

ORIGINAL PAPER

Angiotensin II receptor blocker attenuates stress pressor response in young adult African Americans

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Abstract

African Americans (AAs) are susceptible to hypertension (HTN) and its associated organ damage leading to adverse cardiovascular (CV) outcomes. Psychological stress is proposed to contribute to the development of HTN; however, the potential role of the renin-angiotensin system (RAS) in stress-related HTN in AAs is largely unknown. In this study, we tested the hypothesis that activation of RAS is a potential contributing factor for altered CV responses to stress, and suppression of angiotensin II (Ang II) activity will improve hemodynamic responses to a prolonged mental stressor in healthy young AAs. Utilizing a double-blind, randomized, crossover study design, 132 normotensive AAs (25 ± 7 years) were treated with either a placebo (PLC) or 150 mg/d irbesartan (an Ang II type 1 receptor blocker; ARB) for 1 week. On the final day of each treatment, hemodynamic measures and urinary sodium excretion (UNaV) were collected before, during and after a 45 minute-mental stress. The magnitude of stress-induced increase in blood pressure with ARB was blunted and delayed compared to PLC. Systolic blood pressure at the end of recovery on ARB was significantly lower compared to either PLC (110 ± 13 vs 117 ± 12 mm Hg respectively; $P < 0.001$) or the prestress level on ARB ($P = 0.02$). ARB treatment reduced overall vasoconstriction and improved poststress UNaV. ARB attenuated blood pressure responses to mental stress and improved the poststress BP recovery process which were partly linked to reduced overall vasoconstriction and improved stress-induced UNaV in young adult AAs prior to the development of disease conditions. These results suggest that treatment approaches that inhibit RAS action could have significant relevance to potentially lower susceptibility to stress responses and eventually the premature development of HTN in AAs.

1 | INTRODUCTION

Hypertension (HTN) is highly prevalent¹ leading to increased cardiovascular (CV) morbidity and mortality burden in African Americans (AAs).^{2,3} AAs are among the socially and economically disadvantaged ethnic groups which are linked to elevated levels of perceived stress.⁴ Psychological stress contributes to the susceptibility and severity of HTN, although the precise mechanisms

are not fully understood. Large prospective studies demonstrated that individuals with altered CV response patterns to mental stress are predisposed to future HTN and stress-induced CV diseases.^{5,6} Particularly, augmented blood pressure (BP) responses to mental stress and impaired BP recovery back to the prestress level are associated with increased risk for development of HTN in healthy normotensive adults.^{7,8} Exaggerated hemodynamic responsiveness to various stressors has been demonstrated in young and

apparently healthy AAs,^{9,10} which may link the stress to the pathogenesis of HTN in the context of repeated exposure to daily stress. Therefore, it is of clinical importance to elucidate the mechanism by which stress-induced hemodynamic responses contribute to the development of HTN in AAs.

Several lines of evidence implicated the renin-angiotensin system (RAS) as a modulator of stress-related disease.¹¹⁻¹⁴ Angiotensin II (Ang II), an effector peptide of RAS, is recognized to be a mechanistic mediator for the stress-induced physiological responses that contribute to the development of stress-associated CV diseases.^{11,12} Blockage of Ang II type 1 receptors attenuates the pressor response to emotional stress in animal models.^{13,14} In humans, vasodilation is proposed to be the main mechanism of the hypotensive effect following inhibition of Ang II activity, although evidence only refers to resting BP.¹⁵ Ang II also plays a critical role in the control of renal sodium handling and has been implicated to contribute to salt-dependent HTN.¹⁶ Our group previously demonstrated that a significant percentage of healthy AAs display impaired sodium excretory function in response to stress-induced increases in BP.¹⁷ Evidence from animal studies indicates that mental stress provokes sodium retention mediated by an exaggerated increase in renal sympathetic nerve activity via the action of Ang II.^{18,19} However, limited research exists on the role of RAS-mediating agents for CV outcomes in AAs in part due to their known racial biological profile of low renin physiology and the suboptimal efficacy as mono-hypotensive drugs compared to white counterparts.^{20,21}

Thus, the purpose of the present study was to investigate the mechanistic role of Ang II on stress-induced hemodynamic changes in young normotensive AAs. We hypothesized that mental stress-induced CV reactivity is mediated in part by the action of Ang II, and administration of an Ang II receptor blocker can improve the pressor response during and after mental stress, which may, at least in part,

be attributed to vasodilation and improved urinary sodium regulation in young healthy AAs.

2 | METHODS

2.1 | Study participants

Among a total of 213 subjects screened, 132 subjects met the inclusion/exclusion criteria and completed the study protocol between 2008 and 2013 (Figure 1). Inclusion criteria included (a) AA by self-report and (b) 18-50 years old. Exclusion criteria included (a) on prescribed BP medication, (b) pregnant, (c) food allergy, (d) hemoglobin <14 mg/dL, (e) history of angioedema, (f) history of cardiac arrhythmia, (g) serum creatinine >1.6 mg/dL, (h) serum potassium >5.5 meq/L, or (i) during the menses phase of the menstrual cycle. Informed consent was obtained from all participants prior to any measurements and a brief physical examination was done by a physician prior to testing. All procedures were approved by the Human Assurance Committee of Augusta University in accordance with the institutional guidelines.

2.2 | Study design

This study was a randomized, double-blind, placebo-controlled, crossover design aimed to determine the effects of an Ang II type 1 receptor blocker (ARB) on the hemodynamic and natriuretic responses during mental stress in AAs. After screening, the subjects underwent a pretest protocol prior to the treatment randomization to ensure that they did not have an adverse reaction to the ARB. This protocol included monitoring BP for 2 hours following ingestion of a single dose of the ARB with a physician available in the event of an adverse reaction, which never occurred. Subsequently, participants were randomly assigned to receive

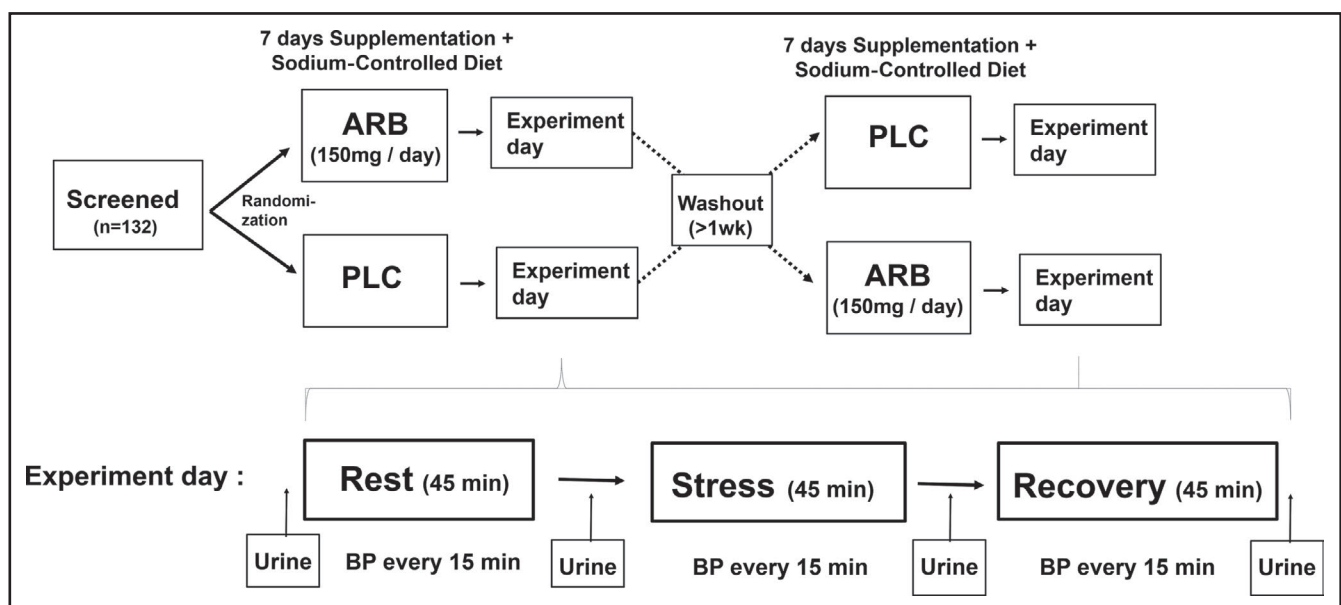


FIGURE 1 Study design. ARB, angiotensin II receptor blocker (irbesartan); BP, blood pressure; PLC, placebo

either placebo (PLC) or irbesartan (ARB, 150 mg PO) for 1 week during which participants were on a fixed sodium-controlled diet to allow similar levels of sodium balance at the time of testing. A nutritionist identified foods with their sodium and potassium levels and subjects selected their own diet to equal 4000 ± 200 mg of sodium and 2600 ± 200 mg of potassium per day. Overnight urine samples were collected for each night to assess dietary compliance. This method has been shown to successfully reduce the variability of sodium intake, as estimated by overnight sodium excretion in free-living individuals.²² On the final day of treatment, the subject performed the stress test protocol described below. This was followed by a one to 2-week washout period. The subject then performed the same procedure while on the second treatment (Figure 1). Randomization (PLC/ARB) was performed and maintained by the university pharmacy. Irbesartan was chosen for its ability to block both vasoconstriction and the aldosterone-secreting effect by selectively blocking the binding of Ang II to the AT1 receptor.²³ The steady-state concentrations are reached within 3 days with a half-life of 11-15 hours.²⁴ Participants were asked to refrain from drinking caffeinated or alcoholic beverages on the day of testing.

2.3 | Stress testing protocol

The mental stress protocol was a modified version of the standard stress testing protocol we have used successfully up to this point in over 1000 subjects as described previously in both adult²⁵ and pediatric populations.^{17,26-28} The stressor was a competitive video game task played against another individual for monetary reward. On the testing day, the subjects were tested in a private room in a comfortable chair. The subjects took their last dose of treatment immediately before the stress testing. The testing period included 45 minutes of rest (Rest), 45 minutes of mental stress (Stress), in which the subjects played a racing or sport video game against one another for a cash prize (PlayStation 2xtreme, PlayStation 2 NBA Live08), followed by another 45 minutes of rest (Recovery). The subjects watched a movie chosen for their preference not containing extreme stimulating scenes during Rest and Recovery periods.

2.4 | Measurements

The hemodynamic responses were monitored by an automated BP machine (Dinamap Model 1864 SX; Critikon Inc) for systolic blood pressure (SBP) and diastolic blood pressure (DBP) and thoracic bioimpedance (NCCOM-3; Bo Med Medical Manufacturing Ltd) for stroke volume (SV), heart rate (HR), and cardiac output (CO). Total peripheral resistance (TPR) was calculated as $[(DBP + 1/3 (SBP - DBP))/CO]$. Measurements were made at 15-minute intervals throughout the testing period. Urine samples were obtained before and after Rest, Stress, and Recovery periods. The subjects were required to drink 200 mL of water every hour to ensure that they remained hydrated and were able to provide adequate urine samples. Volume-corrected urinary sodium

excretion (UNaV) was analyzed by the NOVA 16 Analyzer (NOVA Biomedical) that uses an ion selective electrode technique. The intra-assay coefficient of variation for UNaV was <3%, and the inter-assay coefficient was 4%.

2.5 | Statistical analysis

Values are presented as mean \pm SD unless otherwise noted. Differences in participant characteristics between treatment days were determined using independent *t* tests. Carryover effects were examined for the potential influence of the order of treatments in our crossover design,²⁹ and no significant effects were found. Therefore, no adjustment was made in the subsequent analysis. Repeated measure analysis of variance (ANOVA) was used to identify the effect of treatments (PLC and ARB) on the changes in hemodynamic and urinary excretion variables across different conditions (Rest, Stress, and Recovery) as well as 15-minute interval changes in each condition. Bonferroni test was used for post hoc analysis when a significant main effect was found. The degree of association between the magnitude of changes in BP and other hemodynamic variables and UNaV was analyzed by Pearson's correlation coefficient. Statistical significance was set at an alpha level of 0.05. All analyses were performed using SPSS version 24.0 (IBM Corporation).

3 | RESULTS

3.1 | Participant characteristics

Descriptive characteristics of the 132 participants that completed the crossover experiments without adverse events are presented in Table 1.

3.2 | The effects of ARB on stress-induced hemodynamic changes

3.2.1 | Change in mean SBP across Rest, Stress, and Recovery

There was a significant Treatment (ARB vs PLC) \times Time (Rest, Stress, and Recovery) interaction effect for brachial SBP ($F_{(2, 252)} = 5.44$, $P = 0.005$). While SBP and DBP levels were significantly lower throughout Rest, Stress, and Recovery period with ARB treatment compared to PLC, the magnitude of difference between the treatments was greater during Stress (5.3 ± 8.7 mm Hg; $P = 0.089$ for comparison with Rest) and Recovery (6.3 ± 8.6 mm Hg; $P = 0.002$ for comparison with Rest) compared to the difference during Rest (3.3 ± 9.04 mm Hg; Figure 2A,B). The mean SBP and DBP were significantly increased in response to Stress from Rest with each of PLC and ARB treatment at a similar magnitude ($P < 0.01$ for all, Table 2). HR increased from Rest to Stress with each of PLC and ARB treatment ($P < 0.01$ for all, Table 2).

TABLE 1 Participant characteristics prior to treatments

Characteristics (n = 134)	Mean ± SD
Age (y)	25.1 ± 9.2
BMI (kg/m ²)	28.9 ± 7.7
Height (cm)	171.3 ± 9.7
Weight (kg)	85.0 ± 23.5
Gender (male, %)	72 (54.1)
Blood chemistry	
Albumin (g/dL)	4.4 ± 0.3
Potassium (mEq/L)	4.0 ± 0.3
Creatinine (mg/dL)	0.9 ± 0.2
Glucose (mg/dL)	74 ± 26
Calcium (mg/dL)	9.5 ± 0.4
SBP (mm Hg)	113 ± 9
DBP (mm Hg)	64 ± 7

Abbreviations: BMI, body mass index; DBP, brachial diastolic blood pressure; SBP, brachial systolic blood pressure; SD, standard deviation.

3.2.2 | Change in SBP at 15-minutes interval during Stress and Recovery

SBP change during Stress measured every 15 minutes showed a Treatment × Time interaction ($F_{(3, 372)} = 3.67, P = 0.012$). The stress-induced increase in SBP stayed elevated throughout Stress with PLC, whereas the SBP increase was delayed with ARB treatment with a significant increase from Rest only after 30 minutes into Stress ($\Delta\text{SBP}_{\text{Stress } 30 \text{ min} - \text{Rest}} = 3.6 \pm 9.5, P < 0.01$ on ARB). During Recovery, there was a significant Treatment × Time interaction ($F_{(3, 369)} = 3.23, P = 0.026$) in SBP; the stress-induced increase in SBP was continuously attenuated during Recovery following ARB (SBP in the beginning of Recovery was significantly higher than SBP at 15, 30, and 45 minutes into Recovery, $P < 0.001$ for all), as opposed to a maintained elevation in SBP throughout Recovery with PLC. Notably, SBP at the end of Recovery with ARB treatment, that is, 45 minutes into Recovery, was significantly lower compared to PLC (110 ± 13 vs 117 ± 12 mm Hg, respectively; $P < 0.001$) and was also significantly decreased from Rest following ARB (mean difference; -2 ± 9 mm Hg; $P = 0.02$; Figure 2A).

3.2.3 | Change in TPR, HR, SV, and CO across Rest, Stress, and Recovery

Ang II type 1 receptor blocker treatment resulted in a lower mean TPR during Rest, Stress, and Recovery compared to PLC while responses of SV, CO, and HR were all similar between the two treatments throughout the different time periods (Figure 2C,F, Table 2).

There were positive relationships between SBP and TPR at Rest, Stress, and Recovery ($r = 0.234, 0.196, \text{ and } 0.326, P = 0.015, 0.041, \text{ and } <0.001$, respectively, on PLC; $r = 0.266, 0.229, \text{ and } 0.466, P = 0.004, 0.014, \text{ and } <0.001$, respectively, on ARB), which remained significant after controlling for SV and HR, other determinants of

BP ($r = 0.240, 0.390, \text{ and } 0.558, P = 0.008, <0.001, \text{ and } <0.001$, respectively, on PLC; $r = 0.374, 0.557, \text{ and } 0.652, P < 0.001, 0.001, \text{ and } 0.001$, respectively, on ARB). Positive relationships were also observed between the changes in SBP and HR from Rest to 45 minutes into Stress ($r = 0.147, P = 0.017$) and from Rest to Recovery ($r = 0.134, P = 0.030$).

3.3 | The effects of ARB on stress-induced UNaV

Urinary sodium excretion levels were similar at Rest between PLC and ARB treatments (0.23 ± 0.15 and 0.22 ± 0.17 mEq/min, respectively, $P > 0.05$). In response to stress, UNaV was significantly increased on each treatment with a greater increase on ARB compared to PLC ($\Delta\text{UNaV}_{\text{stress} - \text{rest}} = -0.09 \pm 0.11$ mEq/min, 0.05 ± 0.15 mEq/min respectively, $P = 0.045$), leading to a significantly higher UNaV level at the end of Stress following ARB compared to PLC ($P = 0.048$; Table 2).

For pressure-natriuretic responses, each of the mean SBP during Stress and SBP at 45 minutes into Stress period was positively correlated with UNaV collected at the end of Stress while on ARB treatment ($r = 0.242$ and $0.292, P = 0.011$ and 0.02 , respectively), but not with PLC ($r = 0.131$ and $0.136, P = 0.164$ and 0.149 respectively).

4 | DISCUSSION

Racial minority populations including AAs experience greater levels of stress than their white counterparts, which can lead to significant health disparities.³⁰ The major finding of this study is that an ARB has a beneficial impact on stress-induced hemodynamic changes in young adult AAs. Exaggerated responses or impaired recovery following mental stressors are risk factors for essential HTN and CVD morbidity and mortality.^{5,31-33} The present study is the first to that we are aware to identify a potential role of Ang II in the stress-induced hemodynamic regulation in young healthy AAs prior to the development of disease conditions. Specifically, the stress-induced increase in SBP persisted throughout the stress period with PLC treatment, whereas the SBP levels were not significantly increased until 30 minutes into the stress period following ARB treatment. Furthermore, SBP continued to decrease throughout the poststress period with ARB treatment leading to a lower SBP at the end of recovery compared to the rest value while SBP stayed elevated until the end of the recovery with PLC. Furthermore, ARB treatment reduced overall vasoconstriction contributing to the overall reduction in BP and improved poststress UNaV. These findings suggest the presence of an Ang II-dependent action in stress-associated CV regulation in AAs.

Hyper-CV reactivity and prolonged recovery to mental stress are linked to increased risk for the development of HTN, BP-related target-organ damage, and atherosclerotic CV disease.^{6,31-33} Ang II in the RAS has emerged to be involved in complex roles of the CV response to emotional stress by binding to its type-1A receptors.^{11,12} The present study is the first to demonstrate the mechanistic role

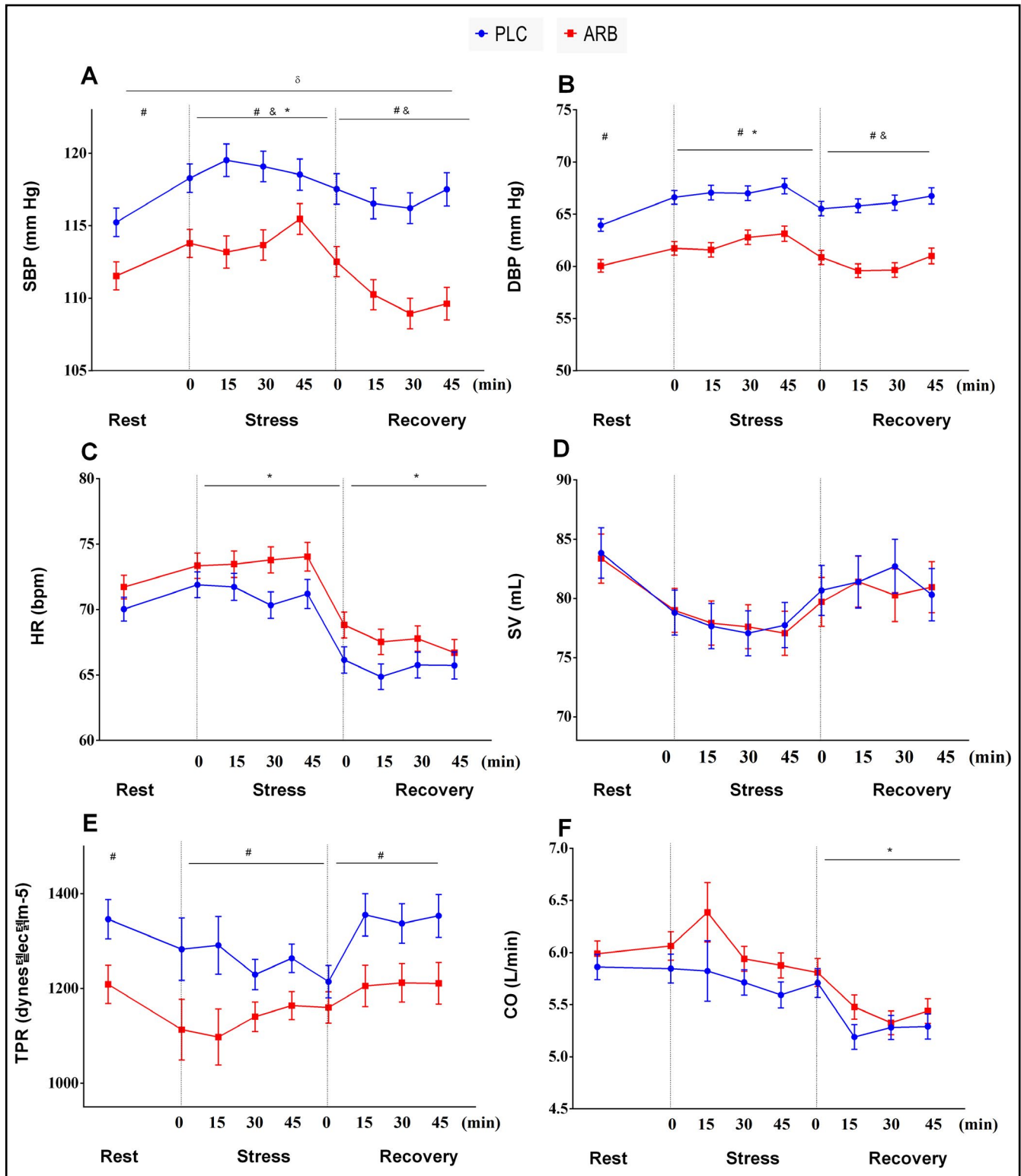


FIGURE 2 A-F, Effect of ARB on stress-induced hemodynamic changes. ARB, angiotensin II receptor blocker (irbesartan); CO, cardiac output; DBP, diastolic blood pressure; HR, heart rate; PLC, placebo; SBP, systolic blood pressure; SV, stroke volume; TPR, total peripheral resistance. *: significantly different from Rest ($P < 0.05$). #: a significant treatment effect ($P < 0.05$). δ : a significant treatment \times time interaction ($P < 0.05$). δ : a significant treatment \times time interaction ($P < 0.05$ for all)

of Ang II in mediating comprehensive hemodynamic responses to mental stress in humans. Our results demonstrate that blocking Ang II action significantly blunted the magnitude of the blood pressure

increase to acute mental stress and accelerated the recovery of poststress BP in normotensive AAs. The stress-induced increase in BP was delayed with lower level of peak BP and a rapid reduction in

Variable	PLC		ARB	
	Stress	Recovery	Stress	Recovery
Δ SBP (mm Hg)	3.6 ± 7.9	1.6 ± 6.4	2.4 ± 7.7	-1.2 ± 7.3 [*]
Δ DBP (mm Hg)	3.0 ± 6.0	1.9 ± 5.3	2.2 ± 4.9	-0.1 ± 1.0 [*]
Δ HR (bpm)	1.3 ± 6.7	-4.3 ± 5.7	1.9 ± 6.0	-3.9 ± 5.6
Δ SV (mL)	-6.1 ± 11.5	-3.6 ± 12.5	-5.4 ± 11.2	-2.9 ± 9.7
Δ TPR (dynes·sec·cm ⁻⁵)	-78 ± 479	-29 ± 134	-75 ± 212	-10 ± 78
Δ CO (L/min)	-0.1 ± 1.0	-0.5 ± 1.0	-0.0 ± 1.0	-0.5 ± 0.8
Δ UNaV (mEq/min)	0.05 ± 0.13	0.02 ± 0.17	0.09 ± 0.17 [*]	0.04 ± 0.17

Note: Values are mean ± SD.

Abbreviations: Bpm, beats per minute; CO, cardiac output; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure; SV, stroke volume; TPR, total peripheral resistance; UNaV, urinary sodium excretion rate.

^{*}Significant difference from PLC at the corresponding condition ($P < 0.05$).

BP following the cessation of the stressor with a week of ARB treatment compared to PLC. Importantly, poststress BP was even lower than the resting BP with ARB treatment as opposed to a maintained elevated BP at poststress with PLC in our normotensive individuals. This reduction in resting BP demonstrated here by a sole ARB treatment, rather than as an adjunct hypotensive agent, is consistent with a recent randomized control study by Johnson et al,³⁴ demonstrating the efficacy of ARB monotherapy in reducing clinic and ambulatory BP in AAs. In addition, an augmented BP reactivity to the same type of stressor (ie, video gaming) predicted increased risks for 5-year BP increase (>8 mm Hg) and early initiation of HTN among 3364 young normotensive adults.⁷ Impaired poststress BP recovery has also been indexed for unfavorable longitudinal BP changes with odds of 3.5 for an increase in SBP >5 mm Hg in 3 years, independent of baseline BP levels in middle-aged healthy individuals.⁸ These reports may strengthen the clinical significance of our findings, such that Ang II's capacity to modify pressor responses to mental stress in healthy young AA individuals may translate into future HTN incidence.

Although the underlying mechanisms of Ang II-mediated changes in hemodynamic responses to acute mental stress remain to be determined, our results indicate Ang II contributes to BP elevation by both vasoconstriction (ie, increased TPR) and volume expansion (ie, salt retention). ARB treatment has a capacity of reversing these actions by reducing vascular tone and promoting UNaV. In the present study, ARB treatment reduced TPR at rest that lasted throughout the stress and the recovery period. Although the stress response pattern of TPR was not directly aligned with BP stress response patterns, it is reasonable to speculate that ARB-mediated overall reduction in vasoconstrictive tone may have blunted stress BP reactivity in a time-independent manner. ARB is known to exert its hypotensive effect by suppressing many actions of Ang II including its powerful vasoconstrictive effect.^{15,35} The vascular effect of a sole usage of RAS inhibitors in AAs is difficult to determine due to disproportionately lower representation of drug use in AAs compared to their white counterparts in the existing literature.^{21,36} Investigation of vascular contribution to stress-associated BP regulation may be

TABLE 2 Changes in cardiovascular hemodynamic values and urinary sodium excretion rates immediately after (Stress) and 45 min after (Recovery) mental stress from rest following placebo (PLC) or angiotensin II receptor blocker (ARB) treatment

of high clinical importance given previous observations of peripheral vascular hyper-reactivity to a variety of physical and psychological stressors in AAs.^{37,38} Ang II is suggested to be involved in regulation of autonomic arousal during emotional stress at the brain level and its resultant autonomic and endocrine outputs to the periphery sites.³⁹ Our results may indicate the potential vascular benefits of inhibiting Ang II activity in the management of resting and stress-associated BP levels in AAs.

Ang II type 1 receptor blocker-induced change in UNaV was found only when associated with stress, suggesting a synergic action of Ang II on sodium excretion when sympathetic activation is involved. Notably, higher BP during stress was associated with a greater increase in UNaV at the end of stress, that is, normal pressure-natriuretic response, while on ARB treatment, but not with PLC. Furthermore, a similar magnitude of increase in BP in response to stress yielded a larger amount of sodium excretion after stress with ARB treatment compared to PLC (0.27 ± 0.16 vs 0.32 ± 0.17 mEq/min $P = 0.048$). These data indicate the increased sensitivity of pressure-natriuretic response to stress with ARB treatment. Although speculative, this improved pressure-natriuretic response to stress induced by blocking Ang II activity may have eliminated an extra volume load from the circulatory system in a timely manner which subsequently prevented a sustained elevation in BP during and after the presence of a stressor. We recently reported that impaired stress-induced sodium retention was improved with ARB treatment in individuals who retained sodium despite a stress-induced increase in BP with placebo treatment.⁴⁰ This present study with a larger sample size extends the previous findings by focusing on the time-serial CV responses not only during stress but also during poststress period for the practical implication of lasting effectiveness. In addition, the potential combined mechanisms (ie, vascular reactivity and UNaV) were explored to explain the ARB-induced hemodynamic changes to stress in the present study. The sodium retaining action of Ang II is mainly driven by increased renal tubular reabsorption in which sympathetic activation can precipitate the

process by its resultant increases in renal hemodynamics and the induction of vasoconstriction in the kidneys.⁴¹ Although less is known about the role of renal sympathetic nerve activity in stress-mediated sodium retention in humans, animal studies in HTN models have provided direct evidence that stress-induced anti-natriuresis is mediated by increased renal sympathetic nerve activity in which Ang II plays a critical role.^{18,19} Taken together, our findings suggest that mechanisms of pressor response to mental stress may be mediated by Ang II, at least in part, via its synergistic action of vascular tone and renal sodium handling in AAs. Further studies are warranted to investigate the role of Ang II signaling in hemodynamic control during sympathetic activation regarding the pathophysiology of HTN and stress-associated CV diseases in AAs.

4.1 | Experimental considerations

Our stress modality produced a modest magnitude of pressor response associated with a mild tachycardia without a significant change in SV and CO regardless of treatment. This relatively modest pressor response to stress might have been due to the normal range of baseline BP and the mild level of stressor over a lengthy period (45 minutes), which might have hindered observation of significant timely interactions between the changes in different hemodynamic parameters. Nevertheless, this level of stressor causing <5 mm Hg change in BP is similar to what everyday life stressors could elicit throughout daily routines which may allow for practical application of our results to the real-life setting.

The participants were from a homogeneous ethnic group with no indication of HTN, and thus, the present observations cannot necessarily be extrapolated to other ethnic groups or even patients with HTN. However, our study was designed to provide mechanistic insight of Ang II-mediated hemodynamic regulation in which homogeneity of race, age range, and health status are advantageous for clear data interpretation with minimal clinical confounding factors. Furthermore, the stress-induced hemodynamic response patterns may be a marker for increased risk of elevated BP in AAs.

Although outside the scope of the present study, other upstream RAS inhibiting agents such as ACE inhibitors and renin blockers may generate similar BP-lowering effects by down-regulation of the formation of Ang II. However, their clinical efficacy may not be comparable as used ARB, especially in stress-associated BP. This is because ARB prevents the binding of angiotensin II with its type 1 receptors, and there are ACE-independent pathways for Ang II formation. Nonetheless, no literature is available to directly support the comparable efficacy of other RAS inhibitors with the ARB.

4.2 | Clinical significance

It is well-recognized that stress is a contributing factor to HTN. AAs face greater exposure to sources of psychosocial stress which

may contribute to their disproportionate burdens of morbidity and mortality.^{4,30} Thus, there is a need to develop a novel therapeutic approach to dampen the deleterious health consequences of stress. Activation of Ang II is implicated in the CV response to psychological stress and has been considered to be a therapeutic target for a number of stress-related disorders such as anxiety disorders. However, the use of RAS inhibitors as a mono-hypotensive therapy in AAs has been controversial for the suboptimal efficacy.^{20,21} Our data demonstrate that suppression of Ang II activity attenuated resting BP as well as stress-reactive and recovery BP levels in healthy AAs, which is in part attributed to its dual mechanistic actions of vasodilation and sodium excretion. These results demonstrate the therapeutic potential of ARB in treating unfavorable BP profiles in AAs by targeting both resting and stress-mediated BP levels.

5 | CONCLUSIONS

Our data suggest the mechanisms of hemodynamic regulation during mental stress may be in part mediated by Ang II. Suppression of Ang II activity improved the hemodynamic responses to mental stress as well as reduced resting BP levels in young normotensive AAs who are at elevated risk for the development of HTN. This improved pressor response to mental stress following ARB treatment seems to be mediated, at least in part, by a reduced vasoconstriction and improved pressure-natriuretic action. These data may suggest that treatment approaches that antagonize Ang II's actions could have significant relevance to potentially lower susceptibility to stress-induced dysregulation of BP, which can ultimately help lowering the risk of the premature development of HTN in AAs.

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CONFLICT OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

J.H.J., C.D.H., J.S.P., D.M.P., G.A.H. conceived and designed research; G.K., G.A.H. performed experiments; J.H.J., R.A.H., G.A.H. analyzed data; J.H.J., C.D.H., R.A.H., G.K., J.S.P., D.M.P., G.A.H. interpreted results of experiments; J.H.J., G.A.H. prepared figures; J.H.J., G.A.H. drafted manuscripts; J.H.J., C.D.H., R.A.H., G.K., J.S.P., D.M.P., G.A.H. edited and revised manuscripts; J.H.J., C.D.H., R.A.H., G.K., J.S.P., D.M.P., G.A.H. approved final version of manuscript.

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