Eur J Appl Physiol (2013) 113:631–640
DOI 10.1007/s00421-012-2474-x

ORIGINAL ARTICLE

Training-related modulations of the autonomic nervous system in endurance athletes: is female gender cardioprotective?

Monika Fürholz · Thomas Radtke · Laurent Roten · Hildegard Tanner · Ilca Wilhelm · Jean-Paul Schmid · Hugo Saner · Matthias Wilhelm

Received: 12 June 2012 / Accepted: 1 August 2012 / Published online: 12 August 2012

Abstract The risk of sudden death is increased in athletes with a male predominance. Regular physical activity increases vagal tone, and may protect against exercise-induced ventricular arrhythmias. We investigated training-related modulations of the autonomic nervous system in female and male endurance athletes. Runners of a 10-mile race were invited. Of 873 applicants, 68 female and 70 male athletes were randomly selected and stratified according to their average weekly training hours in a low ($\leq$4 h) and high (>4 h) volume training group. Analysis of heart rate variability was performed over 24 h. Spectral components (high frequency [HF] and low frequency [LF] power in normalized units) were analyzed for hourly 5 min segments and averaged for day- and nighttime. One hundred and fourteen athletes (50 % female, mean age 42 $\pm$ 7 years) were included. No significant gender difference was observed for training volume and 10-mile race time. Over the 24-h period, female athletes exhibited a higher HF and lower LF power for each hourly time-point. Female gender and endurance training hours were independent predictors of a higher HF and lower LF power. In female athletes, higher training hours were associated with a higher HF and lower LF power during nighttime. In male athletes, the same was true during daytime. In conclusion, female and male athletes showed a different circadian pattern of the training-related increase in markers of vagal tone. For a comparable amount of training volume, female athletes maintained their higher markers of vagal tone, possibly indicating a superior protection against exercise-induced ventricular arrhythmias.

Keywords Gender differences · Circadian rhythm · Autonomic nervous system · Vagal tone · Athletes

Communicated by Keith Phillip George.

M. Fürholz · T. Radtke · J.-P. Schmid · H. Saner · M. Wilhelm (✉)
Division of Cardiovascular Prevention, Rehabilitation and Sports Cardiology, University Clinic for Cardiology, Inselspital, University Hospital and University of Bern, 3010 Bern, Switzerland
e-mail: matthias.wilhelm@insel.ch

L. Roten · H. Tanner
Division of Electrophysiology, University Clinic for Cardiology, Inselspital, University Hospital and University of Bern, Bern, Switzerland

I. Wilhelm
University Clinic for Anaesthesiology, Inselspital, University Hospital and University of Bern, Bern, Switzerland

Introduction

Sports activity enhances the risk of sudden cardiac death in adolescent and young adults (Corrado et al. 2003). In the general population, sports-related sudden deaths are rare events, but they occur with a striking male predominance of more than 90 % (Marijon et al. 2011). Gender differences in the risk of sudden death have also been demonstrated in competitive athletes like long-distance runners (Kim et al. 2012), triathletes (Harris et al. 2010), and student-athletes, participating in different types of sports (Harmon et al. 2011). Most of the cases are associated with an underlying heart disease, like hypertrophic cardiomyopathy in younger and atherosclerotic coronary artery disease in older athletes, predisposing to myocardial ischemia during high-intensity exercise (Marijon et al. 2011; Maron et al. 2009). However, the predominant occurrence of cardiac arrests in the last quarter of a long-distance race, and the increasing incidence with race

duration suggest an elevated adrenergic tone as an additional risk factor (Kim et al. 2012; Redelmeier and Greenwald 2007). Animal studies suggested that, especially in the presence of myocardial ischemia, sympathetic activation can trigger malignant arrhythmias, whereas vagal activity may exert a protective effect (Schwartz et al. 1992). Since women exhibit lower adrenergic and higher vagal markers of autonomic tone (Ramaekers et al. 1998; Wilhelm et al. 2011), their autonomic nervous system (ANS) may be cardioprotective. Endurance training is associated with an increase in vagal activity, both in male and female athletes (Aubert et al. 2003). Animal studies have demonstrated that endurance training enhanced cardiac parasympathetic regulation, restored a more normal β-adrenoceptor balance, and protected against ventricular fibrillation induced by acute myocardial ischemia (Billman 2009). In humans, regular physical activity reduced the risk of sudden death and acute myocardial infarction from vigorous exertion in men (Albert et al. 2000; Mittleman et al. 1993). Training-related effects of ANS modulations have not been compared between female and male endurance athletes. We hypothesized, that for a comparable amount of training volume, female athletes would maintain their higher markers of vagal tone, indicating a superior cardioprotection. We examined nonelite endurance athletes using 24-h Holter monitoring with analysis of time- and frequency-domain parameters of heart rate variability (HRV).

Methods

Design and population

The Grand Prix of Bern is one of the most popular 10-mile races in Switzerland with over 25,000 participants. Nonelite athletes were recruited by an open invitation letter published on the event's homepage. We included runners with and without a history of former marathon participations, aged 30 years and older. We excluded subjects with a history of hypertension (blood pressure >140/90 mmHg at rest), or other known cardiovascular diseases. All athletes applied via email and provided age and race time. From all applicants, 70 male and 68 female athletes were randomly selected. Baseline examination consisted of a comprehensive questionnaire to ascertain personal and sports history. Measurement of training years started in adulthood. Calculation of average weekly endurance and strength training hours of the last 3 months was based on the athletes' estimation and/or exercise diary. Athletes were stratified in a low training ($\leq$4 h) and high training (>4 h) group, based on their information and/or training diary. Measurement of resting heart rate and blood pressure were performed in a quiet room after 5 min in supine position. Further assessment included echocardiography, cardiopulmonary exercise testing on a treadmill, and 24-h Holter monitoring with time- and frequency-domain analysis of HRV. One experienced cardiologists blinded for the athletes' performance performed all analyses. All athletes provided written informed consent and the protocol was approved by the local ethics committee.

Transthoracic echocardiography

Standard transthoracic echocardiography was performed (iE33, Phillips Healthcare, Zurich, Switzerland, S5-1 2.5 MHz transducer) and the images were stored digitally and analyzed off-line. Left ventricular (LV) mass and LV end-diastolic volume were calculated according to current recommendations and indexed for body surface area (Lang et al. 2006). The LV ejection fraction (EF) was derived from the end-diastolic and end-systolic volumes. Pulsed-wave tissue Doppler imaging was performed in the apical four-chamber view to acquire peak early septal mitral annular velocity (e') (Nagueh et al. 2009).

Cardiopulmonary exercise test

Spiroergometric testing was performed on a treadmill. We used a ramp protocol starting at 7.2 km/h, with speed increasing 0.2 km/h every 20 s until exhaustion. Athletes were encourage to reach at least a respiratory exchange ratio >1.05. Respiratory parameters were measured continuously in an open spirometric system (CS 200, Schiller-Reomed AG, Dietikon, Switzerland) and registered as averaged values over 30 s. Blood pressure was measured at peak exercise.

24-h Holter monitoring and analysis of HRV

An ambulatory electrocardiogram (ECG) was performed over a period of 24 h. Athletes were allowed to perform up to 90 min of moderate intensity training during the recording. Athletes were asked to rest in supine position from 11 p.m. to 6 a.m. and to record sleep time. The monitor (Lifecard CF, Del Mar Reynolds Medical Inc., Irvine, CA, USA) provides ECG data with high accuracy (12-bit resolution) and a sampling frequency of 1,024 Hz. The data was manually analyzed and interpreted using the Pathfinder Software (Del Mar Reynolds Medical Inc., Irvine, CA, USA). Premature atrial and ventricular contractions were classified according to onset and QRS morphology. For the analysis of HRV, the program eliminated one RR interval before, and two intervals after each nonsinus beat. Two standard 24-h time-domain measures were calculated: the standard deviation of

normal-to-normal intervals (SDNN), and the square root of the mean squared differences of successive normal-to-normal intervals (RMSSD). In addition, frequency-domain analysis was performed. Power spectral density of 5 min segments were analysed using the Fast Fourier Transform algorithm with a Hamming window (HRV Tools Software, Del Mar Reynolds Medical Inc., Irvine, CA, USA). The total power (TP) and three main spectral components were distinguished: very low frequency (VLF, 0.003–0.04 Hz), low frequency (LF, 0.04–0.15 Hz), and high frequency (HF, 0.15–0.4 Hz) power (Aubert et al. 2003; Camm 1996). LF and HF power components were measured in absolute values of power (ms^2) and in normalized units (nu) which represent the relative value of each power component in proportion to the TP minus the VLF component (Pagani et al. 1986). For analysis of the circadian rhythm, the first 5 min segment from every hour with more than 90 % valid data was recorded. For comparisons of training volumes, recordings between 7 a.m. and 10 p.m. were averaged and reported as daytime autonomic modulations. Recordings between 11 p.m. and 6 a.m. were averaged and reported as nighttime autonomic modulations.

Data analysis

The data was analyzed with SPSS Software for Windows, Version 17.0. Distribution of the data was examined using the Shapiro–Wilk test. Data are presented as mean ± standard deviation (SD) or median (inter-quartile range), depending on whether the data were normally distributed or not. Data were analyzed with the Students *t* test or Mann–Whitney *U* test, as appropriate. Categorical data were analyzed using the χ^2 test. Multiple linear regression analysis was performed to assess the influence of prespecified variables (gender, weekly endurance training hours, peak oxygen uptake, and minimum heart rate during Holter monitoring) on time-domain measures and spectral components of daytime HRV. TP (ms^2), LF power (nu), and HF power (nu) were log-transformed (ln) to achieve a normal distribution. Gender differences in hourly measures of ln LF power (nu) and ln HF power (nu) were analyzed by analysis of variance with repeated-measures. If the sphericity assumption was violated ($p < 0.05$), the Huynh–Feldt correction was used. A Tukey HSD test was performed to determine significant gender differences in individual time-points. Averaged night- and daytime measures of ln TP (ms^2), ln LF power (nu), and ln HF power (nu) were compared between female and male athletes and the low and high training groups using Students *t* tests. A *p* value of less than 0.05 was considered to indicate statistical significance.

Results

Eight hundred and seventy-three runners applied for participation, and 138 athletes (68 female and 70 male) were randomly selected. Twenty-four runners had to be excluded (nine could not participate in the race due to muscular problems, one had mitral valve prolapse, three had an undiagnosed arterial hypertension with diastolic dysfunction, four did not perform the examinations, and seven had insufficient Holter recordings). One hundred and fourteen runners entered the final analysis. There were no significant gender differences in age, former marathon participations, endurance training years, and average endurance, and strength training hours per week. Female athletes had a significantly lower body mass index and body surface area. They participated more often in 10-mile races and had a non-significantly longer 10-mile race time. Heart rate at rest and peak heart rate after the exercise test showed no gender differences. Female athletes had a lower systolic blood pressure at rest and at peak exercise. They had a lower peak oxygen uptake. LV end-diastolic volume index, and LV mass index were lower in female athletes. They showed a higher systolic EF, while diastolic function was comparable to male athlete (Table 1).

During 24-h Holter monitoring, female athletes exhibited a higher minimum heart rate. LV end-diastolic volume index and stroke volume were inversely associated with minimum heart rate. In a multiple linear regression model, LV end-diastolic volume index was the strongest predictor of minimum heart rate (β −0.393; $p < 0.001$), followed by gender (β −0.204; $p = 0.020$) and endurance training hours (β −0.191; $p = 0.030$). Premature atrial and ventricular contractions were low and equally distributed between female and male athletes. No sustained atrial or ventricular arrhythmias occurred. An equal proportion of female and male athletes exercised during the period of Holter monitoring. They showed no differences in exercise time of the day, exercise duration and exercise intensity (measured as percentage of mean exercise heart rate in relation to heart rate at the anaerobic threshold, determined during exercise testing) (Table 2).

TP was significantly higher in male athletes during nighttime and showed a tendency towards higher values during daytime. LF power (in ms^2) was significantly higher in male athletes during daytime and showed a tendency towards higher values during nighttime. HF power (in ms^2) showed no gender differences during night- and daytime. Female athletes exhibited higher values for HF power (nu) and lower values for LF power (nu) during day- and nighttime (Table 2).

Over the 24-h period, LF power (nu) and HF power (nu) showed a circadian rhythm with a significant time effect ($p < 0.001$), both in female and male athletes. There were

Table 1 Characteristics of study participants

Variable	Female athletes ($n = 57$)	Male athletes ($n = 57$)	p Value
Baseline data			
Age (years)	43 ± 7	41 ± 7	0.102
Body mass index (kg/m^2)	20.4 ± 1.8	23.3 ± 1.9	<0.001
Body surface area (m^2)	1.63 ± 0.11	1.93 ± 0.12	<0.001
Previous marathons (n)	3 (6)	3 (7)	0.124
Previous 10-mile races (n)	6 (6)	4.5 (9)	0.027
Endurance training (years)	11.0 (12.0)	14.0 (12.0)	0.907
Endurance training (h/week)	4.5 (2.3)	4.0 (3.5)	0.261
Strength training (h/week)	0.8 (0.9)	0.5 (1.0)	0.324
10-mile race time (min:s)	82:31 ± 11:38	78:58 ± 11:33	0.091
Exercise test			
Heart rate at rest (bpm)	57 ± 8	55 ± 9	0.264
Systolic BP at rest (mmHg)	110 ± 11	123 ± 9	<0.001
Peak heart rate (bpm)	178 ± 11	181 ± 9	0.134
Peak systolic BP (mmHg)	169 ± 19	180 ± 15	<0.001
VO_2 peak (ml/min/kg)	50.1 ± 5.9	53.6 ± 6.8	0.002
Echocardiography			
LV end-diastolic volume index (ml/m^2)	49.4 ± 8.7	54.3 ± 9.1	0.004
LV mass index (g/m^2)	84.8 ± 16.1	107.1 ± 16.8	<0.001
LV EF (%)	67.1 ± 6.5	63.5 ± 4.3	0.001
LV stroke volume (ml)	53.8 ± 11.1	66.5 ± 12.0	<0.001
Peak e' (cm/s)	10.6 ± 1.5	11.0 ± 1.5	0.154

Data are expressed as mean ± standard deviation or median (inter-quartile range)

Bpm beats per minute, *BP* blood pressure, VO_2 oxygen uptake, and *LV* left ventricular

no significant gender × time interactions, but significant gender differences ($p < 0.001$). Female athletes exhibited lower values for LF power (nu) and higher values for HF power (nu) (Fig. 1).

In multiple linear regression analysis, female gender was associated with a higher RMSSD, a lower LF power (in nu) and higher HF power (in nu). Average endurance training hours were an independent predictor of a higher RMSSD, a higher TP, a lower LF power (in nu), and a higher HF power (in ms^2 and nu). Peak oxygen uptake was only related to a higher LF power (in ms^2). Minimum heart rate during 24-h Holter monitoring was the strongest predictor of SDNN, RMSSD, and TP, LF power and HF power (in ms^2) (Table 3).

Between the low and high training groups, both female and male athletes differed significantly with regard to 10-mile race time, and minimum heart rate during 24-h Holter monitoring. Furthermore, higher training hours were associated with a higher peak oxygen uptake, and a larger LV end-diastolic volume. However, these differences were only significant in male athletes. In the low training groups, female and male athletes showed no significant differences concerning 10-mile race time, peak oxygen uptake, and LV end-diastolic volume. In the high training groups, these variables showed significant gender differences. Minimum heart rate was significantly lower in male athletes, both in the high and low training groups (Table 4).

TP increased with training hours during night- and daytime, both in female and male athletes. Male athletes exhibited a higher TP in the high training group. Ln LF power (nu) decreased with training hours, in female athletes during nighttime, and in male athletes during daytime. Overall, ln LF power (nu) was higher in male athletes. Ln HF power (nu) increased with training hours, in female athletes during nighttime, and in male athletes during daytime. Overall, female athletes exhibited a higher ln HF power (nu) (Fig. 2).

Discussion

Our study provided two relevant new findings. First, female and male athletes showed a different circadian pattern of the training-related increase in markers of vagal tone. Second, for a comparable amount of training volume, female athletes maintained higher markers of vagal tone during day- and nighttime.

Table 2 24-h Holter monitoring and analysis of HRV

Variable	Female athletes ($n = 57$)	Male athletes ($n = 57$)	p Value
Holter data			
Holter wear time (h:min)	24:26 (0:47)	24:32 (1:29)	0.792
Minimum heart rate (bpm)	46 (10)	43 (9)	0.006
Premature atrial contractions (n)	4.8 (9.9)	4.8 (10.2)	0.582
Premature ventricular contractions (n)	1.9 (4.0)	2.0 (6.0)	0.359
Athletic activity			
Athletes exercising during Holter monitoring (%)	44	33	0.248
Exercise time of the day (h:min)	13:00 (9:00)	13:30 (6:00)	0.118
Exercise duration (min)	60 (30)	60 (15)	0.495
Mean heart rate/heart rate at AnT (%)	87 (15)	81 (8)	0.247
24-h time-domain HRV			
SDNN	194 (61)	201 (64)	0.169
RMSSD	36 (19)	34 (21)	0.768
Spectral components of nighttime HRV			
TP (ms^2)	5612 (5004)	6869 (5070)	0.024
LF power (ms^2)	1540 (1530)	1951 (1265)	0.093
HF power (ms^2)	746 (945)	653 (804)	0.448
LF power (nu)	65.5 (18.6)	72.0 (20.3)	0.004
HF power (nu)	32.7 (18.0)	25.7 (20.1)	0.011
Spectral components of daytime HRV			
TP (ms^2)	3955 (3466)	5550 (4013)	0.077
LF power (ms^2)	1064 (853)	1507 (1442)	0.002
HF power (ms^2)	272 (334)	258 (283)	0.606
LF power (nu)	74.2 (11.0)	83.6 (9.3)	<0.001
HF power (nu)	22.1 (10.7)	14.2 (10.1)	<0.001

Data are expressed as mean ± standard deviation or median (inter-quartile range) or %

Nighttime (11 p.m. to 6 a.m.), daytime (7 a.m. to 10 p.m.)

Bpm beats per minute, *AnT* anaerobic threshold, *HRV* heart rate variability, *SDNN* standard deviation of normal-to-normal intervals, and *RMSSD* root of the mean squared differences of successive normal-to-normal intervals

Analysis of HRV is an established tool to examine the ANS in athletes (Aubert et al. 2003). While time-domain analysis is preferably used for long-term recordings, frequency-domain methods allow short-term recordings and the assessment of circadian patterns (Aubert et al. 2003; Camm 1996). HF power (nu) is predominantly a marker of vagal tone. In contrast, both branches of the ANS contribute to LF power (nu) (Berntson et al. 1997). LF power is therefore no direct measure of the adrenergic tone and reflect most likely baroreceptor sensitivity (Rahman et al. 2011). However, in selected conditions like an orthostatic load, LF power exhibits parallel changes to muscle sympathetic nerve activity and may reflect sympathetic outflow (DeBeck et al. 2010). This is compatible with the circadian pattern of LF power (nu) in our study. Male athletes exhibited a higher LF power (nu) at all time-points which may indicate their higher adrenergic tone.

Higher markers of vagal tone in women have been demonstrated in several studies on sedentary and athletic individuals, using time- and frequency-domain analysis of HRV and short- and long-term recordings (Antelmi et al. 2004; Hedelin et al. 2000; Ramaekers et al. 1998; Ryan et al. 1994). In our athletic population, we demonstrated a circadian rhythm of HF power (nu) in both male and female athletes. Importantly, female athletes exhibited higher markers of vagal tone at all time-points of the 24-h period. Beside gender, average weekly endurance training hours were an independent predictor of HF power (nu) in multiple linear regression analysis. This is consistent with reports on a training-related increase in markers of vagal tone of sedentary individuals and athletes (Aubert et al. 2001, 2003; Hedelin et al. 2000).

Interestingly, female and male athletes showed a different circadian pattern of the training-related modulation of the ANS. In female athletes, higher training hours were associated with a lower LF power and a higher HF power during nighttime. In male athletes, the same was true

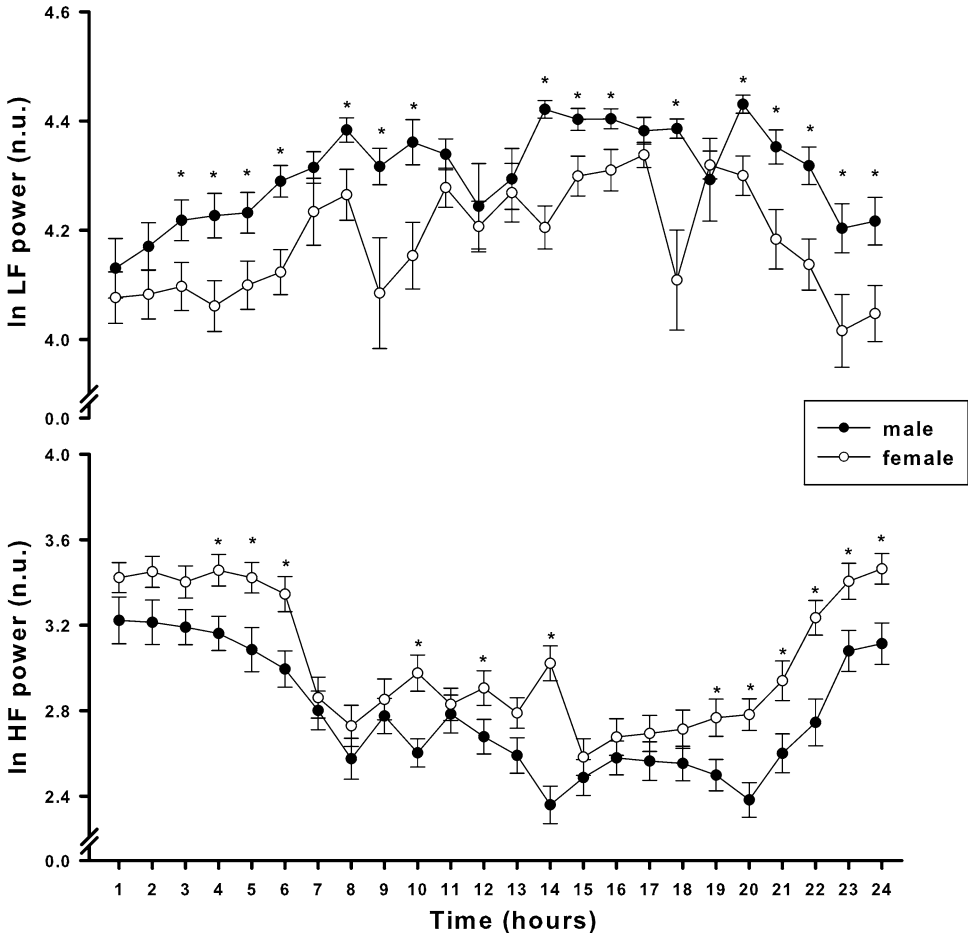

Fig. 1 Gender differences of circadian rhythm of the autonomic tone. Two spectral components of HRV are displayed. LF and HF power are presented log-transformed (ln) and in nu. *Indicates a p value <0.05. *Bars* represent one standard error

during daytime. This suggests a gender-specific adaptation of the ANS to exercise conditioning.

Despite their higher markers of vagal tone during nighttime, minimum heart rate was higher in female athletes. LV volume index was the strongest predictor of minimum heart rate. LV volume index and stroke volume were inversely associated with minimum heart rate, highlighting the fact that absolute heart rate does not mirror sympatho-vagal balance. Although an increase in training hours was accompanied by an increase in markers of vagal tone and a reduction of minimum heart rate, both in female and male athletes, this cannot be interpreted as a causal relationship. Higher endurance training hours were also associated with a greater LV volume index as an expression of the athlete's heart (Maron and Pelliccia 2006), possibly explaining the lower minimum heart rate in the high training groups. Moreover, our observation is consistent with other studies, indicating that not vagal efferent activity but intrinsic sinus node electrophysiologic adaptations are responsible for a lower heart rate in endurance athletes (Scott et al. 2004; Stein et al. 2002). Daytime heart rate at rest showed no gender differences, possibly related to the higher LV EF in female athletes.

Studies on sedentary individuals found heart rate to be a major predictor for time-domain parameters of HRV and components of spectral power in absolute values (Ramaekers et al. 1998; Tsuji et al. 1996). We found the similar association in endurance athletes and demonstrated that minimum heart rate was the strongest predictor for SDNN, RMSSD, TP, and LF and HF power in absolute values.

Because male athletes had larger end-diastolic volumes and a lower minimum heart rate, their TP was higher, compared to female athletes. In this regard, the lower TP of female athletes does not reflect a lower overall strength of the ANS like in patients with heart failure or diabetic neuropathy (Camm 1996). Importantly, only LF and HF power in nu were independent from minimum heart rate and were therefore used for the analysis of autonomic tone.

During 24-h Holter monitoring, ventricular ectopy was low. No athlete exhibited complex ventricular arrhythmias or more than 100 premature ventricular beats per 24 h, both in female and male athletes. This is consistent with data from Biffi et al., who reported a low prevalence of ventricular arrhythmias in athletes (2 %, 335 out of 15,889). Especially those with less than 100 premature ventricular beats per 24 h had no underlying heart disease and

Table 3 Independent predictors of 24-h time-domain parameters and spectral components of daytime HRV

	β Coefficient	Standard error β	Standardized β	p Value
SDNN (ms) ($R^2 = 0.539$)				
Gender[a]	−6.56	6.43	−0.075	0.310
Endurance training (h/week)	0.01	0.02	0.009	0.898
Peak oxygen uptake (ml/min/kg)	0.45	0.52	0.068	0.383
Minimum heart rate (bpm)	−4.92	0.53	−0.718	<0.001
RMSSD (ms) ($R^2 = 0.608$)				
Gender[a]	−5.76	1.85	−0.210	0.002
Endurance training (h/week)	0.01	0.01	0.173	0.012
Peak oxygen uptake (ml/min/kg)	0.14	0.15	0.068	0.341
Minimum heart rate (bpm)	−1.50	0.15	−0.700	<0.001
TP (ms^2) ($R^2 = 0.546$)				
Gender[a]	99.35	432.71	0.017	0.819
Endurance training (h/week)	2.92	1.27	0.168	0.023
Peak oxygen uptake (ml/min/kg)	22.28	34.71	0.049	0.522
Minimum heart rate (bpm)	−297.61	35.86	−0.641	<0.001
LF power (ms^2) ($R^2 = 0.458$)				
Gender[a]	150.87	115.40	0.104	0.194
Endurance training (h/week)	0.01	0.34	0.003	0.972
Peak oxygen uptake (ml/min/kg)	21.50	9.26	0.195	0.022
Minimum heart rate (bpm)	−59.62	9.56	−0.526	<0.001
HF power (ms^2) ($R^2 = 0.443$)				
Gender[a]	−76.06	42.53	−0.144	0.077
Endurance training (h/week)	0.52	0.12	0.335	<0.001
Peak oxygen uptake (ml/min/kg)	2.29	3.41	0.057	0.503
Minimum heart rate (bpm)	−18.96	3.52	0.460	<0.001
LF power (nu) ($R^2 = 0.323$)				
Gender[a]	7.23	1.64	0.392	<0.001
Endurance training (h/week)	−0.02	0.01	−0.366	<0.001
Peak oxygen uptake (ml/min/kg)	0.10	0.13	0.073	0.435
Minimum heart rate (bpm)	0.08	0.14	0.052	0.583
HF power (nu) ($R^2 = 0.272$)				
Gender[a]	−5.61	1.55	−0.333	<0.001
Endurance training (h/week)	0.02	0.01	0.352	<0.001
Peak oxygen uptake (ml/min/kg)	−0.02	0.12	−0.017	0.862
Minimum heart rate (bpm)	−0.15	0.13	−0.112	0.253

Multiple linear regression analysis including gender, endurance training (h/week), peak oxygen uptake, and minimum heart rate during 24-h Holter recording

SDNN standard deviation of normal-to-normal intervals, *RMSSD* root of the mean squared differences of successive normal-to-normal intervals

[a] 1 = female gender, 2 = male gender

exhibited no cardiovascular events during a mean follow-up of 8 years (Biffi et al. 2002).

Animal data suggest that exercise-induced sympathetic activation can trigger malignant arrhythmias, especially in the presence of myocardial ischemia (Schwartz et al. 1984). An antifibrillatory effect of vagal activation has been confirmed by the prevention of ventricular fibrillation during acute ischemia in dogs susceptible to sudden cardiac death by direct electrical stimulation of the right vagus (Vanoli et al. 1991). Moreover, weak sympathetic reflexes and powerful vagal reflexes in response to exercise-induced myocardial ischemia prevented ventricular fibrillation in dogs (De Ferrari et al. 1991). In the Race Association Cardiac Arrest Event Registry, most of the endurance athletes presenting with a cardiac arrests during a long-distance race had an underlying heart disease like hypertrophic cardiomyopathy or atherosclerotic coronary heart disease, predisposing them to exercise-induced myocardial

Table 4 Characteristic of athletes grouped according to gender and training volume

Variable	Low training group (LT)		High training group (HT)		*p* Values			
	Female (F) ($n = 15$)	Male (M) ($n = 23$)	Female (F) ($n = 42$)	Male (M) ($n = 34$)	LT F vs. M	HT F vs. M	F LT vs. HT	M LT vs. HT
Endurance training (h/week)	3.0 (1.1)	3.0 (1.0)	6.0 (3.5)	6.0 (4.3)	0.237	0.383	<0.001	<0.001
10-mile race time (min:s)	88:38 ± 08:20	84:16 ± 09:01	81:10 ± 11:53	75:39 ± 11:50	0.211	0.047	0.030	0.008
Minimum heart rate (bpm)	51.4 ± 7.6	46.2 ± 5.8	46.1 ± 5.9	41.6 ± 5.4	0.040	<0.001	0.018	0.004
VO_2 peak (ml/min/kg)	47.8 ± 4.8	50.8 ± 7.0	50.2 ± 6.0	55.6 ± 5.9	0.242	<0.001	0.262	0.008
LV end-diastolic volume index (ml/m^2)	47.3 ± 8.1	50.8 ± 8.5	49.7 ± 8.9	56.6 ± 8.9	0.295	0.001	0.425	0.017

Data are expressed as mean ± standard deviation or median (inter-quartile range)

Bpm beats per minute, *VO_2* oxygen uptake, and *LV* left ventricular

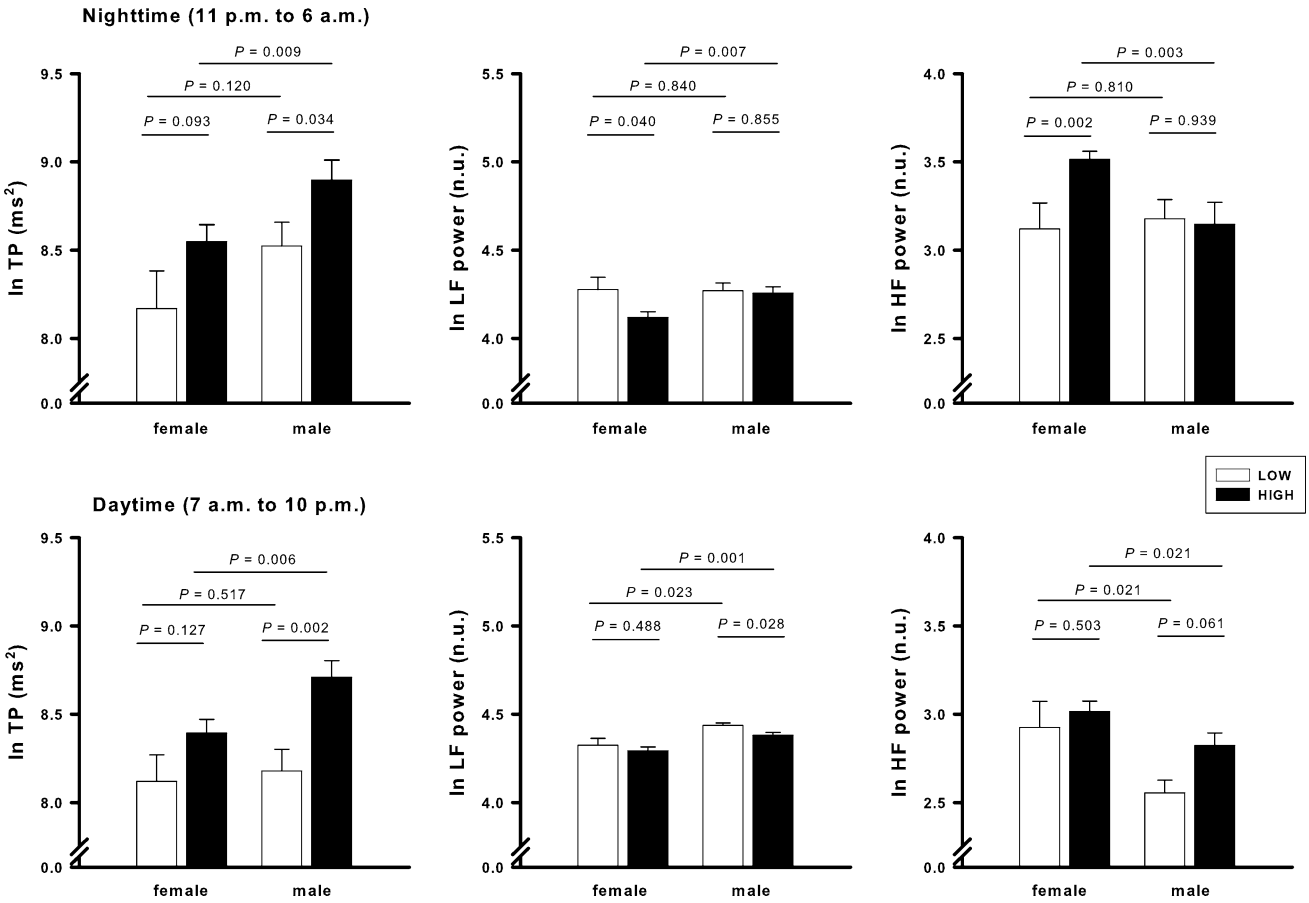

Fig. 2 The impact of gender and training volume (low/high) on autonomic tone during night- and daytime. TP is presented in ms^2, LF and HF power are presented in nu. Data are log-transformed (ln). *Bars* represent one standard error

ischemia (Kim et al. 2012). In highly trained male elite athletes, a conversion from vagal to sympathetic predominance prior to competitions has been observed (Iellamo et al. 2002). In this context, the higher vagal tone of female athletes may protect from malignant arrhythmias, both by an antifibrillatory effect and by mitigating the exercise-induced adrenergic activation.

Clinical implications

Long-distance running has become very popular in middle-aged nonelite athletes and participation rates in half-marathon and marathon events doubled over the last 10 years (Kim et al. 2012). Comparing the years 2000–2004 with 2005–2010, the incidence of cardiac arrest increased in

male athletes more than twofold, from 0.55 to 1.17 per 100,000 athletes, reflecting the participation of less experienced runners. Interestingly, in the same time period, the incidence of cardiac arrest decreased in female athletes from 0.27 to 0.09 per 100,000 athletes (Kim et al. 2012). Animal studies demonstrated that endurance exercise training enhanced cardiac parasympathetic regulation, restored a more normal β-adrenoceptor balance, and protected against ventricular fibrillation induced by acute myocardial ischemia (Billman 2009). Regular physical activity reduced the risk of sudden death and acute myocardial infarction from vigorous exertion in men (Albert et al. 2000; Mittleman et al. 1993), possibly indicating the training-related increase in vagal tone. In our study, we could demonstrate that higher training volumes were associated with a higher vagal tone, both in male and female athletes. Before participating in competitions, a structured and regular exercise training program is essential and should be recommended to all leisure-time athletes.

Study limitations

We performed a cross-sectional observational study and group size was relatively small. Power spectral analysis of HRV is an indirect method to assess autonomic function and does not reflect autonomic tone (Berntson et al. 1997). Especially, LF and HF power as measures of the sympatho-vagal balance are strongly debated in the literature (Eckberg 1997). However, there is evidence that HRV parameters reflect neural cardiovascular regulation at least in certain situations (Pagani et al. 1997), and may be regarded as markers of autonomic modulations (Berntson et al. 1997). Because we performed 24-h recordings, we could not control for respiration which can modulate LF power (DeBeck et al. 2010). Moreover, ambulatory recordings of HRV have a problem with stationarity of heart rate. Slow or irregular trends in the time series can potentially distort analyses and lead to misinterpretation (Berntson et al. 1997). We did not perform polysomnography to control for sleep stages. Active sleep induces rapid and complex fluctuations in autonomic function and may have influenced nighttime autonomic modulations (Murali et al. 2003). Analysis in female athletes was not synchronized with their menstrual cycle. A higher sympathetic activity in the luteal phase has been reported (Yildirir et al. 2002).

Most importantly, it can only be speculated that a higher vagal tone is cardioprotective in humans, since data are derived from experimental studies in animals (Billman 2009; Schwartz et al. 1992). The lower incidence of cardiac arrests in female athletes may also be related to gender differences in cholesterol profile, blood pressure, incidences of underlying cardiovascular diseases, or different exercise intensities during competitions. However, the assumption that a higher vagal tone protects from life-threatening ventricular arrhythmias is plausible and supported by other authors (Billman 2009; Iellamo et al. 2002; Ramaekers et al. 1998; Schwartz et al. 1992).

Conclusions

Female and male athletes showed a different circadian pattern of the training-related increase in vagal tone. For a comparable amount of training volume, female athletes maintained their higher vagal tone, possibly indicating a superior protection against exercise-induced ventricular arrhythmias. This may contribute to their lower risk of sports-related sudden cardiac deaths. Our data support a long-term endurance training program to augment vagal tone prior to participation in competitions, especially for male leisure-time athletes.

Acknowledgments This study was supported by an internal grant of the Inselspital, University Hospital of Bern.

Conflict of interest The authors have no conflicts of interest.

References

Albert CM, Mittleman MA, Chae CU et al (2000) Triggering of sudden death from cardiac causes by vigorous exertion. N Engl J Med 343:1355–1361

Antelmi I, de Paula RS, Shinzato AR et al (2004) Influence of age, gender, body mass index, and functional capacity on heart rate variability in a cohort of subjects without heart disease. Am J Cardiol 93:381–385

Aubert AE, Beckers F, Ramaekers D (2001) Short-term heart rate variability in young athletes. J Cardiol 37(Suppl 1):85–88

Aubert AE, Seps B, Beckers F (2003) Heart rate variability in athletes. Sports Med 33:889–919

Berntson GG, Bigger JT Jr, Eckberg DL et al (1997) Heart rate variability: origins, methods, and interpretive caveats. Psychophysiology 34:623–648

Biffi A, Pelliccia A, Verdile L et al (2002) Long-term clinical significance of frequent and complex ventricular tachyarrhythmias in trained athletes. J Am Coll Cardiol 40:446–452

Billman GE (2009) Cardiac autonomic neural remodeling and susceptibility to sudden cardiac death: effect of endurance exercise training. Am J Physiol Heart Circ Physiol 297:H1171–H1193

Camm J (1996) Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 93:1043–1065

Corrado D, Basso C, Rizzoli G et al (2003) Does sports activity enhance the risk of sudden death in adolescents and young adults? J Am Coll Cardiol 42:1959–1963

De Ferrari GM, Vanoli E, Stramba-Badiale M et al (1991) Vagal reflexes and survival during acute myocardial ischemia in conscious dogs with healed myocardial infarction. Am J Physiol 261:H63–H69

DeBeck LD, Petersen SR, Jones KE, Stickland MK (2010) Heart rate variability and muscle sympathetic nerve activity response to acute stress: the effect of breathing. Am J Physiol Regul Integr Comp Physiol 299:R80–R91

Eckberg DL (1997) Sympathovagal balance: a critical appraisal. Circulation 96:3224–3232

Harmon KG, Asif IM, Klossner D, Drezner JA (2011) Incidence of sudden cardiac death in National Collegiate Athletic Association Athletes. Circulation 123:1594–1600

Harris KM, Henry JT, Rohman E et al (2010) Sudden death during the triathlon. JAMA 303:1255–1257

Hedelin R, Wiklund U, Bjerle P, Henriksson-Larsen K (2000) Pre- and post-season heart rate variability in adolescent cross-country skiers. Scand J Med Sci Sports 10:298–303

Iellamo F, Legramante JM, Pigozzi F et al (2002) Conversion from vagal to sympathetic predominance with strenuous training in high-performance world class athletes. Circulation 105: 2719–2724

Kim JH, Malhotra R, Chiampas G et al (2012) Cardiac arrest during long-distance running races. N Engl J Med 366:130–140

Lang RM, Bierig M, Devereux RB et al (2006) Recommendations for chamber quantification. Eur J Echocardiogr 7:79–108

Marijon E, Tafflet M, Celermajer DS et al (2011) Sports-related sudden death in the general population. Circulation 124:672–681

Maron BJ, Pelliccia A (2006) The heart of trained athletes: cardiac remodeling and the risks of sports, including sudden death. Circulation 114:1633–1644

Maron BJ, Doerer JJ, Haas TS et al (2009) Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980–2006. Circulation 119:1085–1092

Mittleman MA, Maclure M, Tofler GH et al (1993) Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. Determinants of Myocardial Infarction Onset Study Investigators. N Engl J Med 329:1677–1683

Murali NS, Svatikova A, Somers VK (2003) Cardiovascular physiology and sleep. Front Biosci 8:s636–s652

Nagueh SF, Appleton CP, Gillebert TC et al (2009) Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr 10:165–193

Pagani M, Lombardi F, Guzzetti S et al (1986) Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circ Res 59:178–193

Pagani M, Montano N, Porta A et al (1997) Relationship between spectral components of cardiovascular variabilities and direct measures of muscle sympathetic nerve activity in humans. Circulation 95:1441–1448

Rahman F, Pechnik S, Gross D et al (2011) Low frequency power of heart rate variability reflects baroreflex function, not cardiac sympathetic innervation. Clin Auton Res 21:133–141

Ramaekers D, Ector H, Aubert AE et al (1998) Heart rate variability and heart rate in healthy volunteers. Is the female autonomic nervous system cardioprotective? Eur Heart J 19:1334–1341

Redelmeier DA, Greenwald JA (2007) Competing risks of mortality with marathons: retrospective analysis. BMJ 335:1275–1277

Ryan SM, Goldberger AL, Pincus SM et al (1994) Gender- and age-related differences in heart rate dynamics: Are women more complex than men? J Am Coll Cardiol 24:1700–1707

Schwartz PJ, Billman GE, Stone HL (1984) Autonomic mechanisms in ventricular fibrillation induced by myocardial ischemia during exercise in dogs with healed myocardial infarction. An experimental preparation for sudden cardiac death. Circulation 69:790–800

Schwartz PJ, La Rovere MT, Vanoli E (1992) Autonomic nervous system and sudden cardiac death. Experimental basis and clinical observations for post-myocardial infarction risk stratification. Circulation 85:I77–I91

Scott AS, Eberhard A, Ofir D et al (2004) Enhanced cardiac vagal efferent activity does not explain training-induced bradycardia. Auton Neurosci 112:60–68

Stein R, Medeiros CM, Rosito GA et al (2002) Intrinsic sinus and atrioventricular node electrophysiologic adaptations in endurance athletes. J Am Coll Cardiol 39:1033–1038

Tsuji H, Venditti FJ Jr, Manders ES et al (1996) Determinants of heart rate variability. J Am Coll Cardiol 28:1539–1546

Vanoli E, De Ferrari GM, Stramba-Badiale M et al (1991) Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction. Circ Res 68:1471–1481

Wilhelm M, Roten L, Tanner H et al (2011) Gender differences of atrial and ventricular remodeling and autonomic tone in nonelite athletes. Am J Cardiol 108:1489–1495

Yildirir A, Kabakci G, Akgul E et al (2002) Effects of menstrual cycle on cardiac autonomic innervation as assessed by heart rate variability. Ann Noninvasive Electrocardiol 7:60–63