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High blood pressure response to exercise predicts future development of hypertension in young athletes

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Aims Due to superior exercise performance, athletes show higher blood pressure (BP) at peak exercise compared to untrained individuals. Thus, higher reference values for peak exercise systolic and diastolic BP were reported specifically for athletes. However, the prognostic significance of high blood pressure response (HBPR) to exercise has not yet been clarified in this population.

Methods and results One hundred and forty-one normotensive athletes with HBPR to exercise were compared to 141 normotensive athletes with normal blood pressure response (NBPR) to exercise, matched for gender, age, body size, and type of sport. All athletes were followed up for 6.5 ± 2.8 years. Over follow-up, no cardiac events occurred; 24 athletes were diagnosed essential hypertension (8.5%). Specifically, 19 (13.5%) belonged to the HBPR compared with 5 (3.5%) in the NBPR group ($P = 0.003$). Kaplan–Meier analysis confirmed that the incidence of hypertension during follow-up was higher in the HBPR group (log-rank χ^2 *P*-value = 0.009). Multivariable analysis by Cox proportional hazard survival model showed that resting BP and HBPR at baseline evaluation were the strongest predictors of incident hypertension (χ^2 for the model 30.099; $P < 0.001$). Specifically, HBPR was associated with a hazard ratio of 3.6 (95% confidence interval 1.3–9.9) of developing hypertension. Over follow-up exercise capacity, as well as morphologic and functional cardiac parameters in athletes from both groups did not change significantly.

Conclusion The present study showed that an exaggerated BP response to exercise increased the risk for incident hypertension in highly trained and normotensive athletes over a middle-term period.

Keywords Hypertension • Athletes • Exercise test • Follow-up

Introduction

Exercise testing is commonly performed in young athletes to derive information regarding cardiovascular adaptations to effort and to detect subclinical conditions, such as coronary artery anomalies or arrhythmogenic diseases.[1–4] Assessment of blood pressure (BP) during exercise is an integral part of the test and provides important haemodynamic information with relevant clinical value, such as the hypotensive response in patients with obstructive hypertrophic cardiomyopathy or valvular heart diseases.[5,6] Besides, an exaggerated BP response to exercise has been reported as a prognostic factor for incident hypertension or cardiovascular disease in the general population.[7–11]

Athletes are capable of a superior exercise performance compared with sedentary subjects and the BP achieved at maximal exercise has been reported to be higher compared with the general population.[4,12] However, it is not clear whether an exaggerated BP

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response to exercise in highly trained athletes should be considered a simple adaptation to superior exercise performance (with no clinical significance), or may represent a mismatch of cardiac output and peripheral vascular resistance, and expression of subclinical impairment of vascular relaxation with potential adverse clinical implications.[2,9,12]

We, therefore, planned the present study to evaluate the clinical outcome, in terms of incident hypertension or cardiovascular events, in athletes presenting an abnormally high blood pressure response (HBPR) to exercise.

Methods

Study population

The present study was conducted at the Institute of Sports Medicine and Science in Rome, which is the referral centre for the evaluation of Italian competitive athletes before participating to National or International competitions. Between January 2008 and December 2012, we evaluated 1937 athletes; of these, 61 were excluded because of cardiovascular abnormalities ($n = 3$) or definite diagnosis of hypertension ($n = 58$)[13,14]; therefore, the eligible population was composed of 1876 normotensive healthy athletes.

To the scope of our investigation, we identified two groups of athletes: (i) a group of 141 normotensive athletes with HBPR to exercise testing, here defined as >220 mmHg in male and >200 mmHg in female for peak systolic BP and/or >85 mmHg in male and 80 mmHg in female for peak diastolic BP. These threshold values were derived from a large cohort of elite athletes undergoing maximal exercise testing and corresponded to the 95th percentile[12]; (ii) as a control group we identified 141 normotensive athletes with normal blood pressure response (NBPR) to exercise. The controls were selected from the same large database of athletes, by matching 1:1 with the HBPR group in terms of gender, age (±1 year), body surface area (BSA; ±0.02 m^2), and type of sport participated. Type of sport was defined as skill ($n = 40$), power ($n = 36$), mixed ($n = 92$), or endurance ($n = 114$), as previously reported.[15] All the athletes were of Caucasian ethnicity.

Written informed consent was waived for all athletes undergoing a standard clinical evaluation pursuant to Italian law and Institute policy. The study design was approved by the Review Board of the Institute and funded by the Italian National Olympic Committee.

Clinical evaluation

Cardiovascular evaluation included clinical history, physical examination, and resting 12-lead electrocardiogram (ECG). Office resting BP was measured by an experienced cardiologist in the sitting position, after at least 5 min of rest and prior to the exercise test.[13,14,16] Body height and weight were obtained in each subject before exercise testing. Body surface area and body mass index (BMI) were calculated.

Exercise testing

The exercise testing was performed on a bicycle ergometer (Cubestress XR400, Cardioline SpA, Italy). The starting load was 0.5 W/kg, with subsequent increase of 0.5 W/kg every 2 min until exhaustion, identified as the time when the athlete was unable to maintain the power output despite encouragement. Digital 12-lead ECG was monitored before the test, continuously during the exercise, and for at least 5 min during the recovery phase. To measure the BP in a reliable and consistent fashion over the test, the patient was asked to put the left arm in an extended and relaxed position with the hand over the doctor's shoulder. Both systolic and diastolic BPs were manually measured at rest, at every incremental step until peak exercise and during recovery.[12]

Echocardiography

Two-dimensional and Doppler echocardiography was performed using iE33 (Philips Medical System, Andover, MA, USA). Two-dimensional measurements of left ventricular (LV) cavity, wall thickness, left atrium, and aortic root diameters were performed according to the European Association of Cardiovascular Imaging and American Society of Echocardiography.[17] Left ventricular mass was measured by Devereux's formula and normalized to BSA. Diastolic function was evaluated as previously reported and conformed to current recommendations.[18]

Follow-up

Athletes were followed-up according to our medical programme for elite athletes.[19] Data from the most recent clinical evaluation were reviewed. Onset of hypertension was defined when BP was ≥140/90 mmHg on at least two consecutive measurements, or when a specific pharmacological treatment was started.[13,14] Cardiovascular events were considered any of death, stroke, myocardial infarction, or coronary revascularization.

Statistical analysis

Continuous data were expressed as mean ± standard deviation and categorical data as number of observations and frequencies. Differences between groups were evaluated with unpaired *t*-test and Levene's test for the equality of variance; differences between proportions were calculated by χ^2 test. Statistical significance was set for a *P*-value <0.05. Change in measurements over time within the same subject was assessed by paired samples *t*-test; additionally, difference in measurements at follow-up and baseline evaluation was performed and average changes were compared across groups with unpaired samples *t*-test.

The effect of HBPR on incident hypertension was assessed by Kaplan–Meier analysis with log-rank test. Additionally, Cox proportional regression analysis was used to identify those variables that were associated with incidence of hypertension. Factors with a univariate value of $P < 0.05$ were included in a stepwise multivariable logistic regression analysis. Categorical variables included family history, smoking habit, and type of sport. The impact of type of sport was assessed by a binary categorical variable using $N-1$ dummy variables, with skill disciplines chosen as the reference value. For the multivariable analysis, resting systolic and diastolic BP were recoded as ordinal variables with 5 mmHg increment. Statistical analysis was performed with SPSS software (version 24; SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

The baseline and follow-up characteristics of athletes with HBPR and controls are summarized in *Table 1*. The mean age at baseline evaluation of the overall group was 26 ± 6 years and 66% were male. No significant difference was found in terms of family history of hypertension (45 vs. 31; $P = 0.060$) or smoking habit (5 vs. 1; $P = 0.099$) between HBPR and NBPR groups. Both resting and exercise BP were higher in the HBPR group at baseline evaluation, while peak bicycle ergometer workload was not significantly different. In terms of cardiac adaptations, echocardiography showed similar cardiac dimensions in the two groups and no significant differences for LV systolic and/or diastolic function.

Table 1 Baseline and follow-up characteristics of athletes with normal blood pressure response (NBPR) or high blood pressure response (HBPR) to exercise

Parameters	NBPR	HBPR	*P*-value
Age (years)	26.0 ± 5.9	25.9 ± 6.1	0.953
Follow-up	32.4 ± 6.5	32.5 ± 6.4	0.861
Difference	6.4	6.6	0.602
BSA (m^2)	1.98 ± 0.22	1.99 ± 0.24	0.473
Follow-up	1.98 ± 0.23	2.01 ± 0.26	0.293
Difference (95% CI)	0.001 (-0.006 to 0.007)	0.11 (0.001–0.021)[a]	0.089
BMI (kg/m^2)	23 ± 3	24 ± 3	0.106
Follow-up	23 ± 3	24 ± 4	0.051
Difference (95% CI)	0.13 (0.01–0.24)[a]	0.28 (0.08–0.48)[a]	0.203
Resting systolic BP (mmHg)	116 ± 11	121 ± 9	<0.001
Follow-up	117 ± 10	122 ± 12	<0.001
Difference (95% CI)	0.97 (-0.51 to 2.45)	0.79 (-1.12 to 2.69)	0.879
Resting diastolic BP (mmHg)	74 ± 8	77 ± 6	0.007
Follow-up	75 ± 8	77 ± 7	<0.001
Difference (95% CI)	0.30 (-0.74 to 1.33)	0.53 (-0.72 to 1.79)	0.770
Maximal workload (W)	257 ± 62	262 ± 61	0.429
Follow-up	261 ± 60	261 ± 60	0.962
Difference (95% CI)	4.03 (0.19–7.87)[a]	-1.45 (-6.51 to 3.60)	0.089
Max systolic BP (mmHg)	185 ± 20	208 ± 22	<0.001
Follow-up	187 ± 19	203 ± 26	<0.001
Difference (95% CI)	1.25 (-1.13 to 3.63)	-4.86 (-8.86 to -0.86)[a]	0.010
Max diastolic BP (mmHg)	74 ± 7	83 ± 9	<0.001
Follow-up	75 ± 8	82 ± 11	<0.001
Difference (95% CI)	1.21 (-0.18 to 2.61)	-0.75 (-2.23 to 0.74)	0.059
Maximal wall thickness (mm)	10 ± 1	10 ± 1	0.294
Follow-up	10 ± 1	10 ± 1	0.235
Difference (95% CI)	0.06 (-0.02 to 0.15)	0.08 (-0.02 to 0.20)	0.760
LV cavity diameter (mm)	54 ± 5	54 ± 5	0.823
Follow-up	54 ± 4	54 ± 4	0.736
Difference (95% CI)	0.16 (-0.07 to 0.38)	0.10 (-0.20 to 0.41)	0.767
Ejection fraction (%)	64 ± 6	64 ± 6	0.876
Follow-up	65 ± 6	65 ± 5	0.442
Difference (95% CI)	0.83 (-0.17 to 1.84)	0.22 (-0.68 to 1.12)	0.368
Left atrial diameter (mm)	36 ± 4	36 ± 4	0.658
Follow-up	36 ± 4	36 ± 5	0.969
Difference (95% CI)	0.23 (-0.17 to 0.62)	-0.01 (-0.71 to 0.69)	0.565
Aortic root diameter (mm)	31 ± 4	31 ± 4	0.884
Follow-up	32 ± 4	32 ± 4	0.719
Difference (95% CI)	0.56 (0.28–0.84)[a]	0.66 (0.36–0.96)[a]	0.635
LV mass index (g/m^2)	102 ± 23	103 ± 21	0.779
Follow-up	103 ± 24	105 ± 21	0.650
Difference (95% CI)	0.60 (-0.92 to 2.11)	1.02 (-0.75 to 2.78)	0.720
E/A	1.9 ± 0.5	1.9 ± 0.5	0.981
Follow-up	1.87 ± 0.48	1.8 ± 0.5	0.476
Difference (95% CI)	-0.03 (-0.08 to 0.03)	-0.08 (-0.15 to -0.01)[a]	0.215
TDI *e′*	14 ± 2	14 ± 2	0.484
Follow-up	13 ± 4	14 ± 5	0.406
Difference (95% CI)	-0.07 (-0.87 to 0.74)	-0.32 (-0.89 to 0.25)	0.616
E/e′	6.1 ± 1.1	6.4 ± 1.4	0.101
Follow-up	6.3 ± 1.2	6.5 ± 1.4	0.363
Difference (95% CI)	0.11 (-0.09 to 0.31)	0.05 (-0.15 to 0.25)	0.660

First row for each parameter reports values at baseline evaluation, second row (follow-up) reports values at last follow-up evaluation, and third row (difference) reports the difference: follow-up value—baseline value, with 95% confidence interval.

BMI, body mass index; BP, blood pressure; BSA, body surface area; CI, confidence interval; LV, left ventricle; TDI, tissue Doppler imaging.

[a]Follow-up value significantly different compared to baseline with $P < 0.05$.

Follow-up evaluation

Average follow-up was 6.5 ± 2.8 years and not significantly different between the two groups ($P = 0.602$). All athletes continued training regularly and none was disqualified from competitions. No cardiac events occurred, including death, stroke, myocardial infarction, or coronary revascularization. Few athletes complained of symptoms during follow-up ($n = 15$; 5%), including palpitations in 11 (recognized as reciprocating atrioventricular node tachycardia in two, who underwent successful radiofrequency ablation), vasodepressor, neuromediated syncope in three, and hemicrania in one; overall incidence of symptoms was not significantly different between groups (4% vs. 6%; $P = 0.426$).

During follow-up, 24 athletes (20 males and four females) were diagnosed essential hypertension (8.5%); of these, 19 were in the HBPR (13.5%) and five in the control group (3.5%; χ^2 *t*-test *P* value = 0.003; *Figure 1*). In terms of gender, incident hypertension occurred in four females out of 48 (8.3%) in the HBPR group compared with none in the control group ($P = 0.041$) and 15 males out of 93 (16%) in the HBPR group compared with 5 (5%) in the control group ($P = 0.018$).

Kaplan–Meier analysis showed a higher incidence of hypertension among the HBPR athletes (log-rank χ^2 *P*-value =0.009; *Figure 2*). Consistently, pharmacological treatment (including angiotensin-converting enzyme inhibitors in three, angiotensin receptor blocker in three and beta-blocker in one) was more frequently started in athletes within the HBPR group ($n = 6$) compared with controls ($n = 1$; $P < 0.001$).

Of note, maximum exercise capacity was similar in both groups and did not change significantly over the follow-up; in athletes with HBPR we observed a trivial (but statistically significant) reduction in peak systolic BP at the last evaluation, which was not seen in the control group. This reduction of peak systolic BP remained significant in the HBPR group even after removing the small subset of athletes taking medications (peak systolic BP at baseline 208 ± 23 mmHg vs. 202 ± 26 mmHg at follow-up, $P = 0.008$; peak diastolic BP at baseline 83 ± 10 mmHg vs. 82 ± 10 mmHg at follow-up, $P = 0.115$). In terms of cardiac morphology, both groups showed a minimal but significant change in aortic root size, which did not differ significantly across groups. No other morphologic or functional cardiac parameters changed significantly over follow-up (*Table 1*).

Table 2 shows results from univariate and multivariable analyses. Resting BP and HBPR at baseline evaluation were the strongest predictors of incident hypertension (χ^2 for the model 30.099; $P < 0.001$). Specifically, HBPR was associated with a hazard ratio of 3.6 (95% confidence interval from 1.30 to 9.93) of developing hypertension.

Discussion

The most important finding of our study was that in young normotensive athletes, an abnormally high systolic and/or diastolic BP response to exercise testing was an independent and significant predictor of incident hypertension, during an average follow-up of almost 7 years. Specifically, athletes with HBPR had a hazard ratio of developing hypertension 3.6 times higher compared with those with normal BP response during exercise.

Findings from our study further expand several previous observations reporting an association between hypertensive response to exercise and cardiovascular outcome and/or incident hypertension. A meta-analysis by Schultz *et al.*,[10] including 12 studies and >46 000 subjects followed-up for 15 ± 4 years, reported that exaggerated BP response at moderate exercise intensity was associated with a 36% increase in cardiovascular events and mortality, independently of age, gender, resting BP, and cardiac risk factors. A recent study by Berger *et al.*[20] on >7000 normotensive subjects reported that over a follow-up period of 5 ± 3 years, almost 15% developed hypertension; specifically, this risk was related to quartiles of peak systolic and diastolic BP on exercise testing, with individuals in the fourth quartile having 35% probability of developing hypertension.

Of note, most of the studies published to date reported data derived from general population, in the middle-age range, while less is known regarding young individuals and specifically those involved in regular and intensive training programmes.

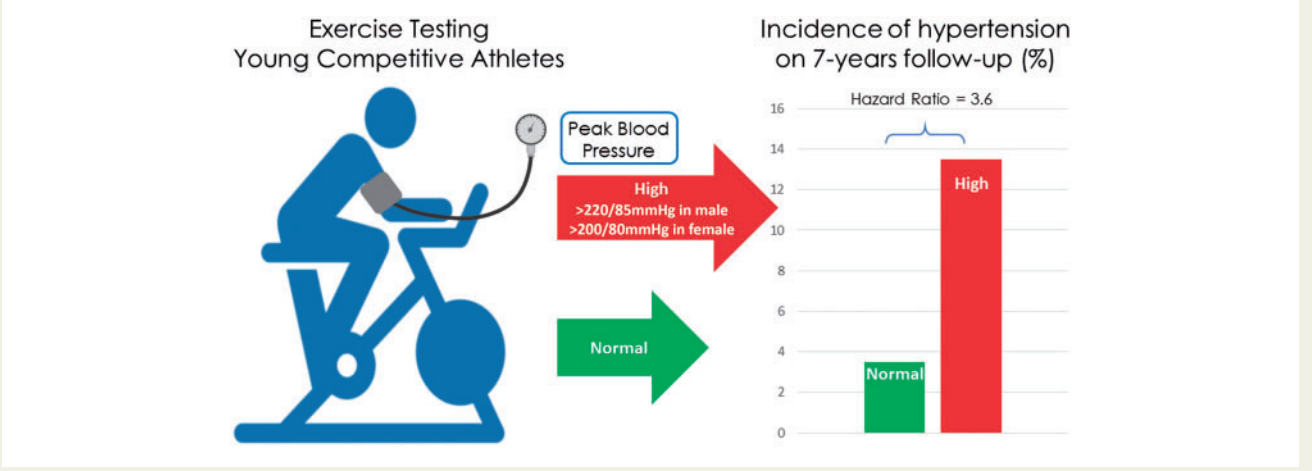

Figure 1 Incidence of hypertension in athletes according to peak exercise blood pressure at baseline evaluation.

In a previous study, we observed that athletes with HBPR to exercise were most commonly engaged in endurance and mixed sporting disciplines, had higher BMI and resting BP values, showed a higher degree of LV remodelling on echocardiography and were able to attain higher workload on exercise testing in comparison to those with normal BP response.[12] In consideration of these findings, it was not clear whether the higher BP values we observed at peak exercise were related simply to the higher performance on bicycle ergometer and could be considered an expression of a superior cardiac adaptation, deprived of any clinical significance.

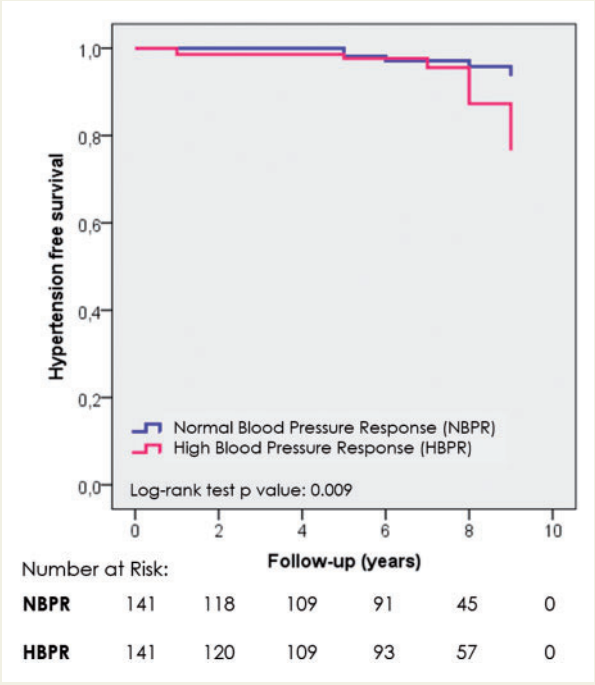

Figure 2 Kaplan–Meier analysis showing hypertension free survival of athletes according to normal blood pressure response or high blood pressure response to exercise.

Our results showed that an exaggerated BP response to exercise was associated with incident hypertension in 13.5% of athletes, compared with only 3.5% in those with normal BP at exercise test. Interestingly and potentially related to the young age at baseline evaluation, the development of hypertension was observed in the later phase of follow-up and, as shown in *Figure 2*, the separation of curves occurred only 7 years after the baseline evaluation.

During the follow-up, we did not record any major adverse cardiovascular event, which was also likely related to the young age, and the excellent cardiovascular fitness (as well as the low risk profile) of our athlete's population.[21]

Several mechanisms have been proposed to explain the excessive increase in BP during exercise, including high-sympathetic tone, decreased aortic distensibility, endothelial dysfunction, and increased activation of the renin-angiotensin-aldosterone system.[2,22,23] Shim *et al.*[24] reported different neuro-hormonal changes in normotensive individuals with or without HBPR to exercise. They observed that an exaggerated BP response to exercise was associated with increased angiotensin II levels compared with those with NBPR; conversely, no difference was found between groups in terms of rise of catecholamines, aldosterone, and plasma renin activity.

In a recent study, Tzemos *et al.*[25] reported that an exaggerated BP response was related to endothelial dysfunction, decreased proximal aortic compliance, and increased neuro-hormonal activation, all conditions able to predict future cardiovascular morbidity. Another possible explanation could be related to masked hypertension, not clinically evident during office evaluation but that may become overt during follow-up.[26] Eventually, pathophysiological mechanisms linking the exaggerated BP response to exercise and incident hypertension are not yet fully understood and remain largely a matter of controversy.

An interesting observation on our study population (and other previous reports) is that athletes with HBPR to exercise also

Table 2 Results of univariate and multivariable analyses to identify variables associated with incident hypertension

	Univariate		Multivariable		Hazard ratio (95% CI)
	B	*P*-value	*B*	*P*-value	
Age (1 year)	0.06	0.072			
Gender (male)	-0.95	0.082			
Power discipline	0.59	0.239			
Mixed discipline	-0.86	0.118			
Endurance discipline	-0.35	0.426			
Family history	0.89	0.030			
Body surface area (m^2)	2.37	0.005			
Body mass index (kg/m^2)	0.16	<0.001			
Resting SBP on baseline evaluation (5 mmHg)	0.46	<0.001	0.37	0.003	1.45 (1.13–1.85)
Resting DBP on baseline evaluation (5 mmHg)	0.77	<0.001	0.41	0.041	1.50 (1.02–2.22)
HBPR	1.21	0.015	1.28	0.014	3.59 (1.30–9.93)

For categorical variables, female gender, skill sports, negative family history, and normal blood pressure response to exercise were chosen as the reference condition. For systolic and diastolic blood pressure, the *B* coefficient and hazard ratios refer to a 5 mmHg increase.
DBP, diastolic blood pressure; HBP, high blood pressure response to exercise; SBP, systolic blood pressure.

presented higher resting BP at baseline evaluation, even though none with overt hypertension. Miyai *et al.*[8] reported that in individuals with a high-normal resting BP and exaggerated increase of BP during exercise the risk for future hypertension was increased by 2.3 times. Therefore, a practical consequence is that individuals with high-normal BP at rest may be better evaluated and risk stratified after the exercise testing.

In consideration of the absence of events or major symptoms in the follow-up, the identification of athletes with HBPR to exercise should not raise concerns in terms of sport participation. We believe it appropriate for these individuals to enter a periodical follow-up programme with controls every 1–2 years. The overall cardiovascular risk profile should be assessed, and lifestyle modification advised including weight control, reduced intake of salt, supplements, alcohol, and anti-inflammatory drugs; these recommendations are frequently sufficient to achieve an optimal BP control in athletes.[16] Additionally, the timely identification and correction of risk factors in the early phase of sport participation plays an important role in the context of the cardiovascular prevention of the athlete in the long term: indeed, at the end of their career, when the beneficial effects of intense exercise may decrease, some athletes may further increase their overall risk profile.[27–29]

Moreover, despite some individuals having developed hypertension, no significant changes in terms of cardiac remodelling occurred during follow-up (except for a minimal increase in aortic root size, likely related to the aging process). Therefore, the beneficial effects of prolonged and continued exercise activity seem to (at least partially) counterweight the effects of hypertension on athlete's heart.

It is worth mentioning that our investigation also presents certain limitations, including the relatively young age of athletes at the most recent evaluation, which justifies the low incidence of major symptoms or cardiovascular diseases. Our study population was entirely comprised of Caucasian individuals and, therefore, our results should not be extrapolated to different ethnic population such as Afro-Caribbean or African athletes (where hypertension is more prevalent).

We also acknowledge that due to the small sample size of our population some risk factors, such as hypertensive family history and cigarette smoking were not significantly related to incident hypertension. Finally, our protocol did not include cardiac magnetic resonance imaging, and therefore, we were not able to confirm the recent finding of focal areas of late gadolinium enhancement compatible with areas of interstitial fibrosis in male triathletes with a history of exercise induced hypertension.[30]

Conclusion

In conclusion, an exaggerated BP response to exercise in normotensive athletes should not be disregarded as a benign adaptation to the high-exercise performance but should be considered as a risk factor for incident hypertension over a middle-term period.

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Conflict of interest: none declared.

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