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

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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 II 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 also been reported to have associated with marathon running in healthy runners.[7,8] 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.[9,10]

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.[10] EIH increases the risk for future resting hypertension,[10] and is an independent risk factor for cerebro-cardiovascular disease.[11]
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.\textsuperscript{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\textsubscript{2}) measured previous to the marathon and to performance in a highly demanding test.\textsuperscript{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,\textsuperscript{16} and angiotensin II activity is associated with EIH in patients with dyspnea.\textsuperscript{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.\textsuperscript{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.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{chart.png}
\caption{Flow chart of the study participants. CHG = complex hypertension group, EIHG = exercise-induced hypertension group, GXT = graded exercise testing, NBPG = normal blood pressure group.}
\end{figure}
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: SWUIRB 2018-009).

2.2. Measurements

2.2.1. GXT. The symptom-limited GXT was performed using a treadmill (T170 DE, hp, Columbus, 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 centrifuged at 3000 rpm for 10 minutes to separate the serum, and stored in a −70°C freezer for RAAS analysis. Blood samples were taken before GXT and stored in a −70°C freezer for RAAS analysis. Blood samples were taken before GXT and stored in a −70°C freezer for RAAS analysis. Blood samples were taken before GXT and stored in a −70°C freezer for RAAS analysis.

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 mm Hg 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 group, DBP ≥20 mm Hg at maximal exercise.

![Table 1 Characteristics of demographics, hemodynamic, and cardiopulmonary fitness in study participants.](https://md-journal.com)

| 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±6.5       |
| BMI (kg/m²)                | 23.4±1.9         | 23.2±2.0         | 23.0±2.2       |
| FFM (kg)                   | 57.3±5.2         | 56.4±7.2         | 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       |
| HRrest, (BPM)              | 60±7.5           | 60±10.1          | 65±7.6         |
| HRmax, (BPM)               | 172±12.2         | 170±23.4         | 176±9.8        |
| SBP (mm Hg)                | 122±7.9          | 128±6.7          | 145±11.0       |
| DBP (mm Hg)                | 79±5.1           | 81±6.0           | 95±8.9         |
| SBPmax (mm Hg)             | 198±8.8          | 233±16.8         | 226±16.5       |
| DBPmax (mm Hg)             | 79±5.1           | 78±11.5          | 81±13.7        |
| **Homodynamic characteristics**|                |                  |                |
| HRrest (BPM)               | 144±12.2         | 145±11.8         | 151±13.3       |
| HRmax (BPM)                | 122±11.3         | 121±13.0         | 130±14.1       |
| HRrest (BPM)               | 110±11.5         | 111±11.5         | 120±18.4       |
| SBP (mm Hg)                | 185±15.1         | 220±20.20        | 220±21.9       |
| SBPmax (mm Hg)             | 186±13.0         | 221±21.8         | 230±19.3       |
| DBP (mm Hg)                | 76±9.3           | 75±11.1          | 80±14.0        |
| DBPmax (mm Hg)             | 77±9.4           | 79±11.3          | 83±9.7         |
| **Physical performance**   |                  |                  |                |
| VO2max (mL/kg/min)         | 51.7±6.5         | 51.4±7.1         | 53.5±9.0       |
| Total Ex. (time)           | 860±88           | 860±85           | 826±104        |
| METsmax                     | 14.8±1.9         | 14.7±2.1         | 15.3±4.3       |

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

BMI = body mass index, 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.
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 SBPmax: 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 VO₂max, 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

| 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     | 210.4±53.1        |
| Marathon completed (number)      | 35.0±18.5        | 75.5±87.5        | 60.0±29.2      | 74.4±82.5         |
| Exercise frequency (times/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.

![Figure 2](image-url)
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 greater in EHIG than the NBPG (Table 3 and Fig. 1B). This shows that angiotensin II activity—which is involved in vasoconstriction and NO explain the impairment of vasodilation patients with EIH. We observed that the EHIG 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[31] are 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 myocar dial volume-pressure, during a 100km ultramarathon in runners with EIH.[6,8] 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 VO2max, 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

### Table 3

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

| Variables      | NBPG  | EHIG  | CHG   |
|----------------|-------|-------|-------|
| Renin (ng/mL/L)|       |       |       |
| 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  |       |       |       |
| Pre            | 0.738±0.143 | 0.742±0.954 | 0.629±0.508 |
| Post           | 0.738±0.153 | 0.678±0.382 | 0.768±0.101 |
| Post-Pre       | 0.000±0.533 | -0.070±0.887 | 0.193±0.007 |
| Angiotensin II |       |       |       |
| Pre            | 0.262±0.22  | 0.222±0.014  | 0.196±0.016  |
| Post           | 0.221±0.017   | 0.216±0.014   | 0.206±0.020   |
| Post-Pre       | -0.041±0.012a | -0.006±0.007b | 0.010±0.010b |
| Aldosterone    |       |       |       |
| Pre            | 8.96±0.84   | 12.47±1.09   | 12.73±2.42   |
| Post           | 13.03±1.37   | 17.91±1.50a  | 15.72±2.71a  |
| Post-Pre       | 4.07±0.95   | 4.84±1.06    | 3.03±1.51    |
| T-Nitric oxide |       |       |       |
| Pre            | 71.0±4.04   | 102.6±69.9   | 80.1±36.0    |
| Post           | 68.1±4.03   | 93.1±66.2a   | 73.7±35.4a   |
| Post-Pre       | -2.8±11.2    | -9.4±14.6b   | -6.4±7.6b    |

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.
angiotensin II receptor inhibitors. Kim and Ha\textsuperscript{[13]} 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.\textsuperscript{[14]} 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.

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**

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