Clinical Efficacy of Efonidipine Hydrochloride, a T-type Calcium Channel Inhibitor, on Sympathetic Activities — Examination Using Spectral Analysis of Heart Rate/Blood Pressure Variabilities and $^{123}$I-Metaiodobenzylguanidine Myocardial Scintigraphy —

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Dihydropyridine Ca antagonists cause reflex tachycardia related to their hypotensive effects. Efonidipine hydrochloride has inhibitory effects on T-type Ca channels, even as it inhibits reflex tachycardia. In the present study, the influence of efonidipine hydrochloride on heart rate and autonomic nervous function was investigated. Using an electrocardiogram and a tonometric blood pressure measurement, autonomic nervous activity was evaluated using spectral analysis of heart rate/systolic blood pressure variability. Three protocols were used: (1) a single dose of efonidipine hydrochloride was administered orally to healthy subjects with resting heart rate values of 75 beats/min or more (high-HR group) and to healthy subjects with resting heart rate values less than 75 beats/min (low-HR group); (2) efonidipine hydrochloride was newly administered to untreated patients with essential hypertension, and autonomic nervous activity was investigated after a 4-week treatment period; and (3) patients with high heart rate values (≥75 beats/min) who had been treated with a dihydropyridine L-type Ca channel inhibitor for 1 month or more were switched to efonidipine hydrochloride and any changes in autonomic nervous activity were investigated. In all protocols, administration of efonidipine hydrochloride decreased the heart rate in patients with a high heart rate, reduced sympathetic nervous activity, and enhanced parasympathetic nervous activity. In addition, myocardial scintigraphy with $^{123}$I-metaiodobenzylguanidine showed significant improvement in the washout rate and H/M ratio of patients who were switched from other dihydropyridine Ca antagonists to efonidipine hydrochloride. Efonidipine hydrochloride inhibits increases in heart rate and has effects on the autonomic nervous system. It may be useful for treating hypertension and angina pectoris, and may also have a cardiac protective function. (Circ J 2003; 67: 139–145)

Key Words: Autonomic nervous function; Blood pressure variability; Efonidipine hydrochloride; Heart rate variability; T-type Ca channel

Recent molecular biology research has classified voltage-sensitive Ca channels into several types and shown how localization and function vary among these subtypes, which have been named L (long-lasting), T (transient), N (neuronal neither), P/Q (purkinje) and R (residual drug-resistant). L-type Ca channels are distributed in cardiac muscle, smooth muscle, and skeletal muscle, and act on excitation–contraction coupling (ie, vasoconstriction, enhancement of myocardial contractility). T-type Ca channels are distributed in the sinoatrial node, involved in pacemaker activity, and are not inhibited by standard Ca antagonists. P/Q-type Ca channel blockers decrease heart rate (HR), but do not influence cardiac contractility. A drop in the HR decreases cardiac muscle oxygen consumption and increases the ratio of the relaxation period, both of which may be effective in securing coronary blood flow.

Because efonidipine hydrochloride inhibits both L- and T-type Ca channels, it is called a dual Ca channel blocker. It may, therefore, differ from standard Ca antagonists in exhibiting protective effects on the heart. An L-type Ca channel antagonist, nifedipine, has been reported to enhance sympathetic nervous activity and reduce parasympathetic nervous activity; however, none of the previous studies have reported on the influence of efonidipine hydrochloride on autonomic nervous activity. In the present study, we investigated the influence of efonidipine hydrochloride on HR and autonomic nervous function using spectral analysis of heart rate/blood pressure (HR/BP) variabilities and sympathetic myocardial scintigraphy with $^{123}$I-metaiodobenzylguanidine (MIBG).

Methods

Single-Dose Oral Administration to Healthy Adults

The protocol included 12 healthy volunteers (7 men, 5 women, mean age: 37.2±6.1 years) without a history of
cardiovascular disorder whose physical findings, standard 12-lead electrocardiogram (ECG) and chest X-ray findings were normal. Patients with hypertension or diabetes mellitus, or who had taken medication that alters the autonomic function in the preceding month, were excluded.

The subjects were divided into 2 groups based on their resting HR in a supine position for 30 min: 6 subjects with a resting HR of 75 beats/min or more (high-HR group: 4 men, 2 women, mean age: 36.3±6.3 years) and 6 subjects with a resting HR less than 75 beats/min (low-HR group: 3 men, 3 women, mean age: 38.1±5.9 years).

A single dose of efonidipine hydrochloride (40 mg po) was administered at 08.00 h. The subjects had fasted from 20.00 h the day before the study and were requested to refrain from smoking for 3 h after drug administration. Water intake was controlled, with 200 ml given at the time of drug administration and again 2 h later. In addition, subjects were requested to refrain from consuming alcohol and foods/drinks containing caffeine during the day before the study and for 24 h after.

Before administration of efonidipine hydrochloride and at 1, 2, and 3 h after administration, the ECG and continuous tonometric monitoring of BP were carried out while the subject was resting in a supine position, and using spectral analysis of HR/BP variabilities, autonomic nervous activity was evaluated.

New Administration to Patients With Essential Hypertension

The protocol included 8 patients with essential hypertension (new-HT group: 5 men, 3 women, mean age: 63.1±9.3 years). Resting, seated systolic BP was measured twice in volunteers who had just completed 4 weeks of hypochloric diet therapy. We selected those patients who had a mean systolic blood pressure of 160 mmHg or greater, or a diastolic BP more than 95 mmHg despite this preparation. We excluded patients with severe hypertension (diastolic BP ≥120 mmHg), secondary or malignant hypertension, diabetes mellitus, arrhythmia, a history of myocardial infarction or stroke, liver injury, nephropathy, and autonomic neuropathy, as well as pregnant and lactating women. Ca antagonists, other than efonidipine hydrochloride, ß-blockers, sympathetic blocking agents, ß-blockers, ß-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor antagonists, vasodilators, autonomic agents, and any other agents that may influence BP and HR were not concurrently administered.

Efonidipine hydrochloride (40 mg/day) was administered with 200 ml of water 30 min after breakfast, and 4 weeks later, tonometric BP measurement and ECG were performed after a 30-min supine rest. Autonomic nervous activity was evaluated using spectral analysis of HR/BP variabilities.

Switching to Efonidipine Hydrochloride

The protocol included 8 patients with high HR (≥75 beats/min) who had received dihydropyridine L-type Ca channel inhibitors (ie, dihydropyridine Ca antagonists other than efonidipine hydrochloride, amiodipine besilate, and cilnidipine) for 1 month or more. These patients were switched to efonidipine hydrochloride (switching-HT group: 5 men, 3 women, mean age: 61.4±7.9 years). Prior to the administration of efonidipine hydrochloride, sustained-release nifedipine, manidipine hydrochloride, and nisoldipine had been prescribed in 4, 2, and 2 patients, respectively.

Once they had discontinued their original prescriptions, these patients began a program of 40 mg/day of efonidipine hydrochloride, administered with 200 ml of water 30 min after breakfast, and 4 weeks after switching, tonometric BP measurement and ECG were performed after a 30-min rest in the supine position. Autonomic nervous activity was evaluated using spectral analysis of HR/BP variabilities. In addition, 123I-MIBG myocardial scintigraphy was performed to evaluate cardiac sympathetic function in the switching-HT group, both before the switch and after 4 weeks of efonidipine hydrochloride therapy.

Written informed consent was obtained from all subjects after the following information was sufficiently explained: study purpose, significance, study methods, expected side effects, and the patient’s right to withdraw from the study at any time for any reason without disadvantage caused by such a decision.

Tonometric Measurement of BP and ECG Monitoring

Using a patient monitor (BP-508, COLIN Corp, Tokyo, Japan), real-time continuous measurement of BP and ECG monitoring were performed. To measure BP, a tonometric pulse pressure wave sensor was placed on the radial artery, and the beat-to-beat BP was noninvasively monitored. The pulse pressure sensor consists of 30 elements; it facilitates measurement of BP per beat by automatically correcting the element pulse pressure in each position and the BP measured by the oscillometric method.

Analysis of Autonomic Nervous Function

The data on continuous BP and ECG R-R data in each patient monitor were sent to a personal computer (Windows 98) via an RS232C device, and processed using software for analyzing autonomic nervous function (COLIN Corp).

Spectral analysis of systolic BP variability with tonometric continuous BP data was performed for 256 heartbeats; BP data in the presence of arrhythmia were excluded. For spectral analysis of systolic BP variabilities, heartbeat change spectra within the range of 0–0.5 Hz were analyzed using Hanning’s window. The low-frequency component (LF: power: 0.04–0.15 Hz), high-frequency component (HF: power: 0.15–0.40 Hz), and the LF/HF ratio were calculated.

Spectral analysis of HR variabilities based on the R-R interval on the ECG was performed using a similar algorithm. For 256 heart beats, the LF: power (0.04–0.15 Hz), HF: power (0.15–0.40 Hz), and LF/HF ratio were calculated.

123I-MIBG Myocardial Scintigraphy

Both planar and single photon emission computed tomography (SPECT) images were taken at 15 min (early images) and 3 h (delayed images) after an intravenous injection of 111 MBq of 123I-MIBG into the cubital vein. A 3-head rotating gamma camera (Prism 3000, Picker Inc, Ohio, USA) with a low-energy all-purpose collimator was used for imaging. Planar images were collected in a 256×256 matrix for 2–3 min; the collection time was 30 s/frame. For the SPECT imaging, 360-degree data were obtained taken using 72 image steps (5-degree steps; 24 directions×3 heads); a super computer (ODYSSEY, Shimazu Corporation, Kyoto, Japan) was used for data processing and analysis.

On the anterior planar images, regions of interest (ROIs)
Effects of Efonidipine on Autonomic Nervous Function

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Table 1 Changes in Autonomic Nervous Activity After Single-Dose Oral Administration of Efonidipine Hydrochloride in High-HR and Low-HR Groups

<table>
<thead>
<tr>
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<th>Time after administration (h)</th>
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<tr>
<td></td>
<td>Before</td>
<td>1</td>
<td>2</td>
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<tr>
<td>HR, heart rate</td>
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<td>BP, blood pressure</td>
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<td>LF (mmHg²/Hz)</td>
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<td>HF (mmHg²/Hz)</td>
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<td>LF/HF</td>
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<tr>
<td>HR variability</td>
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<td>LF (ms²/Hz)</td>
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<tr>
<td>LF/HF</td>
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</tbody>
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HR, heart rate; BP, blood pressure; LF, low frequency; HF, high frequency; LF/HF, ratio of LF power to HF power. Mean±SD, *p<0.05 vs Before.

Results

Single-Dose Oral Administration to Healthy Adults

The changes in the R-R interval on the ECG and the BP after single-dose oral administration of efonidipine hydrochloride were compared between the high-HR and low-HR groups (Fig 1). In the high-HR group, the R-R interval on ECG significantly increased 1–3 h after administration of efonidipine hydrochloride, whereas it significantly decreased 2 h after administration in the low-HR group. At 1–3 h after administration of efonidipine hydrochloride, systolic BP in both groups had decreased by approximately 10 mmHg from the baseline. There was no significant difference between the groups in the rate of decrease of BP.

Table 1 shows the changes in autonomic nervous activity after single-dose oral administration of efonidipine hydrochloride in both groups using spectral analysis of HR/systolic BP variabilities. In the high-HR group, there were significant decreases in the LF power and LF/HF ratio as well as a significant increase in the HF power after drug administration (p<0.05). Analysis of HR variabilities showed significant increases in both the LF and HF power and a decrease in the LF/HF ratio (p<0.05).

In the low-HR group, analysis of systolic BP variabilities showed significant decreases in both the LF and HF power after administration of efonidipine hydrochloride, as well as a significant increase in the LF/HF ratio (p<0.05). Analysis of HR variabilities showed a sig-
significant increase in the LFRR power and a significant decrease in the LFRR/HFRR ratio (p<0.05). There was no significant change in the LFRR power.

New Administration of Efonidipine Hydrochloride to Patients With Essential Hypertension

Fig2 shows the changes in BP and R-R interval on the ECG from the new-HT group. Administration of efonidipine hydrochloride significantly decreased both systolic and diastolic BP (p<0.05), significantly prolonged the R-R interval on ECGs (p<0.05), and reduced the HR.

Table 2 shows the changes in autonomic nervous activity in the new-HT group based on spectral analysis of HR/ systolic BP variabilities during the pre-treatment observation period and the 4 weeks after new administration of efonidipine hydrochloride. Analysis of systolic BP variabilities showed significant decreases in the LFRR power and LFRR/HFRR ratio, as well as a significant increase in the HFRR power after administration of efonidipine hydrochloride (p<0.05). Analysis of HR variabilities showed a significant increase in the HFRR power (p<0.05). There were no significant changes in the LFRR power or LFRR/HFRR ratio.

Table 2 Changes in Autonomic Nervous Activity Based on Spectral Analysis of Heart Rate/Systolic Blood Pressure Variabilities During Pre-Treatment Observation Period and After New Administration of Efonidipine Hydrochloride

<table>
<thead>
<tr>
<th>BP variability</th>
<th>Before treatment</th>
<th>4 weeks after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>LFRR (mmHg²/Hz)</td>
<td>0.64±0.29*</td>
<td>0.33±0.15*</td>
</tr>
<tr>
<td>HFRR (mmHg²/Hz)</td>
<td>12.2±2.33</td>
<td>2.15±1.31*</td>
</tr>
<tr>
<td>HR variability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF (ms²/Hz)</td>
<td>2.64±1.62</td>
<td>2.2±1.11</td>
</tr>
<tr>
<td>HF (ms²/Hz)</td>
<td>13.6±8.5</td>
<td>48.4±21.8*</td>
</tr>
<tr>
<td>LF/HF</td>
<td>3.28±1.08</td>
<td>2.64±1.95</td>
</tr>
</tbody>
</table>

HR, heart rate; BP, blood pressure; LF, low frequency; HF, high frequency; LF/HF, ratio of LF power to HF power. Mean±SD, *p<0.05 observation period vs 4 weeks after treatment.

Table 3 Changes in Autonomic Nervous Activity Based on Spectral Analysis of Heart Rate/Systolic Blood Pressure Variabilities During Administration of Other DHP Ca Antagonists and After Treatment With Efonidipine Hydrochloride

<table>
<thead>
<tr>
<th>BP variability</th>
<th>Before</th>
<th>After</th>
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</thead>
<tbody>
<tr>
<td>LFRR (mmHg²/Hz)</td>
<td>0.96±0.38</td>
<td>0.23±0.20*</td>
</tr>
<tr>
<td>HFRR (mmHg²/Hz)</td>
<td>0.26±0.11</td>
<td>0.35±0.25</td>
</tr>
<tr>
<td>HR variability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF (ms²/Hz)</td>
<td>35.4±19.2</td>
<td>41.0±17.1</td>
</tr>
<tr>
<td>HF (ms²/Hz)</td>
<td>23.6±18.5</td>
<td>45.4±13.8*</td>
</tr>
<tr>
<td>LF/HF</td>
<td>2.0±1.76</td>
<td>1.66±1.03</td>
</tr>
</tbody>
</table>

HR, heart rate; BP, blood pressure; LF, low frequency; HF, high frequency; LF/HF, ratio of LF power to HF power; DHP, dihydropyridine. Mean±SD, *p<0.05 Before vs After treatment.
Switching to Efonidipine Hydrochloride

Fig. 3 shows the changes in BP and R-R interval in the switching-HT group. After patients were switched to efonidipine hydrochloride, BP was favorably controlled without any significant changes. However, the R-R interval was significantly prolonged (p<0.05), and the HR was reduced.

Table 3 shows the results from spectral analysis of HR/systolic BP variabilities during administration of other dihydropyridine Ca antagonists and at 4 weeks after switching to efonidipine hydrochloride. There were significant decreases in the LF/HF and LF/HF ratio (p<0.05), but no significant changes in the HF/HR power. Analysis of HR variabilities showed a significant increase in the HR/HF ratio (p<0.05). There were no significant changes in the LF/HR power or LF/HF/HF ratio.

In the bull’s-eye images on MIBG myocardial scintigraphy, there were no significant decreases in perfusion before or after the start of treatment with efonidipine hydrochloride in the switching-HT group. The washout rates after administration of efonidipine hydrochloride were lower in the 4 patients who had been taking sustained-release nifedipine. Similar findings were obtained in all segments, including the septum, anterior wall, lateral wall, and inferior wall.

Fig. 4 shows the washout rates obtained from the bull’s eye images and planar images (Fig. 4A, B) and the delayed H/M ratio (Fig. 4C) before and after treatment with efonidipine hydrochloride in the switching-HT group. After administration, the washout rate significantly decreased (p<0.05) and in addition, the delayed H/M ratio significantly increased (p<0.05).

Discussion

The dihydropyridine Ca antagonist, efonidipine hydrochloride, inhibits both the L-type Ca and T-type Ca channels, as does mibefradil. In clinical practice, mibefradil reportedly inhibits increases in HR, and the results of the present study suggest that efonidipine hydrochloride, a T-type Ca channel inhibitor, reduced the HR and had favorable effects on the autonomic nervous system. Particularly in patients with higher HR, the agent decreased HR, reduced sympathetic nervous activity, and enhanced parasympathetic activity; it may also have protective effects for organs, including the heart.

The results of a clinical trial showed that efonidipine decreased BP in patients with mild to moderate essential hypertension. In particular, hypotensive reflex tachycardia, which is frequently observed after the administration of Ca antagonists, was rarely observed in hypertensive patients treated with efonidipine. In addition, the results of studies evaluating the efficacy of efonidipine also suggest it inhibits increased HR, and those findings provide one possible explanation for the low incidence of adverse reactions with efonidipine. An overall improvement rate of 73.3% was obtained in patients with angina pectoris after administration of efonidipine. A phase III clinical trial using a treadmill exercise tolerance test demonstrated that efonidipine significantly inhibited increases in HR during the exercise tolerance test, and in comparison with a preparation of nifedipine, it prolonged the maximal duration of exercise. Moreover, efonidipine showed significantly better results than nifedipine for improvement of exercise tolerance, overall improvement rates, and availability. Therefore, inhibition of increased HR by efonidipine might result in improved myocardial oxygen consumption and tissue blood flow in the ischemic region.

In the Framingham study, which demonstrated the correlation between increased HR and the incidence and mortality rates of cardiovascular diseases, patients were divided into 4 groups, based on HR (≤65, 66–74, 75–84, and ≥85 beats/min), before analysis. It was found that the incidence and mortality rates of cardiovascular diseases increased with the HR. When the patients are divided into 2 groups based on HR, the median HR. Therefore, we consider that it was appropriate to divide the present patients into 2 groups based on HR, using 75 beats/min as the marginal HR.

Influence of T-type Ca Channels on Heart Rate and Autonomic Nervous Activity

L-type Ca channels are abundant in the inherent cardiac muscle (ie, atrial and ventricular muscle), and are involved in the development of the action potential and excitation–contraction coupling. The density of T-type Ca channels in the inherent cardiac muscle is very low and they are not involved in excitation–contraction coupling. Recent studies have reported that T-type channels are involved in cardiac hypertrophy, remodeling after myocardial infarction, myocardial failure, and remodeling in atrial fibrillation.

Amlodipine besilate and cilnidipine have been reported to inhibit the release of noradrenalin from the sympathetic terminal by inhibiting the N-type Ca channels that are localized in the sympathetic nerve, thus inhibiting hypotension-related reflex tachycardia. T-type Ca channel inhibitors show potent hypotensive effects, as with the standard Ca antagonists. However, T-type Ca channel inhibitors have been reported to inhibit the hypotension-related increases in HR that compromise the effectiveness of many
Ca antagonists, and do not influence cardiac contractility. It has been reported that bradycardia depends on stimulation/frequency; that is, inhibitors of HR are more dramatically effective when the HR is initially high. Thus, in the present study, in the high-HR group of healthy adults, HR significantly decreased after single-dose administration of efonidipine hydrochloride, but there were no marked changes in the low-HR group.

The special resistance of the T-type agents to HR increase may be related to the relatively large number of T-type Ca channels present in the sinoatrial and atrioventricular nodes, and the impulse-conducting systems such as Purkinje’s fibers, and the important role these channels play in the formation and regulation of pacemaker potential. In other words, inhibition of the latter half of the slow depolarization phase (4th phase) of the sinoatrial node potential may decrease the HR. Therefore, T-type Ca channel inhibitors inhibit myocardial oxygen consumption while maintaining cardiac contractility, and may improve exercise tolerance and prevent myocardial ischemic attacks. These agents may be appropriate for patients with hypertension or angina pectoris.

Previous studies have reported the effects of T-type Ca channel inhibitors on autonomic nervous activity. Though nifedipine, which is selective for L-type channels, inhibits parasympathetic nervous activity, the T-type Ca channel inhibitor, mibebradil, has been reported to enhance parasympathetic nervous activity and favorably influence the autonomic nervous system. In the present study, analysis of HR/BP variabilities suggested that efonidipine hydrochloride, the only agent used as a T-type Ca channel inhibitor in clinical practice, not only enhances parasympathetic nervous activity, but also inhibits sympathetic nervous activity.

Changes in Autonomic Nervous Activity From the Spectral Analysis of Heart Rate/Blood Pressure Variabilities

Recent advances in computer technology have led to the widespread use of a procedure for evaluating autonomic nervous function based on HR/BP variabilities because it enables physicians to evaluate simultaneous changes in both sympathetic and parasympathetic activity.

The significance of the 3 autonomic parameters (ie, LFβ power, HFβ power, LFβ/HFβ ratio) in the analysis of BP variabilities differs slightly from those in the analysis of HR variabilities. Briefly, the LFβ power represents sympathetic nervous activity on the spectral analysis of BP variabilities, but the HFβ power and LFβ/HFβ ratio should by no means be regarded as indices of either parasympathetic or sympathetic activities.

In the present study, we investigated the influence of efonidipine hydrochloride on autonomic nervous activity using 2 procedures: analysis of HR variability and analysis of BP variability. The HFβ power in the analysis of HR variability was used as an index of parasympathetic nervous activity, whereas the LFβ power in the analysis of BP variability was used as an index of sympathetic nervous activity.

In patients to whom efonidipine hydrochloride was newly administered and in patients who were switched from other dihydropyridine Ca antagonists to efonidipine hydrochloride, sympathetic activity (ie, LFβ power) significantly decreased with decreases in HR, while parasympathetic activity (ie, HFβ power) significantly increased. Single-dose oral administration of efonidipine hydrochloride significantly decreased the LFβ power and significantly increased the HFβ power even in patients with a relatively high HR (≥75 beats/min). Our study suggests that these effects were not the result of simple hypotensive actions, but are related to the inhibitory effects of efonidipine hydrochloride on T-type Ca channels.

Changes in Cardiac Sympathetic Nervous Activity Evaluated Using Myocardial Scintigraphy With MIBG

In the present study, we did not evaluate blood concentrations of catecholamines. However, Nishiyama et al administered efonidipine to hypertensive patients for 3 months to evaluate its influence on plasma epinephrine and norepinephrine concentrations, and reported that the plasma norepinephrine concentration was only slightly increased within the normal range and that of plasma epinephrine did not significantly change during the observation period. In addition, another study in patients with essential hypertension demonstrated that plasma concentrations of norepinephrine and active renin did not significantly change in some patients during either the acute or chronic phase of the disease when amlodipine, an N-type Ca channel blocker that inhibits increased sympathetic nervous activity, was changed to efonidipine. Thus, plasma concentrations of nervous humoral factors have been frequently measured in order to evaluate sympathetic nervous activity. Some other studies have also suggested the inhibition of sympathetic nervous activity by efonidipine. In the present study, we evaluated changes in cardiac sympathetic nervous activity using 123I-MIBG myocardial scintigraphy.

In MIBG myocardial scintigraphy, cardiac sympathetic nervous activity is determined from the myocardial accumulation or washout of MIBG, a cardiac sympathetic nervous system analogue, MIBG. To evaluate cardiac autonomic nervous function, the accumulation of MIBG tracer, the H/M ratio, and the washout ratio (WR) of both the planar and Bull’s eye images are used as the data base. It has been reported that WR increases when cardiac sympathetic activity is enhanced.

In the present study, both the washout and H/M ratios significantly improved after administration of efonidipine hydrochloride to patients who had been switched from other dihydropyridine Ca antagonists. These results suggest that efonidipine hydrochloride inhibits sympathetic nervous activity, but the mechanisms of T-type Ca channels in nerves remain to be clarified by further research.

In conclusion, the present study suggests that efonidipine hydrochloride decreases the HR and exhibits favorable effects on the autonomic nervous system. This action may be very significant, as high HR and increased sympathetic nervous activity are important cardiovascular risks or factors influencing prognosis in patients with hypertension. Efondipine hydrochloride may prove an effective medication for hypertension and angina pectoris, and may exert a protective influence on the heart and other organs.

References


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