Lysis of left ventricular thrombi with urokinase

Peter Kremer, M.D., Rainer Fiebig, M.D., Volkmar Tilsner, M.D., Walter Bleifeld, M.D., and Detlef G. Mathey, M.D.

ABSTRACT In 16 patients with recent myocardial infarction (3 to 12 week old) and with large left ventricular thrombi systemic thrombolysis with urokinase was performed. Left ventricular thrombi were diagnosed by two-dimensional echocardiography; in all patients the mural thrombus was located in the area of recent myocardial infarction. Each of three patients suffered an embolic episode before the initiation of thrombolytic therapy and the episode caused a stroke in one. Urokinase was infused intravenously at a rate of 60,000 U/hr for 2 to 8 days in combination with intravenous heparin (200 units/kg × 12 hr). Left ventricular thrombi were successfully lysed in 10 of 16 patients, as determined by two-dimensional echocardiography. In four of the six remaining patients only partial thrombolysis was achieved and in two thrombolytic treatment failed. There was no evidence of embolic events during thrombolysis in any of the 16 patients. The success of thrombolysis seemed to depend on the age of the thrombus: the thrombus was dissolved in eight of nine patients undergoing thrombolysis within 4 weeks of the acute myocardial infarction vs in two of seven patients receiving treatment later (p = .057). The presence of a left ventricular aneurysm or depressed left ventricular function also appeared to reduce the likelihood of successful thrombolysis. All patients were discharged on oral anticoagulants. At 6 months follow-up (n = 9) no recurrence of left ventricular thrombus was found. These results show that left ventricular thrombi can be safely lysed by intravenous urokinase. However, for better definition of the risk and benefit of this new therapy further investigation is necessary.


Mural left ventricular thrombi are common in patients with acute myocardial infarction.1–4 As calculated from autopsy reports, the incidence of mural thrombi in patients who died of myocardial infarction ranged from 14% to 68%.5–9 Thrombi are more common in patients with large than in those with small infarcts.1,2,4,10 Although a mural thrombus adheres to the endocardium, it can produce systemic emboli. The incidence of embolism varies considerably depending on whether the mural thrombus is detected during life or at autopsy. Autopsy studies3,8,10–14 have reported a 22% to 64% incidence of embolism in patients with cardiac thrombus, whereas in clinical studies, in which the left ventricular thrombus was diagnosed by angiography, two-dimensional echocardiography, or at operation, a lower incidence (0 to 36%) has been described.2,4,15–22 In one study, half of the emboli were cerebral.23

Left ventricular thrombi are commonly found by two-dimensional echocardiography in patients in the early stages of acute myocardial infarction, especially those with an extensive anterior infarction.1,2,4,22,24–28 However, no generally accepted therapy for patients with left ventricular thrombi has been found. Some authors advise use of anticoagulation2,3,29,30 or anti-thrombotic therapy in the presence of a left ventricular thrombus; in some patients with large, protruding thrombi surgery is recommended because of the high risk of embolization.

In this report, thrombolytic therapy with urokinase as an alternative therapeutic method is described in a series of 16 patients with large, protruding left ventricular thrombi developing early after infarction.

Methods

Patients. In 16 patients (age 40 to 69 years) with left ventricular thrombi systemic thrombolysis with urokinase was performed. The clinical characteristics of the patients are summarized in table 1. All patients had their first myocardial infarction 3 weeks to 3 months before study entry. Selection criteria for inclusion in the study were (1) large, protruding left ventricular thrombi located in the area of myocardial infarction, (2) time after acute myocardial infarction of 3 weeks to 3 months, and (3) no contraindications to systemic thrombolytic therapy with urokinase.

Immediately before initiation of thrombolytic therapy five patients were on heparin (three on low-dose heparin [100 units/kg body weight sc every 12 hr], two on full-dose heparin [200 units/kg body weight]) for a mean of 22 days. Patients were all asymptomatic during the 3 weeks to 3 months before study entry, and all were in New York Heart Association class I or II.
THERAPY AND PREVENTION—VENTRICULAR THROMBI

TABLE 1
Patient characteristics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/sex</th>
<th>Infarct location</th>
<th>Time between MI and urokinase therapy</th>
<th>Anticoagulation before urokinase therapy</th>
<th>Anticoagulation after urokinase therapy</th>
<th>LV EF (%)</th>
<th>Effect of thrombolytic therapy on LV thrombus</th>
<th>Duration of thrombolytic therapy (days)</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62/M</td>
<td>A (aneur)</td>
<td>4 wk</td>
<td>Dicumarol</td>
<td>Pos.</td>
<td>32</td>
<td>↓</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>63/M</td>
<td>A</td>
<td>3 mo</td>
<td>None</td>
<td>Neg.</td>
<td>46</td>
<td>+ (late)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>57/F</td>
<td>A (aneur)</td>
<td>2 mo</td>
<td>Aspirin</td>
<td>Pos.</td>
<td>38</td>
<td>↓</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>40/M</td>
<td>A</td>
<td>4 wk</td>
<td>None</td>
<td>Neg.</td>
<td>52</td>
<td>+ (late)</td>
<td>8</td>
<td>Hematuria requiring discontinuation</td>
</tr>
<tr>
<td>5</td>
<td>69/M</td>
<td>1 (aneur)</td>
<td>2 mo</td>
<td>None</td>
<td>Pos.</td>
<td>60</td>
<td>+</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>53/F</td>
<td>A</td>
<td>3 wk</td>
<td>Full-dose heparin</td>
<td>Pos.</td>
<td>33</td>
<td>+</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>68/F</td>
<td>A</td>
<td>3 mo</td>
<td>Dicumarol</td>
<td>Neg.</td>
<td>38</td>
<td>↓</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>50/M</td>
<td>A</td>
<td>3 wk</td>
<td>Low-dose heparin</td>
<td>Neg.</td>
<td>57</td>
<td>+</td>
<td>3</td>
<td>Systemic embolus: A. tibialis anterior</td>
</tr>
<tr>
<td>9</td>
<td>63/M</td>
<td>1</td>
<td>4 wk</td>
<td>None</td>
<td>Equivocal</td>
<td>55</td>
<td>+</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>55/M</td>
<td>A (aneur)</td>
<td>3 mo</td>
<td>Dicumarol</td>
<td>Neg.</td>
<td>29</td>
<td>−</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>52/M</td>
<td>A</td>
<td>4 wk</td>
<td>Full-dose heparin</td>
<td>Pos.</td>
<td>35</td>
<td>+</td>
<td>8</td>
<td>Systemic embolus: Mild hematuria</td>
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<tr>
<td>12</td>
<td>45/M</td>
<td>A (aneur)</td>
<td>5 wk</td>
<td>Low-dose heparin</td>
<td>Neg.</td>
<td>30</td>
<td>−</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>49/M</td>
<td>A</td>
<td>4 wk</td>
<td>Dicumarol</td>
<td>Pos.</td>
<td>49</td>
<td>+</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>59/M</td>
<td>A</td>
<td>4 wk</td>
<td>Dicumarol</td>
<td>Pos.</td>
<td>34</td>
<td>+</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>61/M</td>
<td>A</td>
<td>4 wk</td>
<td>Low-dose heparin</td>
<td>Neg.</td>
<td>37</td>
<td>+</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>54/F</td>
<td>A</td>
<td>2.5 mo</td>
<td>Dicumarol</td>
<td>Pos.</td>
<td>50</td>
<td>↓</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

A = anterior; I = inferior; aneur = left ventricular aneurysm; LV = left ventricular; EF = ejection fraction; ↓ = reduction in thrombus size; + = resolution of thrombus; − = no change.

units/kg in over 12 hr), six were on dicumarol, and one was on aspirin (500 mg tid). Four patients received no anticoagulants or antithrombotic drugs. Dicumarol and aspirin were discontinued before the initiation of thrombolytic therapy.

Three patients had clinical evidence of systemic emboli before the institution of thrombolytic therapy; one patient (No. 4) suffered a stroke resulting in temporary right-sided hemiparesis. The two other patients (Nos. 8 and 11) had systemic emboli in the left A. tibialis anterior and the left A. tibialis posterior, respectively, resulting in temporary numbness and paresthesia of the affected areas. All patients were fully informed of the benefits and risks associated with thrombolytic therapy and of the investigational nature of this procedure. They all gave their consent to participate in the study.

The first case of successful lysis of a left ventricular thrombus was incidental. The patient (No. 6) had undergone bypass surgery and afterward had suffered an anterior myocardial infarction. Two weeks later a large left ventricular thrombus was seen on two-dimensional echocardiographic examination despite continuous heparin therapy.

Three weeks after bypass surgery and while still on a full dose of heparin, the patient experienced deep-vein thrombosis resulting in massive swelling of the right leg. To resolve the venous thrombosis intravenous heparin therapy was initiated. To our surprise, not only the venous thrombosis, but also the left ventricular thrombus had disappeared after 7 days of therapy; there was no evidence of systemic or pulmonary embolization.

In a next step we performed intravenous thrombolysis in three patients who had a large mobile left ventricular thrombi despite heparin therapy and who were considered candidates for surgical thrombectomy. Because two of the patients had undergone bypass surgery in the weeks before and had poor left ventricular function, reoperation carried a major risk. In these patients thrombolysis resulted in complete dissolution of the left ventricular thrombus with no complications.

After these positive experiences we were encouraged to perform thrombolysis in patients with large, mobile left ventricular thrombi likely to embolize. In most of the patients these had developed despite use of anticoagulant therapy.

Two-dimensional echocardiography. Two-dimensional echocardiograms were obtained with a Diasonics 3400 R phased-array sector scanner. A standard two-dimensional echocardiographic examination consisting of parasternal short- and long-axis views and apical two- and four-chamber views was performed in all patients; additionally, multiple tangential views from the apex were recorded to measure maximal thrombus size.

In all patients thrombus size was such that the two-dimensional echocardiographic study was considered definitely positive for left ventricular thrombus by three different observers. Thrombus was defined as an echo-dense mass adjacent to an asynergic left ventricular segment protruding into the left ventricular cavity. As described by Stratton and Ritchie, maximal thrombus thickness was estimated by measuring the distance between the thrombus-blood interface and the thrombus-endocardial interface. Between a first and second analysis intraobserver reproducibility was as follows: mean thickness of the left ventricular thrombus was 3.8 ± 1.3 and 3.7 ± 1.2 cm, respec-
platelet scintigraphy immediately 40%.

formed before starting thrombolytic therapy. The circumscribed bulging at bus) or dyskinesis was and four-chamber views; the average thickness neither increased nor decreased more than 8 mm on serial studies. Thus, a reduction of greater than 8 mm in thrombus thickness was considered a reduction in thrombus size.

An aneurysm was defined echocardiographically as a well-circumscribed bulging segment of myocardium demonstrating dyskinesis or akinesis.

Global left ventricular ejection fraction was estimated from the apical two- and four-chamber view by tracing the endocardium of the left ventricle (excluding the left ventricular thrombus) at end-diastole (peak R wave) and end-systole (smallest left ventricular area in both views) with a Philips light-pen unit. Global ejection fraction was calculated separately for the two- and four-chamber views; the average between the two measurements was used in the analysis. A significant left ventricular dysfunction was defined as a global ejection fraction of less than 40%.

Two-dimensional echocardiographic examination was performed before starting thrombolytic treatment, every day during intravenous urokinase therapy, and 2 days and 1 week after termination of thrombolytic therapy.

Follow-up studies by two-dimensional echocardiography were performed 3, 6, and 12 months after thrombolysis.

Thrombolytic therapy. After an initial intravenous bolus injection of 250,000 U urokinase (Ukidan R, Serono Pharmaceutical Company, Freiburg, West Germany), the drug was infused intravenously at a rate of 60,000 U/hr for 2 to 8 days in combination with heparin (mean dosage 200 units/kg iv over 12 hr). After termination of thrombolytic therapy dicumarol was administered and heparin was withheld as soon as dicumarol was effective. All patients were discharged on dicumarol.

Results

Effects of thrombolysis. Left ventricular thrombi were successfully lysed in 10 of 16 patients as evidenced by the absence of residual thrombus visible on the two-dimensional echocardiogram (figures 1 to 4). In four patients only partial thrombolysis was achieved, i.e., there was a reduction in thrombus size of greater than 8 mm as compared with the initial echocardiogram. In two patients no reduction in thrombus size was seen

![FIGURE 1. Echocardiogram from the two-chamber view demonstrating a large left ventricular thrombus protruding into the left ventricular outflow tract.](image-url)
after thrombolytic therapy. The time required for thrombolysis differed considerably: in eight patients in whom the left ventricular thrombus disappeared completely, thrombolysis occurred within 2 to 8 days of urokinase therapy. In two patients (Nos. 2 and 4) with residual thrombus after 8 days of urokinase the thrombus had completely disappeared by 1 week after termination of urokinase therapy. In the four patients in whom only partial thrombolysis could be demonstrated infusion of urokinase was maintained for 8 days, as in the two patients who failed to respond.

On follow-up, nine of the 10 patients in whom thrombolysis was successful were restudied by two-dimensional echocardiography 6 months after treatment. In no case was there evidence of reoccurrence of thrombus.

The follow-up to this point dates back 12 months in five patients: reexamination by two-dimensional echocardiography in this subset also did not reveal reformation of left ventricular thrombus.

**Determination of successful thrombolysis.** On retrospective analysis patient data revealed some differences concerning the efficacy of thrombolytic therapy. The chances for successful thrombolysis were best when the age of the thrombus was 4 weeks or less. In eight of nine patients undergoing thrombolytic therapy 3 to 4 weeks after acute myocardial infarction left ventricular thrombi were successfully dissolved by systemic urokinase. However, thrombolysis was successful in only two of seven patients with a myocardial infarction between 5 and 12 weeks old (p = .057).

Left ventricular ejection fraction estimated by two-dimensional echocardiography was moderately or severely depressed in all but one of the six patients in whom thrombolysis was partial or did not occur (36 ± 8%, n = 6); only four of 10 patients in whom thrombolysis was successful had evidence of significant left ventricular dysfunction, whereas the remaining six patients had a normal or mildly depressed left ventricular ejection fraction (46 ± 10%, n = 10).

In each of five patients a left ventricular aneurysm was demonstrated by two-dimensional echocardiography; four patients had a left ventricular apical aneurysm after acute myocardial infarction and one patient had a posterior wall aneurysm. In all four patients with an apical aneurysm thrombolytic therapy was unsuccessful, in contrast to the case in the one patient with a posterior wall aneurysm in whom thrombolysis was successful.

Immediately preceding thrombolytic therapy 99mTc-platelet imaging was performed in eight patients. At the time the platelet scan was performed four patients were on anticoagulants, three were on dicumarol, and one was on full-dose heparin. Four patients received...
no antithrombotic or anticoagulant drugs. Only two patients, one of them on dicumarol, demonstrated ongoing platelet deposition on the $^{99m}$Tc-platelet scan. Despite demonstration of thrombus activity, thrombolysis was effective in only one of the two patients; in the other patient (No. 1), who had an apical aneurysm, thrombus size decreased slightly during therapy, but the larger part of the apical clot remained unchanged.

FIGURE 3. Large apical left ventricular thrombus in a patient after acute myocardial infarction.

FIGURE 4. Same patient as in figure 3. Thrombus resolved after 8 days of thrombolytic treatment with intravenous urokinase.
Five patients had negative platelet scans; despite the failure to demonstrate thrombus activity by this technique thrombolyis was successful in three patients. Additionally, successful thrombolysis was achieved in one patient with an equivocal scan.

Complications. During thrombolytic therapy and at follow-up there was no clinical evidence of embolic events in any of 16 patients. One patient developed hematuria during thrombolytic therapy, which required discontinuation of the therapy after 5 days of treatment. At that time, the left ventricular thrombus had been partially dissolved. Reexamination by two-dimensional echocardiography 1 week and 6 months later revealed no further reduction in thrombus size. Another patient developed only mild hematuria after 3 days of therapy with intravenous urokinase. Thrombolytic treatment was continued and resulted in complete thrombolysis of a large left ventricular thrombus that initially protruded into the left ventricular outflow tract.

Discussion

Systemic embolic are a well-known complication of mural thrombi in patients with transmural myocardial infarction. Since left ventricular mural thrombi can now easily be diagnosed by two-dimensional echocardiography, patients at risk of systemic embolism can be identified. The question arises, however, as to how these patients should be treated to prevent embolization. Long-term anticoagulation is considered by many a method of diminishing the risk of embolization after myocardial infarction. However, to our knowledge no prospective studies are available demonstrating a lower incidence of emboli with anticoagulant therapy in patients with proven left ventricular thrombi. Anticoagulation is thought to prevent further apposition of the thrombus by enhancing organization and endothelialization. Edwards, however, reports that thrombi larger than 5 mm are rarely organized, regardless of their age.

Recently published data suggest that full-dose heparin or warfarin anticoagulation may lead to thrombus resolution in the setting of acute myocardial infarction. According to the report of Visser et al., oral anticoagulant therapy resulted in thrombus resolution in only two of 15 patients within a period of 4 months. In contrast, Asinger et al. reported that in six of seven patients on oral anticoagulants left ventricular thrombi were found to be resolved 9 ± 5 months after acute myocardial infarction. These authors also found that resolution of thrombus occurred in some patients without anticoagulation or with antithrombotic drugs.

In seven of 10 patients on coumarin therapy Tramarin et al. observed the disappearance of left ventricular thrombi within 5 weeks after myocardial infarction.

However, in contrast to our patient population, the patients of Tramarin et al. did not begin anticoagulant therapy until their left ventricular thrombi were observed by two-dimensional echocardiography. Since the left ventricular thrombi in our patients had developed despite anticoagulation in the majority of cases, it appears unlikely that they would have been dissolved by the same medication.

If recurrent systemic emboli develop despite adequate anticoagulation surgical removal of the thrombus becomes necessary. This may also be true for large protruding and mobile thrombi that are likely to embolize.

In this report we introduce an alternative method of treatment of mural left ventricular thrombi, i.e., systemic thrombolysis with urokinase. By use of this method left ventricular thrombi less than 3 months old that were adherent to an area of myocardial infarction were dissolved in two of three of patients. All patients were fully heparinized during the acute stage of myocardial infarction, i.e., they received heparin for at least 72 hr or until they were ambulatory. Half of the patients (eight of 16) were on oral anticoagulants or were fully heparinized before thrombolysis.

Left ventricular thrombi of patients in this study were remarkably large, with an average maximal diameter of 3.7 ± 1.2 cm. Nevertheless, it took only several days of thrombolytic therapy to completely resolve them. Although some of the thrombi were attached to the left ventricular wall with a stalk, no emboli occurred during or after thrombolysis independent of the result. During a follow-up period of 6 months, no recurrence of thrombus or embolism was noted.

These data suggest that intravenous lysis with urokinase is an effective and probably safe method of dissolving large left ventricular thrombi. In our opinion, lysis should be attempted (1) in patients being considered for surgical removal of thrombus, (2) in patients with peripheral recurrent emboli despite adequate anticoagulation, and (3) possibly in patients with large protruding thrombi likely to embolize.

The potential benefit of thrombolysis has to be weighed against the risks of urokinase-induced bleeding and embolization. In the small series of 16 patients reported here bleeding complications in the form of hematuria was seen in two and required termination of urokinase therapy in one. Urokinase-induced
embolization was not noted at all. However, the number of patients is too small to provide conclusive evidence concerning the risk related to urokinase-induced thrombolysis of left ventricular thrombi. Additionally, since this study had no control group, the likely behavior of the left ventricular thrombi in the absence of thrombolytic treatment cannot be judged. Therefore, the suggestions above should be considered preliminary. For a definite answer regarding the benefit and risks of the new method a prospective randomized trial is required.

References
Lysis of left ventricular thrombi with urokinase.
P Kremer, R Fiebig, V Tilsner, W Bleifeld and D G Mathey

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