Thrombolytic therapy reduces the incidence of left ventricular thrombus after anterior myocardial infarction

Relationship to vessel patency and infarct size

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Background Controversial evidence exists as to whether thrombolytic therapy reduces the incidence of left ventricular thrombus in acute myocardial infarction and, if so, how this relates to successful reperfusion.

Methods Four hundred and eighteen consecutive patients underwent echocardiography and coronary angiography within 3 weeks of an acute myocardial infarction. A dys-synergic score was calculated by analysing regional wall motion in 18 left ventricular segments. The infarct-related artery was considered patent if TIMI grade 2 or 3 flow and less than 90% stenosis were present. Retrograde perfusion by Rentrop's grade 2 or 3 collaterals was considered significant.

Results Large anterior myocardial infarctions were associated with the highest prevalence (39%) of left ventricular thrombosis. Thrombus was also very frequent if the left anterior descending coronary artery was occluded and no collaterals to the infarct area were seen (75%). Anticoagulant therapy reduced the prevalence of left ventricular thrombus, regardless of whether the infarct-related vessel was patent or not. Conversely, in patients undergoing thrombolysis the incidence of left ventricular thrombosis was lower when the left anterior descending coronary artery was patent, and especially when an early creatine kinase peak, suggestive of reperfusion, was recorded (7%). Finally, the presence of left ventricular thrombosis was inversely related to the asynergy score.

Conclusion These observations suggest that the presence of left ventricular thrombus is related to the extent of myocardial damage. Thrombolytic therapy reduces thrombus probably by salvaging myocardium at risk.

Key Words: Left ventricular thrombus, acute myocardial infarction, thrombolytic therapy.

Introduction

Anterior myocardial infarction is frequently associated with left ventricular thrombus\textsuperscript{1-2} especially when apical akinesia is present\textsuperscript{3,4}. The high risk of systemic embolization (20% approximately) suggests the use of anticoagulants in patients with anterior myocardial infarction and documented thrombus\textsuperscript{5-7}, but whether thrombolytic agents prevent its formation and reduce the incidence of embolization is not clear\textsuperscript{8-11}.

Fibrinolytic agents may beneficially affect left ventricular thrombosis after acute myocardial infarction by (1) direct lysis of the thrombus (2) reduction of myocardial damage by early reperfusion. In a large cohort of patients with acute myocardial infarction, we assessed the effects of systemic thrombolysis on the prevalence of left ventricular thrombosis. In particular, we studied the role of recanalization of the infarct-related artery in preventing the development of left ventricular thrombosis as well as the relationship between the thrombus and the extent of myocardial damage.

Methods

Study patients

We prospectively studied 418 consecutive patients admitted to our Unit between November 1990 and May 1993. We evaluated the presence of left ventricular thrombus by transthoracic echocardiography within 3 weeks of the acute event.
1994 and presenting with a first acute myocardial infarction. We excluded patients aged more than 75 years and those with inadequate echocardiograms, complete left bundle branch block, primary myocardial or valvular heart disease and systemic illnesses that could affect left ventricular function or long-term prognosis.

All study patients had been admitted to the Coronary Care Unit within 48 h of the onset of symptoms and had a proven diagnosis of acute myocardial infarction based on history, ECG changes and abnormal increases in cardiac enzymes. A 16-lead electrocardiogram (standard precordial and peripheral leads, V1, V6 and V3R, V4R) was obtained from all patients immediately after admission and then at least every 4 h, together with serum enzyme determinations. Additional electrocardiograms and blood samples were obtained whenever appropriate. An early peak of the creatine kinase release curve was considered to have occurred when observed within 12 h of the onset of symptoms.

Of the 418 patients enrolled (322 males, mean age 57.7 ± 9.6, range 19–75 years), in 333 there was ST segment elevation of 1 mm or more in at least two adjacent leads; 85 had T wave inversion or ST depression. Infarct location was established as the site of electrocardiographic alterations and of regional wall motion abnormalities recorded on the two-dimensional echocardiogram. The ST segment elevation was inferior in 102 patients, infero-postero-lateral in 50, and anterior in 181. In all cases, there was concordance between the electrocardiographic site of necrosis and regional wall motion abnormalities.

Anterior myocardial infarction was defined as large when (1) the ST segment elevation involved lead V1 or aVL, or both, as well as at least four precordial leads and (2) occlusion, or stenosis, or wall irregularities of the proximal segment of the left anterior descending coronary artery (before the first septal perforator) was observed at angiography.

A larger anterior myocardial infarction was present in 138 patients: these were further subdivided according to the treatments received: thrombolysis (rTPA or streptokinase), intravenous heparin, subcutaneous heparin and aspirin.

**Early fibrinolytic, anticoagulant and antiplatelet therapy**

All patients admitted to the Coronary Care Unit within 6 h of the onset of chest pain, who had diagnostic ST segment elevation and no contraindications, received thrombolytic treatment (42%).

Of the 138 patients with a larger anterior myocardial infarction, 68 (49%) were treated with thrombolytic therapy. Of these, 34 patients received streptokinase (1 500 000 IU i.v. over 1 h) and 34 had rTPA (100 mg i.v. in 2 h). The administration of both thrombolytics was immediately followed by heparin: a 5000 IU bolus followed by a continuous infusion, targeted to maintain the partial thromboplastin time ratio at about 2 (range 1.7–2.3). Before discharge from the Coronary Care Unit, heparin was gradually tapered (median 6–5 range 4–12 days after MI). Antiplatelet therapy with aspirin (150 mg) was started on the first day of treatment in all patients.

Seventy patients with a larger anterior myocardial infarction did not receive fibrinolytic treatment, either because of contraindications (30 patients) or because of the late arrival (40 patients). Of these, 22 received intravenous (titrated to the partial thromboplastin time ratio) and 30 subcutaneous (25 000 IU daily) heparin. In both instances the drug was continued for the whole period of bed confinement (5 to 13 days). The remaining 18 patients, in whom anticoagulant therapy was also contraindicated, received only antiplatelet agents.

All patients studied underwent the following investigations. Two-dimensional echocardiography was performed by experienced operators unaware of the therapy each patient had received. Examinations were conducted using a Sonos 500 Hewlett Packard echocardiograph and employing a 2·5 or 3·5 MHz transducer, or both. In all patients, the examination was performed after discharge from the Coronary Care Unit, within 2 weeks of the acute event (average 10·2, range 7–15 days), when the patients were clinically stable and only took oral therapy.

Echocardiograms were recorded on videotape and reviewed in real time, slow motion and stop frame mode by three experienced echocardiographers, blinded to the study protocol. Each study included all standard echocardiographic views; left ventricular diameters were measured in the parasternal short axis at papillary muscle level.

Standard criteria for identifying left ventricular thrombus were used and the diagnosis was established when the following conditions were met: (1) an echo-dense mass with distinct borders was identified in different echocardiographic views, and was easily visible throughout the cardiac cycle; (2) the wall motion of the adjacent myocardium was abnormal (dyskinetic or akinetic).

The regional wall motion was assessed in 18 left ventricular regions (Fig. 1) which were assigned an asynergy score (0 = normal; 1 = hypokinesia; 2 = akinesia; 3 = dyskinesia). A global score was then obtained by adding individual segment values; the apical score was calculated from distal segments.

**Coronary arteriography**

Biplane left ventriculography (30°RAO and 60°LAO) and selective coronary angiography were performed by the Judkins technique in all patients within 3 weeks of the infarction. The left and right coronary arteries were imaged in multiple views, before and after intracoronary nitrates (200 μg, slow bolus) to overcome the potential effects of vasoconstriction.
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Inferior Anterior wall
Posterior Anterior wall septum
Segments:
Distal
Middle
Proximal

Figure 1  Echocardiographic analysis of regional wall motion abnormalities: at three standard apical views the left ventricle was divided in 18 segments as shown in the figure.

Whenever present, coronary arterial lesions were evaluated semiquantitatively by two independent angiographers: end-diastolic cine frames were selected for optimal visualization of stenosis and magnified five times. Eccentric stenoses were evaluated in two orthogonal views. A normal arterial segment was identified immediately proximal and distal to the lesion and measured with a caliper. A stenosis was considered significant if it reduced the coronary diameter by at least 50%. If no significant lesions were present on the infarct-related artery, the location of irregularities of the vessel wall was also recorded.

Angiograms were also analysed for the presence of collaterals to the infarct region and Rentrop’s scale was used for grading collaterals141. Angiographic perfusion of the infarct zone was considered significant either when the infarct-related vessel was patent (with or without residual stenosis) and exhibited TIMI grade 2 or 3 flow or when Rentrop’s grade 2 or 3 collaterals were present.

Follow-up
All patients were followed up for at least one month after the myocardial infarction and all embolic events identified both clinically and by laboratory investigations were recorded. Echo Doppler analysis of carotid arteries was performed in all patients who developed neurological ischaemic events.

Statistical analysis
Continuous data are expressed as mean ± SD. The chi-square test and two-tailed Student’s t-test for unpaired data were used as appropriate. Correlations between continuous variables were assessed with multivariate regression analysis.

Differences were considered significant for a probability value of 0-05 or less.

Results

Left ventricular thrombus: relation to infarct location and type of treatment

Left ventricular thrombi were detected in 67 of the 418 study patients (16%). Table 1 shows the prevalence of left ventricular thrombus according to the site of myocardial infarction. Of the 85 patients initially presenting with ST segment depression or T wave inversion on the admission electrocardiogram, only three had left ventricular thrombus: all these patients eventually developed abnormal Q waves.

The prevalence of thrombus was low in inferior infarctions (2-9%), but higher (6%) in the presence of posterolateral extension. Patients with a small area of anterior necrosis and exhibiting a similar asynergy score (inferoposterior: 12-5 ± 6-4, anterior: 13-9 ± 7-3, P=ns) had a similar prevalence of left ventricular thrombus (7-3%). The highest prevalence was recorded in patients with anterior ST segment elevation and significant lesion or occlusion of the proximal left anterior descending coronary artery (39%).

Overall, the prevalence of thrombus in the different treatment groups (thrombolysis, i.v. heparin, s.c. heparin, aspirin) was not significantly different, probably because of the low prevalence (16%) in the whole study population. However, when the effects of treatment were assessed in the highest prevalence group (i.e. large anterior infarctions), statistically significant differences became apparent (Fig. 2).

Patients receiving thrombolytics showed a lower prevalence of left ventricular thrombosis (26%) than the other patients (45%, P=0-04). Patients treated with either intravenous or subcutaneous heparin had a significantly (P<0-05) lower prevalence (respectively 45% and 47%) than those treated with aspirin, who exhibited a 67% prevalence. The difference was even more striking in patients treated with streptokinase (32%, P=0-03) and rt-PA (recombinant tissue plasminogen activator) (20%, P=0-002). Patients undergoing thrombolysis had a
Table 1  Left ventricular thrombus prevalence according to the site of myocardial infarction and ST segment alterations on the admission ECG

<table>
<thead>
<tr>
<th>ECG</th>
<th>ST segment depression</th>
<th>ST segment elevation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Site of myocardial infarction</td>
<td>Angiography</td>
</tr>
<tr>
<td></td>
<td>Inferior</td>
<td>Inf. post. lat.</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>n patients</td>
<td>85</td>
</tr>
<tr>
<td>LV thrombosis %</td>
<td>59 ± 44</td>
<td>56 ± 5</td>
</tr>
<tr>
<td>Global score</td>
<td>7.7 ± 2</td>
<td>8.6 ± 2</td>
</tr>
<tr>
<td>Apical score</td>
<td>3.8 ± 0.4</td>
<td>2.9 ± 0.7</td>
</tr>
</tbody>
</table>

* vs all P<0.05.
** vs *P<0.05.

Table 2  Age, risk factors and treatment given during the acute phase and after discharge in patients with a large anterior myocardial infarction

<table>
<thead>
<tr>
<th>Thrombolysis</th>
<th>i.v. Heparin</th>
<th>s.c. Heparin</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>68</td>
<td>22</td>
<td>30</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55 ± 8</td>
<td>56 ± 9</td>
<td>57 ± 12</td>
</tr>
<tr>
<td>Risk factors (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td>58</td>
<td>41</td>
<td>27</td>
</tr>
<tr>
<td>Smoking</td>
<td>59</td>
<td>59</td>
<td>67</td>
</tr>
<tr>
<td>Hypercholesterol</td>
<td>43</td>
<td>59</td>
<td>43</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28</td>
<td>54</td>
<td>40</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16</td>
<td>23</td>
<td>30</td>
</tr>
<tr>
<td>Treatment (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrates</td>
<td>100</td>
<td>100</td>
<td>97</td>
</tr>
<tr>
<td>β-block</td>
<td>21</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Ca&quot;+ Ant</td>
<td>8</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>59</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Chronic phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrates</td>
<td>8</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>β-block</td>
<td>37</td>
<td>45</td>
<td>37</td>
</tr>
<tr>
<td>Ca&quot;+ Ant</td>
<td>49</td>
<td>41</td>
<td>63</td>
</tr>
<tr>
<td>ACE I</td>
<td>20</td>
<td>18</td>
<td>43</td>
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</tbody>
</table>

β-block = beta-adrenergic blocking agents.
Ca"+ Ant = calcium channel antagonists.
ACE I = ACE inhibitors.

lower prevalence of thrombus than those receiving i.v. heparin (P<0.05).
The five treatment groups were similar with regard to age, risk factors and concomitant treatment (Table 2), except for lidocaine administration, because of the high incidence of reperfusion arrhythmias in thrombolysed patients.

**Angiographic perfusion of the infarct area and left ventricular thrombus in anterior infarction**

As shown in Fig. 3, the patency of the infarct-related vessel was greater in thrombolysed patients than in the

Figure 2  Prevalence of left ventricular thrombus in the four treatment groups in the large anterior myocardial infarction.
Successful thrombolysis prevents LV thrombosis

Thrombolysis
Heparin
Aspirin

Figure 3 Coronal angiographic results in the three groups of patients with a large anterior myocardial infarction. ■=closed coronary; □=perfusion of the occluded coronary by collateral vessels; ○=patent coronary without early creatine kinase peak; ●=patent coronary with early creatine kinase peak.

Figure 4 Percent prevalence of left ventricular thrombus and residual perfusion of myocardial infarction-related area. ■=closed coronary; ○=perfusion of the occluded coronary by collateral vessels; □=patent coronary without early creatine kinase peak; ●=patent coronary with early creatine kinase peak.

No significant differences were found among the five treatment groups as regards the asynergy score (global and apical), the number of segments with hypokinesia, akinesia and dyskinesia and the left ventricular diameters. However, the ischaemic score was significantly lower in patients with a patent infarct-related artery, especially when associated with clinical signs of reperfusion. The decrease of both apical and global ischaemic score was accompanied by a parallel reduction in the prevalence of left ventricular thrombus (Fig. 5).

Multivariate regression analysis of the clinical and echocardiographic data obtained in the whole study
Figure 5 The percent prevalence of left ventricular thrombus (bars) are shown for patients with closed coronary (●), retrograde perfusion of closed coronary by collateral vessels (□), patent coronary (□) or early creatine kinase peak (⊙). Mean values (circles) and standard deviation of the asynergy score for each group are also represented.

Embolic events

Five patients developed embolic events (two strokes; two transient ischaemic attacks; one peripheral embolism). All had sustained an anterior myocardial infarction and four had a proximal-LAD lesion and left ventricular thrombus: only one of these received thrombolysis but without clinical and angiographic evidence of reperfusion. Of five patients suffering an embolic event, only one had no echocardiographic evidence of thrombosis before and after the event; the angiographic study showed a significant stenosis of the left main coronary artery with severe reduction of left ventricular function, significant mitral regurgitation and left atrial enlargement. In the four patients with cerebrovascular accidents, echo Doppler examination of carotid arteries excluded significant local disease.

Discussion

Prevalence of left ventricular thrombosis in acute myocardial infarction

Our study confirms the results of previous reports by documenting the high prevalence of left ventricular thrombi in patients with anterior myocardial infarction. In fact, the overall incidence in our population was 31%.

Thrombus developed more frequently when the antero-apical region was involved and when the infarct area was large, as suggested by the strong relationship with the severity of the echocardiographic asynergy score. In fact, the highest incidence was observed in patients with a proximal LAD lesion or occlusion. Conversely, patients with ST segment elevation in inferior leads or ST segment depression had a low prevalence of thrombus (respectively 2.9 and 3.5%), and small dysfunctional areas. Indeed, the prevalence of thrombus increased when inferior necrosis extended towards the postero-lateral wall. When this was the case, the prevalence was similar to that observed in anterior myocardial infarctions of comparable extension.

Table 3 Multivariate regression analysis for left ventricular thrombus in patients with a large anterior myocardial infarction

<table>
<thead>
<tr>
<th></th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>ns</td>
</tr>
<tr>
<td>Males</td>
<td>ns</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td>ns</td>
</tr>
<tr>
<td>Smoking</td>
<td>ns</td>
</tr>
<tr>
<td>Hypertension</td>
<td>ns</td>
</tr>
<tr>
<td>Hypercholesterol</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetes</td>
<td>ns</td>
</tr>
<tr>
<td>Beta-blocking agents</td>
<td>ns</td>
</tr>
<tr>
<td>End-diastolic diameter</td>
<td>ns</td>
</tr>
<tr>
<td>End-systolic diameter</td>
<td>ns</td>
</tr>
<tr>
<td>Segments with hypokinesia</td>
<td>ns</td>
</tr>
<tr>
<td>Segments with akinesia</td>
<td>ns</td>
</tr>
<tr>
<td>Segments with dyskinesia</td>
<td>ns</td>
</tr>
<tr>
<td>Global score</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Apical score</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Absence of perfusion</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

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Fibrinolytic and anticoagulant therapy and left ventricular thrombus

Despite the widespread clinical use\[18,19\], the impact of thrombolysis upon the formation of left ventricular thrombus during acute myocardial infarction varies in different reports. Some studies reported a significant reduction in the prevalence of left ventricular thrombus\[8,20-22\]; in others the reduction did not achieve statistical significance\[7\], others found no differences\[6,23\].

Patients' inclusion criteria, the dose of heparin and the time at which its administration was started vary quite widely in these reports, and may explain their conflicting results. Also, none of the previous studies separated large from small anterior infarctions: a different proportion of the two types in the study population might have significantly affected the prevalence of left ventricular thrombus. Moreover, not taking into account infarct size may represent a confounding factor for evaluating the potential effects of various treatments.

Also, previous studies often showed significant differences in treatment strategies; in our study all patients underwent systemic thrombolysis, if not contraindicated, immediately followed by full anticoagulation with i.v. heparin. In addition, our study is the first one in which the patients were stratified according to the site of coronary occlusion and the size of the infarct area. There is no doubt that a balanced mix of severity, obtained by a large consecutive series, represents an advantage in the analysis of the results since anticoagulant and fibrinolytic therapies obviously cannot be randomized. Indeed, a statistically significant reduction in left ventricular thrombosis by fibrinolytic agents was evident only in patients with a large anterior myocardial infarction, probably because of the relatively low prevalence of thrombus observed in the other groups.

As in previous reports\[24-27\], anticoagulant therapy with heparin reduced the prevalence of thrombus regardless of the route of administration.

Reduction of left ventricular thrombus by thrombolysis: possible mechanisms

The mechanisms by which thrombolytic agents may reduce the prevalence of left ventricular thrombus have not been investigated. Theoretically, the effect may be related to the ability of these agents to directly lyse the thrombus; alternatively, the reduction may be secondary to the improvement of left ventricular function caused by an early reperfusion. Finally, a combination of the two mechanisms cannot be excluded.

In the group of patients treated with full doses of i.v. heparin, the prevalence of left ventricular thrombus was lower than in patients who only received aspirin and similar regardless of whether the infarct-related artery was patent or not. Probably, the subsequent heparin therapy justifies the comparable incidence of thrombus observed in patients with thrombolysis was unsuccessful. The further reduction in the prevalence of thrombus was restricted to the patients who received thrombolytics and had reperfusion or whose myocardium was protected by collateral vessels.

Two previous studies reported a relationship between the absence of thrombus and the patency of the infarct-related vessel\[28,29\]. However, none obtained a statistically significant difference, perhaps because of the small sample size. Only a recent preliminary report showed a significant inverse relationship between early development of left ventricular thrombosis and coronary patency observed 48 h after admission\[30\].

Left ventricular thrombus and embolism

An increased risk of embolism has been demonstrated in patients with thrombi and our data agree with previous reports\[38,29\]: in the first month from the acute event we observed embolic complications only in patients with anterior myocardial infarction. The presence of left ventricular thrombus on echocardiography considerably increased the risk of this complication: among patients without evidence of thrombosis we observed only one case of transient ischaemic attack, whilst four events were recorded in patients with left ventricular thrombosis. In our series only patients with mobile, protruding thrombi and hyperkinesia of the adjacent myocardium received chronic anticoagulant therapy\[30-33\]; of the five patients with embolic events, only one had a thrombus with these features and was treated with anticoagulants. A more extensive use of chronic anticoagulation in all patients with left ventricular thrombosis may be indicated in order to prevent this complication\[34\].

Conclusions

These data suggest that left ventricular thrombosis development is inversely related to myocardial reperfusion of the infarct area and its timing. The evidence of a very low rate of left ventricular thrombosis in patients with patent vessels and early creatine kinase peak suggests that the salvage of myocardium at risk may be the mechanism by which thrombolytic agents are effective in reducing this complication.

The presence of left ventricular thrombus in a large anterior myocardial infarction identifies patients with reduced left ventricular function and may be a marker of unsuccessful thrombolytic therapy. A long-term follow-up with serial echocardiograms is ongoing in our institution and will hopefully provide further data on the value of ventricular thrombus detection for predicting left ventricular function outcome.

References


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