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Exercise-induced hypertension is associated with angiotensin II activity and total nitric oxide

Chul-Hyun Kim, PhD[a], Yongbum Park, MD[b], Min Young Chun, MD[c], Young-Joo Kim, PhD[d,*]

Abstract

Angiotensin II mediates exercise-induced hypertension (EIH), which adversely impacts future cardiovascular health. There is paucity of data on the association between EIH and angiotensin II in well-trained middle-aged marathoners. Therefore, we investigated the renin-angiotensin-aldosterone-system and total nitric oxide activity in middle-aged marathoners with EIH.

Seventy middle-aged marathoners were divided into 3 groups: normal blood pressure ([NBPG] [n = 21]), EIH group ([EIHG] [n = 35]), and complex hypertension group ([CHG] [n = 14]). We defined NBPG as resting systolic BP/diastolic BP (SBP/DBP) of ≤140/90 mm Hg and maximal exercise SBP of ≤210 mm Hg, EIHG as resting SBP/DBP ≤140/90 mm Hg and maximal exercise SBP of ≥210 mm Hg, and CHG as resting SBP/DBP ≥140/90 mm Hg and maximal exercise SBP of ≥210 mm Hg. Renin-angiotensin-aldosterone-system and NO levels were measured before and 30 minutes after the graded exercise test.

Renin level was elevated while angiotensin level was reduced after 30 minutes of graded exercise test. There was no change in angiotensin I and angiotensin converting enzyme levels. Comparing the groups, renin level was only elevated in the CHG during recovery, while aldosterone level was higher than the baseline level in the recovery phase in all groups. Angiotensin I level remained unchanged in all groups. Angiotensin II level reduced significantly in the NBPG group but remained at the baseline in the EIHG and CHG groups. NO level was unchanged in the NBPG group but reduced in the EIHG and CHG groups after exercise. At 3 minutes of recovery, SBP was the highest in the NBPG group, followed by the EIHG and CHG groups ($P < .05$).

In conclusion, angiotensin II activity and reduced NO level are associated with EIH in middle-aged long-distance runners. Angiotensin II inhibitors may; therefore, be the more appropriate antihypertensive medication for runners with EIH.

Abbreviations: ACE = angiotensin converting enzyme, BP = blood pressure, CHG = complex hypertension group, EIH = exercise-induced hypertension, EIHG = exercise-induced hypertension group, GXT = graded exercise test, HR = heart rate, NBPG = normal blood pressure group, NO = nitric oxide, RAAS = renin-angiotensin-aldosterone-system, SBP = systolic blood pressure.

Keywords: exercise-induced hypertension, marathon, renin-angiotensin-aldosterone-system

1. Introduction

Regular exercise ameliorates risk factors of cerebro-cardiovascular diseases[1,2] while lowering mortality and promoting cardiovascular health.[3] However, in runners participating in long-distance running such as marathon, arterial stiffness and pressure increased[4] and the prevalence of critical arrhythmia such as atrial fibrillation, was significantly higher than the general population.[5,6] Coronary atherosclerosis and myocardial damage has been also reported to have associated with marathon running in healthy runners.[7–9] In prospective follow-up study of 10.4 years, running or walking decreased cardiovascular disease mortality risk progressively at most levels of exercise in patients after a cardiac event. However, the benefit of exercise on cardiovascular disease or ischemic heart disease related mortality was attenuated at the highest levels of exercise like running above 7.1 km/d.[10]

Recent reports show that the incidence of exercise-induced hypertension (EIH) is high[7] among long-distance runners and that runners with EIH show a greater elevation of cardiac troponin I, a marker for myocardial injury, and N-terminal fragment of the prohormone brain-type natriuretic peptide, a marker for myocardial volume-pressure, than normal runners during a marathon or ultramarathon,[8,9] raising concerns for the risk of cardiac events during exercise. EIH is defined as a normal resting blood pressure (BP) of <140/80 mm Hg with a maximum systolic BP (SBP) ≥210 mm Hg.[11] EIH increases the risk for future resting hypertension.[10] and is an independent risk factor for cerebro-cardiovascular disease.[12,13]

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

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Furthermore, prehypertension and isolated or combined with exaggerated BP response affect cardiac remodeling such as myocardial hypertrophy or further left atrial enlargement in middle aged amateur marathon runners.[14] Gabrielli et al reported athletes with more intensive training load had larger left ventricular mass and left atrial size with increased left atrial contraction. This increase in the left atrial contraction was related to the maximum oxygen consumption (VO_2) measured previous to the marathon and to performance in a highly demanding test.[15]

Therefore, the preventive treatment for exercise induced hypertension is very important in the cardiovascular health of runners. Especially, the marathon race is an extremely vigorous and competitive exercise that requires regular and intense training. Nevertheless, the acute adverse effects of marathon race on arterial stiffness and clinical outcomes, as well as regulatory mechanism of BP, have not clearly been elucidated. A recent study found renin-angiotensin-aldosterone system (RAAS) involved in the elevation of BP and heart rate (HR) during exercise,[16] and angiotensin II activity is associated with EIH in patients with dyspnea.[17]

For this purpose, this study aimed to identify factors in the RAAS, which regulates BP, that are activated in addition to the responses of nitric oxide (NO), which has vasodilatory, antiplatelet, and antithrombotic action, in well-trained runners with EIH.[18]

2. Materials and methods

2.1. Subjects and the study protocol

The study protocol is illustrated in Figure 1. The inclusion criteria for participants in this study were: healthy middle-aged men aged 40 to 60 years with a training history of 3 years or longer, exercise frequency of 2 times/wk or more, and at least 5 completed full marathons. Individuals with hypertension, diabetes mellitus, or cerebro-cardiovascular disease, those who had exercised on the day of the study before the graded exercise test (GXT), and those who failed to answer all items on the questionnaire were excluded

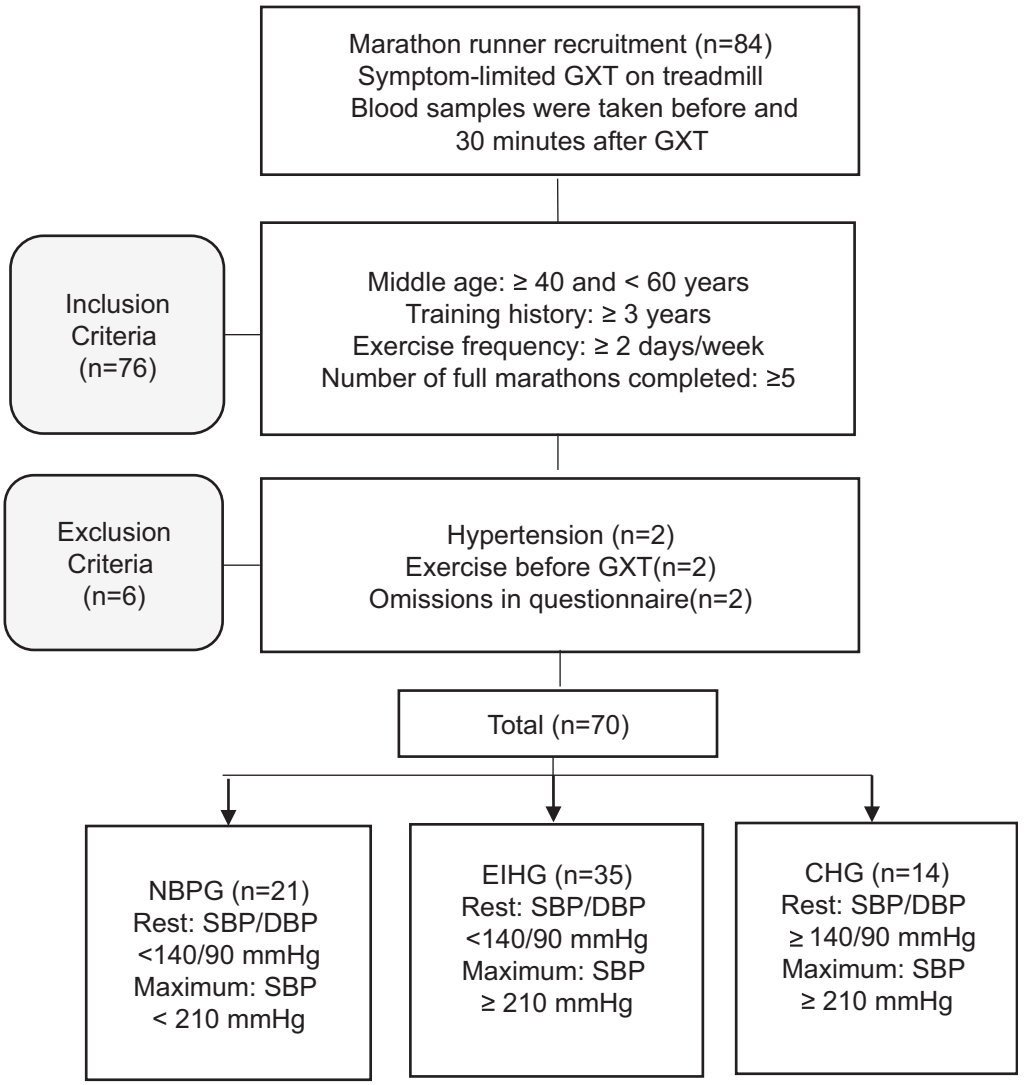

Figure 1. Flow chart of the study participants. CHG = complex hypertension group, EIHG = exercise-induced hypertension group, GXT = graded exercise testing, NBPG = normal blood pressure group.

from the study. There were no meal restrictions before GXT. Symptom-limited GXT was performed on 84 study participants, and their blood samples were taken before and 30 minutes after GXT and stored in a −70°C freezer for RAAS analysis.

This study was approved by the institutional review board at Sungshin Women's University per the 1975 Declaration of Helsinki (IRB number: SSWUIRB 2018-009).

2.2. Measurements

2.2.1. GXT. The symptom-limited GXT was performed using a treadmill (T170 DE, hp cosmos, Traunstein, Germany), respiratory gas analyzer (Quark CPET, COSMED, Lavio, Italy). Electrocardiography system (CH2000, Cambridge Heart, MA) and automated BP monitor (Tango+, SunTech, NC) measured cardiopulmonary fitness (ECG, HR, BP) at rest and during exercise. The Bruce protocol was used for the GXT. Subjects rated the difficulty of the exercise using the rating of perceived exertion (Borg scale) at each stage of exercise. To increase the accuracy of BP measurements, we placed a high-performance microphone over the radial artery on the upper arm and measured BP by listening to the sounds during the systolic and diastolic phases. The GXT was concluded as per the ACC/AHA guideline.[19]

2.2.2. Blood sampling and blood analysis. Blood samples were taken before GXT and after 30 minutes of rest following a GXT. To measure angiotensin converting enzyme (ACE), aldosterone, and total NO, blood samples were taken in a serum separator tube (BD Vacutainer Serum Separator Tube) containing gel and blood clotting promoter in a vacuum state, centrifuged at 3000 rpm for 10 minutes to separate the serum, and stored in a freezer at −70°C.

To measure renin activity, blood samples were collected in an EDTA tube, stored at room temperature for >30 minutes, and centrifuged at 3000 rpm for 10 minutes to take the supernatant, which was stored in a freezer at −70°C. To measure angiotensin-1 and angiotensin-2, blood samples were collected in an EDTA tube, shaken several times to mix in the anticoagulant, and transferred to a new centrifuge tube. After adding 0.6 TIU of aprotinin to 1 mL of blood (0.6 TIU/mL of blood), the tube was shaken several times. The mixture was centrifuged at 3000 rpm for 10 minutes, and the supernatant was taken and stored at −70°C.

ACE was analyzed using enzymatic assay with the ACE kinetic reagent. Total NO was analyzed with colorimetry via the total NO and nitrate/nitrite assay. Aldosterone and renin activity were analyzed using radioimmunoassay (RIA) with the RIA aldosterone reagent and the angiotensin I RIA KIT reagent, respectively. Angiotensin I and angiotensin II were analyzed using enzyme-linked immunosorbent assay with the angiotensin I and angiotensin II (Human, Rat, Mouse) EIA kit extraction free reagents.

The normal reference values for each parameter were: ACE (7.5–53.0 U/L), aldosterone (Supine: 4.2–20.9 ng/dL, Upright: 6.7–33.5 ng/dL), and renin activity (Early morning, Supine: 0.32–1.84 ng/mL/h, Upright, 2 hours: 0.60–4.18 ng/mL/h).

2.3. Statistical analysis

Data obtained in this study were analyzed using descriptive statistics (mean and standard deviation). Before analyzing the difference among groups or time periods, data for each parameter were tested for normal distribution using skewness, kurtosis, and the Kolmogorov-Smirnov Test. For data requiring parametric tests, pre- and post- differences for each group were analyzed using paired *t*-tests, and intergroup differences were analyzed using 1-way analysis of variance followed by a Scheffe test for significant parameters. For data requiring nonparametric tests, pre- and post- differences were analyzed using the Wilcoxon signed rank test, and intergroup differences were analyzed using the Kruskal–Wallis test followed by the Mann–Whitney *U* test. Bonferroni correction was conducted to correct post-hoc error at an adjusted *P*-value of .05/3. Statistical significance (alpha) was set to .05 for a 2-tailed test, and angiotensin II and NO activities were analyzed using a 1-tailed test. All data were collected and statistically analyzed using the SPSS statistics version 21.

3. Results

3.1. Anthropometric and biochemical characteristics

Seventy subjects were classified into 3 groups: the normal blood pressure group (NBPG, n = 21, 30%) with a resting SBP/diastolic BP (DBP) ≤ 140/90 mmHg and SBP ≤ 210 mm Hg at maximal exercise during the GXT, exercise-induced hypertension group (EIHG, n = 35, 50%) with a resting SBP/DBP ≤140/90 mm Hg and SBP at maximal exercise ≥210 mm Hg, and complex

Table 1

Characteristics of demographics, hemodynamic, and cardiorespiratory fitness in study participants.

Variables	NBPG (N = 21, 30%)	EIHG (N = 35, 50%)	CHG (N = 14, 20%)
General characteristics			
Age (yr)	53.6 ± 4.9	53.9 ± 4.8	52.1 ± 5.1
Height (cm)	167.4 ± 21.5	170.6 ± 4.4	173.6 ± 5.3
Weight (kg)	69.2 ± 7.2	67.4 ± 6.5	69.3 ± 6.3
BMI (kg/m^2)	23.4 ± 1.9	23.2 ± 2.0	23.0 ± 2.2
FFM (kg)	57.3 ± 5.2	56.4 ± 57.2	57.2 ± 4.6
FM (kg)	12.0 ± 4.5	11.1 ± 3.7	12.1 ± 4.1
%Fat (%)	17.0 ± 5.2	16.2 ± 4.3	17.2 ± 4.8
$HR_{rest,}$ (BPM)	60 ± 7.5	60 ± 10.1	65 ± 7.6
$HR_{max,}$ (BPM)	172 ± 12.2	170 ± 23.4	176 ± 9.8
SBP (mm Hg)	122 ± 7.9[a]	126 ± 6.7[a]	145 ± 11.0[b]
SBP_{max} (mm Hg)	198 ± 8.8[a]	233 ± 16.5[b]	236 ± 16.5[b]
DBP (mm Hg)	79 ± 5.1[a]	81 ± 6.0[a]	95 ± 8.9[b]
DBP_{max} (mm Hg)	80 ± 10.3	78 ± 11.5	81 ± 13.7
Hemodynamic characteristics			
HRR_{1min} (BPM)	144 ± 12.2	145 ± 11.8	151 ± 13.3
HRR_{2min} (BPM)	122 ± 11.3	121 ± 13.0	130 ± 14.1
HRR_{3min} (BPM)	110 ± 11.5	111 ± 11.5	120 ± 18.4
SBP_{1min} (mm Hg)	185 ± 15.1[a]	226 ± 20.7[b]	220 ± 21.9[b]
SBP_{2min} (mm Hg)	188 ± 13.0[a]	221 ± 21.8[b]	230 ± 19.8[b]
SBP_{3min} (mm Hg)	180 ± 16.0[a]	206 ± 21.8[b]	222 ± 20.8[c]
DBP_{1min} (mm Hg)	76 ± 9.3	75 ± 11.1	80 ± 14.0
DBP_{2min} (mm Hg)	77 ± 9.4	79 ± 11.3	83 ± 9.7
DBP_{3min} (mm Hg)	77 ± 9.3	78 ± 10.8	81 ± 9.3
Physical performance			
VO_{2max} (mL/kg/min)	51.7 ± 6.5	51.4 ± 7.1	53.5 ± 9.0
Total Ex. (time)	865 ± 88	860 ± 85	826 ± 104
$METs_{max}$	14.8 ± 1.9	14.7 ± 2.1	15.3 ± 4.3

Mean ± SD. Different superscripts mean significant different at $P < .05$.

BPM = beat per minute, CG = complex group, DBP = diastolic blood pressure, EIHG = exercise-induced hypertension group, HR = heart rate, METs = maximal metabolic equivalents, NG = normal group, SBP = systolic blood pressure, Total Ex. Time = total exercise time.

Table 2

Participant's careers in marathon.

Variables	NBPG (N = 21, 30%)	EIHG (N = 35, 50%)	CHG (N = 14, 20%)	Total (N = 70, 100%)
Training history (yr)	15.4 ± 5.5	13.1 ± 4.5	14.0 ± 5.0	14.0 ± 5.0
Marathon time (min)	201.8 ± 38.3	194.7 ± 27.9	212.4 ± 35.5	200.4 ± 33.1
Marathon completed (number)	82.0 ± 98.5	75.5 ± 87.5	60.0 ± 29.2	74.4 ± 82.5
Exercise frequency (times per week)	3.4 ± 0.8	3.8 ± 1.4	3.9 ± 1.3	3.7 ± 1.2
Exercise intensity (Borg RPE scale)	13.0 ± 1.8	13.4 ± 1.4	13.4 ± 1.6	13.3 ± 1.6

Mean ± SD.

CG = complex hypertension group, EIHG = exercise-induced hypertension group, NBPG = normal blood pressure group.

hypertension group (CHG, n = 14, 20%) with a resting SBP/DBP ≥140/90 mm Hg and SBP at maximal exercise ≥210 mm Hg. Table 1 delineates the general and hemodynamic characteristics, and physical performance of the study subjects. The NBPG, EIHG, and CHG were similar in age, height, body weight, and body composition. All of the 3 groups had similar resting and maximum HR as well as maximal DBP. However, EIHG shows similar resting BP and significantly higher maximal SBP than NBPG (NBPG vs EIHG for SBP_{max}: 198 ± 8.8 mm Hg, 233 ± 16.5 mm Hg, $P < .05$). CHG has significantly higher resting SBP and DBP than NBPR (NBPG vs CHG for SBP: 122 ± 7.9 mm Hg, 145 ± 11.0 mm Hg, $P < .05$; NBPG vs CHG for DBP: 79 ± 5.1 mm Hg, 95 ± 8.9 mm Hg, $P < .05$).

3.2. Hemodynamic changes during recovery following maximal exercise

HR significantly decreased 1, 2, and 3 minutes into recovery immediately after exercise in all of the 3 groups with no significant differences among the groups. There were also no significant differences of DBP in the recovery phase after exercise among the 3 groups. However, SBP was significantly elevated in the EIHG and CHG than in the NBPG during the recovery phase immediately after exercise. In particular, SBP was significantly higher in the EIHG and CHG than in the NBPG at 1 and 2 minutes into recovery (for 1 minute recovery, NBPG vs EIHG, 185 ± 15.1 vs 226 ± 20.7, $P < .05$; NBPG vs CHG, 185 ± 15.1 vs 220 ± 21.9, $P < .05$; for 2 minutes recovery, NBPG vs EIHG, 188 ± 13.0 vs 221 ± 21.8, $P < .05/3$; NBPG vs CHG, 188 ± 15.1 vs 230 ± 19.8, $P < .05/3$ based on the Bonferroni correction), with the highest SBP in the CHG, followed by the EIHG and NBPG at 3 minutes into recovery (NBPG > EIHG > CHG, 180 ± 16.0 > 206 ± 21.8 > 222 ± 20.8, $P < .05$). Physical performance including VO_{2max}, total exercise time, and maximal metabolic equivalents shows similar values among the 3 groups. The exercise careers of the subjects are described in Table 2. The 3 group has comparable careers among them showing 14.0 ± 5.0-year training history, 200.4 ± 33.1-minute marathon time, 74.4 ± 82.5 times of completed marathon, 3.7 ± 1.2 times per week of exercise, and 13.3 ± 1.6 RPE of exercise intensity in average. Changes in SBP in all the groups at rest, maximal exercise, and 3 minutes recovery after exercise are shown in Figure 2A. The EIHG and CHG groups had significantly higher maximum SBP than the NBPG group and this level significantly differed at the 3 minutes recovery in the following order: NBPG > EIHG > CHG (NBPG > EIHG > CHG, 180 ± 16.0 > 206 ± 21.8 > 222 ± 20.8, respectively, $P < .05$).

3.3. Response of RAAS

In Table 3 and Figure 2, 30 minutes after performing the GXT on a treadmill, the NBPG showed significantly elevated renin and aldosterone levels, and significantly reduced angiotensin II levels, while angiotensin I was consistent. After the GXT, the EIHG showed no changes in renin, angiotensin I, ACE, and angiotensin II, but had a significant elevation of aldosterone. The CHG had

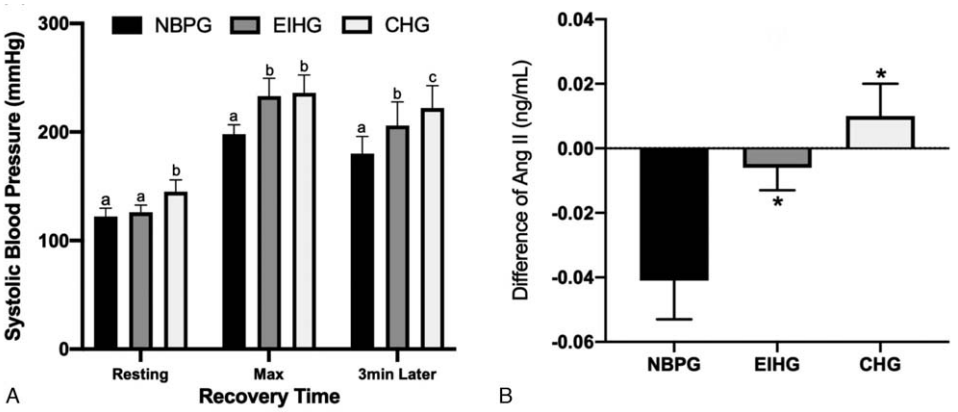

Figure 2. Response of systolic blood pressure (SBP) and angiotensin II to strenuous maximal exercise. (A) Variations of SBP before and after the strenuous maximal exercise; (B) Difference of in activity of angiotensin II before and after strenuous maximal exercise. *P-value is $<.05$; different letters indicate significant difference at $P < .05$. BP = blood pressure, CHG = complex hypertension group, EIHG = exercise-induced hypertension group, NBPG = normal BP group.

Table 3

Responds of RAAS and NO to the strenuous maximal exercise on treadmill.

Variables	NBPG (N = 21, 30%)	EIHG (N = 35, 50%)	CHG (N = 14, 20%)
Renin (ng/mL/h)			
Pre	1.58 ± 0.66	1.30 ± 0.15	1.14 ± 0.18
Post	1.91 ± 0.70*	1.48 ± 1.19	1.62 ± 0.40*
Post-Pre	0.33 ± 0.12	0.18 ± 0.13	0.48 ± 0.32
Angiotensin I (ng/mL)			
Pre	0.738 ± 0.143	0.742 ± 0.954	0.629 ± 0.508
Post	0.738 ± 0.133	0.672 ± 0.382	0.768 ± 0.101
Post-Pre	0.000 ± 0.353	−0.070 ± 0.087	0.139 ± 0.067
Angiotensin II (ng/mL)			
Pre	0.262 ± 0.22	0.222 ± 0.014	0.196 ± 0.016
Post	0.221 ± 0.01*	0.216 ± 0.014	0.206 ± 0.020
Post-Pre	−0.041 ± 0.012[a]	−0.006 ± 0.007[b]	0.010 ± 0.010[b]
Aldosterone (ng/dL)			
Pre	8.96 ± 0.84	12.47 ± 1.09	12.73 ± 2.42
Post	13.03 ± 1.37*	17.31 ± 1.50*	15.72 ± 2.71*
Post-Pre	4.07 ± 0.95	4.84 ± 1.06	3.03 ± 1.51
T-Nitric oxide (μmol/L)			
Pre	71.0 ± 40.4	102.6 ± 69.9	80.1 ± 36.0
Post	68.1 ± 40.3	93.1 ± 66.2*	73.7 ± 35.4*
Post-Pre	−2.8 ± 11.2[a]	−9.4 ± 11.4[b]	−6.4 ± 7.6[ab]

Mean ± SD. Different superscripts mean significant different at $P < .05$. ACE = angiotensin converting enzyme, T-nitric oxide = total nitric oxide.
* $P < .05$ from the Pre.

significantly elevated renin and aldosterone levels in the recovery phase with no changes in ACE, angiotensin I, and angiotensin II. These results show that angiotensin II levels were significantly reduced in the NBPG while it remained similar to the baseline in the EIHG and CHG in the recovery phase after exercise (for angiotensin II, NBPG vs EIHG, −0.04 ± 0.012 vs −0.006 ± 0.007, $P < .05/3$; and NBPG vs CHG, −0.04 ± 0.012 vs 0.010 ± 0.010, $P < .05$). Table 3 for the total NO shows that there were trends to decrease the total NO after the post-exercise compared to the pre-exercise. As a result, the reduction in total NO is significantly greater in EHIG than the NBPG (−2.8 ± 11.2 vs −9.4 ± 11.4, $P < .05$).

4. Discussion

This study examined the changes in RAAS and total NO, which are involved in BP regulation, after maximal exercise in middle-aged long-distance runners with EIH. The study participants were classified into the NBPG, EIHG, and CHG, and RAAS and NO measurements were taken before a GXT and 30 minutes after the GXT. The results showed that angiotensin II levels were significantly reduced from the baseline in the NBPG but remained at the baseline in the EIHG and CHG (Table 3 and Fig. 1B). This suggests that runners with EIH and CH showed persistent angiotensin II activity even in the recovery phase after exercise.

The NBPG showed no changes in NO in the recovery phase after exercise, but the EIHG and CHG showed reduced NO levels, with the EIHG showing a more significant reduction than the NBPG. Hypotheses explaining the reduction of NO after exercise involve elevated oxidative stress, shear rate, BP, baseline artery diameter, and SNS activity.[20] Particularly, strenuous exercise increases the production of free radicals, such as superoxide, that cause oxidative stress, which substantially lowers the bioavailability and production of NO and diminishes epithelial functions and FMD.[21] Further, NO eliminates free radicals, thereby decreasing NO availability.[22] In general, oxidative stress increases with increasing exercise intensity,[23] and this is related to an excessive reduction of FMD.[24] A biphasic response occurs in which FMD declines 30 minutes to 1 hour after vigorous exercise, and this phenomenon is associated with the reduction of NO.[20] High levels of BP lead to associated increases in shear that, over a prolonged period, may result in the decreased release of NO from the endothelium.[25] As previously mentioned, the decrease in FMD immediately after exercise may be less apparent in trained individuals.[26,27] However, in patients with EIH and general hypertension, they already have endothelial dysfunction, which is normal, because they lack protection against high shear rates due to increase in BP after exercise.

Therefore, the clear reduction of NO 30 minutes after maximal exercise in the EIHG and CHG and the relatively lower reduction in angiotensin II activity—which is involved in vasoconstriction—in the EIHG and CHG explain the impairment of vasodilation patients with EIH. We observed that the EIHG and CHG had higher BP than the normal group at 3 minutes of recovery after GXT. EIH occurs because of an increase in post load caused by increased arterial stiffness and arterial endothelial dysfunction.[28,29]

In this study, we found that 50% of long-distance runners had EIH, and 20% of the participants had complex hypertension. It is unclear whether the high prevalence of elevated BP during exercise is caused by the higher exercise capacity of the participants or by a pathological factor such as increased arterial stiffness. Recent reports have shown a high incidence of EIH in long-distance runners, but the cause for this remains unknown.[6,7] The incidence of atrial fibrillation,[5] as well as sudden death[30] and arterial stiffness[4] is high among individuals who engage in vigorous exercise. In fact, runners who participate in intense exercises such as marathons engage in exercise 5 to 10 times higher than the recommended amount of exercise in the cardiovascular prevention guidelines,[31] raising concerns for the potential side effects of excessive exercise. Individuals with EIH are 5 to 10 times more likely to develop resting hypertension,[10] and although EIH is a risk factor for stroke and predictor of mortality,[11] it is unknown whether this is also true for long-distance runners.

Recently, studies have confirmed the elevation of cardiac troponin I, which is expressed upon myocardial infarction, and the elevation of N-terminal fragment of the prohormone brain-type natriuretic peptide, which increases myocardial volume-pressure, during a 100 km ultramarathon in runners with EIH.[8,9] This proves that runners with EIH participate in long-distance running with greater myocardial burden than runners with normal BP. In addition, in a study of 588 long-distance runners, Kim et al found that the group of runners with arrhythmia such as critical atrial fibrillation had higher VO_2max, greater exercise intensity, and longer exercise career than the group of normal runners, and that both groups had prehypertension and EIH.[6] This evidence suggests that excessive exercise itself may adversely impact the cardiovascular system, and longitudinal studies are needed to investigate whether the incidence of future cardiac events such as myocardial hypertrophy, arterial stiffness, arrhythmia, and sudden death may be elevated among those with EIH.

Warner et al[32] reported that the maximum SBP was lowered by 33 mm Hg in patients with exaggerated BP response by

angiotensin II receptor inhibitors. Kim and Ha[33] stated that angiotensin receptor inhibitors or ACE inhibitors can be recommended for patients with EIH. Moreover, Liakos et al reported that angiotensin receptor blocker were effective at suppressing the exercise induced acute phase inflammatory response.[34] Our finding that runners with EIH and CH showed persistent angiotensin II activity even in the recovery phase after exercise could be accompanied by a significant clinical impact; it can be speculated that angiotensin receptor blockers can be suggested at protecting long distance runner with EIH against the triggering of acute coronary syndrome and the developing of sudden critical arrhythmia during vigorous exercise. Nevertheless, this suggestion needs to be proven by future studies with hard endpoints in terms of morbidity and mortality.

Some limitations of this study and recommendation for future studies were discussed. First, the size of sample was small and there was no randomization with groups, which would possibly affect generalizability of the findings. It is suggested that a larger sample size and randomization of the groups should be considered in the further studies. Secondly, the sample was only consisted of well-trained Korean healthy middle-aged runner, it is possible that results from this study may not be generalizable to various groups with other physical conditions. In the future, it is recommended involving a more various racial groups with different physical conditions. Thirdly, we were unable to adjust for the subjects' family histories and control for their involvement in other exercises. Fourth, we also did not perform FMD testing before and after exercise. Absence of echocardiography to differentiate between the potential diseases affecting cardiac structure and functions and not using the 24-hour ambulatory BP test to accurately examine BP further limited the study. Finally, this study used only blood analysis for evaluation for arterial stiffness or hemodynamic changes. Follow-up assessments through diagnostic imaging test such as ultrasonography or computerized tomography scan would be suggested in future studies

Despite these limitations, this study has its significance by verifying the factors in the RAAS, which regulates BP, that are activated in addition to the responses of NO in well-trained runners with EIH.

In conclusion, angiotensin II and NO reduction, which hinder vasodilation, are involved in EIH among long-distance runners. Therefore, angiotensin II blockers should be considered for pharmacological therapy for them when necessary.

Author contributions

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

References

[1] D'Isabella NT, Shkredova DA, Richardson JA, et al. Effects of exercise on cardiovascular risk factors following stroke or transient ischemic attack: a systematic review and meta-analysis. Clin Rehabil 2017; 31:1561–72.
[2] Miele EM, Headley SAE. The effects of chronic aerobic exercise on cardiovascular risk factors in persons with diabetes mellitus. Curr Diab Rep 2017;17:97.
[3] Paffenbarger RSJr, Hyde RT, Wing AL, et al. The association of changes in physical-activity level and other lifestyle characteristics with mortality among men. N Engl J Med 1993;328:538–45.
[4] Vlachopoulos C, Kardara D, Anastasakis A, et al. Arterial stiffness and wave reflections in marathon runners. Am J Hyperten 2010;23:974–9.
[5] Flannery MD, Kalman JM, Sanders P, et al. State of the art review: atrial fibrillation in athletes. Heart Lung Circ 2017;26:983–9.
[6] Kim YJ, Kim CH, Park KM. Excessive exercise habits of runners as new signs of hypertension and arrhythmia. Int J Cardiol 2016;217:80–4.
[7] Kim YJ, Park Y, Kang DH, et al. Excessive exercise habits in marathoners as novel indicators of masked hypertension. Biomed Res Int 2017; 1342842.
[8] Kim YJ, Shin YO, Lee YH, et al. Effects of marathon running on cardiac markers and endothelin-1 in EIH athletes. Int J Sports Med 2013; 34:777–82.
[9] Kim YJ, Kim CH, Shin KA, et al. Cardiac markers of EIH athletes in ultramarathon. Int J Sports Med 2012;33:171–6.
[10] Williams PT, Thompson PD. Increased cardiovascular disease mortality associated with excessive exercise in heart attack survivors. Mayo Clin Proc 2014;89:1187–94.
[11] Singh JP, Larson MG, Manolio TA, et al. Blood pressure response during treadmill testing as a risk factor for new-onset hypertension. The Framingham Heart Study. Circulation 1999;99:1831–6.
[12] Kurl S, Laukkanen JA, Rauramaa R, et al. Systolic blood pressure response to exercise stress test and risk of stroke. Stroke 2001;32: 2036–41.
[13] Mundal R, Kjeldsen SE, Sandvik L, et al. Exercise blood pressure predicts mortality from myocardial infarction. Hypertension 1996;27:324–9.
[14] Małek ŁA, Czajkowska A, Mróz A, et al. Left ventricular hypertrophy in middle-aged endurance athletes: is it blood pressure related? Blood Press Monit 2019;24:110–3.
[15] Gabrielli L, Herrera S, Contreras-Briceño F, et al. Increased active phase atrial contraction is related to marathon runner performance. Eur J Appl Physiol 2018;118:1931–9.
[16] Fallo F. Renin-angiotensin-aldosterone system and physical exercise. J Sports Med Phys Fitness 1993;33:306–12.
[17] Shim CY, Ha JW, Park S, et al. Exaggerated blood pressure response to exercise is associated with augmented rise of angiotensin II during exercise. J Am Coll Cardiol 2008;52:287–92.
[18] Jin RC, Loscalzo J. Vascular nitric oxide: formation and function. J Blood Med 2010;1:147–62.
[19] Gibobons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). J Am Coll Cardiol 2002;40:1531–40.
[20] Dawson EA, Green DJ, Cable NT, et al. Effects of acute exercise on flow-mediated dilatation in healthy humans. J Appl Physiol 2013;115:1589–98.
[21] Rognmo O, Bjornstad TH, Kahrs C, et al. Endothelial function in highly endurance-trained men: effects of acute exercise. J Strength Cond Res 2008;22:535–42.
[22] Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. Circ Res 2000;87:840–4.
[23] Goto C, Higashi Y, Kimura M, et al. Effect of different intensities of exercise on endothelium-dependent vasodilation in humans: role of endothelium-dependent nitric oxide and oxidative stress. Circulation 2003;108:530–5.
[24] Birk GK, Dawson EA, Batterham AM, et al. Effects of exercise intensity on flow mediated dilation in healthy humans. Int J Sports Med 2013; 35:409–14.
[25] Bilfinger TV, Stefano GB. Human aortocoronary grafts and nitric oxide release: relationship to pulsatile pressure. Ann Thorac Surg 2000; 69:480–5.
[26] Varady KA, Bhutani S, Church EC, et al. Adipokine responses to acute resistance exercise in trained and untrained men. Med Sci Sports Exerc 2010;42:456–62.
[27] Phillips SA, Das E, Wang J, et al. Resistance and aerobic exercise protects against acute endothelial impairment induced by a single exposure to hypertension during exertion. J Appl Physiol 2011;110:1013–20.

[28] Stewart KJ, Sung J, Silber HA, et al. Exaggerated exercise blood pressure is related to impaired endothelial vasodilator function. Am J Hypertens 2004;17:314–20.
[29] Wilson MF, Sung BH, Pincomb GA, et al. Exaggerated pressure response to exercise in men at risk for systemic hypertension. Am J Cardiol 1990; 66:731–6.
[30] Noakes TD. Heart disease in marathon runners: a review. Med Sci Sports Exerc 1987;19:187–94.
[31] Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Circulation 2007; 116: 1081–93.
[32] Warner JGJr, Metzger DC, Kitzman DW, et al. Losartan improves exercise tolerance in patients with diastolic dysfunction and a hypertensive response to exercise. J Am Coll Cardiol 1999;33:1567–72.
[33] Kim D, Ha JW. Hypertensive response to exercise: mechanisms and clinical implication. Clin Hypertens 2016;22:17.
[34] Liakos Cl, Vyssoulis GP, Michaelided AP, et al. The effect of angiotensin receptor blockers vs. calcium channel blockers on the acute exercise-induced inflammatory and thrombotic response. Hypertens Res 2012;35:1193–200.