Benifical effects of timolol on infarct size and late ventricular tachycardia in patients with acute myocardial infarction

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ABSTRACT This investigation was undertaken to study the effects of β-adrenergic blockade with timolol on infarct size and on the incidence of late ventricular tachycardia in patients with acute myocardial infarction of less than 6 hr of evolution. Patients were assigned randomly either to a placebo-treated group (98 patients) or to a timolol-treated group (102 patients). The patients were treated with 5.5 mg iv timolol (or matched placebo) as a bolus divided into four doses during the first 2 hr followed by 10 mg orally twice daily for 1 month. Cumulative total creatine kinase (CK) release, which reflects the amount of myocardial necrosis was 1677 ± 132 IU/liter in the placebo group (n = 83) and 1274 ± 73 IU/liter in the timolol group (n = 81, p<.01), a 24% reduction. Cumulative release of CK-MB was 138 ± 8 IU/liter in the placebo group and 106 ± 8 IU/liter in the timolol group (p<.01), a 23% reduction. Twenty-four hour Holter electrocardiograms were obtained on days 7, 14, 21, and 28 after the onset of the acute myocardial infarction in 80 patients in the placebo group and 82 patients in the timolol group. The incidence of ventricular tachycardia was lower in the timolol than in the placebo group (7 vs 16 patients, p = .05). We conclude that early administration of intravenous timolol followed by oral treatment in patients with acute myocardial infarction reduces infarct size as assessed by CK and CK-MB serum activity, and decreases the occurrence of late ventricular tachycardia.


THE PROGNOSIS of patients with acute myocardial infarction is related to the extent of the infarcted zone,1,2 to the occurrence of serious late ventricular arrhythmias,3–6 and to the recurrence of myocardial ischemia.7,8

Experimental studies have shown that β-adrenergic blockade reduces myocardial ischemic damage when administered early after coronary artery occlusion.9–14 Initial clinical studies that examined the effects of β-adrenergic-blocking agents on myocardial damage showed promising results.10,15,16 Results of subsequent investigations, however, were conflicting. Some of these investigations have been criticized because of the lack of an adequate control group,16 the small number of patients studied,15,17 or because of the relative delay in starting treatment.18 Recently, timolol was shown to decrease myocardial infarct size as judged by enzymatic and vectorcardiographic criteria.19

The purpose of our investigation was to establish the efficacy of timolol in limiting infarct size and to evaluate its effects on the incidence of late ventricular tachycardia. This was carried out in a multicenter, randomized, double-blind study of patients with acute myocardial infarction of less than 6 hr of evolution.

Methods

Organizational aspects. The TIARA Group (acronym for the Spanish words Timolol en Infarto Agudo, Republica Argentina, which means Timolol in Acute Myocardial Infarction, Republic of Argentina), was organized to carry out this multicenter study in 11 coronary care units.

All clinical data were analyzed at the coordinating center. The enzymatic determinations and the analysis of 12-lead electrocardiograms (ECGs) and Holter monitoring tapes were performed in core laboratories. The planning and progression of the
study as well as data analysis were monitored by an independent ethics committee.

**Patient recruitment and therapy.** Recruitment was carried out between November 1, 1982 and March 18, 1985. During this period, 2094 consecutive patients with chest pain suggestive of acute myocardial infarction and lasting more than 30 min were admitted to the participating coronary care units. Patients were admitted to the study if a diagnosis of acute myocardial infarction was made based on the following criteria: (1) history of pain that strongly suggested acute myocardial infarction with a duration of 30 min or more and an onset of less than 6 hr previously, (2) elevation of serum enzymes during the 24 hr after onset of chest pain (total CK activity of more than 100 IU/liter and plasma CK-MB activity of more than 10 IU/liter, corresponding to at least 6% of the CK), and (3) informed consent. No electrocardiographic criteria were used. Exclusion criteria are listed in table 1.

On admission, history, physical examination, an ECG, and a blood sample for CK and CK-MB determinations were obtained. Thereafter patients were randomized (blocks of 6 patients) and treatment was initiated. Every treatment was started before 6 hr from the onset of chest pain. Placebo or timolol maleate was administered intravenously. The total amount of timolol given was 5.5 mg, 1 mg as an initial dose, 1.5 mg 10 min later, and the same dose repeated 1 and 2 hr after the initial dose. Two hours after the last intravenous dose, oral treatment with placebo or timolol maleate (10 mg) every 12 hr was initiated and continued for 1 month.

Treatment was discontinued if any of the following events occurred: (1) systolic arterial hypotension (<90 mm Hg) or bradycardia (<45 beats/min) that was symptomatic or persisted for more than 1 hr, (2) second- or third-degree atrioventricular block, (3) left ventricular failure, (4) bronchospasm requiring treatment, (5) cerebrovascular accident, or (6) need for coronary artery surgery. All patients in whom treatment was discontinued were followed as indicated by protocol and were considered in the final analysis according to the intention-to-treat approach.

Mortality during treatment and for the following 2 years was assessed, although this study was not designed for this purpose because the patient population was not large enough.

**Clinical and electrocardiographic evaluation.** Systemic arterial pressure and heart rate were determined every 20 min until completion of the intravenous phase and from then on every 3 hr until the end of day 7.

Chest pain was scored on a scale of 0 to 4 in which 0 indicated absence of pain; 1, chest discomfort; 2, moderate thoracic pain without radiation requiring analgesics; 3, intense thoracic pain with radiation; and 4, severe chest pain with radiation, restlessness, and perspiration.

An ECG was obtained at admission and repeated 8, 16, and 24 hr later, every 12 hr during the following 6 days, and on days 14, 21, and 28. ECGs were referred to the core laboratory to determine infarct location and the diagnosis of bundle branch block.

The following criteria were used to localize the infarcted area: anterior when acute changes were present in the precordial leads or in lead I or aVL; inferior when the abnormal findings appeared in lead II, III, or aVF. Q wave infarctions were diagnosed when new abnormal waves (>0.2 mV and >0.04 sec) were present.

Acute indeterminate infarction was diagnosed when localization as anterior or inferior was not possible because of lack of new Q waves or lack of pathognomonic ST segment deviation evolution or presence of left bundle branch block.

Complete right bundle branch block, complete left bundle branch block, left anterior fascicular block, and left posterior fascicular block were diagnosed according to the criteria described by the Ad Hoc Task Force of the World Health Organization. All four were considered bundle branch blocks.

Left ventricular failure was established by the existence of both a third heart sound and crepitant basilar rales. If only one of these signs was present, the evidence of lung congestion on chest x-ray was used to confirm the diagnosis. A chest x-ray was taken at admission, on days 3 and 7, and on the predischARGE day.

**Estimation of infarct size (total CK and CK-MB).** To determine CK and CK-MB levels, blood samples were obtained every 2 hr during the first 12 hr, every 4 hr during the following 36 hr, every 6 hr during the next 24 hr, and every 8 hr during the last 24 hr.

Blood samples were immediately centrifuged at 2000 rpm over 10 min. After addition of 5 mmol of mercaptoethanol, the serum was stored at −20°C and transported to the central laboratory on dry ice. CK and CK-MB were determined by immunoinhibition (Merck creatine kinase Nac-activated kit) with the use of a Flexigen Analyzer System (Electro Nucleonic).

For each patient, the following variables were determined: (1) peak plasma CK and CK-MB activity, (2) time elapsed between the onset of pain and peak plasma activity of CK and CK-MB, and (3) the cumulative release of CK and CK-MB, which was calculated according to the method developed by Shell et al. with the use of an individual decay constant.

**Evaluation of late ventricular tachycardia by serial Holter recordings.** On days 7, 14, 21, and 28 continuous 24 hr, two-channel electrocardiograms (Holter recording) were obtained. The tapes were analyzed in a central laboratory with an Advanced Med equipment (Eliminator). All beats were printed and the analysis of ventricular tachycardia was performed manually by two independent observers. Ventricular tachycardia was defined as three or more consecutive aberrant beats at a rate greater than 100 beats/min and accelerated idioventricular rhythm (AIVR) was defined as three or more consecutive aberrant beats at a rate between 55 and 99 beats/min.

Patients did not receive antiarrhythmic drugs from the sixth to the twenty-ninth day.

**Statistical analysis.** Sample size was selected to detect a 30% difference in cumulative CK release between timolol and placebo groups, with a power of 80% at a significance level of .05. For continuous variables two-tailed Student tests were used. Analysis of variance (ANOVA) tables followed by Newman-

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**TABLE 1 Patient selection**

<table>
<thead>
<tr>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened</td>
<td>2094</td>
</tr>
<tr>
<td>Enrolled in study</td>
<td>200</td>
</tr>
<tr>
<td>Causes of exclusion</td>
<td>1894</td>
</tr>
<tr>
<td>Evolution &gt;6 hr</td>
<td>41</td>
</tr>
<tr>
<td>Drug treatment at entry</td>
<td>30</td>
</tr>
<tr>
<td>Left ventricular failure</td>
<td>10</td>
</tr>
<tr>
<td>Refusal to participate</td>
<td>5</td>
</tr>
<tr>
<td>Diabetes (insulin dependent)</td>
<td>3</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>2</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>1</td>
</tr>
<tr>
<td>Severe concomitant disease</td>
<td>1</td>
</tr>
<tr>
<td>Nonischemic heart disease</td>
<td>1</td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>1</td>
</tr>
<tr>
<td>Previous cardiac surgery</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
</tbody>
</table>

Some patients were excluded for more than one reason.

**β**-blockers, amiodarone, calcium-channel blockers, or digitalis.
Keuls statistics were used when complications were analyzed. Life table methods were used for survival analysis and the chi-square test and contingency tables were used for qualitative variables.

Differences between groups were considered nonsignificant when the p > .05. All data are presented as mean ± standard error.

Results

Ninety-eight patients were randomly assigned to placebo and 102 received timolol. The characteristics of the groups at admission did not differ significantly (table 2).

Infarct size. Myocardial infarction was not confirmed by a rise in CK-MB in eight patients in the placebo group and in six in the timolol group. Adequate enzyme curves were not obtained in seven patients from the placebo group (two died before 24 hr of evolution, two entered after plasma CK peaked, and in three samples were insufficient in number or quality for calculation of CK cumulative release), and in 15 patients from the timolol group (two died before 24 hr of evolution, four entered after the plasma CK peak, and in nine samples were insufficient in number or quality for calculation of CK cumulative release).

Cumulative release of CK, reflecting infarct size, was 24% smaller in the timolol than in the placebo group (placebo, 1677 ± 132 IU/liter; timolol, 1274 ± 73 IU/liter; p < .01; table 3). Peak plasma level of CK was 23% less in the timolol than in the placebo group (placebo, 1082 ± 81 IU/liter; timolol 833 ± 52 IU/liter; p < .01). CK-MB cumulative release was 23% less in the timolol- than in the placebo-treated group (placebo, 138 ± 8 IU/liter; timolol, 106 ± 8 IU/liter; p < .01; table 3). A reduction of 22% was observed when the peak plasma CK-MB level was considered (placebo, 98 ± 6 IU/liter; timolol 76 ± 5 IU/liter; p < .005; table 3).

In the timolol-treated group, CK-MB cumulative release at 0 to 4 hr after symptom onset was 109 ± 11 IU/liter (n = 41) and at 4 to 6 hr it was 100 ± 8 IU/liter (n = 40, p = NS).

Differences in distribution of patients according to release of CK-MB in timolol and placebo groups were statistically significant (p < .05; figure 1). A reduction in the number of large infarcts was seen among timolol-treated patients.

The time from onset of chest pain to peak CK and CK-MB plasma levels was similar in the two groups: 19.2 ± 0.7 hr in the placebo group and 20.0 ± 0.7 hr in the timolol group (p = NS), and 17.7 ± 0.6 hr in the placebo group and 18.3 ± 0.6 hr in the timolol group (p = NS), respectively.

The downward slope of CK and CK-MB curves (i.e., the decay constant or Kd), which reflects the disappearance of the enzyme from the intravascular space, was similar in the placebo- and timolol-treated patients (CK, placebo 0.0502 ± 0.0014 and timolol 0.0493 ± 0.0015; MB-CK, placebo 0.0520 ± 0.019 and timolol 0.0544 ± 0.0024, p = NS).

Late ventricular tachycardia. Eighteen patients in the placebo group did not undergo Holter monitoring: eight did not have acute myocardial infarction, five died during the first week, and in five there were technical difficulties. Data from 20 patients in the timolol group were not analyzed: six did not have acute myocardial infarction, three died during the first week, and in 11 there were technical reasons. In the remaining 80 patients of the placebo group and 82 patients of the timolol group, 281 and 271 Holter recordings, respectively, were obtained on days 7, 14, 21, and 28. The average number of analyzable hours from the 24 hr Holter recordings obtained on these days was 20.8, 21.0, 20.9, and 20.8 hr, respectively, in the placebo group and 21.6, 20.8, 20.2 and 20.0 hr, respectively, in the timolol group. Three or four Holter recordings were obtained in 83% of the patients.

One or more episodes of ventricular tachycardia occurred in 16 patients in the placebo group (20%) and

### TABLE 2

<table>
<thead>
<tr>
<th>Patient characteristics at entry</th>
<th>Placebo group (n = 98)</th>
<th>Timolol group (n = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (%)</td>
<td>91.0</td>
<td>84.0</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52 ± 1.0</td>
<td>53 ± 1.0</td>
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<tr>
<td>Weight (kg)</td>
<td>79 ± 1.2</td>
<td>79 ± 1.5</td>
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<tr>
<td>Electrocardiographic signs of a previous myocardial infarction (%)</td>
<td>5.1</td>
<td>3.9</td>
</tr>
<tr>
<td>History of arterial hypertension (%)</td>
<td>29.6</td>
<td>32.4</td>
</tr>
<tr>
<td>Time from onset of pain to randomization (hr)</td>
<td>4.3 ± 0.1</td>
<td>4.1 ± 0.1</td>
</tr>
<tr>
<td>Heart rate at randomization (beats/min)</td>
<td>83 ± 1.2</td>
<td>80 ± 1.3</td>
</tr>
<tr>
<td>Systolic arterial pressure at randomization (mm Hg)</td>
<td>138 ± 3.8</td>
<td>134 ± 3.7</td>
</tr>
<tr>
<td>Diastolic arterial pressure at randomization (mm Hg)</td>
<td>89 ± 2.4</td>
<td>89 ± 3.3</td>
</tr>
<tr>
<td>Location of myocardial infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>38</td>
<td>41</td>
</tr>
<tr>
<td>Inferior</td>
<td>49</td>
<td>48</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Type of myocardial infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Q wave</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Q wave</td>
<td>81</td>
<td>88</td>
</tr>
</tbody>
</table>

All data are mean ± SE. p = NS (> .05) for all comparisons between the groups.
TABLE 3
Cumulative release and peak plasma levels of total CK and CK-MB

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Timolol</th>
<th>p value</th>
<th>Reduction in the timolol group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients entered</td>
<td>98</td>
<td>102</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients contributing data</td>
<td>83</td>
<td>81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative release of total CK (IU/l)</td>
<td>1677 ± 132</td>
<td>1274 ± 73</td>
<td>&lt;.01</td>
<td>24</td>
</tr>
<tr>
<td>Peak plasma of total CK (IU/l)</td>
<td>1082 ± 81</td>
<td>833 ± 52</td>
<td>&lt;.01</td>
<td>23</td>
</tr>
<tr>
<td>Cumulative release of CK-MB (IU/l)</td>
<td>138 ± 8</td>
<td>106 ± 8</td>
<td>&lt;.01</td>
<td>23</td>
</tr>
<tr>
<td>Peak plasma of CK-MB (IU/l)</td>
<td>98 ± 6</td>
<td>76 ± 5</td>
<td>&lt;.005</td>
<td>22</td>
</tr>
</tbody>
</table>

All data are mean ± SE.

*See text for explanation.

In seven patients in the timolol group (8.5%, p = .05). The number of patients with episodes of AIVR was similar in both groups, with seven in the placebo group (8.75%) and eight in the timolol group (9.75%, p = NS).

The ventricular rate of tachycardia in timolol-treated patients was 126 ± 6.65 beats/min and in placebo-treated patients it was 138 ± 1.8 beats/min. The number of beats in each episode of ventricular tachycardia was 5.05 ± 0.53 and 3.9 ± 0.18 in placebo and timolol groups, respectively. The number of episodes of ventricular tachycardia was 55 in the placebo group and 10 in the timolol group. These differences did not reach statistical significance.

Relationship between infarct size, left ventricular failure, and bundle branch block in the placebo group. In the placebo group the infarct size (as reflected by the cumulative release of CK-MB) was 111.2 ± 9.9 IU/liter in patients without left ventricular failure or bundle branch block (group I, figure 2). Patients with left ventricular failure (group II) had a significantly greater infarct size of 174.3 ± 31.4 IU/liter (p < .01). Patients who developed bundle branch block (group III) had yet higher values, with a mean of 215.3 ± 34.7 IU/liter (p < .01 compared with group I). In patients in whom both left ventricular failure and bundle branch block occurred (group IV), the mean cumulative release of

FIGURE 1. Patient distribution according to cumulative release of CK-MB in the placebo (n = 83) and timolol (n = 81) groups. Placebo vs timolol, p < .05. There were fewer patients with large infarcts in the timolol group. Open circles = placebo group; solid circles = timolol group.

FIGURE 2. Mean cumulative release of CK-MB in placebo-treated patients. Groups are as defined in the text. * p < .01 compared with Group I; ** p < .001 compared with group I; † p < .01 compared with group II; ‡ † p < .001 compared with group II. Bar denotes ± SE; numbers inside the columns are numbers of patients.

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CK-MB was the highest 275.3 ± 44.3 IU/liter. This value was significantly greater than the infarct size for patients with no complications (group I) or with left ventricular failure alone (group II, p<.001, figure 2). In patients without bundle branch block (with or without left ventricular failure), the cumulative release of CK-MB was 125.4 ± 14.2 IU/liter. Patients who developed bundle branch block (with or without left ventricular failure) had a mean cumulative release of CK-MB of 233.6 ± 37.6 IU/liter (p<.001 compared with patients without bundle branch block).

Patients with left ventricular failure and bundle branch block considered in this analysis did not have evidence of previous myocardial infarction, either by history or by electrocardiographic criteria. The same type of analysis could not be performed in the timolol group because of the small number of patients who developed these complications.

Relationship between infarct size and ventricular tachycardia on Holter recordings. In the placebo group, cumulative CK-MB release in patients without late ventricular tachycardia was 135 ± 11 IU/liter and in those who had late ventricular tachycardia it was 139 ± 22 IU/liter (p = NS). In the timolol group these values were 108 ± 7 and 80 ± 14 IU/liter, respectively (p = NS).

Clinical evolution and side effects. Heart rate fell in the timolol group (p<.01; figure 3). There was no difference in systolic arterial pressure (figure 3). A significant decrease in the number of patients with a pain score higher than 2 was observed 2 hr after starting timolol (p<.05; figure 3).

No significant differences were observed either in the meperidine consumption in the first 24 hr (placebo group, 60 ± 5 mg; timolol group, 45 ± 3 mg; p = NS), or in the consumption of furosemide during the first week (placebo group, 117 ± 17 mg; timolol group, 99 ± 16 mg, (p = NS). The number of patients in the timolol vs placebo group with various complications was three vs six for reinfarction, 10 vs 18 for left ventricular failure, and 0 vs three for nonfatal ventricular fibrillation, respectively, indicating favorable but nonsignificant trend. Ventricular tachycardia during the first week, i.e., before Holter monitoring, occurred in 10 patients in the placebo group and six patients in the timolol group (p = NS).

Twelve patients with anterior myocardial infarction developed a new bundle branch block: 11 in the placebo group (seven complete right bundle branch block and four left anterior fascicular block) and one patient in the timolol group (incomplete left bundle branch block, p<.01).

In the group treated with timolol there was a significantly higher incidence of transient arterial hypotension and bradycardia (p<.01).

Treatment was discontinued in 17 and 13 patients in the placebo and timolol groups, respectively (p = NS).

Mortality. During the first 30 days seven of the 98 patients receiving placebo (7.1%) and three of 102 receiving timolol (2.9%) died. In the placebo group, one of the deaths was secondary to a dissecting aneurysm of the aorta, two patients died due to severe left ventricular failure, and the remaining four deaths were sudden and unexpected. The three patients in the timolol group who died had severe left ventricular failure.

The mean follow-up was 24 months (6 to 35 months). Mortality was 12.2% in the placebo group and 6.9% in the timolol group (p = NS).

Discussion

The results of this randomized, placebo controlled, double-blind study demonstrate that the early treatment of patients with acute myocardial infarction with intravenous timolol followed by its oral administration reduces infarct size as measured by total CK and
CK-MB release and decreases significantly the number of patients with one or more episodes of ventricular tachycardia throughout the first month.

**Infarct size.** There is no direct method to measure infarct size in patients, but the measurement of total CK, or its cardiac isoenzyme MB, results in a satisfactory estimation of damage as indicated by its close relationship with left ventricular failure. Ventricular arrhythmias, left ventricular performance, and short-term and long-term mortality. A close correlation has been established in humans between anatomic and enzymatic (CK) estimation of infarct size. The introduction of quantitative techniques for the measurement of serum CK-MB permits the estimation of infarct size with a specific myocardial isoenzyme, avoiding overestimations due to liberation of CK from skeletal muscle.

Maroko and Braunwald and their colleagues have shown that by improving the imbalance between oxygen supply and demand before irreversible ischemic changes have occurred it is possible to limit infarct size. Clinical studies have yielded a wide range of results, which is at least partially a consequence of differences in the techniques used to assess myocardial ischemic damage and/or necrosis, the time elapsed from chest pain to the beginning of the intervention, and the population studied. Improvement in electrocardiographic variables has been observed after administration of propranolol, timolol, and atenolol. However, a more recent study with propranolol did not show any differences in the electrocardiographic variables after the drug. With the use of enzymatic indexes (total CK, CK-MB, or lactic dehydrogenase isoenzyme) it was noted that adrenergic-blocking agents reduced infarct size when given in the preinfarction period or within 4 hr of the onset of infarct. Subsequently, larger studies showed that adrenergic blockade (metoprolol, timolol, or atenolol) reduced necrosis. Again, no differences were found in a recent study after propranolol.

Two studies are of special relevance in comparison with ours. The Multicenter Investigation of the Limitation of Infarct Size (MILIS) an extremely sophisticated clinical trial that showed no difference between placebo- and propranolol-treated patients, used as indexes of infarct size electrocardiographic criteria, CK-MB activity, and pyrophosphate scintigraphy. In this study, however, only 2% of patients entered within 4 hr and 22% entered within 6 hr of the onset of infarction. In contrast, in the present study, 51% of patients were treated within 4 hr and 100% were seen within 6 hr. This may explain the difference in results and corresponds to the experimental data that show the importance of early treatment.

The International Collaborative Study Group carried on the only previous investigation that examined the effects of timolol on infarct size. They reported a reduction in necrosis assessed by total CK and vectorcardiographic criteria. Our results agree closely with those of that study since they noted a reduction in the cumulative release of CK of 29.5% and in our study there was a reduction of 24%. Our study goes a step further since it shows this beneficial effect with respect to myocardial salvage assessed not only by total CK but also by the specific myocardial isoenzyme CK-MB. Chest pain, measured by a subjective pain score, decreased in both studies; we did not find, however, a reduction in the use of opiates in our patients receiving timolol.

The favorable effect of β-blocking agents or other interventions on infarct size decreases with the time elapsed from coronary artery occlusion. This study, however, was not designed to explore this important question. The subgroup analysis showed that the resulting cumulative release of CK-MB was similar in the timolol-treated group whether the time elapsed between the initiation of pain and treatment was less than 4 hr or between 4 and 6 hr.

An unexpected finding was the significant reduction in the occurrence of bundle branch block in the timolol group, and this is clearly related to infarct size. This result is in accordance with a previous study showing a correlation between bundle branch block and heart failure.

The hypotheses about the mechanisms of action by which adrenergic blockade decreases infarct size were not addressed in this study. However, it can be postulated that their effects are partially related to the observed fall in heart rate and to a reduction in myocardial contractility (which was not evaluated in this study), since both changes decrease myocardial oxygen consumption. It may also be relevant that experimentally timolol and metoprolol are more efficacious, in equivalent blocking doses, than propranolol in reducing infarct size, although the changes in both hemodynamic and metabolic variables do not completely explain this disparity.

**Late ventricular tachycardia.** Late ventricular tachycardia has been identified as a predictor of sudden cardiac death in acute myocardial infarction. β-Adrenergic–blocking drugs have shown antiarrhythmic properties in experimental and electrophysiologic studies. Timolol and propranolol are effective in preventing ventricular tachycardia or fibrillation induced by programmed ventricular stimulation
in subacute myocardial infarction, and increase significantly the ventricular fibrillation threshold.39 Timolol given to patients early after acute myocardial infarction reduces the incidence of ventricular tachycardia on the first day.40 Long-term clinical trials using \( \beta \)-blockers after the fifth day of acute myocardial infarction have shown a reduction in the occurrence of sudden death.41 42

Because of the variability in the appearance of ventricular tachycardia during the first month after acute myocardial infarction,43 we performed 24 hr Holter monitoring on days 7, 14, 21, and 28 after the onset of acute myocardial infarction to examine its occurrence. A significant reduction in the number of patients with ventricular tachycardia was observed in the timolol group. This reduction was not due to a slowing of rate of tachycardia to below 100 beats/min since the number of patients with AIVR was the same in both groups. Infarct size did not predict the appearance of late ventricular tachycardia. This suggests that the reduction in the incidence of this arrhythmia may be related to an antiarrhythmic effect of timolol.

Systolic hypotension and bradycardia were more frequent in the timolol group. These effects were transient, and apparently did not have any deleterious consequences.

It has been reported that patients with acute myocardial infarction who develop bundle branch block have an increased mortality risk.35 In the placebo group, 11 patients exhibited a new bundle branch block, while this was evident in only one patient in the timolol group. This was a significant and unexpected finding, probably related to infarct size. A correlation between the size of myocardial infarction and the occurrence of heart failure and bundle branch block was detected in this study. The smallest infarcts were found in patients without those complications. Increasingly larger infarcts were found in patients with heart failure, bundle branch block, and the combination of both. These results need confirmation by prospective studies designed with this goal in mind.

In summary, this study showed that in patients with acute myocardial infarction, timolol reduces myocardial damage, the occurrence of late ventricular tachycardia, and bundle branch block.

The beneficial effects of early administration of intravenous timolol followed by oral treatment in patients with evolving acute myocardial infarction and the low frequency and severity of the side effects suggest that this therapy should be considered in patients without contraindication to timolol admitted soon after the onset of pain.

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The TIARA Study Group

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