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Exaggerated Blood Pressure Response to Exercise Is Associated With Augmented Rise of Angiotensin II During Exercise

Chi Young Shim, MD, Jong-Won Ha, MD, PHD, Sungha Park, MD, PHD, Eui-Young Choi, MD, Donghoon Choi, MD, PHD, Se-Joong Rim, MD, PHD, Namsik Chung, MD, PHD

Seoul, South Korea

Objectives The aim of this study was to investigate the association between an exaggerated blood pressure (BP) response to exercise and augmented angiotensin (Ang) II rise during exercise.

Background Although a central pressor effect of Ang II has been implicated in the pathogenesis of hypertension, the relationship between Ang II and exaggerated BP response to exercise is unclear.

Methods Thirty-six subjects with an exaggerated BP response to exercise (18 men, age 50 ± 16 years, Group II) were compared with 36 age- and gender-matched control subjects (18 men, age 50 ± 16 years, Group I) with normal BP reactivity. The subjects who had resting BP ≥140/90 mm Hg or were treated with any antihypertensive drugs were excluded. The blood was sampled at rest and immediately after peak exercise for measurement of renin, Ang II, aldosterone, and catecholamine.

Results At rest, there were no significant differences in BP, renin, aldosterone, and catecholamine levels between the 2 groups. The renin, aldosterone, and catecholamine were increased during exercise, but there were no significant differences between the groups. However, log Ang II at rest (0.78 ± 0.32 vs. 0.98 ± 0.38, $p = 0.004$) and peak exercise (0.84 ± 0.35 vs. 1.17 ± 0.51, $p < 0.001$) and the magnitude of the increment of log Ang II with exercise (0.06 ± 0.12 vs. 0.19 ± 0.20, $p = 0.003$) were significantly higher in the exaggerated BP response group.

Conclusions An exaggerated BP response to exercise was associated with augmented rise of Ang II during exercise. (J Am Coll Cardiol 2008;52:287–92) © 2008 by the American College of Cardiology Foundation

An exaggerated blood pressure (BP) response to exercise is associated with a 2 to 3 times greater risk of future development of hypertension (1–3) and a greater prevalence of left ventricular (LV) hypertrophy (4,5) in otherwise normotensive participants. The association between an abnormal rise in systolic BP during exercise and cardiovascular morbidity has been suggested, but its mechanism has not been clearly elucidated. It has been suggested that BP and heart rate increments during exercise are related to stimulation of the sympathetic nervous system and the renin-angiotensin-aldosterone system during exercise (6–8). However, neurohormonal differences have not been studied fully between subjects who have an exaggerated BP response to exercise and who have normal BP reactivity. In the present study, we hypothesized that an exaggerated BP response to exercise is associated with augmented angiotensin (Ang) II rise during exercise. To prove our hypothesis, we investigated neurohormonal changes such as renin, Ang II, aldosterone, and catecholamine at rest and immediately after peak exercise in subjects with an exaggerated BP response to exercise and compared them with neurohormonal changes in control subjects who have normal BP reactivity.

Methods

Study subjects. The study subjects consisted of patients who were referred for exercise Doppler echocardiography for the evaluation of coronary artery disease or exercise-induced diastolic dysfunction as the cause of exertional dyspnea during the period between October 2005 and May 2006. At the initial enrollment, patients underwent a complete physical examination, a baseline electrocardiogram, and laboratory assessment. Inclusion criteria included resting BP <140/90 mm Hg, LV ejection fraction ≥55% by 2-dimensional echocardiography, no valvular heart disease, no significant systemic disease, and no evidence of renal

From the Cardiology Division, Yonsei Cardiovascular Center, Yonsei University College of Medicine, Seoul, South Korea. This work was supported by the Korea Science and Engineering Foundation (KOSEF) grant funded by the Korean government (M10642120001-06N4212-00110).

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Abbreviations and Acronyms

Ang = angiotensin
BP = blood pressure
Epi = epinephrine
LV = left ventricle/ventricular
NE = norepinephrine
PRA = plasma renin activity
SV = stroke volume

insufficiency (serum creatinine <1.5 mg/ml). The subjects who were treated with any antihypertensive drugs or vasodilators were also excluded. Among the 286 subjects who received the exercise stress echocardiography, 131 subjects (61 men, mean age 48 ± 16 years) satisfied the entry criteria completely. Each subject provided informed, written consent to the protocol that had been approved by our institutional review board. The mean change in systolic BP with exercise echocardiography was 55 ± 21 mm Hg in men and 46 ± 25 mm Hg in women. Among the 131 subjects, 26 men and 23 women met the definition of an exaggerated BP response to exercise defined as difference of peak and baseline systolic BP ≥60 mm Hg in men and ≥50 mm Hg in women during exercise echocardiography. After the exercise test, 3 subjects (2 men, 1 woman) who showed positive exercise echocardiogram for inducible ischemia and 10 subjects (6 men, 4 women) with insufficient blood samples either at rest or immediately after peak exercise were additionally excluded. Finally, 36 subjects with an exaggerated BP response to exercise (Group II, 18 men, mean age 50 ± 16 years) and 36 age- and gender-matched control subjects with normal BP reactivity (Group I) were analyzed. Among the 72 subjects analyzed, 16 subjects (9 in Group I, 7 in Group II) were previously diagnosed with essential hypertension. However, the resting BP of all subjects was <140/90 mm Hg without any antihypertensive treatments.

Exercise protocol. The exercise test with simultaneous respiratory gas analysis was performed using a variable load bicycle ergometer (Medical Positioning Inc., Kansas City, Missouri) at a supine position. Echocardiographic examination was performed simultaneously as described previously (9). Briefly, after obtaining the rest of the images, a multistage supine bicycle exercise test was performed. From the resting images, standard 2-dimensional measurements were performed as a recommendation of the American Society of Echocardiography (10). Stroke volume (SV) was calculated by multiplying LV outflow tract area by the time integral of the outflow tract velocity measured by pulsed wave Doppler. Left ventricular outflow tract area was determined as $(D/2)^2$, where D is its diameter measured from a zoomed systolic freeze frame in the parasternal long-axis view. End-systolic pressure was approximated by [(2 × systolic BP + diastolic BP)/3]. The effective arterial elastance was the ratio of end systolic pressure to SV (11).

The subjects pedaled at a constant speed beginning at a workload of 25 W, with an incremental workload of 25 W every 3 min until limited by their symptoms. Peak exercise time was recorded in seconds. Peak workload was estimated as metabolic equivalents. The BP was measured at the end of each stage of exercise on the left arm using an oscillometric BP monitoring device (Solar 8000M patient monitoring device, GE Medical Systems, Milwaukee, Wisconsin).

Neurohormonal assessment. A small flexible intravenous cannular was inserted into the forearm vein for blood sampling. The blood samples were obtained with the subjects at rest (after 5 min of rest in supine position) and immediately after peak exercise for measurements of plasma renin, Ang II, serum aldosterone, and plasma catecholamine (epinephrine [Epi] and norepinephrine [NE]). Samples were drawn into ethylenediaminetetraacetic acid–treated tubes and plain tubes. The tubes were immediately placed in ice and immediately centrifuged. The plasma and serum then were separated and stored at −70°C until analysis. Plasma Epi and NE levels were measured by high-performance liquid chromatography (normal range of Epi: <300 pg/ml, NE: <800 pg/ml) (12). Plasma renin activity (PRA), plasma Ang II concentration, and serum aldosterone were measured using commercially available radioimmunoassay kits, level of PRA (Renin RIA beads, SRL Inc., Tokyo, Japan, normal range 0.68 to 1.36 ng/ml/h), Ang II (Angiotensin II kits, SRL Inc., Tokyo, Japan, normal range 9 to 47 pg/ml), and aldosterone (Coat-a-Coung, DPC, Los Angeles, California, normal range 10 to 105 pg/ml). The interassay and intra-assay precision (coefficient of variation) of NE was 4.7% and 3.6%. Those of Epi were 3.9% and 3.4%. Those of PRA were 4.0% and 2.5%. The interassay and intra-assay coefficients of variation were 7.7%, 7.2% in Ang II and 6.5%, 3.2% in aldosterone.

Statistical analysis. Continuous variables were presented as mean ± SD and categorical variables as absolute and relative frequencies (%). Differences between the 2 groups were analyzed using a paired *t* test for continuous variables and the McNemar test for categorical variables. In each group, between at-rest and at-peak exercise, neurohormonal data were compared using a paired *t* test. To normalize the distribution, a natural logarithmic transformation was applied to variables that were not in the normal distribution. A p value of <0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS software (version 13.0, SPSS Inc., Chicago, Illinois).

Results

Baseline characteristics. Clinical characteristics of the study population are presented in Table 1.

There were no significant differences in clinical variables such as body mass index, smoking, diabetes mellitus, and dyslipidemia. Four subjects were treated with statins, but there were no significant differences between the groups. There were no subjects who were taking insulin-sensitizing drugs such as thiazolidinediones. In addition, there were no subjects on exogenous hormone therapy, either contraceptives or post-menopausal hormone treatment. Systolic BP, diastolic BP, pulse pressure, and heart rate at rest were not

Table 1 Baseline Characteristics of the Study Subjects

	Group I (n = 36)	Group II (n = 36)	p Value*
Age, yrs	50 ± 16	50 ± 16	1.000
Gender, M:F	18:18	18:18	1.000
Height, cm	163.4 ± 8.7	163.9 ± 8.8	0.779
Weight, kg	64.4 ± 10.4	67.1 ± 10.9	0.209
Body surface area, m^2	1.70 ± 0.17	1.74 ± 0.17	0.282
Body mass index, kg/m^2	24.0 ± 2.6	24.9 ± 3.1	0.117
Diabetes mellitus, n (%)	2 (5.6)	4 (11.2)	0.453
Dyslipidemia, n (%)	4 (11.2)	5 (13.9)	1.000
Smoking, n (%)	8 (22.4)	13 (36.1)	0.267
Statin, n (%)	1 (2.8)	3 (8.3)	0.500
Resting SBP, mm Hg	131 ± 9	130 ± 11	0.450
Resting DBP, mm Hg	80 ± 9	79 ± 10	0.540
Resting PP, mm Hg	51 ± 9	51 ± 11	0.930
Resting HR, beats/min	64 ± 9	65 ± 10	0.446
Resting ESP, mm Hg	115 ± 15	114 ± 15	0.101
Stroke volume, ml	67.6 ± 12.9	67.7 ± 12.0	0.978
Ea, mm Hg/ml	1.72 ± 0.41	1.71 ± 0.41	0.271
LVEF, %	67.5 ± 6.1	67.9 ± 5.8	0.785
LV mass index, g/m^2	92.6 ± 20.6	92.1 ± 15.4	0.909
Relative wall thickness	0.38 ± 0.06	0.39 ± 0.06	0.636
LA volume index, ml/m^2	21.3 ± 6.6	21.0 ± 6.6	0.854

*$p < 0.05$ is considered statistically significant.

DBP = diastolic blood pressure; Ea = arterial elastance; ESP = end-systolic pressure; HR = heart rate; LA = left atrium; LV = left ventricle; LVEF = left ventricular ejection fraction; PP = pulse pressure; SBP = systolic blood pressure.

different between the groups. There was no difference in SV, end-systolic pressure, and arterial elastance between the groups. Left ventricular ejection fraction, LV mass index, relative wall thickness, and left atrium volume index were also similar in the 2 groups.

Hemodynamic response to exercise. Total exercise duration was similar between the 2 groups. The reason for stopping exercise was not different between the 2 groups. The most common limiting symptom was leg fatigue. Peak systolic and peak diastolic BP during exercise and increment of systolic and diastolic BP were significantly higher in Group II compared with that in Group I because of the study design. Heart rate at rest was not different between 2 groups, but heart rate at peak exercise was significantly higher in Group II compared with that of Group I (Table 2).

Neurohormonal response to exercise. There were no significant differences in resting PRA, aldosterone, and catecholamine level between 2 groups. The PRA, aldosterone, and catecholamine levels increased during exercise, but there were no significant differences between groups. However, log Ang II at rest (Group I 0.78 ± 0.32 vs. Group II 0.98 ± 0.38, $p = 0.004$) and peak exercise (0.84 ± 0.35 vs. 1.17 ± 0.51, $p < 0.001$) and the magnitude of increment of log Ang II with exercise (0.06 ± 0.12 vs. 0.19 ± 0.20, $p = 0.003$) were significantly higher in Group II subjects (Table 3, Fig. 1). These different neurohormonal responses to exercise between the 2 groups were consistent in both genders.

Discussion

The present study demonstrated that an exaggerated BP response to exercise was associated with augmented rise of Ang II during exercise. Catecholamines such as NE and Epi also increased during exercise, but there was no significant difference between the 2 different BP response groups.

The mechanism of an exaggerated BP response to exercise is poorly understood. Several mechanisms for this unique phenomenon have been proposed. The sympathoadrenal and renin-angiotensin systems play an important role in BP control and regulation of cardiovascular function during exercise (13). An exaggerated BP response to exercise has been thought to be related to excess stimulation of the sympathetic nervous system and increased activation of the renin-angiotensin-aldosterone system (6–8). The renin-angiotensin and sympathoadrenal systems do not operate independently but mutually interact with each other in accomplishing their cardiovascular regulatory function (14,15). In our study, all neurohormones were increased with exercise compared with at rest. Plasma catecholamine was increased as expected, but no difference was found between subjects with or without an exaggerated BP response to exercise. This result can be explained by 2 factors influencing the neurohormonal response. First, we selected only normotensive subjects at rest, although most of all previous studies had focused on neurohormonal changes in hypertensive patients. Second, in the present study, most of the subjects underwent exercise workloads of 5 to 7 metabolic equivalents, equivalent to routine daily activities. Because of these factors, the amount of catecholamine secreted by the sympathetic nerve endings might not be sufficient enough to increase its systemic concentration with a statistical significance. However, in the same setting, Ang II level at peak exercise was significantly increased in subjects with an exaggerated BP response to

Table 2 Hemodynamic Response to Exercise

	Group I (n = 36)	Group II (n = 36)	p Value*
Total exercise duration, s	617 ± 203	636 ± 184	0.652
METs	6.1 ± 1.4	6.2 ± 1.3	0.339
Peak-exercise SBP, mm Hg	164 ± 27	200 ± 20	<0.001
Peak-exercise DBP, mm Hg	88 ± 16	94 ± 18	0.019
Peak-exercise HR, beats/min	120 ± 21	130 ± 20	0.012
Increment of SBP, mm Hg	33 ± 19	73 ± 19	<0.001
Increment of DBP, mm Hg	8 ± 14	15 ± 19	0.001
Increment of HR, beats/min	56 ± 20	65 ± 18	0.070
Reason for stopping exercise, n (%)			
Dyspnea	8 (22.2)	9 (25.0)	NS
Chest discomfort	0 (0.0)	1 (2.8)	NS
Leg fatigue	23 (63.9)	22 (61.1)	NS
Others	4 (11.1)	5 (13.9)	NS

*$p < 0.05$ is considered statistically significant.

MET = metabolic equivalent; other abbreviations as in Table 1.

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Table 3 Neurohormonal Response to Exercise in Subjects With or Without an Exaggerated BP Response to Exercise

Neurohormones	Group I (n = 36)	Group II (n = 36)	p Value*
Log NE, pg/ml			
Rest			
All	2.35 ± 0.24	2.37 ± 0.20	0.951
Men	2.31 ± 0.24	2.35 ± 0.20	0.251
Women	2.39 ± 0.23	2.38 ± 0.20	0.237
Peak exercise			
All	2.43 ± 0.26	2.48 ± 0.22	0.453
Men	2.36 ± 0.20	2.45 ± 0.28	0.062
Women	2.50 ± 0.29	2.51 ± 0.15	0.695
Increment			
All	0.08 ± 0.31	0.12 ± 0.29	0.521
Men	0.04 ± 0.07	0.11 ± 0.09	0.692
Women	0.10 ± 0.08	0.12 ± 0.06	0.626
Log Epi, pg/ml			
Rest			
All	1.69 ± 0.22	1.67 ± 0.36	0.558
Men	1.61 ± 0.22	1.64 ± 0.44	0.304
Women	1.75 ± 0.20	1.70 ± 0.27	0.121
Peak exercise			
All	1.80 ± 0.25	1.81 ± 0.23	0.598
Men	1.81 ± 0.30	1.82 ± 0.21	0.681
Women	1.78 ± 0.20	1.80 ± 0.25	0.738
Increment			
All	0.10 ± 0.28	0.15 ± 0.32	0.299
Men	0.19 ± 0.35	0.19 ± 0.37	0.451
Women	0.04 ± 0.18	0.11 ± 0.28	0.055
Log PRA, ng/ml/h			
Rest			
All	0.10 ± 0.44	0.12 ± 0.45	0.773
Men	0.21 ± 0.45	0.21 ± 0.38	0.724
Women	−0.03 ± 0.41	0.02 ± 0.51	0.967
Peak exercise			
All	0.22 ± 0.37	0.29 ± 0.35	0.372
Men	0.33 ± 0.40	0.39 ± 0.35	0.897
Women	0.10 ± 0.31	0.18 ± 0.33	0.121
Increment			
All	0.09 ± 0.22	0.14 ± 0.33	0.473
Men	0.12 ± 0.20	0.18 ± 0.24	0.897
Women	0.07 ± 0.25	0.10 ± 0.40	0.121
Log Ang II, pg/ml			
Rest			
All	0.78 ± 0.32	0.98 ± 0.38	0.004
Men	0.78 ± 0.27	0.98 ± 0.32	0.009
Women	0.77 ± 0.38	0.98 ± 0.44	0.167
Peak exercise			
All	0.84 ± 0.35	1.17 ± 0.51	<0.001
Men	0.86 ± 0.33	1.18 ± 0.45	0.002
Women	0.81 ± 0.38	1.16 ± 0.57	0.036
Increment			
All	0.06 ± 0.12	0.19 ± 0.20	0.003
Men	0.08 ± 0.11	0.19 ± 0.20	0.016
Women	0.04 ± 0.14	0.18 ± 0.21	0.034
Log ALDO, pg/ml			
Rest			
All	1.46 ± 0.33	1.46 ± 0.35	0.912
Men	1.42 ± 0.35	1.54 ± 0.33	0.873
Women	1.49 ± 0.31	1.39 ± 0.37	0.989
Peak exercise			
All	1.54 ± 0.31	1.59 ± 0.36	0.532
Men	1.55 ± 0.30	1.65 ± 0.35	0.947
Women	1.54 ± 0.32	1.52 ± 0.37	0.348
Increment			
All	0.09 ± 0.17	0.12 ± 0.22	0.524
Men	0.12 ± 0.17	0.11 ± 0.14	0.761
Women	0.05 ± 0.17	0.13 ± 0.28	0.154

*$p < 0.05$ is considered statistically significant.

ALDO = aldosterone; Ang = angiotensin; BP = blood pressure; Epi = epinephrine; NE = norepinephrine; PRA = plasma renin activity.

exercise. There was indirect evidence that Ang II is an important neurohormone in subjects with an abnormal BP rise. Warner et al. (16) found that 2 weeks of therapy with the Ang II receptor blocker reduced peak systolic BP by a mean of 33 mm Hg during exercise in patients with an exaggerated BP response to exercise. This observation suggested the role of Ang II acting through Ang I receptors in contributing to an exaggerated BP response to exercise. However, that study also included hypertensive patients who were taking a variety of common antihypertensive medications. Furthermore, the neurohormonal measurements were not performed. The results of the present study provide the role of Ang II on an exaggerated BP response to exercise.

Study limitations. Limitations of this study need to be addressed. First, the exercise was performed in the supine position using a bicycle ergometer. It is possible that the neurohormonal response to exercise might be different with the response to upright exercise. Second, habitual physical activity was not taken into account in this study, although that has been considered as an important factor of neurohormonal response to exercise. However, the subjects of 2 different groups performed a similar amount of symptom-limited exercise, and total exercise duration was not different between the 2 groups. Therefore, we think that the habitual physical activity might have been similar between the 2 groups. Third, studied subjects had some comorbidities, such as diabetes mellitus, smoking, and dyslipidemia, which could have confounding effects. However, we compared the neurohormonal changes of the exaggerated BP response group with age- and gender-matched control subjects, and the baseline characteristics including comorbidities were not significantly different between the 2 groups. Fourth, the participants in the study were all Asian, and it is possible that results from the present study may not be generalizable to other ethnic and racial groups.

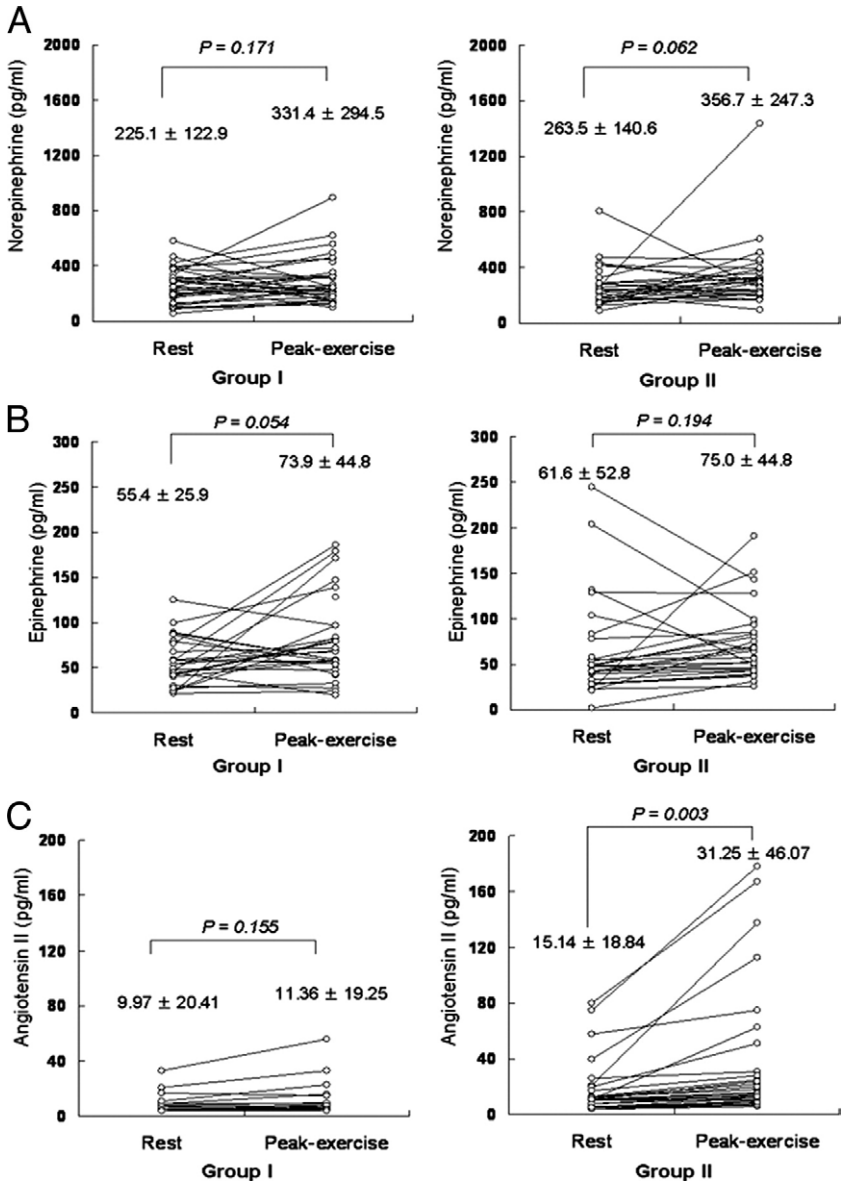

Figure 1 Neurohormonal Response to Exercise

(A) Norepinephrine; **(B)** epinephrine; **(C)** angiotensin II.

Perspectives. Recently, the early pharmacologic treatment for preventing hypertension has been issued. In the TROPHY (TRial Of Preventing HYpertension) study, it has been demonstrated that treatment with Ang II receptor blocker reduced the risk of hypertension in subjects with pre-hypertension (17,18). We believe that an exaggerated BP response to exercise is not a benign phenomenon, but the treatment strategy is uncertain. Treating the exaggerated BP response during exercise in subjects without hypertension is still controversial, and there are no guidelines for medical therapy, although it is associated with adverse cardiovascular outcomes. From the results of this study, Ang II can be considered the most important neurohormone affecting an exaggerated BP response to exercise. The neurohormonal observation in this study might provide important information about the mechanism of an exaggerated BP response to exercise. It can be suggested that Ang II receptor blockers can be recommended in subjects with an exaggerated BP response to exercise.

Conclusions

The exaggerated BP response to exercise was associated with augmented production of Ang II during exercise. Our data may provide important information about the neuro-

hormonal mechanism of an exaggerated BP response to exercise.

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Reprint requests and correspondence: Dr. Jong-Won Ha, Cardiology Division, Yonsei Cardiovascular Center, Yonsei University College of Medicine, SeodaemunGu 120-752, Seoul, South Korea. E-mail: jwha@yuhs.ac.

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Key Words: angiotensin II ■ catecholamine ■ blood pressure ■ exercise.