PATHOPHYSIOLOGY AND NATURAL HISTORY
VENTRICULAR THROMBI

Increased occurrence of left ventricular thrombi during early treatment with timolol in patients with acute myocardial infarction

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ABSTRACT To examine whether early intervention with timolol influences the occurrence of left ventricular thrombi in acute anterior myocardial infarction, 40 patients with acute anterior myocardial infarction admitted to hospital within 6 hr of onset of symptoms were randomly assigned to receive intravenous followed by oral timolol maleate or placebo. Five (25%) of 20 patients in the placebo group and 14 (73.7%) of 19 patients with confirmed infarction in the timolol group developed a left ventricular apical thrombus as detected by two-dimensional echocardiography from 2 to 10 days after inclusion (p < .005). Patients received anticoagulants only after a left ventricular thrombus had been diagnosed. Only one patient with thrombus suffered peripheral embolization (timolol group). The treatment groups were comparable with respect to location of regional left ventricular dysfunction, electrocardiographic changes, and infarct size estimated by creatine kinase release. However, computer-assisted regional wall motion analysis demonstrated significantly reduced apical wall motion in the timolol group compared with the placebo group (p < .01). Also, the mean heart rate during the first 10 days after the acute infarction was reduced by 13% in the timolol group (p < .001). The reduction in heart rate and left ventricular apical wall motion caused by timolol in patients with acute anterior myocardial infarction may increase the occurrence of left ventricular thrombi.


LEFT VENTRICULAR thrombi diagnosed by two-dimensional echocardiography have been reported in 28% to 40% of patients with acute anterior myocardial infarction.1-6 The occurrence of thrombi has been associated with transmural1-5 and large1-3 myocardial infarction, and apical akinesis of the left ventricle is a constant finding in patients with left ventricular thrombi.1-6

Early treatment with β-adrenergic blocking drugs in acute myocardial infarction reduces the extent of myocardial damage.7-9 β-Blockers may reduce the contractility of normal10 and ischemic11-13 myocardium and the platelet aggregation in ischemic heart disease,14 thus influencing possible pathogenetic factors in the development of ventricular thrombi in anterior myocardial infarction.

In a study of reduction of infarct size with the early use of the β-blocker timolol in acute myocardial infarction,8 we observed that four of five (80%) patients included at our hospital with anterior infarctions who received timolol developed a left ventricular thrombus. The use of β-blockers in acute myocardial infarction may reduce infarct size, but ventricular thrombi may have serious clinical consequences.2,4,5 Therefore, in this study we wished to test the hypothesis that treatment with a β-blocker might be associated with an increased occurrence of ventricular thrombi in patients with acute anterior infarctions.

Methods

Subjects. Consecutive patients of any age were included in the study if admitted to the hospital within 6 hr after onset of symptoms of a suspected first myocardial infarction and with electrocardiographic changes indicating an anterior location of the infarction. The electrocardiographic criterion for inclusion, present in at least two leads in a standard 12 lead electrocardiogram, was new ST segment elevation of more than 1 mm in lead I and aVL or more than 2 mm in precordial leads.

Patients were excluded from the study if they had any of the following clinical findings: heart rate below 50 beats/min, systolic blood pressure below 100 mm Hg, clinical signs of left ventricular failure, bronchial obstruction, or any degree of heart block. Patients on concurrent treatment with digitalis, β-blockers, calcium antagonists, or any other cardioactive drugs were also excluded.
Drug treatment. The study was double blind, and patients giving informed consent were randomly assigned to treatment with timolol maleate or placebo. The treatment was started with 6 hr after onset of symptoms with an intravenous injection of 1 mg of timolol in a 10 ml bolus or 10 ml of isotonic saline; the dose was repeated after 10 min. After another 10 min a constant infusion of timolol at a dose of 0.6 mg/hr or an equal volume of saline was started and continued for 24 hr. Oral treatment with timolol (10 mg bid) or matching placebo was started after the infusion and continued for 10 days.

Concomitant treatment with drugs shown to have influence on the contractility of ischemic myocardium was avoided, and heart failure was treated exclusively with intravenous or oral furosemide. Prophylactic antiarrhythmic treatment was not used. One patient in each group developed ventricular fibrillation on the day of admission, and both were defibrillated successfully.

Intramuscular injections were not allowed, and pain was treated with oxygen, intravenous morphine, or oral propoxyphene (Apropex).

Anticoagulation treatment with oral warfarin was started in all patients with a diagnosed ventricular thrombus, and thrombotest values between 3% and 10% were regarded as therapeutic levels.

Creatine kinase analysis. Blood for analysis of cumulative creatine kinase enzyme release was drawn and analyzed as described elsewhere. The criterion for confirmed myocardial infarction was transient creatine kinase elevation to more than twice the upper normal limit.

Echocardiography. Cross-sectional echocardiography was performed with a Toshiba SSH-10 phased-array sector scanner. All registrations were recorded on a videorecorder (Umatric) allowing real-time (50 frames/sec) and slow-motion playback as well as stop-frame analysis.

Patients were examined in the left lateral decubitus position with the head slightly elevated, and all were examined daily from the day after inclusion for a total of 10 days for detection of left ventricular thrombi. Our diagnostic criteria for thrombi were (1) definite margin of an intracavitary mass, (2) acoustic distinction from underlying myocardium, (3) clear delineation of the endocardium at the site of the intraventricular mass, and in addition at least one of the following: (a) independent movement during the cardiac cycle and (b) changes of intracavitary structure during serial examinations. These criteria had to be fulfilled with at least two different sector orientations to avoid false-positive interpretations. The diagnosis was made by two independent observers not involved in the daily care of the patients and without knowledge of each other’s interpretation or the treatment of the patient.

The analysis of wall motion, volumes, and ejection fractions were made from the recordings on the fifth or sixth day after admission, since all surviving patients were hemodynamically stable and no patient had suffered reinfarction at this time. The apical four-chamber view was always used for these calculations to enable visualization of the entire circumference of the ventricular area, including the apical region. The recordings were made with the transducer at the point of maximal apical impact.

With the identity number of the patients blinded, the echocardiographic registrations were analyzed with a Cardio 80 computer (Kontron). The outline of the left ventricular cavity was drawn manually clockwise along the endocardial border with an overlay technique. Minor irregularities in the endocardial outline were smoothed, and papillary muscles and intraventricular masses were excluded from the drawings. The end-diastolic silhouette was chosen at the peak of the R wave of the QRS complex in standard lead I, and the end-systolic silhouette was chosen as the smallest left ventricular area of the same cardiac cycle. All cases used for analysis followed at least 3 normal heartbeats. All results were calculated as the arithmetic means of three different cycles by two independent observers. Mean interobserver and intraobserver variation was under 15% both for end-diastolic and end-systolic measures.

Calculations. Ventricular volumes were calculated according to the area–long axis method. Computerized regional wall motion was analyzed both as systolic fractional area change of six subareas (A1 to A6) and as systolic fractional radial shortening of 36 radians (R1 to R36) by means of ventricular silhouettes from the apical four-chamber view and a fixed reference system with polar coordinates.

The mean fractional area change and fractional radial shortening of the septal, apical, and lateral regions were calculated as (A1 + A2)/2 and (R1 - R12)/12, (A3 + A4)/2 and (R13 - R24)/12, and (A5 + A6)/2 and (R25 - R36)/12, respectively.

The radial shortening was also evaluated by two other methods. From all patients in both treatment groups, the means of radians 13 to 24 were calculated, and the number of mean radians in each group with fractional radial shortening of 0 or less was used as a measure of the extension of the akinetic area in the apical region and compared in the two groups. The second approach to the analysis of radial shortening was done in a similar manner to that reported by Weyman et al. In a representative systole from each patient, the number of frames in the systole was counted and 10 points in the systole were defined, each separated from another by an equal number of frames. In each patient, the mean radial shortening of radians 13 to 24 was calculated for each of the frames at these 10 time points according to the formula:

\[
\text{Mean FRS}(i) = \frac{1}{12} \times \frac{24}{13} \times \frac{Rd(j) - R(i,j)}{Rd(j)} \times 100%
\]

where FRS(i) is the radial shortening, Rd(j) the end-diastolic and R(i,j) the corresponding radial in the ith frame, i = 1 to 10. In both treatment groups, the mean radial shortening at each time point was calculated, and the means from the 10 systolic points were used to calculate a time-dependent wall motion curve in each group.

Statistical analysis. Because of the possible hazard of ventricular thrombi and the unknown effect of the β-blocker treatment, care was taken to minimize the number of study patients necessary to reach a statistically significant conclusion. In our previous reports, we have observed left ventricular thrombi in 28% of patients with acute anterior infarction, and a 30% incidence of ventricular thrombi was therefore assumed in the placebo group. Based on the preliminary observation that four of five patients with acute anterior infarction treated with timolol developed thrombi, it was hypothesized that the occurrence of thrombi in the timolol group might be as high as 80%. With \( \alpha = 0.01 \) and \( 1 - \beta = 0.90 \), it was calculated that at least 20 patients had to be included in each treatment group by a one-sided test.

Fisher’s exact test was used to analyze categorical data, and analysis of variance and Wilcoxon rank sum test were used to compare continuous variables from the two treatment groups. Statistical evaluations were two-sided, and p values below .05 were considered significant.

Results

After 40 patients had been included in the study, a left ventricular thrombus had been diagnosed in 20 patients (5/20 patients in the placebo group and 15/20 patients in the timolol group; \( p < .0025 \).
By the creatine kinase analysis, acute myocardial infarction was confirmed in all patients but one, who was in the timolol group. Echocardiographically and electrocardiographically, he had signs of an anterior myocardial infarction and an intraventricular mass in the apical region of the left ventricle, but his infarction was assumed to be older.

One patient in the placebo group who did not develop a thrombus had accidentally received oral warfarin and was therefore excluded from the later analysis.

Therefore only 19 patients in each group were considered for the final analysis, 14 patients with a thrombus in the timolol group and five in the placebo group (p < .005).

The two groups were comparable with respect to infarct size estimated as cumulative creatine kinase release, and all patients had normal thrombocyte counts and thrombotest levels.

Heart rate at admission to hospital was 82 ± 14 and 77 ± 15 beats/min (p = NS) in the placebo and timolol group, respectively, whereas the mean heart rate during the first 10 days was 13.6% lower in the timolol group when compared with the placebo group (70 ± 4 vs 81 ± 4 beats/min, respectively; p < .001) (table 1). The corresponding mean heart rate during the same period in the 19 patients with a thrombus was 75.5 ± 4 beats/min as compared with 75.4 ± 3 in the 19 patients without a thrombus (p = NS). The range of heart rates on the echocardiographic registration at the fifth day after the infarction were 43 to 112 beats/min in the timolol group and 60 to 118 beats/min in the placebo group.

Results from the regional wall motion analysis are listed in table 2. Two patients in the timolol group died 8 hr and 5 days after the infarction. The latter had a diagnosed ventricular thrombus, whereas the former did not. In the placebo group, three patients developed persistent atrial fibrillation needing digitalis and other antiarrhythmic drugs. Therefore they were excluded from the wall motion analysis. Accordingly, wall motion data were analyzed for only 17 patients in the timolol group and 16 patients in the placebo group.

The ventricular dysfunction measured as reduced wall motion was centered at radian 16 in the placebo group and radian 20 (p = NS) in the timolol group, and the change in mean systolic fractional area and mean systolic fractional radial shortening in the apical but not in the other regions were significantly reduced in the timolol group (p < .05 and p < .01, respectively). In this group, there was also a significant extension of the area of apical akinesis or dyskinesia estimated as the number of radians with radial shortening of 0 or less in this region (p < .001) (figure 1). The time-dependent wall motion curves of the apical region

### TABLE 1

**Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 16)</th>
<th>Timolol (n = 17)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulated creatine kinase release (U/l)</td>
<td>3904 ± 1625</td>
<td>3445 ± 1568</td>
<td>NS</td>
</tr>
<tr>
<td>Peak aspartate aminotransferase (U/l)</td>
<td>265 ± 119</td>
<td>298 ± 112</td>
<td>NS</td>
</tr>
<tr>
<td>Cardi thoracic ratio</td>
<td>0.48 ± 0.3</td>
<td>0.54 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>End-diastolic volume (ml)</td>
<td>178 ± 74</td>
<td>197 ± 50</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>45 ± 11</td>
<td>34 ± 14</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>84 ± 17</td>
<td>65 ± 16</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>82 ± 14</td>
<td>77 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>Mean, on admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean, during first 10 days after infarction</td>
<td>81 ± 4</td>
<td>70 ± 4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dose of furosemide first 4 days (mg/day)</td>
<td>50.5 ± 60</td>
<td>58 ± 30</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.
demonstrated reduced wall motion at all time points of systole in the timolol group when compared with the placebo group (p < .005) (figure 2).

One patient in the timolol group suffered peripheral emboli in the abdominal circulation verified by angiography during the study period of 10 days.

**Discussion**

These results demonstrate a significant increase in the occurrence of left ventricular thrombi during early treatment with timolol in patients with acute anterior myocardial infarction when compared with placebo. The occurrence of thrombi in the placebo group is in accordance with our previous observations.2, 20, 21

The two patient groups were balanced with respect to infarct location based on left ventricular dysssynergy, the infarct size estimated as cumulative creatine kinase release, peak aspartate aminotransferase, platelet counts, and thrombotest levels. A reduction of the creatine kinase release in the timolol group by 11.7% did not reach significance. The 13.6% reduction (p < .001) in heart rate in the timolol group is in accordance with previous observations.7

The wall motion of the anterior septal and apical regions where the myocardial infarctions were located was significantly reduced in the timolol group, whereas there were no significant differences in the wall motion of other parts of the left ventricle. A larger region of apical akinesis was seen in the timolol group, and the apical wall motion was reduced at all time points in systole.

The lower mean heart rate in the timolol group could have caused a difficulty in blinding those reading the echocardiographic films with respect to treatment groups. However, the overlap in range of heart rates between the two groups made it impossible to guess the treatment of individual patients.

Lieberman et al.22 and Jugdutt et al.23 have shown that the border of an infarct may contain up to 10% infarcted tissue in the form of interdigitizing islands of necrotic and ischemic tissue and that the endocardial motion of this adjacent tissue is intermediate between that of distant normal and infarcted regions. The reduction in apical wall motion observed in the timolol group in our study may therefore have been caused by reduced contractility of partially infarcted and ischemic tissue in the border of the infarction. This may have increased the apparent apical akinesis by inducing akinesis in regions that were otherwise only hypokinetic.

On the other hand, it might be argued that the presence of an apical thrombus reduces apical wall motion.24 Thus the reduced apical wall motion in the timolol group might have been caused by the increased occurrence of ventricular thrombi in this group. However, this explanation is unlikely for the following reasons: only nine of the thrombi in the timolol group were present on the fifth day after the infarction when the wall motion analysis was performed, and three of the thrombi in the timolol group present at that time protruded into the ventricular lumen and were attached to only a small area of the endocardium. Thrombi were present in three patients in the placebo group at the same time. However, it is possible that broad-based thrombi, once formed, may interfere with the local ventricular wall motion.

It is also possible that timolol may change the cardiac movement and thereby the ventricular long axis in a manner that produces an apparent change in wall motion in a fixed-reference system. However, the fact that the wall motion in the septal and lateral regions on both sides of the apical region was similar in both treatment groups makes this possibility unlikely.

The observed reduction of wall motion and heart rate in the timolol group may be a measure of reduced myocardial contractility of the apical region in these patients. Apical akinesis and large infarction have been associated with left ventricular thrombi,1, 2, 6 and infarct size may be reduced by timolol maleate.8 The increased apical akinesis in the timolol group was out of proportion to the infarct size compared with that in the placebo group. Our results therefore suggest that reduced myocardial contractility in the apical region, more than the size of the infarction, is a predisposing factor for the development of left ventricular thrombi.

Since left ventricular thrombi have been associated with peripheral emboli,2, 4 the increased occurrence of

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**FIGURE 2.** Fractional radial shortening (FRS) (mean ± SD) of the apical region (mean of radians 13 to 24) in the placebo (P) (n = 16) and timolol (T) (n = 17) groups during systole.
left ventricular thrombi after early intervention with timolol in acute anterior myocardial infarction may therefore have clinical importance.

We conclude that the reduction in heart rate and left ventricular apical wall motion caused by timolol in patients with acute anterior myocardial infarction may increase the occurrence of left ventricular thrombi.

References
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