Fate of Left Ventricular Thrombi in Patients With Remote Myocardial Infarction or Idiopathic Cardiomyopathy

John R. Stratton, MD, John W. Nemanich, MD, Karl-Arne Johannessen, MD, and Arthur D. Resnick, MD

Although left ventricular thrombi that form acutely after myocardial infarction frequently resolve spontaneously or with anticoagulant therapy, the fate of left ventricular thrombi in patients with remote myocardial infarction or with idiopathic cardiomyopathy remains unknown. To determine the natural history of such chronic left ventricular thrombi, we performed serial echocardiograms on 51 patients with remote myocardial infarction (≥3 months; mean, 31±41 months) and on nine patients with idiopathic dilated cardiomyopathy. Mean follow-up was 24±22 months during which 3.5±1.4 echocardiograms were obtained. Studies were interpreted by blinded observers, and an increase or decrease of more than 5 mm in maximal thrombus thickness was defined as significant. Among all 60 patients left ventricular thrombi were unchanged in 24 (40%), completely resolved in 24 (40%), decreased in size in four (7%), increased in size in five (8%), and decreased and then increased in size in three (5%). Results in patients with remote infarction and idiopathic cardiomyopathy were similar. Warfarin therapy, which was at the discretion of the primary physician, was associated with a higher prevalence of thrombus resolution compared with no therapy (59% vs. 29%, p=0.02). Definite systemic emboli occurred in seven patients (12%), all at times while they were not anticoagulated. Among the 48 thrombi that were present on two or more echocardiograms, changes in thrombus shape (classified as protruding or flat) occurred in only 16%, and changes in thrombus movement (classified as mobile or immobile) occurred in only 10%. We conclude that left ventricular thrombi in patients with remote infarction or idiopathic cardiomyopathy usually persist in the absence of anticoagulant therapy and usually retain the same shape and motion characteristics. (Circulation 1988;78:1388–1393)

Left ventricular thrombi that form in the setting of acute myocardial infarction have been studied extensively, and several studies document that either spontaneous or anticoagulant-induced resolution is relatively common. In the first 1–12 months after acute myocardial infarction, approximately 20–40% of thrombi undergo spontaneous resolution without anticoagulant therapy1–3 and approximately 42–88% resolve with anticoagulant therapy.2–5 In addition, of thrombi that persist early after myocardial infarction, spontaneous variations in shape and mobility patterns occur frequently (41% and 29%, respectively).6 However, the fate of left ventricular thrombi present in other populations is largely unknown. The purpose of the present prospective study was to determine by serial echocardiography the rate of thrombus resolution in patients with left ventricular thrombi attributable to either remote myocardial infarction (≥3 months) or idiopathic dilated cardiomyopathy. In addition, we evaluated sequential changes over time in the morphological features of protrusion and mobility that have been associated with an increased embolic risk. Last, we assessed the effects of warfarin anticoagulation, which was administered at the discretion of the patients’ primary physicians, on the rate of thrombus resolution.

Patients and Methods

Patients

Patients with left ventricular thrombus diagnosed by echocardiography between October 1979 and January 1987 were eligible for entry. Beginning in

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April 1983, we attempted to obtain serial echocardiograms at 6–9-month intervals on all patients who had previously been identified as having a definite left ventricular thrombus. From April 1983 on, we prospectively entered all consenting patients with newly diagnosed thrombi and obtained serial echocardiograms at 6–9-month intervals. A total of 95 patients had left ventricular thrombi by echocardiography. Of these, 25 could not be restudied because of death (n=13), refusal (n=1), distance (n=3), or loss of follow-up (n=8), and an additional 10 patients were excluded because they had thrombi detected only during the first 3 months after an acute myocardial infarction. The remaining 60 patients were divided into two groups, remote myocardial infarction and cardiomyopathy, depending on whether they had evidence of a previous myocardial infarction more than 3 months before the initial echocardiogram. Infarction was defined as present if there was a definite Q wave infarction on the electrocardiogram and/or documentation of typical electrocardiographic and enzyme changes. Data regarding survival status, radionuclide ejection fraction (available in 48 patients), the time and type of all previous myocardial infarctions, embolic events, and warfarin therapy were obtained by chart review. The diagnosis of a peripheral embolic event required either surgical or autopsy documentation. The diagnosis of a definite cerebral embolic event required either autopsy documentation or that the criteria developed by Hart et al.\textsuperscript{7,8} be met. Decisions regarding anticoagulation therapy were made by the patients’ primary physicians.

Two-dimensional Echocardiography

Echocardiographic examinations in multiple standard and nonstandard views were performed with a wide-angle, phased-array scanner (Toshiba Medical Systems, Japan) or a mechanical sector scanner (ATL Ultramark 8, Bellevue, Washington) with previously described methods.\textsuperscript{9} At the conclusion of the study, all echocardiograms were interpreted by two observers who were blinded to all patient data. Studies on a given patient were read at a single session but in a random order. Left ventricular thrombus was defined as a mass of echoes that was distinct from the endocardium, present throughout the cardiac cycle, identified in at least two views, and located in an area of asynergy. The sensitivity (95%) and the specificity (86%) of the echocardiographic diagnosis of left ventricular thrombus in our laboratory are relatively high.\textsuperscript{9} Studies were read independently by each observer; in cases of disagreement, the studies were reviewed again to arrive at a consensus. Each study was graded as positive, equivocally positive, or negative for left ventricular thrombus. The eight studies interpreted as equivocally positive by consensus reading of both observers were excluded from all subsequent analyses. Three thrombus characteristics were evaluated on all studies. Thrombi were defined as protruding if they projected into the ventricular cavity and as flat if they did not.\textsuperscript{8,10} Thrombi were classified as mobile if a portion of the thrombus moved independently of the underlying myocardium and as immobile if there was no independent motion.\textsuperscript{8,10} Thrombus thickness was estimated by a one-dimensional measurement of maximal thrombus thickness; the measurement was made perpendicular to the myocardium from the epicardial-pericardial interface to the innermost border of the thrombus-blood interface as previously described.\textsuperscript{11}

\begin{table}[h]
\centering
\caption{Patient Characteristics at Entry}
\begin{tabular}{lcc}
\hline
 & Remote & Idiopathic  \\
 & infarction & cardiomyopathy  \\
(n=51) & (n=9) &  \\
\hline
Age (yr) & 59±8 & 61±13  \\
Anterior MI (%) & 82 & 0  \\
Inferior MI (%) & 20 & 0  \\
Left bundle branch block (%) & 6 & 0  \\
Interval from last MI (mon) & 31±14 & . . .  \\
Ejection fraction & 0.31±0.14 & 0.24±0.17  \\
Left atrial size (cm) & 4.4±0.7 & 5.1±0.9  \\
LV end diastole (cm) & 6.2±0.8 & 6.1±0.8  \\
LV end systole (cm) & 4.9±1.0 & 5.2±0.6  \\
Shortening fraction (%) & 21±10 & 13±4  \\
\hline
\end{tabular}
\end{table}

LV, left ventricle; MI, myocardial infarction.
TABLE 2. Follow-up Data: Duration, Death, Myocardial Infarction, and Antithrombotic Therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Remote Infarction (n=51)</th>
<th>Idiopathic Cardiomyopathy (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiograms (n)</td>
<td>3.5±1.5</td>
<td>3.7±1.3</td>
</tr>
<tr>
<td>Follow-up duration (mon)</td>
<td>24±21</td>
<td>22±25</td>
</tr>
<tr>
<td>Death (%)</td>
<td>31</td>
<td>33</td>
</tr>
<tr>
<td>MI during follow-up (%)</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Systemic emboli (%)</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Warfarin (%)</td>
<td>31</td>
<td>33</td>
</tr>
<tr>
<td>Warfarin therapy duration (mon)</td>
<td>9±11</td>
<td>4±3</td>
</tr>
<tr>
<td>Platelet inhibitory drugs (%)</td>
<td>43</td>
<td>22</td>
</tr>
</tbody>
</table>

MI, myocardial infarction.

A significant increase or decrease in thrombus size was defined as present if there was a change in thrombus thickness of more than 5 mm. We have previously documented the intraobserver, interobserver, and test-retest reproducibility of this estimate of thrombus size. Thrombus resolution was defined as conversion of a positive echocardiogram to negative (Figure 1).

Statistical Analysis

Discrete variables were compared by Fisher’s exact test or Pearson’s χ² test, and continuous variables were compared by an unpaired t test. Data were expressed as the mean±SD.

Results

Patient Characteristics

The clinical features, as well as the left atrial and left ventricular dimensions of the patients in the remote infarction and cardiomyopathy groups, are listed in Table 1. All patients except one were male. In the remote infarction group, the mean interval from the most recent infarction was 31±41 months, and most subjects (82%) had had an anterior infarction. Global ventricular function, as assessed by the radionuclide ejection fraction in 48 patients, was depressed in both groups.

Follow-up duration was similar in patients with remote infarction and cardiomyopathy (24±21 and 22±25 months) as was the mean number of echocardiograms (3.5±1.5 and 3.7±1.3). Death during follow-up was frequent, whereas recurrent myocardial infarction was uncommon (Table 2). Of patients with remote infarction, 43% received platelet inhibitory agents during follow-up, as did 22% of the idiopathic cardiomyopathy group. One third of both groups received warfarin anticoagulation during follow-up, and two thirds did not. Definite systemic emboli occurred in 14% of patients with remote infarction (n=7) during follow-up and in none of the idiopathic cardiomyopathy group (p=NS).

Changes in Thrombus Size, Shape, or Mobility

Among patients with remote infarction, 41% (21 of 51) had no change in thrombus size during echocardiographic follow-up, 37% (19 of 51) had thrombus resolution, 8% (four of 51) had a decrease, 8% (four of 51) had an increase, and 6% (three of 51) had a decrease followed by increase in thrombus size (Table 3). Patients with idiopathic cardiomyopathy had similar findings (Table 3). Thus, among all 60 patients, 40% (24 of 60) had no change in thrombus size, whereas 38% (23 of 60) had thrombus resolution and 7% (four of 60) had a reduction in thrombus size. None of the seven systemic emboli occurred in patients after thrombus resolution had occurred.

Overall, 12 thrombi had completely resolved between the first and second studies; therefore, data regarding serial changes in thrombus shape and motion were available on 48 patients (Tables 4 and 5). Overall, approximately one half of thrombi were initially flat and the other one half protruded. Changes in this thrombus characteristic were uncommon, with only 12% of all thrombi exhibiting any change over time. In regards to thrombus mobility, most thrombi were initially immobile and remained so. Only one thrombus that was immobile on the initial study later exhibited mobility in conjunction with an increase in size. Similarly, of the initially mobile thrombi, most (nine of 12) remained mobile, whereas three of 12 later became immobile.

Comparison of Patients With and Without Thrombus Resolution

Clinical and echocardiographic features of patients with and without thrombus resolution are presented in Table 6. Age, follow-up duration, interval after infarction, ejection fraction, and the use of platelet inhibitory drugs were similar in the two groups. Warfarin therapy was significantly more common in patients who had thrombus resolution (54% vs. 25%, p=0.02). In addition, thrombus thickness on the initial echocardiogram was somewhat less in patients who ultimately had thrombus resolution compared with patients who did not (23±5 vs. 29±13 mm, p=0.01).

Table 3. Changes in Thrombus Size During Follow-up

<table>
<thead>
<tr>
<th></th>
<th>No change</th>
<th>Resolution</th>
<th>Decreased size</th>
<th>Increased size</th>
<th>Decreased, then increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remote infarction (n=51)</td>
<td>21 (41%)</td>
<td>19 (37%)</td>
<td>4 (8%)</td>
<td>4 (8%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Idiopathic cardiomyopathy (n=9)</td>
<td>3 (33%)</td>
<td>5 (56%)</td>
<td>0 (0%)</td>
<td>1 (11%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>All patients (n=60)</td>
<td>24 (40%)</td>
<td>24 (40%)</td>
<td>4 (7%)</td>
<td>5 (8%)</td>
<td>3 (5%)</td>
</tr>
</tbody>
</table>
Warfarin Therapy

Nineteen patients with remote infarction received warfarin therapy for a mean of 9 ± 11 months and 32 did not. Three patients with idiopathic cardiomyopathy received warfarin for a mean of 4 ± 3 months and six did not. Thrombus resolution occurred in 58% of warfarin-treated patients with remote infarction and in two of three warfarin-treated patients with idiopathic cardiomyopathy (Table 7). Among all patients from both groups, thrombus resolution occurred in 59% (13 of 22) of warfarin-treated patients compared with 29% (11 of 38) of untreated patients (p = 0.02) (Figure 2). Among all 24 patients with thrombus resolution (treated and untreated), the time to thrombus resolution was shorter in the warfarin-treated patients than in the untreated patients (10 ± 9 vs. 23 ± 19 months, p = 0.03).

Discussion

The present study sought to define prospectively the course of left ventricular thrombi in patients who had experienced myocardial infarction at least 3 months earlier and in patients who had idiopathic dilated cardiomyopathy. This study differs from most previous studies of the fate of left ventricular thrombi in that patients with left ventricular thrombi due to recent (<3 months) myocardial infarction were excluded because of the relatively extensive data already available. We have used the term “acute” thrombi to denote thrombi present in patients with recent myocardial infarction, whereas the term “chronic” thrombi has been applied to thrombi in patients with remote infarction or idiopathic cardiomyopathy. Although there were relatively few patients in the cardiomyopathy group, the fate of thrombi in these patients appeared similar to patients with remote myocardial infarction.

Over a mean follow-up of 2 years, 40% of patients had no change in thrombus size, and 40% had thrombus resolution. Small numbers of patients showed either an increase (8%) or decrease (7%) of more than 5 mm or a variable change (5%) in thrombus size.

Changes in Shape and Motion Over Time

In addition to the size of the thrombus, we assessed serial changes in two other morphological characteristics: shape (protruding vs. flat) and motion (mobile vs. immobile). Several studies have suggested that left ventricular thrombi that protrude into the ventricular cavity or that exhibit independent mobility are associated with a higher rate of embolization than thrombi without these features.8,10,12,13 However, by performing serial echocardiography on 59 untreated patients, Domenicucci et al6 recently found that these morphological features demonstrated marked spontaneous variability in the first several months after acute infarction and therefore suggested that the assessment of these features was not helpful. They noted that 41% of 59 thrombi had significant changes in shape and 29% had changes in mobility.

In the current study of thrombi largely attributable to remote myocardial infarction, approximately one half of all thrombi were flat, and one half were protruding when first detected. In contrast to the findings of Domenicucci et al,6 nearly all thrombi in the present study that did not resolve retained a stable appearance. Only 10% of all thrombi were initially protruding but became flat, and only 5% of thrombi were initially flat but became protruding.

Most thrombi were immobile at study entry and remained so. Only one of 31 initially immobile thrombi became mobile during follow-up. Of the nine initially mobile thrombi, six remained mobile, whereas three became immobile. Thus, in a population with chronic thrombi, morphological features appear to be relatively stable over time.

Warfarin Anticoagulation

In the present study, decisions regarding the use of warfarin anticoagulation were made by the patients’ primary physicians. However, demographic and clinical features of the group receiving warfarin were not significantly different from the untreated group. Thrombus resolution was twice as common in
warfarin-treated patients as in untreated patients (59% vs. 29%, \(p=0.02\)). Similar results have been noted in the only randomized trial of anticoagulant therapy for established thrombi, although it entered only patients with recent, not remote, myocardial infarction; among warfarin-treated patients, thrombi resolved in 88% of patients during 12 months of treatment, whereas thrombi resolved in only 24% of untreated patients (\(p<0.05\)). In other uncontrolled trials in patients with left ventricular thrombi early after myocardial infarction, thrombi have resolved in 20% (three of 15) and 42% (eight of 19) of untreated patients. Among treated patients, the rates of resolution have been generally higher, being 42% (eight of 19), 80% (eight of 10), and 86% (six of seven) in three studies but only 19% (four of 21) in a fourth study. The differences in results in warfarin-treated patients are difficult to reconcile. However, the only randomized study and the present study, which is the largest single study to date that includes moderate numbers in both treated and untreated groups, are concurrent in suggesting that chronic warfarin increases thrombus resolution compared with no therapy. In the current trial, there was no suggestion that platelet inhibitory therapy caused thrombus resolution.

**TABLE 6. Comparison of Patients With and Without Thrombus Resolution During Follow-up**

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Thrombus resolution (n=24)</th>
<th>No resolution (n=36)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>60±10</td>
<td>59±9</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up duration (mon)</td>
<td>27±23</td>
<td>21±20</td>
<td>NS</td>
</tr>
<tr>
<td>Echocardiograms (n)</td>
<td>4.0±1.7</td>
<td>3.5±1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Interval after infarction (mon)</td>
<td>21±24</td>
<td>38±49</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection fraction (n=48)</td>
<td>28±16</td>
<td>31±14</td>
<td>NS</td>
</tr>
<tr>
<td>Echocardiographic features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombus thickness (mm)</td>
<td>23±5</td>
<td>29±13</td>
<td>0.01</td>
</tr>
<tr>
<td>Platelet inhibitory drugs (%)</td>
<td>38</td>
<td>42</td>
<td>NS</td>
</tr>
<tr>
<td>Warfarin therapy</td>
<td>54</td>
<td>25</td>
<td>0.02</td>
</tr>
<tr>
<td>Warfarin therapy duration (mon)</td>
<td>9±12</td>
<td>8±8</td>
<td>NS</td>
</tr>
<tr>
<td>MI during follow-up</td>
<td>17</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Protrusion on first echocardiogram</td>
<td>63</td>
<td>57</td>
<td>NS</td>
</tr>
<tr>
<td>Mobility on first echocardiogram</td>
<td>29</td>
<td>25</td>
<td>NS</td>
</tr>
</tbody>
</table>

MI, myocardial infarction.

**FIGURE 2.** Warfarin therapy was associated with a higher rate of complete left ventricular thrombus resolution compared with no warfarin therapy.

**Study Limitations**

Anticoagulant therapy was not controlled as part of this study. Thus, although the treated and untreated groups were similar in regard to known clinical variables and the rate of thrombus resolution appeared to be greater in the treated group, the results must be considered suggestive but not definitive. An additional limitation was the lack of follow-up in many potential patients, frequently because of death. Although no emboli occurred after thrombus resolution had been documented, the patient-years of follow-up are currently insufficient to state with absolute certainty that left ventricular thrombus resolution is associated with a reduction in embolic risk in an individual patient. However, in a cross-sectional study, we have previously documented that patients with left ventricular thrombi documented by echocardiography have a clearly increased risk of systemic emboli compared with a control group without left ventricular thrombi.

**Implications**

The present study documents that most left ventricular thrombi in untreated patients with remote myocardial infarction or cardiomyopathy are unchanged in size, shape, and mobility over a 2-year period; approximately 30% resolve. Warfarin therapy may increase the rate of thrombus resolution by approximately twofold. In view of the increased embolic risk associated with chronic left ventricular thrombi and because warfarin is probably effective in causing thrombus resolution, ran-
domized clinical trials to assess the effects of chronic anticoagulation on embolization may be helpful. However, until the risk-benefit ratio of warfarin therapy in patients with chronic left ventricular thrombi is defined by clinical trials, it would be reasonable to withhold treatment, given the known hemorrhagic complications of chronic anticoagulation, which include an approximate 5% risk of major bleeding and a 1% risk of fatal bleeding in patients with ischemic heart disease.15

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References


Key Words • left ventricular thrombi • myocardial infarction • echocardiography • anticoagulation • warfarin
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