Enhanced Blood Pressure–Lowering Effect of Olmesartan in Hypertensive Patients With Chronic Kidney Disease–Associated Sympathetic Hyperactivity: HONEST Study

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To investigate the blood pressure (BP)-lowering effect of olmesartan in relation to chronic kidney disease (CKD)-associated sympathetic nerve activity, a subanalysis was performed using data from the first 16 weeks of the Home BP Measurement With Olmesartan-Naive Patients to Establish Standard Target Blood Pressure (HONEST) study, a prospective observational study of hypertensive patients. Essential hypertensive patients who took no antihypertensive agent at baseline were classified based on baseline morning home systolic BP (MHSBP) in quartiles. In each class, patients were further classified based on baseline morning home pulse rate (MHPR). A subgroup analysis in patients with/without chronic kidney disease (CKD) was performed. A total of 5458 patients (mean age, 63.0 years; 51.6% women) were included. In the 4th quartile of baseline MHSBP (>165 mmHg), patients with MHPR ≥70 beats per minute had a greater BP reduction (by 3.2 mmHg) than those with MHPR <70 beats per minute after 16 weeks of olmesartan-based treatment (P=.0005). An even greater BP reduction (by 6.6 mm Hg) was observed in patients with CKD than in patients without CKD in this group (P=.0084). Olmesartan was more effective in hypertensive patients with high MHSBP and MHPR ≥70 beats per minute, especially in patients with CKD. Olmesartan may have enhanced BP-lowering effects by improving renal ischemia in hypertensive CKD patients with potential increased sympathetic nerve activity. J Clin Hypertens (Greenwich). 2013;15:555–561.

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Hypertensive patients commonly have increased sympathetic nerve activity.1 Morning hypertension and morning surge in blood pressure (BP) are particularly known to be caused by increased sympathetic nerve activity as well as lack of sustained effects of antihypertensive drugs.2–4 A marked increase in sympathetic nerve activity has been reported at the time of awakening.5 In addition, heart rate, which is associated with progression of hypertensive patients, is also known as an indicator of increased sympathetic nerve activity.6,7 Therefore, compared with clinic BP and pulse rate (PR), morning home BP and PR are thought to reflect the status of sympathetic nerve activity more accurately.

Moreover, patients with conditions such as obesity leading to the metabolic syndrome and chronic kidney disease (CKD), who have a marked increase in sympathetic nerve activity, often have concomitant morning hypertension.8–11 Particularly in patients with CKD, increased sympathetic nerve activity is observed from the early stages and becomes more prominent according to the disease progression.12 Two mechanisms are thought to be involved in the activation of renal sympathetic nerves in patients with CKD. The first mechanism is that mild ischemia of renal tissues activates the hypothalamic area and the sympathetic nervous system center in the medulla oblongata through the afferent nerve pathway. The second one is that ischemia of renal tissues activates the renin-angiotensin system, and the resultant angiotensin II (Ang II) activates the central sympathetic nervous system.13 Consequently, we proposed the following hypothesis: In hypertensive patients with high PR (indicating increased sympathetic nerve activity), angiotensin receptor blockers (ARBs) yield a potent BP-lowering effect through suppression of sympathetic nerve activity. Especially in hypertensive patients with concomitant CKD who are characterized by increased sympathetic nerve activity, an even greater BP reduction can be obtained. In order to verify this hypothesis, we conducted the present analysis using data from a large-scale observational study of an ARB, olmesartan. The Home BP Measurement With Olmesartan-Naive Patients to Establish Standard Target Blood Pressure (HONEST) study is a prospective observational study following >20,000 patients receiving olmesartan-based antihypertensive treatment for 2 years. The time from start of treatment to first occurrence of cardiovascular events is the primary endpoint.14
Here, we evaluated patients untreated with antihypertensive drugs using data as of 16 weeks from the HONEST study in order to test our hypothesis. Morning home BP was used to evaluate the BP-lowering effect, and morning home PR (MHPR) was used to evaluate effects on sympathetic nerve activity.

**METHODS**

The aims and protocol of the HONEST study have already been reported. This study was a large-scale prospective observational study with a 2-year follow-up by September 30, 2012. The study was registered at http://www.umin.ac.jp/ctr/index.htm with the unique trial number UMIN000002567. The study protocol was approved by the Ethical Committee of Daiichi Sankyo Co., Ltd., and it conformed with the pharmaceutical affairs laws of Japan and was approved by the Ministry of Health, Labour and Welfare of Japan before commencement. This study was carried out in medical institutions registered in compliance with Good Post-marketing Study Practice in Japan and internal regulations for clinical studies at each institution.

Briefly, participants were olmesartan-naive with essential hypertension. Written informed consent was obtained from all patients at the start of the study. Patients were excluded if they had a history of recent cardiovascular events (eg, myocardial infarction, stroke, and cardiovascular interventions), or if cardiovascular interventions were planned. Olmesartan (generally 10 mg/d or 20 mg/d) was administered at each participating physician’s discretion. No restriction was placed on prior antihypertensive drug treatment, with the exception of prior use of olmesartan, or on the use of combination antihypertensive drug treatment during the study. The data included patient characteristics (eg, disease history and complications), clinic BP and home BP, clinic PR, MHPR, clinical laboratory test values, and the incidence of cardiovascular events and adverse events during the study period. The present analysis used the first 16 weeks of data from the HONEST study for patients who received olmesartan and took no antihypertensive agent before the study, avoiding the influence of prior antihypertensive drug treatment.

**Home BP Measurements**

Patients who already owned a sphygmomanometer based on the cuff-oscillometric principal were registered, but electrical devices for home BP measurements were not standardized. All such devices available in Japan have been validated and approved by the Ministry of Health, Labour and Welfare of Japan. At the time of obtaining informed consent, patients were asked to measure home BP twice in the morning and twice at bedtime according to the Japan Society of Hypertension 2009 guidelines, namely, in the morning (within 1 hour after waking up, after urination, before dosing in the morning, before breakfast, and 1 or 2 minutes after resting in a sitting position), and at bedtime (after 1 or 2 minutes of resting in a sitting position). We analyzed only the first measurement of home BP and PR in the morning at baseline and at 16 weeks. Home BP at each measurement point is defined as an averaged value over 2 days.

**Definition of Patients With CKD**

The patients with CKD at baseline were defined as having an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m², or proteinuria ≥2+ on dipstick test, or proteinuria 1+ and renal disease as a complication at study entry, or both. eGFR was calculated by the following formula devised for the Japanese population: eGFR=194×age (years)\(^{-0.287}\)×SCr\(^{-1.094}\) (×0.739 in women), where serum creatinine (SCr) levels measured within 12 months prior to study onset were used.

**Data Analysis**

Patients were classified based on baseline morning home systolic BP (MHSBP) in quartiles. Patients were also stratified into high and low MHPR groups using the cut-off value of MHPR 70 beats per minute (bpm) according to previous reports. For the comparison of changes in MHSBP and MHPR after 16 weeks of olmesartan-based treatment by quartiles of baseline MHSBP, by baseline MHPR, or by low and high MHPR in quartiles of MHSBP, analysis of variance was performed with adjustments for sex, age, disease duration, diabetes mellitus, smoking status, and alcohol drinking status. For comparison of baseline characteristics between CKD and non-CKD patients, chi-square test was used for categorical variables and t test for continuous variables. As to the comparison of BP-lowering effect, age and smoking status were used as adjustment factors. Patients with missing values of BP and PR were excluded from the analyses. Effect modification by CKD, on differences of the changes in MHSBP and MHPR between patients with/without CKD. All tests were two-sided, and \(P<.05\) was considered statistically significant. Continuous variables and categorical variables were expressed as mean±standard deviations. SAS release 9.2 (SAS Institute, Cary, NC) was used for all statistical analyses.

**RESULTS**

**Patient Disposition**

The subanalysis was conducted in 5458 unmedicated hypertensive patients at baseline with the data of MHSBP and MHPR both at baseline and at 16 weeks after olmesartan administration.

**Patient Background**

The baseline characteristics of the patients are presented in the Table I. The mean age of the patients was 63.0 years (range, 16–96 years); 51.6% of patients were women. Of 5458 patients, 891 (16.3%) had concomitant CKD. Compared with patients without
CKD (non-CKD), CKD patients had a higher percentage of female patients, an older mean age, longer duration of disease, and higher percentages of patients with a history of cerebrovascular/cardiovascular disease (P<.05 for all comparisons). Moreover, in CKD patients, body mass index, percentages of current smokers and regular alcohol drinkers, and morning home and clinic diastolic BP were lower (P<.001 for all comparisons). There was no significant difference in the morning home and clinic systolic BP and PR between the two groups.

### Dose of Olmesartan

Patients visited the hospital several times during the study period, and physicians adjusted the dose of olmesartan by checking for effective BP control. The mean (±standard deviation) dose of olmesartan in all patients, in CKD patients, and in non-CKD patients increased from 16.86±6.00, 17.04±6.45, and 16.83±5.89 mg at baseline to 17.97±6.94, 18.08±7.29, and 17.96±6.85 mg at 16 weeks, respectively.

### Changes in MHSBP and MHPR by Quartiles of Baseline MHSBP

Figure 1a and 1b show the changes in MHSBP and MHPR after 16 weeks of olmesartan treatment in patients classified into quartiles based on their baseline MHSBP. Significantly greater decreases in MHSBP and MHPR were noted in patients with higher baseline MHSBP (P<.0001 for both comparisons). Specifically, the changes from baseline in MHSBP (ΔMHSBP) and MHPR (ΔMHPR) were 35.6 mm Hg and 3.8 bpm, respectively, in the fourth quartile, whereas they were 9.1 mm Hg and 1.2 bpm, respectively, in the first quartile. A similar significant reduction pattern was also observed when the relation was analyzed by percentage reduction. The percentage reduction in each quartile from MHSBP quartile 1 (Q1) to MHSBP quartile 4 (Q4), was 6.4%, 11.6%, 14.6%, and 20.1% for MHSBP (P<.0001) and 1.1%, 2.0%, 2.3%, and 4.3% for MHPR (P<.0001), respectively.

### Changes in MHSBP and MHPR by Baseline MHPR

Figure 1c and 1d compare the changes in MHSBP and MHPR between patients with high (≥70 bpm) and low (<70 bpm) baseline MHPR after 16 weeks of olmesartan treatment. Compared with the group with low baseline MHPR, the group with high baseline MHPR had significantly greater decreases in MHPR and MHSBP, with the differences being 6.6 bpm and 2.3 mm Hg, respectively (P<.0001 for both comparisons). A similar significant reduction pattern was also observed when the relation was analyzed by percentage reduction. The percentage reductions of MHPR <70 bpm and MHPR ≥70 bpm was −2.7% and 6.1% for MHPR (P<.0001) and 12.6% and 13.7% for MHSBP (P<.0001), respectively.

### Changes in MHSBP by Baseline MHSBP and MHPR

To exclude the possibility that BP- and PR-lowering effects of olmesartan accounted only for consequence of phenomenon of regression to the mean, we stratified study patients by baseline MHSBP and MHPR, and compared changes in MHSBP after 16 weeks of olmesartan treatment (Figure 2). In the first to third quartile, no significant difference was observed between patients with high and low baseline MHPR. By contrast, in the fourth quartile, patients with high baseline MHPR had a significantly greater reduction in MHSBP by

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**TABLE 1. Baseline Characteristics**

| Patients       | All Patients (N=5458)^a | CKD (−) (n=4542) | CKD (+) (n=891) | P Value^b |
|----------------|-------------------------|------------------|-----------------|-----------|
| Women, %       | 51.6                    | 50.9             | 55.4            | .0127     |
| Age (range), y | 63.0±12.0               | 61.9±11.7        | 68.9±11.5       | <.0001    |
|                | (16–96)                 | (16–95)          | (27–96)         |           |
| BMI, kg/m^2    | 24.12±3.57              | 24.22±3.58       | 23.63±3.46      | .0001     |
| Duration of hypertension, y | 3.15±4.00          | 2.96±3.89        | 4.19±4.45       | <.0001    |
| Cerebrovascular disease, % | 3.4                  | 3.0              | 5.1             | .0014     |
| Cardiovascular disease, % | 1.5                  | 1.2              | 3.3             | <.0001    |
| Dyslipidemia, % | 38.6                   | 38.2             | 40.1            | .3005     |
| Diabetes mellitus, % | 14.5                 | 14.2             | 15.8            | .1951     |
| Current smoker, % | 13.5                | 14.2             | 9.5             | .0003     |
| Regularly drinks alcohol, % | 17.1                | 18.2             | 11.6            | <.0001    |

**BP parameters**

| Patients       | All Patients (N=5458)^a | CKD (−) (n=4542) | CKD (+) (n=891) | P Value^b |
|----------------|-------------------------|------------------|-----------------|-----------|
| Morning home SBP, mm Hg | 156.2±15.1             | 156.2±15.0       | 156.2±15.2      | .9658     |
| Morning home DBP, mm Hg | 90.8±11.0              | 91.2±10.9        | 88.8±11.1       | <.0001    |
| Morning home pulse rate, bpm | 71.8±9.7              | 71.8±9.6         | 71.9±10.0       | .6903     |
| Clinic SBP, mm Hg | 159.2±17.3             | 159.3±17.2       | 159.1±17.6      | .6768     |
| Clinic DBP, mm Hg | 91.5±12.2              | 92.0±12.1        | 89.4±12.5       | <.0001    |
| Clinic pulse rate, bpm | 74.4±10.8              | 74.4±10.7        | 74.4±11.4       | .9928     |

**Abbreviations:** BMI, body mass index; BP, blood pressure; bpm, beats per minute; CKD, chronic kidney disease; DBP, diastolic blood pressure; SBP, systolic blood pressure. Data are shown as means ± standard deviation or number of patients (percentage). ^a Including 25 patients with unknown status of CKD. ^b CKD(−) vs (+).
3.2 mm Hg compared with those with low baseline MHPR \((P=.0005)\). A similar pattern of reduction was also observed when the relation was analyzed by percentage reductions from baseline MHSBP (Q1–Q3, not significant; Q4, \(P=.0010\)).

**Changes in MHSBP by Baseline MHSBP and MHPR in Patients With or Without CKD**

Figure 3 compares the changes in MHSBP after 16 weeks of olmesartan-based treatment in patients classified by baseline MHSBP and MHPR and the presence of concomitant CKD. In the first to third quartile, differences between patients with high and low baseline MHPR were similar in both CKD and non-CKD patients as compared with all patients. By contrast, in the fourth quartile, CKD patients with high baseline MHPR had a significantly greater reduction in MHSBP by 6.6 mm Hg compared with those with low baseline MHPR \((P=.0084)\). Similarly, non-CKD patients had a significantly greater reduction in MHSBP by 2.2 mm Hg than those with low baseline MHPR \((P=.0254)\). A similar pattern of reduction was also
FIGURE 2. Change in morning home systolic blood pressure (MHSBP) after 16 weeks of olmesartan treatment classified by MHSBP and morning home pulse rate (MHPR) at baseline. △MHSBP is adjusted by sex, age (3 stages), duration of hypertension, diabetes mellitus, smoking, and alcohol. *P<.001: analysis of variance (MHPR <70 vs ≥70 beats per minute).

FIGURE 3. Changes in morning home systolic blood pressure (MHSBP) of patients with chronic kidney disease (CKD) and no CKD after 16-week olmesartan treatment classified by MHSBP and morning home pulse rate (MHPR) at baseline. △MHSBP(CKD) is adjusted by age (3 stages) and smoking and △MHSBP(non-CKD) is adjusted by sex, age (3 stages), duration of hypertension, history of drug allergy, and alcohol. *P<.01: MHPR <70 vs ≥70 beats per minute. #P<.05: analysis of variance (MHPR <70 vs ≥70 bpm).
observed when the relation was analyzed by percentage reductions from baseline MHSBP (CKD Q4, \( P=.0123 \); non-CKD Q4, \( P=.0398 \)). Differences of the changes in MHSBP between high and low MHPR were significantly modified by CKD and non-CKD patients (\( P=.0004 \)).

**DISCUSSION**

In this study, a greater reduction in MHPR was observed in essential hypertensive patients with higher baseline MHSBP (\( \geq 165 \) mm Hg) after olmesartan-based treatment. Furthermore, a greater BP-lowering effect was noted in patients with high baseline MHPR (\( \geq 70 \) bpm) who had increased sympathetic nerve activity than those with low baseline MHPR (\(< 70 \) bpm). This tendency was more evident in patients who had concomitant CKD. To our knowledge, this is the first study that reported the enhanced antihypertensive effect of olmesartan associated with sympathetic nerve activity in the clinical setting.

A significant reduction in PR was observed not only in patients with high baseline MHPR but also in those with a higher baseline BP who had a greater reduction in PR. Whereas sympathetic overdrive causes the development of hypertension, sympathetic nerve activity is also more potentiated according to the severity of hypertension.\(^{19}\) Although in this study we did not measure muscle sympathetic nerve activity (MSNA), which is a useful indicator of sympathetic nerve activity, an association between heart rate and MSNA has been reported.\(^{7}\) Thus, we consider that patients included in this study who had elevated BP and PR are highly likely to have concomitant CKD. Because of its effects on sympathetic nerve activity, the renin-angiotensin system and sympathetic nerve system activate each other, resulting in a vicious circle.\(^{33-35}\) ARBs suppress sympathetic nerve activity. A significant decrease in MSNA was observed in CKD patients who received treatment with an oral ARB.\(^{25-27}\) Thus, the effects of olmesartan on sympathetic nerve activity may be mediated through inhibition of Ang II in the brain and suppression of renal afferent nerve activity due to improvement of renal ischemia.

Our recent analysis of Jichi Medical University ABPM Study Wave 1 has shown that in hypertensive patients with CKD who also have elevated blood norepinephrine concentration, risk of stroke increases in a synergistic manner.\(^{36}\) Furthermore, in CKD patients, increased sympathetic nerve activity as shown by heart rate is associated with increased risks of developing end-stage renal disease or total mortality.\(^{37,38}\) Therefore, olmesartan may be particularly effective in the treatment of hypertensive patients who have concomitant CKD because of its effects on sympathetic nerve activity. In fact, a difference in BP reduction by 3 mm Hg has been reported to produce a reduction of cardiovascular events by 15%.\(^{39}\) Thus, olmesartan may be most beneficial for patients with elevated BP and PR, particularly when they have concomitant CKD. However, further prospective studies should be conducted to determine its effects in preventing events.

**STUDY LIMITATIONS**

This study has several limitations. Firstly, this is a post-hoc analysis of an observational study with no control arm. Secondly, PR used in the present study, as an indicator of sympathetic nerve activity, is not a direct measurement. Nevertheless, there is clearly a close association between heart rate and renal sympathetic nerve activity, as shown by a marked decrease in heart rate following renal denervation.\(^{40}\) The results of the present study showing the antihypertensive effects of olmesartan using PR in the real-world setting are considered important regarding the possibility of an application in clinical practice.
CONCLUSIONS

Olmesartan yielded statistically and clinically significant BP-lowering effects in patients with untreated essential hypertension with MHSBP ≥165 mm Hg in patients with high baseline MHPR compared with those with low baseline MHPR. Furthermore, in a subgroup of patients with CKD, an even greater reduction of MHSBP was noted in patients with high baseline MHPR than those with low baseline MHPR.

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References

1. Smith PA, Graham LN, Mackintosh AF, et al. Relationship between central sympathetic activity and stages of human hypertension. Am J Hypertens. 2004;17:217–222.
2. Kario K, Pickering TG, Umeda Y, et al. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. Circulation. 2003;108:1401–1406.
3. Kario K, White WB. Early morning hypertension: what does it contribute to overall cardiovascular risk assessment? J Am Soc Hypertens. 2008;2:397–402.
4. Kario K. Morning surge in blood pressure and cardiovascular risk: evidence and perspectives. Hypertension. 2010;56:765–773.
5. Tuck ML, Stern N, Sowers JR. Enhanced 24-hour norepinephrine and renin secretion in young patients with essential hypertension: relation with the circadian pattern of arterial blood pressure. Am J Cardiol. 1985;55:112–115.
6. Palatini P, Julius S. Heart rate and the cardiovascular risk. J Hypertens. 1997;15:3–17.
7. Grassi G, Vailati S, Bertamini G, et al. Heart rate as marker of sympathetic activity. J Hypertens. 1998;16:1635–1639.
8. Straznicky NE, Lambert EA, Lambert GW, et al. Effects of dietary weight loss on sympathetic activity and cardiac risk factors associated with the metabolic syndrome. J Clin Endocrinol Metab. 2005;90:2988–6005.
9. Tamaki S, Nakamura Y, Yoshino T, et al. The association between morning hypertension and metabolic syndrome in hypertensive patients. Hypertens Res. 2006;29:783–788.
10. Klein IH, Ligtenberg G, Neumann J, et al. Sympathetic nerve activity is inappropriately increased in chronic renal disease. J Am Soc Nephrol. 2003;14:3239–3244.
11. Ishikawa J, Hoshide S, Shibusaki S, et al. Relationship between morning hypertension and sympathetic nerve activity: effect of home blood pressure monitoring and brain natriuretic peptide and estimated glomerular filtration rate: the Japan Morning Surge 1 (JMS-1) Study. J Clin Hypertens (Greenvich). 2008;10:34–42.
12. Grassi G, Quarti-Trevano F, Seravalle G, et al. Early sympathetic activation in the initial clinical stages of chronic renal failure. Hypertension. 2011;57:846–851.
13. Siddiqui L, Joles JA, Grassi G, Blankestijn PJ. Is kidney ischemia the central mechanism in parallel activation of the renin and sympathetic nervous system? J Hypertens. 2009;27:1341–1349.
14. Saito I, Kario K, Kashihiro T, et al. Rationale, study design, baseline characteristics and blood pressure at 16 weeks in the HONEST Study. Hypertension Res. 2012;35:177–182.
15. Oshiga T, Kikuchi K, Matsuoka H, et al. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). Hypertens Res. 2009;32:3–107.
16. Committee of KJ Initiative, Japanese Society of Nephrology. Clinical practice guidebook for diagnosis and treatment of chronic kidney disease. Clin Exp Nephrol. 2009;13:187–256.
17. Hozawa A, Okubo T, Kikuha M, et al. Prognostic value of home heart rate for cardiovascular mortality in the general population: the Ohkama study. Am J Hypertens. 2004;17:1005–1010.
18. Fox K, Ford I, Steg PG, et al; BEAUTIFUL Investigators. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomized controlled trial. Lancet. 2008;372:817–821.
19. Grassi G. Assessment of sympathetic cardiovascular drive in human hypertension: achievements and perspectives. Hypertension. 2009;54:690–697.
20. Julius S, Jamerson K. Sympathetics, insulin resistance and coronary risk in hypertension: the chicken-and-egg question. J Hypertens. 2013;31:485–502.
21. Kuramoto K, Ikhikawa S, Hirai A, et al. Azelnidipine and amlopidine: a comparison of their pharmacokinetics and effects on ambulatory blood pressure. Hypertens Res. 2003;26:201–208.
22. Hoshide S, Kario K, Ikhikawa J, et al. Comparison of the effects of cilnidipine and amlopidine on ambulatory blood pressure. Hypertens Res. 2005;28:1003–1008.
23. Kario K, Ando S, Kido H, et al. The effects of the l-type calcium channel blocker (cilnidipine) on sympathetic hyperactive morning hypertension: results from achieve-one. J Clin Hypertens. 2013;15:133–142.
24. Litgenberg G, Blankstein PJ, Oey PL, et al. Reduction of sympathetic hyperactivity by enalapril in patients with chronic renal failure. N Engl J Med. 1994;330:1321–1328.
25. Klein IH, Litgenberg G, Oey PL, et al. Enalapril and losartan reduce sympathetic hyperactivity in patients with chronic renal failure. J Am Soc Nephrol. 2003;14:425–430.
26. Neumann J, Litgenberg G, Oey L, et al. Moxonidine normalizes sympathetic hyperactivity in patients with eprosartan-treated chronic renal failure. J Am Soc Nephrol. 2004;15:2902–2907.
27. Neumann J, Litgenberg G, Klein IH, et al. Sympathetic hyperactivity in hypertensive chronic kidney disease patients is reduced during standard treatment. Hypertension. 2007;49:506–510.
28. Siddiqui L, Oey PL, Blankstein PJ. Alikiren reduces sympathetic nerve activity and blood pressure in chronic kidney disease patients. Nephrol Dial Transplant. 2011;26:2930–2934.
29. Ye S, Ozgur B, Campese VM. Renal afferent impulses, the posterior hypothalamus, and hypertension in rats with chronic renal failure. Kidney Int. 1997;51:722–727.
30. Reid IA. Interactions between ANG II, sympathetic nervous system, and baroreceptor reflexes in regulation of blood pressure. Am J Physiol. 1992;262:E763–E778.
31. Williams JL, Barnes KL, Bronsnian KM, Ferrario CM. Area postrema: a unique regulator of cardiovascular function. News Physiol Sci. 1992;7:30–34.
32. Kumagi H, Oshima N, Matsuura T, et al. Importance of rostral ventrolateral medulla neurons in determining efferent sympathetic nerve activity and blood pressure. Hypertension Res. 2012;35:132–141.
33. Sakata K, Kumagi H, Osaka M, et al. Potentiated sympathetic nerve and renin-angiotensin systems reduce nonlinear correlation between sympathetic activity and blood pressure in conscious spontaneously hypertensive rats. Am J Physiol. 2006;290:620–625.
34. Matsuura T, Kumagi H, Kawai A, et al. Rostral ventrolateral medulla neurons of neonatal Wistar-Kyoto and spontaneously hypertensive rats. Hypertension. 2012;40:560–565.
35. Brooks VL, Hayward JA, Johnson AK. Transition of salt retention to central activation of the sympathetic nervous system in hypertension. Clin Exp Pharmacol Physiol. 2005;32:462–463.
36. Yano Y, Hoshide S, Etoh T, et al. Synergistic effect of chronic kidney disease and high circulatory norepinephrine level on stroke risk in Japanese hypertensive patients. Atherosclerosis. 2011;219:273–279.
37. Zoccali C, Leonards D, Ena G, et al. Heart rate, age and the risk of progression to kidney failure in patients with CKD. J Nephrol. 2012;25(suppl 19):205–209.
38. Beddu S, Ngwekar SU, Ma X, Greene T. Associations of resting heart rate with insulin resistance, cardiovascular events and mortality in chronic kidney disease. Nephrol Dial Transplant. 2009;24:2482–2489.
39. Neal B, MacMahon S, Chapman N; Blood Pressure Lowering Treatment Trialists’ Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designedoverviewsof randomised trials. Blood Pressure Lowering Treatment Trialists’ Collaboration. Lancet. 2000;356:1955–1964.
40. Ukena C, Mahfoud F, Spies A, et al. Effects of renal sympathetic denervation on heart rate and atrioventricular conduction in patients with resistant hypertension. Int J Cardiol. 2012;Aug 20. doi:10.1016/j.ijcard.2012.07.027 [Epub ahead of print].