The Natural History of Left Ventricular Thrombus in Myocardial Infarction: A Rationale in Support of Masterly Inactivity

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One hundred five unselected and consecutive patients were prospectively studied after acute transmural myocardial infarction to assess the incidence of mural thrombus formation and to relate the presence of thrombus to patient outcome in terms of systemic embolic events, functional class and survival. In 87 patients, optimal quality two-dimensional echocardiographic studies were obtained and were repeated at daily intervals to detect mural thrombus formation. The site of infarction was anterior in 53 patients and inferior in 34. On admission, all patients received subcutaneous heparin and antiplatelet agents (aspirin, dipyridamole); none received full anticoagulant therapy.

Left ventricular mural thrombus was visualized between 2 and 11 days (median 6) after the clinical onset of infarction in 21 (40%) of the 53 patients with anterior infarction. No patients with inferior infarction had echocardiographic evidence of thrombus formation. During follow-up of 22 to 51 months (mean 39), none of the 21 patients with mural thrombus had clinical evidence of systemic embolism. One patient with inferior and one with anterior infarction had a cerebral embolus 7 days and 9 months, respectively, after the acute event, but neither of these patients had echocardiographic evidence of left ventricular thrombus at any stage. Echocardiography performed at 1 and 2 years of follow-up showed persistent evidence of thrombus in only 8 (31%) and 5 (24%) of the 21 patients, respectively.

On admission, the functional class of patients with anterior myocardial infarction and thrombus was similar to that of patients without ventricular thrombus. Early inhospital mortality was higher in those without thrombus (9 [28%] of 32 versus 2 [9%] of 21) (p < 0.001) and occurred earlier in time (mean 24 h versus 8 days) (p < 0.001). At 1 year of follow-up, patients with anterior infarction and thrombus formation had improvement in functional class compared with those who did not (p < 0.001).

It is concluded that left ventricular mural thrombus is a common finding in patients sustaining anterior myocardial infarction. The incidence of systemic embolism, however, is low and does not justify full anticoagulation. Furthermore, as early mortality and morbidity were lower in patients with than in those without mural thrombus, mural thrombus, by offering mechanical support to infarcted myocardium, may protect against left ventricular rupture and improve functional class in the long term.

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Methods

Patient selection. Over a 2 year period before thrombolytic therapy became widely used, 105 consecutive patients with a diagnosis of a first acute transmural myocardial infarction underwent two-dimensional echocardiographic examination in the coronary care unit. The diagnosis was based on chest pain of <24 h duration, typical evolutionary ST segment, QRS and T wave changes in at least two continuous electrocardiographic (ECG) leads and a diagnostic increase followed by a decrease of serum creatine kinase enzyme levels. Seventy-nine patients were male and 26 female with an average age of 61 years (range 32 to 82). Patients undergoing early thrombolytic therapy or patients with previous myocardial infarction or a second cardiac disease (e.g., prosthetic heart valve, cardiomyopathy or congenital heart disease) were excluded from the study.

Early management. Within the first 24 h patients were treated routinely with bed rest, nitrates, a calcium channel antagonist and a beta-adrenergic blocker alone or in combination according to the patient’s clinical condition. An intravenous dose of diamorphine was administered when pain was present and low dose subcutaneous calcium heparin (5,000 U) was given on admission and repeated every 12 h for a minimum of 72 h or until the patient was ambulant. Low dose aspirin (75 mg) and dipyridamole (300 mg three times daily) were also instituted on hospital admission and continued for ≥1 year after discharge. No patient was given full anticoagulation (intravenous heparin or warfarin). Clinical assessment of the cardiovascular status was made according to the Killip classification (16) on admission and daily throughout the patient’s hospitalization. At discharge from the hospital, functional class was assessed according to the New York Heart Association classification. The approximate size of myocardial infarction was assessed from peak levels of creatine kinase.

Follow-up. Follow-up data were obtained on all patients from subsequent regular visits or by written or telephone contact with the patient or the patient’s family or general practitioner. The mean follow-up period was 39 months (range 22 to 51).

Two-dimensional echocardiography. This procedure was performed in all patients immediately after admission to the coronary care unit. A high resolution cardiac ultrasound system with 3.5 and 3.75 MHz short focus transducers was used (Hewlett Packard and Toshiba SSH 65A). All studies were recorded on videotape for subsequent replay and frame by frame analysis.

The patients were systematically studied with strict adherence to a standardized examination protocol (17). Particular care was taken to obtain optimal images of the cardiac apex from both long- and short-axis projections (18) with use of all the depths of field settings and minimizing potential near field artifact while maintaining optimal left ventricular wall resolution and, in particular, the endocardial boundaries. Patients whose cardiac apex was not optimally visualized or in whom endocardial definition was limited were excluded from the study. The remaining patients were examined with the same echocardiographic protocol at daily intervals throughout their hospital stay.

Left ventricular thrombus was diagnosed by two-
VENTRICULAR THROMBUS IN MYOCARDIAL INFARCTION

Table 1. Clinical Characteristics of 87 Patients

<table>
<thead>
<tr>
<th>Anterior Infarction</th>
<th>Inferior Infarction</th>
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<tbody>
<tr>
<td></td>
<td>With LVT</td>
</tr>
<tr>
<td>No. of patients</td>
<td>21</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>61 (43 to 79)</td>
</tr>
<tr>
<td>Male/female (no.)</td>
<td>19/2</td>
</tr>
<tr>
<td>Killip classification</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>6</td>
</tr>
<tr>
<td>III</td>
<td>11</td>
</tr>
<tr>
<td>IV</td>
<td>4</td>
</tr>
<tr>
<td>Hospital deaths</td>
<td>2 (9%)</td>
</tr>
</tbody>
</table>

LVT = left ventricular thrombus formation.

dimensional echocardiography when an echogenic mass, distinct from the ventricular wall, was seen in association with a wall motion abnormality from both the apical four chamber or long-axis view and the short-axis view of the left ventricle and cardiac apex (Fig. 1). All echocardiograms were performed by one of two operators and interpreted by an independent observer; all were highly experienced in echocardiography. When the operator and observer disagreed, a repeat study was obtained on the same day.

A total of 856 echocardiographic studies were performed in the 87 patients judged to have a first study of suitable quality, (average 9.2 studies per patient). The operator and observer were in complete agreement on the presence or absence of thrombus in 89.6% of studies. In all 12 studies in which disagreement occurred consensus was reached after repeat study. In 9 of these 12 studies, the disagreement concerned whether a left ventricular thrombus had totally disappeared or had diminished in size in patients with a previous diagnosis of thrombus.

Abnormal segmental wall motion was defined by a determination of regional motion abnormalities according to criteria previously described (19). Briefly, akinesia was defined as an absence of systolic wall thickening. An increase in echogenicity of a segment was considered indicative of myocardial scarring. Dyskinesia was defined as an outward motion of a segment of the left ventricular wall during systole (19). Normal motion was described when all left ventricular segments showed uniform, symmetric inward motion with segmental wall thickening during systole.

Statistical analysis. Data on clinical, enzymatic and ECG variables are presented as mean values ± SD. Comparison of values in the various clinical groups were made with the Student's t test for unpaired data. The change in the patient's functional class at discharge and at 1 year was assessed with the Wilcoxon signed rank test with use of normal approximation (two-tail). A chi-square test was used to evaluate the differences in functional class among the subgroups of patients with myocardial infarction and thrombus formation. Differences were considered significant at a p value <0.05.

Results

Patient characteristics (Table 1). Of the 105 consecutive patients with an acute myocardial infarction, 87 (83%) had echocardiographic studies of sufficient technical quality to be suitable for serial evaluation. Fifty-three patients (61%) had an anterior and 34 (39%) an inferior myocardial infarction. On admission to the coronary care unit, the majority of patients with an anterior infarction (79%) were in Killip class III or IV (p < 0.001). All patients who developed left ventricular thrombus had an anterior infarction. Their initial clinical characteristics did not differ from those of patients with anterior infarction who did not develop mural thrombus. The size of the anterior infarction was similar in patients with and without thrombus (Fig. 2).

Incidence of left ventricular thrombus formation and characteristics of the thrombus. The first echocardiographic examination was performed 11.3 ± 8 h after the onset of chest pain. No patient had left ventricular thrombus on this first examination. In 21 (40%) of the 53 patients with anterior myocardial infarction, a left ventricular thrombus was visualized on at least one study between day 2 and day 13 (median 6 days) after the acute event. No thrombus was detected in any of the 34 patients with inferior infarction. In 6 (28%) of the 21 patients with a mural thrombus, it was pedunculated, presenting a small degree of mobility during the first 5 days (Fig. 3); in 5 others (24%), it was judged as rounded and immobile, occupying the left ventricular apex.
Figure 3. Apical four chamber view on day 4 after an acute anterior myocardial infarction. Note the presence of a pedunculated apical thrombus (arrows) protruding into the left ventricular (LV) cavity. LA = left atrium; RA = right atrium; RV = right ventricle.

The remaining 10 thrombi (48%) were observed to be laminar, lying along and appearing to "pack" the adjacent abnormal myocardium (Fig. 4). In one patient a large rounded thrombus was seen on day 8 along the distal portion of the ventricular septum adjacent to a large apical dyskinetic segment with additional clouds of fine intracavitary echoes within the distal left ventricular cavity (Fig. 5). In the remaining 32 patients with anterior infarction, as well as in patients with an inferior infarction, no thrombus was visualized at any time.

A left ventricular aneurysm, defined at echocardiography as a localized dyskinetic segment of the left ventricular wall, was noted in 14 patients with anterior and in 2 with inferior infarction; in 9 patients, the aneurysm was apical. Left ventricular aneurysm in patients with anterior infarction was equally present in patients with and without mural thrombus formation.

In-hospital course after acute infarction. Patients without left ventricular thrombus had a higher in-hospital mortality rate when compared with those with mural thrombus (p < 0.001) (Table 1). Twelve (14%) of the 87 patients died in the hospital; 5 of the 12, of whom none had thrombus formation, died during the first 72 h (mean 24), seven died between day 4 and day 10 (mean 7.1 days) after the acute event, of whom only two, who died on day 7 and day 8, respectively, had thrombus formation. The cause of death was attributed to acute pump failure or cardiac rupture (including ventricular septal defect) in eight patients and to recurrent ischemia or infarction in four. Five patients had an acute ventricular septal defect and underwent immediate surgery, which was successful in only one. In the patients who died during the

Figure 4. Apical four chamber view on day 3 from a patient after extensive anterior myocardial infarction. Note the presence of a laminar thrombus (arrows) lying distally along the anterior portion of the ventricular septum. The "head" of the thrombus is slightly detached from the endocardial surface and protrudes into the left ventricular cavity exhibiting a small degree of mobility.

Figure 5. Apical four chamber view. The arrowheads indicate the presence of an apical thrombus. Note the fine echoes surrounding the thrombus demonstrating swirling of low velocity intracardiac blood flow at the left ventricular (LV) apex. Abbreviations as in Figure 3.
Table 2. Possible Systemic Embolic Events in 87 Patients

<table>
<thead>
<tr>
<th></th>
<th>Anterior Infarction (n = 53)</th>
<th>Inferior Infarction (n = 34)</th>
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<tbody>
<tr>
<td></td>
<td>With LVT</td>
<td>Without LVT</td>
</tr>
<tr>
<td>Left hemiparesis</td>
<td>--</td>
<td>1</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Arm weakness</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
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LVT = left ventricular thrombus.

in-hospital course, diagnosis of the presence or absence of thrombus was established on clinical grounds in all and by autopsy in 10 of the 12 patients. Autopsy confirmed the absence of left ventricular thrombus in eight patients, including four patients with an acute ventricular septal defect. Autopsy also confirmed the echocardiographic findings of mural thrombus in the remaining two patients.

One patient had a left hemiparesis on day 6 after inferior myocardial infarction. No thrombus had been visualized at any stage. Computed tomography of the head confirmed the presence of localized infarction in the right parietal lobe of the brain.

Ten (11%) of the 87 patients experienced transient arm weakness or blurred vision during the in-hospital early stage of infarction. Left ventricular thrombus was seen in 3 of these 10 patients (Table 2) and its presence did not appear to be related to the occurrence of these transient ischemic episodes. Indeed, in 6 of the 10 patients the transient ischemic episode occurred immediately after an episode of chest pain with ECG repolarization changes, but in none did computed tomography of the head show evidence of localized infarction.

Follow-up course (after hospital discharge). Seventy-five (86%) of the 87 patients (42 with anterior and 33 with inferior infarction) survived hospitalization. At discharge, 29 (69%) of the 42 patients with anterior and 1 patient with inferior infarction were in functional class III of the New York Heart Association classification (p < 0.01), whereas 13 (31%) of the 42 patients with anterior and 18 (55%) of the 33 patients with inferior infarction were in functional class II (Fig. 6). Fourteen patients (42%) with an inferior infarction were asymptomatic at discharge.

At the end of 1 year after infarction, two more patients died. One had a second myocardial infarction and died on admission to the hospital and the other died suddenly at home. Both initially had had an extensive anterior infarction and were in functional class III when discharged. Neither had evidence of left ventricular thrombus at any stage and, in the patient who died during readmission, no thrombus was found at autopsy. One additional patient had a left hemiparesis 9 months after myocardial infarction; no left ventricular thrombus was seen at any stage of his recovery.

The clinical condition of all patients had improved at the end of 1 year after the initial discharge (Fig. 6); the majority of patients had been in New York Heart Association functional class I or II. However, patients with anterior infarction and left ventricular mural thrombus were less symptomatic than were patients who did not have mural thrombus formation (p < 0.001).

Of the initial 21 patients with left ventricular thrombus, only 8 (38%) at the end of 1 year and 5 (24%) at the end of 2 years of follow-up had persistent evidence of left ventricular thrombus. In all later studies in which thrombus was present, the thrombus appeared to be smaller and more highly echo-dense and to be firmly attached to the adjacent akinetic myocardium (Fig. 7). No patient had an embolic event after hospital discharge.

Discussion

Visualization of the left ventricular thrombus. The incidence rate of left ventricular thrombus formation in this study was 40%, similar to that reported in other echocardiographic (4,20,21), surgical (22) and autopsy series (23-25). The presence of left ventricular thrombus can be better assessed with two-dimensional echocardiography (26-31) than with angiography (32,33), and echocardiography is generally recognized as the reference standard for in vivo diagnosis. There are, however, several technical considerations that may lead to false diagnosis. Increased echo densities originating from structures close to the transducer may mask the presence of the thrombus when viewed from the apical window. Also, a transducer related fixed artifact in the near field may give the false impression of a rounded apical mass (27). Assinger et al. (34) emphasized the danger...
of false positive diagnoses and they suggested criteria for diagnosing left ventricular thrombus that included the serial identification of an echo-dense mass with a margin distinct from the ventricular wall, an apical location and associated akinesia of the adjacent myocardial wall. We have applied these criteria with particular care in the visualization of the cardiac apex from both apical long-axis and serial short-axis projections. We would emphasize the importance of these latter projections when the study is performed with the transducer located at the apex of the heart.

**Systemic thromboembolic events.** The incidence of systemic embolism is controversial and, as judged by autopsy data (25,35), is almost uniformly higher than that reported in clinical studies (6,12,22,36,37). This discrepancy between autopsy and clinical data is striking but not surprising. Patients incurring myocardial infarction are also at high risk for peripheral vascular disease, including strokes, so that systemic embolization should not necessarily be attributed to embolus from the heart. Most patients coming to autopsy will have a larger infarction and arterial occlusion of cerebral vessels may be produced by embolism, thrombosis in situ or atherosclerotic narrowing, alone or associated with shock or local alterations of blood flow (35). Many arterial occlusions reported as thromboembolic may be due to thrombus formation in situ, and Blumer (38) has stressed the difficulty encountered in determining at necropsy whether a given lesion is thrombotic or embolic in origin.

Clinical evidence of systemic embolism occurs <5% in the reported large clinical studies (6,7,12). A precise description of the reported embolic events, however, is lacking in these multicenter studies and it may be that a number of presumed systemic emboli do not relate to left ventricular thrombus. This hypothesis may be supported by the wide differences in the reported occurrence of embolism in relation to time of infarction. Some authors (26) suggest that embolism is a typically late complication in infarction, occurring after 2 weeks. Others (21,39) reported that the majority of suspected cases of systemic embolism occur within 2 weeks of myocardial infarction. However, these reports involve few cases of suspected systemic embolization, which in themselves are difficult to attribute only to the presence of thrombus without the existence of bias (8).

Of our 87 patients followed up serially with twodimensional echocardiography, 10 (11%) had a transient ischemic cerebral attack within the 1st week of myocardial infarction. The episode may have been regarded as a thromboembolic event by some. However, we hold the view that other factors may be operating, including a transient fall in blood pressure occurring, for example, during an episode of myocardial ischemia leading to cerebral ischemia without arterial occlusion. This view is supported by an absence of cerebral infarction assessed by computed tomography. Atherosclerotic changes of the aorta and peripheral arteries may also provide an alternative explanation for thromboembolic events in patients with ischemic heart disease. Finally, other mechanisms such as transient alterations of the patient's coagulation state (40,41) may be responsible for the early postinfarction "thromboembolic events."

**Anticoagulant therapy.** Therapeutic trials (6,7,12) assessing the role of anticoagulant therapy for preventing embolic events are difficult to interpret. They all suggest a significant reduction in the frequency of clinically evident thromboembolic complications in broad groups receiving anticoagulant treatment. The majority of these complications, however,
are venous thromboses and pulmonary emboli which, perhaps not surprisingly, may have a high incidence rate in the nontreated group of patients because bed rest after infarction and heart failure predisposes to venous thrombosis and subsequent pulmonary embolism. Although these studies also demonstrated a reduction in the incidence of systemic embolism, the number of these events was small and, when analyzed separately from venous events, is statistically inconclusive.

Echocardiography is able to detect mural thrombus with high sensitivity. The improved diagnostic specificity of this technique, therefore, has provided support for those favoring anticoagulant therapy (8). Observational investigations have reported both positive (42) and negative (9,13,43,44) effects of such therapy in reducing the frequency of left ventricular thrombus and embolization. However, because the overall incidence of systemic embolism is very low, larger numbers of patients will have to be recruited to sustain these claims.

Although short-term treatment with low dose heparin is effective in preventing venous thromboembolism in high risk patients (45-47), no effect has been convincingly demonstrated in the prevention of systemic embolism. All patients in this study were treated with low dose heparin and antiplatelet agents (aspirin and dipyridamole).

It is possible that early thrombolyis for acute myocardial infarction would prevent left ventricular mural thrombus formation either directly, by lysis of the thrombus, or indirectly, by reducing the infarct size and thus the amount of necrotic endocardium after early revascularization (48). Only two prospective studies have been so far performed (48,49) and their results are conflicting regarding the effects on the formation of left ventricular mural thrombus. Both studies failed to demonstrate systemic embolization in either the treated or the untreated group of patients. Both studies (48,49), however, involved few patients and further large randomized studies are necessary to measure the effects of early thrombolytic treatment on left ventricular thrombus formation. Thrombus formation after complete myocardial infarction appeared after 2 days in our study, at a time when systemic heparin therapy would normally be continued after successful thrombolysis. In the clinical situation of "culprit" artery recanalization, there would be no or limited myocardial infarction and thus no left ventricular thrombus. In unsuccessful thrombolysis, heparin may or may not have been discontinued; in these patients with complete infarction our data would support a less favorable outcome if thrombolysis were to prevent left ventricular thrombus. Further studies in this group appear to be justified.

Relation of left ventricular thrombus and prognosis. All of our patients with left ventricular thrombus had a large anterior infarction and the patient age, functional class on admission and extent of infarction were not different from those of patients in whom no thrombus was visualized. Previous studies on left ventricular thrombus (1-3,13,29-31,50,51) have not examined the influence of thrombus formation on short- and long-term patient outcome. In our study, in-hospital mortality was lower and the 2 year outcome more favorable in patients with early mural thrombus than in patients without early thrombus. Moreover, mural thrombus did not occur in any patients whose early postinfarction course was complicated by rupture of the left ventricle. Therefore it appears that the presence of mural thrombus may have short- and long-term beneficial effects in patients with transmural myocardial infarction.

Myocardial infarct expansion, regional thinning and dilation of the infarct zone occur in the setting of a large transmural infarction (52). When infarcted myocardium dilates, wall stress will increase (wall stress = pressure \times \text{radius}^2 \times \text{wall thickness}). This unlimited increase in wall stress may lead to ventricular aneurysm or even to cardiac rupture. Mechanisms that prevent or limit this change in left ventricular geometry are not fully understood, but it is clear that wall thickness is an important determinant of infarct expansion (53). We therefore speculate that left ventricular thrombus has a positive role in the acutely infarcted myocardium. After endocardial damage, collagen is exposed, thereby initiating platelet aggregation, which begins the formation of thrombus (54). This thrombus will act as a foreign body provoking an inflammatory reaction of the underlying myocardium, which will later be followed by a healing response in which fibroblasts and capillary buds invade the thrombus (54). The thrombus becomes firmly attached to its site of origin, enhancing the underlying myocardial scar, limiting potential infarct expansion and partially restoring a full thickness myocardium. In consequence bulging is reduced, resulting in a more effective myocardial contraction. Often, however, expansion of the infarct zone occurs very early after infarction, before thrombus would have time to "organize." This may explain the formation of left ventricular aneurysm and myocardial rupture, which had not been prevented by thrombus.

Conclusions. This prospective study confirms the high incidence of mural thrombosis in acute myocardial infarction. However, it shows that the incidence of clinically detected systemic embolism is low both immediately after the infarction and over a 2 year follow-up period. The presence of a left ventricular aneurysm or mural thrombus, or both, did not appear to influence the occurrence of embolic phenomena. We propose that the presence of a mural thrombus after myocardial infarction should not by itself be an indication for full anticoagulant treatment. The lower incidence of in-hospital mortality and the improved long-term symptomatic status in patients with left ventricular thrombus raises the intriguing possibility that thrombus formation, by participating in the healing myocardial process, confers short- and long-term benefit.
References


