

Comparison of Effects of Enalapril and Nitrendipine on Cardiac Sympathetic Nervous System in Essential Hypertension

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Objectives. The purpose of this study was to assess the effects of enalapril and nitrendipine on the cardiac sympathetic nervous system.

Background. Angiotensin-converting enzyme inhibitors and long-acting calcium channel blockers have been widely used in the treatment of cardiovascular diseases, in some of which sympathetic overactivity plays a major role in the pathophysiology and prognosis. However, little information is available on the effects of these drugs on the cardiac sympathetic nervous system.

Methods. ^{123}I -metaiodobenzylguanidine (MIBG) cardiac imaging was performed before and 3 months after drug administration in 46 patients with mild essential hypertension. Twenty-two patients were treated with 5 to 10 mg of enalapril once a day, and the other 24 with 5 to 10 mg of nitrendipine once a day. For comparison, 20 normotensive subjects were also studied.

Results. There were no significant differences between the basal

characteristics in the 2 hypertensive groups. In both hypertensive groups, both systolic and diastolic blood pressures were significantly reduced to similar levels after the 3-month drug treatment. Before the drug treatment, the 2 hypertensive groups had a significantly higher washout rate and lower MIBG uptake than the normotensive subjects. The heart-to-mediastinum ratio significantly increased ($p < 0.0001$), with decreased ($p < 0.002$) washout rate after drug treatment in the enalapril group, but with no significant changes in the nitrendipine group.

Conclusion. Enalapril could suppress cardiac sympathetic activity and nitrendipine had no effect on it. The knowledge of antihypertensive drugs on the cardiac sympathetic nervous system appears to be helpful in selecting appropriate treatment in cardiovascular diseases.

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Sympathetic overactivity is proposed as a pathophysiologic finding in several cardiovascular diseases (1-6). This is supported, in part, by the widespread use of beta-blocking agents to treat these cardiovascular diseases effectively (7-9). Recently, numerous investigators (10-12) have recommended the use of angiotensin-converting enzyme (ACE) inhibitor in cardiovascular diseases because of its beneficial effects on the cardiovascular system, among them a proposed effect on the sympathetic nervous system (13). On the other hand, the issue that the use of short-acting calcium channel blockers is associated with increased risk of acute myocardial infarction and mortality (14) or does not reduce the incidence of cardiac events (15) has cast doubt on the usefulness of long-acting calcium channel blockers in cardiovascular diseases. Neurohormonal activation is considered to be an important variable participating in the unexpected results obtained with short-acting calcium channel blockers (16). To date, no large-scale long-term clinical trials of long-acting calcium channel blockers in patients with cardiovascular diseases have been reported

other than one recent clinical trial in patients with hypertension (17). That study revealed that nitrendipine reduced the overall incidence of cardiac events in elderly hypertensives. The effect of nitrendipine on the sympathetic nervous system, however, remains unknown, despite the known association between sympathetic activation and heart disease. Cardiac sympathetic activity seems to be particularly important because sympathetic outflow is not necessarily uniformly distributed across the organs (18) and the cardiac sympathetic nervous system is associated with prognosis of heart failure (19,20).

Although it was previously difficult to assess cardiac sympathetic nerve activity in vivo, ^{123}I metaiodobenzylguanidine (MIBG), an analog of guanidine that shares the same neuronal transport and storage mechanisms with norepinephrine, is now used to evaluate the sympathetic activity and innervation of the left ventricle (20-27), where most severe forms of heart disease originate.

Using MIBG imaging in patients with essential hypertension, we compared the effects on the cardiac sympathetic nervous function of enalapril, an ACE inhibitor, with those of nitrendipine, a long-acting calcium channel blocker.

Methods

Patients. We selected 46 male patients with mild essential hypertension over 39 years of age (range 40 to 69) who were

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Abbreviations and Acronyms

ACE	=	angiotensin-converting enzyme
H/M ratio	=	heart-to-mediastinum ratio
LVM	=	left ventricular mass
LVMI	=	left ventricular mass index
MIBG	=	¹²³ I metaiodobenzylguanidine

referred to cardiac catheterization because of chest pain and/or electrocardiographic abnormalities that revealed normal coronary arteries without spasm and normal cardiac function. According to the Guidelines Sub-committee of the WHO/ISH Mild Hypertension Liaison Committee (28), mild hypertension was defined as persistent resting levels of diastolic blood pressure between 90 and 105 mm Hg and/or systolic blood pressure between 140 and 180 mm Hg. All hypertensive patients in the present study met these criteria. They were allocated randomly into 2 groups: 22 of the men received oral enalapril (5 to 10 mg) once a day and the other 24 men received oral nitrendipine (5 to 10 mg) once a day. We also selected 20 normotensive male subjects (122 ± 16 mm Hg/ 76 ± 8 mm Hg) with normal coronary and left ventricular function as a control group. None of the study patients had diabetes mellitus or any other disease affecting the autonomic nervous system. They underwent MIBG imaging within one month after cardiac catheterization and also repeat MIBG imaging 3 months after the start of the drug treatment. All hypertensive patients were newly diagnosed and had not received any antihypertensive therapy except for diet therapy before first MIBG imaging. Informed consent was obtained from each patient. This study protocol was approved by the hospital's ethics committee.

Coronary angiography. Coronary angiography with the acetylcholine provocation test was performed by the standard Judkins technique in all patients.

Echocardiography. Echocardiograms were recorded, with the patient in the supine position turned 30° on his left side, using an SSD-870 echocardiograph (Aloka Co., Ltd., Tokyo, Japan) with a 3.5-MHz transducer. M-mode echocardiograms were recorded under 2-dimensional guidance, and the tracing was recorded at a paper speed of 100 mm/s. Measurements were obtained to the nearest millimeter for at least 4 cardiac cycles during quiet respiration, and the average values were used for analysis. All echocardiograms were recorded with the patient in the same position, in the same intercostal and left ventricular area, just below the tip of the mitral leaflets. All measurements were obtained by the same observer according to the guidelines of the American Society of Echocardiography (29). The parameters measured or calculated were the left ventricular end-diastolic and end-systolic dimensions, and the septal and posterior wall thickness in systole and diastole. In addition, the left ventricular mass (LVM) was calculated as follows (30): $1.05 \times \pi/3 \{ [2 (\text{left ventricular end-diastolic dimension}) + (\text{septal} + \text{posterior wall thickness in diastole})] \times [\text{left ventricular end-diastolic dimension} + (\text{septal} + \text{posterior}$

wall thickness in diastole)]²/2} - (\text{left ventricular end-diastolic dimension})³. LVM was divided by the body surface area to obtain the LVM index (LVMI) (g/m²). LV ejection fraction (EF) was also calculated according to the American Society of Echocardiography criteria by the area-length method (31).

MIBG scintigraphy. After an overnight fast, a dose of 111 MBq of commercially available MIBG (Daiichi Radioisotopes Labs, Ltd., Tokyo, Japan) was administered intravenously. A 5-minute static acquisition was made every 15 minutes and 3 hours after injection of MIBG in the anterior view. Cardiac images were acquired after each static acquisition, using a three-head gamma camera (Toshiba GCA 9300A/HG, Tokyo, Japan) equipped with parallel-hole, high-resolution collimators. Energy discrimination was provided by a 15% window centered at 159 keV. Data processing was performed on a Toshiba GMS 5500A system.

Left ventricular MIBG activity and washout rate were measured by using square region-of-interests placed over the left ventricle with the peak count density and over the upper mediastinum. The heart-to-mediastinum ratio (H/M ratio) on the delayed image was calculated to quantify cardiac MIBG uptake as a fraction of the mean count per pixel in the heart divided by those in the upper mediastinum (20). The myocardial washout rate was defined as the percent change in activity from the initial to the delayed images within the left ventricle and calculated as follows: washout rate (%) = $(A - B)/A \times 100$, where A = average count/pixel in the left ventricle on the initial image and B = average decay-corrected count/pixel in the same region on the delayed image. Decay correction was performed assuming that the half-life of the radionuclide (¹²³I) was 13 hours.

Hormone analysis. After the patient had rested in the supine position for 30 minutes in a warm, quiet, darkened room between 8:00 and 9:00 AM before MIBG imaging, his blood pressure was measured and venous blood samples were drawn from an indwelling catheter inserted in the median cubital vein. Blood samples were stored at -70°C. The plasma norepinephrine concentration was determined by a high-performance liquid chromatography (32). This method detects norepinephrine levels as low as 10 pg/ml. The intra- and interassay coefficient of variation were 1.1% and 0.5%, respectively.

Statistical analysis. Data are expressed as mean \pm SD. Comparisons among 3 groups (normotensive subjects, patients with enalapril and patients with nitrendipine) were performed by one-way analysis of variance (ANOVA) followed by Bonferroni multiple comparison test. Statistical evaluation was also performed by ANOVA with repeated measurements, which included the effects of enalapril and nitrendipine and comparisons between groups, and, if significant differences were detected by ANOVA, the paired *t* test was performed on the relevant data pair. Chi-square or Fisher's exact test was used to determine the significance of differences in the observed occurrence rates. A *p* value less than 0.05 was considered significant.

Table 1. Distribution of Clinical Variables

Group	Normotensive Subjects (n = 20)	Hypertensive Patients Treated With enalapril (n = 22)	Hypertensive Patients Treated With nitrendipine (n = 24)
Age (yr)	59 ± 8	61 ± 8	65 ± 7
Smoking	6	5	6
Hypercholesteremia	4	6	5
FH	8	8	6
Hyperuricemia	4	4	3
Body mass index (kg/m ²)	23 ± 2	24 ± 3	24 ± 2
Echocardiographic variables			
LVM (g)	141 ± 17	150 ± 23	154 ± 23
LVMi (g/m ²)	91 ± 11	97 ± 15	100 ± 14
EF (%)	68 ± 9	65 ± 6	67 ± 5

Values are expressed as mean ± SD. EF = ejection fraction; FH-family history of coronary artery disease; LVM-left ventricular mass; LVMi-left ventricular mass index.

Results

Baseline characteristics. Baseline clinical characteristics of the hypertensive patients and normotensive subjects are listed in Table 1. There were no significant differences in age, body mass index and coronary risk factors among the 3 groups, and no difference in blood pressure levels was recognized between the 2 hypertensive groups. In addition, echocardiographic findings were comparable across the 3 groups.

Changes in hemodynamics and hormones. Changes in blood pressure, heart rate and plasma norepinephrine concentration before and after drug treatment are presented in Table 2. There were no significant differences in any of the parameters between the 2 groups before and 3 months after drug treatment. In both groups, both systolic and diastolic blood pressures were significantly reduced after drug treatment, although heart rate did not change significantly. In addition,

Table 2. Changes in Hemodynamics and Plasma Norepinephrine Concentration

	Enalapril	Nitrendipine
Systolic BP (mm Hg)		
Before	164 ± 10	174 ± 20
After	140 ± 11*	140 ± 15*
Diastolic BP (mm Hg)		
Before	97 ± 4	97 ± 10
After	80 ± 6*	77 ± 8*
HR (beats/min)		
Before	72 ± 4	70 ± 5
After	70 ± 6	73 ± 2
Norepinephrine(ng/L)		
Before	299 ± 134	276 ± 120
After	244 ± 108	269 ± 99

*p < 0.001, compared with the value before drug treatment. There was no significant difference in any variable between the 2 groups. Values are expressed as mean ± SD. BP-blood pressure; HR-heart rate.

plasma norepinephrine concentration did not change significantly after drug administration in either group.

Changes in scintigraphic variables after drug treatment. Compared with the normotensive group before drug treatment, the 2 hypertensive groups had significantly higher washout rates (5.4 ± 3.8 in normotensive subjects vs. 18.1 ± 11.4 in the enalapril group [p < 0.0001] and vs. 13.3 ± 9.3 in the nitrendipine group [p < 0.005]) and lower H/M ratio (2.22 ± 0.21 vs. 1.89 ± 0.34 [p < 0.0003] and vs. 2.00 ± 0.27 [p < 0.01], respectively) (Fig. 1). Figure 2 shows the scintigraphic variables before and 3 months after drug treatment in the 2 hypertensive groups. In the enalapril group, the H/M ratio significantly increased (1.89 ± 0.34 vs. 2.08 ± 0.35, p < 0.0001) after drug treatment, but there was no significant change in the ratio in the nitrendipine group (2.00 ± 0.27 vs. 2.01 ± 0.26, p = NS). In addition, the washout rate significantly changed in the enalapril group (18.1 ± 11.4 vs. 13.9 ± 11.0, p < 0.002) but not in the nitrendipine group (13.3 ± 9.3 vs. 12.3 ± 9.1, p = NS).

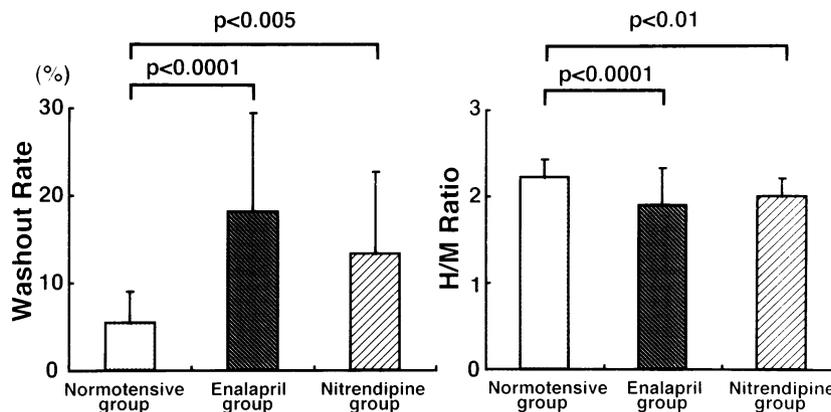
Ten of the normotensive subjects underwent repeat MIBG imaging 3 months after the first MIBG imaging. The H/M ratio was 2.20 ± 0.23 at the first and 2.16 ± 0.20 at the second test (p = NS), and the washout rate was 5.7 ± 3.3 and 5.8 ± 3.3 (p = NS), respectively. Correlation analysis revealed high reproducibility of both the H/M ratio (r = 0.93, p < 0.001) and washout rate (r = 0.96, p < 0.0001).

Discussion

Essential hypertension and the cardiac sympathetic nervous system. The present study demonstrated that hypertensive patients had lower MIBG uptake and higher washout rate than normotensive subjects. These MIBG findings in essential hypertension are consistent with those in cardiovascular diseases with cardiac sympathetic overactivity (20,21,23,24,26). Furthermore, recent microneurographic studies (2,3) have demonstrated that the central sympathetic neural outflow is augmented in essential hypertension. Likewise, activation of the cardiac sympathetic nervous system in essential hypertension was documented using power spectral analysis (4) and measurement of tritiated norepinephrine (1). Therefore, it is reasonable to assume that the abnormalities of MIBG imaging in the present study result from cardiac sympathetic overactivity in essential hypertension.

The reliability of the MIBG-imaging process for quantitatively assessing sympathetic nerve activity has been demonstrated in a large number of MIBG studies. Experimentally, Sisson et al. (22) demonstrated that movements of MIBG in the heart largely mimic those of tritiated norepinephrine, indicating that MIBG release from the heart reflects sympathetic nerve activity. In addition, Takatu et al. (23) demonstrated that accelerated MIBG washout in Syrian hamsters was due to increased firing of the sympathetic nerves. Clinically, Schofer et al. (24) demonstrated that the H/M ratio was related to MIBG activity and norepinephrine concentration in the human myocardium. Using a quantitative method similar to ours, Imamura et al. (26) suggested that MIBG washout was

Figure 1. Comparisons of heart/mediastinum (H/M) ratio and washout rate among 20 normotensive subjects, 22 patients with essential hypertension before enalapril administration, and 24 patients with essential hypertension before nitrendipine administration.



more closely associated with sympathetic activity than MIBG uptake in heart failure, since MIBG washout is independent of the number of neurons available, whereas the H/M ratio is not. In addition, Morozumi et al. (25) demonstrated that the H/M ratio and MIBG washout rate correlated with sympathetic nerve activity, which was determined by power spectral analysis of heart rate variability. These results corroborate our theory that quantitative analysis of cardiac MIBG images is a reliable method to assess cardiac sympathetic nerve activity. In considering the report by Imamura et al. (26) and the responses of MIBG washout and uptake to atropine (27), MIBG washout appears to be more closely associated with sympathetic nerve activity than MIBG uptake.

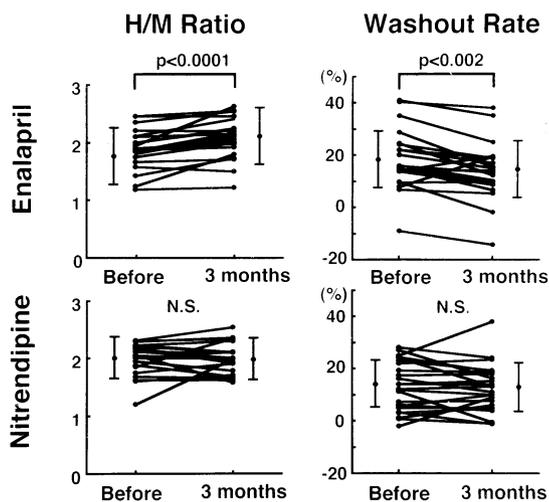
Effect of enalapril on the cardiac sympathetic nervous system. Using MIBG imaging, several investigators have demonstrated that enalapril increases MIBG uptake and reduces MIBG washout rate in heart failure, suggesting that enalapril has a beneficial effect on the cardiac sympathetic nervous system in heart failure (33). However, ACE inhibitors are shown to have beneficial hemodynamic effects that reduce

norepinephrine release in heart failure. Therefore, it is unclear whether improvement in sympathetic activity is due to the direct influence of ACE inhibitors on the sympathetic nervous system or to their beneficial systemic effects in patients with heart failure. Noll et al. (34) demonstrated that captopril did not reduce muscle sympathetic activity compared with its resting activity, but did so when compared with placebo despite reduction in diastolic blood pressure that appears to be important for baroreceptor-mediated activation of the sympathetic nervous system (35). In contrast, we demonstrated that enalapril increased MIBG uptake and reduced MIBG washout rate in essential hypertension, suggesting that enalapril suppresses cardiac sympathetic overactivity. However, enalapril did not affect a global index of sympathetic activity, such as plasma norepinephrine concentration, in patients with essential hypertension. Thus, enalapril could suppress cardiac sympathetic activity without affecting plasma norepinephrine concentration despite a significant reduction in diastolic blood pressure.

Several mechanisms contributing to the inhibition of sympathetic nervous activity by ACE inhibitors have been proposed. ACE inhibitors may reduce norepinephrine release by reducing angiotensin II concentration. Angiotensin II facilitates norepinephrine release at presynaptic sites (36) and stimulates sympathetic outflow by activating specific binding sites in the brainstem (37). In addition, ACE inhibition may lead to enhanced prostaglandin formation via accumulation of bradykinin (38), which may inhibit norepinephrine release at presynaptic sites (39). On the basis of an interaction between the sympathetic nervous system and the renin-angiotensin system, enalapril may decrease the enhanced cardiac sympathetic nervous system in essential hypertension.

Calcium channel blocker and sympathetic activity. The reflex increase in sympathetic activity induced by short-acting dihydropyridine calcium channel blockers has been demonstrated (16). This increase is considered to be one of the major adverse factors of cardiovascular diseases (40). However, it remains unknown whether this reflex increase is associated with the short-term and with the rapid action of dihydropyridine calcium channel blockers. Frohlich et al. (16) demonstrated that long-acting nifedipine does not increase plasma

Figure 2. Comparison of heart/mediastinum (H/M) ratio and washout rate before and 3 months after drug treatment in hypertensive patients treated with enalapril and in those treated with nitrendipine.



norepinephrine concentration but that short-acting nifedipine does. They suggested that the duration as well as the strength of the action of antihypertensive drugs may affect the sympathetic nervous system. However, recent studies demonstrated that long-acting dihydropyridine calcium channel blockers, such as amlodipine and felodipine, could activate the sympathetic nervous system (41,42). In contrast, we demonstrated that nitrendipine (5 to 10 mg) did not change the cardiac MIBG kinetics and plasma norepinephrine concentration despite lowering systemic blood pressure to a degree similar to that produced by enalapril; this suggests that nitrendipine did not influence the cardiac sympathetic nervous system and did not induce an increase in plasma norepinephrine concentration, probably resulting from baroreceptor-mediated activation of the sympathetic nervous system. Thus, nitrendipine did not affect the sympathetic nervous system, although sympathetic activation may depend on used dosages of the drug.

Clinical implications. Among patients with heart diseases, those with sympathetic activation have a high mortality rate (19). Therefore, modulation of the cardiac sympathetic nervous system by medication is worth considering as a treatment for such patients. Because decreased MIBG uptake and increased MIBG washout are shown to be associated with unfavorable prognosis (20), we expect that enalapril could improve the prognosis in such patients. In fact, enalapril has been shown to have beneficial effects on the prognosis of patients with heart failure (10,11) whose reported MIBG findings (20,26) were similar to those of patients with essential hypertension in this study. Nitrendipine, on the other hand, does not seem to affect the cardiac sympathetic nervous system. Regarding the question of whether this feature offers an advantage to patients receiving long-term treatment with nitrendipine, a recent study—the Systolic Hypertension in Europe (SYST-EUR) Trial (17)—demonstrated that active treatment with nitrendipine for elderly patients with isolated systolic hypertension decreased all fatal and nonfatal cardiac events significantly, although the effect on cardiovascular mortality did not reach statistical significance. Therefore, nitrendipine could improve cardiovascular mortality and morbidity in hypertensive patients. Further investigations are needed to examine whether nitrendipine is more beneficial to patients with essential hypertension and/or other cardiovascular diseases than ACE inhibitors or beta blockers.

We were able to assess the effects of antihypertensive drugs on the cardiac sympathetic nervous system with MIBG findings. In addition, because increased cardiac sympathetic nervous activity is associated with poor prognosis in heart disease and we have found that degrees of MIBG uptake and washout are different at each clinical stage of essential hypertension (43), MIBG findings in essential hypertension have implications with regard to clinical information about each patient's condition and a risk for developing cardiovascular complications.

Conclusions. In essential hypertension, enalapril improved MIBG kinetics, whereas nitrendipine had no effect on MIBG kinetics, although these drugs did not affect plasma norepi-

nephrine concentration. These results suggest that enalapril could suppress cardiac sympathetic activity, but nitrendipine had no effect on it in essential hypertension. Consideration of the different effects of antihypertensive drugs on the cardiac sympathetic nervous system may be helpful in finding more effective and beneficial treatments for patients with cardiovascular disease.

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