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Exercise-induced hypertension can increase the prevalence of coronary artery plaque among middle-aged male marathon runners

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Abstract

Marathon runners demonstrate a high incidence of coronary artery plaque; however, studies on runners with exercise-induced hypertension (EIH) are sparse. We aimed to investigate the prevalence of coronary artery plaque among marathon runners with EIH.

Veteran male marathon runners (≥40 and <60 years) underwent an exercise stress test. They were divided into 2 groups: normal blood pressure group (NBPG, n=22), with resting systolic blood pressure (SBP)/diastolic blood pressure <140/90 mm Hg and maximal exercise SBP <210 mm Hg, and EIH group (EIHG, n=28), with resting blood pressure <140/90 mm Hg and maximal exercise SBP ≥210 mm Hg. Coronary artery plaque and stenosis were compared using multi-detector computed tomography.

The proportion of subjects with a coronary artery calcium (CAC) score ≥10 or ≥100 units, 1 or ≥2 plaques, or plaques in ≥2 blood vessels was higher in the EIHG than in the normal blood pressure group (NBPG) ($P<.05$). The absolute CAC score was higher in the EIHG (42.6 ± 67.8) than in the NBPG (2.8 ± 6.0; $P<.05$). The CAC score distribution was higher in the EIHG (5–300 units) than in the NBPG ($P<.05$). The prevalence of coronary plaques and maximal luminal artery stenosis was higher in the EIHG than in the NBPG ($P<.05$). The EIHG showed 12 cases of stenosis, whereas the NBPG showed only 1 case ($P<.05$).

In marathon runners, EIH was associated with increased prevalence of coronary artery plaques and could be a new risk factor for coronary artery plaque formation. Therefore, preventive measures and EIH monitoring using an exercise stress test, alongside multi-detector computed tomography, are recommended.

Abbreviations: BP = Blood pressure, CAC = coronary artery calcium, DBP = diastolic blood pressure, ECG = electrocardiogram, EIH = exercise-induced hypertension, GXT = graded exercise test, MDCT = multi-detector computed tomography, NBPG = normal blood pressure group, SBP = systolic blood pressure.

Keywords: coronary plaques, coronary stenosis, exercise-induced hypertension, marathon

1. Introduction

Proper exercise is beneficial for preventing and treating cardiovascular disease,[1] improving chronic kidney failure,[2] and reducing glycated hemoglobin in patients with diabetes mellitus.[3] However, athletes who participate in chronic high-intensity exercise, such as marathon runners, are known to demonstrate higher arterial stiffness[4] and significantly higher prevalence of fatal arrhythmia, such as atrial fibrillation, than those among the general population.[5] Exercise-induced hypertension (EIH) is defined as a resting systolic blood pressure (SBP)/diastolic blood pressure (DBP) of <140/90 mm Hg and a maximal exercise SBP of ≥210 mm Hg in males and ≥190 mm Hg in females.[6,7] Recently, long-distance runners, such as marathon runners, have been found to show a higher frequency of EIH,[8,9] which has been reported as an independent cardiovascular and cerebrovascular risk factor.[10,11] The most important cause in the pathogenesis of EIH is impaired endothelium-dependent dilation in the arteries.[12] A high incidence of resting hypertension is seen among individuals with EIH.[13] No criteria for excessive exercise have been established; however, to adapt to endurance exercise, such as marathons, athletes must participate in intense exercise for 90 to 300 min/d and accumulate 200 to 300 maximal metabolic equivalent × hr/wk, which is approximately 5 to 10 times higher than the recommended exercise levels in the guidelines for the prevention of cardiovascular disease.[14] Recently, marathon runners have been reported to show a higher prevalence of coronary artery plaque than that among the general population.[15] Middle-aged marathon runners, especially, show coronary artery calcium (CAC) deposits in cardiovascular CT in approximately 50% of cases, despite

Editor: Wen-Jun Tu.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

CHK and YP have contributed equally to this work as first authors.

This work was supported by the Ministry of Education of the Republic of Korea and the National Research Foundation of Korea (NRF-2017S1A5A2A03068634)

This work was funded by the Soonchunhyang University Research Fund.

The authors have no conflicts of interest to report.

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How to cite this article: Kim CH, Park Y, Chun MY, Kim YJ. Exercise-induced hypertension can increase the prevalence of coronary artery plaque among middle-aged male marathon runners. Medicine 2020;99:17(e19911).

Received: 3 February 2020 / Received in final form: 15 March 2020 / Accepted: 17 March 2020

http://dx.doi.org/10.1097/MD.0000000000019911

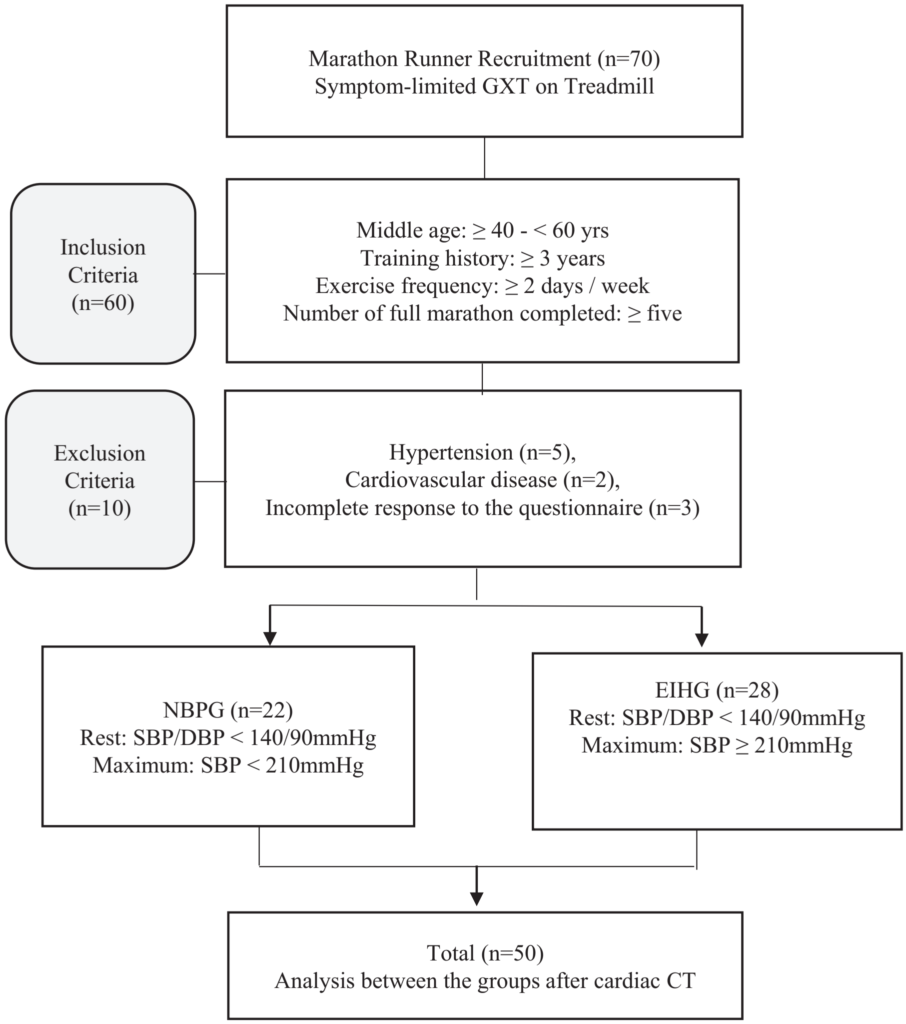

Figure 1. Flow chart of the study participants. DBP = diastolic blood pressure, EIHG = exercise-induced hypertension group, GXT = graded exercise testing, NBPG = normal blood pressure group, SBP = systolic blood pressure.

demonstration of normal ST segment in an exercise stress test.[16] To test the hypothesis that EIH is a risk factor for coronary artery stenosis, this study compared runners who had EIH, which could increase the load on cardiac muscle during exercise, with runners who had normal blood pressure (BP). This is the first study to investigate the prevalence of coronary artery plaques and the extent of stenosis in middle-aged male marathon runners with EIH.

2. Materials and methods

2.1. Subjects and the study protocol

The study protocol is shown in Figure 1. A symptom-limited graded exercise test (GXT) was administered to 70 applicants. The inclusion criteria for participation in the study were age ≥40 years and <60 years, exercise experience ≥3 years, exercise frequency ≥2 times/wk, and number of marathons completed ≥5. Individuals who did not meet these criteria (n = 10), had hypertension (n = 5) or cardiovascular disease (n = 2), or provided an incomplete response to the questionnaire (n = 3) were excluded from the study. In the GXT, subjects who showed resting SBP/DBP <140/90 mm Hg and maximal exercise SBP <210 mm Hg were classified in the normal blood pressure group (NBPG), while subjects with resting SBP/DBP <140/90 mm Hg and maximal exercise SBP ≥210 mm Hg were placed in the EIH group (EIHG). The subjects underwent cardiac CT, and results were compared between the 2 groups.

This study was approved by the Sungshin Women's University institutional review board and was conducted in accordance with the 1975 Declaration of Helsinki guidelines (IRB number: SSWUIRB 2018-009).

2.2. Measurements

2.2.1. GXT. To analyze the subjects' hemodynamic responses, the heart rate and BP were measured at rest, at maximal exercise, and in the recovery phase. The test was performed on a treadmill (T170DE, hp cosmos, Traunstein, Germany) using the Bruce protocol, VO2max was measured using a respiratory gas analyzer (Quark CPET, Cosmed, Lavio, Italy), and electrocardiography (CH2000, Cambridge heart, Massachusetts, USA) was used to monitor myocardial ischemia and arrhythmia. An automatic BP monitor (Tango+, Suntech, NC) was used to measure BP by stages, at rest and during maximal exercise, to minimize the mechanical measurement error. A high-performance microphone was attached over the brachioradial artery, and measurements were taken while listening directly to the sounds in the systolic and diastolic phases. The rating of perceived exertion, which indicates the difficulty experienced by the subject during the GXT, was measured on a scale of 6 to 20 using the Borg criteria. The criteria for stopping the test, based on the ACC/AHA guidelines, were when the SBP/DBP were ≥250/115 mm Hg or when the subject was unable to continue.[17]

2.2.2. Multi-detector computed tomography (MDCT). MDCT was performed using a 64-slice MDCT scanner VCT XT (Toshiba, Tustin, CA). Images were acquired using a standard protocol for coronary angiography (64 × 0.625 mm slice collimation, 350 ms rotation time, 120 kV tube voltage, 500–800 mA tube current according to the patient body habitus). For the contrast agent, 80 mL of 400 mg/mL iodine (Omnipaque 300 GE healthcare Carrigtwohill, Ireland) was infused at a rate of 4 mL/s, following which 50 mL of physiological saline was infused at the same rate.

For infusion of the contrast agent, an 18- to 20-gauge intravenous catheter was placed in the right arm. The heart rate was monitored simultaneously, and images were acquired using prospective and retrospective electrocardiogram (ECG) gating for heart rate <60 beats/min and ≥60 beats/min, respectively. Using a mono-segment and multi-segment algorithms, respectively, for heart rates <75 beats/min and ≥75 beats/min, images were reconstructed in the mid-diastolic phase.

The mean effective dose for cardiac CT was 4.7 ± 1.6 mSv. Subjects were instructed to fast and avoid caffeine for at least 4 h before MDCT. Subjects who had not previously taken beta-blockers and had a heart rate ≥65 beats/min were given atenolol 25 to 75 mg 1 h before MDCT to keep their heart rate ≤65 beats/min. Before imaging, ECG was performed, and heart rate and BP were measured 1 h, 30 min, and 5 min before imaging. Subjects were given sublingual nitroglycerine 0.6 mg 1 min before MDCT. The ECG was monitored throughout the imaging process.

During scanning, the subject maintained maximal inhalation for approximately 8 to 10 s, and oxygen was supplied as necessary to increase the time that the subject could hold their breath. All cardiac CT scans were analyzed and interpreted by the same investigator.

2.3. Statistical analysis

For all demographic, hemodynamic, cardiorespiratory fitness and Agatston score data obtained in this study, descriptive statistics (mean and standard deviation) were calculated. To test differences between the 2 groups, first, the kurtosis, skewness, and Kolmogorov-Smirnov test were analyzed for each variable. Based on the results, the independent *t*-test was performed to analyze the differences in the parametric variables, and the Mann–Whitney *U* test was used to analyze differences in non-parametric variables. For the prevalence of the CAC scores, a 2 × 2 cross-tabulation analysis was performed. Cross-tabulation and linear analysis were performed for 4 × 2 cross-tabulation, and for separate analysis between variables, a 2 × 2 cross-tabulation analysis or 2 × 2 Fisher exact test was performed. The type-1 error rate was set to 0.05. SPSS version 21 was used for all data collection and statistical analysis.

3. Results

3.1. Anthropometric and biochemical characteristics

Table 1 shows the general characteristics, hemodynamic characteristics, and physical performance of the subjects. General characteristics comprising age, height, body weight, and body composition were comparable between the NBPG and EIHG. Resting heart rate and BP were also comparable between the 2 groups. However, while maximal heart rate was comparable between the 2 groups, maximal SBP was significantly higher in the EIHG than that in the NBPG (maximal SBP; NBPG vs EIHG: 198 ± 8.2 vs 238 ± 15.5, $P < .001$; Table 1).

In terms of hemodynamic characteristics, during the recovery phase after high-intensity exercise, both groups showed similar decreasing trends in the recovery phase heart rate and DBP. However, SBP measured every minute for 3 min during the recovery phase was significantly higher in the EIHG at all time points (NBPG vs EIHG: 187 ± 16.3 vs 231 ± 21.5, 190 ± 12.6 vs 228 ± 19.6, 178 ± 12.3 vs 214 ± 19.6, $P < .001$; SPB recovery at 1 min, 2 min, and 3 min, respectively).

Physical performance, comprising training experience, number of completed marathons, personal minimum time, maximum oxygen uptake, total exercise time, and maximal metabolic equivalents showed no significant differences between the 2 groups.

Table 1

Anthropometric, hemodynamic, and cardiorespiratory fitness characteristics of the study subjects.

Variables	NBPG (n = 22)	EIHG (n = 28)	*P*-value
Age (yr)	51.7 ± 4.9	54.5 ± 5.0	.060
Height (cm)	171.9 ± 5.4	170.5 ± 4.0	.300
Weight (kg)	67.9 ± 6.2	68.2 ± 6.8	.849
BMI (kg/m^2)	23.0 ± 1.7	23.4 ± 1.9	.447
%Fat (%)	16.2 ± 4.4	16.5 ± 4.3	.760
HR_{rest} (BPM)	58 ± 5.3	60 ± 10.4	.334
HR_{max} (BPM)	171 ± 12.0	171 ± 26.0	.919
SBP (mm Hg)	123 ± 8.6	127 ± 7.1	.070
SBP_{max} (mm Hg)	198 ± 8.2	238 ± 15.5	.000
DBP (mm Hg)	79 ± 5.4	81 ± 6.4	.230
DBP_{max} (mm Hg)	79 ± 12.5	78 ± 11.0	.650
Hemodynamic characteristics			
HRR_{1min} (BPM)	142 ± 12.5	147 ± 11.0	.154
HRR_{2min} (BPM)	119 ± 13.9	122 ± 12.3	.340
HRR_{3min} (BPM)	108 ± 13.8	112 ± 10.6	.316
SBP_{1min} (mm Hg)	187 ± 16.3	231 ± 21.5	.000
SBP_{2min} (mm Hg)	190 ± 12.6	228 ± 19.6	.000
SBP_{3min} (mm Hg)	178 ± 12.3	214 ± 19.6	.000
DBP_{1min} (mm Hg)	75 ± 10.9	76 ± 10.5	.768
DBP_{2min} (mm Hg)	77 ± 11.7	78 ± 10.9	.702
DBP_{3min} (mm Hg)	75 ± 11.5	78 ± 9.8	.286
History of cardiovascular disease	18.2% (4)	10.7% (3)	.362
Physical performance			
Training experience	14.1 ± 4.9	14.3 ± 5.5	.893
Number of completed marathons	52.5 ± 43.5	82.1 ± 92.6	.142
Personal minimum time	11062 ± 2756	12175 ± 1760	.093
VO_{2max} (kg/mL/min)	53.3 ± 6.8	51.9 ± 6.5	.457
Total ex. time	874 ± 89.9	856 ± 84.1	.467
MET_{max}	15.2 ± 1.9	14.8 ± 1.9	.457

Values are presented as means ± standard deviations; BMI = body mass index, BPM = beat per minute, DBP = diastolic blood pressure, HR = heart rate, MET = maximal metabolic equivalent, SBP = systolic blood pressure, Total ex. Time = total exercise time.

3.2. Coronary artery calcium score

CAC score (Agatston score) was normal in 15 out of 22 subjects (68.2%) in the NBPG and 14 out of 28 subjects (50.0%) in the EIHG. The percentage of subjects with a score ≥10 units was

Table 2

Coronary artery calcium score in normal and exercise-induced hypertension marathoners.

Variables	NBPG (n=22)	EIHG (n=28)	*P*-value
Agatston score	2.8±6.0	42.6±67.8	.036
CAC >0 Agatston units	7 (31.8)	14 (50)	.098
CAC >10 Agatston units	4 (18.2)	13 (46.4)	.035
CAC >100 Agatston units	0 (0.0)	5 (17.9)	.046
≧ 1 plaque	2 (9.1)	10 (35.7)	.029
≧ 2 plagues	0 (0.0)	5 (17.9)	.046
≧ 2 vessels with plaques	0 (0.0)	5 (17.9)	.046

Values are n (%). CAC=coronary artery calcium, LAD = left anterior descending artery, LCX = left circumflex artery, OM = left circumflex artery, RCA = right coronary artery.

significantly higher in the EIHG (13 out of 28 subjects, 46.4%) than that in the NBPG (4 out of 22 subjects, 18.2%) ($P<.05$), and there were 5 subjects in the EIHG with a score ≥100 units (>100 Agatston units; NBPG vs EIHG: 0(0%) vs 5 (17.9%), $P<.05$; Table 2).

The percentage of subjects with ≥1 plaque or ≥2 plaques was significantly higher in the EIHG, and the percentage of subjects with plaques in ≥2 blood vessels was significantly higher (Table 2, ≥1 plaque 10 (35.7%) in the EIHG, ≥ 2 plaque 5 (17.9%) at EIHG, and ≥ 2 vessels 5 (17.9%) at EIHG for $P<.05$; only ≥1 plaque 2 (9.1%) at NBPG, $P<.05$).

The absolute value for CAC score was significantly higher in the EIHG (42.6±67.8) than that in the NBPG (2.8±6.0) (Table 2, Fig. 2(A), $P<.05$). There was a significantly higher percentage of subjects with higher elevated coronary CAC (5–300 units) in the EIHG than that in the NBPG (Fig. 2(B)).

3.3. Coronary plaques and luminal stenosis

The EIHG showed a higher prevalence of coronary plaques than the NBPG (Table 2, Fig. 2). At least 1 instance of luminal stenosis was observed in 2 out of 22 subjects (9.1%) in the NBPG; however, in 10 out of 28 subjects (36%) in the EIHG, where 5 subjects (17.9%) showed luminal stenosis in 1 blood vessel, 4 subjects (14.3%) showed luminal stenosis in 2 blood vessels, and 1 subject (3.6%) showed luminal stenosis in ≥3 blood vessels, demonstrating a significantly higher number of blood vessels with luminal stenosis than that in the NBPG (Fig. 3(B)).

The main locations showing stenosis in the EIHG were the left anterior descending artery (7 cases), right coronary artery (2 cases), left circumflex artery (2 cases), and obtuse marginal artery (1 case), accounting for 12 cases in total; the NBPG only showed 1 case in the RCA ($P<.05$; Fig. 2(B)). The EIHG also showed a higher prevalence than the NBPG for each stage of maximal luminal artery stenosis (Fig. 3(C)) (7 with no stenosis in NBPG; 7 with no stenosis, 5 with <25% stenosis, 3 with 25%–49% stenosis, 1 with 50%–69% stenosis in EIHG; $P<.05$)

4. Discussion

This study aimed to assess the prevalence of coronary artery plaque among marathon runners with EIH and found that EIH is associated with an increased prevalence of coronary artery plaques and may be a novel risk factor for the formation of the coronary artery plaque. Since resting hypertension is a clinical risk factor for myocardial hypertrophy, cardiac failure, and coronary artery disease, there are systematic guidelines for the treatment and prevention of hypertension.[18] In contrast, although EIH is associated with a 5- to 10-fold increase in the development of resting hypertension later on[13] and is an independent risk factor for cardiovascular and cerebrovascular disease,[10,11] no guidelines are available to date.

Recent studies reported that after completing a marathon or ultramarathon, long-distance runners with EIH show elevated N-terminal pro-brain natriuretic peptide levels, which is indicative of myocardial load, and high expression of cardiac troponin-I, which is an indicator of myocardial injury.[19,20] These results suggest that runners with EIH are chronically exposed to high BP during marathons and everyday exercise. When an individual persistently performs excessive exercise, repeated chronic high pressure on the arterial walls causes mechanical fatigue, which can increase arterial stiffness.[4]

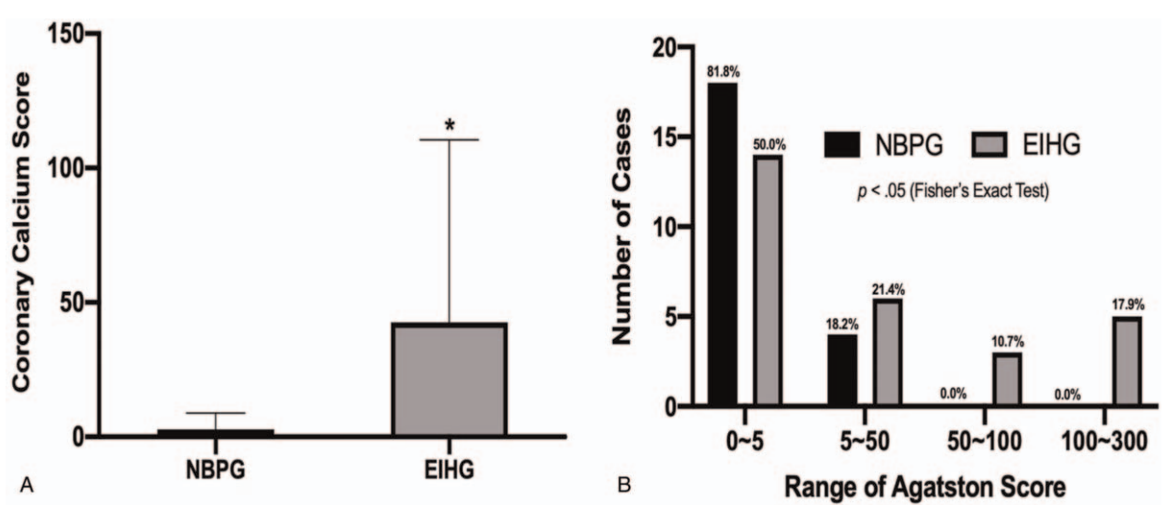

Figure 2. Coronary artery calcium scores in exercise-induced hypertension group and normal blood pressure group. Values are coronary artery calcium score in Agatston units. (A) Agatston scores between NBPG and EIHG. (B) Distribution of coronary artery calcium scores severity between NBPG and EIHG. EIHG= exercise-induced hypertension group, NBPG=normal blood pressure group. *$P<.05$ from the NBPG.

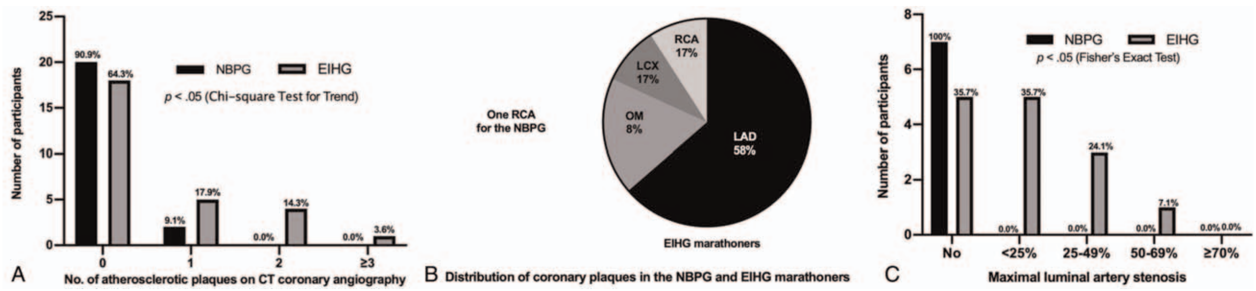

Figure 3. Coronary artery plaques and luminal stenosis artery in NBPG and EIHG. EIHG = exercise-induced hypertension group, LAD = left anterior descending artery, LCX = left circumflex artery, OM = left circumflex artery, NBPG = normal blood pressure group, RCA = right coronary artery.

Runners with EIH may especially be exposed to high arterial pressures, and this may be an independent risk factor for the development of atherosclerosis in the coronary arteries. In the present study, compared to the NBPG, the EIHG showed higher CAC scores (18.2% vs 46.4% participants with a score ≥10 units), and the prevalence of plaque and the number of blood vessels affected by plaque were also significantly higher in the EIHG (Table 2). In particular, the absolute CAC score was higher in the EIHG (42.6 ± 67.8) than the NBPG (2.8 ± 6.0; Table 2, Figure (A)), and a greater proportion of subjects in the EIHG showed higher elevated CAC scores (5–300 units; Fig. 1(B)). Although the sample size was small, these results were considerably significant. Tsiflikas et al[16] studied 50 middle-aged male marathon runners without a control group and detected coronary artery stenosis in 50% of the subjects, with 3 subjects showing moderate coronary atherosclerosis.

Recently, Merghani et al[15] reported that marathon runners show higher CAC scores than the general population, but the calcified plaques were more stable in nature in the marathon runners. However, regardless of the plaque characteristics, a higher incidence of coronary artery plaques in long-distance runners participating in excessive exercise can still increase the risk of sudden death during exercise. The main cause of sudden death in athletes aged <35 years is congenital disease, such as hypertrophic cardiomyopathy, but in athletes aged ≥35 years, it is coronary artery disease.[21] Thus, the findings of the present study indicated that the prevalence of coronary artery stenosis was higher among the middle-aged marathon runners with EIH and that these runners presented with a greater number of stenotic blood vessels and a greater severity of stenosis than those runners in the NBPG (Fig. 2(B-C)).

The mechanism of excessive BP elevation during exercise is associated with the epithelial cell injury causing arterial vasodilation dysfunction, resulting in an increased post-load.[12,22] In particular, excessive exercise itself causes chronic atrial overload and dilation, leading to atrial fibrillation, which is 5 times more prevalent than in the general population.[5] Kim et al reported that atrial fibrillation is 2.5 times more common in long-distance runners and these athletes show higher cardiopulmonary stamina and exercise intensity than normal runners; they also reported that among all runners, the long-distance runners showed EIH.[8] It is not known whether the high prevalence of EIH among long-distance runners is the result of elevated arterial stiffness due to excessive exercise or whether the excessive increase in BP is due to high cardiopulmonary capacity.

In the present study, coronary artery plaque in long-distance runners may be produced by inflammation due to oxidative stress resulting from excessive exercise; runners with EIH are especially exposed to higher exercise intensity than the NBPG, resulting in increased plaque generation; therefore, measures are needed to prevent plaque development in these runners. Specifically, antioxidants[23,24] or antihypertensives, such as angiotensin II receptor blocker,[25] may be considered, and it may also be necessary to adjust the exercise intensity. However, as precise prevention guidelines are not available to date, large-scale studies are warranted in the future.

The present study indicated that, in middle-aged male marathon runners participating in excessive exercise, EIH may be a risk factor for new coronary artery plaque formation; based on the results, cardiovascular CT and an exercise stress test are recommended for these individuals.

There are several limitations of this study. It was not possible to examine the 24-hour ambulatory BP to precisely measure the BP in the subjects, and data, such as family history, may not have been accurate as they could only be obtained via a questionnaire. In addition, it was not possible to control other factors that could affect the subjects' cardiovascular function, including blood lipid levels, dietary habits, sleep patterns, stress, and performing additional exercise, other than marathons.

In conclusion, the prevalence of coronary artery plaque was higher in middle-aged male marathon runners with EIH than in marathon runners with normal BP; therefore, prevention strategies and countermeasures are required. EIH may be a risk factor for new coronary artery plaque formation; hence, EIH must be evaluated in these individuals using an exercise stress test together with MDCT scans.

Author contributions

Data curation: Chul-Hyun Kim, Yongbum Park.
Investigation: Yongbum Park.
Software: Chul-Hyun Kim.
Supervision: Min Young Chun.
Validation: Chul-Hyun Kim, Yongbum Park, Min Young Chun.
Writing – original draft: Chul-Hyun Kim, Yongbum Park.
Writing – review & editing: Min Young Chun.

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