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

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Original

Hemodynamic and ECG responses to stress test in early adolescent athletes explain ethnicity-related cardiac differences / Demola, P., Crocamo, A., Ceriello, L., Botti, A., Cremonini, I., Pattoneri, P., Corradi, D., Visioli, F., Goldoni, M., Pelà, G.. - In: INTERNATIONAL JOURNAL OF CARDIOLOGY. - ISSN 0167-5273. - 289:(2019), pp. 125-130. [10.1016/j.ijcard.2019.04.084]

Availability:

This version is available at: 11381/2859643 since: 2021-10-26T12:07:54Z

Publisher:

Elsevier Ireland Ltd

Published

DOI:10.1016/j.ijcard.2019.04.084

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note finali coverpage

(Article begins on next page)

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
Corresponding Author	Giovanna Pelà
Corresponding Author's Institution	Department of Medicine and Surgery
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Suggested reviewers	Antonio Pelliccia

Submission Files Included in this PDF

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IJC_2019_166 Answers to reviewers.doc [Response to Reviewers]

IJC_2019_166 Highlights REV.docx [Highlights]

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revised marked manuscript.docx [Manuscript File]

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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. Whilst 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^o 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 ($\text{height}^{2.7}$) is preferred principally in obese patients to overcome the underestimation of left ventricular hypertrophy

We also considered LVM indexed to $\text{height}^{2.7}$ 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 Crocarno, 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 self-

administered, 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.

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

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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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4 **1 Hemodynamic and ECG responses to stress test in early adolescent athletes**
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6 **2 explain ethnicity-related cardiac differences**
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9 **3**

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25 **13 All authors take responsibility for all aspects of the reliability and freedom from bias of**
26 **14 the data presented and their discussed interpretation.**

27 **15 Declarations of interest: none’.**
28

29 **17 Word Count.**34843385 (excluding abstract, disclosures, references and figure legends)
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32 **19 Tables. 2**
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34 **20 Figures. 2**
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36 **21 Supplementary figures. ~~4~~2**
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38 **22 Supplementary methods**
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62 **Abstract**
63

64 **Background:** Ethnicity is an important determinant of athletes' cardiovascular adaptation.
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66 Black adolescent and adult athletes exhibit a left ventricular (LV) hypertrophy with a
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68 concentric remodelling higher than their Caucasian counterparts. Scant data, however, are
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72 exercise and its relation with heart remodelling. We evaluated if race-specific, sport-related
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74 structural and electrical remodelling in adolescent athletes of Caucasian and African ethnicity
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80 Black (BA). All participants underwent thorough clinical, echocardiographic and stress test
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88 WA had a significant shorter QRS duration in each step considered with a significant greater
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92 strongly influenced by ethnicity and less by SBP at peak of exercise (PE), although
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102 hemodynamic profile to physical activity.
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107 **Keywords:** athlete's heart; cardiac remodeling; left ventricular geometry; QT dispersion;
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109 black-white differences in exercise blood pressure; echocardiography
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121 **1.Introduction**
122

123 60 Africans have higher left ventricular (LV) mass compared to Caucasians [1]. This holds true
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125 61 for both the general population and different situations triggered by physiological and
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127 62 pathological stimuli such as physical exercise and hypertension [1-3]. The exaggerated left
128
129 63 ventricular hypertrophy, quantified by echocardiography as LV mass (LVM) and thicknesses,
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131 64 sometimes mirrors the classical features of hypertrophic cardiomyopathy (HCM). This is an
132
133 65 issue in pre-participation cardiovascular screening process of sports eligibility.
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136 ~~66 As compared with their Caucasian counterparts, black athletes also develop more~~
137
138 ~~67 pronounced ECG abnormalities such as LV hypertrophy (LVH), ST trait elevation, negative~~
139
140 ~~68 T waves, and right ventricular hypertrophy [4]. Accordingly, ethnicity-specific parameters~~
141
142 ~~69 and guidelines are needed to discriminate common training-related findings from abnormal~~
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144 ~~70 findings stemming from underlying pathological cardiac conditions unrelated to regular~~
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146 ~~71 training, as the guidelines for ECG interpretation in athletes outline [5].~~
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149 72 We recently demonstrated that LV wall thicknesses and mass is higher in adolescent
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151 73 amateur black versus white soccer players [64]. This has been previously demonstrated in
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153 74 adult athletes, despite their much lower level of sport training and activity [64]. At difference
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155 75 with white athletes, such changes are associated with a concentric pattern of left ventricular
156
157 76 remodelling independent of the type of exercise; hence, concentric heart adaptation to sport
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159 77 activity is, likely, a peculiar phenotype of black ethnicity [64]. ~~Similar to adults [4],~~
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161 ~~78 adolescent black athletes exhibit greater ECG sports-related adaptations, e.g. early~~
162
163 ~~79 repolarization pattern in right precordial leads followed by negative T wave, inverted T~~
164
165 ~~80 waves in inferior or lateral leads, biphasic T waves, or higher QRS voltages, that must be~~
166
167 ~~81 taken into account in the assessment of sports eligibility [6]. In brief, there is need for age-~~
168
169 ~~82 and race-specific structural and electrical cardiac parameters' registries in this specific~~
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171 ~~83 setting.~~ Yet, whether such structural ~~and electrical~~ ethnic differences could be intrinsically
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180 84 related to race or, rather, to a different hemodynamic response to exercise is still an
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182 85 unresolved issue.

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185 86 Further, excessive elevation in systolic blood pressure during physical exercise is
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187 87 associated to an increased left ventricular mass in pre-hypertensive individuals. [5]

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189 88 Recently an independent relationship between exercise BP and cardiovascular
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191 89 structure has been demonstrated in a large cohort of apparently healthy adolescents [6].

192
193 90 These findings suggest that the systolic BP at exercise is an important determinant of cardiac
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195 91 structure and would be involved in the different remodeling of left ventricle in the two
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197 92 ethnicities.

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199 93 Epidemiological studies showed that African ethnicity correlates with a higher risk of
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201 94 sudden death (SD) as compared with Caucasian, with greater incidence in adolescence [7,8].
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203 95 Moreover, HCM (the first cause of sudden death in competitive athletes in the USA, mostly
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205 96 affecting black athletes) is more difficult to diagnose in this population, not only for its
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207 97 overlapping with physiological hypertrophy, but also because some typical features of this
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209 98 disease, e.g. familiarity for HCM, subvalvular obstruction, and systolic anterior motion of
210
211 99 mitral valve, are often absent [9,10].

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214 100 Therefore, we need to define the physiological LV adaptation to exercise in African
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216 101 athletes and the mechanisms through which LV hypertrophy develops, to differentiate it from
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218 102 its pathological analogue.

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220 103 We undertook this study to address the aforementioned issues and to assess a possible
221
222 104 relationship between peculiar LV remodelling (more concentric hypertrophy) and
223
224 105 haemodynamic response to physical exercise (e.g. greater blood pressure response) in
225
226 106 adolescent athletes of African ethnicity compared to counterpart of Caucasians. ~~We enrolled~~
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228 107 ~~adolescent athletes from black and Caucasian ethnicities and we compared their response to~~
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230 108 ~~the ergometer stress test, monitoring blood pressure and heart rate and including the analysis~~
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~~109 of conventional and innovative ECG parameters recently introduced for the stratification of
110 arrhythmic risk, e.g. QT dispersion (maximum QT interval minus minimum QT interval,
111 QTd). The latter is an index of the spatial dispersion of ventricular recovery times and,
112 therefore, is an index of inhomogeneity potentially involved in the genesis of arrhythmias.~~

113

114 **2. Methods**

115 *2.1 Study population*

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

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

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

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133 *2.2 Echocardiography*

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299 134 M-mode, two-dimensional, and Doppler ECHO were performed by an
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301 135 ultrasonography-experienced cardiologist, using a commercially available, multi-hertz sector,
302
303 136 2-4 MHz probe-equipped machine (Vivid S5, GE Healthcare, USA). The interventricular
304
305 137 septal (SWT) and posterior wall (PWT) thicknesses, systolic (ESD) and diastolic (EDD) LV
306
307 138 diameters, absolute left ventricular mass (LVM) and indexed to body surface area
308
309 139 (LVM/BSA) were calculated as previously described [64]. LVM was also normalized to
310
311 140 height^{2.7}, an estimate of lean body mass. RWT was calculated as: (SWT+ PWT)/ EDD.
312
313 141 According to the ASE guidelines, we calculate LV remodelling categories (normal,
314
315 142 concentric remodelling, concentric and eccentric hypertrophy) in the two groups [12], based
316
317 143 on LVM and RWT. Cut-off values was based on 95th percentiles for this population (see
318
319 144 Supplementary methods), using the 0.42 cut-off to define eccentric (≤ 0.42) or concentric
320
321 145 (≥ 0.42) remodelling [12]. Simpson's biplane rule-based end-diastolic (EDV) and systolic
322
323 146 (ESV) volumes and ejection fraction (EF) were calculated, while Fractional Shortening (FS)
324
325 147 was: [(EDV – ESV)/EDV] x 100.

328 148 Mitral inflow pattern were analysed from apical 4-chamber view and E and A wave
329
330 149 and their ratio were considered as peak flow velocity and time velocity integral, in order to
331
332 150 evaluate the conventional diastolic function. From the same projection, DTE analysis was
333
334 151 performed at lateral site and postero-septum of mitral annulus. All echo measurements were
335
336 152 undertaken at rest

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344 156 *2.3 Stress Test*

346 157 All participants performed a cycle ergometer stress test (Cubestress Cardioline S.p.A.,
347
348 158 Italy) until volitional exhaustion, via 30 watts resistance increases every 2 min, during which

355
356
357 159 the ECG was recorded continuously. We calculated heart rates from the ECGs. Systolic
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359 160 (SBP) and diastolic (DBP) blood pressures were measured by trained and certified
360
361 161 technicians either using manual sphygmomanometers or an automated system (with small
362
363 162 blood pressure cuffs when appropriate).

364
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366 163 The average of both pressure values was computed at six points: basal time (BT); 2nd (2E), 4th
367
368 164 (4E) min and peak of exercise (PE); 2nd (2R) and 5th (5R) minute during the recovery time
369
370 165 (RT). The test was stopped when at least 80% of predicted HR was attained or when the
371
372 166 participant was exhausted.

373
374 167 HR x BP (DP) was considered in each of the six points and some ECG parameters such as P
375
376 168 wave duration, PR interval, QRS, QT, and QTd in four of them (BT, 2E, PE, 2R) were
377
378 169 assessed off-line, after the stress test, using the magnification system of the cycle ergometer
379
380 170 software. The QTd was calculated as the difference between the maximum and the minimum
381
382 171 QT interval in the 12-lead ECG.

383 384 385 172 386 387 173 *2.4 Statistical analysis*

388
389 174 We report data as means \pm SD and we compared, after testing for normality (Kolmogoroff-
390
391 175 Smirnov), groups using two-tailed Student's *t* test (SPSS 20.0 software package, IBM,
392
393 176 Armonk, New York, USA). To consider the effect size taking into account the differences
394
395 177 between groups' sample sizes, was used the values of Hedges' *g*. The interpretation is the
396
397 178 same as Cohen's *d*: Small effect (cannot be discerned by the naked eye) = 0.2; Medium
398
399 179 Effect = 0.5; Large Effect (can be seen by the naked eye) = 0.8. Our sample size was
400
401 180 generally sufficient to see medium effects (significance with *g* values between 0.4 and 0.5).

402
403
404 181 Univariate analysis was performed to analyse the relationship of cardiac structural
405
406 182 parameters, such as RWT and LVM/BSA and BP at BT and PE including also relative
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416 183 pressure peak (Δ SBP: difference between SBP at PE and at BT). Of note, we report BPs
417
418 184 taken before stress tests.

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421 185 Mixed factorial ANOVA was used to test the effect of time and ethnicity (inter-subject
422
423 186 factor) on quantitative variables, assessing a different trend by the significance of the
424
425 187 interaction race x time.

426
427 188 Multiple regression analysis was used to analyse the relationship between RWT and
428
429 189 LVM/BSA to ethnicity with age, HR, body surface area (BSA, not used for LVM/BSA), and
430
431 190 BP as the covariates. In the analysis BP, from time to time, was included both to the BT, PE
432
433 191 and Δ SBP.

434
435 192 We performed univariate analyses to assess the relationship between ECG-derived variables
436
437 193 (such as QRS duration and QTd) and structural cardiac parameters in the two groups. A 2-
438
439 194 tailed p value < 0.05 was considered as statistically significant.

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443 196 **3. Results**

444 197 *3.1 Baseline characteristics*

445
446 198 All athletes were engaged in organized amateur-level training for approximately ~~eight~~ seven
447
448 199 hours/week (Table 1). The two groups had similar age, height, weight, BSA, and body mass
449
450 200 index. SBP and DBP were higher and HR was lower in BA than WA (Table 1). BA
451
452 201 exhibited higher S1+R5 voltages (38 ± 10 vs 30 ± 10 in WA; $p < 0.001$) with greater prevalence
453
454 202 of ECG-based LVH (19/30, 63% vs 18/60, 30% in WA; $p < 0.001$) and ST elevation (28/30,
455
456 203 93% vs 32/60, 53% in WA; $p < 0.001$) and that of partial right- bundle branch block was
457
458 204 lower (7/30, 23% vs 30/60, 50% in WA; $p < 0.001$) compared with WA. We did not find
459
460 205 differences in inverted T waves.

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463 206

464 207 *3.2 Echocardiographic results*

473
474
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476 208 SWT, PWT and LVM were significantly greater in BA compared with WA with an
477
478 209 increased RWT suggesting a concentric remodelling despite mainly endurance training
479
480 210 (Table 1).

481
482 211 ~~–~~This fits within in agreement with our previous report of a peculiar geometry due to black
483
484 212 ethnicity [64]. By using the LVM and RWT cut-off values to define the distribution of LV
485
486 213 remodeling in the two groups, none of the WA was above the cut-off value for LVM and
487
488 214 5% was above the cut-off value for RWT. On the contrary, the percentage for BA were
489
490 215 23.3% and 13.3%, respectively. Therefore, the distribution of adolescents in the two higher
491
492 216 quadrants was significantly higher in BA (p<0.001). (see Supplementary Figure 2).

493
494 217 LV diameters and volumes were similar in the two groups. LV systolic and diastolic
495
496 218 functions, assessed by conventional and Doppler tissue imaging, were also similar between
497
498 219 groups.(data not shown)

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233 84±11 ms, p= 0.01; 2R: 93±11 vs 84±12 ms, p= 0.002) with a consistently significant greater
234 QTd (Table 2). The other ECG parameters, i.e. P wave duration, PR interval and QT, did not
235 differ between BA and WA.

237 *3.4 Statistical analyses*

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

244 After univariate analysis, the highest correlation coefficient was found between
245 LVM/BSA and SBP at PE for both BA and WA (SBP at PE- WA: r=0.45, p<0.001; BA: r=
246 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,
247 p<0.001; BA: r=0.30, p= ns) whilst RWT correlated with SBP at PE and ΔSBP only in WA
248 (SBP at PE- r=0.35, p<0.01; ΔSBP- r=0.29, p<0.05).

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

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

256 Among the ECG-parameters we analyzed, a significant relationship between
257 LVM/BSA and QTd was found at 2R (r=0.44; p=0.014) in BA, suggesting that

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593 258 inhomogeneity of ventricular recovery time is related to LVM in blacks (Supplementary
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595 259 Figure [1](#), A). No correlations between LVM (Supplementary Figure [1](#), B) and QTd were seen
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598 260 in Caucasians. QRS was not related to structural characteristics of LV in either group.
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600 261

602 262 **4. Discussion**

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604 263 This is the first work that targets the different response to effort stress test between
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606 264 adolescent athletes of two different ethnicities. The main goal was to clarify the physiological
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608 265 mechanisms that underlie the structural and electrical heart differences of the African vs.
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610 266 Caucasian races, in the context of sport medicine.

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612 267 We previously showed that pubertal African athletes have higher LVM compared to
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614 268 their Caucasian counterparts, which is associated to a peculiar concentric, ethnicity-
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616 269 determined remodeling, resulting in a distinct LV phenotype [[64](#)]. Moreover, more
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618 270 pronounced ECG sport-related adaptations, such as LV hypertrophy and early repolarisation,
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620 271 were observed in Black vs Caucasian adolescents athletes [[64](#)]. Here, we report different
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623 272 hemodynamic and ECG changes occurring in the two groups during stress tests. Namely, BA
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625 273 vs WA exhibited higher SBP at rest, both during clinical examinations and at T_0 of a cycle-
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627 274 ergometer test. This difference was maintained during the whole exercise and actually
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629 275 increased at its peak. The converse was detected for HR, which was lower in BA vs WA with
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631 276 significant differences at 4E and at PE. Therefore, the double product was unchanged in the
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633 277 two groups in all steps. A significantly lower HR was also observed during clinical
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635 278 evaluation (yet not at base time of the ergometer test), which we suggest is due to the
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637 279 different clinical context, the different pressure measurement mode (an automated blood
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639 280 pressure system rather than ECG), and a likely greater autonomic response in the Caucasian
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641 281 race as already as demonstrated by other authors [[13](#)].
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652 282 As regards DBP, the effort test confirmed lower values in WA (in agreement with
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654 283 what we observed during the clinical visit), although this difference disappeared during the
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656 284 effort to reappear at R5.
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658
659 285 Population studies indicate that both adult and young Africans have higher blood
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661 286 pressure values; whether this phenomenon is due to different genetics or to social-economic
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663 287 factors is yet to be elucidated [14]. Indeed, clinical studies confirmed these findings, but
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665 288 accumulated data are still controversial [15,16].
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667 289 A higher increase in SBP during treadmill exercise tests was observed in adult black
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669 290 men (from 35 to 40 years) compared to white ones, suggesting that the exaggerated vascular
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671 291 reactivity to physical exercise of the former might be responsible for their major incidence of
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673 292 hypertension [17]. Similar observations were done in pediatric subjects: children from
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675 293 Caucasian and African ethnicities - between 6 to 15 years - were submitted to an effort test
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677 294 and their pressure response was compared [18]. In all age ranges, except for the younger
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679 295 group, a significant higher SBP at peak was detected in black subjects, even though, at base
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681 296 time, their SBP was comparable to that of their Caucasian counterparts [18]. Of note, other
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683 297 investigators did not confirm these results [19,20].
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685

686 298 In a longitudinal study that lasted over 15-years, ethnic differences in ambulatory BP
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688 299 (ABPM) have been reported: African-Americans compared to European-Americans have
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690 300 higher systolic BP both during daytime and nighttime, with a greater increase with age [21].
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692 301 Using ABPM, researchers showed that black adolescents had higher SBP than white ones
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694 302 during sleep, but not during daytime [22].
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697 303 We confirm that black adolescent athletes have higher SPB compared to their
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699 304 Caucasian counterparts and that such difference is more evident during the exercise test. Our
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701 305 results were obtained by using a dual method for BP evaluation, manual and automatic
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712 306 systems integrated to the cycle-ergometer. This allows overcoming the well-known technical
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714 307 difficulties of BP's assessment during exercise and increases the diagnostic accuracy.

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716 308 From an anatomical viewpoint, we confirm the close relationship previously found
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718 309 between cardiac geometry and race [64,23]. The multivariate analysis showed that ethnicity
719
720 310 was strictly related to RWT. The latter weakly correlated with SBP at PE, but not with SBP at
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722 311 BT and age.

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724 312 No correlation between LVM and SBP at rest was found, suggesting that altered BP is
725
726 313 not representative of the global pressure profile determining left ventricular remodelling/LV
727
728 314 mass. Rather, SBP at PE is the strongest predictor of LVM demonstrating that BP measured
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730 315 during the stress test is more stable (being less influenced by neuro-endocrine factors) and is
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732 316 a more accurate estimation of cardiac workload. These results are in agreement with Schultz
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734 317 MG -et al. who recently demonstrated the association between exercise blood pressure,
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736 318 measured immediately after submaximal step-test, and cardiovascular structure (LVM in
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738 319 particular) in a large non-selected cohort of adolescents of both sexes [246]. The association
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740 320 between LVM and SBP developed during physical exercise has been reported also both in
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742 321 healthy subjects and in hypertensive patients [2524,2625].

743
744 322 In summary, the main determinants of LVM and RWT are different: SBP at PE for the
745
746 323 former and race for the latter. Africans conceivably develop higher LVM as a compensation
747
748 324 mechanism for because they are exposed to a higher workload- pressure overload (as detected
749
750 325 by the effort test), whereas their geometry appears to be primarily related to genetic traits
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752 326 rather than SBP (Figure 2).

753
754 327 Race-related differences in cardiac structure become evident during development
755
756 328 when more pronounced changes in myocardial anatomy could be measured [27,2826,27]. In a
757
758 329 prospective study of 687, 8 - 27 years old subjects, followed for more than ten years, ethnicity
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760 330 was a strong predictor of LVM [2726]. This feature was noticeable from puberty and was
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770 331 independent of socioeconomic status, anthropometric characteristics, and hemodynamic
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772 332 stimuli. Expanding on a previous publication, we suggest that the younger, i.e. six months
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775 333 age of athletes explains the lower extent of cardiac morphology differences [2726,2827].
776

777 334 From a mechanistic viewpoint, we suggest that a larger increase of myocytes' size
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779 335 (and not their number) in Africans compared to Caucasians partially explains the cardiac
780
781 336 structure differences in the transpuberal age [2928]. Further, black adolescent athletes might
782
783 337 exhibit increased LVM because of a different hemodynamic load.
784

785 338 Finally, genome-wide association studies recently identified a single nucleotide
786
787 339 polymorphism in intron 16 of the cardiac sodium channel gene *SCN5A* linked with QRS
788
789 340 duration among African Americans that can be related to shorter duration of this interval
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791 341 [3029]. Polymorphisms of *SCN5A* could be related to an overall predominance of transient
792
793 342 outward epicardial currents determining also the early repolarization, more frequent in
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795 343 Africans [3130].
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798 344 LVM also significantly influenced QTd in BA, demonstrating that only the
799
800 345 inhomogeneity of the ventricular repolarization in the African race is related to cardiac
801
802 346 structure. Other studies did not report associations between athlete's heart and ventricular
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804 347 repolarization heterogeneity compared with healthy sedentary controls, despite physiological
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806 348 and structural changes. Thus, an increase in left ventricular mass, in the frame of athlete's
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808 349 heart, does not influence QTd [3231]. Our results indicate differences in the spread of the
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810 350 electric stimulus between the two ethnicities and suggest that the higher QTd of Africans
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812 351 could be employed to assess the risk for arrhythmia in this setting, helping the prognostic
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814 352 stratification of adolescent black athletes. The higher QTd of Africans might also be a marker
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816 353 of a 'midway' condition between physiological and pathological hypertrophy. In summary,
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818 354 ECG measurements differ depending on ethnicity, having Africans shorter QRS duration and
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355 increased QTd; and such differences did not fluctuate with heart rate variations during stress
356 tests.

357
358 *4.1 Limitations*

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

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

368
369 **5. Conclusion**

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

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

383

384 **Disclosures**

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

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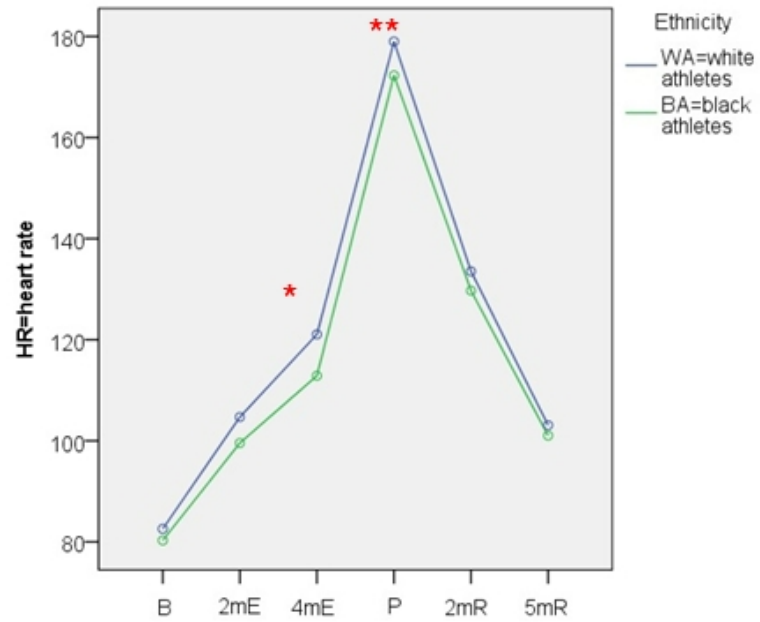
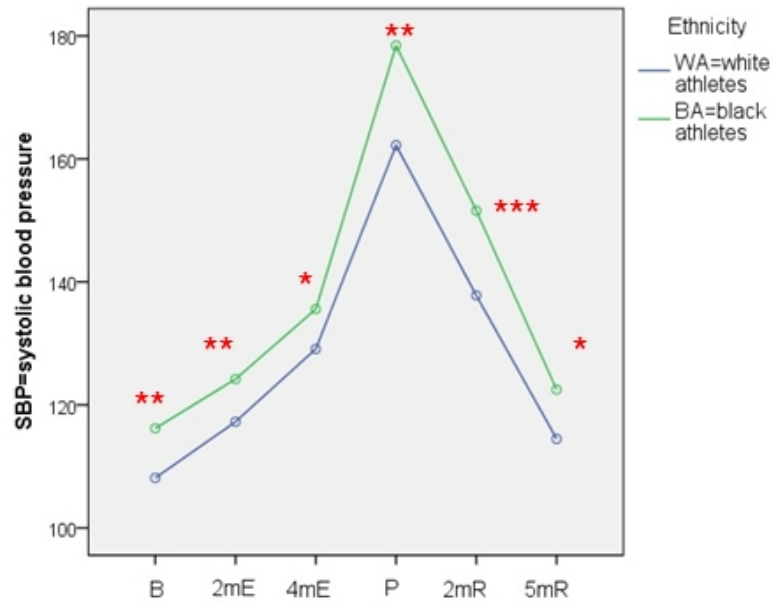
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492 **Figure legends**

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

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



DETERMINANTS OF LEFT VENTRICULAR MASS (LVM) AND GEOMETRY (RWT)

LVM

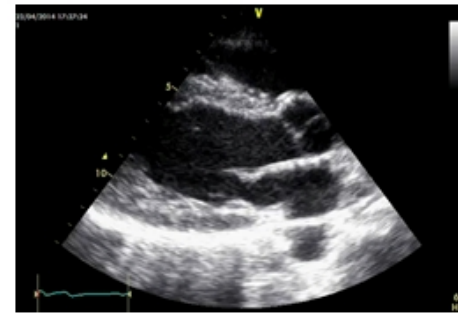
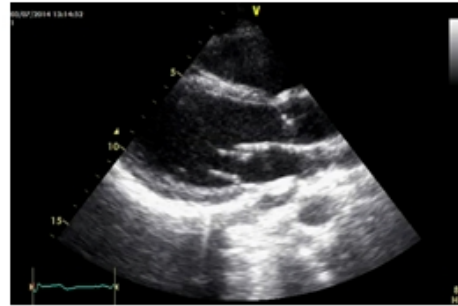
Maximal BP at exercise

Age

A



B



RWT

Ethnicity

Maximal BP at exercise

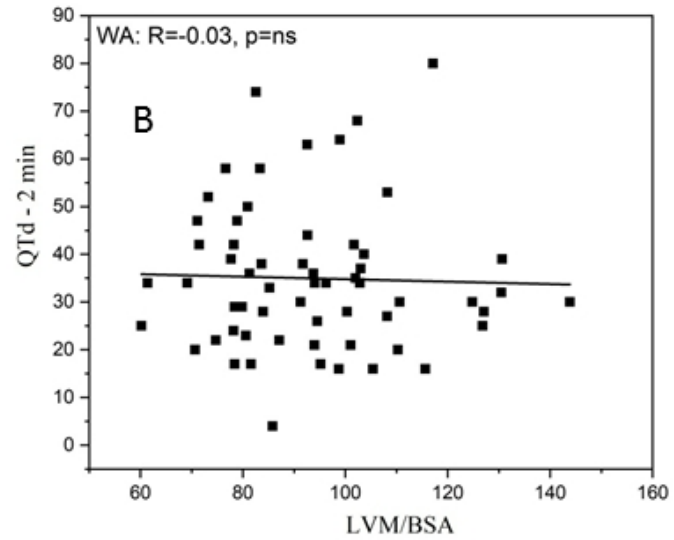
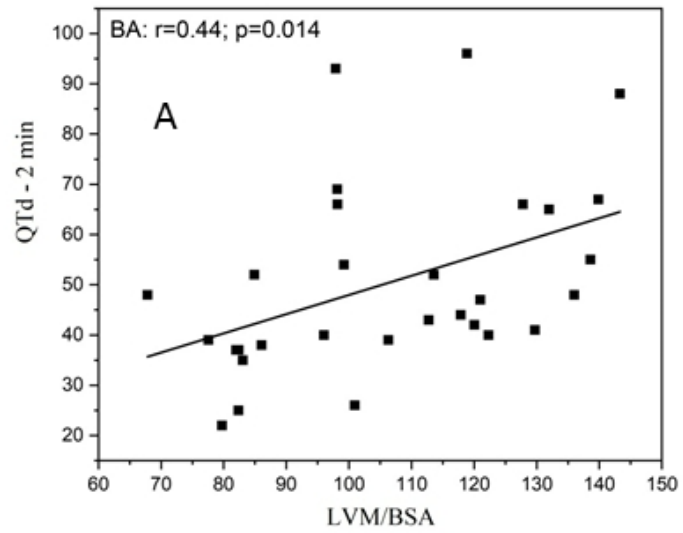
White ethnicity

Black ethnicity



C

D



1 **Table 1**

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

Parameter	WA <i>n</i> =60	BA <i>n</i> =30	<i>p</i> value	<i>Hedges' g</i> <i>Size effect</i>
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

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

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Table 2

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

SBP	WA		BA		<i>p value</i>	<i>Hedges' g Size effect</i>
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		<i>p value</i>	
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		<i>p value</i>	
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		<i>p value</i>	
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		<i>p value</i>	
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 \pm 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].

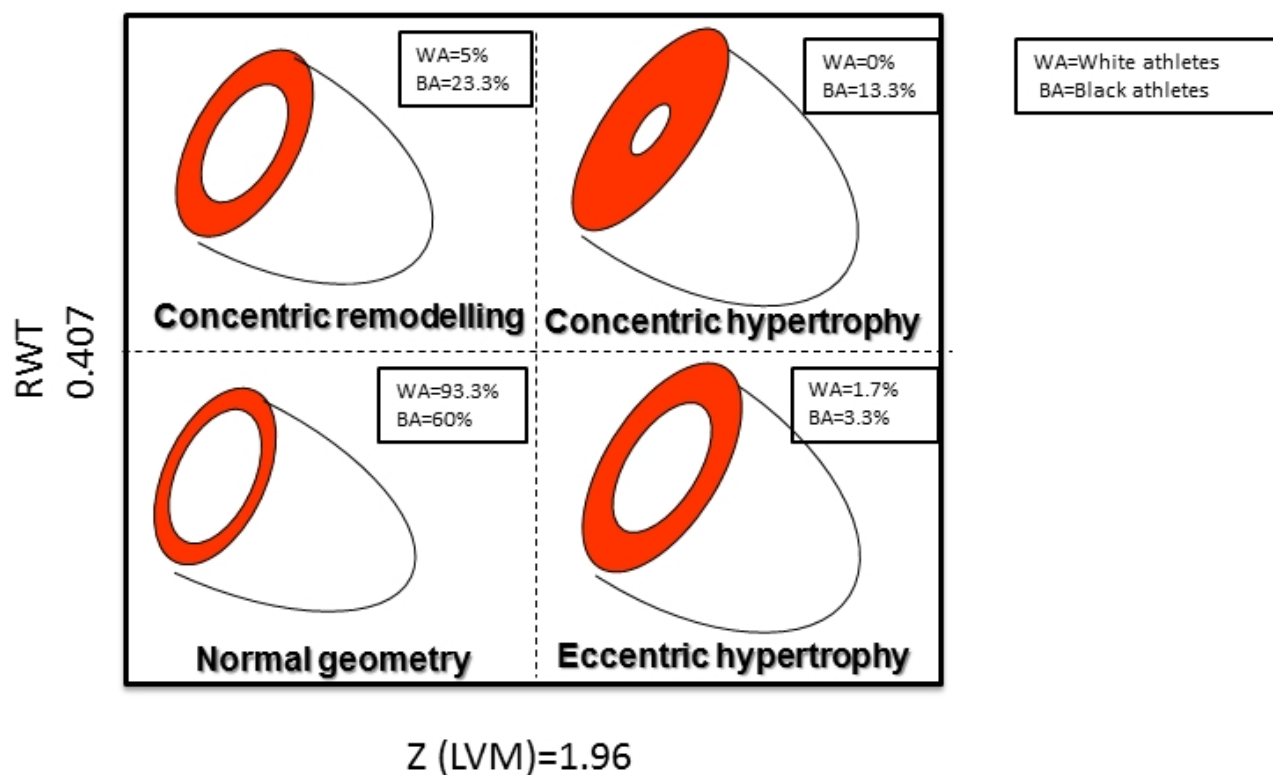
We performed this study in the middle of the sport season and all participants underwent physical examinations with 12-lead resting ECG, ECHO and ergometer stress test.

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 ≥ 35 mm) 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