

Tiapamil, a new calcium antagonist: hemodynamic effects in patients with acute myocardial infarction

H. G. EICHLER, M.D.,* T. A. MABIN, M.B.Ch.B., M.R.C.P.,
P. J. COMMERFORD, M.B.Ch.B., F.A.C.C., E. A. LLOYD, M.D., F.A.C.C.,
W. BECK, M.Sc., F.R.C.P., F.A.C.C., AND L. H. OPIE, M.D., D.Phil., F.A.C.C.

With the technical assistance of J. Boniaszczuk

ABSTRACT The afterload reduction and myocardial oxygen sparing that results after administration of calcium antagonists suggests a possible role for these drugs in intervention after onset of acute myocardial infarction, but their use in this setting is limited by the possibility that left ventricular failure will develop. Tiapamil is a new verapamil congener. The hemodynamic effects of this drug (1 mg/kg followed by 25 μ g/kg/min over 36 hr) were studied in 30 patients randomly assigned in a double-blind manner to a tiapamil or control group within 12 hr of the onset of acute myocardial infarction as diagnosed by Swan-Ganz catheterization and gated blood pool scans. Tiapamil reduced heart rate from 83 ± 20 beats/min (mean \pm SD) before to 74 ± 19 beats/min after drug (over an average 36 hr), arterial pressure from $128 \pm 22/87 \pm 14$ to $118 \pm 16/74 \pm 11$ mm Hg, rate-pressure product from $10,695 \pm 3492$ to 8800 ± 2550 units, and systemic vascular resistance from 1732 ± 351 to 1400 ± 350 dynes \cdot sec \cdot cm $^{-5}$. Tiapamil also increased stroke volume index from 34.7 ± 12.1 to 41.6 ± 12.0 ml/m 2 , left ventricular ejection fraction from $50.1 \pm 14.8\%$ to $56.4 \pm 17.4\%$ (at 24 hr), left ventricular end-diastolic volume index from 71.3 ± 23.1 to 80.5 ± 23.7 ml/m 2 , and peak diastolic filling rate (an index of diastolic relaxation) from 2.1 ± 0.9 to 2.6 ± 0.8 end-diastolic volumes/sec ($p < .05$ for all changes). Cardiac index, wedge pressure, left ventricular end-systolic volume, and PR interval remained unchanged. Without precipitating left ventricular failure, tiapamil reduced afterload and heart rate and maintained cardiac index while apparently improving diastolic compliance.

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IN 1971 Maroko et al.¹ proposed that pharmacologic interventions that reduce myocardial oxygen consumption (MVO $_2$) and/or increase blood supply to ischemic myocardium during the very first hours after onset of infarction should reduce infarct size. Clinical studies have supported this principle of early intervention, showing beneficial effects of early β -receptor blockade on the indexes of infarct size.² Although β -blockers effectively reduce MVO $_2$ (mainly by reducing heart rate), their cardiodepressive effects may result in heart failure, especially in patients with large infarcts. There is also concern that β -blockers, particularly non-cardioselective compounds, might give rise to vasoconstriction of coronary arteries.³

Calcium antagonists could become an alternative and promising approach to early intervention in patients with acute myocardial infarction. They reduce MVO $_2$ primarily by peripheral vasodilatation and may facilitate blood flow to the ischemic zone by coronary arterial vasodilatation. These two properties and an associated reflex increase in sympathetic tone compensate for their intrinsic negative inotropic effect.^{4,5} Nifedipine has been studied in this context in patients with acute myocardial infarction and, although it markedly reduced afterload (and did not precipitate heart failure), it gave rise to a reflex increase in heart rate.⁶ A calcium antagonist with a direct negative chronotropic effect would thus be more suitable for early intervention.

Although tiapamil, a new calcium antagonist, is chemically similar to verapamil (figure 1),⁷ the two drugs showed different hemodynamic and antiarrhythmic properties in preclinical studies: In a direct comparison with verapamil, tiapamil did not depress myocardial contractility in dogs over a wide dose range,

From the Cardiac Clinic and Department of Medicine and Nuclear Medicine, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa.

Address for correspondence: Dr. T. A. Mabin, Cardiac Clinic, Groote Schuur Hospital, Cape Town 7925, South Africa.

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*Current address: 1. Medical Clinic, Vienna University Hospital, Lazarettgasse 14, A-1090 Vienna, Austria.

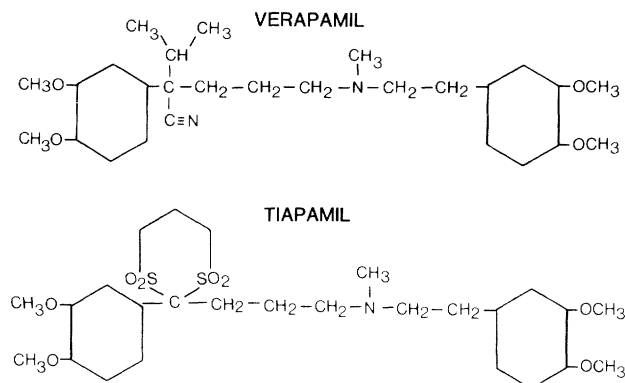


FIGURE 1. Structures of tiapamil and verapamil.

whereas verapamil did, but both drugs were similarly effective in reducing afterload and increasing coronary flow.⁸ Tiapamil was more effective than verapamil, nifedipine, or diltiazem in preventing ventricular fibrillation during coronary artery ligation and simultaneous stimulation by epinephrine in isolated perfused rat hearts.⁹

As a vasodilator, tiapamil showed some selectivity for coronary arteries (small rather than larger arteries) in dogs.⁸ In a baboon preparation tiapamil reduced infarct size as estimated by release of creatine kinase and ST segment mapping when administered 20 min after coronary artery ligation.¹⁰

Very few clinical studies of tiapamil are available to date, but it improved regional coronary flow to ischemic areas on thallium myocardial images¹¹ in patients with angina and decreased afterload^{4, 12} while either reducing heart rate^{13, 14} or leaving it unchanged.⁴ Tiapamil did not, however, depress myocardial contractility in patients with coronary artery disease.⁴ Several investigators have reported that tiapamil has a beneficial effect in those with supraventricular arrhythmias and also in those with ventricular premature contractions.¹⁴⁻¹⁶

Tiapamil might thus be a suitable agent for reducing size of myocardial infarction. In this double-blind, placebo-controlled study we investigated the safety of tiapamil and its effects on the hemodynamic indexes of MVO_2 in the early stages of acute myocardial infarction.

Patients and methods

The study protocol was approved by the University's Ethical Committee; all patients gave informed consent.

Patient selections. Thirty-two consecutive patients with histories and electrocardiographic changes characteristic of acute transmural myocardial infarction who were admitted to the Coronary Care Unit within 12 hr from onset of chest pain were selected for the study. Myocardial infarction was confirmed in each patient by a documented increase in creatine kinase (CK) (more than two times normal, with MB-CK present). Patients

with second- or third-degree atrioventricular block, sustained ventricular tachycardia, systolic arterial pressure less than 90 mm Hg, symptomatic heart failure (with wedge pressure >25 mm Hg), and patients on current antiarrhythmic, β -blocker, digitalis, or calcium antagonist therapy were excluded from the study. Patients were randomly assigned in a double-blind manner to a tiapamil or a control group.

Procedures. A Swan-Ganz thermodilution catheter was inserted and heart rate, systolic and diastolic arterial pressures (sphygmomanometer cuff), cardiac output (five readings/measurement), and pulmonary arterial wedge pressure (PAWP) were measured at the times indicated in table 2 and figure 3. At 0, 2, and 24 hr multigated equilibrium blood pool scans (MUGA) were done to determine left ventricular ejection fraction, peak diastolic filling rate (PDFR), and peak systolic ejection rate (PSER). The patients' electrocardiograms were monitored continuously and recorded by a central computerized arrhythmia monitoring unit. Values for routine biochemical and hematologic parameters were obtained before and after completion of the study. Premature end points of the study were as follows: developing indications for therapy with β -blockers or positive inotropic agents, symptomatic sustained elevated PAWP unresponsive to furosemide, and ventricular arrhythmias causing hemodynamic deterioration (atrial and ventricular arrhythmias were not treated otherwise).

MUGA. Twenty minutes after intravenous administration of 1 mg stannous pyrophosphate, 10 ml heparinized blood was withdrawn and incubated with 25 mCi technetium-99m (as per technetate). Thereafter the labeled blood was reinjected and after 24 hr labeling was repeated. Images were acquired in the left anterior oblique view at an angle giving the best septal separation. The same angle and camera position were used for all three consecutive acquisitions. Imaging was performed with a Siemens LEM scintillation camera interfaced to an A2 Medical Data Systems dedicated minicomputer. Acquisitions were performed in 64×64 byte mode to a total of 200 K counts in full field with use of 28 frames per RR interval. Data were stored on a disk and left ventricular ejection fraction was determined by an experienced, blinded operator with commercial MDS A2 software (A2 MUGA program with automatic edge detection and background correction). A reproducibility study had previously been performed with this method in 55 patients on two occasions. There was no medical intervention or evidence of any change in cardiac status between the two MUGA scans. Left ventricular ejection fraction was again calculated without knowledge of the previous result. In accord with the results of this study ($R = .974$) a change in left ventricular ejection fraction of 5% was considered significant at $p = .05$.

PSER and PDFR were obtained from the first derivative of the volume curve. This provides frame-by-frame ejection and filling rates. The early peak negative deflection of this first derivative curve was defined as PSER and the late positive peak as PDFR.¹⁷ Both variables are expressed in terms of end-diastolic volumes/second (EDV/sec) (figure 2).

Calculations. The various hemodynamic parameters were calculated as follows: mean arterial pressure (MAP in mm Hg) = $(\text{SAP} + 2 \text{DAP})/3$, where SAP and DAP are systolic and diastolic arterial pressures; systemic vascular resistance (in $\text{dynes} \cdot \text{sec} \cdot \text{cm}^{-5}$) = $80 \times \text{MAP}/\text{CO}$, where CO is cardiac output; cardiac index (CI in $\text{liters}/\text{m}^2/\text{min}$) = $\text{CO}/\text{body surface area}$; stroke volume index (SVI in $\text{ml}/\text{m}^2/\text{beat}$) = $1000 \times \text{CI}/\text{HR}$, where HR is heart rate; rate-pressure product (in units) = $\text{SAP} \times \text{HR}$; left ventricular end-diastolic volume index (LVEDVI in ml/m^2) = $\text{SVI}/\text{LVEF} \times 100$, where LVEF is left ventricular ejection fraction; and left ventricular end-systolic volume index (in ml/m^2) = $\text{LVEDVI} - \text{SVI}$. Heart rate, cardiac output, and ejection fraction were obtained simultaneously.

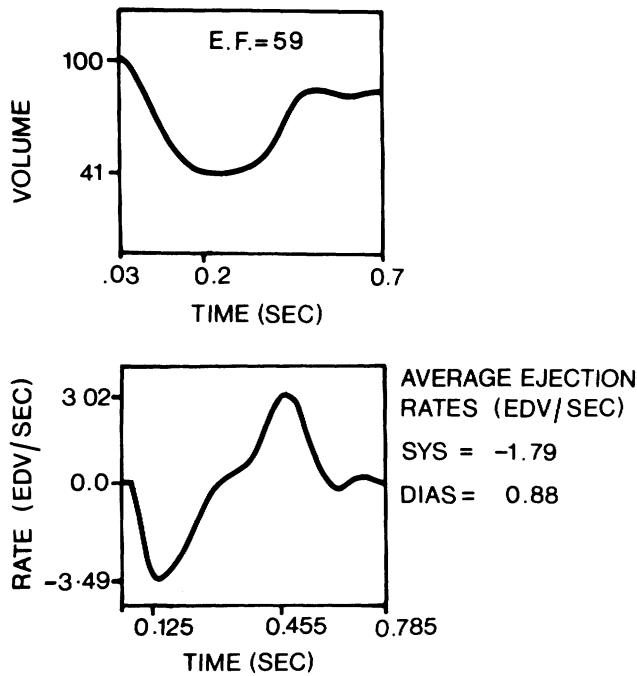


FIGURE 2. MUGA scans. Volume curve (*top*) and first derivative curve (*bottom*). EF = left ventricular ejection fraction; EDV/sec = end-diastolic volume/second. In this example PDFR and PSER are 3.02 and -3.49 EDV/sec, respectively.

Treatment. After baseline measurements (0 hr in figures 3 and 4 and tables 2 and 3) patients in the tiapamil group received a loading dose of 1 mg/kg of the drug over 3 min. In patients with inferior infarcts, first-degree atrioventricular block, or PAWP between 20 and 25 mm Hg, the loading dose was reduced to 0.5 mg/kg (eight of 15 patients). This was followed by an infusion of 25 μ g/kg/min over 36 hr in each patient. Control patients received equivalent volumes of saline solution. The treatment period was followed by a 36 hr observation period without medication. Concurrent treatment with other cardioactive drugs was avoided when possible.

Statistical methods. Data were analyzed by analysis of variance. Comparisons were made between mean values at individual time intervals with use of contrast coefficients. When sample variance lacked homogeneity, logarithmic transformations were used. A $p < .05$ was considered significant. Groups were poorly matched for left ventricular ejection fraction, left ventricular volumes, PDFR, and PSER. For these variables only 0 and 24 hr values in the treatment group were compared by paired t test. Fisher's exact test¹⁸ was used to analyze incidences of chest pain and nitroglycerin administration.

TABLE 1
Patient characteristics

Group	n	Age (years)		Sex (M/F)	Height (mean \pm SD cm)	Weight (mean \pm SD kg)	BSA (mean \pm SD m ²)	Infarct site ^A		Time after onset ^B	
		Mean \pm SD	Range					Inf.	Ant.	Mean \pm SD	Range
T	15	55.1 \pm 10.5	38–69	11/4	168 \pm 9	73 \pm 15	1.79 \pm 0.23	6	9	7.6 \pm 2.5	3–11
C	15	51.6 \pm 11.6	30–69	13/2	170 \pm 9	78 \pm 16	1.88 \pm 0.23	8	7	6.9 \pm 2.1	3–11
Total	30	53.4 \pm 7.8	30–69	24/6	169 \pm 9	75 \pm 15	1.83 \pm 0.23	14	16	7.3 \pm 1.6	3–11

T = tiapamil; C = control; BSA = body surface area; inf = inferior; ant = anterior.

^AAll infarcts were transmural.

^BHours between onset of chest pain and initiation of therapy.

Results

Thirty-two patients entered the study. There were no deaths. Two patients had to withdraw from the study early: one patient in the tiapamil group who required direct-current shock for ventricular fibrillation withdrew at 1 hr and one control patient who required β -blockade for chest pain, tachycardia, and hypertension withdrew at 3 hr. Hemodynamic data were thus obtained from 15 patients in each group. The tiapamil infusion was maintained in all 15 patients for 36 hr, according to the protocol. Groups were well matched for age, sex, body measurements, site of infarct, and time between onset of chest pain and initiation of therapy (table 1). Because of technical defects MUGA scans could be obtained for only 14 patients in the tiapamil group and nine patients in the control group.

Hemodynamic effects

Heart rate. Heart rate was consistently reduced from 83 ± 20 beats/min (mean \pm SD) before drug to an average of 74 ± 19 beats/min during tiapamil infusion and rose to levels above baseline (90 ± 20 at 48 hr) after tiapamil was discontinued. The difference from control heart rate reached significance at 18 and 24 hr (table 2, figure 3). One patient receiving tiapamil who entered the study with a sinus rate of 52 beats/min developed transient sinus bradycardia at a rate of 42 beats/min after 3 hr, but this responded to a single dose of atropine.

Arterial pressures. Systolic and diastolic arterial pressures decreased from $128 \pm 22/87 \pm 14$ (mean arterial pressure 101 ± 16) to an average of $118 \pm 16/74 \pm 11$ mm Hg (mean arterial pressure 89 ± 10) during the infusion of tiapamil. The decrease was significant compared with control at most time points. As with heart rate, there was an "overshoot" at 48 hr, after which pressures returned to their baseline levels (table 2, figure 3).

Stroke volume index and cardiac index. Stroke volume index was consistently and for the most part significantly increased during administration of tiapamil

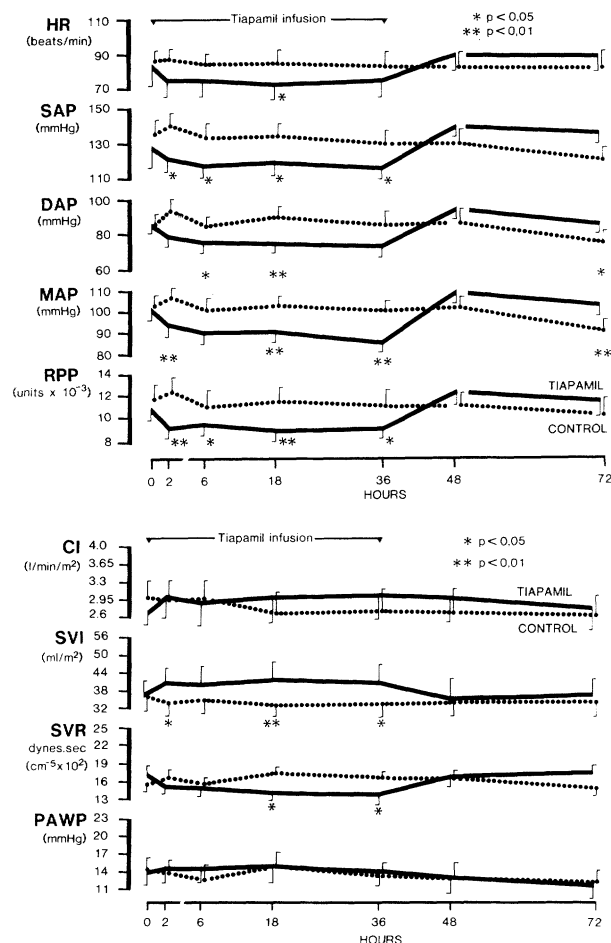


FIGURE 3. Hemodynamic parameters in 15 patients receiving tiapamil and 15 control patients. HR = heart rate; MAP = mean arterial pressure; RPP = rate-pressure product; SVI = stroke volume index; CI = cardiac index; SVR = systemic vascular resistance. * $P < .05$; ** $p < 0.01$.

(34.7 ± 12.1 vs 41.6 ± 12.0 ml/m²/beat before vs during drug), and returned to the baseline level after tiapamil was discontinued (figure 3). Because of the concomitant decrease in heart rate, cardiac index remained largely unchanged (2.7 ± 0.7 vs 2.9 ± 0.5 liters/m²/min; NS), but it exceeded baseline and control values throughout the infusion period (table 2, figure 3).

Systemic vascular resistance. Systemic vascular resistance was consistently decreased during administration of tiapamil (from 1732 ± 351 to 1400 ± 350 dynes·sec·cm⁻⁵) and returned to baseline after the infusion ended. The difference between tiapamil and control values reached significance at 1, 18, and 36 hr (figure 3).

Rate-pressure product. Rate-pressure product was consistently reduced from $10,695 \pm 3492$ units before to an average of 8800 ± 2550 units during infusion of tiapamil. There was an overshoot of values at 48 hr ($12,551 \pm 3285$), but thereafter levels returned to near

baseline (figure 3). The decrease in rate-pressure product was significant vs control at all time points.

PAWP (table 2, figure 3). Average PAWP remained constant and within the normal range (12 ± 3 to 15 ± 6 mm Hg) from 0 to 72 hr in both groups (NS), but four patients on tiapamil and three in the control group required furosemide and/or nitroglycerin for increased PAWPs (>25 mm Hg) during the first 36 hr.

Left ventricular ejection fraction and left ventricular volumes. Patients in the two groups were poorly matched for these variables (see Statistical methods). In the control group ($n = 9$) neither left ventricular ejection fraction nor left ventricular end-diastolic or end-systolic volume index changed over time. In the tiapamil group ($n = 14$) there was a slight increase in left ventricular ejection fraction from $50.1 \pm 14.8\%$ to $56.4 \pm 15.0\%$ at 2 hr (figure 4). This rise was sustained until 24 hr ($56.4 \pm 17.4\%$; $p < .025$ vs 0 hr). Of the four patients on tiapamil with left ventricular ejection fractions of less than 40%, three had the same or increased left ventricular ejection fractions during infusion of drug. In one patient left ventricular ejection fraction decreased from 38% to 30% at 24 hr, but this was not accompanied by a rise in PAWP. Left ventricular end-diastolic volume index increased marginally during infusion of tiapamil from 71.3 ± 23.1 to 74.4 ± 20.4 ml/m² at 2 hr and further to 80.5 ± 23.7 ml/m² by 24 hr ($p < .01$ vs 0 hr). Left ventricular end-systolic volume index remained unchanged with tiapamil (table 3).

PSER and PDFR. The results of MUGA in three tiapamil patients were inadvertently lost from the magnetic disk before analysis of the data, which was thus performed on results in 11 patients only. Groups were poorly matched for PSER and PDFR (see Statistical methods). In the control group ($n = 9$) both variables decreased marginally. In patients receiving tiapamil PSER increased from -2.58 ± 0.7 to -3.03 ± 0.7 EDV/sec at 2 hr and to -3.13 ± 1.2 EDV/sec at 24 hr ($p < .05$ vs 0 hr). PDFR increased from 2.06 ± 0.9 to 2.74 ± 0.9 EDV/sec at 2 hr and to 2.61 ± 0.8 EDV/sec at 24 hr ($p < .025$ vs 0 hr) (table 3).

Atrioventricular conduction and arrhythmias. Groups were poorly matched with respect to PR intervals, but tiapamil did not increase the average values for this parameter, which remained constant in both groups throughout the study period (table 2). After 1 hr one patient on tiapamil developed intermittent atrioventricular block, which was successfully abolished with a single dose of atropine; this was the same patient who developed bradycardia (see above). At 9 hr one control patient developed complete atrioventricular block that

TABLE 2
Mean \pm SD hemodynamic measurements and PR intervals

	Time (hr)											
	0	½	1	2	6	12	18	24	36	48	60	72
Heart rate (beats/min)												
T	82.9	75.6	76.2	75.1	74.9	72.4	72.0 ^A	73.5 ^A	74.9	90.2	86.3	87.5
	± 20.2	± 19.7	± 19.9	± 17.9	± 17.3	± 19.5	± 18.1	± 17.8	± 19.6	± 20.3	± 19.5	± 21.2
C	86.5	87.0	86.8	86.7	84.2	80.1	84.7	87.5	83.5	83.4	80.1	81.7
	± 11.6	± 13.0	± 13.0	± 12.0	± 11.2	± 16.1	± 18.1	± 17.7	± 17.5	± 16.0	± 18.1	± 15.8
Systolic arterial pressure (mm Hg)												
T	128	115 ^B	114 ^B	122 ^A	118 ^A	116 ^A	120 ^A	122	117 ^A	139	128	135
	± 22	± 21	± 21	± 15	± 15	± 13	± 14	± 9	± 9	± 17	± 18	± 19
C	135	136	141	139	134	129	135	134	131	132	128	124
	± 24	± 32	± 23	± 25	± 24	± 18	± 16	± 14	± 14	± 25	± 20	± 19
Diastolic arterial pressure (mm Hg)												
T	87	79 ^A	69 ^B	78 ^A	75	72	73 ^B	73 ^A	71 ^B	94	81	88 ^A
	± 14	± 14	± 20	± 11	± 11	± 10	± 9	± 13	± 9	± 11	± 14	± 15
C	87	93	95	93	84	82	90	88	86	88	80	77
	± 19	± 21	± 17	± 17	± 19	± 17	± 14	± 13	± 18	± 24	± 18	± 16
Cardiac index (l/min/m²)												
T	2.72	3.03	2.95	3.00	2.93	2.89	2.98	2.96	2.99	2.96	2.85	2.86
	± 0.71	± 1.04	± 0.86	± 0.81	± 0.73	± 0.54	± 0.53	± 0.41	± 0.46	± 0.43	± 0.49	± 0.57
C	2.98	2.86	2.90	2.93	2.96	2.73	2.68	2.77	2.71	2.76	2.91	2.71
	± 0.80	± 0.82	± 0.93	± 0.87	± 0.62	± 0.64	± 0.64	± 0.72	± 0.62	± 0.64	± 0.98	± 0.67
PAWP (mm Hg)												
T	13.9	14.0	15.2	14.2	14.2	14.9	14.8	15.2	14.2	13.8	12.1	11.8
	± 4.5	± 5.5	± 5.5	± 3.8	± 3.7	± 3.9	± 3.6	± 4.3	± 4.0	± 5.0	± 5.2	± 3.2
C	14.2	14.5	13.7	13.5	12.2	13.1	14.9	13.4	13.1	13.8	14.9	13.5
	± 7.7	± 8.2	± 6.5	± 5.5	± 4.2	± 5.8	± 8.0	± 5.2	± 4.9	± 5.8	± 7.7	± 5.9
PR intervals (msec)^C												
T	160	157	157	165	162	160	159	161	156	147	150	146
	± 26	± 23	± 16	± 19	± 16	± 21	± 21	± 16	± 15	± 19	± 17	± 20
C	145	145	147	140	142	138	138	138	135	133	135	136
	± 29	± 30	± 23	± 23	± 19	± 20	± 19	± 19	± 13	± 21	± 16	± 16

T = tiapamil group (n = 15); C = control group (n = 15).

^Ap < .05; ^Bp < .01.

^Cn = 13 for both groups.

was unresponsive to atropine. She remained hemodynamically stable with a junctional escape rhythm of 50 beats/min and so was not withdrawn from the study.

Two patients in the tiapamil group entered the study while in atrial fibrillation; in both it was converted to sinus rhythm (after 2 and 10 hr). Before conversion, tiapamil reduced the ventricular rate in the patients from 90 to 50 and from 75 to 50 beats/min. One control patient remained in atrial fibrillation (constant ventricular rate) throughout the observation period.

The incidence of ventricular arrhythmias was very low in both groups: During the first 36 hr of the study (treatment period) five patients in the tiapamil group developed a total of 13 short runs of self-limiting ventricular tachycardia (3 or more consecutive beats); seven control patients also experienced a total of 13 runs of self-limiting tachycardia. None of these required

antiarrhythmic treatment. At 1 hr one additional patient on tiapamil developed ventricular fibrillation requiring direct-current shock and was consequently withdrawn from the study. At that time her plasma K⁺ level was 2.9 mmol/liter.

Ischemic chest pain. Chest pain was reported by one patient in the tiapamil group and eight patients in the control group over the first 36 hr (p < .01).

Concomitant medication. One patient in each group received atropine for atrioventricular conduction disturbances and/or bradycardia (see above). Three patients in the control group and four in the tiapamil group received intravenous furosemide for increased PAWPs (>25 mm Hg). One patient on tiapamil received intravenous nitroglycerin from hours 4 to 32 for chest pain and 10 control patients (p < .01 between groups) received nitroglycerin over periods ranging

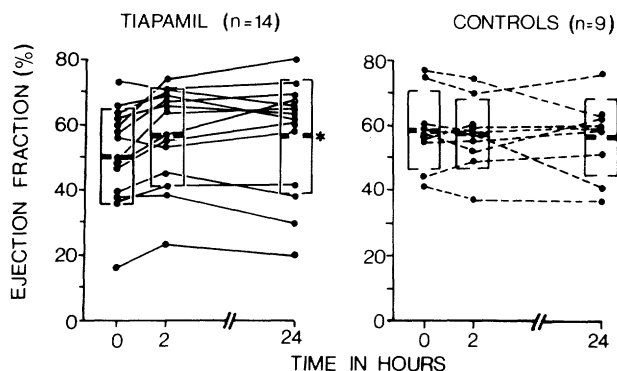


FIGURE 4. Left ventricular ejection fractions in the two groups of patients. Bars represent mean \pm SD. * $p < .025$ vs zero time.

from 2 to 72 hr for one or more of the following indications: ischemic chest pain (eight patients), hypertension (five), and PAWP greater than 25 mm Hg developing after the start of the study (three).

Tolerance to drug and side effects. Two patients vomited and two complained of nausea after injection of the tiapamil loading dose. No other side effects were observed.

Laboratory tests. Results of standard laboratory tests showed no difference in kidney and liver function or hematologic parameters before and after the study.

Discussion

One of the current aims in the treatment of acute myocardial infarction is to decrease the workload of the heart while maintaining cardiac output, i.e., to

TABLE 3

Mean \pm SD left ventricular ejection fraction and volumes and peak volume change rates

	Time (hr)		
	0	2	24
LVEF (%)			
T (n = 14)	50.1 \pm 14.8	56.4 \pm 15.0	56.4 \pm 17.4 ^B
C (n = 9)	58.6 \pm 12.0	57.0 \pm 10.9	56.3 \pm 11.8
LVEDVI (ml/m²)			
T (n = 14)	71.3 \pm 23.1	74.4 \pm 20.4	80.5 \pm 23.7 ^C
C (n = 9)	63.7 \pm 20.4	66.0 \pm 18.0	65.2 \pm 20.4
LVESVI (ml/m²)			
T (n = 14)	37.1 \pm 22.0	33.8 \pm 18.4	37.9 \pm 25.9
C (n = 9)	28.2 \pm 14.9	29.9 \pm 15.1	30.4 \pm 16.9
PDVR (EDV/sec)			
T (n = 11)	2.06 \pm 0.88	2.74 \pm 0.90	2.61 \pm 0.77 ^B
C (n = 9)	2.79 \pm 1.15	2.34 \pm 1.02	2.58 \pm 0.57
PSER (EDV/sec)			
T (n = 11)	-2.58 \pm 0.74	-3.03 \pm 0.71	-3.13 \pm 1.19 ^A
C (n = 9)	-3.56 \pm 1.13	-3.39 \pm 1.02	-3.38 \pm 0.99

T = tiapamil group; C = control group; LVEF = left ventricular ejection fraction; LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index.

^A $p < .05$ vs zero time; ^B $p < .025$ vs zero time; ^C $p < .01$ vs zero time.

economize heart work. Calcium antagonists can be expected to achieve this aim by a combination of their vasodilator and negative inotropic properties. However, there are relatively few studies concerning the hemodynamic effects of these drugs in patients with acute myocardial infarction. Nifedipine has a marked vasodilator effect,^{19, 20} while verapamil reduces both systemic vascular resistance and cardiac output, and decreases enzyme release.^{21, 22} The present study is, to our knowledge, the first report of tiapamil in patients with acute myocardial infarction. Tiapamil appeared to economize heart work by decreasing heart rate and arterial pressure. Both of these variables and the resultant rate-pressure product are major determinants of MVO_2 . The cardiac output index, on the other hand, remained unchanged during administration of tiapamil. These potentially beneficial hemodynamic effects were accompanied by fewer episodes of chest pain (one vs eight patients, $p < .01$) and a decreased requirement for nitroglycerin (one vs 10 patients, $p < .01$) in the tiapamil vs the control group. The greater use of intravenous nitroglycerin for pain or hypertension or the development of elevated PAWPs in control patients makes interpretation of the results more difficult. In the case of pain, nitroglycerin was given only for short periods, with few hemodynamic consequences. In the case of elevated PAWPs, only three of the 15 control patients were affected and this would not alter the interpretation of the data with respect to effects of tiapamil (figure 3). Five of 15 control patients were treated by intravenous nitroglycerin for hypertension and the consequent reduction in arterial pressure in these patients makes the results achieved with tiapamil (figure 3) all the more significant.

In dogs, tiapamil has a direct negative chronotropic effect, even after cardiac denervation.⁸ Another possible effect of tiapamil is an increase in reflex sympathetic tone in response to vasodilation. This was demonstrated in the case of verapamil by elevated catecholamine levels²³ and in the case of nifedipine by increased heart rate.⁶ In our patients the direct effect of tiapamil on heart rate exceeded the indirect effect. In view of the detrimental effects of reflex tachycardia on MVO_2 this is an important beneficial property of this drug.

Tiapamil increased left ventricular end-diastolic volume. According to LaPlace's law, whereby wall tension is directly related to intracavity pressure and cavity radius, this could lead to increased wall tension and, consequently, increased MVO_2 . However, the net effect of tiapamil on wall tension was difficult to assess because the volume effect was counteracted by a de-

crease in systolic arterial pressure. To add to the complexity of the interpretation of our results, the volume increase (which is possibly the result of improved relaxation in localized ischemic areas) could have been associated with changes in ventricular geometry. This, to a degree, would preclude conclusions about global ventricular radius and global wall tension.

Although tiapamil decreased heart rate, cardiac index was maintained. This was brought about by a marked increase (20%) in stroke volume. The increase in stroke volume (and the concomitant marginal increase in ejection fraction and peak systolic ejection rate) can be ascribed to the combined effect of (1) decreased impedance to left ventricular ejection effected by peripheral vasodilation,^{4, 5} (2) increased preload, as demonstrated by the increase in left ventricular end-diastolic volume index, and/or (3) a reflex increase in the sympathetic tone. It is therefore difficult to assess the effect of the increase in stroke volume on MVO_2 . However, an increase in stroke volume effected by reduced afterload does not cause the same marked increase in MVO_2 that results when afterload or the rate-pressure product are kept constant.²⁴ The greater stroke volume index in tiapamil-treated patients could result from either a direct effect on the heart (e.g., improved diastolic filling) or from reflex sympathetic activation after peripheral vasodilation and a fall in systemic vascular resistance. However, 2 hr after the onset of therapy with tiapamil, when stroke volume index rose and systolic arterial pressure fell, the heart rate and systemic vascular resistance were unchanged. It is not likely that these changes were those of reflex sympathetic activation. Later, when systemic vascular resistance fell (18 hr), so did the heart rate, so that although the stroke volume index was still increased, the cardiac index was unchanged. These changes suggest a direct negative chronotropic effect of tiapamil.⁸ Although the initial systemic vascular resistance values in our study were relatively low, in patients without acute myocardial infarction even lower values were also reduced by tiapamil.¹² It is therefore unlikely that the effects of tiapamil in our patients chiefly represent the effects in a selected group with high systemic vascular resistances.

Myocardial ischemia not only impairs systolic function, but also diastolic compliance²⁵; the major mechanism may be impairment of relaxation with a reduced rate of decrease in early diastolic wall tension.²⁶ Conversely, an improvement in diastolic relaxation could be beneficial by lowering filling pressure and thereby improving coronary flow.²⁶ Although compliance is usually expressed as volume change/pressure change,

use of radioisotope volume curves is reported to be a suitable method for detecting changes in diastolic function.^{17, 26-28} Tiapamil significantly increased peak diastolic filling rates in our patients, as did oral verapamil in patients with coronary artery disease.²⁶ This effect of tiapamil reflects a change in compliance that is possibly due to more rapid ventricular relaxation, which is normally prolonged by ischemia.²⁹ The increase in peak diastolic filling rate with tiapamil is all the more remarkable because it occurred together with a decrease in heart rate and arterial pressure, whereas a reduction in heart rate would be expected to be associated with a decrease in peak filling rate,²⁶ and a reduction in systemic arterial pressure decreases the rate of ventricular relaxation.²⁹

The observed increase in left ventricular end-diastolic volume index (in the absence of an increase in wedge pressure) also indicates improved left ventricular compliance. If left ventricular end-diastolic volume index were increased as a result of left ventricular failure, it would have been accompanied by a rise in PAWP. These findings further support the concept of improved diastolic function in patients given tiapamil.

At least three mechanisms may explain the improvement in left ventricular diastolic filling during administration of tiapamil: (1) Relaxation is an energy-requiring process and we postulate that the improvement in filling may at least partly reflect an improvement in regional O_2 balance. (2) Experimental evidence suggests that disturbances of intracellular calcium metabolism during myocardial ischemia may account, at least in part, for incomplete or impaired relaxation,²⁶ so that tiapamil or other agents that reduce calcium ion flux across the myocardial membrane may improve ventricular relaxation. (3) In experimental acute myocardial infarction, compliance may decrease in the infarct zone because of an increased cytosolic calcium ion concentration, which may respond to tiapamil, or because of changes in the connective tissue after 40 min of occlusion,³⁰ which may not respond to tiapamil.

The use of tiapamil was safe in our group of patients with uncomplicated infarcts and indexes of left ventricular failure (left ventricular end-systolic volume and average PAWP) remained unchanged. Tiapamil could also be used in patients with low ejection fractions (figure 3), but since all of our patients started the study with PAWPs less than 25 mm Hg, we cannot draw conclusions about the safety of tiapamil in patients with acute infarct and severe left ventricular failure.

Further studies are required to demonstrate true patient benefit from tiapamil early after onset of acute

myocardial infarction. However, even in the absence of such studies, it can be stated that the hemodynamic effects of tiapamil compare well with those of β -blockers: β -blockers reduce cardiac output by reducing heart rate so that stroke volume is largely unchanged and systemic vascular resistance is either unchanged or even increased.³¹ Tiapamil maintained cardiac output by increasing stroke volume while it reduced systemic vascular resistance. Thus, like β -blockers,³² tiapamil reduces heart rate and arterial pressure but, in contrast to β -blockers, it maintains cardiac output and improves diastolic compliance. Tiapamil might therefore become a potentially useful alternative to β -blockers for early intervention after acute myocardial infarction.

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