CLINICAL STUDIES

Natural History of Left Ventricular Thrombi: Their Appearance and Resolution in the Posthospitalization Period of Acute Myocardial Infarction

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A series of 198 consecutive patients with acute myocardial infarction were prospectively studied before hospital discharge and during 24.0 ± 8.6 months of follow-up. A predischarge thrombus was found in 38 (31%) of 124 patients with anterior infarction but in none of 74 patients with inferior infarction (p < 0.001). Early thrombolytic therapy in 34 patients did not decrease the rate of thrombus occurrence. Acute anterior infarction, ejection fraction ≤35% and apical dyskinesia or aneurysm (but not akinesia) were significantly related to the appearance of thrombus during hospitalization by stepwise logistic regression analysis.

Echocardiographic follow-up of 159 patients for at least 6 months (mean 26.6 ± 8.4) revealed that thrombus disappeared in 14 (48%) of 29. Disappearance of thrombus was related to predischarge apical akinesia (but not dyskinesia) and to warfarin therapy during the follow-up period. A new thrombus first appeared after hospital discharge in 13 of 130 patients, and in 7 of the 13 it resolved during further follow-up. Thus, 30% (13 of 42) of thrombi in these patients appeared after discharge from the hospital.

Three factors were related to occurrence of new thrombi during the follow-up period: deterioration in left ventricular ejection fraction, predischarge ejection fraction ≤35% and ventricular aneurysm or dyskinesia. Systemic embolism occurred in six patients, all with a predischarge thrombus (p < 0.001). Mobility of the thrombus was the only variable significantly related to subsequent embolic events (p = 0.001) by logistic regression analysis. Thus, the predischarge echocardiogram identifies patients with thrombus and those at highest risk of embolic events. It can indicate patients who are likely to have thrombus resolution and those at risk of developing a new thrombus after hospital discharge. Follow-up echocardiograms may help in guiding the length of long-term anticoagulant therapy.

Left ventricular thrombus occurs frequently in the course of acute myocardial infarction and is associated with increased embolic risk (1–6). Acute anterior infarction and severe apical asynergy have been uniformly correlated with formation of thrombus (7–19). Clinical (8–10,18–21) and laboratory (15–17) markers of the extent of myocardial damage as well as administration of anticoagulant (22–26) or fibrinolytic (27–30) therapy during the acute phase of infarction have been shown to have a variable influence on the incidence of thrombi. A thrombus disappearance rate ranging from 20% to 71% (8,10,11,19,20,27,31–33) and first appearance of left ventricular thrombus after hospital discharge (8,18,20) have been reported. Factors related to thrombus appearance in the posthospitalization period and its embolic potential have not been systematically evaluated in prospective studies.

Echocardiography is both sensitive and specific in the detection and morphologic characterization of ventricular thrombus (21,34–37). Protrusion and mobility of the thrombus have been variably (13% to 83%) associated with increased risk of embolization (12–18), but it has been claimed (18) that spontaneous variability in thrombus shape and
mobility significantly decreases the prognostic value of these characteristics.

The present study prospectively investigated 198 consecutive patients with acute transmural myocardial infarction. The patients had long-term clinical, echocardiographic and nuclear angiographic follow-up evaluations to attempt to define 1) factors related to the formation of thrombus during the acute phase of infarction; 2) factors related to disappearance of thrombus during the follow-up period; 3) the frequency of and factors related to appearance of a new thrombus during the follow-up period; and 4) the risk of embolization of thrombus detected either before or after hospital discharge. Pertinent experience is reported in four additional patients in whom fibrinolytic therapy was used during the late phase of acute infarction to achieve lysis of a mobile thrombus.

Methods

Study patients. The study group included 198 consecutive patients who survived an acute transmural myocardial infarction, had technically adequate predischarge echocardiograms and had no additional cardiac or systemic illness that could affect left ventricular function or long-term prognosis. They represented 93% of the 212 patients with acute infarction discharged from the hospital between February 1985 and January 1987. Excluded were 2 patients with inadequate echocardiograms and 10 with primary myocardial or valvular heart disease, emergency surgery or coronary angioplasty during hospitalization or a systemic illness that could affect long-term prognosis. Two additional patients with previous infarction and echocardiographic documentation of left ventricular thrombus <12 h after their hospitalization were excluded because thrombus appearance could not be attributed with certainty to the new infarction.

Of the 198 patients included in the study, 168 were men and 30 were women; the mean age was 62.3 ± 11.8 years (range 32 to 86). Echocardiography was performed 10.6 ± 4.1 days (range 7 to 21) after the acute event. Transmural myocardial infarction was diagnosed by typical history, characteristic increase in serum creatine kinase, glutamic oxaloacetic transaminase and lactate dehydrogenase enzyme levels, and development of diagnostic Q waves on the electrocardiogram (ECG). The location of the infarction was defined from the ECG (38). Patients with previous infarction and those who received streptokinase shortly after admission had their first echocardiogram performed within 12 h of hospitalization. Each study included all standard echocardiographic views (36). In assessing the apical area, images were recorded with different gain settings and angulations of the transducer, and a short focused transducer was used in each patient to minimize near field artifacts and to differentiate muscular trabeculae and aberrant bands from thrombus (21,34,36).

Left ventricular thrombus was defined as an echo-dense mass, contiguous but distinct from the endocardium, located in an area of asynchrony that was seen in both systole and diastole in at least two echocardiographic views (8,21,34-36). The agreement of two independent reviewers was required for diagnosis of thrombus and other echocardiographic variables. There was 96% interobserver agreement for thrombus and 92% agreement for characteristics of wall motion abnormalities adjacent to the cardiac mass. In cases of disagreement, a decision was reached by joint review of the case.

A thrombus was classified as either mural (if the free margin of the mass was concave following the curvature of the endocardial surface) or protruding (if the free margin was convex in relation to the adjacent endocardium); it was considered mobile if any portion of it moved independent of the underlying myocardium (6,12-15). The area of the thrombus was defined by tracing its contour on a still frame image (16) using the built-in calibrated measurement system of the echocardiographic machine. During follow-up evaluations, a ≥50% change in thrombus area was considered to be a significant change in thrombus size. Left ventricular aneurysm was defined as a localized area of akinesia or dyskinesia that deformed the ventricular contour in both systole and diastole (6,15,20).

Wall motion of the apical area, where most of the thrombi predictably (6-16) occurred, was qualitatively graded as normal, hypokinetic, akinetic or dyskinetic; 90% of dyskinetic segments were located in the area of an apical aneurysm. Therefore, apical dyskinesia and left ventricular aneurysm (the latter associated in some cases with apical akinesia) were analyzed as a single category for statistical correlations. Akiness without aneurysm was separately evaluated. Changes from hypokinesia to akinesia or from akinesia to dyskinesia were defined as deterioration in wall motion, and improvement was diagnosed when the opposite changes occurred.

Nuclear angiography. Left ventricular ejection fraction was evaluated using multiple gated technetium blood pool scans on an Elscint 400 Apex gamma camera. A change of
>5% in ejection fraction was defined as deterioration or improvement in global ventricular contractility (39).

Early fibrinolytic and long-term anticoagulant therapy. Thirty-four patients admitted to the emergency room within 4 h of the onset of typical chest pain, with ST segment elevation at least two ECG leads and lack of response to sublingual nitrates received fibrinolytic therapy (27). After intravenous infusion of hydrocortisone (100 mg), streptokinase (1.5 million U) and heparin (15 IU/kg per h) were also given intravenously. The hemostatic effect of the medication was assessed by repeat fibrinogen level and partial thromboplastin time measurements. After 24 h, the heparin dose was adjusted to maintain the partial thromboplastin time in the therapeutic range (70 to 140 s). Successful reperfusion was defined using clinical and angiographic criteria (30). Patency of the infarct-related artery was evaluated in each case on coronary arteriograms obtained 5 to 10 days after hospitalization. Before hospital discharge, oral warfarin was started, and heparin administration was stopped when the prothrombin time reached the therapeutic range (20% to 30%). Changes in the warfarin regimen and bleeding complications were recorded.

Systemic embolism. The criteria for systemic embolization were similar to those described in previous studies (11,15-17). The diagnosis of embolism to a limb required the presence of sudden circulatory compromise and pathologic confirmation. A cerebrovascular embolic event was diagnosed in the presence of a sudden neurologic deficit in the absence of a previous transient ischemic attack and a carotid artery bruit, normal carotid Doppler recording and independent confirmation of the embolic nature of the event by a neurologist. In patients with hypertension, nonlacunar cerebrovascular infarction had to be demonstrated by computed tomography.

Statistical analysis. Clinical, echocardiographic and nuclear angiographic variables were evaluated by univariate and multivariate analysis. Continuous variables were expressed as mean values ± SD. Differences between two mean values were evaluated by a paired or unpaired two-tailed Student t test. Differences among three mean values were evaluated with one-way analysis of variance. Categoric variables were tested by chi-square test or Fisher's exact test where indicated.

Stepwise logistic regression analysis (40) was used to define explanatory variables for four major events ("risk groups"). 1) The risk of thrombus formation during hospitalization was evaluated in the original 198 patients; 2) the risk of systemic embolization was evaluated in 189 patients (9 patients were lost to follow-up) who had a clinical follow-up period of 24.0 ± 8.6 months (range 1 to 48); 3) factors related to the disappearance of thrombus; and 4) the risk of new thrombus appearance during the follow-up period were evaluated in 159 patients with ≥6 months of echocardiographic follow-up study (range 6 to 48 months, mean 26.6 ± 8.4). Thus, patients who had an echocardiographic follow-up period of <6 months because of death, cardiac surgery or coronary angioplasty performed before that time period were excluded from this analysis.

The stepwise regression analysis defined the beta coefficient and its standard error as well as the corrected odds ratio (comparing the risk and reference groups) for each explanatory variable selected (40).

Attempt to lyse left ventricular thrombi. After conclusion of our study, four additional patients had a large protruding mobile ventricular thrombus. Each received intravenous streptokinase or urokinase in an attempt to achieve lysis of the thrombus. Streptokinase was given in doses usually described by Kremer et al. (43), as a 250,000 IU bolus followed by 70,000 IU/h and heparin, 1,000 U/h. Urokinase was given as previously described by Cremer et al. (43), as a 250,000 IU bolus followed by 75,000 IU/h and heparin, 1,000 U/h. After this, warfarin therapy was started. Two of these patients have been previously described (44,45), but the complications noted and the relevance of these cases to those described in the consecutive series warrant inclusion of this experience.

Results

Incidence and factors related to ventricular thrombus before hospital discharge (Fig. 1). A left ventricular thrombus was found on predischarge echocardiograms in 38 (31%) of 124 patients with anterior and none of 74 patients with inferior infarction (p < 0.001). Of the 38 thrombi, 18 (47%) were mural and 20 (53%) were protruding. Six (16%) of the

Figure 1. Myocardial infarction (MI) location, therapy and presence of left ventricular thrombus (LVT+) during initial hospitalization of 96 patients. Ant = anterior; Inf = inferior; STK + = streptokinase administered within 3 h of chest pain; STK - = no streptokinase administered.
Table 1. Predischarge Clinical and Echocardiographic Correlations in 124 Patients With Anterior Wall Myocardial Infarction (univariate analysis)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Present (n = 38)</th>
<th>Absent (n = 86)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left Ventricular Thrombus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>59 ± 13</td>
<td>64 ± 11</td>
<td>0.02</td>
</tr>
<tr>
<td>Male</td>
<td>36 (95%)</td>
<td>71 (83%)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous MI</td>
<td>3 (85%)</td>
<td>22 (26%)</td>
<td>NS</td>
</tr>
<tr>
<td>Ant + inf MI</td>
<td>4 (11%)</td>
<td>10 (12%)</td>
<td>NS</td>
</tr>
<tr>
<td>Maximal CK*</td>
<td>7.4 ± 3.9</td>
<td>7.0 ± 4.6</td>
<td>NS</td>
</tr>
<tr>
<td>CHF</td>
<td>14 (37%)</td>
<td>43 (50%)</td>
<td>NS</td>
</tr>
<tr>
<td>Arhythmiasf</td>
<td>10 (26%)</td>
<td>21 (24%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiogenic shock or CPR</td>
<td>4 (11%)</td>
<td>14 (16%)</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>32 ± 11</td>
<td>40 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF ≤35%</td>
<td>34 (89%)</td>
<td>57 (66%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Apical wall motion (echo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokinesia</td>
<td>0</td>
<td>18 (21%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Aakinesia</td>
<td>22 (58%)</td>
<td>52 (60%)</td>
<td>NS</td>
</tr>
<tr>
<td>Dyskinesia/aneurysm</td>
<td>16 (42%)</td>
<td>16 (19%)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*Multiples of upper normal limit of creatine kinase (CK) level. †Atrial fibrillation, ventricular tachycardia or fibrillation, complete heart block. Ant = anterior; CHF = congestive heart failure; CPR = cardiopulmonary resuscitation; echo = echocardiography; inf = inferior; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

38 thrombi were mobile; all 6 were of the protruding type. Mean thrombus size was 3.2 ± 1.6 cm² (range 0.5 to 7.1).

Comparison of clinical and laboratory data in patients with anterior infarction with and without thrombus (Table 1)

showed similar findings in the two groups, except that patients with a thrombus were younger (p = 0.02) and had a higher prevalence of left ventricular ejection fraction <35% (p = 0.01). The incidence of hypokinetic apical contractility was higher in patients without a thrombus (p = 0.01), whereas dyskinesia or left ventricular aneurysm, or both, were more frequently found in patients with a thrombus (p = 0.006).

Stepwise logistic regression analysis (Table 2) showed that anterior location of the infarct, decreased left ventricular ejection fraction (35%) and apical dyskinesia or aneurysm had the highest association with left ventricular thrombus during hospitalization.

Effect of early thrombolytic therapy. Streptokinase was given to 34 patients (Fig. 1); 26 had anterior infarction and 11 (42%) of these had an apical thrombus. Six (55%) of the 11 thrombi were mural, 4 (36%) were protruding and 1 (9%) was mobile. The mean thrombus size was 2.7 ± 1.9 cm². None of these patients had evidenced thrombus on the first echocardiogram performed within 12 h of hospitalization. Among these 26 patients, thrombus was found in 5 (63%) of 8 patients without and in 6 (33%) of 18 patients with reperfusion (p = NS). Among the 98 patients with anterior infarction and no streptokinase therapy, 27 (28%) had a left ventricular thrombus (p = NS compared with treated patients). No significant differences were found among clinical features, ejection fraction, type of thrombus or apical wall motion between patients with and without streptokinase therapy.

Table 2. Results of Stepwise Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta</th>
<th>Standard Error</th>
<th>Odds Ratio</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predischarge LV thrombus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior MI (Pre)</td>
<td>2.22</td>
<td>1.08</td>
<td>9.20</td>
<td>0.04</td>
</tr>
<tr>
<td>LVEF ≤35% (Pre)</td>
<td>1.49</td>
<td>0.52</td>
<td>4.42</td>
<td>0.005</td>
</tr>
<tr>
<td>Aneurysm (Pre)</td>
<td>1.00</td>
<td>0.45</td>
<td>2.73</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Follow-up: New LV thrombus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deterioration in LV contractility (FU)</td>
<td>2.46</td>
<td>0.90</td>
<td>11.80</td>
<td>0.006</td>
</tr>
<tr>
<td>LVEF ≤35% (Pre)*</td>
<td>1.54</td>
<td>0.69</td>
<td>4.69</td>
<td>0.02</td>
</tr>
<tr>
<td>Aneurysm (Pre)†</td>
<td>1.46</td>
<td>0.90</td>
<td>4.31</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Follow-up: Disappearance of LV thrombus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No dyskinesia/aneurysm (Pre)</td>
<td>1.59</td>
<td>0.80</td>
<td>4.90</td>
<td>0.03</td>
</tr>
<tr>
<td>Long-term anticoagulant therapy (FU)</td>
<td>1.38</td>
<td>0.92</td>
<td>4.00</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Systemic embolism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV thrombus mobility (Pre)</td>
<td>1.80</td>
<td>0.43</td>
<td>6.10</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Because follow-up and predischarge left ventricular ejection fraction (LVEF) ≤35% showed a high correlation coefficient (r = 0.79), the model arbitrarily included one of these variables. †Because follow-up and predischarge ventricular aneurysm showed a high correlation coefficient (r = 0.81), the model arbitrarily also included one of these variables. ‡Apical aneurysm during follow-up showed a negative correlation coefficient (r = -0.98) with apical akinesia and could replace it in the model. §Presence of predischarge left ventricular thrombus showed a high correlation coefficient (r = 0.89) with thrombus mobility. FU = follow-up; LV = left ventricular; Pre = predischarge; other abbreviations as in Table 1.
Deterioration in overall left ventricular contractility during the follow-up period, 2) pre-discharge left ventricular ejection fraction ≤ 35%, and 3) predischarge ventricular aneurysm or dyskinesia.

Disappearance and changes in morphology of predischarge thrombus (Fig. 2). Three of the 38 patients with a predischarge thrombus were lost to follow-up study, 3 died and 3 underwent surgical procedures before repeat echocardiographic studies. The remaining 29 patients were followed up by echocardiography for ≥ 6 months. Fourteen (48%) of the 29 predischarge thrombi disappeared during 6.5 ± 3.7 months (range 2 to 13), and 10 of these 14 thrombi disappeared within 6 months. The thrombus persisted until the end of the follow-up period in the other 15 patients (52%), and 13 (87%) of these showed no significant change in size.

The clinical features in the 14 patients with and the 15 without disappearance of thrombus were similar. However, the predischarge echocardiogram disclosed apical akinesia in 11 (79%) of the 14 patients with disappearance but in only 6 (40%) of the 15 with persistence of thrombus (p = 0.03). Apical aneurysm or dyskinesia was found in three patients (21%) with thrombus disappearance and in nine (60%) of those with thrombus persistence (p = 0.03). Improvement or deterioration in left ventricular global and apical contractility was similar in patients with and without persistence of thrombus.

The morphology of the 14 thrombi that disappeared (6 mural, 6 protruding and 2 mobile) and their size were similar to those of the thrombi that persisted.

Changes in shape and mobility could be evaluated in 27 thrombi (2 thrombi could not be detected on the first echocardiographic study after discharge). In 6 (22%) of the 27 thrombi, a change occurred in thrombus shape; 5 protruding thrombi became of the mural type and 1 mural thrombus evolved into the protruding type. In four patients, the thrombus lost its mobility during follow-up.

Stepwise logistic regression analysis (Table 2) disclosed that two variables were related to disappearance of predischarge thrombi: 1) apical akinesia on the predischarge echocardiogram, and 2) long-term anticoagulant therapy.

Long-term anticoagulant therapy. This was administered to 19 of 130 patients without a predischarge thrombus; a thrombus did not occur in the 16 patients who continued receiving anticoagulant therapy until the end of the follow-up period (Fig. 3). Thrombus occurred in 13 (11%) of 114 patients without any or without continuous long-term anticoagulant therapy (p = NS) (Fig. 4). Three of these 13
patients had aneurysm and no thrombus while receiving anticoagulant therapy for 3 to 21 months, but a thrombus did occur 1.5 to 3 months after cessation of anticoagulant therapy. After diagnosis of a new thrombus, treatment with warfarin was begun in all 13 patients, and the thrombus resolved in 7 during a further follow-up period of 3 to 18 months (mean 6.8 ± 4.9) (Fig. 3 and 4).

Among the 29 patients with a predischarge thrombus, long-term anticoagulant therapy was administered to 9 (Fig. 3). The thrombus disappeared in 7 (78%) of the 9 patients.

Figure 3. Correlation between changes in echocardiographic incidence of left ventricular thrombus and long-term anticoagulant therapy during follow-up. Ac+= long-term anticoagulants administered; Ac-= no anticoagulant therapy given; other abbreviations as in Figure 2.

Figure 4. Formation of a left ventricular thrombus after hospital discharge. Upper panel: A, Patient with apical dyskinesia without predischarge thrombus. B, Protruding thrombus (T) found 3 months later. C, Resolution of the thrombus after 5 months of warfarin therapy. Lower panel: A, Patient with left ventricular (LV) aneurysm (an). Thrombus was not found before discharge and during 12 months of echocardiographic follow-up study while warfarin was administered. B, A mobile thrombus (T) detected 3 months after cessation of anticoagulant therapy, which resolved (C) within 2 months of renewed anticoagulant therapy. LA = left atrium; RA = right atrium; RV = right ventricle.
with and 7 (35%) of the 20 patients without anticoagulant therapy (p < 0.001). In five patients (three with aneurysm and two with apical akinesia), warfarin therapy was stopped 3 to 12 months after resolution of the thrombus. However, thrombus recurred in two patients with aneurysm and disappeared again after renewal of anticoagulant therapy. In none of the seven patients with thrombus resolution without long-term anticoagulant therapy was recurrence of a thrombus seen.

Systemic embolism. Six (17%) of the 35 patients with a thrombus on the predischarge evaluation had systemic embolism during the follow-up period. None of the 154 patients without a thrombus had systemic embolism (p < 0.001). Among the 13 patients who developed a new thrombus during the follow-up period and received long-term anticoagulant therapy thereafter, none had systemic embolism. The time interval between hospital discharge and embolization was 10.9 ± 14.0 months (range 1 to 36), but four patients had embolism within 6 months. Two emboli were to a limb and organized thrombus was retrieved at surgery. In four patients, an ischemic type cerebrovascular accident was diagnosed, and two of these patients died. Systemic embolism occurred in 1 (7%) of 14 patients with a predischarge mural thrombus, 1 (7%) of 15 with a protruding nonmobile thrombus and 4 (66%) of the 6 with a protruding mobile thrombus (p < 0.001).

Long-term anticoagulant therapy. Twenty-one patients (9 with thrombus on the predischarge echocardiogram and 13 with a new thrombus during follow-up period) received long-term anticoagulant therapy and none had systemic embolism. Of the 26 patients with a thrombus without anticoagulant treatment, 6 (23%) had an embolic event (p < 0.02). Stepwise logistic regression analysis (Table 2) related subsequent embolic events to presence of a protruding mobile thrombus (p = 0.001).

Prognostic significance of a left ventricular thrombus. Twenty-nine patients (15%) died among the 189 patients observed during the 2 year follow-up period. Cause of death was congestive heart failure in 12, recurrent myocardial infarction in 5, sudden cardiac death in 8, cerebrovascular accident in 2 and unknown in 2. The mortality rate was 23% (8 of 35) in those with anterior infarction associated with a predischarge thrombus, 15% (13 of 84) in those with anterior infarction without a thrombus and 11% (8 of 70) in those with inferior infarction (p = NS). There were no significant complications related to warfarin therapy.

Thrombolytic therapy for apical mobile thrombus (Table 3). Urokinase or streptokinase was used in four patients who were not part of the consecutive series described here; Data on patients 1 and 2 have been previously published (44,45). All four patients had anterior infarction with apical akinesia or dyskinesia, and the diagnosis of thrombus was made on days 5 to 16. Ejection fraction ranged from 28% to 46%. After diagnosis of thrombus, systemic heparinization was applied for 48 to 72 h. During heparin therapy, Patient 1 had a transient ischemic attack, with disappearance of the smallest of three apical thrombi originally found. Because heparin therapy did not change thrombus size or mobility, urokinase or streptokinase was started. In all four cases, a significant decrease in size of the thrombus, together with a marked increase in its mobility was seen 8 to 12 h later. In Patients 1 and 2, the thrombus disappeared without complications. In Patient 3, diplopia occurred 9 h after the start of streptokinase infusion. Heparin infusion was continued, but streptokinase administration was stopped for 24 h until complete resolution of diplopia. The renewed streptokinase infusion led to complication-free resolution of the thrombus.

Patient 4 had a large protruding mobile apical thrombus that decreased significantly in size after 52 h of uncomplicated infusion of streptokinase. One hour later, the patient suddenly lost consciousness and developed signs of a right hemispheric stroke. Disappearance of the apical thrombus was documented by immediate echocardiography; computed tomography excluded cerebral hemorrhage and showed the presence of extensive right hemispheric infarction (Fig. 5). The patient died a few days later.

Patients 1, 2 and 3 were discharged on long-term anticoagulant treatment. During 20 to 32 months of follow-up, thrombus recurred in one patient after cessation of warfarin, but disappeared again after renewal of anticoagulant therapy.
Discussion

Determinants of ventricular thrombus appearance before hospital discharge. Logistic regression analysis showed that anterior location of the infarction, left ventricular ejection fraction ≤35% and apical dyskinesia or aneurysm were the major variables related to thrombus formation. The 31% incidence rate of left ventricular thrombus in anterior infarction and its absence in inferior infarction are in agreement with previous reports (8–14). In anterior infarction, further clinical variables (such as previous infarction, congestive heart failure, cardiogenic shock, maximal serum enzyme levels) did not separate patients with and without predischarge thrombus. Thus, on the basis of clinical criteria, all patients with anterior infarction should be considered at high risk of thrombus formation. Decreased ejection fraction was an independent predictor of (46) but not a prerequisite for (11) thrombus formation. Thrombus is rare in the presence of a preserved or only mildly decreased left ventricular ejection fraction, but may occur in patients with an apical aneurysm, as seen in four patients in this series. Similar to findings in other studies (8,46), apical dyskinesia or aneurysm correlated better with thrombus occurrence by univariate (p = 0.006) (Table 1) or multivariate (p = 0.03) (Table 2) analysis than did akinesia (p = NS).

Effect of early fibrinolytic therapy. This study did not demonstrate a beneficial effect of early fibrinolytic therapy on left ventricular ejection fraction and the incidence of thrombus. Sharma et al. (29) observed thrombus within 24 h of streptokinase administration. In the present study, thrombus was found only after the lytic phase, while patients were fully anticoagulated. The unusually high incidence of thrombus (42%) found in our patients with anterior infarction receiving streptokinase may be related to the small number of patients evaluated. However, two randomized (28,30) and one uncontrolled (29) study showed an incidence of 26% to 55% of thrombus in similar patients. In contrast, Eigler et al. (27) compared 12 patients treated with and 10 patients without early thrombolytic therapy and found a significant improvement in both ejection fraction and thrombus incidence in the treated group. Our present study and a previous study (30) showed a statistically nonsignificant trend toward fewer thrombi in patients with successful reperfusion.

Appearance of ventricular thrombi during follow-up. Prospective echocardiographic studies have shown that 33% to 62% of thrombi detected during hospitalization are present within 48 h of the acute event (18,20,24,27) and some may be found at admission (20). Few data (8,18,20) are available concerning the appearance of thrombi after hospitalization. In 13 (10%) of our 130 patients, a thrombus first developed during the follow-up period. This was found in 15% of patients with anterior and 5% of those with inferior infarction. All patients with inferior infarction had either a large inferior wall aneurysm or severe inferoapical asynergy. The new thrombus occurred within 6 months of the infarction in 69% of cases, and in 38% of the cases, it was of the protruding type (Fig. 4). None of the 16 patients on continuous anticoagulant therapy developed a thrombus during the follow-up period compared with 11% of patients without anticoagulant therapy (p = NS).

Logistic regression analysis showed three factors to be related to the occurrence of thrombus after hospital discharge: 1) deterioration in left ventricular ejection fraction during the follow-up period, 2) initially low ejection fraction, and 3) ventricular aneurysm or dyskinesia during hospitalization or follow-up. Previous infarction and congestive heart failure showed a significant correlation with the occurrence of thrombus by univariate but not by stepwise logistic regression analysis.

Disappearance of thrombus during follow-up. Logistic regression analysis revealed that the type of apical wall motion before and warfarin therapy after hospital discharge
were the major factors associated with disappearance of thrombus in 48% of the patients with a predischarge thrombus. Thrombus disappeared in 65% of patients with apical akinesia but in only 25% of those with apical aneurysm or dyskinesia ($p = 0.03$). Seven of the 13 new thrombi found after hospital discharge disappeared during further follow-up (Fig. 4). Improvement in wall motion adjacent to the thrombus has been suggested as a possible mechanism for thrombus resolution ($p < 0.05$). The current study and others ($20,22$) do not support this observation.

Thrombus disappeared in 78% of patients with compared with only 35% of those without long-term anticoagulant therapy ($p < 0.05$). A randomized study ($32$) of warfarin therapy in patients with thrombus after acute myocardial infarction demonstrated 88% versus 24% disappearance rates in treated and untreated patients, respectively. In nonrandomized studies ($8,10,11,18,20,27,33$) thrombus disappearance rates have ranged from 42% to 84% with and 14% to 40% without long-term anticoagulant therapy. The beneficial effect of long-term anticoagulant therapy has been supported by indium-111 platelet imaging, which showed prolonged (months to years) surface activity of thrombi with active platelet deposition ($47,48$) and inhibition of this activity by warfarin in some cases ($48$). Furthermore, there are reports ($8,20$) of thrombus reappearance after cessation of anticoagulation therapy. In this study and another study ($20$), thrombus recurred after cessation of anticoagulants only in patients with aneurysm or dyskinesia, not in those with apical akinesia.

**Systemic embolism.** Previous studies ($8-21,25,26,33$) have demonstrated systemic embolism in 147 (20%) of 746 patients (range 4% to 63%) with echocardiographically documented ventricular thrombus, but in only 16 of 785 patients (2%, range 0 to 4%) without thrombus. In this study, systemic embolism occurred in 6 (17%) of 35 patients with a thrombus, but in none of the 154 patients without a predischarge thrombus ($p < 0.001$). Clinical and nuclear angiographic variables were not predictive of embolic events. Although most embolic events occur within 6 months of infarction, ventricular thrombus continued to represent an increased risk for systemic embolism in the current and previous ($12-15$) reports.

**Thrombus mobility on predischarge echocardiography showed the best correlation with subsequent embolic events ($p < 0.001$). The incidence of embolism in patients with a mobile thrombus has ranged from 13% to 83% ($11-17$) and, in most cases, mobile thrombi were of the protruding type ($13-20$). The reported average rates of systemic embolism were 55% (47 of 86) in protruding mobile, 18% (18 of 102) in protruding nonmobile and 10% (25 of 255) in mural thrombi ($11-16,18$). Changes in thrombus shape and mobility were common when evaluated from the first day of infarction ($18$), but were rare in patients evaluated ≥3 months after the acute event ($33$). In the present study, the morphologic characteristics of persistent thrombus defined before hospital discharge remained relatively stable and were predictive of subsequent embolic events. A thrombus formed after hospital discharge was not associated with systemic embolism. However, in this group, there was only one patient with a mobile thrombus, and long-term anticoagulant therapy was given to all patients immediately after detection of thrombus. Further studies are needed to evaluate the embolic potential of thrombi formed during follow-up.

It has been suggested that long-term anticoagulant therapy is not indicated in patients with ventricular aneurysm because of a low incidence of embolism ($6,49-51$). In the current series, three of six emboli occurred in patients with a ventricular aneurysm. Moreover, cessation of anticoagulant therapy after periods of up to 2 years was associated with both recurrence or first appearance of a new thrombus only in patients with aneurysm. Similar to our results, other investigators ($12,15,17$) found the same incidence of embolism in patients with and without aneurysm, and Reeder et al. ($52$) demonstrated that in patients with aneurysm, the frequency of systemic embolism decreased significantly with longer periods of anticoagulant therapy.

**Fibrinolytic therapy in patients with a mobile apical thrombus.** Kremer et al. ($43$) reported lysis of a protruding thrombus in 10 of 16 patients after acute myocardial infarction. At least three of their patients had a mobile thrombus. The treatment was successful in eight of nine patients within 4 weeks of the acute infarction. None of the patients had clinical embolism, and only in one was therapy discontinued because of hematuria. Shenoy et al. ($53$) reported successful lysis of an apical mural thrombus with streptokinase. Considering the foregoing discussion, we selectively applied this therapy to four patients with a protruding mobile thrombus. In the first two previously reported cases ($44,45$), lysis of thrombus was achieved without complication. In the latter two cases, however, systemic embolism occurred, with transient diplopia in one and stroke followed by death in the other. This experience confirms that fibrinolytic agents are capable of lysing ventricular thrombi but suggests that the risks of this therapy may be higher than previously assumed.

**Limitations of the study.** This was an observational study in which anticoagulant and fibrinolytic therapies were not controlled and were applied to a small number of patients. Therefore, the results regarding these therapies are not conclusive. The data regarding resolution and appearance of a new thrombus during the follow-up period can be applied only to long-term survivors on medical therapy because echocardiographic follow-up of ≥6 months was not available in approximately 20% of the patients, mostly because of death or operative interventions during that time period. The results of univariate statistical analysis should be considered with caution given the multiple comparisons made. However, we also used logistic regression analysis, which eliminated fortuitous statistical significance.
Clinical implications. The results of this study support the view that echocardiography should be routinely performed before hospital discharge in all patients with acute anterior myocardial infarction (54,55) to 1) diagnose patients with ventricular thrombus and those with a protruding mobile thrombus who are at especially high risk of embolization; 2) define patients at risk of developing thrombus after hospital discharge; and 3) identify patients who may undergo resolution of thrombus during follow-up. We did not demonstrate a reduction in incidence of ventricular thrombus by early fibrinolytic therapy and a full dose of anticoagulants during the acute phase of infarction. However, long-term anticoagulant therapy applied to a relatively small number of patients in the posthospitalization period was associated with an increased resolution rate of thrombus and with prevention of systemic embolism in patients with documented thrombus. Long-term anticoagulant therapy under echocardiographic guidance is probably indicated until resolution of the thrombus is seen on the follow-up echocardiogram. Weighing the risk-benefit ratio, long-term anticoagulant therapy may be given indefinitely to selected patients with left ventricular aneurysm, decreased or deteriorating left ventricular ejection fraction (that is, in the presence of the factors that predispose to occurrence of a new thrombus during the follow-up period). Lysis of fresh thrombi with thrombolytic agents is feasible, but may be associated with death. More data are needed before thrombolysis is accepted as the therapy of choice in patients with a mobile thrombus (56).

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References


