Hemodynamic and ECG responses to stress test in early adolescent athletes explain ethnicity-related cardiac differences

Manuscript Details

Manuscript number	IJC_2019_166_R1
Title	Hemodynamic and ECG responses to stress test in early adolescent athletes explain ethnicity-related cardiac differences
Article type	Original article

Abstract

Background: Ethnicity is an important determinant of athletes' cardiovascular adaptation. Black adolescent and adult athletes exhibit a left ventricular (LV) hypertrophy with a concentric remodelling higher than their Caucasian counterparts. Scant data, however, are available on race-related differences in hemodynamic response of adolescent athletes to exercise and its relation with heart remodelling. We evaluated if race-specific, sport-related structural and electrical remodelling in adolescent athletes of Caucasian and African ethnicity exclusively depends on race itself rather than on different cardiovascular responses to physical exercise. Methods: We examined 90 adolescent athletes, 60 Caucasian (WA) and 30 Black (BA). All participants underwent thorough clinical, echocardiographic and stress test evaluations. Results: BA had greater indexed LV mass (LVM/BSA) with increased relative wall thickness (RWT) implying a concentric remodelling. BA showed higher systolic blood pressure (SBP) compared to WA during the whole exercise test. ECG data showed that BA vs WA had a significant shorter QRS duration in each step considered with a significant greater QT dispersion. BA reached a higher relative pressure peak as compared to WA. RWT was strongly influenced by ethnicity and less by SBP at peak of exercise (PE), although LVM/BSA was significantly related to SBP at PE and just marginally to age and not significantly to race. Conclusions: Black adolescent athletes showed higher SBP during all steps of exercise associated to a different trend. Ethnicity was the main determinant of RWT, suggesting that LV geometry is principally race-related rather than influenced by a different hemodynamic profile to physical activity.

Keywords	athlete's heart; cardiac remodeling; left ventricular geometry; QT dispersion; black-white differences in exercise blood pressure; echocardiography
Taxonomy	Basic Science
Manuscript category	Original clinical research studies, basic science/translational research papers
Manuscript region of origin	Europe

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April 8th, 2019

Prof. Paolo G. Camici

Editor-in-Chief

International Journal of Cardiology

Dr Osto

Managing Editor

International Journal of Cardiology

Dear Professor Camici/Dr. Osto

Thank you for your evaluation of our manuscript IJC_2019_166. We carefully revised our paper according to the reviewers' suggestions and we are now submitting a new version for your kind consideration.

We hope you will find this improved version acceptable for publication and we thank you very much for your kind assistance.

Sincerely,

Giovanna Pelà MD, PhD

Ref: IJC_2019_166
Title: Hemodynamic and ECG responses to stress test in early adolescent athletes explain ethnicity-related cardiac differences
Journal: International Journal of Cardiology

Comments from the editors and reviewers:
-Reviewer 1

This work is an interesting study aiming to address some of the factors contributing to different LV structural and functional parameters in African and Caucasian adolescent athletes. The study is largely well-written, although this reviewer found it difficult to understand how the rationale of the study connected to the analysis approach taken. As such, whilst potentially important findings were seen, a clearer and more direct analysis path is required to enhance the appeal of the paper. The following comments are provided for the authors consideration and clarity surrounding these points should enhance the final product of the paper.

Response
Thank you for the comments. We carefully revised the manuscript according to your suggestions.

Major comments:

1. The bulk of the introduction does not directly lead to the rationale for the study. i.e. the introduction should be more directed towards describing how ethnicity may impact on the relationship between type of cardiac remodelling and exercise hemodynamics, or even more specifically, the BP response to exercise? Presently, the introduction is far too broad and does not specially draw the reader to the rationale of the study performed.

   Response
   We agree with this comment. The introduction was revised and the text focused on the objective of the study, which was to interpret the higher LVM in adolescent athletes of African ethnicity

2. The final paragraph of the introduction is not required to outline specific methodologies and parameters tested in the study – a simple statement of the aim and/or hypotheses would be sufficient and the later moved to the methods section.

   Response
   The final paragraph of introduction was shortened and part of it was moved to the Methods section

3. Please state that all echo measurements were undertaken at rest

   Response
   We now state (in Methods) that measurements were taken at rest.

4. Table 1 – please report the actual p values for all differences, even if not significant.

   Response
   Table 1 was revised and the actual p values for all differences were added

5. The type of remodelling is only inferred from greater LVM and RWT. Whist this is ok, a more thorough understanding of the type of LVH underlying the hemodynamic differences to exercise is required. Please calculate LV remodelling categories (normal, concentric remodelling, concentric

hypertrophy, eccentric hypertrophy) according to the ASE guidelines on the basis on LVM and RWT. Given the age of participants, please create LVM and RWT cut-offs based on 95th percentiles for this population group, rather than relying on the adult thresholds given in the guidelines, since you may or may not find very few individuals exceed the adult thresholds.

Response
Thank you for the suggestion to apply the four models of left ventricular remodeling in the field of athlete's heart to show the distribution in the two ethnicities. We have, therefore, divided the population according to your comments. Cut-off levels for LVM were calculated by Z scores according to the formula proposed by Foster B.J. et al. *Circulation* 2008, with a cut-off of 1.96. On the contrary, we have no proposed cut-off values and/or a formula for the calculation of z-score in children in literature for RWT. Therefore, we have considered the 95° percentile of the white children (0.407) we studied, which is very consistent with the data reported by Pelà et al, 2015. By using these two cut-off values, none of the white children was above the cut-off value for LVM and 5% was above the cut-off value for RWT. On the contrary, the percentages for black children were 23.3% and 13.3%, respectively. Therefore, the distribution of children in the two higher quadrants was significantly higher in black children ($p< 0.001$). The results are showed in Supplementary Figure that demonstrates how Africans have a tendency to a concentric remodeling both with normal or increased LV mass despite mainly endurance training.

6. Table 1 & 2 - Given the somewhat disproportionate groups sizes, please report the effect sizes for the differences in each parameter, rather than relying solely on the p values.

   Response
   We added the values of Hedges' g, which takes into account the differences between simple sizes of the groups. The interpretation is the same as Cohen's d: Small effect (cannot be discerned by the naked eye) = 0.2; Medium Effect = 0.5; Large Effect (can be seen by the naked eye) = 0.8. Our sample size is generally sufficient to see medium effects (minimum d values between 0.4 and 0.5).

7. I see the dependent variable in this study as being the BP response to exercise. If so, then the researchers should try to undertake analysis comparing what LV structural and functional parameters are associated with the BP response, and determine whether they differ between the 2 ethnic groups. Presently, it is difficult to interpret the results due to the potential for varying causal relationships/pathways between structure, function and BP response to exercise. Can the authors undertake such an analysis?

   Response
   The BP response to exercise is a predictor in the multiple regression analysis in which the dependent variable is LVM or RWT. We do agree with the referee that it is difficult to interpret the results due to the potential for varying causal relationships/pathways between structures. However, the goal of this multivariate model is to find possible independent factor that may predict alterations in RWT and LVM that are used to formulate a diagnosis. It is not necessarily a cause-effect relationship, which is complicated to establish on the basis on the available variables.

8. The term 'higher workload' is not appropriate to describe the exposure of the BA. Higher workload means greater work performed (i.e. mets achieved, watts achieved, intensity) and cannot be inferred from the BP response. Indeed, BA had high resting LVM, meaning they would be able to generate higher output during exercise (starling mechanism) of the same relative intensity or workload, and this alone may contribute to the higher SBP achieved during exercise. Please change your wording throughout to remove 'exposure to higher workload' and consider designing a model to determine if

the difference in SBP response between BA and WA is independent of the resting LVM difference. If any functional variables are available (e.g. SV) they may help to formulate conclusions

Response
The term "higher workload" has been replaced by maximal pressure at exercise.
The main aim of the manuscript is not to demonstrate the variables that influence the BP variations during effort test, but to assess whether the differences in BP during the test are best predictors for LVM and RWT, which remain the main target of our research for diagnostic reasons. Therefore, the introduction of LVM as covariate, although mathematically possible, makes the analysis contradictory, because it flip-flops predictors and outcome. The trend of BP as related to ethnicity has the main aim to exclude multicollinearity between predictors to include in the multivariate model and whether the temporal trend is different based on an interaction between ethnicity and time.

Minor comment:

Line 6 – introduction: 'pre-partecipation' – please correct spelling

Response
The word was corrected (participation instead of partecipation)

-Reviewer2

Hemodynamic and ECG responses to stress test in early adolescent athletes explain ethnicity-related cardiac differences – *International Journal of Cardiology* review
Dr Demola and colleagues present a manuscript detailing the paediatric cardiovascular responses to exercise testing among athletes of different ethnicities. They expand upon prior work from the group to include exercise stress testing focusing on blood pressure measurement with the aim of understanding the relationship between ethnicity and cardiac remodelling. In doing so they found that peak exercise blood pressure may explain the increased ethnic variation of physiological LVM enlargement, while ethnicity itself is more likely the determinant of relative wall thickness. The manuscript reads well is clear in its message and the work they present is novel.
The general premise is an interesting one and definitely worth attention within sports cardiology. The addition of the ECG derived QT dispersion analysis particularly at the end of the discussion I don't feel is particularly well placed and a slight deviation from the overall general message of the paper. It is interesting but if short on words I may suggest leaving attention to focus on the BP response to exercise.

Response
Thank you for the positive comments on our paper. Actually our first aim was to link the different LV structure and geometry in adolescent athletes of African ethnicity with the response to stress test. However, cardiac structure may be associated to electrical changes. A greater LV mass could be associated to greater repolarization dispersion as we demonstrated in Africans. Cycle-ergometer stress test gave us the opportunity to study not only the BP changes during the effort but also the ECG parameters

Comments
Page 3, line 79: Just note inferolateral TWI is not a sports related finding, so please exclude this.

Response
We deleted this paragraph as suggested by Reviewer 1

Page 5, line 110: This is a long shot but given their youth, do you happen to have information regarding how long the football players had been engaged in systematic training?

Response

We do not have these data, but – generally - our adolescent boys have a sports history of at least 4-5 years.

Page 5, line 110: Within the supplementary materials you add the important information of

Page 5, line 111: You add extra information regarding the origin of the black athletes within the supplementary material but I would suggest briefly mentioning this within the actual methods section. Work from Riding *et al* 2018 has highlighted the difference in electrical and structural adaptation between East and West/Central Africa in particular, so your inclusion of athletes only from these regions is particularly noteworthy.

Response

We agree with you, but we had to consider the maximum number of words allowed by the journal. In the revised paper we added the country of origin of African adolescents.

Page 5, line 111: For reference, please highlight that there are extra study details within the supplementary materials.

Response

We inserted references to the supplementary materials

Page 5, line 111: You state that athlete practiced different endurance sports. Despite including the information within the supplementary materials could you alter the phrasing of this as only 22% of your cohort are classified as endurance athletes. On page 13, line 326 you state that "All Africans except one practiced football". According to the EAPC recommendations (see below) soccer is denoted as a "mixed" sport and not an endurance sport. It may seem overly pedantic but it's worth changing to address any potential confusion.

Secondly on this point, a maximum of one black athlete could possibly be classified as partaking in endurance sport (3.3%) compared to at least 32% of white athletes, I feel like this deserves some attention given that type of sport was not included as a covariate in any of your analyses.

Response

We agree with the comment that football is a "mixed" sport . Soccer is mostly, though not exclusively, an endurance sport because explosive bursts of activity are frequently required and include jumping, kicking, tackling, turning, sprinting, changing pace, sustaining forceful contractions to maintain balance and to control the ball against pressure of opponent players; these actions account for 10-15% of total running time (Hoff & Helgerud, 2004; Pelà et al., 2004). Professional elite soccer players also routinely undergo remarkable isometric, strength-training programs similar to those typical of power sports (Hoff & Helgerud, 2004) and standard programs (including one competitive game on week-ends) consist in 12 to 15 hours of training per week, distributed in 6 days (Di Paolo et al., 2012; Hoff & Helgerud, 2004; Pelà et al., 2004).

However, in adolescent athletes the intensity of training is much lower than that of elite adult athletes and strength-training programs are limited. We added "**Soccer is mainly an endurance sport in adolescents".** The type of sport is not included in the analysis because we did not find any significant differences both for LVM, RWT and the pressure profile during effort among the different sports

Page 5, line 124: I know LVM/BSA is used as standard within cardiology and its recommendation in standard echo guidelines, particularly within the determination of relative wall thickness however please be aware of the methodological flaws of this ratiometric approach to normalising for body surface area. The use of allometric scaling better adjusts for the relationships observed between body size and cardiac dimensions. Ideally this is the approach you would have used, maybe consider checking the data again using a simple allometric approach.

Response

We thank you for the observation. LVM was indexed by BSA because it is most often used in clinical studies, as underlined by the latest Guidelines published in 2015. Indexing LV mass for the power of its allometric or growth relation with height (height2.7) is preferred principally in obese patients to overcome the underestimation of left ventricular hypertrophy

We also considered LVM indexed to height 2.7 and, as reported in Table 1, the difference between the two ethnic groups was significant (p= 0.021). However, this index was highly correlated with both LVM (R= 0.83) and LVM/BSA (R= 0.95). Given: (1) the lower significance at univariate; (2) the high correlation with LVM-LVM/BSA, the multivariate model with this index is redundant and we do not think it would strengthen the paper. However, we are willing to insert it, should the reviewer find it indispensable. It was added in the text and shown below the result with this model.

Page 7, line 171: Here you state the athletes trained for approximately 8 hours. Can you please expand to include this within table 1, with a specific split between average training hours between white and black athletes, including the standard deviation or CI here too. This I feel is a pertinent point as hours spent training per week was also not included as a covariate within your analysis.

Additionally, with regards to training hours, does this approximate 8 hours of training within the present study come from the calculation within the previous 2014 study where only for football players it was broken down to 2 sessions of 2.5 hours per week with one game?

Supplementary materials: Within this section you once again refer back to your previous 2014 study. This is seemingly a different study group of athletes given the years of study, so were you simply following the same protocol here and thus the reference? Or was there in fact a cross over with athletes?

Response

There was a typesetting error. The overall training time was about 7 and not 8 hours/week and include standard program during the week and one competitive game on week-ends, similar for all type of sports. These data do not include non-organized exercise activity as well as that performed at school and with friends. There were no differences in hours of training (self-reported data) between white and black adolescents (added in Table 1), and this variable was not significantly related to RWT and LVM/BSA. Therefore, this variable was not included in the multivariate model.

This a different study group of athletes and included slightly younger adolescents (mean age 13.5 + 1.5 vs 14.0 ± 1.7 years). However, we used the same protocol reported in the previous paper

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

"Each participant entered the study and, under physician and parents' supervision, completed a questionnaire that included: his own and family cardiovascular and clinical history; a survey on food habits, using a 7-days food and beverage record of the week previous to the examination; and detailed information on type, intensity and duration of sport activity, assessed through the selfadministered, 9-item Physical Activity Questionnaire for Adolescents (PAQ-A) (Crocker et al., 1997; Kowalski et al.; 1997, Booth et al., 2002; Gurd et al., 2003)".

Page 5, line 113: Was the exercise stress testing performed in these athletes for any particular reason (suspicion of pathology, symptoms etc) or were they simply selected consecutively within the screening process? Maybe a line stating this would again be a nice addition.

Response
The exercise stress test was part of the protocol in healthy athletes

Highlights

- In adolescent athletes of Caucasian and African ethnicities, the maximal exercise blood pressure, measured during cycle ergometry, is the strongest predictor of LVM
- Africans develop higher LVM because they develop higher BP when they exercise.
- Ethnicity is the main determinant of relative wall thickness, suggesting that left ventricular geometry is principally race-related
- An integrated and multi-parametric evaluation of cardiovascular adaptation in black athletes is needed

Abstract

Background: Ethnicity is an important determinant of athletes' cardiovascular adaptation. Black adolescent and adult athletes exhibit a left ventricular (LV) hypertrophy with a concentric remodelling higher than their Caucasian counterparts. Scant data, however, are available on race-related differences in hemodynamic response of adolescent athletes to exercise and its relation with heart remodelling. We evaluated if race-specific, sport-related structural and electrical remodelling in adolescent athletes of Caucasian and African ethnicity exclusively depends on race itself rather than on different cardiovascular responses to physical exercise. **Methods:** We examined 90 adolescent athletes, 60 Caucasian (WA) and 30 Black (BA). All participants underwent thorough clinical, echocardiographic and stress test evaluations. **Results:** BA had greater indexed LV mass (LVM/BSA) with increased relative wall thickness (RWT) implying a concentric remodelling. BA showed higher systolic blood pressure (SBP) compared to WA during the whole exercise test. ECG data showed that BA vs WA had a significant shorter QRS duration in each step considered with a significant greater QT dispersion. BA reached a higher relative pressure peak as compared to WA. RWT was strongly influenced by ethnicity and less by SBP at peak of exercise (PE), although LVM/BSA was significantly related to SBP at PE and just marginally to age and not significantly to race. **Conclusions:** Black adolescent athletes showed higher SBP during all steps of exercise associated to a different trend. Ethnicity was the main determinant of RWT, suggesting that LV geometry is principally race-related rather than influenced by a different hemodynamic profile to physical activity.

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
No conflicts of interest to declare. The authors received no financial support for the research, authorship, and/or publication of this article.

Word Count.3385 (excluding abstract, disclosures, references and figure legends)

Tables. 2

Figures. 2

Supplementary figures. 2

Supplementary methods

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Declarations of interest: none'.

Word Count.~~3484~~3385 (excluding abstract, disclosures, references and figure legends)

Tables. 2

Figures. 2

Supplementary figures. ~~1~~2

Supplementary methods

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Abstract

Background: Ethnicity is an important determinant of athletes' cardiovascular adaptation. Black adolescent and adult athletes exhibit a left ventricular (LV) hypertrophy with a concentric remodelling higher than their Caucasian counterparts. Scant data, however, are available on race-related differences in hemodynamic response of adolescent athletes to exercise and its relation with heart remodelling. We evaluated if race-specific, sport-related structural and electrical remodelling in adolescent athletes of Caucasian and African ethnicity exclusively depends on race itself rather than on different cardiovascular responses to physical exercise. **Methods:** We examined 90 adolescent athletes, 60 Caucasian (WA) and 30 Black (BA). All participants underwent thorough clinical, echocardiographic and stress test evaluations. **Results:** BA had greater indexed LV mass (LVM/BSA) with increased relative wall thickness (RWT) implying a concentric remodelling. BA showed higher systolic blood pressure (SBP) compared to WA during the whole exercise test. ECG data showed that BA vs WA had a significant shorter QRS duration in each step considered with a significant greater QT dispersion. BA reached a higher relative pressure peak as compared to WA. RWT was strongly influenced by ethnicity and less by SBP at peak of exercise (PE), although LVM/BSA was significantly related to SBP at PE and just marginally to age and not significantly to race. **Conclusions:** Black adolescent athletes showed higher SBP during all steps of exercise associated to a different trend. Ethnicity was the main determinant of RWT, suggesting that LV geometry is principally race-related rather than influenced by a different hemodynamic profile to physical activity.

Keywords: athlete's heart; cardiac remodelling; left ventricular geometry; QT dispersion; black-white differences in exercise blood pressure; echocardiography

1.Introduction

Africans have higher left ventricular (LV) mass compared to Caucasians [1]. This holds true for both the general population and different situations triggered by physiological and pathological stimuli such as physical exercise and hypertension [1-3]. The exaggerated left ventricular hypertrophy, quantified by echocardiography as LV mass (LVM) and thicknesses, sometimes mirrors the classical features of hypertrophic cardiomyopathy (HCM). This is an issue in pre-partecipation cardiovascular screening process of sports eligibility.

~~As compared with their Caucasian counterparts, black athletes also develop more pronounced ECG abnormalities such as LV hypertrophy (LVH), ST-trait elevation, negative T waves, and right ventricular hypertrophy [4]. Accordingly, ethnicity-specific parameters and guidelines are needed to discriminate common training-related findings from abnormal findings stemming from underlying pathological cardiac conditions unrelated to regular training, as the guidelines for ECG interpretation in athletes outline [5].~~

We recently demonstrated that LV wall thicknesses and mass is higher in adolescent amateur black versus white soccer players [~~6~~4]. This has been previously demonstrated in adult athletes, despite their much lower level of sport training and activity [~~6~~4]. At difference with white athletes, such changes are associated with a concentric pattern of left ventricular remodelling independent of the type of exercise; hence, concentric heart adaptation to sport activity is, likely, a peculiar phenotype of black ethnicity [~~6~~4]~~. Similar to adults [4], adolescent black athletes exhibit greater ECG sports-related adaptations, e.g. early repolarization pattern in right precordial leads followed by negative T wave, inverted T waves in inferior or lateral leads, biphasic T waves, or higher QRS voltages, that must be taken into account in the assessment of sports eligibility [6]. In brief, there is need for age- and race-specific structural and electrical cardiac parameters' registries in this specific setting.~~ Yet, whether such structural ~~and electrical~~ ethnic differences could be intrinsically related to race or, rather, to a different hemodynamic response to exercise is still an unresolved issue.

Further, excessive elevation in systolic blood pressure during physical exercise is associated to an increased left ventricular mass in pre-hypertensive individuals. [5]

Recently an independent relationship between exercise BP and cardiovascular structure has been demonstrated in a large cohort of apparently healthy adolescents [6]. These findings suggest that the systolic BP at exercise is an important determinant of cardiac structure and would be involved in the different remodeling of left ventricle in the two ethnicities.

Epidemiological studies showed that African ethnicity correlates with a higher risk of sudden death (SD) as compared with Caucasian, with greater incidence in adolescence [7,8]. Moreover, HCM (the first cause of sudden death in competitive athletes in the USA, mostly affecting black athletes) is more difficult to diagnose in this population, not only for its overlapping with physiological hypertrophy, but also because some typical features of this disease, e.g. familiarity for HCM, subvalvular obstruction, and systolic anterior motion of mitral valve, are often absent [9,10].

Therefore, we need to define the physiological LV adaptation to exercise in African athletes and the mechanisms through which LV hypertrophy develops, to differentiate it from its pathological analogue.

We undertook this study to address the aforementioned issues and to assess a possible relationship between peculiar LV remodelling (more concentric hypertrophy) and haemodinamic response to physical exercise (e.g. greater blood pressure response) in adolescent athletes of African ethnicity compared to counterpart of Caucasians . ~~We enrolled adolescent athletes from black and Caucasian ethnicities and we compared their response to the ergometer stress test, monitoring blood pressure and heart rate and including the analysis~~

~~of conventional and innovative ECG parameters recently introduced for the stratification of arrhythmic risk, e.g. QT dispersion (maximum QT interval minus minimum QT interval, QTd). The latter is an index of the spatial dispersion of ventricular recovery times and, therefore, is an index of inhomogeneity potentially involved in the genesis of arrhythmias.~~

2. Methods

2.1 Study population

The local ethics' committee approved this study. Written informed consent was obtained from the athletes' parents.

We enrolled 90 amateur level, male adolescent athletes, 60 of which were white (WA) and 30 black (BA), practicing different endurance disciplines. All BA were coming from the Central/West Africa, namely Burkina Faso, Cameroon, Ghana, Ivory Coast, Nigeria, and Senegal. All participants underwent physical examinations with 12-lead resting ECG, ECHO and ergometer stress test. S1+R5 in precordial leads were calculated using the Sokolow-Lyon voltage criteria to assess the presence of ECG-based LVH [11] . The analysis of ECG also include the innovative parameter recently introduced for the stratification of arrhythmic risk, e.g. QT dispersion (maximum QT interval minus minimum QT interval, QTd). The latter is an index of the spatial dispersion of ventricular recovery times and, therefore, is an index of inhomogeneity potentially involved in the genesis of arrhythmias. .

We assessed blood pressure (BP) and heart rate (HR) (OMRON 705 IT) during the clinical evaluation, with three consecutive measurements whose data were averaged. (see Supplementary Methods for details)

2.2 Echocardiography

M-mode, two-dimensional, and Doppler ECHO were performed by an ultrasonography-experienced cardiologist, using a commercially available, multi-hertz sector, 2-4 MHz probe-equipped machine (Vivid S5, GE Healthcare, USA). The interventricular septal (SWT) and posterior wall (PWT) thicknesses, systolic (ESD) and diastolic (EDD) LV diameters, absolute left ventricular mass (LVM) and indexed to body surface area (LVM/BSA) were calculated as previously described [~~6~~4]. LVM was also normalized to height $^{2.7}$, an estimate of lean body mass. RWT was calculated as: (SWT+ PWT)/ EDD. According to the ASE guidelines, we calculate LV remodelling categories (normal, concentric remodelling, concentric and eccentric hypertrophy) in the two groups [12], based on LVM and RWT. Cut-off values was based on 95th percentiles for this population (see Supplementary methods).~~, using the 0.42 cut-off to define eccentric (≤0.42) or concentric (≥0.42) remodelling [12].~~ Simpson's biplane rule-based end-diastolic (EDV) and systolic (ESV) volumes and ejection fraction (EF) were calculated, while Fractional Shortening (FS) was: [(EDV – ESV)/EDV] x 100.

Mitral inflow pattern were analysed from apical 4-chamber view and E and A wave and their ratio were considered as peak flow velocity and time velocity integral, in order to evaluate the conventional diastolic function. From the same projection, DTE analysis was performed at lateral site and postero-septum of mitral annulus. All echo measurements were undertaken at rest

2.3 Stress Test

All participants performed a cycle ergometer stress test (Cubestress Cardioline S.p.A., Italy) until volitional exhaustion, via 30 watts resistance increases every 2 min, during which the ECG was recorded continuously. We calculated heart rates from the ECGs. Systolic (SBP) and diastolic (DBP) blood pressures were measured by trained and certified technicians either using manual sphygmomanometers or an automated system (with small blood pressure cuffs when appropriate).

The average of both pressure values was computed at six points: basal time (BT); 2^{nd} (2E), 4^{th} (4E) min and peak of exercise (PE); 2^{nd} (2R) and 5^{th} (5R) minute during the recovery time (RT). The test was stopped when at least 80% of predicted HR was attained or when the participant was exhausted.

HR x BP (DP) was considered in each of the six points and some ECG parameters such as P wave duration, PR interval, QRS, QT, and QTd in four of them (BT, 2E, PE, 2R) were assessed off-line, after the stress test, using the magnification system of the cycle ergometer software. The QTd was calculated as the difference between the maximum and the minimum QT interval in the 12-lead ECG.

2.4 Statistical analysis

We report data as means ± SD and we compared, after testing for normality (Kolmogoroff-Smirnoff), groups using two-tailed Student's *t* test (SPSS 20.0 software package, IBM, Armonk, New York, USA). To consider the effect size taking into account the differences between groups' sample sizes, was used the values of Hedges' g. The interpretation is the same as Cohen's d: Small effect (cannot be discerned by the naked eye) = 0.2; Medium Effect = 0.5; Large Effect (can be seen by the naked eye) = 0.8. Our sample size was generally sufficient to see medium effects (significance with g values between 0.4 and 0.5). Univariate analysis was performed to analyse the relationship of cardiac structural parameters, such as RWT and LVM/BSA and BP at BT and PE including also relative pressure peak (ΔSBP: difference between SBP at PE and at BT). Of note, we report BPs taken before stress tests.

Mixed factorial ANOVA was used to test the effect of time and ethnicity (inter-subject factor) on quantitative variables, assessing a different trend by the significance of the interaction race x time.

Multiple regression analysis was used to analyse the relationship between RWT and LVM/BSA to ethnicity with age, HR, body surface area (BSA, not used for LVM/BSA), and BP as the covariates. In the analysis BP, from time to time, was included both to the BT, PE and ΔSBP.

We performed univariate analyses to assess the relationship between ECG-derived variables (such as QRS duration and QTd) and structural cardiac parameters in the two groups. A 2-tailed p value < 0.05 was considered as statistically significant.

3. Results

3.1 Baseline characteristics

All athletes were engaged in organized amateur-level training for approximately ~~eight~~ seven hours/week (Table 1). The two groups had similar age, height, weight, BSA, and body mass index. SBP and DBP were higher and HR was lower in BA than WA (Table 1). BA exhibited higher S1+R5 voltages (38 ± 10 vs 30 ± 10 in WA; $p< 0.001$) with greater prevalence of ECG-based LVH (19/30, 63% vs 18/60, 30% in WA; $p< 0.001$) and ST elevation (28/30, 93% vs 32/60, 53% in WA; $p< 0.001$) and that of partial right- bundle branch block was lower (7/30, 23% vs 30/60, 50% in WA; $p< 0.001$) compared with WA. We did not find differences in inverted T waves.

3.2 Echocardiographic results

SWT, PWT and LVM were significantly greater in BA compared with WA with an increased RWT suggesting a concentric remodelling despite mainly endurance training (Table 1).

~~.~~This fits with~~is in agreement with~~ our previous report of a peculiar geometry due to black ethnicity [~~6~~4]. By using the LVM and RWT cut-off values to define the distribution of LV remodeling in the two groups, none of the WA was above the cut-off value for LVM and 5% was above the cut-off value for RWT. On the contrary, the percentage for BA were 23.3% and 13.3%, respectively. Therefore, the distribution of adolescents in the two higher quadrants was significantly higher in BA ($p<0.001$). (see Supplementary Figure 2).

LV diameters and volumes were similar in the two groups. LV systolic and diastolic functions, assessed by conventional and Doppler tissue imaging, were also similar between groups.(data not shown)

3.3 Stress test

At BT of the stress test and during the whole exercise test, BA had a significantly higher SBP than WA, consistent with their clinical evaluation (Table 2). At PE, such differences increased then returned to basal values during the recovery time (Figure 1, on the left).

No significant differences were observed in DBP, except at BT and at 5R, whilst HR and SBP contrastingly behaved during the effort as the former increased less in BA than in WA; this difference reached statistical significance at 4E and PE (Table 2 and Figure 1, on the right). DP did not change at any step.

During ECG monitoring, BA showed significant shorter QRS durations than WA at each point (BT: 93±12 vs 85±10 ms, $p< 0.01$; 2E: 93±12 vs 86±12, $p= 0.01$; PE: 94±17 vs

84±11 ms, p= 0.01; 2R: 93±11 vs 84±12 ms, p= 0.002) with a consistently significant greater QTd (Table 2). The other ECG parameters, i.e. P wave duration, PR interval and QT, did not differ between BA and WA.

3.4 Statistical analyses

Concerning SBP, mixed factorial ANOVA showed that time and ethnicity were significantly different ($p<0.001$ and $p=0.002$ respectively). Their interaction was also significantly different ($p= 0.013$). Specifically, BA reached a higher ΔSBP as compared to WA. As regards HR, time and ethnicity were significantly different ($p<0.001$ and $p=0.039$, respectively), but their interaction was not significant different. Finally, concerning DBP, only time was significant ($p<0.001$).

After univariate analysis, the highest correlation coefficient was found between LVM/BSA and SBP at PE for both BA and WA (SBP at PE- WA: $r=0.45$, $p<0.001$; BA: $r= 0.38$, $p<0.05$; SBP at BT - WA: $r=0.27$, $p<0.05$; BA: $r=0.28$, p= ns; ΔSBP WA: $r=0.40$, $p<0.001$; BA: $r=0.30$, p= ns) whilst RWT correlated with SBP at PE and ΔSBP only in WA (SBP at PE- $r=0.35$, $p<0.01$; ΔSBP- $r=0.29$, $p<0.05$).

Still after multivariate data analysis that included ethnicity, age, HR, and SBP at BT or at PE as covariates, RWT was strongly influenced by ethnicity ($p<0.001$) and less by SBP at PE ($p=0.02$).

SBP at PE, but not at BT, was significantly related to LVM/BSA ($p=0.003$) suggesting that the under hemodynamic stress load rather that at baseline influences the weight of LV, which was also marginally related to age ($p<0.05$), but not significantly to race ($p=0.061$).

Among the ECG-parameters we analyzed, a significant relationship between LVM/BSA and QTd was found at 2R ($r=0.44$; $p=0.014$) in BA, suggesting that inhomogeneity of ventricular recovery time is related to LVM in blacks (Supplementary Figure 1, A). No correlations between LVM (Supplementary Figure 1, B) and QTd were seen in Caucasians. QRS was not related to structural characteristics of LV in either group.

4. Discussion

This is the first work that targets the different response to effort stress test between adolescent athletes of two different ethnicities. The main goal was to clarify the physiological mechanisms that underlie the structural and electrical heart differences of the African vs. Caucasian races, in the context of sport medicine.

We previously showed that pubertal African athletes have higher LVM compared to their Caucasian counterparts, which is associated to a peculiar concentric, ethnicity-determined remodelling, resulting in a distinct LV phenotype [~~6~~4]. Moreover, more pronounced ECG sport-related adaptations, such as LV hypertrophy and early repolarisation, were observed in Black vs Caucasian adolescents athletes [~~6~~4]. Here, we report different hemodynamic and ECG changes occurring in the two groups during stress tests. Namely, BA vs WA exhibited higher SBP at rest, both during clinical examinations and at T_0 of a cycle-ergometer test. This difference was maintained during the whole exercise and actually increased at its peak. The converse was detected for HR, which was lower in BA vs WA with significant differences at 4E and at PE. Therefore, the double product was unchanged in the two groups in all steps. A significantly lower HR was also observed during clinical evaluation (yet not at base time of the ergometer test), which we suggest is due to the different clinical context, the different pressure measurement mode (an automated blood pressure system rather than ECG), and a likely greater autonomic response in the Caucasian race as already as demonstrated by other authors [13].

As regards DBP, the effort test confirmed lower values in WA (in agreement with what we observed during the clinical visit), although this difference disappeared during the effort to reappear at R5.

Population studies indicate that both adult and young Africans have higher blood pressure values; whether this phenomenon is due to different genetics or to social-economic factors is yet to be elucidated [14]. Indeed, clinical studies confirmed these findings, but accumulated data are still controversial [15,16].

A higher increase in SBP during treadmill exercise tests was observed in adult black men (from 35 to 40 years) compared to white ones, suggesting that the exaggerated vascular reactivity to physical exercise of the former might be responsible for their major incidence of hypertension [17]. Similar observations were done in pediatric subjects: children from Caucasian and African ethnicities - between 6 to 15 years - were submitted to an effort test and their pressure response was compared [18]. In all age ranges, except for the younger group, a significant higher SBP at peak was detected in black subjects, even though, at base time, their SBP was comparable to that of their Caucasian counterparts [18]. Of note, other investigators did not confirm these results [19,20].

In a longitudinal study that lasted over 15-years, ethnic differences in ambulatory BP (ABPM) have been reported: African-Americans compared to European-Americans have higher systolic BP both during daytime and nighttime, with a greater increase with age [21]. Using ABPM, researchers showed that black adolescents had higher SBP than white ones during sleep, but not during daytime [22].

We confirm that black adolescent athletes have higher SPB compared to their Caucasian counterparts and that such difference is more evident during the exercise test. Our results were obtained by using a dual method for BP evaluation, manual and automatic systems integrated to the cycle-ergometer. This allows overcoming the well-known technical difficulties of BP's assessment during exercise and increases the diagnostic accuracy.

From an anatomical viewpoint, we confirm the close relationship previously found between cardiac geometry and race [~~6~~4,23]. The multivariate analysis showed that ethnicity was strictly related to RWT. The latter weakly correlated with SBP at PE, but not with SBP at BT and age.

No correlation between LVM and SBP at rest was found, suggesting that altered BP is not representative of the global pressure profile determining left ventricular remodelling/LV mass. Rather, SBP at PE is the strongest predictor of LVM demonstrating that BP measured during the stress test is more stable (being less influenced by neuro-endocrine factors) and is a more accurate estimation of cardiac workload. These results are in agreement with Schultz MG ~~–~~et al. who recently demonstrated the association between exercise blood pressure, measured immediately after submaximal step-test, and cardiovascular structure (LVM in particular) in a large non-selected cohort of adolescents of both sexes [~~24~~6]. The association between LVM and SBP developed during physical exercise has been reported also both in healthy subjects and in hypertensive patients [~~25~~24,~~26~~25].

In summary, the main determinants of LVM and RWT are different: SBP at PE for the former and race for the latter. Africans conceivably develop higher LVM as a compensation mechanism for ~~because they are exposed to a higher workload~~ pressure overload (as detected by the effort test), whereas their geometry appears to be primarily related to genetic traits rather than SBP (Figure 2).

Race-related differences in cardiac structure become evident during development when more pronounced changes in myocardial anatomy could be measured [~~27,28~~26,27]. In a prospective study of 687, 8 - 27 years old subjects, followed for more than ten years, ethnicity was a strong predictor of LVM [~~27~~26]. This feature was noticeable from puberty and was independent of socioeconomic status, anthropometric characteristics, and hemodynamic stimuli. Expanding on a previous publication, we suggest that the younger, i.e. six months age of athletes explains the lower extent of cardiac morphology differences [~~27~~26,~~28~~27].

From a mechanistic viewpoint, we suggest that a larger increase of myocytes' size (and not their number) in Africans compared to Caucasians partially explains the cardiac structure differences in the transpuberal age [~~29~~28]. Further, black adolescent athletes might exhibit increased LVM because of a different hemodynamic load.

Finally, genome-wide association studies recently identified a single nucleotide polymorphism in intron 16 of the cardiac sodium channel gene SCN5A linked with QRS duration among African Americans that can be related to shorter duration of this interval [~~30~~29]. Polymorphisms of *SCN5A* could be related to an overall predominance of transient outward epicardial currents determining also the early repolarization*,* more frequent in Africans [~~31~~30].

LVM also significantly influenced QTd in BA, demonstrating that only the inhomogeneity of the ventricular repolarization in the African race is related to cardiac structure. Other studies did not report associations between athlete's heart and ventricular repolarization heterogeneity compared with healthy sedentary controls, despite physiological and structural changes. Thus, an increase in left ventricular mass, in the frame of athlete's heart, does not influence QTd [~~32~~31]. Our results indicate differences in the spread of the electric stimulus between the two ethnicities and suggest that the higher QTd of Africans could be employed to assess the risk for arrhythmia in this setting, helping the prognostic stratification of adolescent black athletes. The higher QTd of Africans might also be a marker of a ''midway'' condition between physiological and pathological hypertrophy. In summary, ECG measurements differ depending on ethnicity, having Africans shorter QRS duration and increased QTd; and such differences did not fluctuate with heart rate variations during stress tests.

4.1 Limitations

The main limitation of our study is the small number of BA we enrolled. However, that sample was homogeneous for gender, age, ethnic/geographic origin (all from West-African descent), time spent in Italy, socio-economic environment, lifestyle, and food habits. All Africans except one practiced football, the most prevalent sport in Caucasians. However, no differences were observed between football players and athletes of other disciplines in the Caucasian group.

The main strength of our work is the accurate assessment of blood pressure during stress tests, which we performed by two methods, i.e. manual sphygmomanometer and an automated system.

5. Conclusion

Black adolescent athletes exhibit higher SBP when they exercise; their SBP at PE is the strongest predictor of LVM/BSA. These results suggest that the more pronounced left ventricular remodelling of black athletes could be related to a potentially higher hemodynamic ~~workload~~ afterload during sport exercise. Conversely, ethnicity is the main determinant of RWT, suggesting that LV geometry is principally race-related rather than influenced by a different hemodynamic response to physical activity. African adolescent athletes display greater inhomogeneity of ventricular recovery time (as evaluated through QTd), which could reveal different risk for arrhythmia, worth further appropriate investigations.

An integrated and multi-parametric evaluation of cardiovascular adaptation in black athletes could reduce the grey zone between physiological heart remodeling associated with exercise and the phenotype aspects of hypertrophic cardiomyopathy, which is the first cause of sudden death in the black population.

Disclosures

No conflicts of interest to declare. The authors received no financial support for the research, authorship, and/or publication of this article. All authors have materially participated in the research and/or article preparation. All authors have approved the final article.

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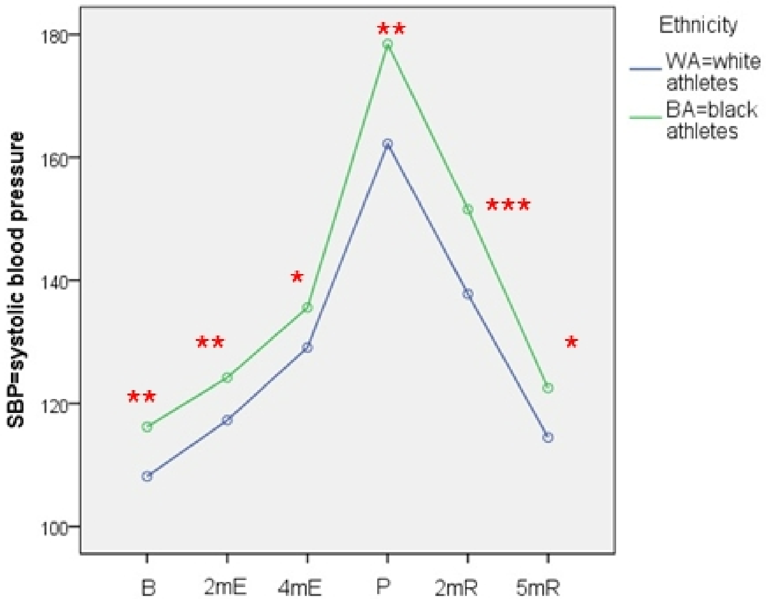
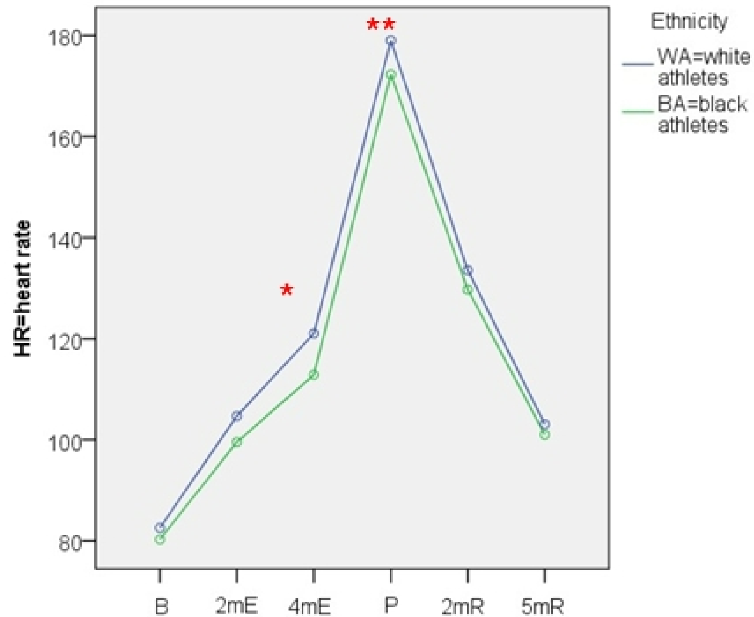
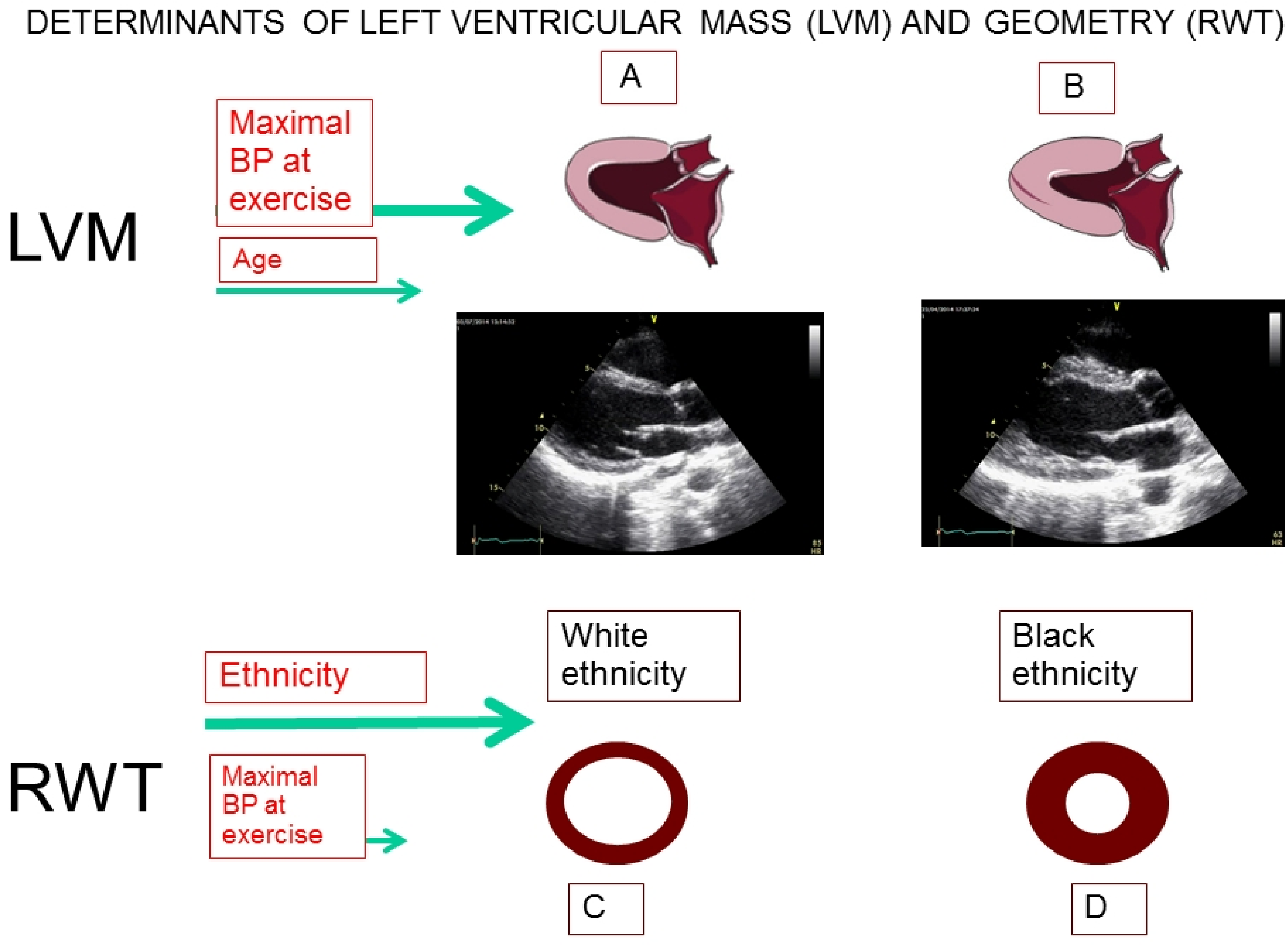
Figure legends

Figure 1. Trend of systolic blood pressure (on the top) and heart rate (on the bottom) during exercise stress test in the two groups of athletes. *p< 0.05; **p< 0.01; ***p< 0.001

Figure 2. Determinants of structural characteristics of left ventricle in the two groups of adolescent athletes. ~~Maximal workload, expressed as t~~The systolic blood pressure at peak of exercise, is the main determinant of left ventricular mass (LVM) (shift from model A to B with growing LVM). On the contrary, Geometry, in terms of Relative wall thickness (RWT), is strictly related to ethnicity, with eccentric geometry (C) being peculiar in Caucasians, while concentric geometry (D) in Africans.


SBP=systolic blood pressure
180
160
140
120
100
B
2mE
4mE
P
2mR
5mR
Ethnicity
WA=white athletes
BA=black athletes


HR=heart rate
180
160
140
120
100
80
B
2mE
4mE
P
2mR
5mR
Ethnicity
WA=white athletes
BA=black athletes


DETERMINANTS OF LEFT VENTRICULAR MASS (LVM) AND GEOMETRY (RWT)
A
B
LVM
Maximal BP at exercise
Age
RWT
Ethnicity
Maximal BP at exercise
White ethnicity
Black ethnicity
C
D

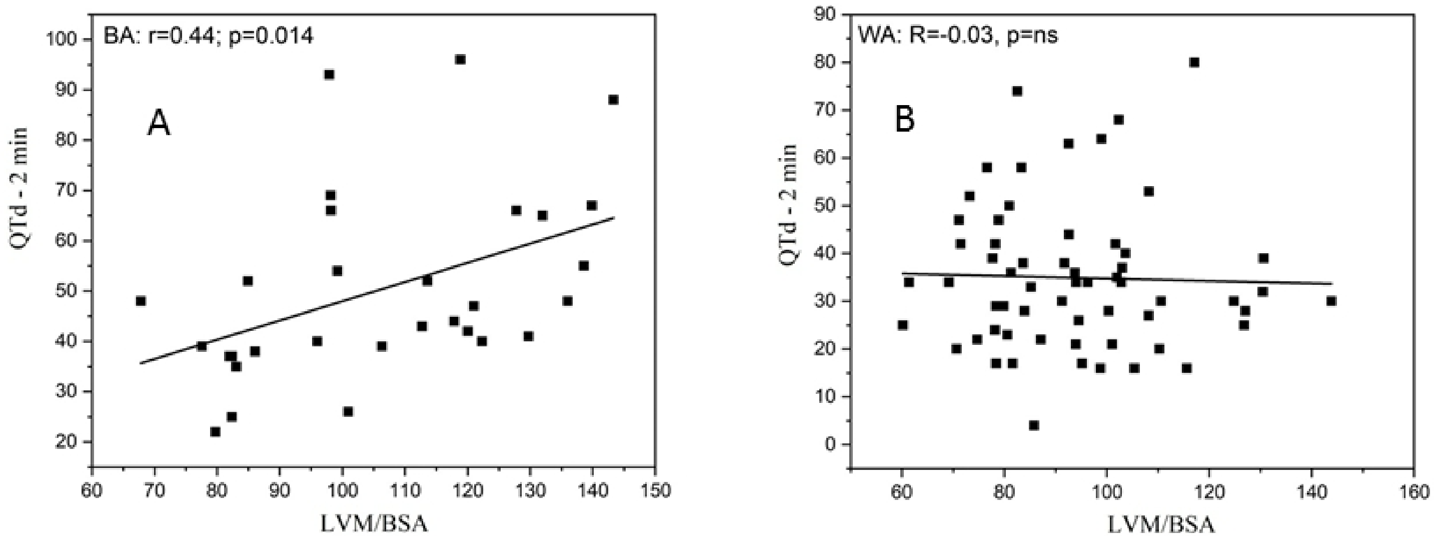

BA: r=0.44; p=0.014
A
QTd - 2 min
LVM/BSA
WA: R=-0.03, p=ns
B
QTd - 2 min
LVM/BSA

Table 1

Clinical and echocardiographic data in adolescent white and black, amateur-level athletes

Parameter	WA *n=60*	BA *n=30*	*p* value	*Hedges' g Size effect*
Age (years)	13.3 ± 1.5	13.8 ± 1.6	0.17	0.33
Training (hours/w)	6.3± 2.0	7.0 ± 1.8	0.11	0.36
Height (cm)	1.64 ± 0.12	1.68 ± 0.08	0.11	0.37
Weight (kg)	53.1 ± 13.5	56.8 ± 10.9	0.27	0.29
BMI (kg/m^2)	19.4 ± 3.0	19.9 ± 2.3	0.61	0.18
BSA (m^2)	1.56 ± 0.25	1.64 ± 0.19	0.18	0.34
SBP (mmHg)	105 ± 12	113 ± 13	0.018	0.65
DBP (mmHg)	64 ± 9	71 ± 8	0.006	0.81
HR (beats-per-minute)	76 ± 11	70 ± 8	0.005	0.59
EDD (mm)	46.4 ± 4.3	46.1 ± 4.2	0.63	0.07
ESD (mm)	28.3 ± 3.6	28.5 ± 4.0	0.98	0.05
EDV (ml)	97 ± 26	100 ± 25	0.67	0.12
ESV (ml)	32 ± 11	32 ± 9	0.77	<0.01
SWT (mm)	7.8 ± 1.1	8.9 ± 1.1	<0.0001	1.00
PWT (mm)	7.9 ± 1.4	9.0 ± 1.3	<0.0001	0.80
RWT	0.34 ± 0.04	0.39 ± 0.04	<0.0001	1.25
LVM (g)	149± 46	175 ± 47	0.009	0.56
LVM/BSA (g/m^2)	94 ± 18	106 ± 22	0.005	0.62
LVM/h $^{2.7}$ (g/m$^{2.7}$)	38 ± 7	43 ± 9	0.021	0.65

Data are means ± standard deviation. BA, black athletes; BMI, Body mass index; BSA, Body surface area; DBP, Diastolic blood pressure; EDD, End-diastolic diameter; EDV, End-diastolic volume; ESD, End-systolic diameter; ESV, End-systolic volume; HR, Heart rate; h, Height; LVM, absolute left ventricle mass; LVM/BSA, indexed left ventricle mass; MWT Maximal wall thickness; PWT Posterior wall thickness; RWT, relative wall thickness; SBP, Systolic blood pressure; SWT, Septal wall thickness; WA, white athletes.

Table 2

Exercise test in adolescent white and black, amateur-level athletes: Hemodynamic and ECG data

SBP	WA		BA		*p value*	*Hedges' g Size effect*
Basal	108	±13	116	±13	0.007	0.62
2° min	117	±11	124	±13	0.008	0.60
4° min	129	±13	136	±16	0.029	0.50
Peak exercise	162	±22	178	±27	0.004	0.67
2° min rec	138	±17	152	±22	0.001	0.74
5° min rec	115	±13	123	±16	0.016	0.57
DBP	**WA**		**BA**		***p value***	
Basal	66	±9	70	±8	0.027	0.58
2° min	64	±8	67	±8	0.069	0.38
4° min	65	±8	68	±10	0.14	0.34
Peak exercise	72	±11	73	±12	0.76	0.09
2° min rec	58	±9	60	±11	0.43	0.021
5° min rec	58	±7	61	±9	0.046	0.39
HR	**WA**		**BA**		***p value***	
Basal	83	±12	80	±14	0.43	0.24
2° min	105	±14	100	±10	0.078	0.39
4° min	121	±18	113	±12	0.027	0.49
Peak exercise	179	±10	172	±11	0.005	0.68
2° min rec	133	±13	130	±15	0.23	0.22
5° min rec	103	±19	101	±13	0.60	0.12
QRS DURATION	**WA**		**BA**		***p value***	
Basal	93	±12	85	±10	0.004	0.70
2° min	93	±12	86	±12	0.01	0.58
Peak exercise	94	±17	84	±11	0.012	0.65
2° min rec	93	±11	84	±12	0.002	0.79
QT DISPERSION	**WA**		**BA**		***p value***	
Basal	27	±8	37	±13	<0.001	1.01
2° min	28	±12	36	±17	0.006	0.58
Peak exercise	24	±10	29	±9	0.019	0.52
2° min rec	31	±23	51	±19	0.001	0.92

Data are means ± standard deviations. BA, black athletes; DBP, diastolic blood pressure; HR, heart rate; min, minute; SBP, systolic blood pressure; rec, recovery time; WA, white athletes.

Author Agreement Form – International Journal of Cardiology

Manuscript Title: **Hemodynamic and ECG responses to stress test in early adolescent athletes explain ethnicity-related cardiac differences**

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This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *International Journal of Cardiology.*

We attest that the article is the Authors' original work, has not received prior publication and is not under consideration for publication elsewhere. We adhere to the statement of ethical publishing as appears in the International of Cardiology (citable as: Shewan LG, Rosano GMC, Henein MY, Coats AJS. A statement on ethical standards in publishing scientific articles in the International Journal of Cardiology family of journals. Int. J. Cardiol. 170 (2014) 253-254 DOI:10.1016/j.ijcard.2013.11).

On behalf of all Co-Authors, the corresponding Author shall bear full responsibility for the submission. Any changes to the list of authors, including changes in order, additions or removals will require the submission of a new author agreement form approved and signed by all the original and added submitting authors.

All authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. If there are no conflicts of interest, the COI should read: “The authors report no relationships that could be construed as a conflict of interest”.

Supplementary Methods

The local ethics' committee approved this study. Written informed consent was obtained from the athletes' parents.

Between January 2015 and December 2016, we enrolled 90 amateur level, male athletes, 60 of which were white (WA) and 30 black (BA). Their age ranged from 11.0 to 16.9 years (13.5 ± 1.57, mean ± SD), with 48 of them younger than 14 years.

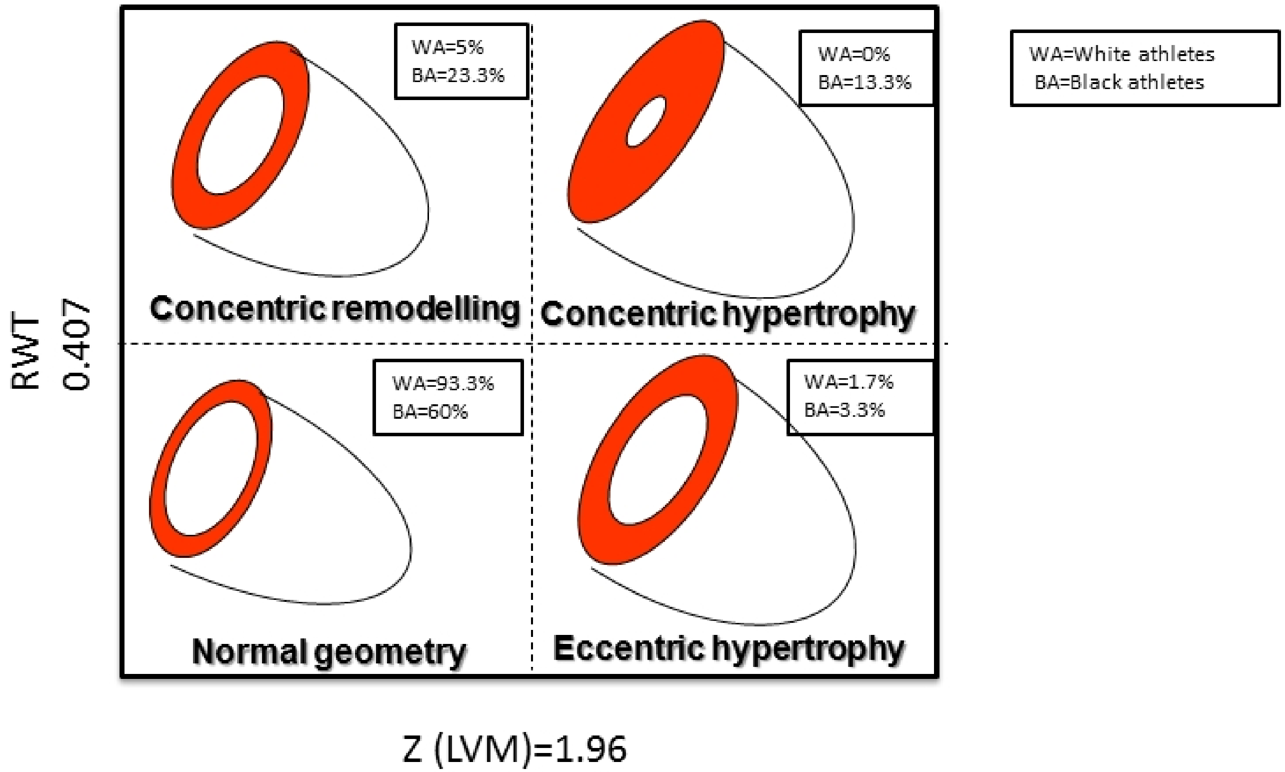
All participants competed in local, amateur-level leagues of different endurance disciplines, predominantly soccer (54/90, 60% of the total), but also athletics (n= 19), basketball (n= 5), judo (n= 4), tennis (n= 3), karate (n= 2), volleyball (n= 1), rugby (n= 1), swimming (n= 1). Participant entered the study and, under their physician's and parents' supervision, completed a questionnaire that included their own and family cardiovascular and clinical history and detailed information on type, intensity, and duration of sport activity, as previously reported [6].

We performed this study in the middle of the sport season and all participants underwent physical examinations with 12-lead resting ECG, ECHO and ergometer stress test.

Twelve-lead, 25 mm/second, supine-position ECGs were performed at enrolment. S1+R5 in precordial leads were calculated using the Sokolow-Lyon voltage criteria (positive if ≥ 35mm) to assess the presence of LVH. We also assessed the presence and shape (concave or domed) of ST-segment elevation (≥ 1 mm in ≥ 2 adjacent leads), prevalence of inverted T-waves (≥ 2 mm in depth in ≥ 2 adjacent leads, excluding aVR and III) [11].

The four models of left ventricular remodeling in the two ethnicities were created on the basis of LVM and RWT. Cut-off levels for LVM were calculated by Z scores according to the formula proposed by Foster B.J. et al. *Circulation* 2008, with a cut-off of 1.96. On the contrary, we have no proposed cut-off values and/or a formula for the calculation of z-score in children in literature for RWT. Therefore, we have considered the 95° percentile of white children (0.407), which is consistent with the data reported in Pelà et al, 2015. By using these two cut-off values, none of the white children was above the cut-off value for LVM and 5% was above the cut-off value for RWT.

Distribution of left ventricular remodelling in adolescent athletes



Supplementary Figure 2