Use of heart rate spectral analysis to study the effects of calcium channel blockers on sympathetic activity after myocardial infarction

We used spectral analysis of heart rate variability (HRV) to study the effects of the calcium channel blockers diltiazem and nifedipine and the β-blocker metoprolol on the sympathetic nervous system in patients following myocardial infarction. Energy in the low-frequency range (0.04 to 0.12 Hz) in the standing (tilt) position was used as a quantitative index of sympathetic activity. Twenty-seven male patients, mean age 62 ± 13 years, were studied 2 to 6 weeks after myocardial infarction. Eight patients received metoprolol, 100 mg twice daily; nine patients received diltiazem, 60 mg three times daily; and 10 patients received nifedipine, 10 mg three times daily. HRV and arterial blood pressure were recorded before and 5 to 7 days after initiation of therapy. None of the drugs had significant effects on the systolic blood pressure, and only nifedipine significantly reduced the diastolic blood pressure. Metoprolol and diltiazem reduced the low-frequency HRV in all patients studied, but nifedipine had no consistent effects. Our results suggest that diltiazem had a depressant effect on sympathetic activity similar to β-adrenergic blockers. This effect was not observed with nifedipine. The reduction in sympathetic activity by diltiazem may contribute to its therapeutic effects in the post-infarction period. (Am Heart J 1990;119:79.)

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Not since the introduction of β-adrenergic blockers has a class of drugs emerged as important in the treatment of cardiovascular disease as the calcium (Ca^{2+}) channel blockers. Some experimental studies have suggested that Ca^{2+} channel blockers may interfere with the release of noradrenaline from sympathetic nerve endings and that part of their action in vivo may be explained by a reduction of sympathetic activity.[1, 2] While the clinical effects of calcium channel antagonists resemble somewhat those of β-blockers, their clinical protective effects are not as consistent.[3-8] These differences may be related in part to varying effects of these drugs on the sympathetic nervous system.

Spectral analysis of heart rate variability has recently been shown to be a reliable noninvasive test for quantitative assessment of cardioneural regulatory responses.[9-16] In the standing position, spectral energy in the low-frequency range (0.04 to 0.12 Hz) has been suggested as a quantitative index of sympathetic activity[9-12] and can be suppressed by β-adrenergic blocking agents.[10-13] We utilized this technique to determine whether the Ca^{2+} channel blockers diltiazem and nifedipine in therapeutic doses modulate the sympathetic nervous system and to compare their effects with the β-blocking agent metoprolol in the post-infarction patient.

METHODS

Patients. Twenty-seven male patients, ages 40 to 78 years (mean ± standard deviation, 62 ± 13 years), who had previous myocardial infarction based on clinical, electrocardiographic, and enzymatic criteria were included in the study. All patients were studied within 2 to 6 weeks after myocardial infarction. Patients with congestive heart failure, renal insufficiency, diabetes, neuropathy, or electrocardiographic (ECG) evidence of sinus node dysfunction were excluded from the study. None of the patients showed changes in systolic blood pressure of more than 10 mm Hg when tilted from the supine to the standing position. None of the patients was receiving any cardioactive drugs or angiotensin-converting enzyme inhibitor drugs at the time of the study. All patients were in sinus rhythm and had a QRS interval of less than 0.1 second in duration. Patients with frequent premature beats were excluded

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Supported in part by Grant HL 31341 from the National Institutes of Health, Bethesda, Md., and by Coronary Heart Disease Research, a Program of the American Heart Assistance Foundation.

Received for publication Apr. 24, 1989; accepted Aug. 15, 1989.

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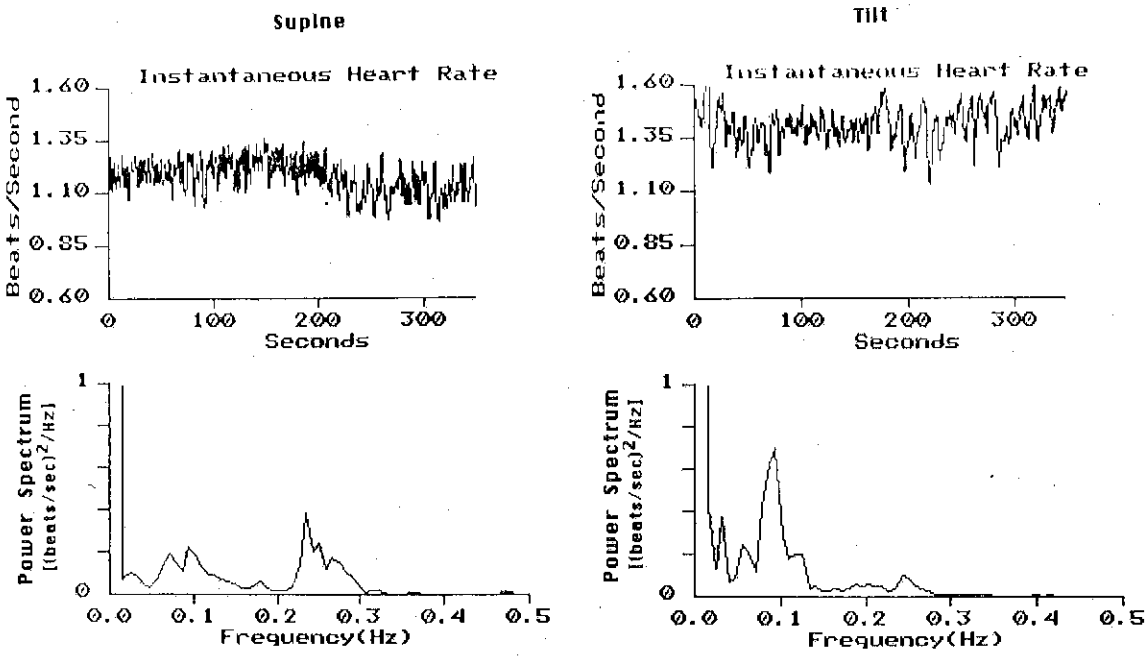

Fig. 1. Response of heart rate power spectrum to changes in posture. Instantaneous heart rate *(IHR)* is shown on the *top* and power spectrum on the *bottom*. Note relatively small low-frequency peak and prominent high-frequency peak in supine position. During tilt, the peak of the low-frequency oscillations significantly increased while the high-frequency peak markedly diminished. The power spectrum is measured as $[(\text{beat/sec})^2/\text{Hz}] \times 10^{-3}$.

Table I. Clinical characteristics of study groups

	Metoprolol	*Diltiazem*	*Nifedipine*	*p*
No. of patients	8	9	10	
Age, mean ± SD (yr)	63 ± 8	66 ± 7	65 ± 13	NS
Site of MI				
Anterior	3	3	4	NS
Inferior	5	6	6	NS
LVEF (%)	53 ± 7	48 ± 8	46 ± 12	NS

MI, Myocardial infarction; LVEF, left ventricular ejection fraction.

from the study. Patients were assigned sequentially to one of the three test drugs. Patients received either metoprolol, 100 mg twice daily; diltiazem, 60 mg three times daily; or nifedipine, 10 mg three times daily. Serum drug levels were not obtained but patient compliance was tested by counting the number of pills in the returned bottles. Only patients with 100% compliance were included in the analysis. Eight patients receiving metoprolol, 9 patients receiving diltiazem, and 10 patients receiving nifedipine completed the study protocol.

Study Protocol. All patients gave their written consent after being informed about the study and they were all in a stable condition. Patients were studied on an electrically driven tilt table connected to an Electronics for Medicine VR 12 physiologic recorder (PPG Biomedical Systems, Pleasantville, N.Y.) and an eight-channel FM tape recorder (No. 3968A, Hewlett-Packard Co., Andover, Mass.) connected to the ECG signal. After a period of 20 to 30 minutes for stablization, a continuous two-lead ECG recording for 20 minutes was obtained in the supine position. The ECG was recorded for another 20 minutes after the table was passively moved to an upright 90-degree position (tilt position). All recordings were made between 10 AM and 12 noon. Every patient received one of his scheduled doses at 6 AM every day of therapy including the day of testing. Control recordings were obtained before the initiation of drug therapy. Each patient was restudied 5 to 7 days after the initiation of therapy. The arterial blood pressure was measured by a sphygmomanometer in both the supine and tilt positions. All patients were breathing normally within a frequency of 12 to 15/min.

Data analysis. The ECG was recorded onto FM tape (4.75 cm/sec) and played back at the same speed for analysis of heart rate variability (HRV). Of the 20 minutes of ECG recording, the last 10 minutes were utilized for analysis of HRV. The ECG signals were band-pass filtered between 0.01 to 100 Hz and a QRS timing circuit was used to generate an accurate pulse for each normal QRS complex, rejecting premature ventricular beats and noise.[17] The triggered pulses corresponding to each R wave were sampled at 1000 Hz and approximately 600 R-R intervals were stored in the computer. The non-sinus beats were recognized according to interval criteria, and were corrected using an interpolation algorithm.[17] The instantaneous heart rate (IHR) was calculated according to previously published algorithm.[18,19] A measure of overall HRV was provided by the standard deviation of IHR.

Frequency analysis of IHR data was done by performing power spectrum calculations on approximately 10 minutes of IHR by fast Fourier transform based on a windowed

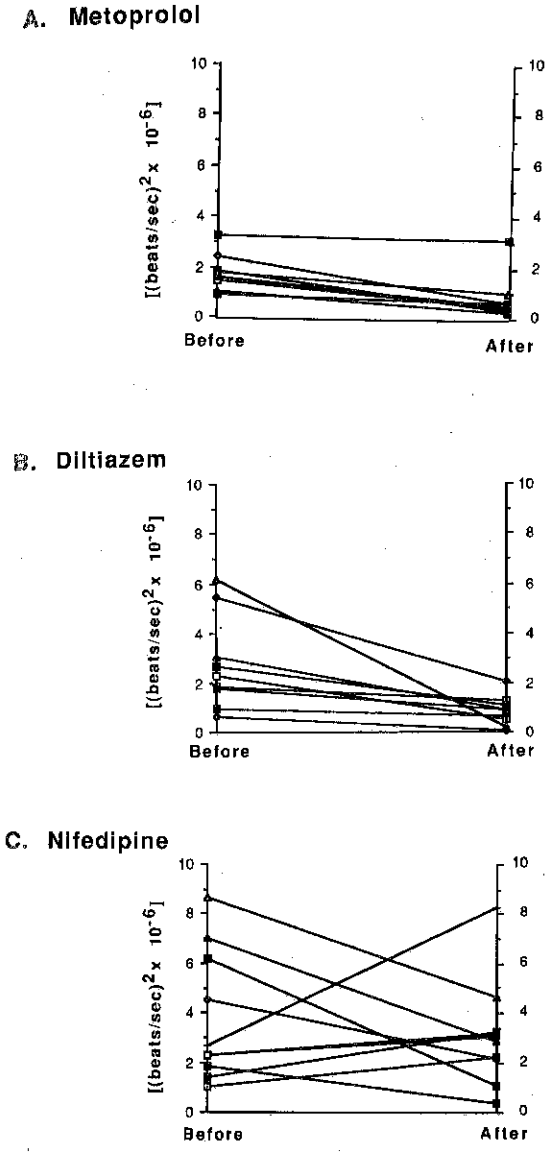

Fig. 2. Graphic representation of the effects of metoprolol, diltiazem, and nifedipine on low-frequency energy during tilt in individual patients. See text for details.

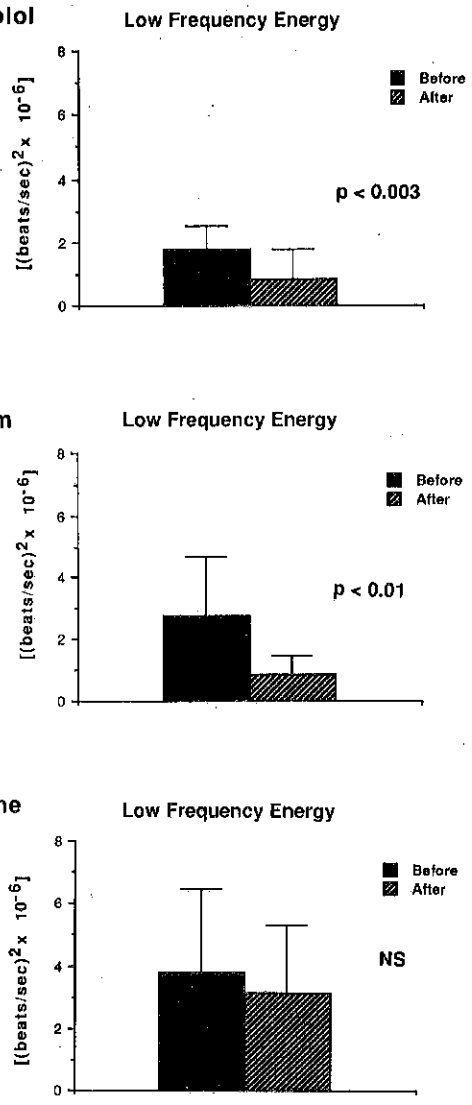

Fig. 3. Mean and standard deviation of low-frequency energy during tilt in patients before and after metoprolol, diltiazem, and nifedipine. Both metoprolol and diltiazem resulted in significant reduction of low-frequency energy.

periodogram technique.[18, 19] The power spectral energy was expressed in (beats/sec)$^2 \times 10^{-6}$. The spectral density estimations for different ranges of frequency from 0.0 to 0.5 Hz were calculated.

In the supine position, there were two frequency bands of interest: a low-frequency band (0.04 to 0.12 Hz) and a high-frequency band (0.22 to 0.28 Hz).[9, 11] In the tilt position the peak within the low-frequency band, occurring approximately at 0.1 Hz, increased by five- to 10-fold from supine values, while both the area and peak of the high-frequency band were markedly decreased[11] (Fig. 1). The high-frequency band is a direct measure of respiratory sinus arrhythmia.[9, 11, 12] On the other hand, the energy within the low-frequency band in the tilt position is a quantitiative index of sympathetic activity.[9-13] We therefore confined our analysis to the effects of metoprolol, diltiazem, and nifedipine on the low-frequency energy in the tilt position.

Statistical analysis. The difference in the low-frequency spectral energy during tilt between the three patient groups was analyzed by nonpaired Student's t test. The spectral energy of the low-frequency band, the mean and standard deviation of IHR, and the mean and standard deviation of the R-R interval in the tilt position before and after administration of the tested drug were compared using a paired Student's t test. Differences were considered significant at $p < 0.05$.

RESULTS

Table I summarizes the clinical data in the study groups. There was no significant difference in age, site of infarction, left ventricular ejection fraction,

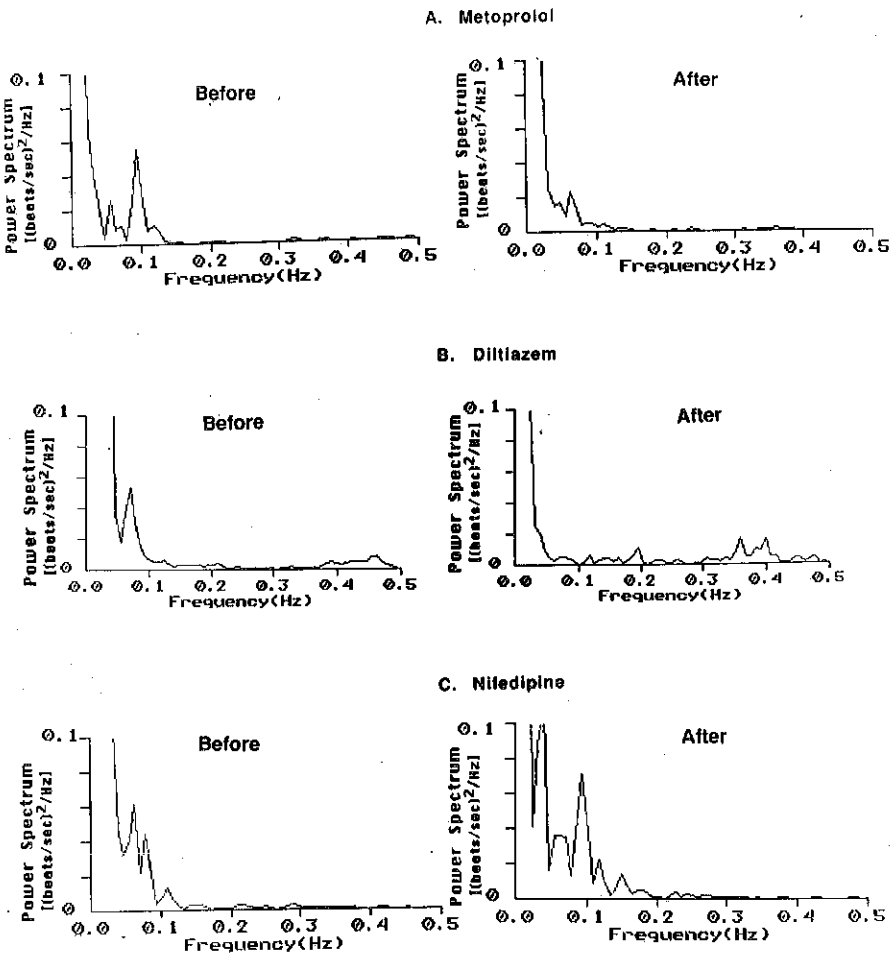

Fig. 4. Illustrative examples of power spectra during tilt position in three patients who received metoprolol **(A)**, diltiazem **(B)**, or nifedipine **(C)**. Both metoprolol and diltiazem resulted in significant reduction of the low-frequency energy, while nifedipine resulted in an increase of the low-frequency energy. The power spectrum is measured as $[(\text{beat/sec})^2/\text{Hz}] \times 10^{-3}$.

and time of study in the post-infarction period between the three groups.

Arterial blood pressure. In all patients there was a decrease in both systolic and diastolic pressures in the standing position after they had received the tested drug, but this reduction did not reach statistical significance except for nifedipine (Table II). Nifedipine significantly reduced the diastolic arterial pressure from a mean of 91 ± 12 mm Hg to 80 ± 10 mm Hg ($p < 0.05$).

Heart rate analysis. The effects of metoprolol, diltiazem, and nifedipine on the mean and standard deviation of IHR, and the R-R interval and its standard deviation, are shown in Table II. Metoprolol significantly reduced the mean IHR and its standard deviation ($p < 0.01$). Diltiazem resulted in a slight and insignificant decrease in mean IHR. However, there was a significant decrease in HRV represented by a decrease in IHR standard deviation ($p < 0.05$). Nifedipine did not have a significant effect on IHR or its standard deviation.

The mean R-R interval was significantly reduced by metoprolol ($p < 0.01$) and was not affected by diltiazem or nifedipine. None of the drugs tested changed the standard deviation of the R-R interval significantly.

Effects on spectral energy. There was some variability among the three study groups in terms of the mean and standard deviation of the low-frequency spectral energy during tilt in the control phase. The mean low-frequency spectral energy during tilt was higher in the group receiving nifedipine (3.792 ± 2.66) compared with those receiving diltiazem (2.77 ± 1.89) and metoprolol (1.77 ± 0.76). These differences were not statistically significant and are assumed to be due to random variations, since the groups were assigned randomly.

Metoprolol consistently reduced the low-frequency

Table II. Effects of metoprolol, diltiazem, and nifedipine on arterial pressure, instantaneous heart rate (IHR) and its standard deviation (SD), and R-R interval and its SD

	Metoprolol		*Diltiazem*		*Nifedipine*	
	Control	*Drug*	*Control*	*Drug*	*Control*	*Drug*
Arterial pressure (mm Hg)						
Systolic	128 ±18	121 ±16	129 ±21	120 ±13	125 ±25	118 ±17
Diastolic	91 ±10	85 ±7	86 ±12	81 ±13	91 ±12	80 ±10*
IHR (beats/min)	82.42 ±12.65	63 ± 23†	77.23 ±13.39	74.08 ±1.39	80.35 ±8.47	83.35 ±8.03
SD	3.64±1.35 ±1.35	1.73† ±0.62	3.62 ±1.01	2.1* ±1.7	3.86 ±0.71	3.97 ±2.43
R-R (msec)	745.44 ±134.21	1029.67† ±171.14	815.9 ±187.49	824.8 ±122.96	753.6 ±77.17	728.2 ±78.74
SD	25.33 ±10.01	26.44 ±11.17	32.7 ±20.42	33.1 ±23.72	32.5 ±12.69	55.8 ±65.18

*$p < 0.05$.
†$p < 0.01$.

spectral energy during tilt in all eight patients tested (Fig. 2, *A*). The mean value of the low-frequency energy significantly decreased from 1.77 ± 0.76 during control recordings to 0.87 ± 0.93 after metoprolol ($p < 0.003$) (Fig. 3, *A*). Similar to metoprolol, diltiazem also consistently reduced the low-frequency energy in all nine patients (Fig. 2, *B*). The mean value significantly decreased from 2.77 ± 1.89 during control recordings to 0.83 ± 0.6 after diltiazem ($p < 0.01$) (Fig. 3, *B*). On the other hand, nifedipine had inconsistent effects on the low-frequency energy. In five patients the low-frequency energy decreased, while in the other five patients it increased compared with control recordings (Fig. 2, *C*). There was no significant difference of the mean value of low-frequency energy during control recordings (3.79 ± 2.66) and following nifedipine (3.12 ± 2.18) (Fig. 3, *C*). Fig. 4 shows samples of power spectra during control recordings and following administration of each of the three drugs.

Because nifedipine resulted in significant reduction of diastolic blood pressure during tilt, we analyzed the relationship between the degree of reduction in diastolic blood pressure and the changes in low-frequency energy. The increase or decrease of low-frequency energy following nifedipine did not correlate with the degree of reduction of diastolic blood pressure.

DISCUSSION

Ca^{2+} channel blockers and sympathetic activity. Our results showed that both metoprolol and diltiazem reduced HRV, based on both time domain analysis (standard deviation of IHR) and frequency domain analysis (low-frequency spectral energy during tilt). The fact that a parallel reduction in the standard deviation of R-R intervals was not seen is consistent with the findings of previous studies that showed the low sensitivity and accuracy of this parameter as a measurement of HRV.[16, 18]

Our results with metoprolol confirm the findings of previous reports on the depressant effect of β-adrenergic blockers on the low-frequency component of the heart rate power spectrum.[10-12] The reduction in the low-frequency HRV index by diltiazem similar to that observed for metoprolol, suggests a common action of the two drugs in reducing sympathetic nervous activity. On the other hand, nifedipine showed no consistent effects on the low-frequency energy. The nifedipine results could be partially related to the differences in the low-frequency spectral energy during the control phase between the three groups of patients, even though these differences were not statistically significant. It could also be argued that a higher nifedipine dosage could produce different results. However, the results may also suggest that sympathetic inhibition is not a general property of Ca^{2+} channel blockers. Nifedipine and diltiazem differ markedly in chemical structure and in their potency of action on various cardiovascular functions.[1, 2] The net hemodynamic and electrophysiologic effects of Ca^{2+} channel blockers in general, and of nifedipine in particular, may result from a complex interplay of indirect and reflex phenomena.[2]

The technique of spectral analysis of HRV cannot distinguish between changes in the different components of the neural reflex arc or in target organ responsiveness.[13] Thus the exact mechanism and site

of action of diltiazem that explain its effects on the low-frequency spectrum must await further studies. Further, the possibility that at least part of the effects of diltiazem have resulted from a nonspecific membrane-depressant action rather than from specific blockade of voltage-dependent Ca^{2+} channels[20] can not be excluded. The effects of metoprolol and diltiazem on the low-frequency componets of the heart rate power spectrum can not be explained on the basis of normal evolutionary changes in the sympathetic tone during the 1-week study period. Recent studies that utilized repeated measurements of the heart rate power spectrum have shown that the increased sympathetic activity found 2 weeks after infarction gradually normalized over a much slower time course of 6 to 12 months.[13]

There are few clinical data available to suggest the mechanism whereby diltiazem or other calcium channel blockers may affect the sympathetic nervous system. Initial reports on verapamil suggested that it may act as a β-adrenergic antagonist based on its hemodynamic effects and antagonism of β-agonist-stimulated effects.[21] Subsequently, verapamil's effects as a Ca^{2+} channel blocker were elucidated and its primary pharmacologic action was attributed to this mechanism.[22] More recently, verapamil and norverapamil were shown to have competitive antagonistic effects on human lymphocyte $beta_2$-adrenergic receptors.[23] In the same study, subjects were shown to have 50% reduction in plasma catecholamine levels after 1 week of verapamil treatment, which may have reflected a decrease in central sympathetic outflow.

Ca^{2+} channel blockers and secondary prevention trials in the post-infarction period. Numerous clinical studies have demonstrated the efficacy of β-blockers in reducing morbidity and mortality after myocardial infarction.[8] This may be explained by one or more of the multiple pharmacologic effects of β-blockers.[8] The effects of Ca^{2+} channel blockers closely resemble those of β-blockers and they similarly have multiple mechanisms of action on the cardiovascular system.[1] This has led to several secondary prevention trials of therapy with Ca^{2+} channel blockers to reduce morbidity and mortality in the post-infarction period.[3-7] However, compared with β-blockers, the results of trials of Ca^{2+} channel blockers are less consistent. Neither of the two studies of nifedipine[4, 5] showed a salutary effect on infarct size or mortality, and one actually suggested a higher acute phase mortality in the treatment group. Similar negative results were reported with verapamil.[3] On the other hand, diltiazem seemed to show beneficial effects in patients with non-Q wave infarction[6] and in post-infarction patients with good left ventricular function.[7]

It is possible that the different effects of various Ca^{2+} channel blockers in the post-infarction patient are real and reflect a different pharmacologic profile. In this regard, our finding that diltiazem but not nifedipine can decrease the sympathetic activity[13] in the post-infarction patient may have important clinical implications. However, further studies are necessary to confirm the validity of the technique of spectral analysis of HRV as a quantitative index of the autonomic tone and to investigate the effects of different doses of Ca^{2+} channel blockers in a large cohort of patients.

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