Sex-related differences in left ventricular structure in early adolescent non-professional athletes

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Abstract:	Background: Professional athletes exhibit lower left ventricular (LV) wall thicknesses, diameters and mass (in females), with less frequent training-related ECG changes, as compared with controls. Methods: We studied the association of sex with LV structure in trained early adolescents. 206 adolescent Caucasian athletes (mean age 13.8+1.6, range 11.8-16.9 years), 158 males (M) and 48 females (F), with similar degree of training underwent ECG and echocardiographic measurements of LV diameters, thicknesses, and mass (LVM), with relative wall thickness (RWT) as the remodelling index. Results: As compared with F, M exhibited greater maximal wall thickness (MWT: M=8.7+1.2 vs F=7.9+0.8) and indexed LVM (100±18 gr/m2 vs. 79±12, $p<0.001$), without differences in RWT (M=0.35+0.04 vs. F=0.34+0.04) and with higher prevalence of ECG-based LV hypertrophy (LVH), sinus bradycardia, and ST-elevation. An ANCOVA analysis, using age, body surface area, systolic blood pressure, heart rate and sex as the covariates, reported that sex is a strong predictor of LVM, MWT, LV

	diastolic diameter, and ECG-based LVH. In a binary logistic regression model analysis sex, like LVM, predicted ST-trait elevation. Conclusions: Our results suggest that, in early adolescence, female athletes have lower LVM and thicknesses compared with males, without geometrical differences. Therefore, sex, independent of age, is a strong determinant of structural parameters also in early adolescent athletes. These data indicate that sex- specific parameters are needed in the pre-participation cardiovascular screening of adolescent athletes.

RE: EJPC-D-15-00344, entitled "Sex-related differences in left ventricular structure in early adolescent non-professional athletes"

Dear Prof. Pela',

The reviewers have returned their comments on your manuscript and have found a few areas where they believe the manuscript can be improved. Please find their comments listed below. We anticipate that you will easily be able to answer the points raised by the reviewers.

If you are willing to revise the manuscript, please include with your revised submission an itemized, point-by-point response to the comments of the reviewers.

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With kind regards,

Rosemary Allpress
Managing Editor
European Journal of Preventive Cardiology

September 4th, 2015

Rosemary Allpress

Managing Editor

European Journal of Preventive Cardiology

Dear Managing Editor,

Many thanks for your rapid and thorough evaluation of our manuscript. The revised paper (revisions in red) include two citations to papers recently published in EJPC. As indicated in the specific responses to the reviewers, we added more detailed information about the sport disciplines in which subjects were engaged. We know that soccer and volleyball should be computed together, but soccer is the most popular sport in Italy. Yet, it is unusual for girls do practice this type of sport activity.

Unfortunately, we were unable to provide data about actual conditioning because athletes did not perform cardiopulmonary exercise tests when we screened them. This is a consequence of the observational nature of the study, which was designed and performed in athletes referred to our Sport Medicine Service and Laboratory of Clinical Physiology for pre-participation screening, which is specifically required in Italy at any level of competitive sport activity, regardless of age.

Once again, thank you for your kind assistance, we look forward to hearing from you soon.

Sincerely Yours

Prof. Giovanna Pelà

RE: EJPC-D-15-00344, entitled "Sex-related differences in left ventricular structure in early adolescent non-professional athletes"

Reviewer Comments:

Reviewer #1:

The potentially interesting and important manuscript describes differences in left ventricular structure between male and female caucasian adolescent athletes. More than 150 male and around 50 female athletes with a mean age of 13.8 years were investigated for a set of cardiovascular parameters. The major finding of the study is the difference of LVM including lower LV thicknesses and diameters between male and female without alteration of the ventricular structure. It is concluded from the data that sex becomes a strong determinant of structural and functional parameters of athletes' heart from the early adolescence and sex- and age- specific parameters are needed to discriminate in the guidelines for pre participation cardiovascular screening evaluation. The study is well done from cardiovascular screening side but has substantial limitation for the documentation of training-/sport-level and aerobic fitness. These limitations reduce the potential impact of study.

Specific comments:

1. More detailed information should be given for the sport load. It seems from distinct importance for the interpretation of the data to give not only the time per week of training. It is important to know more about the intensity of the training load.

Response: Unfortunately, detailed quantification of physical activity, training levels, and performance was not feasible in our observational study in amateur-level athletes, who greatly differ from elite, professional athletes precisely because of the lack of such measurements during their routine training. Nonetheless, the detailed, questionnaire-based survey of training - which is being often employed - reliably estimates the exercise load in amateur athletes. See Methods, page 7, lines 114 to 115 (see ref 14) .

2. It would also be interesting to compare the training time per week with the LVM and the other parameter of the left ventricular structure.

Response: Training time was not significantly related with LVM and other parameters (data not shown). It should be noted that this parameter had low variability because the training programs are quite similar in adolescents regardless the type of sport in males and females.

3. Specific and detailed information about the sport disciplines should be given.

Response: Good point. Information about sport disciplines is now added to the Methods section (page 7, lines 107 to 113).

4. It would be preferable to have also data of the aerobic capacity of the young athletes

Response: We agree, but, unfortunately, we are unable to provide data about actual conditioning because athletes did not perform cardiopulmonary exercise tests. This is a consequence of the observational nature of the study, which was designed and performed in athletes referred to our Sport Medicine Service and Laboratory of Clinical Physiology for pre-participation screening, which is specifically required in Italy at any level of competitive sport activity, regardless of age.

Reviewer #2:

In the paper of Pelà et al. 206 adolescent Caucasian athletes (158 males -M and 48 females -F), with similar degree of training underwent ECG and echocardiographic measurements of LV diameters, thicknesses, and mass (LVM), with relative wall thickness (RWT) as the remodelling index.
Authors found that M exhibited greater maximal wall thickness, indexed LVM, without differences in RWT and with higher prevalence of ECG-based LV hypertrophy (LVH), sinus bradycardia, and ST-elevation. At ANCOVA analysis, using age, body surface area, systolic blood pressure, heart rate and sex as the covariates, sex resulted a strong predictor of LVM, MWT, LV diastolic diameter, and ECG-based LVH. In a binary logistic regression model analysis sex, like LVM, predicted ST-trait elevation. I believe that the paper is well written and study results clearly explained. Moreover, the specific focus on early adolescence, may add relevant information to previous studies performed in later ages.

My only concern, as reported by authors in the study limitation, is that males and females recruited in this cohort, practice different sports (soccer and volleyball), which cannot be considered the same.
Response: Indeed, soccer and volleyball should not be computed together, but soccer is the most popular sport in Italy, yet girls rarely engage in this type of sport activity.

Furthermore, we only know the average time of training but no information was given about the actual conditioning. It would have been of interest to have had a cardiopulmonary exercise test to correct for this relevant factor. This is particularly important as no control group of sedentary adolescent is incorporated in the analysis.
Response: This was also of concern to Referee 1. We agree, but, unfortunately, we are unable to provide data about actual conditioning because athletes did not perform cardiopulmonary exercise tests. This is a consequence of the observational nature of the study, which was designed and performed in athletes referred to our Sport Medicine Service and Laboratory of Clinical Physiology for pre-participation screening, which is specifically required in Italy at any level of competitive sport activity, regardless of age.

In addition, I do believe that a plasma sampling of sexual hormones would have been of interest.
Response: This is a good point. However, blood collection and cardiopulmonary exercise test are not routinely included during the screenings for fitness and we cannot provide such data. We will incorporate these measurements/tests in future investigations.

I would finally suggest to check for multicollinearity at ANCOVA analysis.
Response: All of the variables included as predictors in the models had R values (Pearson's correlation test) below 0.5. Furthermore, multicollinearity was tested in a multiple regression model, which gives mathematically the same significances of ANCOVA, looking at the VIF (Variance Inflation Factor) values, always below 2. A cut-off value of 10 is usually considered to assess multicollinearity. (*Kutner M.H.,Nachtsheim C.J., Neter J., 2004. Applied Linear regression models, 4th ed., McGraw-Hill)*.

We now expand on this in the Methods section (see page 10, lines 162 to 164).

Sex-related differences in left ventricular structure in early adolescent non-professional athletes

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Abstract

Background: Professional athletes exhibit lower left ventricular (LV) wall thicknesses, diameters and mass (in females), with less frequent training-related ECG changes, as compared with controls.

Methods: We studied the association of sex with LV structure in trained early adolescents. 206 adolescent Caucasian athletes (mean age 13.8±1.6, range 11.8-16.9 years), 158 males (M) and 48 females (F), with similar degree of training underwent ECG and echocardiographic measurements of LV diameters, thicknesses, and mass (LVM), with relative wall thickness (RWT) as the remodelling index.

Results: As compared with F, M exhibited greater maximal wall thickness (MWT: M=8.7±1.2 vs F=7.9±0.8) and indexed LVM (100±18 gr/m^2 vs. 79±12, $p<0.001$), without differences in RWT (M=0.35±0.04 vs. F=0.34±0.04) and with higher prevalence of ECG-based LV hypertrophy (LVH), sinus bradycardia, and ST-elevation. An ANCOVA analysis, using age, body surface area, systolic blood pressure, heart rate and sex as the covariates, reported that sex is a strong predictor of LVM, MWT, LV diastolic diameter, and ECG-based LVH. In a binary logistic regression model analysis sex, like LVM, predicted ST-trait elevation.

Conclusions: Our results suggest that, in early adolescence, female athletes have lower LVM and thicknesses compared with males, without geometrical differences. Therefore, sex, independent of age, is a strong determinant of structural parameters also in early adolescent athletes. These data indicate that sex- specific parameters are needed in the pre-participation cardiovascular screening of adolescent athletes.

Key words: athlete’s heart; echocardiography; left ventricular mass; left ventricular geometry; pre-participation screening process.

Introduction

Regular physical training induces structural and electrical cardiac changes, such as left ventricular (LV) hypertrophy and low heart rate, resulting in the so-called "athlete's heart". [1-3]

Such changes are thought not only to depend on the type and intensity of exercise, but also to be influenced by other factors such as age, ethnicity, and sex. [4,5] However, even though the characteristics of cardiac remodelling have been extensively studied in male athletes of different sport disciplines [2], scant data are available on the prevalence of athlete's heart in females vs. males. Pelliccia et al. [6,7] first demonstrated - in a population of mostly adult professional athletes - lower LV thicknesses, diameters, and mass in females, with less frequent training-related ECG changes. [8] In contrast to male athletes, female maximal wall thickness (MWT) never exceeded the upper normal value of 12 mm, consistent with the notion of no overlapping of LV thicknesses with the pathological range compatible with hypertrophic cardiomyopathy (HCM). [6,7,9-11]

Even fewer studies have been performed to assess sex-related differences in cardiac remodelling in adolescent athletes. Sharma et al. [12] studied a group of 16-years-old trained persons and suggested that sex itself may be an independent determinant of LV adaptation to regular exercise in adolescence, because of lower LV thicknesses and mass in girls vs. boys. Age is a critical determinant of LV diameters, thicknesses, and mass (LVM), which increase from birth to adolescence and youth in both sexes, independent of sport activity. [13] In addition, wide between-sex physiological LV structural differences develop in the early adolescence, along with sexual maturation. Within the 12-to-14 years age interval, LVM - only marginally different between boys and girls in the childhood - becomes much greater in males, showing an age-related progressively greater increase which reaches 30% vs. females at the age of 16. [13]

In short, the appearance of *between-sex* differences in LV parameters in adolescent athletes may not only reflect, as generally thought [12], sex-related different responses of LV to training, but also the physiological age-dependent divergence in LV parameters in the early adolescence. Furthermore, in the 12-to-14 years age interval, sex-related differences in body size are much less pronounced than in 16-years-old people, thus limiting the specific influence of anthropometric characteristics on LV.[13] It may be thus of interest to study LV parameters in adolescent athletes of both sexes within their trans-pubertal age. For this purpose, we investigated ECG- and ECHO-findings in 206 adolescent female (F) and male (M) amateur-level endurance athletes, practising sports in local, non-professional tournaments. Of note, their age averaged 13.8±1.6 years (range 11.8-to-16.9), which is approximately 2-years earlier than that of participants in the only previous study in adolescent athletes of both sexes. [12]

Our aims were 1): to determine whether and to what extent between-sex differences in LV thicknesses and mass already were detectable in amateur-level athletes within the early, trans-pubertal phase of adolescence; 2): to contribute defining age- and sex-specific cardiac parameters at the pre-participation cardiovascular screening of adolescents, in an effort to differentiate athlete's heart from structural cardiac diseases such HCM, which may cause sudden death in the youth. [9]

Methods

Participants

This study was approved by the Medical Ethical Committee of Parma. Written informed consent was obtained from the parents of athletes.

Between 2006 and March 2014, we consecutively selected 206 Caucasian amateur level adolescent athletes (158 M and 48 F) from within the adolescent athletes referred to the sport pre-participation screening in the Parma AUSL Sport Medicine Service and Laboratory of Clinical Physiology (Parma, Italy). Screening criteria were: age lower than 17 years (range 11.8-16.9 years; average 13.8 ± 1.6 SD), Caucasian ethnicity, absence of symptoms, structurally normal heart, and blood pressure (BP) within the normal range. All participants competed in local, amateur-level leagues of different endurance disciplines. Soccer was by far most prevalent sport activity in M (102/158, 65% total), who also participated in other disciplines including basketball (n=13), athletics (n=9), judo (n=3), rugby (n=7), baseball (n=3), handball (n=2), volleyball (4), cycling (n=4), karate (n=2), tennis (n=3), triathlon (n=2), fencing (n=1), and water polo (n=3). Girls predominantly played volleyball (n=21), but also gymnastics (n=4), athletics (n=6), soccer (n=2), basketball (n=5), swimming (n= 2), softball (n=4), judo (n=1), rugby (n=1), kick boxing (n=1), and skating (n=1).

A 9-item Physical Activity Questionnaire for Adolescents (PAQ-A) was used to assess the type, intensity, and duration of sport activity. [14] All evaluations were performed during periods of intensive training, with physical examinations and 12-lead resting ECG and 2-D ECHO. BP was assessed on two occasions, with three consecutive measurements (OMRON 705 IT).

ECG

Twelve-lead, 25 mm/second, supine-position ECGs were interpreted [15] by three investigators (GP, ML, AC) blinded to the type of subject. Heart rate (HR), QRS-axis, PR-interval, QRS-duration, and corrected QT-interval were measured. S1+R5 in precordial leads were calculated using the Sokolow-Lyon voltage criteria (positive if ≥ 35mm) to define the presence of LV hypertrophy (LVH). Prevalence of Q-waves (≥ 2mm in depth in ≥ 2 adjacent leads), presence and shape (concave or domed) of ST-segment elevation (≥ 1mm in ≥2 adjacent leads), prevalence of inverted T-waves (≥ 2 mm in depth in ≥ 2 adjacent leads, excluding aVR and III), were also assessed.

Transthoracic ECHO

M-mode, two-dimensional, and Doppler ECHO were performed by one ultrasonography-experienced cardiologist (GP), using commercially available, multi-hertz sector, 2-4 MHz probe-equipped machines (Aspen, Siemens Acuson, Mountain View, California, USA; Vivid S5, GE Healthcare, USA). With the subject set in the left lateral position, images based on three consecutive heart cycles were obtained from standard projections.

Interventricular septal (SWT) and posterior wall (PWT) thicknesses were measured at the parasternal long-axis view according to the Penn convention and the greatest measure was considered as the maximal wall thickness (MWT), with systolic (ESD) and diastolic (EDD) LV diameters measured in the same projection. [16,17] RWT was calculated as: (SWT+ PWT)/ EDD, using the 0.42 cut-off to define eccentric (≤0.42) or concentric (≥0.42) remodelling. [18] Penn convention-based LVM also was normalized - when necessary - to body surface area (BSA) or to $height^{2.7}$, an estimate of lean body mass (LBM). [18,19] Simpson’s biplane rule-based end-diastolic and systolic LV volumes and ejection fraction (EF) were calculated, while Fractional Shortening (FS) was: [(EDD – ESD)/EDD] x 100. Blood flow across the mitral valve was monitored using the pulsed-Doppler technique in the apical four-chamber view, with the sample volume placed at the tip of the valve. The blood flow profile contains diastolic E and A waves and peak flow velocity and its time-integral were measured for each wave. The intra-observer percent variability for MWT was < 3.5 as previously reported. [20]

Statistical analyses

Data are expressed as means ± SD after testing for normality (Kolmogoroff-Smirnoff) and sex as univariate factor was assessed by means of two-tailed Student's *t* test (SPSS 20.0 software package, IBM, Armonk, New York, USA), χ-square, or Fisher F-test, when appropriate. ANCOVA, calculating also marginal means, was used to analyze sex differences in ECHO-based variables (LVM, MWT, EDD) and ECG-based LVH using age, HR, BSA, and systolic BP as covariates. Dichotomous ECG variable such as ST elevation and inverted T wave were analysed with a binary logistic regression model including as covariates sex, age, HR, BSA, systolic BP, LVM and EDD. Multicollinearity among predictors was excluded from all multivariate models (correlation coefficients between couples of variables were always < 0.5 and VIF – Variance Inflation Factor <2).

A 2-tailed p value < 0.05 was considered as significant.

Results

All athletes engaged in organized, sport-specific training for approximately 2.5 hours twice a week and participated (usually during weekends) in one amateur-level local competition. Total sport load was approximately eight hours/week in both groups. M and F had similar age and body mass index (BMI), but height, weight and BSA were higher in M than in F (Table 1).

Systolic and diastolic BP were significantly lower, but HR was higher in F compared with M (Table 1).

ECG Findings

The prevalence of LVH and high S1+R5 voltages was greater in M, as were those of ST-elevation and sinus bradycardia, with similar PR and QRS duration; QRS-axis; QT-interval; prevalence of enlarged left atrium; and inverted T-waves in the two groups (Table 2). Pathological Q-waves were not observed in any athlete. The ANCOVA analysis revealed that S1+R5 voltage-based LVH was strongly and independently predicted by sex only ($p<0.01$). In the binary logistic regression model analysis, sex and LVM significantly predicted ST-trait elevation ($p<0.05$ for both), without any effects of others physiological variables. Negative T wave was only determined by age ($p<0.01$).

Left Ventricular Dimensions and Geometry

M exhibited greater SWT, PWT, MWT, and LVM compared with F (Table 3). Normalization of LVM for BSA, weight, height, or LBM did not abolish the differences we observed between sexes.

LV cavity size, as assessed by diameters and volumes, was lower in F compared to M whilst the two groups did not differ for their geometry, as evaluated by RWT (Table 3).

Figure 1 shows that frequency distribution of LVM (A), MWT (B), and EDD (C) was distinctly right-shifted for M, with the upper limit for MWT that never exceeded 10 mm in F (range 6.1 to 9.6 mm) and 13 in M (range 6.5 to 12.3 mm).

Systolic function, as assessed by FS and EF, was slightly higher (FS: 40±6 % vs 38± 5, p=ns; EF: 68±6 % vs 67±6, p=0.07) and stroke volume was significantly lower (60±12 ml vs. 72±17, $p<0.001$) in F compared with M, without differences in diastolic function (data not shown).

The ANCOVA-analysed association of LVM, indexed LVM, MWT, and EDD (the dependent variables) with age, BSA, systolic BP, HR, and sex (the independent variables) showed that sex is a strong independent predictor of all structural ECHO-parameters (for all $p<0.001$) with similar effects of BSA. Systolic BP was significantly related to MWT and indexed values of LVM (for all $p<0.05$), with HR being a predictor of absolute and indexed LVM (for both $p<0.01$) and MWT ($p<0.05$) without any predicting correlation computed for EDD.

Discussion

The foremost result of the present study is that adolescent male athletes have significantly greater LV mass, thicknesses, and cavity size compared with age-matched female athletes with comparable degree of training. LV structure is, hence, very different according to the sex also in adolescent athletes, similar to adult elite athletes [6,7]. This is consistent with the significantly lower (in females vs males) EDD, MWT, and LVM found in a large group of adolescent athletes by Sharma et al. [12], who first indicated sex as an important determinant of LV adaptation to exercise in the adolescence. However, participants in the present study (aged 13.8 ± 1.6 years) were substantially younger than those of Sharma et al. [12] (the age of whom averaged 16 years); thus, our data indicate that sex-related differences in LV structure can be detected even in early adolescence. The approximately two-year age difference vs. the study of Sharma et al. [12] may be important, because population studies[13] indicate that the age-related physiological LVM growth curves, which can be superimposed before puberty, diverge from the 12-to-14 years interval. Indeed, markedly greater LVM growth in males, start to be seen close to pubertal development. Sexual characterization, mostly triggered by the increase of testosterone in boys vs. oestrogens in girls, is indeed thought to exert differential growth effects on the myocardium, stimulating a greater increase in the size of myocytes in males, in turn contributing to the appearance - in the trans-pubertal age - of sex-related differences in cardiac structures. [21]

Sex-dependent phenotype maturation is similar in both sexes as shown by large increases in height, weight, BSA, and LBM; however, such changes are much more pronounced in males than in females.[13] Because body size is a strong physiological-, sex-, and age-independent determinant of LV structure[13,22], the marked anthropometric differences between the sex subgroups recorded in our study could partially explain the greater LVM observed in males. However, as the 24% greater absolute LVM in males vs females was essentially maintained after normalizing LVM for any anthropometric variable, sex *per se* appears to be an independent strong predictor of LVM in the trans-pubertal phases of adolescence, as also indicated by the ANCOVA analysis.

In addition to the physiological training-independent, age-related, between-sex divergence in cardiac growth curves, the higher LVM of male trans-pubertal athletes could reflect the contribution of other factors, namely sex-related different heart responses of LV to physical activity training. [4,5] However, because female and male sedentary control groups were not tested in the present investigation and in previous echocardiographic studies in adult or adolescent athletes [6,7,12], this issue remains unresolved. Yet, a recent MR study in adult athletes reported similar LV hypertrophic changes to training in females vs. males, consistent with the lack of any sex-specific LVM response to exercise. [23]

Other factors potentially involved in LV remodeling in athletes were different between the males and females of our cohort, including a slightly higher BP and a lower HR seen in males. Both parameters were predictive of LVM (according to the ANCOVA analysis), although to a much lesser extent when compared with sex and body size. A lower HR in athletes is generally thought to reflect a higher training intensity[24], which could also have been facilitated in the male subgroup as suggested by the markedly greater LBM. In brief, some differences in the level of physical activity might have played some roles in cardiac remodeling. Hemodynamic loads could also have affected LVM in adolescent male athletes, similar to what has been previously observed in adult athletes[25,26] and as indicated by the association of LVM with systolic BP. However, the association of systolic BP and HR with LVM were much weaker than those of sex and body size, consistent with the hypothesis that cardiac workloads strongly influence LVM variability in the adulthood but not in the adolescence. [22]

Similar to LVM, LV diameters and thicknesses were greater in the male subgroup, with sex and body size strongly and independently predicting EDD and MWT. Conversely, EDD and MWT were poorly predicted by systolic BP and HR. MWT has been proposed as a diagnostic tool in adolescent and adult athletes undergoing pre-participation screening, to discriminate between training-related LV thickening and pathological LVH and to contribute preventing the HCM-related sudden death in athletes. As showed in Figure 1, the frequency distribution of MWT was right-shifted in males, with upper limits not exceeding 13 mm in males and 10 mm in females, which were significantly lower than those reported by Sharma et al. [12] in 16- years old athletes (11 mm in females vs 14 mm in males). Our data are consistent with the sex-related difference in the age-dependent LV growth curve and also indicate the need of sex-specific MWT-based criteria to improve the pre-participation assessment of early adolescent athletes.

RWT-based LV geometry study did not show between-sex differences, consistent with similar growth-related increases in LV chamber dimensions and wall thicknesses in both sexes. Furthermore, RWT was 0.35 in males and 0.34 in females, similar to that we found in white, male early adolescent athletes.[20] RWT in male black counterparts was 0.44, consistent with a concentric remodeling pattern linked to African ethnicity, as opposed to a sex-independent, eccentric-type LV remodeling in Caucasian people.[20] An even more pronounced eccentric LV remodelling in Japanese football players suggests a varied spectrum of LV remodelling patterns across various ethnicities. [27]

Concerning the exercise-related ECG changes, increased S1+R5 voltages and prevalence of ST elevation, sinus bradycardia, and positive LVH criteria were less frequent in females, with sex strongly and independently predicting ECG-based LVH and ST-trait elevation, which also was related to the ECHO-based LVM. Therefore, sex is a determinant not only of structural, but also of electrical LV remodeling in early adolescent athletes.

Prevalence of “juvenile” inverted T waves was low in our study group and only related to age, in agreement with their tapering down in the pubertal age. [28]

Limitations

The main limitation of our study is the small proportion (23 vs 77%) of female athletes in the cohort. This proportion reflects the tipically lower participation of girls vs boys in competitions. Indeed, fewer (25 vs 75 %) adolescent female than male athletes usually undergo clinical examinations at the Parma AUSL Sport Medicine Service. This is comparable with the study of Sharma et al.[12]. However, all ECHO measurements were performed by one single experienced cardiologist, thus minimizing variability.

We did not perform cardiopulmonary test; therefore, we cannot exclude different levels of training in the two groups. We also must take into account that the type of sport such as soccer (more prevalent in male) and volley (more popular among females) might differentially affect LV remodelling in the two groups.

Conclusion

In conclusion, our results confirm that, in the early phase of adolescence, between-sex differences in LV structure are already detectable in amateur-level Caucasian athletes, with lower LV thicknesses, mass, and diameters (but not geometry) in female than male athletes. Exercise-related ECG abnormalities also are less prevalent in females. In short, sex becomes a strong determinant of structural and functional parameters of athletes' heart from the early adolescence. Finally, we suggest that sex- and age- specific parameters and guidelines are needed to discriminate physiological and HCM-related pathologic hypertrophy in the pre-participation cardiovascular screening evaluation of non-professional early adolescent athletes.

Conflict of interest

The authors declare that there is not conflict of interest.

References

1. Maron BJ. Structural features of the athlete heart as defined by echocardiography. *J Am Coll Cardiol* 1986; 7: 190-203.
2. Pluim BM, Zwinderman AH, Van der Laarse A, et al. The Athlete's Heart. A Meta-analysis of cardiac structure and function. *Circulation* 2000;101: 336-344.
3. Weiner RB, Baggish AL. Exercise-Induced cardiac remodeling. *Prog Cardiovasc Dis* 2012;54:380–386.
4. Sharma S. Athlete's heart – effect of age, sex, ethnicity and sporting discipline. *Exp Physiol* 2003;88:665-669.
5. Di Paolo FM, Pelliccia A. The "athlete's heart": relation to gender and race. *Cardiol Clin* 2007;25:383-389.
6. Pelliccia A, Maron BJ, Culasso F, et al. Athlete's heart in women. Echocardiographic characterization of highly trained elite female atletes. *Jama* 1996;76:211-215.
7. Pelliccia A, Di Paolo FM. Cardiac remodeling in women athletes and implications for cardiovascular screening. *Med Sci Sports Exerc* 2005;37:1436-1439.

8. Pelliccia A, Maron BJ, Culasso F, et al. Clinical significance of abnormal electrocardiographic patterns in trained athletes. *Circulation* 2000;102:278-396.

9. Maron BJ. Distinguishing hypertrophic cardiomyopathy from athlete's heart physiological remodelling: clinical significance, diagnostic strategies and implications for preparticipation screening. *Br J Sports Med* 2009; 43:649-656.

10. Pelliccia A, Maron BJ, Spataro A, et al. The upper limit of physiologic cardiac hypertrophy in highly trained elite athletes. *N Eng J Med* 1991;324:295-301.

11. Pelliccia A, Maron Ms, Maron BJ. Assessment of left ventricular hypertrophy in a trained athlete: differential diagnosis of physiologic athlete’s heart from pathologic hypertrophy. *Prog Cardiovasc Dis* 2012;54:387-396.

12. Sharma S, Maron BJ, Whyte G, et al. Physiologic limits of left ventricular hypertrophy in elite junior athletes: relevance to differential diagnosis of athlete's heart and hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002;40:1431-1436.

13. De Simone G, Devereux R, Daniels SR, et al. Gender differences in left ventricular Growth. *Hypertension* 1995; 26:979-983.

14. Booth ML, Okely AD, Chey T, et al. The reliability and validity of the Adolescent Physical Activity Recall Questionnaire. *Med Sci Sports Exerc* 2002; 34; 1986–199.

15. Corrado D, Pelliccia A, Heidbuchel H, et al. Recommendations for interpretation of 12-lead electrocardiogram in the athlete. *Eur Heart J* 2010; 31: 243-259.

16. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man: anatomic validation of the method. *Circulation* 1977;55: 613-618.

17. Pelà G, Bruschi G, Montagna L, et al. Left and right ventricular adaptation assessed by Doppler tissue echocardiography in athletes. *J Am Soc Echocardiogr* 2004; 17: 205-211.

18. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. *Eur J Echo* 2006;7:79-108.

19. Pressler A, Haller B, Scherr J, et al. Association of body composition and left ventricular dimensions in elite athletes. *Eur J Prev Cardiol* 2012;19:1194-1204.

20. Pelà G, Li Calzi M , Crocamo A, et al. Ethnicity related variations of left ventricular remodelling in adolescent amateur football players. *Scand J Med Sci Sports* 2015;25:382-389.

21. Janz KF, Dawson JD, Mahoney LT. Predicting heart growth during puberty: the Muscatine Study. *Pediatrics* 2000;105:1-8.

22. De Simone G, Devereux R, Kimball TR, et al. Interaction between body size and cardiac workload. Influence on left ventricular mass during body growth and adulthood. *Hypertension* 1998; 31:1077-1082.

23. Petersen SE, Hudsmith LE, Doll A, et al. Sex-Specific Characteristics of Cardiac Function,Geometry, and Mass in Young Adult Elite Athletes. *Journal of Magnetic Resonance Imaging* 2006;24:297–303.

24. Boyett MR, D'Souza A, Zhang H, et al. Viewpoint: Is the resting bradycardia in athletes the result of remodelling of sinoatrial node rather than high vagal tone? *J Appl Physiol* 2013;114:1351-1355.

25. Wilhelm M, Roten L, Tanner H, et al. Gender differences of atrial and ventricular remodeling and autonomic tone in Nonelites Athletes . *Am J Cardiol* 2011;108: 1489-1495.

26. Furholz M, Radtke T, Roten L, et al. Training-related modulations of the autonomic nervous system in endurance athletes: is female gender cardioprotective? *Eur J Appl Physiol* 2013; 113:631–640.

27. Kervio G, Pelliccia A, Nagashima J, et al. Alterations in echocardiographic and electrocardiographic features in Japanese professional soccer players:

comparison to African-Caucasian ethnicities. *Eur J Prev Cardiol* 2013;20:880-888.

28. Migliore F, Zorzi A, Michieli P, et al. Prevalence of cardiomyopathy in Italian asymmptomatic children with electrocardiographic T-wave inversion at preparticipation screening. *Circulation* 2012;125:529-538.

Figure Legend

Figure 1. Percent distribution of left ventricular mass index (LVM/BSA) (A), maximal wall thickness (MWT) (B), and left ventricular end diastolic diameter (LVEDD) (C) in adolescent male (black bars) and female (white bars), amateur-level athletes. The upper limit for MWT was 12.3 for males and 9.6 for females. None exceed the upper limit of 13 mm.

Table 1

Table 1. Anthropometry and clinical data in female and male adolescent amateur-level athletes

Parameter	**Males (=158)**	**Females (n=48)**	**p value**
Age (years)	13.8 ± 1.6	13.7 ± 1.4	ns
Height (cm)	1.67 ± 0.11	1.61 ± 0.07	<0.01
Weight (kg)	60 ± 13	52 ± 9	<0.05
BMI (kg/m^2)	20.2 ± 3.0	19.7 ± 2.4	ns
BSA (m^2)	1.62 ± 0.24	1.54 ± 0.15	<0.05
SBP (mmHg)	117 ± 11	112 ± 10	<0.01
DBP (mmHg)	70 ± 7	67 ± 7	< 0.05
HR (beats-per-minute)	71 ± 11	76 ± 11	< 0.01

Data are expressed as mean values ± standard deviation. BMI, Body mass index; BSA, Body surface area; DBP, Diastolic blood pressure; HR, Heart rate; SBP, Systolic blood pressure; F, female athletes; M, male athletes

Table 2

Table 2. ECG findings in female and male adolescent amateur-level athletes

Parameters	**Males**	**Females**	**p value**
PR interval (ms)	139 ± 23	134 ± 22	NS
QRS complex duration (ms)	83 ± 16	80 ± 12	NS
QT_c interval (ms)	403 ± 36	404 ± 28	NS
QRS axis (°)	64 ± 30	69 ± 26	NS
S_1+R_5 wave voltages (mm)	30 ± 11	22 ± 6	< 0.001
Synus Bradicardia	18 % (26/146)	0 % (0/42)	<0.01
Left Ventricular Hypertrophy (Sokolow-Lyon criteria)	38 % (56/146)	2 % (1/42)	< 0.001
Partial right bundle branch block	38 % (56/146)	33 % (14/42)	NS
ST segment elevation	47 % (69/146)	10 % (4/42)	< 0.001
Inverted T waves	14 % (20/146)	10 % (4/42)	NS
Left Atrial enlargement	3 % (5/146)	10 % (4/42)	NS

Data are expressed as mean values ± standard deviation. Synus bradycardia, heart rate < 60 b.p.m.; F, female; M, male.

Table 3

Table 3. ECHO-based left ventricular morphology in female and male adolescent amateur-level athletes: sex-related differences.

Parameters	**Males**	**Females**	**p value**
End-diastolic diameter (mm)	47 ± 4	44 ± 3	< 0.001
End-systolic diameter (mm)	29± 4	27 ± 4	< 0.001
End-diastolic volume (ml)	109 ± 25	89 ± 17	< 0.001
End-systolic volume (ml)	37 ± 12	28± 8	< 0.001
Septal thickness (mm)	8.4 ± 1.2	7.6 ± 0.9	< 0.001
Posterior wall thickness (mm)	8.1 ± 1.2	7.2 ± 0.9	< 0.001
Maximal wall thickness (mm)	8.7 ± 1.2	7.9 ± 0.8	< 0.001
RWT	0.35 ± 0.04	0.34 ± 0.04	ns
Absolute LVM (g)	163 ± 43	122 ± 25	< 0.001
LVM/BSA (g/m^2)	100 ± 18	79 ± 12	< 0.001
LVM/W	2.9±0.5	2.4±0.4	< 0.001
LVM/h	97±22	75±13	< 0.001
LVM/LBM ($g/h^{2.7}$)	40±8	33±5	<0.001

Data are expressed as mean values ± standard deviation.
F, female athletes; h, height; LVM, absolute left ventricle mass; LVM/BSA, indexed LVM for body surface area; LVM/LBM, indexed LVM for lean body mass; RWT, relative wall thickness; M, male athletes; W, weight.

Figure 1

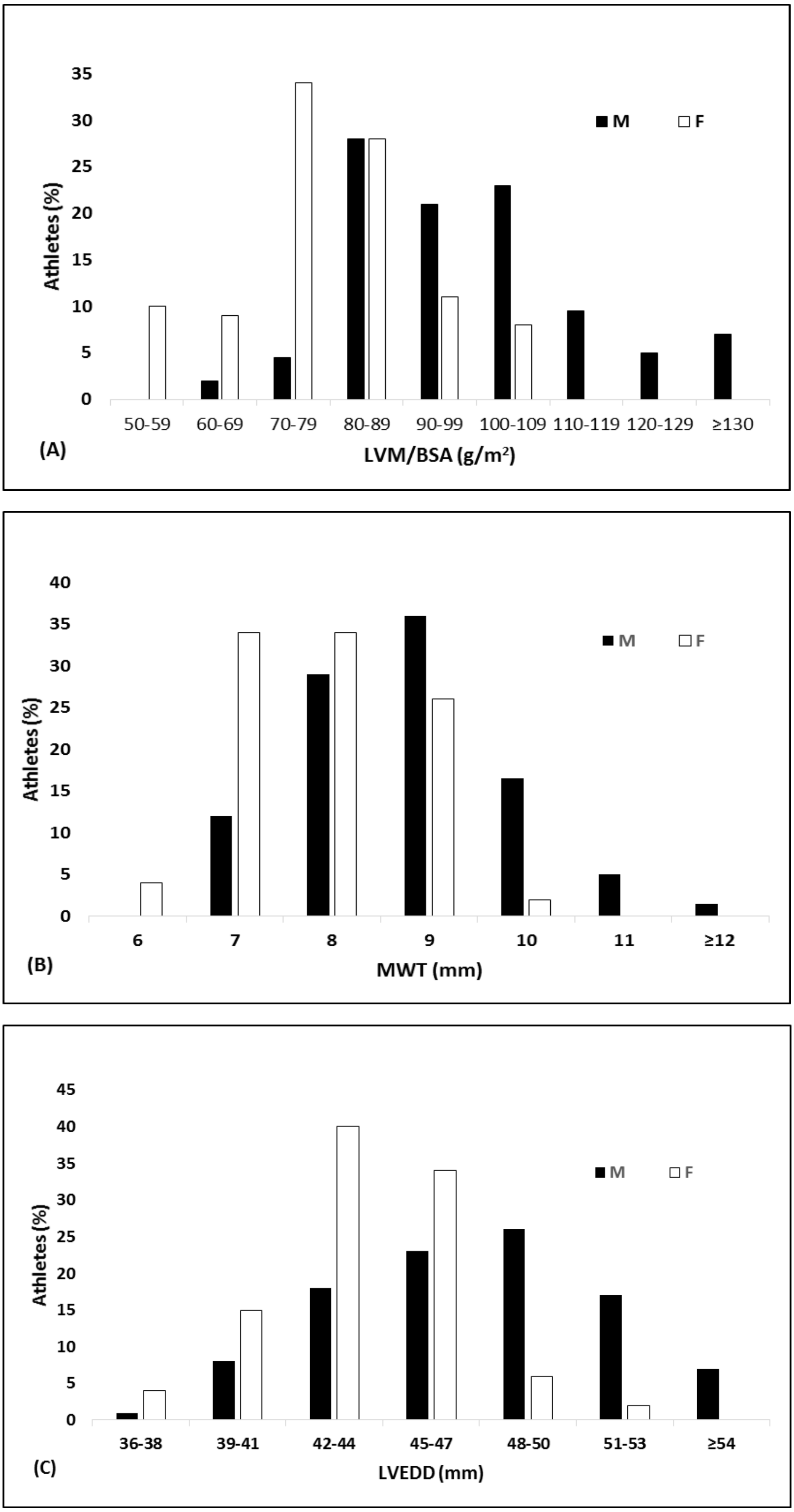

Figure I. The distribution of Left Ventricular Mass Index (LVM/BSA) (A), Maximal Wall Thickness (MWT) (B), and Left Ventricular End Diastolic Diameter (LVEDD) (C) in Males (M) (black bars) and Females (F) (white bars) athletes.

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