (mV)	.08 (.20)	.11 (.12)	-.03 (-.20 to .15)	.75
T wave amplitude in lead V_5 (mV)	.42 (.13)	.46 (.20)	-.04 (-.13 to .06)	.42
T wave amplitude in lead II (mV)	.26 (.06)	.30 (.09)	-.04 (-.09 to .01)	.08
5 MZ pairs				
LVM (g)	153.0 (34.9)	186.6 (38.5)	-33.6 (-70.0 to 2.9)	.06
LVM/BSA (g·m^{-2})	77.1 (12.3)	93.2 (12.4)	-16.1 (-33.2 to .8)	.06
LVM/body height (g·m^{-1})	86.0 (15.8)	104.2 (18.4)	-18.2 (-40.0 to 3.5)	.08
LVM/body weight (g·kg^{-1})	1.9 (.3)	2.3 (.2)	-.4 (-.8 to .0)	.04
LVEDD (mm)	63.2 (9.5)	63.6 (6.3)	-.4 (-9.5 to 8.8)	.92
LVEDD/BSA (mm·m^{-2})	32.0 (2.9)	32.1 (1.1)	-.1 (-3.4 to 3.2)	.96
EF (%)	59.1 (11.6)	62.6 (12.6)	-3.5 (-17.9 to 10.8)	.53
Resting heart rate (bpm)	69.6 (5.1)	60.0 (6.9)	9.6 (-4.2 to 23.4)	.13
RR interval (ms)	858.8 (83.4)	997.6 (102.5)	-138.8 (-363.0 to 85.4)	.16
P duration (ms)	86.4 (19.7)	110.8 (13.0)	-24.4 (-60.4 to 11.6)	.13
PR interval (ms)	158.4 (26.2)	167.6 (27.8)	-9.2 (-31.5 to 13.1)	.32
QRS duration (ms)	90.8 (16.0)	88.4 (13.7)	2.4 (-13.6 to 18.4)	.70
QT interval (ms)	394.8 (25.3)	424.4 (24.6)	-29.6 (-44.6 to -14.6)	.005
QTc (ms)	424.4 (33.2)	422.0 (19.6)	2.4 (-35.4 to 40.2)	.87
Sokolow Lyon voltage (mV)	2.8 (.7)	2.9 (.6)	-.1 (-1.3 to 1.1)	.89
Cornell voltage (mV)	1.1 (.5)	1.5 (.7)	-.4 (-1.4 to .6)	.32
Cornell product (mV x ms)	102.0 (44.9)	141.0 (75.2)	-39.0 (-126.5 to 48.6)	.29
P axis (degree)	49.6 (5.5)	39.6 (14.1)	10.0 (-2.3 to 22.3)	.09
QRS axis (degree)	34.8 (6.6)	36.2 (25.5)	-1.4 (-28.3 to 25.5)	.89
T axis (degree)	42.8 (15.6)	39.2 (3.7)	3.6 (-15.1 to 22.3)	.62
T wave amplitude in lead V_1 (mV)	.10 (.27)	.12 (.14)	-.02 (-.42 to .39)	.93
T wave amplitude in lead V_5 (mV)	.37 (.16)	.37 (.15)	.00 (-.17 to .17)	1.00
T wave amplitude in lead II (mV)	.23 (.07)	.27 (.07)	-.04 (-.12 to .04)	.21
7 DZ pairs				
LVM§ (g)	108.0 (44.4)	108.9 (43.3)	-.9 (-75.5 to 73.7)	.98
LVM/BSA§ (g·m^{-2})	57.2 (20.7)	62.6 (19.8)	-5.4 (-40.6 to 29.8)	.69
LVM/body height § (g·m^{-1})	63.4 (24.3)	65.5 (24.2)	-2.1 (-43.1 to 38.8)	.89
LVM/body weight§ (g·kg^{-1})	1.4 (.5)	1.7 (.4)	-.3 (-1.1 to .6)	.49
LVEDD** (mm)	55.2 (5.2)	56.0 (11.9)	-.8 (-15.4 to 13.8)	.89
LVEDD/BSA** (mm·m^{-2})	29.3 (2.8)	31.9 (4.4)	-2.6 (-8.7 to 3.5)	.33
EF** (%)	54.9 (8.7)	63.1 (9.5)	-8.2 (-19.8 to 3.4)	.13
Resting heart rate (bpm)	66.9 (13.0)	58.6 (4.0)	8.3 (-4.0 to 20.6)	.15
RR interval (ms)	933.4 (160.1)	1021.7 (67.0)	-88.3 (-245.9 to 69.3)	.22
P duration (ms)	95.7 (12.5)	98.9 (9.3)	-3.2 (-20.7 to 14.4)	.68
PR interval (ms)	156.9 (20.5)	166.0 (28.1)	-9.1 (-28.6 to 10.3)	.29

* For the difference between the inactive and active co-twins, based on paired samples Student's t-test for normally distributed variables and Wilcoxon signed ranks test for non-normally distributed variables. † n = 10. ‡ n = 11. § n = 5. ** n = 6. LVM = left ventricular mass (see the calculation in Methods section); BSA = body surface area (see the calculation in Methods section); LVEDD = left ventricular end-diastolic diameter; EF = ejection fraction.

Table 2. Continue.

Characteristic	Inactive co-twins, mean (SD)	Active co-twins, mean (SD)	Mean difference (95% CI)	p value*
QRS duration (ms)	87.4 (4.9)	89.7 (15.3)	-2.3 (-17.1 to 12.6)	.72
QT interval (ms)	404.9 (26.9)	420.3 (14.0)	-15.4 (-48.1 to 17.3)	.29
QTc (ms)	423.3 (22.2)	414.0 (13.0)	9.3 (-10.4 to 28.9)	.29
Sokolow Lyon voltage (mV)	2.7 (.7)	2.9 (1.1)	-.2 (-1.6 to 1.3)	.87
Cornell voltage (mV)	1.3 (.5)	1.5 (.6)	-.2 (-.6 to .4)	.56
Cornell product (mV x ms)	116.6 (42.2)	133.6 (67.9)	-17.0 (-69.7 to 35.7)	.46
P axis (degree)	49.1 (24.4)	50.4 (17.4)	-1.3 (-18.9 to 16.4)	.86
QRS axis (degree)	30.0 (26.6)	43.3 (22.5)	-13.3 (-55.7 to 29.1)	.47
T axis (degree)	34.1 (11.9)	40.1 (19.1)	-6.0 (-28.5 to 16.5)	.54
T wave amplitude in lead V_1 (mV)	.07 (.16)	.10 (.12)	-.03 (-.27 to .20)	.74
T wave amplitude in lead V_5 (mV)	.45 (.10)	.52 (.22)	-.07 (-.21 to .09)	.35
T wave amplitude in lead II (mV)	.27 (.05)	.32 (.10)	-.05 (-.13 to .04)	.25

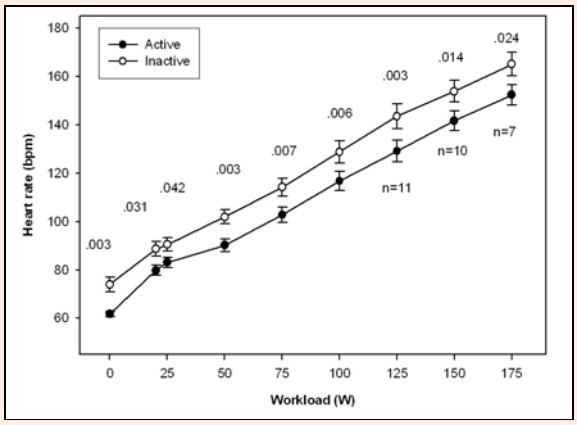

Figure 3. Heart rate (mean ± SEM) before and during the symptom-limited clinical exercise test in the active and inactive co-twins (n = 12).

of both resting heart rate and submaximal heart rate, and to some extent, also increased LVM relative to body weight. These adaptations are in the same direction as those reported in highly trained athletes. The use of a twin design enabled total (MZ pairs) or partial (DZ pairs) adjustment for genetic factors. The childhood environments of both MZ and DZ twin pairs are usually similar. Therefore, the results of our study suggest that physical activity has beneficial effects on cardiac structure and function, even after partially or fully controlling for genetic liability and childhood environment. This is of note since participation in exercise (Stubbe et al., 2006) as well as cardiac structure (Sharma et al., 2006) and function (Mutikainen et al., 2009) are genetically influenced.

Both longitudinal and case-control studies have reported, almost without exception, decreased resting heart rates as a consequence of physical training (Bjørnstad et al., 1991; Parker et al., 1978; Sharma et al., 1999; Stolt et al., 1997). Factors which may contribute to this adaptation include lower intrinsic heart rate, increased parasympathetic tone and decreased sympathetic tone (Fagard, 2003). Decreased resting heart rate is an independent predictor of reduced cardiovascular mortality (Kannel et al., 1987; Shaper et al., 1993). In our study, the resting heart rate (measured in supine position) of the active co-twins was nearly 10 bpm lower than that of their inactive co-twins [59 (SD 5) vs. 68 (SD 10) bpm, respectively]. Similar and even larger difference was seen when the heart rate was measured in the sitting position before the beginning of the clinical exercise test. According to a previous study (Shaper et al., 1993), the difference in resting heart rate observed in our study is clinically significant. Shaper et al. (1993) reported that those with higher resting heart rates (similar to the values in our inactive co-twins, i.e. 60-69 bpm) have 40% greater risk of coronary heart disease mortality and 60% greater risk of sudden cardiac death than those whose resting heart rate is < 60 bpm (as in our active co-twins), even after controlling for classical coronary heart disease risk factors.

Similar heart rate difference between the co-twins was also seen at submaximal stages during the clinical exercise tests. At each stage, beginning from the learning stage, heart rates were significantly lower in the active co-twins. However, peak heart rates were still the same between the co-twins. These are well-known adaptations to physical training (Charlton and Crawford, 1997), but our study showed that these adaptations are partially independent of genetic liability. As lowered resting heart rate, also lowered submaximal heart rate is a beneficial adaptation to physical activity since, for example, it reduces myocardial stress and thus its oxygen need during exercise.

We estimated VO_{2peak} from the highest load achieved in the clinical exercise test and it was significantly higher in the active co-twins, showing that the discordance for physical activity was also reflected in the co-twins' cardiorespiratory fitness levels. Many studies have reported that maximal or peak oxygen uptake is a heritable trait (Bielen et al., 1990; Bouchard et al., 1998; Bouchard et al., 1986; Fagard et al., 1991; Fagard et al., 1987). Heritability estimates have varied within broad ranges; in the studies of Bouchard et al. (1986), Bouchard et al. (1998) and Fagard et al. (1991) the heritability estimates ranged approximately from 10% to 80%, depending on adjustments. Also the VO_{2max} response to physical training shows rather strong heritability. For example, it was almost 50% in sedentary adults in the 20-week exercise training study (Bouchard et al., 1999). Cardiorespiratory fitness, in turn, may have influences on resting ECG variables. These influences have been similar as those caused by physical activity or athletic training. For example, resting heart rate is lower and T wave amplitude higher in the athletes with the best fitness level compared with those whose fitness level is clearly lower (Bjørnstad

et al., 1993).

As expected on the basis of the significantly lower resting heart rate, the ECG variables dependent on heart rate (QT interval) were significantly prolonged in the active co-twins. When the QT interval was corrected for heart rate, it was shortened in the active co-twins, but the difference was neither statistically nor clinically significant. Instead, previous case-control studies have reported significantly prolonged QTc intervals in athletes compared with sedentary controls (Bjørnstad et al., 1991; Sharma et al., 1999; Stolt et al., 1997). This has raised concern about the significance of training-induced QTc prolongations, since at least among patients with cardiac diseases, QTc prolongation is associated with sudden cardiac death and other adverse outcomes (Schwartz and Wolf, 1978). However, extreme QTc prolongations in athletes or other physically active persons are rare (Basavarajaiah et al., 2007) and may be associated with inherited or congenital long QT syndromes. In contrast to the studies performed in highly trained athletes, our present study suggests that although the uncorrected QT interval is significantly prolonged, the QTc interval remains unchanged as a consequence of moderate intensity leisure time physical activity.

Our QT intervals were corrected for heart rate using the Bazett's formula, which may not be optimal for the correction, since a previous study (Karjalainen et al., 1994) has reported that the Bazett's formula both overadjusts QT interval at high heart rates and underadjusts it at low heart rates. However, when we corrected for heart rate using the formula QTc = QT interval + [(1000 – RR interval) / 7], in which the changes in RR intervals do not influence the QTc (Katsuoka et al., 1998), the results remained similar, i.e. there were no statistically significant differences between the co-twins.

Some of the medications used in the treatment of cardiovascular diseases may have influences on heart rate. In our study, among the MZ pairs, one pair was discordant for the use of beta-blockers (the inactive co-twin used a $beta_1$ selective blocker). When all heart rate variables and the ECG variables dependent on heart rate were analyzed without this pair, the results (mean differences) remained similar.

There was a tendency for increased LVM per body weight in the active co-twins. When MZ twin pairs were studied separately, the difference between the active and inactive co-twins was statistically significant. Increased LVM is one of the most often documented adaptations in athletes, which results from an enlarged LV cavity and/or thickened LV wall (Pluim et al., 2000). However, LVM is a highly heritable trait; in a large cohort of twins, about 60% of individual differences in LVM were accounted for by genetic factors (Sharma et al., 2006). This may, at least to some extent, be a cause of bias in case-control studies, i.e. persons with congenitally larger hearts may be more prone to participate in vigorous exercise, since it may be easier for them than for persons with smaller hearts. Similar problems may also arise in other population-based studies (such as intervention studies), since genetic factors may also modify the myocardial response to physical training. For example, both the angiotensinogen gene M235T (Karjalainen et al., 1999) and angiotensin-converting enzyme gene I/D polymorphisms (Kasikcioglu et al., 2004; Montgomery et al., 1997; Tanriverdi et al., 2005) have been reported to be associated with the variability in LVM induced by physical training. The greatest LVM values were found in those homozygous either for the T allele or D allele, respectively. In our study, the aforementioned problems were overcome by comparing MZ co-twins, who are genetically identical at the chromosomal sequence level (with the rare exception of somatic mutations); epigenetic differences between MZ twins may exist (Fraga et al., 2005). But despite this, LVM per body weight was increased in the active MZ co-twins, suggesting that physical activity may have independent effects on LVM. Although we did not measure diastolic function to determine whether diastolic abnormalities were present, it is likely that the increased LVM is physiological, since none of the active MZ co-twins had significant hypertension, valvular disorders or other conditions leading to pathologically increased LVM.

Previous studies have also reported other adaptations to physical training, such as increased LVEDD (Pluim et al., 2000), prolonged PR interval (Sharma et al., 1999) and more vertical QRS axis (Bjørnstad et al., 1991; Parker et al., 1978), but these results were not observed in our study. There are a number of possible reasons for this discrepancy. Firstly, moderate intensity physical activity may not be enough to induce adaptations of these kinds in the heart. Secondly, these "adaptations" may not be revealed when genetic factors and childhood environment are taken into account. However, this does not mean that physical training has not contributed to the differences observed in previous athletic studies since the intensity of training in athletes is significantly greater than in our twins and often includes differences in training during childhood and adolescence. Thirdly, the small sample size in our study may have led to lack of statistical power to detect differences between the active and inactive co-twins. The small sample size is due to the strict criteria laid down for physical activity discordance and subsequent difficulties in finding twin pairs who fulfill these criteria. The number of pairs was also too small to allow separate analyses for males and females, although it is known that the adaptation of the heart to physical training is gender-specific (Spirito et al., 1994). In addition, baseline measurements of cardiac structure and function were missing; however, subjects with overt cardiac or pulmonary disease or related symptoms were excluded.

The co-twin control study probably represents the best controlled long-term study design available in humans that allows adjustment for genetic and familial factors because of the complete or close match for genes, age, gender and the intrauterine and childhood environment. The follow-up period was long (32 years), covering most of the participants' adult lives and exceeding the length of training history in many athlete studies. In addition, the amount and/or intensity of physical activity at which positive adaptations were observed is realistically achievable for normal, healthy people compared with the training levels reported in athlete studies.

Conclusion

The main adaptations to long-term leisure time physical activity are lowered resting and submaximal heart rates, even after partially or fully controlling for genetic liability and childhood environment. There is also a tendency toward an increased LVM per body weight and heightened T wave amplitude. These adaptations are in the same direction as previously reported in athletes, suggesting that also less intensive physical activity has beneficial effects on cardiac structure and function. Lowering of resting heart rate is a clinically significant adaptation shown to be associated with decreased cardiovascular mortality, and thus the prevention of cardiovascular disorders should also include engagement in physical activity.

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Key points

- The main adaptation to long-term physical activity is lowering of resting heart rate, even after controlling for genetic liability.
- VO_{2peak} is increased in the active co-twins compared with their inactive co-twins and accordingly, also submaximal heart rates during the clinical exercise test are lower in physically active co-twins.
- There is a tendency for increased LVM per body weight and heightened T wave amplitude in the active co-twins.

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