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Exercise-induced Hypertension and Carotid intima-media thickness in male marathon runners.

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Abstract

This study aimed to identify the relationship between exercise-induced hypertension and carotid artery intima-media thickness in long-distance runners. Sixty healthy male runners aged 40–60 years were assigned to the following three groups based on resting blood pressure and maximal systolic blood pressure during a maximal exercise test: normal blood pressure response, exercise-induced hypertension, and complex hypertension. An exaggerated systolic blood pressure response was defined as a maximal systolic blood pressure ≥210 mmHg during the maximal exercise test, while carotid intima-media thickness was measured using B-mode ultrasonography. The carotid intima-media thickness mean values were the highest in the complex hypertension group (0.72±0.11 mm), followed by exercise-induced hypertension (0.62±0.12 mm) and normal blood pressure groups (0.55±0.13 mm), with a significant difference between the groups ($p<0.002$). In linear regression analysis, the mean intima-media thickness was independently associated with age ($p=0.015$) and maximal systolic blood pressure ($p=0.046$) but not with resting systolic blood pressure. These results suggest that exercise-induced hypertension is associated with carotid intima-media thickness, a surrogate marker of cardiovascular disease, in long-distance runners. Therefore, evaluating the blood pressure response during exercise is important for the early detection of potential cardiovascular disease risks in long-distance runners.

Introduction

Exercise-induced hypertension (EIH), an exaggerated systolic blood pressure (SBP) response to exercise, is a predictor of future hypertension [1]. It is also associated with an increased risk of stroke [2] and cardiovascular mortality [3]. Although regular aerobic exercise reduces the risk of cardiovascular diseases (CVD), high-intensity exercises such as marathons can cause excessive strain on the cardiovascular system. Interestingly, a recent study showed that EIH may be associated with a 3.6-fold increased risk of hypertension in highly trained athletes [4]. In fact, long-distance

runners with EIH have an increased risk of cardiovascular events, including the increased incidence of coronary artery plaque [5], elevated markers of myocardial damage [6,7], and increased arterial stiffness [8], compared to runners with normal blood pressure (BP). Witham and Babbitt [9] highlight the increased risk of cardiac events in long-distance runners and emphasize the importance of healthcare professionals screening and educating runners on cardiac risk factors. Notably, repeated increases in BP can cause structural changes in the blood vessels, such as increased carotid artery intima-media thickness (IMT). Carotid artery IMT is an important subclinical marker that can monitor the process of vascular damage before the onset of clinical CVD, and it has high clinical utility in terms of prevention because it can be measured non-invasively using ultrasound [10]. Furthermore, it is an independent indicator of increased risk for cerebrovascular disease, even after accounting for other traditional CVD risk factors [11,12]. Carotid IMT increases with risk factors for CVD, such as age, hypertension, dyslipidemia, and obesity [13]. However, BP has the greatest impact on carotid IMT [14]. In contrast, it has been suggested that exercise training and fitness can decrease carotid IMT [15,16]. However, most of these studies have been conducted on general adult populations, and there is a lack of research examining carotid IMT in long-distance runners. Gori et al. [17] suggested that prolonged, high-intensity exercise can induce structural changes in athletes' blood vessels, similar to athletes' hearts; however, insufficient evidence supports this. The underlying factors and clinical significance of these findings have been hotly debated. A study comparing trained runners to sedentary controls found that there was no significant difference in cIMT between the two groups [18]. Pressler et al. [19] found that running multiple marathons did not pose an additional risk factor for vascular impairment beyond age. However, Previous studies have shown that an increase in carotid IMT is related to a decrease in endothelial function and compliance, which are the main factors causing increased BP during exercise [20]. Long-distance runners with EIH may be at higher risk if the carotid artery is adversely affected. However, there is insufficient evidence to support this. Therefore, this study aimed to verify the relationship between EIH and carotid IMT in long-distance runners.

Methods

Participants

This study included 60 male runners aged 40–60 years with a minimum of 4 years of marathon

experience and participation in at least 5 full-course marathons. The participants were classified into three groups based on resting BP and maximum SBP at maximal exercise test as follows: normal BP response group (NBPG), exercise-induced hypertension group (EIHG), and complex hypertension group (CHG). EIH was defined as a resting SBP/DBP less than 140/90mmHg and a maximal SBP of 210 mmHg or higher during the maximal exercise test. Complex hypertension was defined as a resting SBP/ DBP of 140/90 mmHg or higher and a maximal SBP of 210 mmHg or higher during exercise. The study design is presented in Figure 1. This study was approved by the Institutional Review Board (IRB NO: SSWUIRB 2019-017).

Resting BP

Resting BP was measured with an automatic sphygmomanometer (Home 3MX1-1; WathchBP, Taipei, Taiwan) after a 10-minute rest. BP was measured twice at 3-minute intervals. The mean value of the two measurements was used.

Carotid artery IMT measurement

Carotid artery IMT was determined using a high-resolution B-mode ultrasound system (ACUSON X300 ultrasound imaging system, Siemens, Mountain View, CA, USA) with an 11.4-MHz linear probe, following the guidelines of the Mannheim IMT consensus [21]. With the subjects in a supine position and their necks rotated to the left, longitudinal images of the common carotid artery were acquired 10 mm below the carotid bulb to determine the carotid artery IMT. IMT was defined as the distance between the leading edge of the lumen-intima interface and that of the media-adventitia interface of the far wall of the carotid artery. The mean value of thickness was defined as IMT_{mean}, which was automatically measured. All measurements were taken at the end of the diastole.

Maximal exercise test

Maximal exercise test was performed using the Bruce protocol on a treadmill (Quinton Cardiology Systems Inc., Bothell, WA, USA). Maximal oxygen uptake (VO2max) was measured using a portable metabolic system (TrueOne 2400; Parvo Medics, Murray, UT, USA), and breath-by-breath data were averaged over 15 seconds. Exercise BP was measured during the last minute of each 3-minute stage using an automatic BP device (Tango, sunTECH, Wuxi, China). An integrated headset was used by a trained researcher to reduce measurement errors and ensure the correct identification of Korotkoff

sounds during blood pressure measurement. The maximal SBP was defined as the highest value measured during the test. The criteria for termination and maximal effort of exercise tests followed the guidelines of the American College of Sports Medicine [22].

Statistical analysis

Data are presented as mean±standard deviation, median (25^{th}–75^{th} percentile), or number (%). Characteristics of the three groups (NBPG, EIHG, and CHG) were compared using one-way ANOVA and the Kruskal-Wallis test for continuous variables. Post-hoc analyses were performed using the LSD and Mann-Whitney U test if there was a significant difference between groups. Furthermore, Pearson correlation analysis and multiple linear regression analysis were conducted to analyze the association between carotid IMT and exercise-induced hypertension. All data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA), and statistical significance was set at $p<0.05$.

Results

Physical characteristics

Among the 60 subjects, 14 (23.3%), 34 (58.3%), and 11 (18.3%) were the NBPG, EIHG, and CHG, respectively. Group comparisons of the characteristics are shown in Table 1. We found that the demographics, anthropometrics, and careers of marathons were similar in all three groups. Additionally, there were no significant differences in the training volume. Although the total exercise testing time did not significantly differ among the three groups ($p>0.05$), NBPG had higher maximal oxygen uptake (VO2max) than EIHG and CHG (NBPG vs. EIHG, $p=0.022$; NBPG vs. CHG, $p=0.015$); however, there was no significant difference in VO2max between the CHG and EIHG ($p>0.050$) (Table 1).

Resting BP and maximal BP during maximal exercise testing

Resting SBP and DBP were the highest in CHG, and there was no significant difference between the NBPG and EIHG ($p>0.05$) (Table 1). In addition, maximal SBP and DBP during exercise testing were significantly higher in EIHG (SBP_{max} 246.01±7.1 mmHg, DBP_{max} 80.1±15.5 mmHg) and CHG (SBP_{max} 244.9±16.8 mmHg, DBP_{max} 73.6±13.4 mmHg) than NBPG (NBPG vs. EIHG, $p<0.001$; NBPG vs. CHG, $p<0.001$), and there was no significant difference between the EIHG and CHG ($p>0.05$) (Table

2).

Carotid artery IMT

Carotid IMT_{mean} was the highest in CHG (0.72±0.11 mm) than in EIHG (0.62±0.12 mm) and NBPG (0.55±0.13 mm, CHG vs. EIHG, p=0.014; CHG vs, NBPG, p=0.001). Additionally, the carotid IMT_{mean} was significantly higher in EIHG than in NBPG (p=0.029) (Fig 2).

Correlation between BP and carotid artery IMT

Pearson correlation analysis showed that IMT_{mean} was positively correlated with both SBP_{rest} (r=0.283, p=0.028) and SBP_{max} (r=0.312, p=0.015) (Figure 3, 4). However, The results of the multiple linear regression analysis using IMT_{mean} as the dependent variable and SBP_{rest}, SBP_{max}, age, marathon career, and training volume as independent variables showed that age (p=0.015) and SBP_{max} (p=0.046) but not resting SBP and exercise volume, were independently associated with IMT_{mean} (Table 3, Fig 5). The regression equation is as follows: IMT_{mean} = -0.656+0.009*age+0.001* SBP_{max}

Discussion

This study investigated the relationship between the EIH and carotid artery IMT in long-distance runners. We found that the CHG had the highest carotid IMT, followed by the EIHG and NBPG. In the correlation analysis between carotid IMT and BP, IMT_{mean} showed a correlation with both resting SBP and SBP_{max}. Although carotid IMT is known to be most influenced by BP [14], the multiple regression analysis to identify factors related to IMT_{mean} in this study showed that only age and SBP_{max} were related to IMT_{mean}, and there was no correlation with resting SBP. This suggests that excessive BP increase during exercise in healthy marathon runners may increase the risk of carotid atherosclerosis. To the best of our knowledge, our results are the first reported regarding the carotid artery in long-distance runners with EIH. There is a dose-response relationship between exercise volume and health benefits [23]; however, excessive exercise, such as marathon running, can place stress on the cardiovascular system [24] and may lead to arterial stiffening [25]. Nevertheless, studies regarding the indicators of carotid atherosclerosis in long-distance runners have reported varying results. Koutlianos et al. [26] found that immediately after the 246 km ultra-marathon race, there was an acute increase in

arterial stiffness and vascular resistance, but the carotid artery thickness of ultra-marathon runners was within normal range. Kroger et al. [27] reported the presence of atherosclerotic lesions in both the carotid and peripheral arteries of marathon runners, while Galetta et al. [28] reported that carotid IMT was lower in elderly long-distance runners compared to an age-matched control group. Additionally, Heffernan et al. [29] and Taylor et al. [18] have suggested that there is no significant difference in carotid IMT between long-distance runners and the general population. The differences in results between these studies raise questions regarding whether high-intensity exercise accelerates the development of atherosclerosis and whether there are factors that cause greater vascular damage in similar exercise conditions. Some previous studies have also suggested that excessive exercise is not a major factor in increasing carotid IMT. In a study by Müller et al. [30], which observed changes in carotid IMT in 38 marathon runners over 4 years, carotid IMT increased by approximately 0.013±0.023 mm per year and a total of 0.05±0.09 mm over 4 years. This was similar to the results of previous studies that suggested an increase in carotid IMT of 0.01–0.03 mm per year in the general population [31]. It also showed that carotid IMT was not related to training volume or marathon participation frequency. In this study, the training volume and marathon experience were similar among all groups, and regression analysis showed that IMT was not related to training indicators. Notably, the IMT_{mean} of the participants in this study was 0.55±0.13 mm in the NBPG, which was lower than that of the Korean age-matched value of 0.65±0.12 mm; 0.62±0.12 mm in the EIHG, which was similar; and 0.72±0.11 mm in the CHG, which was thicker than that of the age-matched group [32]. These findings suggest that even long-distance runners can have lower carotid IMT than the general population if they maintain a normal BP. However, if BP increases during rest or exercise, IMT may be thicker in long-distance runners than in the general population. Therefore, it can be considered that EIH, rather than the effects of high-intensity exercise, is a factor that accelerates the changes in IMT of long-distance runners.

Notably, the increase in carotid IMT has been shown to be an important indicator of elevated BP during exercise in several studies. In Kader et al.'s study [33], the group with high BP during both rest and exercise showed decreased endothelial dilation and higher carotid IMT only at rest compared to the group with high SBP at rest only, emphasizing that excessive SBP during exercise is a significant risk factor for CVD. Jae et al.'s study [34] also showed a close relationship between elevated BP

during exercise and carotid artery sclerosis, with the prevalence of carotid artery sclerosis being 1.57 times higher in the group with the highest increase in BP during exercise. These studies suggest that an excessively high BP during exercise is a meaningful indicator of the risk for carotid artery sclerosis and has clinical significance [35]. According to the previous search findings, an exaggerated blood pressure response to exercise in athletes is not a benign phenomenon [36]. It is, therefore, important to monitor blood pressure during exercise and intervene early to reduce the risk of end-organ damage.

The clear mechanism by which an excessive BP increase during exercise contributes to increased subclinical CVD risk, such as carotid IMT, has not yet been elucidated. However, the following possible mechanisms can be considered. The first is a decreased vascular regulation ability. For example, shear stress exerted by blood flow on the vascular wall is the most important factor regulating vascular remodeling [37]. Excessive BP increase due to a disorder of decreased peripheral vascular resistance and vascular relaxation capacity [38,39] increases shear stress and local distension pressure generated by blood flow, leading to changes in the internal structure of the arterial wall. This ultimately causes the thickening of the carotid artery intima-media layer [40-42]. The second is the development of exercise-induced hypertension and increased carotid IMT due to excessive sympathetic nervous system activation. Abnormal regulation of the autonomic nervous system on blood vessels might fail to reduce peripheral resistance, resulting in increased SBP during exercise [43]. According to a study by Eryonucu et al. [44], individuals who show EIH have increased sympathetic nervous system activity during both rest and exercise compared to those with normal BP responses. Moreover, animal studies have shown that prolonged elevation of sympathetic tone leads to the proliferation of smooth muscle cells and thickening of the vascular endothelium [45]. Another study measuring the femoral artery also found a strong correlation between increased sympathetic activity and IMT [46]. This current study had some limitations. This study was a cross-sectional study; therefore, it cannot determine the causal relationship between exercise-induced hypertension and carotid IMT. Moreover, other clinical factors and lifestyle habits that may affect BP and carotid IMT could not be fully controlled. Future prospective studies and pathophysiological mechanism studies are therefore needed.

Conclusion

In this study, $CIMT_{mean}$ was increased in long-distance runners with EIH compared to runners with normal BP. Age and SBP_{max} were also identified as predictive factors influencing the $CIMT_{mean}$ in long-distance runners. Therefore, regular health screening and management of cardiovascular risk factors, including BP response during exercise, are necessary for safe exercise in long-distance runners.

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301

Figure Legends

Fig. 1. Flow chart of the study procedure.

GXT: graded exercise testing, NBPG: normal blood pressure group, EIHG: exercise-induced hypertension group, CHG: complex hypertension group

Figure 2. Comparison of carotid IMT_{mean} between groups.

IMT: intima-media thickness, NBPG: Normal blood pressure group, EIHG: Exercise-induced hypertension group, CHG: complex hypertension group, †: Significant difference compared to NBPG ($P<0.05$), §: Significant difference compared to EIHG ($P<0.05$). Tested using the Kruskal-Wallis test, with the Mann-Whitney U-test post hoc.

Figure 3. Correlation between carotid IMT_{mean} and resting SBP.

IMT: intima-media thicknessm, SBP: systolic blood pressre.

Figure 4. Correlation between carotid IMT_{mean} and maximal SBP.

IMT: intima-media thickness, SBP: systolic blood pressure.

Figure 5. Correlation between carotid IMT_{mean} and age.

IMT: intima-media thickness

Table Legends

Table 1. Characteristics of participants

IQR : interquartile range, NBPG: Normal blood pressure group, EIHG: Exercise-induced hypertension group, CHG: complex hypertension group, HR: Heart Rate; BPM: beat per minute, SBP: systolic blood pressure, DBP: diastolic blood pressure, †Significant difference compared to NBPG ($P<0.05$), §Significant difference compared to EIHG ($P<0.05$).

Table 2. Hemodynamics value response to treadmill exercise test

NBPG: Normal blood pressure group, EIHG: Exercise-induced hypertension group, CHG: complex hypertension group, HR: Heart Rate, BPM: beat per minute, SBP: systolic blood pressure, DBP: diastolic blood pressure, diff: means the difference between peak and resting, †: Significant difference compared to NBPG ($P<0.05$), §: Significant difference compared to EIHG ($P<0.05$). SBP and DBP tested tested using Kruskal-Wallis Test with Mann-Whitney U Test post hoc.

Table 3. Multiple linear regression analyses for carotid artery intima-media thickness mean

BMI, body mass index, SBP: systolic blood pressure

Table 1. Characteristics of participants

	NBPG (N=14, 23.3%)	EIHG (N=35, 58.3%)	CHG (N=11, 18.3%)
General characteristics			
Age, yr	50.1 ± 4.5	55.0 ± 4.3	51.7 ± 4.7
Height, cm	169.8 ± 4.9	168.8 ± 4.3	168.8 ± 5.6
Weight, kg	65.8 ± 5.3	67.3 ± 7.1	67.3 ± 6.2
BMI, $kg \cdot m^{-2}$	22.8 ± 1.5	23.6 ± 1.9	23.6 ± 1.5
LBM, kg	55.4 ± 4.0	55.4 ± 4.6	55.1 ± 4.8
Fat, %	16.4 ± 2.4	17.6 ± 4.0	18.3 ± 2.8
Smoker, n (%)	3 (21.4%)	5 (14.3%)	3 (27.3%)
Alcohol, time/wk	2.1 ± 2.0	1.9 ± 1.6	2.3 ± 2.6
HR_{rest}, bpm	64.0 ± 10.2	65.0 ± 10.6	65.6 ± 9.4
SBP_{rest}, mmHg	113.9 ± 8.2	119.5 ± 10.0	143.3 ± 6.9†§
DBP_{rest}, mmHg	72.4 ± 6.2	74.0 ± 8.9	85.5 ± 13.9†§
Marathon training history			
Marathon careers, yr (IQR)	10.0(9.5-12.0)	8.0(6.0-11.0)	10.0(7.0-11.0)
Marathon start age, yrs	39.4 ± 6.3	43.4 ± 5.4†	42.1 ± 5.1†
Marathon completed, n (IQR)	40.0(22.3-57.0)	35.0(20.0-50.0)	28.4(20.0-60.0)
Race time, min	203.6 ± 16.6	205.3 ± 21.4	197.7 ± 14.9
Training volume, METs/week (IQR)	1440.0 (1080.0-1680.0)	1440.0 (1080.0-1920.0)	1440.0 (960.0-3840.0)
Training intensity			
Moderate, n (%)	13 (92.9)	30 (85.7)	8 (72.7)

High , n(%)	1 (7.1)	5 (14.3)	3 (27.3)

IQR : interquartile range, NBPG: Normal blood pressure group, EIHG: Exercise-induced hypertension group, CHG: complex hypertension group, HR: Heart Rate; BPM: beat per minute, SBP: systolic blood pressure, DBP: diastolic blood pressure, †Significant difference compared to NBPG ($P<0.05$), §Significant difference compared to EIHG ($P<0.05$).

Table 2. Hemodynamics value response to treadmill exercise test

	NBPG (N=14, 23.3%)	EIHG (N=35, 58.3%)	CHG (N=11, 18.3%)
HR_{max}, bpm	173.6 ± 6.9	168.9 ± 14.4	175.2 ± 10.5
SBP_{peak}, mmHg	194.4 ± 11.6	244.9 ± 16.8†	246.0 ± 17.1†
DBP_{peak}, mmHg	66.4 ± 9.1	73.6 ± 13.4†	80.1 ± 15.5†
SBP_{diff}, mmHg	81.8 ± 13.9	125.0 ± 18.7†	103.4 ± 16.4†§
VO_{2max}, mL/kg/min	50.0 ± 5.0	46.4 ± 4.7†	45.1 ± 5.1†
Exercise testing time, sec	847.8 ± 69.8	812.5 ± 86.7	820.9 ± 56.0

NBPG: Normal blood pressure group, EIHG: Exercise-induced hypertension group, CHG: complex hypertension group, HR: Heart Rate, BPM: beat per minute, SBP: systolic blood pressure, DBP: diastolic blood pressure, diff: means the difference between peak and resting, †: Significant difference compared to NBPG ($P<0.05$), §: Significant difference compared to EIHG ($P<0.05$). SBP and DBP tested tested using Kruskal-Wallis Test with Mann-Whitney U Test post hoc.

Table 3. Multiple linear regression analyses for carotid artery intima-media thickness mean

Variables	ß	SE	t	95%CI	P
Age	.009	.004	2.516	.002-.016	.015
BMI	.008	.009	.868	-.011-.027	.389
SBP_{rest}, mmHg	.001	.001	1.073	-.001-.004	.288
SBP_{peak}, mmHg	.001	.001	2.049	.001-.003	.046
VO_{2max}	.002	.003	.477	-.005-.008	.635
Marathon career	.007	.004	1.724	-.001-.015	.091
Weekly training volume	.001	.001	.436	.001-.001	.664

BMI, body mass index, SBP: systolic blood pressure