Relationship Between Calcium Channel Antagonists and Nocturnal Hypotension and Autonomic Imbalance in Patients With a Previous Myocardial Infarction

Hirofumi Tomiyama, MD; Goki Watanabe, MD; Koichiro Siojima, MD;
Eisuke Nishikawa, MD; Tuyoshi Nakayama, MD; Akira Yamamoto, MD;
Yasuro Ishikawa, MD; Hideo Yoshida, MD; Nobutaka Doba, MD

The present study was conducted to evaluate the effect of calcium channel antagonists on diurnal changes in blood pressure and on autonomic function in 71 patients who were receiving a calcium channel antagonist because they had previously suffered a myocardial infarction. Ambulatory blood pressures and Holter ECGs were recorded simultaneously for 24 h. Autonomic function was assessed by heart rate variability. Nocturnal systolic pressure was ≥ 90 mmHg in 63 patients (group I) and < 90 mmHg in 8 patients (group II). Significant day to night changes in high-frequency power (from 4.3 ± 1.2 to $4.5 \pm 1.0/m^2$) as well as in the ratio of low-frequency power to high-frequency power (from 1.3 ± 0.1 to 1.1 ± 0.2) were observed in group I, whereas such changes were blunted in group II. When the calcium antagonist was discontinued or the dose was reduced in group II, the autonomic imbalance improved along with elevation of nocturnal systolic blood pressure. Thus, nocturnal blood pressure should be monitored when such drugs are administered for the treatment of ischemic heart disease to a patient with a previous myocardial infarction. If nocturnal hypotension occurs, the dose should be reduced or the drug should be discontinued.

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Key Words: Calcium channel antagonist; Myocardial infarction; Heart rate variability

Calcium channel antagonists are often prescribed for patients with ischemic heart disease in order to increase coronary blood flow. Some of these drugs, however, exhibit a marked hypotensive effect that is harmful to ischemic hearts because of the impairment of coronary artery perfusion² and the aggravation of autonomic imbalance.^{3–5} Thus, assessment of changes in blood pressure levels resulting from these drugs is crucial in the management of ischemic heart disease. Owing to the circadian variation in blood pressure,⁶ casual blood pressure is not suitable for assessing the change in blood pressure caused by administered drugs. Ambulatory monitoring of blood pressure seems to be the most useful in this regard,^{7,8} if simultaneous ambulatory ECG monitoring is combined with cardiac ischemia. In addition, power spectral analysis of heart rate variability obtained

from ambulatory ECG monitoring has the potential benefit of quantifying the activity and changes in cardiac autonomic function^{9,10} and its blunting may indicate an increased risk of arrhythmic events after myocardial infarction.^{11,12} Nevertheless, few studies have examined the relationship of diurnal blood pressure levels, myocardial ischemia, and autonomic activity through the long-term administration of drugs for ischemic heart disease. In the present study, we obtained simultaneous recordings of ambulatory blood pressure and the electrocardiogram to assess the relationship between diurnal blood pressure variation, myocardial ischemia, and autonomic activity in patients who were receiving calcium channel antagonists following myocardial infarction. We also sought to determine whether or not myocardial ischemia and autonomic imbalance induced by hypotension are

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Division of Cardiology, Third Department of Internal Medicine, Teikyo University Ichihara Hospital, Ichihara, Chiba, Japan

Mailing address: Hirofumi Tomiyama, MD, Division of Cardiology, Third Department of Internal Medicine, Teikyo University Ichihara Hospital, 3426-3 Anezaki, Ichihara, Chiba 299-01, Japan

reversible.

Patients and Methods

The study was performed between February and May 1995 and involved 71 Japanese patients (age 38–77 years) at Teikyo University School of Medicine Ichihara Hospital who were diagnosed as having had a previous myocardial infarction based on their medical history, electrocardiogram, and coronary angiogram, and who were subsequently treated with a calcium channel antagonist. The protocol of this study was performed at least 6 months after the final myocardial infarction (mean 2.1 ± 1.8 years after the final attack). Excluded from the study were patients with atrial fibrillation or previous coronary bypass surgery, and those who had received a beta-blocker or an angiotensin-converting enzyme inhibitor; these drugs are reported to have a beneficial effect on sympathovagal balance.^{13,14} After informed consent had been obtained, each patient underwent simultaneous ambulatory monitoring of the electrocardiogram and of blood pressure during a normal working day. Ultrasonography and ^{99m}Tc radionuclide ventriculography were also performed to evaluate the morphology of the carotid artery and left ventricular function, respectively. The protocol of this study was approved by the Research Committee of Teikyo University Ichihara Hospital.

Blood Pressure Measurements

Casual blood pressure readings were obtained in the office setting with the patient seated using the manual K-sound method and a sphygmomanometer. Blood pressure was also determined by the same method with the patient in the supine position during ultrasonographic examination of the carotid artery.

Ambulatory Electrocardiographic Recording

Two-channel 24-h ECG recordings (lead CM2 and CM5) were obtained. Holter ECGs were analyzed with a Marquette 8500 scanner (Marquette Electronics, Milwaukee, USA). An ischemic episode was defined as at least 60 sec of horizontal or down-sloping ST-segment depression ≥ 1 mm measured 60 ms after the J-point, and an interval of at least 60 sec between 2 episodes. The standard deviation of all normal RR intervals in the entire 24-h ECG recording (SDNN) and the percent difference between the adjacent normal RR intervals > 50 msec that were computed over the entire 24-h ECG recording (pNN50) were obtained. Heart rate-period power spectra were computed for each 30-min segment of the Holter ECG

recordings. Power spectra were quantified by measuring the area under 2 frequency bandwidths: 0.04–0.15 Hz (low-frequency power, LF) and 0.15–0.40 Hz (high-frequency power, HF). The ratio of LF to HF (LF/HF) was also determined.

Ambulatory Blood Pressure Monitoring

Blood pressure was measured at 30-min intervals from 06.00 to 23.00 h and at 60-min intervals from 23.00 to 06.00 h (Model 90207, Spacelabs, Redmond, USA). The device was calibrated before the recordings by comparison with a mercury sphygmomanometer. All patients were asked to keep a diary and to describe notable events during their waking and sleeping times, and the time spent indoors. We eliminated a pulse pressure < 15 mmHg, a systolic pressure < 70 mmHg, and/or a diastolic pressure < 40 mmHg as erroneous readings.

Definition of Ambulatory Monitoring

Blood pressure and Holter ECG measurements were analyzed at 3 periods taken from the diary: while awake in the daytime (between waking up in the morning and 19.00 h), while awake at night (between 19.30 h until the patient goes to bed), and while asleep (between going to bed and awakening). Diary entries confirmed that all patients remained at home after 19.00 h during the study. Ambulatory monitoring variables were defined as the mean of variables in each period.

Coronary Angiography

Coronary angiography was performed on all subjects up to 3 months before the ambulatory monitorings. Angiograms were evaluated visually, assisted by calipers, with an approximation of the reduction in lumen size for each coronary vessel (left descending artery, circumflex artery, and right coronary artery). Vessels with narrowing that exceeded 75% of the lumen diameter were defined as being significantly stenosed.

Definition and Management of Nocturnal Hypotension

Nocturnal hypotension was defined as a mean systolic pressure during sleeping < 90 mmHg. Patients who were found to have nocturnal hypotension received a reduced dose of the calcium channel antagonist, or the drug was discontinued altogether. Ambulatory Holter ECG and blood pressure monitoring were again repeated 1 or 2 months later.

^{99m}Tc Radionuclide Ventriculography

Recordings were obtained in the supine position and

Table 1 Clinical Characteristics of 71 Patients

	Group I	Group II	p value
Number of patients	63	8	ns
Gender (male/female)	51/12	6/2	ns
Age (years)	59±10	63±10	ns
BMI	23.5±2.1	24.8±2.3	ns
CPs (mmHg)	128±13	117±13	p<0.05
CPd (mmHg)	80±7	73±12	ns
DM	12	2	ns
HBP	27	3	ns
Diseased artery	1.5±0.7	1.8±0.7	ns
EF (%)	50.8±7.6	48.0±7.6	ns
Plaque score	1.8±1.1	2.1±1.2	ns
Carotid Dis (%kPa)	1.8±0.5	1.3±0.2	ns
Nifedipine	30	6	p<0.05
5 mg×3 times/day (B, L, D)	2	1	ND
10 mg×3 times/day (B, L, D)	2	0	ND
5 mg×4 times/day (B, L, D, S)	9	2	ns
10 mg×4 times/day (B, L, D, S)	17	3	ns
Nifedipine long-acting	14	2	ns
20 mg×2 times/day (B, D)	2	0	ND
20 mg×2 times/day (B, S)	7	1	ns
40 mg×2 times/day (B, D)	3	1	ND
40 mg×2 times/day (B, S)	2	0	ND
Diltiazem	17	0	p<0.05
20 mg×2 times/day (B, D)	3	0	ND
30 mg×3 times/day (B, L, D)	14	0	p<0.05
Diltiazem long-acting	2	0	ND
Nitrates	63	8	ns
Nicorandil	22	2	ns

Group I vs group II; ND, not determined; BMI, body mass index; CPs, casual systolic blood pressure; CDd, casual diastolic blood pressure; DM, number of patients with diabetes mellitus; HBP, number of patients with hypertension; EF, left ventricular ejection fraction; Nifedipine, number of patients receiving nifedipine; Nifedipine long-acting, number of patients receiving a long-acting nifedipine; Diltiazem, number of patients receiving diltiazem, Diltiazem long-acting=number of patients receiving a long-acting diltiazem; Nitrates, number of patients receiving nitrates; Nicorandil, number of patients receiving nicorandil; B, take drugs after breakfast; L, take drugs after lunch; D, take drugs after dinner; S, take drugs before go to bed.

the left ventricular ejection fraction was calculated by using the multiple-gated method (Gamma-view R-d, Hitachi, Tokyo) in the left oblique projection.

Ultrasonographic Carotid Artery Examination

Recordings were performed with the patient in the supine position and with the neck slightly hyperextended. The carotid sinus and bifurcation were examined using a 7.5-MHz transducer (SSH140, Toshiba, Tokyo). Atherosclerotic plaque was defined as a thickening of the wall at least 50% greater than that of the surrounding wall. Plaque was measured in the B-mode image, and the plaque score was assigned¹⁵ The B-mode image-guided short-axis M-mode tracings of the common carotid artery approximately 1 cm proximal to the carotid sinus were obtained, and distensibility of the common carotid artery was calculated

according to the following formula¹⁶

$$100 \times (Ds^2 - Dd^2) / [Dd^2 \times (SBP - DBP)]$$

(1 kPa=7.6 mmHg)

where Ds=diameter of right common carotid artery at systole, Dd=diameter of right common carotid artery at diastole, SBP=systolic pressure measured during the ultrasonographic examination of the carotid artery, and DBP=diastolic pressure during the ultrasonographic examination of carotid artery.

Statistics

Data are expressed as means±SD. Statistical analyses were performed by using the SPSS software package (SPSS, Chicago, IL, USA). Differences between 2 groups were evaluated by Wilcoxon's test

Table 2 Variables of Blood Pressure, Heart Rate Variability and Electrocardiogram in Patients With and Without Nocturnal Hypotension

	Group I	Group II	p value
PsD (mmHg)	122±13	110±9	$p<0.01$
PsNa (mmHg)	119±15**	103±9**	$p<0.01$
PsNs (mmHg)	110±14***††	88±2***††	$p<0.01$
PsNsL (mmHg)	92±4	80±3	$p<0.01$
PdD (mmHg)	76±9	66±7	$p<0.01$
PdNa (mmHg)	72±10**	63±9**	$p<0.01$
PdNs (mmHg)	68±8***††	56±5***††	$p<0.01$
PdNsL (mmHg)	54±5	46±3	$p<0.01$
HRD (beats/min)	78±10	77±7	ns
HRNa (beats/min)	72±9**	72±8**	ns
HRNs (beats/min)	63±10***††	64±9***††	ns
TP24 (ln(ms ²))	6.6±1.0	6.6±0.9	ns
TPD (ln(ms ²))	6.6±1.1	6.6±0.6	ns
TPNa (ln(ms ²))	6.4±0.9	6.4±0.7	ns
TPNs (ln(ms ²))	6.7±0.9	6.6±0.5	ns
LF24 (ln(ms ²))	5.3±1.1	5.3±1.0	ns
LFD (ln(ms ²))	5.5±1.3	5.5±0.6	ns
LFNa (ln(ms ²))	5.2±1.1*	5.2±0.8	ns
LFNs (ln(ms ²))	5.3±1.1	5.3±0.7	ns
HF24 (ln(ms ²))	4.3±1.0	4.3±1.0	ns
HFD (ln(ms ²))	4.3±1.2	4.3±1.1	ns
HFNa (ln(ms ²))	4.3±1.0	4.3±1.0	ns
HFNs (ln(ms ²))	4.5±1.0*†	4.3±0.8	ns
LF/HF24	1.2±0.2	1.3±0.2	ns
LF/HLD	1.3±0.1	1.3±0.1	ns
LF/HFNa	1.2±0.1*	1.3±0.2	ns
LF/HFNs	1.1±0.2***†	1.2±0.2	ns
SDNN (ms)	122±37	155±32	ns
pNN50 (%)	6.4±5.3	6.0±6.0	ns
PVCD (beats/h)	5±10	26±57	ns
PVCNa (beats/h)	3±8	34±80	ns
PVCNs (beats/h)	4±8	13±30	ns
PVCrD (times/h)	0.03±0.07	0.13±0.27	ns
PVCrNa (times/h)	0.16±1.05	0.03±0.08	ns
PVCrNs (times/h)	0.02±0.13	0.02±0.06	ns
STDD	16	2	ns
STDNa	8	1	ns
STDNs	9	2	ns

Group I vs group II; * $p<0.05$, ** $p<0.01$ compared with daytime, † $p<0.05$, †† $p<0.01$, compared with night-time waking. Ps, systolic pressure; Pd, diastolic pressure; HR, heart rate; TP, total power; LF, low frequency power; HF, high frequency power; LF/HF, ratio of low frequency power and high frequency power; SDNN, standard deviation of all normal RR interval in the 24-h ECG recording; pNN50, percent of difference between adjacent normal RR intervals >50 ms in the 24-h ECG recording; PVC, number of isolated paroxysmal ventricular conduction in 1 h; PVCr, times of runs of paroxysmal ventricular conduction; STD, number of patient who had ischemic episode in 24-h ECG monitoring; 24, 24-h; D, daytime; Na, night-time waking; Ns, night-time sleeping; NsL, lowest blood pressure at night-time sleeping.

Fig 1. Effects of adjusting medication on blood pressure and autonomic functions in patients with nocturnal hypotension. Open circle, before adjusting medication; closed circle, after adjusting medication; LF, low-frequency power; HF, high-frequency power; LF/HF, ratio of low-frequency power and high-frequency power; D, daytime; Na, awake at night; Ns, asleep at night. * $p<0.05$ compared with before changing medication, † $p<0.05$ compared between awake at night and asleep at night.

or by the chi-squared test. Within-group comparisons were performed by Student's t test. A level of $p<0.05$ was accepted as statistically significant.

Results

Of the 71 patients, 63 patients exhibited a systolic pressure during sleep ≥ 90 mmHg (group I), whereas 8 patients exhibited a systolic pressure during sleep <90 mmHg (group II). Table 1 lists their clinical characteristics. Age, gender, cardiac systolic function, the

Table 3 Changes in Medication to Alleviate Nocturnal Hypotension in 8 Patients

<i>Patients no.</i>	<i>Age/Sex</i>	<i>Initial medication</i>	<i>Adjust in medication</i>
1	70/M	Nifedipine 15 mg Isosorbide dinitrate 60 mg Nicorandil 30 mg	Discontinued Continued Continued
2	67/F	Nifedipine 40 mg Isosorbide dinitrate 40 mg Aspirin 100 mg	Discontinued Continued Continued
3	46/M	Nifedipine 20 mg Isosorbide dinitrate 60 mg	Discontinued Continued
4	54/M	Nifedipine 40 mg Isosorbide dinitrate 40 mg	Amlodipine 5 mg Continued
5	65/M	Nifedipine 20 mg Isosorbide dinitrate 80 mg	Discontinued Continued
6	66/M	A long-acting nifedipine 40 mg Isosorbide dinitrate 40 mg Aspirin 100 mg	Discontinued Continued Continued
7	66/M	A long-acting nifedipine 80 mg Isosorbide dinitrate 80 mg Nicorandil 30 mg	A long-acting nifedipine 40 mg Continued Continued
8	60/F	Nifedipine 40 mg Isosorbide dinitrate 20 mg Aspirin 100 mg	Discontinued Isosorbide dinitrate 40 mg Continued

number of diseased arteries, area of infarction, the distensibility of the carotid arteries, and heart rate were similar in both groups. However, a significantly larger portion of patients in group II than in group I received a short-acting nifedipine and none of the patients in group II received diltiazem.

Table 2 represents the ambulatory monitoring variables in the 2 groups. The HF values increased and the LF/HF ratio decreased significantly from waking to sleeping at night in group I, whereas these changes were blunted in group II. These 2 groups did not differ as to the number of ventricular arrhythmias or the number of patients with ischemic episodes. The increase in systolic blood pressure from 1 h before awakening to 1 h after awakening (group I= 10 ± 5 mmHg, group II= 11 ± 6 mmHg) and heart rate during the ambulatory recordings were similar in both groups. In group II, the number of ventricular arrhythmias was similar while sleeping at night and during normal daytime activities. Management of the 8 patients with nocturnal hypotension is summarized in Table 3.

Anginal attacks were not aggravated by changing the dosage or by discontinuing the drugs, namely the calcium channel antagonist nifedipine. A dosage reduction or the discontinuation of nifedipine led to a significant increase in systolic and diastolic blood

pressure during sleep (from $88 \pm 2/56 \pm 5$ mmHg to $108 \pm 10/67 \pm 8$ mmHg, $p < 0.01$). This adjustment (changing the dosage of or discontinuing the drugs), however, did not alter the number of ventricular arrhythmias, nor did it affect the number of patients who experienced ischemic episodes while asleep at night.

The pNN50 increased from $6.0 \pm 6.0\%$ to $6.6 \pm 5.8\%$ ($p < 0.05$), whereas the HF, LF, and LF/HF ratio and SDNN did not change during the 24-h ECG recording. However, the HF values increased and the LF/HF values decreased significantly between waking and sleeping at night (Fig 1).

Discussion

Although most drugs administered for the treatment of ischemic heart disease exert a hypotensive effect, it is not clear how they affect the diurnal changes in blood pressure, myocardial ischemia, or autonomic activity. The present study assessed the usefulness of ambulatory blood pressure monitoring in determining the effects of antihypertensive drugs, mainly calcium channel antagonists used to treat ischemic heart disease, on the diurnal change in blood pressure. Simultaneous recording of ambulatory blood pressure

and electrocardiogram in the present study demonstrated that 8 of 71 patients with previous myocardial infarction who were receiving a calcium channel antagonist developed nocturnal hypotension in the absence of diurnal changes in heart rate variability. Most of these patients received a short-acting formulation of nifedipine and none received diltiazem. When nocturnal systolic blood pressure rose after an adjustment in drug dose, or after drug discontinuance, the absence of diurnal change in heart rate variability also improved without changing electrocardiographic ST-segment depression. This appears to be the first report suggesting that nocturnal hypotension induced by a calcium channel antagonist, namely nifedipine, in patients with ischemic heart disease is related to an autonomic imbalance, which, however, can be ameliorated by reducing the dose or discontinuing the medication.

Autonomic function is assessed by several methods, including baroreceptor sensitivity,¹⁷ direct recording of muscular sympathetic activity,¹⁸ and analysis of heart rate variability.^{19,20} The analysis of heart rate variability is appropriate for evaluating the relationship between diurnal changes in autonomic balance and blood pressure levels, in a non-invasive and continuous manner. A study of the circadian pattern of heart rate variability in normotensive subjects demonstrated that LF and LF/HF fell to a minimum, whereas HF peaked at night.²¹ In the present study, whereas patients without nocturnal hypotension demonstrated patterns of LF, HF, and LF/HF similar to those seen in normotensive subjects, those with nocturnal hypotension demonstrated a reduction in the circadian pattern of HF and LF/HF. Just as loss of oscillations (significant changes from waking to sleeping) in HF, LF, and LF/HF has been demonstrated in patients with autonomic neuropathy,²² we similarly defined autonomic imbalance as a loss of oscillations in these power components. The autonomic imbalance in patients with nocturnal hypotension was corrected by elevating the nocturnal systolic pressure. pNN50, a parameter of heart rate variability, also improved.

It is essential to understand the pathophysiology underlying autonomic imbalance induced by drug administration. The severity of cardiac dysfunction or the number of diseased coronary arteries has been correlated with the severity of the autonomic imbalance.²³ Our previous study extended these findings by demonstrating that the impaired distensibility of the common carotid artery is related to an impairment of baroreceptor sensitivity in patients with coronary heart disease.¹⁶ However, in the present study, the incidence of factors known to influence autonomic function, such as cardiac systolic function,

number of diseased coronary arteries, presence of hypertension or diabetes mellitus, and distensibility of the common carotid artery, were similar in patients with or without nocturnal hypotension.

Myocardial ischemia has been shown to aggravate an existing autonomic imbalance.²⁴ If nocturnal hypotension induced cardiac ischemia in the present study, autonomic imbalance likewise could have been caused by myocardial ischemia. The severity of cardiac ischemia is assessed by evaluating changes in the ST segment and the increase in the number of arrhythmias using ambulatory electrocardiographic monitoring.²⁵⁻²⁷ However, these parameters never worsened during the period of nocturnal hypotension. In addition, management of nocturnal hypotension did not alter the change in ST segment or number of arrhythmias. Thus, our results did not support the concept that nocturnal hypotension contributes to autonomic imbalance mediated by myocardial ischemia.

As discontinuance or reduction in dosage of the calcium channel antagonist lessened the severity of nocturnal hypotension and autonomic imbalance, we offer 2 possible explanations for autonomic imbalance: nocturnal hypotension induced by the administration of a calcium channel antagonist either aggravated the autonomic imbalance or it induced marked autonomic imbalance and nocturnal hypotension in those patients with a latent autonomic imbalance. The present results do not explain why a calcium channel antagonist would induce nocturnal hypotension and autonomic imbalance in some patients with a previous myocardial infarction. However, casual systolic blood pressure in patients who had nocturnal hypotension was lower than that in patients without nocturnal hypotension, and casual systolic blood pressure <120 mmHg may be a marker to evaluate those patients who experience nocturnal hypotension while undergoing treatment with calcium channel antagonists. Further studies regarding the effects of antihypertensive drugs on blood pressure and autonomic balance are needed for a more effective treatment of ischemic heart disease.

Study Limitation

In the present study, 6 of the 8 patients with nocturnal hypotension received the short-acting calcium channel antagonist nifedipine, which belongs to a class of dihydropyridines, whereas none of these patients received diltiazem, a benzothiazepine. It has been reported that the deteriorative effects of a short-acting dihydropyridine such as nifedipine can adversely affect cardiovascular mortality.⁴ The hypotensive effect is more prominent in nifedipine than in diltiazem.²⁸ However, the present study did not investigate

whether nocturnal hypotension and autonomic imbalance could be induced by drugs other than a short-acting formulation of nifedipine.

According to the so-called "J-curve" hypothesis, an excessive lowering of diastolic blood pressure can increase the risk of coronary artery disease.²⁹ Regardless of the J-curve phenomenon, however, it is recommended that the blood pressure be maintained below 140/90 mmHg.³⁰ Although the present study arbitrarily defined nocturnal hypotension as a nocturnal systolic pressure <90 mmHg, the critical systolic blood pressure that would aggravate autonomic balance is an elusive variable that still remains to be determined. In addition, heart rate variability recorded from 24-h ECG used the risk stratification of after myocardial infarction. In this study, with the exception of pNN50, time-domain and frequency-domain analyses of 24-h ECG recording did not improve after reversal of nocturnal systolic blood pressure in patients with nocturnal hypotension. It is clear whether the increase in heart rate variability in patients after myocardial infarction improves the prognosis of such patients in a clinical setting. Thus, further evaluations are required to evaluate the clinical significance of drug-induced nocturnal hypotension and autonomic imbalance in patients after myocardial infarction. In addition, calcium channel antagonists are frequently prescribed for hypertension or angina pectoris, and the clinical significance of drug-induced nocturnal hypotension and autonomic imbalance should also be evaluated in patients with these pathophysiological conditions.

The reproducibility of ambulatory monitoring has already been discussed elsewhere.^{31,32} In this study, in 7 of 63 patients who did not demonstrate nocturnal hypotension repeated ambulatory blood pressure monitoring and 24-h ECG recording were successful; all of them showed diurnal changes in heart rate variabilities and did not demonstrate nocturnal hypotension.

Conclusion

The administration of a calcium channel antagonist induced nocturnal hypotension associated with autonomic imbalance in some patients with a previous myocardial infarction; ambulatory blood pressure monitoring is useful in such patients during medication to avoid drug-induced autonomic imbalance.

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