Angiotensin II, Independent of Plasma Renin Activity, Contributes to the Hypertension of Autonomic Failure

Amy C. Arnold, Luis E. Okamoto, Alfredo Gamboa, Cyndya Shibao, Satish R. Raj, David Robertson, Italo Biaggioni

Abstract—At least half of primary autonomic failure patients exhibit supine hypertension, despite profound impairments in sympathetic activity. Although the mechanisms underlying this hypertension are unknown, plasma renin activity is often undetectable, suggesting renin–angiotensin (Ang) pathways are not involved. However, because aldosterone levels are preserved, we tested the hypothesis that Ang II is intact and contributes to the hypertension of autonomic failure. Indeed, circulating Ang II was paradoxically increased in hypertensive autonomic failure patients (52±5 pg/mL, n=11) compared with matched healthy controls (27±4 pg/mL, n=10; P=0.002), despite similarly low renin activity (0.19±0.06 versus 0.34±0.13 ng/mL per hour, respectively; P=0.449). To determine the contribution of Ang II to supine hypertension in these patients, we administered the AT1 receptor blocker losartan (50 mg) at bedtime in a randomized, double-blind, placebo-controlled study (n=11). Losartan maximally reduced systolic blood pressure by 32±11 mmHg at 6 hours after administration (P=0.05), decreased nocturnal urinary sodium excretion (P=0.0461), and did not worsen morning orthostatic tolerance. In contrast, there was no effect of captopril on supine blood pressure in a subset of these patients. These findings suggest that Ang II formation in autonomic failure is independent of plasma renin activity, and perhaps Ang-converting enzyme. Furthermore, these studies suggest that elevations in Ang II contribute to the hypertension of autonomic failure, and provide rationale for the use of AT1 receptor blockers for treatment of these patients. (Hypertension. 2013;61:701-706.)

Key Words: angiotensin ■ autonomic nervous system ■ hypertension ■ natriuresis ■ renin

Primary autonomic failure is a neurodegenerative disorder characterized by disabling orthostatic hypotension, in the setting of profound loss of sympathetic activity and absence of baroreceptor reflexes.1 At least half of these patients are also hypertensive while lying down, which can be severe with systolic blood pressure (SBP) reaching >200 mm Hg in some cases.2 The supine hypertension increases nocturnal pressure natriuresis to promote volume depletion and worsening of morning orthostatic tolerance. It also complicates management of these patients by limiting use of daytime pressor agents for treatment of orthostatic hypotension. Finally, supine hypertension increases risk for cardiovascular events and for development of target-organ damage in autonomic failure, including renal impairment and left-ventricular hypertrophy.3,4 These findings provide rationale for pharmacological treatment; however, the precise pathophysiological mechanisms underlying the hypertension and the ideal antihypertensive therapies for these patients remain unclear.

The renin–angiotensin (Ang) system is an important contributor to the development of hypertension, through actions of Ang II at AT1 receptors to stimulate vasoconstriction, baroreflex dysfunction, and aldosterone release.5 Blockade of Ang II formation with Ang-converting enzyme (ACE) inhibitors, or its actions with AT1 receptor blockers (ARBs), is well established for treatment of essential hypertension.6 Previous studies, however, show that autonomic failure patients have very low and often undetectable plasma renin activity, blunted renin responses to postural and pharmacological stimuli, and loss of renin immunoreactive cells in autopsied kidneys.7,8 These collective findings suggest that renin mechanisms are not involved in the hypertension of autonomic failure. However, aldosterone levels are normal in these patients,7 perhaps suggesting preservation of downstream renin–Ang system pathways for cardiovascular modulation.

Thus, we tested the hypothesis that Ang II levels are intact and contribute to the supine hypertension of autonomic failure. Indeed, our results show that circulating Ang II is paradoxically elevated in hypertensive autonomic failure patients compared with healthy subjects, despite similar low renin activity. Given this finding, we performed a randomized, double-blind, crossover study comparing the effects of placebo versus the ARB losartan on supine overnight blood pressure (BP). As a secondary objective, some patients also received the ACE inhibitor captopril on a separate study night, to determine potential mechanisms involved in Ang II production. Finally, to further assess the therapeutic potential of these medications for management of autonomic failure, we measured their effect on nocturnal natriuresis and morning orthostatic tolerance.
Methods
This study was approved by the Vanderbilt Investigational Review Board and written informed consent was obtained from each patient before enrollment (http://clinicaltrials.gov identifier: NCT00223717).

Study Participants
This study included 11 patients with primary autonomic failure diagnosed with either multiple systems atrophy (n=5) or pure autonomic failure (n=6) based on established criteria. All patients had supine hypertension defined as SBP $\geq$ 150 mm Hg or diastolic BP $\geq$ 90 mm Hg. Patients were excluded if they had secondary forms of autonomic failure (ie, diabetes mellitus, amyloidosis) or renal failure. We also studied 10 healthy volunteers matched for age, sex, and body mass index. Healthy volunteers were nonsmokers and were excluded if pregnant, had evidence of systemic illness, or were taking medications known to interfere with regulation of BP, blood volume, or the renin–Ang system.

General Protocol
Autonomic failure patients were admitted to the Clinical Research Center at Vanderbilt University on an inpatient basis. Medications affecting the autonomic nervous system, BP, or blood volume were withheld for 24 half-lives before admission, including fludrocoritolate, statins, diuretics, $\beta$-blockers, or other antihypertensive medications. Patients were placed on a fixed diet consisting of low monoamine, methylxanthine-free food containing 150 mEq sodium and 70 mEq potassium. Healthy volunteers were studied as outpatients, withheld from methylxanthine-containing products or medications for 3 days before the study, and underwent 24-hour urinary sodium levels within normal limits. All subjects were screened with a comprehensive medical history, physical examination, 12-lead ECG, and routine laboratory tests.

Autonomic Function and Orthostatic Stress Testing
Standardized autonomic function tests were performed including sinus arrhythmia, Valsalva maneuver, hyperventilation, cold pressor, and isometric handgrip. BP was measured intermittently with an automated sphygmomanometer cuff (Dinamap, GE Healthcare) and continuously with finger photoplethysmography (Nexfin, BMEYE). Heart rate (HR) was measured by continuous ECG. For orthostatic stress testing, subjects remained supine after an overnight rest and then were asked to stand for 10 minutes, or as long as tolerated. BP was measured in the supine position and again after 1, 3, 5, and 10 minutes of standing with an automated sphygmomanometer (Dinamap). Fasting blood samples were collected at the end of the supine and standing periods for circulating hormone measurements, through an antecubital vein catheter placed at least 30 minutes before testing.

Circulating Hormone Measurements
Plasma norepinephrine was measured by high-performance liquid chromatography with electrochemical detection. Plasma renin activity was measured by conversion of angiotensinogen to Ang I using radioimmunoassay (IgG Corporation). Plasma aldosterone was measured using radioimmunoassay analysis (Diagnostics Products Corporation). For statistical analysis, renin activity or aldosterone levels below detection limits (<0.2 ng/mL per hour or <2.5 ng/dL, respectively) were assigned a value of one-half the detection limit. For Ang II, blood was collected in a peptidase inhibitor cocktail to prevent in vitro metabolism, and harvested plasma was sent to the Hypertension Core Laboratory at Wake Forest University for analysis using radioimmunoassay (ALPCO Diagnostics, RK-A22) as previously described. The analytic sensitivity for this assay is 1.0 pg/mL, with 8% intra-assay and 12% interassay variability. This assay has high cross-reactivity for Ang III and Ang IV metabolites (108% and 96%, respectively).

Overnight Medication Trials
We performed a randomized, double-blind, crossover study comparing the effects of single dose losartan (50 mg, PO) versus placebo on overnight BP in 11 autonomic failure patients. Seven of these patients were also randomized to receive captopril (50 mg, PO) on a separate study night. The primary outcome was the decrease in SBP after drug administration. As secondary end points, we examined for changes in nocturnal pressure natriuresis and morning orthostatic tolerance. Medications were administered with 50 mL of tap water at 8:00 AM and 2:2.5 hours after the last meal. Patients were instructed to remain supine throughout the night, and BP was measured twice in a row at 2-hour intervals with an automated cuff (Dinamap). At 8:00 AM, patients were asked to stand for 10 minutes, with BP and HR measured after 1, 3, 5, and 10 minutes of standing, or as long as tolerated to assess orthostatic tolerance. To determine effects on pressure natriuresis, urine was collected for 12 hours after drug administration. Because these patients often have neurogenic bladder, it is difficult to obtain accurate urine volume measurements. Thus, nocturnal sodium excretion was defined as the ratio of urinary sodium to creatinine, to correct for incomplete bladder emptying. Changes in body weight were also measured as a means to assess overnight volume loss.

Statistical Analysis
Data are reported as means±SEM. Analysis was performed using SPSS for Windows (Version 19.0, IBM Corp). A 2-tailed $\alpha$ level of $<0.05$ was defined as statistical significance. Differences between autonomic failure patients and healthy subjects were compared by Mann–Whitney U nonparametric analysis. To evaluate changes in overnight SBP, we used 2-way ANOVA to test for effects of treatment, time, and their interaction. To summarize overnight SBP changes, area under the curve (AUC) for the 7 measurements was calculated by the trapezoidal rule (AUC$_{\text{trapezoid}}$ = mean SBP x time). Morning orthostatic tolerance was also calculated as AUC for standing SBP, with comparisons made for patients who could stand after all active medications. Changes in AUC for overnight and morning SBP, body weight, and urinary sodium excretion were analyzed by Wilcoxon signed-rank tests. Our preliminary data from 3 patients showed a difference in SBP means of 25 mm Hg, with SD of difference of 22 mm Hg, after placebo versus losartan. Based on these data, we calculated that 10 patients would have 90% power to detect a difference in means between treatments with an $\alpha$ level of 0.05 using paired t test analysis (PS Dupont, Version 3.0.34).

Results
Clinical Characteristics of Study Participants
As shown in Table 1, there were no differences in age, body mass index, or sex between autonomic failure patients and healthy subjects. Respiratory sinus arrhythmia was significantly reduced in autonomic failure, suggesting parasympathetic dysfunction. Sympathetic impairment was evident in autonomic failure as indicated by the following: (1) a decrease in SBP during phase II of Valsalva maneuver; (2) absence of BP overshoot during phase IV of Valsalva maneuver; and (3) blunted SBP responses to isometric handgrip and cold pressor tests. By definition, autonomic failure patients had higher supine BP compared with healthy subjects, with no significant differences in HR (Table 2). Upright posture produced profound decreases in BP in autonomic failure, with an inadequate compensatory HR increase, indicating failure of baroreflex modulation. Plasma norepinephrine, renin activity, and aldosterone significantly increased on standing in both groups. However, postural norepinephrine increases were blunted in autonomic failure, suggesting reduced ability to engage sympathetic activity.

Circulating Ang II Levels and Antihypertensive Effects of Losartan and Captopril
Despite similar low renin activity (Table 2), circulating Ang II was paradoxically increased in hypertensive autonomic failure patients compared with healthy subjects (Figure 1; $P=0.002$).
Based on this finding, we assessed whether losartan could reduce supine overnight BP in these patients. All patients completed placebo and losartan treatment arms, with no differences in baseline SBP between study nights (placebo: 164±11 mm Hg; losartan: 167±6 mm Hg; P=0.799). Losartan maximally decreased SBP by 32±11 mm Hg at 6 hours after administration (95% CI, −58 to −6 mm Hg; Figure 2), resulting in an average SBP of 135±8 mm Hg at this time point. The main treatment effect of losartan was significant (P<0.001; 2-way ANOVA; Figure 2A), as was the AUC for SBP changes after losartan versus placebo (P=0.047; Figure 2B). Losartan also significantly lowered diastolic BP at 6 hours (placebo, 64±4 mm Hg; losartan, −12±6 mm Hg; P=0.015), with no effect on HR (placebo, −4±3 bpm; losartan, −4±2 bpm; P=0.684).

The ACE inhibitor captopril was also administered to 7 of these patients. There was a tendency toward higher baseline SBP on the placebo versus captopril night that did not reach statistical significance (176±11 and 154±7, respectively; P=0.109). Captopril produced a maximal 11±12 mm Hg decrease in overnight SBP (95% CI, −39 to 17 mm Hg), which was not different from placebo (−4±8 mm Hg; 95% CI, −23 to 14 mm Hg; P=0.1508, 2-way ANOVA, Figure 2C; P=0.1094, AUC for overnight SBP, Figure 2D). There was also no significant effect of captopril on diastolic BP (placebo, 5±5 mm Hg; captopril, −4±7 mm Hg; P=0.318) or HR (placebo, −4±3 bpm; captopril, −6±3 bpm; P=0.902).

**Effect of Ang II Blockade on Urinary Sodium Excretion and Morning Orthostatic Tolerance**

Losartan did not significantly alter body weight compared with placebo (Figure 3A; P=0.249); however, urinary sodium excretion was reduced after losartan (Figure 3B; P=0.046). Of the 11 patients studied, only 7 were able to stand after both treatment arms. The AUC for morning SBP was not significantly different after placebo versus losartan (530±194 versus 404±163 mm Hg×min, respectively; P=0.687). Captopril did not produce significant changes in either body weight (placebo, −1.7±0.8 kg; captopril, −1.2±0.4 kg; P=0.127) or nocturnal sodium excretion (placebo, 0.145±0.119 mmol/mg; captopril, 0.119±0.009 mmol/mg; P=0.1364). In the 5 patients who could stand after both placebo and captopril treatments, there was no difference in the AUC for morning SBP (527±248 placebo versus 516±187 mm Hg×min captopril; P=0.8125).

**Discussion**

The present study provides evidence that in autonomic failure patients with supine hypertension, the following occurs: (1) circulating angiotensin II is paradoxically elevated compared with healthy subjects, despite low and often undetectable renin production; (2) plasma angiotensin II (NG/ml per hour) remains significantly higher in autonomic failure patients with supine hypertension relative to matched healthy subjects. **P<0.002 vs healthy.** AF indicates autonomic failure; dashed line, detection limit for renin activity.

### Table 2. Orthostatic Stress Testing and Neurohormonal Profile

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Healthy (n=10)</th>
<th>Autonomic Failure (n=11)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Orthostatic stress tests</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine (≥ 30 min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>116±5</td>
<td>166±5</td>
<td>0.001</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>74±4</td>
<td>89±3</td>
<td>0.005</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>66±4</td>
<td>70±4</td>
<td>0.512</td>
</tr>
<tr>
<td>Standing (1 min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>121±6</td>
<td>92±12</td>
<td>0.043</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>79±3</td>
<td>59±6</td>
<td>0.015</td>
</tr>
<tr>
<td>HR, mm Hg</td>
<td>76±4</td>
<td>83±5</td>
<td>0.353</td>
</tr>
<tr>
<td>Δ SBP (standing–supine)</td>
<td>4±3</td>
<td>−75±13</td>
<td>0.001</td>
</tr>
<tr>
<td>Δ DBP (standing–supine)</td>
<td>4±3</td>
<td>−30±7</td>
<td>0.002</td>
</tr>
<tr>
<td>Δ HR (standing–supine)</td>
<td>10±2</td>
<td>15±3</td>
<td>0.353</td>
</tr>
<tr>
<td><strong>Plasma norepinephrine, pg/mL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>352±65</td>
<td>209±50</td>
<td>0.113</td>
</tr>
<tr>
<td>Upright</td>
<td>689±61†</td>
<td>357±100†</td>
<td>0.046</td>
</tr>
<tr>
<td><strong>Plasma renin activity, ng/mL per hour</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>0.34±0.13</td>
<td>0.19±0.06</td>
<td>0.449</td>
</tr>
<tr>
<td>Upright</td>
<td>0.73±0.29†</td>
<td>0.32±0.11†</td>
<td>0.356</td>
</tr>
<tr>
<td><strong>Plasma aldosterone, ng/dL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>2.4±0.7</td>
<td>2.1±0.5</td>
<td>0.684</td>
</tr>
<tr>
<td>Upright</td>
<td>5.7±1.0†</td>
<td>5.4±0.8†</td>
<td>0.842</td>
</tr>
</tbody>
</table>

Values are mean±SEM. DBP indicates diastolic blood pressure; HR, heart rate; and SBP, systolic blood pressure. †P<0.05 vs supine.
Losartan

∆ 6 am

Placebo
2 am

Capt opril
8 am

∆ -30

8 am

-400

Placebo


In agreement with previous findings, renin activity was below detection limits in 73% of autonomic failure patients compared with loss of renin immunoreactivity in juxtaglomerular cells in autopsied kidneys, suggesting loss of sympathetic innervation for renin release. However, the role of norepinephrine itself in renin release is more complicated, as patients with dopamine β-hydroxylase deficiency, with intact innervation but no norepinephrine, have normal renin activity.

Despite often undetectable renin, Ang II was increased in autonomic failure, to levels seen in severe essential hypertension, and higher than those observed in hypertensive subjects responsive to ARBs. These findings raise the possibility that renin-independent mechanisms are involved in Ang II formation in autonomic failure. Several such mechanisms have been proposed, including alternate enzymes for angiotensinogen cleavage such as cathepsins, tonin, and chymase, prorenin activating the prorenin receptor to generate Ang II independent of renin activation; renin-independent cleavage of Ang1–12 to generate Ang II; and tissue-derived mechanisms have been proposed, including alternate enzymes for Ang II formation is independent of ACE activity in autonomic failure. Several such mechanisms have been proposed, including alternate enzymes for angiotensinogen cleavage such as cathepsins, tonin, and chymase; prorenin activating the prorenin receptor to generate Ang II independent of renin activation; renin-independent cleavage of Ang1–12 to generate Ang II; and tissue-derived enzymes for Ang II formation is independent of ACE activity in autonomic failure.

We and others have shown low and unresponsive renin activity in autonomic failure, and therefore disregarded a contribution of the renin–Ang system to hypertension in these patients. In agreement with previous findings, renin activity was below detection limits in 73% of autonomic failure patients compared with 50% of healthy subjects. Autonomic failure is associated with loss of renin immunoreactivity in juxtaglomerular cells in autopsied kidneys, suggesting loss of sympathetic innervation for renin release. However, the role of norepinephrine itself in renin release is more complicated, as patients with dopamine β-hydroxylase deficiency, with intact innervation but no norepinephrine, have normal renin activity.

Despite often undetectable renin, Ang II was increased in autonomic failure, to levels seen in severe essential hypertension, and higher than those observed in hypertensive subjects responsive to ARBs. These findings raise the possibility that renin-independent mechanisms are involved in Ang II formation in autonomic failure. Several such mechanisms have been proposed, including alternate enzymes for angiotensinogen cleavage such as cathepsins, tonin, and chymase, prorenin activating the prorenin receptor to generate Ang II independent of renin activation; renin-independent cleavage of Ang1–12 to generate Ang II; and tissue-derived enzymes for Ang II formation is independent of ACE activity in autonomic failure. Several such mechanisms have been proposed, including alternate enzymes for angiotensinogen cleavage such as cathepsins, tonin, and chymase, prorenin activating the prorenin receptor to generate Ang II independent of renin activation; renin-independent cleavage of Ang1–12 to generate Ang II; and tissue-derived enzymes for Ang II formation is independent of ACE activity in autonomic failure.

![Figure 2. Effects of losartan and captopril on blood pressure in autonomic failure. Effect of single dose losartan (50 mg, PO; n=11) or captopril (50 mg, PO; n=7) administered at 8:00 pm on overnight systolic blood pressure (SBP) in autonomic failure patients with supine hypertension. Losartan produced significant decreases in SBP compared with placebo as summarized by (A) changes in SBP over time and (B) area under the curve (AUC) for SBP. There was no effect of captopril on overnight SBP in these patients (C, D).](http://hyper.ahajournals.org/)

![Figure 3. Effect of losartan on nocturnal volume loss and sodium excretion. A. There was no significant effect of losartan on changes in body weight, a measure of night-time volume loss, in hypertensive autonomic failure patients. B. Losartan significantly reduced nocturnal urinary sodium (Na⁺) excretion in these patients. *P=0.046.](http://hyper.ahajournals.org/)
hypertension and did not have a placebo comparator arm. Furthermore, because depressor responses did not correlate with renin activity it was concluded that captopril effects were attributable to nonspecific increases in vasodilatory peptides, rather than direct Ang II effects. It could be argued that higher dose captopril could have proven more effective; however, first dose captopril produces exaggerated hypotensive effects, particularly in elderly hypertensive patients. The lower baseline SBP before captopril administration is not likely attributable to carryover effects as medications were randomized with appropriate washout between studies. Whereas the lower baseline pressure could result in a floor effect, we routinely observe that antihypertensive medications lower SBP <140 mm Hg in autonomic failure patients.

The ideal treatment for autonomic failure should not only control night-time hypertension, but also reduce pressure natriuresis to improve morning orthostatic hypotension. Nonpharmacological head-up tilt is one such approach; however, the degree of tilt required in patients with severe hypertension limits this approach. Several medications reduce supine hypertension in autonomic failure, such as nitroglycerin patch, sildenafil, and clonidine. None of these reduce nocturnal pressure natriuresis and improve morning orthostatic tolerance. In this study, losartan effectively lowered nocturnal pressure and urinary sodium excretion. This contrasts effects of chronic losartan to increase sodium and water excretion in essential hypertension, by blocking renal effects of Ang II. However, acute losartan does not alter sodium excretion in hypertensive subjects. Unfortunately, we were unable to demonstrate an improvement in morning orthostatic tolerance after losartan. This could be attributed to residual hypotensive effects, because the maximal SBP decrease occurred at 6 hours after administration. Whereas losartan could be given earlier in the night to prevent morning reductions in BP, further studies are needed before recommending this for patient management.

There are potential limitations to this study. First, the Ang II radioimmunoassay shows cross-reactivity for Ang III and IV metabolites. However, previous studies show that Ang II is the predominant species in venous blood from humans. In addition, the antihypertensive effects of losartan provide functional evidence for presence of biologically significant levels of Ang II. Second, this study included a small number of subjects, especially for captopril. All subjects could not receive captopril based on medication allergies or contraindications. However, because these studies were powered to detect differences in overnight SBP, we would need 66 patients to have 80% power to detect a difference in means between captopril and placebo based on the present data showing a mean difference of 7 mm Hg and a SD of difference of 20 mm Hg. In the patients receiving captopril, we still observed a highly significant BP lowering effect of losartan, suggesting Ang II is important despite no effect of ACE inhibition. Finally, because of the small number of patients, a direct comparison between multiple systems atrophy and pure autonomic failure patients was not made. This will be investigated in future studies given that supine hypertension is driven by different mechanisms in these patients. Although hypertension in multiple systems atrophy is supported by residual sympathetic tone, it is driven by increased vascular resistance in pure autonomic failure. Importantly, Ang II could contribute to hypertension in either multiple systems atrophy or pure autonomic failure, as this peptide increases sympathetic and vascular tone.

**Perspectives**

Based on the finding for low renin activity, therapies targeting Ang II are not commonly used for treatment of supine hypertension in autonomic failure, despite having potential benefit for cardiovascular end-organ damage. The findings in the present study, however, suggest that losartan, and potentially other ARBs, should be considered in management of these patients. Whether losartan provides long-term benefit is unclear and will need to be addressed in future studies. Although primary autonomic failure is a relatively rare condition, these patients provide the unique opportunity to study BP regulation, and the development of hypertension, in the absence of autonomic and traditional renin influences. The identification of mechanisms driving paradoxic elevations in BP in autonomic failure will have important implications for management of these patients. These findings may also improve our understanding of essential hypertension, particularly in the context of low renin forms of the disease and in elderly patients with concomitant orthostatic hypotension.

**Acknowledgments**

We thank our patients and healthy volunteers.

**Sources of Funding**

This work was supported by National Institutes of Health grants P01HL056693, 5U54NS065736, and UL1TR000445. A.C. Arnold is supported by American Heart Association Postdoctoral Fellowship 11POST7330010.

**Disclosures**

I. Biaggioni is a consultant at Chelsea Therapeutics and receives financial support for an investigator-initiated study from Forest Laboratories through Vanderbilt University. The other authors have no conflicts to report.

**References**

by guest on April 19, 2017 http://hyper.ahajournals.org/ Downloaded from


29. Semple PF, Boyd AS, Dawes PM, Morton JJ. Angiotensin II and its heptapeptide (2-8), hexapeptide (3-8), and pentapeptide (4-8) metabolites in arterial and venous blood of man. Circ Res. 1976;39:671–678.


Angiotensin II, Independent of Plasma Renin Activity, Contributes to the Hypertension of Autonomic Failure
Amy C. Arnold, Luis E. Okamoto, Alfredo Gamboa, Cyndya Shibao, Satish R. Raj, David Robertson and Italo Biaggioni

Hypertension. 2013;61:701-706; originally published online December 24, 2012; doi: 10.1161/HYPERTENSIONAHA.111.00377

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/61/3/701

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/