JACC Vol. 25, No. 4
March 15, 1995:915–21

Effects of Oral Pirenzepine on Heart Rate Variability and Baroreceptor Reflex Sensitivity After Acute Myocardial Infarction

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Objectives. **Our aims were 1) to assess whether oral pirenzepine could increase indexes of cardiac vagal activity in postinfarction patients, and 2) to compare the effects of this agent with those of transdermal scopolamine.**

Background. **Depression of vagal tone and reflexes predicts a poor arrhythmic outcome after myocardial infarction. Interventions for shifting the sympathovagal balance toward vagal dominance are now of increased clinical interest. Intravenous pirenzepine increases RR interval variability in normal volunteers, a finding that could have therapeutic implications if confirmed in postinfarction patients after oral administration of the drug.**

Methods. **In a single-blind placebo-controlled crossover trial, short-term RR interval variability and baroreceptor reflex sensitivity were evaluated in 20 patients an average of 19 ± 6 days after infarction. Analysis was performed during control conditions and during administration of placebo, oral pirenzepine and transdermal scopolamine.**

Results. **Compared with placebo, at a dose of 25 mg twice daily, pirenzepine significantly increased all time and frequency domain measures of RR interval variability and augmented baroreceptor reflex sensitivity by 60% (mean ± 1 SD 10.4 ± 5.9 vs. 6.5 ± 3.2 ms/mm Hg, p = 0.0007). Pirenzepine and scopolamine showed a similar vagomimetic effect, but the overall incidence of adverse effects was lower with pirenzepine (1 [5%] of 20 vs. 10 [50%] of 20).**

Conclusions. **In patients with a recent myocardial infarction, oral pirenzepine proved equal to transdermal scopolamine in significantly increasing indexes of cardiac vagal activity. These data suggest that oral pirenzepine may have a therapeutic potential for preventing malignant ventricular arrhythmias after infarction.**

(J Am Coll Cardiol 1995;25:915–21)

A strong correlation between impaired autonomic function and poor arrhythmic outcome after acute myocardial infarction has been found in several clinical studies (1–5). Therefore, manipulation of cardiac sympathovagal interaction may have an important therapeutic potential in preventing life-threatening ventricular arrhythmias after infarction. In one strategy for using this potential, sympathetic activity is antagonized by beta-adrenergic blockade, and the efficacy of beta-blockers in reducing the risk of sudden death after myocardial infarction is well known (6). Experimental studies (7,8) suggest that an alternative strategy may be to increase parasympathetic activity. In humans, atropine is known to induce bradycardia (as a "paradoxic" vagomimetic effect) at low doses and to result in the expected heart rate increase (as the typical antimuscarinic effect) at higher doses (9). Recent studies (10–16) showed that low doses of transdermal scopolamine may induce a significant increase in tonic and reflex cardiac vagal outflow in normal subjects, survivors of myocardial infarction and patients with congestive heart failure. Because pharmacologic vagal stimulation may represent a novel therapeutic approach for preventing malignant ventricular arrhythmias after acute myocardial infarction, further investigation of the vagomimetic power of different drugs is desirable. Low doses of intravenous pirenzepine, an antimuscarinic agent widely used for peptic ulcer therapy, were found to increase the standard deviation (SD) of the RR intervals by 58% in six normal volunteers (9). This finding could have therapeutic implications if the results are confirmed in postinfarction patients after oral administration of the drug.

The aims of the present study were 1) to assess whether low doses of oral pirenzepine could induce a sustained increase in cardiac vagal outflow after acute myocardial infarction, and 2) to compare the autonomic effects and tolerability of oral pirenzepine with those of transdermal scopolamine.

Methods

Study design. The present study was conducted in two sequential phases to determine 1) the oral dose of pirenzepine required to produce the maximal parasympathomimetic effect,

From the Division of Cardiology and the Biomedical Engineering Unit, "Clinica del Lavoro" Foundation, Istituto Ricovero e Cura a Carattere Scientifico (IRCCS), Medical Center of Rehabilitation, Tradate, Italy. This study was supported in part by funds for current research from the Italian Ministry of Health, Rome, Italy.

Manuscript received July 19, 1994; revised manuscript received October 27, 1994, accepted October 31, 1994.

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0735-1097/95/$9.50
0735-1097(94)00468-6

Table 1. Effects of Increasing Doses of Oral Pirenzepine on Baroreceptor Reflex Sensitivity in Eight Postinfarction Patients

	Baroreceptor Reflex Sensitivity (ms/mm Hg)				
		Oral Pirenzepine			
Pt No.	Control Period	12.5 mg BID	25 mg BID	37.5 mg BID	50 mg BID
1	3.6	3.3	4.8	5.1	6.3
2	11.3	21.0*	12.4	—	—
3	3.3	7.2	10.1*	6.6	—
4	11.0	11.0	15.4*	12.8	—
5	6.5	0.8	—	—	—
6	3.0	6.1	4.2	5.3	6.5
7	4.4	7.5	8.8*	5.5	—
8	3.4	5.1	8.4*	4.5	—
Mean	5.8	7.7	9.2	6.6	—
SD	3.5	6.1	4.0	3.1	—

*Baroreceptor reflex sensitivity increase >4 ms/mm Hg from control value. BID = twice daily; Pt = patient; — = test not performed.

and 2) the increase of tonic and reflex vagal cardiac activity induced by pirenzepine and scopolamine in postinfarction patients.

In phase 1 we determined the effect of different doses of oral pirenzepine on baroreceptor reflex sensitivity in eight consecutive patients. All patients were men (mean age ± SD 54 ± 10 years, mean left ventricular ejection fraction 51 ± 8%). Six patients (75%) had a Q-wave infarction, three (37%) an anterior wall infarction and five (62%) an inferior wall infarction. Four patients (50%) underwent thrombolysis in the acute phase of infarction.

After giving informed written consent to the study, all patients underwent a baseline evaluation of baroreceptor reflex sensitivity. Then, the titration phase was started and the patients were given increasing doses of oral pirenzepine (Gastrozepin, Boehringer Ingelheim) every 2 days until a significant increase in baroreceptor reflex sensitivity occurred (Table 1). As we (13) have described elsewhere, a baroreceptor reflex sensitivity increase >4 ms/mm Hg from baseline value was considered a true change. Therefore, baroreceptor reflex sensitivity was reassessed after 2 days of therapy for each oral dose tested. If baroreceptor reflex sensitivity increased by >4 ms/mm Hg, the patient was considered a responder and that dose of pirenzepine was defined as effective. All patients who responded also received the subsequent dose to exclude the possibility of a further increase in vagal activity.

From December 1993 to February 1994, 23 patients who survived an acute myocardial infarction were admitted to our institute for cardiac rehabilitation. Of these, 20 were eligible for the present investigation and underwent phase 2 of the study after giving informed written consent. Eighteen patients were men and two were women (mean age 56 ± 8 years, mean left ventricular ejection fraction 48 ± 6%). Sixteen patients (80%) had a Q wave infarction; 10 (50%) underwent thrombolysis in the acute phase of infarction. Eight patients (40%) had an anterior, 11 (55%) an inferior and 1 patient (5%) a lateral wall myocardial infarction. Three other patients were excluded from the study because of insulin-dependent diabetes mellitus. The other exclusion criteria were age >70 years; flutter or atrial fibrillation (or both); frequent atrial or ventricular arrhythmia that made analysis of sinus cycle impossible; abnormal sinus node function; atrioventricular block; ventricular paced rhythm; blood pressure >160/90 mm Hg with diuretic agents or angiotensin-converting enzyme inhibitors (or both); postinfarction unstable angina; heart failure unresponsive to administration of angiotensin-converting enzyme inhibitors and diuretic agents. All patients were studied between 10 and 36 days (average 19 ± 6) after infarction, and no patient was receiving beta-adrenergic blocking agents, calcium channel antagonists, digitalis or antiarrhythmic drugs at the time of the investigation. Diuretic agents, angiotensin-converting enzyme inhibitors and nitrates were allowed, if needed, to control blood pressure, pulmonary congestion and myocardial ischemia. Eight patients received angiotensin-converting enzyme inhibitor therapy, eight received nitrates and one patient received diuretic agents. No change in drug prescription was allowed during the investigation.

The study protocol consisted of the assessment of heart rate variability and baroreceptor reflex sensitivity in a control period and during administration of placebo, pirenzepine and scopolamine. The study was designed as a single-blind, placebo-controlled, crossover trial. After a baseline evaluation of both baroreceptor reflex sensitivity and heart rate variability, all patients received each of three treatments in random order: placebo (one placebo patch behind one ear plus one placebo tablet twice daily), pirenzepine (one placebo patch behind one ear plus one pirenzepine tablet twice daily) and scopolamine (one patch of transdermal scopolamine behind one ear plus one placebo tablet twice daily). Each treatment was given for 3 days, separated by washout periods of 2 days, and heart rate variability and baroreceptor reflex sensitivity were always assessed after 48 h of therapy. During pirenzepine treatment, all patients were given oral pirenzepine at the dose of 25 mg twice daily, 30 min after breakfast and dinner, respectively. The

therapeutic system (Transcop, Recordati) used delivers a low dose of scopolamine (0.5 mg daily) at a continuous rate over 3 days. The patients were informed about the possible side effects induced by vagal stimulation and asked to report them on a questionnaire at the end of the placebo, pirenzepine and scopolamine treatment periods. The protocol was approved by the committee on human investigation at our institution.

Heart rate variability assessment. During each treatment period, heart rate variability was assessed at the same time of day, ≥3 h after a light meal. Throughout the study, smoking and caffeine consumption were prohibited. The patients were studied at supine rest in a quiet, temperature-controlled room and were asked to relax and to avoid talking and sleeping. The recording was started after 10 min of acclimatization and lasted 20 min. Our heart rate variability analysis system consists of a conventional bedside monitor (Supermon 7210, Kontron Instruments), providing an electrocardiographic (ECG) signal and a respiratory signal obtained by measuring the changing impedance between two leads, and a Compaq 486 computer with 12-bit analog/digital interface. Custom-made software (R. Colombo, PhD, Veruno, Italy) was used for analysis of heart rate variability. The ECG and respiratory signals were acquired at a sampling rate of 1 kHz and 250 Hz, respectively. A preprocessing phase removed artifacts in the acquired time series and replaced them with the expected values by linear interpolation between two preceding and two successive interbeat intervals. An off-line analysis was performed on detrendized, 10-min stationary sections of normal RR intervals. A reverse arrangements test (17) was used to verify stationarity and the significance level was set at p value of 0.05.

Both time domain and power spectral analyses were performed. Time domain variables considered were the mean RR interval and its SD, the mean squared successive difference interval and the percent of sinus cycles differing from the preceding cycle by >50 ms. The power spectral density of the time series was then evaluated by an autoregressive method. The algorithm used to identify the autoregressive model was the Batch Least Square method, by means of Levinson-Durbin recursion usually stopped at the 20th order. The Anderson test and the Portmanteau test were used to check the validity of the model, and the order of the model was chosen by minimization of the Akaike Information Criterion figure of merit. A spectral decomposition method was then applied, and the power and the center frequency of each spectral component were evaluated; the coherence function between heart rate and respiration variabilities was also analyzed. The absolute power of the spectral components was expressed in ms^2.

The time series was created as a function of heart beats; this frequency was converted into hertz equivalent (indicated as Hz) by dividing it by the mean RR interval. Two main components in the spectra of heart rate variability were identified: 1) a high frequency component (from 0.18 to 0.35 Hz on average, with a peak centered at 0.28 Hz), and 2) a low frequency component (from 0.03 to 0.15 Hz on average, with a peak centered at 0.10 Hz). A very low frequency peak was generally not revealed by the spectral decomposition method; therefore, the very low frequency power was calculated by integrating the frequency band (from 0.002 to 0.03 Hz) under the spectral curve. The total power (power in the band up to 0.50 Hz) was also calculated. The principles of our software have been described in more detail elsewhere (18).

Baroreceptor reflex sensitivity assessment. Baroreceptor reflex sensitivity was assessed shortly after heart rate variability testing, according to a method previously described (4,19). Blood pressure was continuously monitored noninvasively by an infrared digital plethysmograph (Finapres 2300, Ohmeda). This signal and one ECG lead were digitized and fed into a Compaq 386 computer with custom-made software (G.D. Pinna, PhD, Montescano, Italy) for analysis of baroreceptor reflexes. After a 10 min rest period, phenylephrine hydrochloride (initial dose 2 μg/kg body weight) was injected into an antecubital vein to obtain an increase in systolic arterial pressure >15 and <40 mm Hg. Systolic blood pressure and RR intervals were calculated as increments with respect to baseline conditions. The RR intervals were plotted against the preceding arterial pulse, and a linear regression analysis was performed for points included between the beginning and the end of the first significant increase in systolic arterial pressure. Only regression lines with a correlation coefficient >0.70 were accepted for analysis. A final slope was obtained by calculating the mean value of three or more determinations. This value was then considered to represent the baroreceptor reflex sensitivity (ms/mm Hg).

With a Marquette CENTRA system, a standard 12-lead ECG was recorded in all patients before the baroreceptor reflex sensitivity analysis, and automatic measurements of the PR interval, QRS complex duration and QT interval corrected for heart rate were available.

Echocardiographic studies. A two-dimensional echocardiogram was obtained by using a Ving Med CFM 750 unit 15 ± 6 days after infarction; left ventricular ejection fraction was obtained by the area-length formula.

Statistical analysis. Continuous variables were expressed as mean value ± 1 SD and tested for normal distribution with the Shapiro and Wilk W statistic (20). For normal distributions (mean RR interval and its SD, PR interval and QT interval corrected for heart rate), the overall difference among mean values in the four study periods (control, placebo, pirenzepine, scopolamine) was analyzed by analysis of variance for repeated measures; for nonnormal distributions (mean squared successive difference interval, percent of sinus cycles differing from the preceding cycle by >50 ms, total power, high frequency, low frequency and very low frequency power, ratio of low to high frequency power and QRS complex duration), the four periods were compared by using the Friedman two-way analysis of variance. A two-tailed p value < 0.05 was required for statistical significance. In a subsequent direct comparison, the *t* test for paired samples or the Wilcoxon signed rank test was used. The following comparisons were performed: control versus placebo, pirenzepine versus placebo, scopolamine versus placebo, pirenzepine versus scopolamine. The limit for significance was set at $p < 0.012$, according to the Bonferroni

Table 2. Time Domain Measures of Heart Rate Variability Calculated From 10-Min Intervals During Control, Placebo, Pirenzepine and Scopolamine Periods in 20 Postinfarction Patients

	Study Period				
Interval	Control	Placebo	Pirenzepine (25 mg BID)	Scopolamine (0.5 mg daily)	p Value
Mean RR (ms)	916 ± 142	907 ± 138	970 ± 137	997 ± 137	< 0.0001
SD (ms)	31 ± 15	31 ± 14	46 ± 18	41 ± 16	< 0.0001
MSSD (ms)*	19 ± 13	16 ± 10	30 ± 17	31 ± 19	< 0.0001
PNN50 (% of beats)*	2.2 ± 4.9	1.7 ± 3.8	5.8 ± 7.0	5.9 ± 7.0	< 0.0001

Data are presented as mean value ± 1 SD. The four groups are compared using analysis of variance for repeated measures or (*) Friedman two-way analysis of variance. BID = twice daily; MSSD = mean squared successive difference interval; PNN50 = percent of sinus cycles differing from the preceding cycle by >50 ms; SD = standard deviation of normal RR intervals.

adjustment. All of these analyses were performed by the BMDP Statistical Software (1990 version).

Results

Dose-ranging studies. The effects of increasing doses of oral pirenzepine on baroreceptor reflex sensitivity are illustrated in Table 1. Of eight patients studied, five (62%) showed a significant increase in baroreceptor reflex sensitivity and were considered responders to pirenzepine; four (80%) of these five responded at a dose of 25 mg twice daily. In all patients who responded, administration of a pirenzepine dose higher than the effective dose did not induce a further increase in baroreceptor reflex sensitivity. During treatment with 25 mg twice daily, pirenzepine increased baroreceptor reflex sensitivity by 59%, and the baroreceptor reflex sensitivity was significantly higher than during control conditions (9.2 ± 4.0 vs. 5.8 ± 3.5 ms/mm Hg, p = 0.007). This dose was selected for phase 2 of the study.

Effects of oral pirenzepine and transdermal scopolamine on time domain measures of heart rate variability. The effects of placebo, pirenzepine and scopolamine on time domain measures of heart rate variability are shown in Table 2. Statistical analysis revealed a significant (p < 0.0001) difference among the four study periods. There was no significant difference in any of the variables between placebo and control conditions or between pirenzepine and scopolamine treatments. During pirenzepine administration, all time domain measures of heart rate variability were significantly higher than during placebo administration: The mean RR interval (p = 0.0001) and its SD (p = 0.0002) increased by 7% and by 48%, respectively; the mean squared successive difference interval increased by 87% (p < 0.0001), and the percent of sinus cycles differing from the preceding cycle by >50 ms increased by 241% (p = 0.0006). A similar result was obtained during scopolamine administration: Compared with the placebo period, the mean RR interval (p < 0.0001) and its SD (p = 0.005) increased by 10% and by 32%, respectively; the mean squared successive difference interval increased by 94% (p = 0.0002), and the percent of sinus cycles differing from the preceding cycle by >50 ms increased by 247% (p = 0.004).

Effects of oral pirenzepine and transdermal scopolamine on frequency domain measures of heart rate variability. In one or more conditions, three patients showed a high coherence between heart rate and respiration variabilities in the low frequency band of the spectrum. We therefore analyzed frequency domain measures of heart period variability in 17 patients (Table 3) and found significant differences among the four study periods in total power (p < 0.0001) and in high (p < 0.0001), low (p = 0.007) and very low (p = 0.005) frequency power. Conversely, the ratio of low to high frequency power did not show a significant difference. There was no difference

Table 3. Frequency Domain Measures of Heart Rate Variability Calculated From 10-Min Intervals During Control, Placebo, Pirenzepine and Scopolamine Periods in 17 Postinfarction Patients

	Study Period				
	Control	Placebo	Pirenzepine (25 mg BID)	Scopolamine (0.5 mg daily)	p Value
Total power (ms^2)	984.17 ± 1037.80	1,006.09 ± 747.42	2,129.26 ± 1,563.69	1,734.25 ± 1,357.89	< 0.0001
HF (ms^2)	120.96 ± 252.30	68.50 ± 105.14	256.17 ± 363.91	251.00 ± 351.15	< 0.0001
LF (ms^2)	140.37 ± 246.12	140.09 ± 160.84	336.71 ± 387.15	382.84 ± 502.87	0.007
VLF (ms^2)	477.06 ± 423.43	524.71 ± 402.05	952.76 ± 793.11	664.68 ± 512.31	0.005
LF/HF ratio	2.09 ± 2.20	3.56 ± 3.62	1.96 ± 1.78	5.66 ± 9.03	0.43

Data are presented as mean value ± 1 SD. The four groups are compared using Friedman two-way analysis of variance. BID = twice daily; HF, LF and VLF, respectively, = high frequency, low frequency and very low frequency spectral components of RR interval variability.

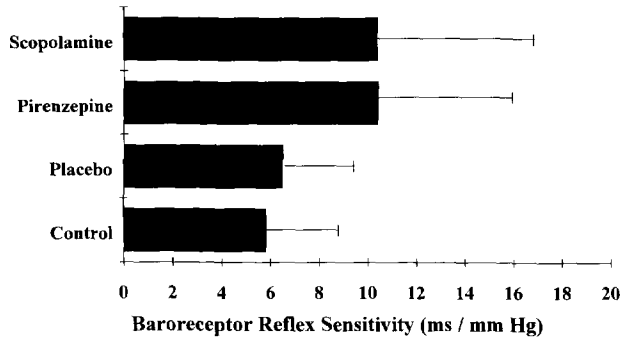

Figure 1. Effects of placebo, pirenzepine and scopolamine treatment on baroreceptor reflex sensitivity. Pirenzepine ($p = 0.0007$) and scopolamine ($p = 0.002$) significantly increased baroreceptor reflex sensitivity compared with values during placebo administration. **Bars** represent mean value ± 1 SD.

in any of the variables between placebo and baseline conditions or between pirenzepine and scopolamine treatments. Compared with placebo, pirenzepine increased the total power by 112% ($p = 0.002$), the high frequency power by 274% ($p < 0.0001$) and the very low frequency power by 81% ($p = 0.009$), respectively. A trend toward a difference was noted for the low frequency component (140% increase; $p = 0.02$). Compared with placebo, transdermal scopolamine significantly increased high ($p = 0.004$) and low ($p = 0.009$) frequency power by 266% and by 173%, respectively. It also increased total power by 72% (statistical analysis showed a borderline p value: $p = 0.019$). Very low frequency power did not differ significantly between the scopolamine and placebo periods.

Effects of oral pirenzepine and transdermal scopolamine on baroreceptor reflex sensitivity. Statistical analysis for the baroreceptor reflex sensitivity disclosed a significant ($p < 0.0001$) difference among the four study periods (Fig. 1). As with the other variables analyzed, no difference was found between control and placebo conditions (5.8 ± 3.4 vs. 6.5 ± 3.2 ms/mm Hg, $p = 0.19$) or between pirenzepine and scopolamine treatments (10.4 ± 5.9 vs. 10.4 ± 6.8 ms/mm Hg, $p = 0.79$). Compared with placebo, both pirenzepine (10.4 ± 5.9 vs. 6.5 ± 3.2 ms/mm Hg, $p = 0.0007$) and scopolamine (10.4 ± 6.8 vs. 6.5 ± 3.2 ms/mm Hg, $p = 0.002$) significantly increased baroreceptor reflex sensitivity by 60%.

Effects of oral pirenzepine and transdermal scopolamine on standard 12-lead ECG. Results of the statistical analysis for the PR interval, QRS complex duration and QT interval corrected for heart rate are illustrated in Table 4. The standard 12-lead ECG disclosed no significant difference in any of the analyzed variables.

Adverse effects of oral pirenzepine and transdermal scopolamine. The overall incidence of adverse effects was lower during treatment with pirenzepine than with scopolamine (1 [5%] of 20 vs. 10 [50%] of 20). During scopolamine administration, eight patients reported dry mouth, two drowsiness and two others blurred vision and nausea, respectively. Conversely, only one patient reported nausea during pirenzepine treatment. No patients required withdrawal of vagomimetic drugs before termination of the study.

Discussion

The present investigation shows that low doses of oral pirenzepine may induce a significant increase in heart rate variability and baroreceptor reflex sensitivity in patients with a recent myocardial infarction. The data suggest that the effects of oral pirenzepine on cardiac sympathovagal interaction are similar to those induced by transdermal scopolamine, which has improved measures of both tonic and reflex cardiac vagal outflow after myocardial infarction (12–15). However, the incidence of adverse effects was lower during treatment with pirenzepine than with scopolamine. Because indexes of cardiac vagal activity are shifted toward values associated with a lower risk of death, especially sudden death (1–5), pharmacologic vagal stimulation by means of oral pirenzepine could have clinical relevance in preventing postinfarction arrhythmic events.

Cardiac autonomic function and ventricular electrical instability. Malignant ventricular arrhythmias and sudden death remain major problems after myocardial infarction. A fatal ventricular arrhythmia is a multifactorial event. As Myerburg et al. (21) suggest, its occurrence is preconditioned by a structural abnormality that is modulated by functional factors such as neurophysiologic interactions and ischemia that can convert chronic ambient arrhythmias into triggering events for potentially fatal ventricular tachycardia and fibrillation (21).

Table 4. Standard 12-Lead Electrocardiogram During Control, Placebo, Pirenzepine and Scopolamine Periods in 20 Postinfarction Patients

	Study Period				
	Control	Placebo	Pirenzepine	Scopolamine	p Value
PR interval (ms)	168 ± 21	169 ± 17	170 ± 24	169 ± 16	0.77
QRS complex duration (ms)*	101 ± 17	102 ± 15	101 ± 14	102 ± 14	0.91
QT interval corrected for heart rate (ms)	441 ± 25	439 ± 27	439 ± 41	435 ± 27	0.71

Data are presented as mean value ± 1 SD. The four groups are compared using analysis of variance for repeated measures or (*) Friedman two-way analysis of variance.

The association between postinfarction arrhythmic events and cardiac autonomic impairment has been documented in clinical investigations (1–5). Moreover, experimental studies (22) showed that sympathetic hyperactivity promotes the occurrence of life-threatening ventricular tachyarrhythmias, whereas augmented vagal tone has a protective antifibrillatory effect (7,8). Therefore, manipulation of cardiac autonomic function could induce a favorable change in the electrophysiologic milieu of the heart. Treatment with thrombolysis and reperfusion, as well as angiotensin-converting enzyme inhibitors, probably has a beneficial effect on sympathovagal balance after myocardial infarction (23–26), and beta-adrenergic blockade has been clearly shown (6) to improve survival in postinfarction patients. Nevertheless, a useful alternative approach may be to increase parasympathetic activity by means of vagal stimulation, especially because of its modest negative inotropic effect (8).

Effects of oral pirenzepine on cardiac autonomic function after acute myocardial infarction. Wellstein and Pitschner (9) found that low doses of intravenous pirenzepine may increase the SD of the RR intervals by 58% in normal volunteers, suggesting the possibility of a cardiac vagomimetic intervention by means of this drug. Because their observation in healthy young adults would not necessarily predict results in older subjects with myocardial infarction, we performed the present investigation. We found a significant increase in time and frequency domain measures of heart rate variability after administration of oral pirenzepine. Pirenzepine increased very low frequency power by 87% compared with placebo: this finding may have particular relevance because spectral measures of heart rate variability in the very low and ultra low frequency bands seem to have a substantially higher prognostic power than that of the reduced vagal components (2). After pirenzepine treatment, the ratio of low frequency to high frequency spectral densities did not change significantly, and the increase in both low and high frequency powers was quantitatively similar. This is not surprising because the low frequency component reflects both parasympathetic and sympathetic nervous modulation (27). After pirenzepine, baroreceptor reflex sensitivity was 60% higher than placebo values. Five patients with a baseline baroreceptor reflex sensitivity <4 ms/mm Hg showed an average increase of 61%, and three patients with a baseline sensitivity <3 ms/mm Hg showed an average increase of 67%. These data are similar to those provided by De Ferrari et al. (14) about autonomic effects of transdermal scopolamine, and they suggest that pirenzepine modulation is also present in patients at high risk of malignant ventricular arrhythmias (i.e., baroreceptor reflex sensitivity <3 ms/mm Hg) (4,5,13).

The mechanism underlying the cholinomimetic effect of low doses of antimuscarinic agents has not been fully explained. It may result from the blockade of cardiac presynaptic M_1 receptors that interrupts a negative auto feedback mechanism (9). Wellstein and Pitschner (9) suggest that acetylcholine could inhibit its own release through the activation of M_1 receptors. Because M_1 receptors have a higher affinity for antimuscarinic drugs than does the postsynaptic M_2 subtype (9), low concentrations of pirenzepine could preferentially bind to them, leaving the M_2 receptors available for higher levels of acetylcholine for any level of neural activation.

Anti-ischemic effect of pirenzepine. Marracini et al. (28) recently found in patients with effort myocardial ischemia that intravenous pirenzepine may significantly increase exercise tolerance over that achieved with saline solution. In their study, time to ischemia and rate-pressure product of ischemia were significantly increased by pirenzepine, and the anti-ischemic effect of pirenzepine was similar to that induced by their reference drug, intravenous isosorbide dinitrate. Whether the oral dose of pirenzepine used to modulate cardiac autonomic function could also induce an anti-ischemic effect is yet to be demonstrated. However, myocardial ischemia and sympathovagal impairment may be involved in the occurrence of a malignant ventricular tachyarrhythmia (21); therefore, the data of Marracini and coworkers, which complement our findings, may have interesting clinical implications.

Pharmacologic modulation of cardiac autonomic function after acute myocardial infarction: oral pirenzepine and transdermal scopolamine. Recent studies (12–16) found that transdermal scopolamine may improve measures of both tonic and reflex cardiac vagal outflow after myocardial infarction and in patients with congestive heart failure. In the present investigation we compared the effects of oral pirenzepine on heart rate variability and baroreceptor reflex sensitivity with those induced by transdermal scopolamine. The data showed that the two drugs had a similar cholinomimetic power in postinfarction patients, but the overall incidence of adverse effects was higher during treatment with scopolamine than with pirenzepine.

Concerning pharmacologic vagomimetic interventions in postinfarction patients, only few data about short-term treatment with transdermal scopolamine are available (12–15). Recently, at our institution, we interrupted a study planned to assess efficacy and safety of transdermal scopolamine after myocardial infarction on a mid-term treatment owing to the high incidence of adverse effects (unpublished data). Of five patients randomized to transdermal scopolamine, four (80%) had to be withdrawn from therapy within the 1st month of treatment. Two patients developed intractable cutaneous erythema in the site of patch application, and the other two reported blurred vision and drowsiness. As recommended by the manufacturer, the transdermal patch of scopolamine is usually applied behind an ear, where the therapeutic system is able to deliver the programmed dose of the drug on the basis of the local cutaneous temperature and blood flow (29). However, because the small area available for the patch application may facilitate the occurrence of cutaneous rash, oral administration of pirenzepine may be preferable for long-term treatment. No patient in our study reported blurred vision or drowsiness during pirenzepine treatment, whereas three patients reported these effects during scopolamine therapy. Thus, oral pirenzepine seems to be better tolerated than transdermal scopolamine, a factor that may be relevant in

evaluating the feasibility of the clinical use of muscarinic receptor blockers after myocardial infarction.

Study limitations. Our study has several limitations. 1) Given the relatively low risk profile of our patient group and the small sample size, we cannot describe the effects of pirenzepine on patients who have a larger infarct size and a lower left ventricular ejection fraction. 2) Our patients were exposed to pirenzepine for only 3 days, and we have not assessed whether the vagomimetic modulation produced by pirenzepine may be maintained over a period of months. 3) The fact that our study was not performed in double-blind fashion may represent a possible bias of our investigation.

Conclusions and clinical implications. We have shown that low doses of oral pirenzepine may induce a sustained improvement in those autonomic indexes that predict a poor arrhythmic outcome after acute myocardial infarction (1–5). This finding suggests that oral pirenzepine could have relevant therapeutic potential for the prophylaxis of postinfarction malignant ventricular arrhythmias. The cholinomimetic power of oral pirenzepine is similar to that of transdermal scopolamine, which was recently found (12–15) to increase tonic and reflex cardiac vagal activity in survivors of an acute myocardial infarction; however, pirenzepine seems to be better tolerated than scopolamine. Whether the effects of oral pirenzepine on cardiac vagal outflow can improve survival in postinfarction patients remains to be assessed. However, the finding that pharmacologic vagal stimulation by means of oral pirenzepine is feasible and well tolerated may warrant further studies in the evaluation of new therapeutic approaches to preventing life-threatening ventricular arrhythmias after acute myocardial infarction.

We are indebted to Cinzia Guicciardi, RN for expert technical assistance and to Giovanni B. Migliori, MD for useful comments.

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