Prospective Assessment of Cholesterol Embolization in Patients With Acute Myocardial Infarction Treated With Thrombolytic vs Conservative Therapy*

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Purpose: To determine whether subclinical cholesterol embolization is a frequent sequela of thrombolytic therapy. Case reports of catastrophic cholesterol embolization temporally associated with thrombolytic therapy in 19 patients have suggested a causal relationship. Patients and methods: We prospectively followed 60 patients with acute myocardial infarction who underwent coronary bypass surgery within 1 month. Twenty-nine received thrombolytic therapy for myocardial infarction; 31 were treated conservatively. Two muscle biopsy specimens and one skin biopsy specimen were obtained from the vein harvest site at the time of bypass surgery. Paraffin block and frozen sections from each biopsy specimen were analyzed for evidence of cholesterol embolization. Results: Cholesterol emboli were found in biopsy specimens from 4 of 29 patients who had undergone thrombolytic therapy (14%) and in 3 of 31 patients who had not undergone thrombolytic therapy (10%, p=NS). Clinical evidence of cholesterol embolization occurred in one patient. Cholesterol emboli were distributed inhomogeneously; they were not observed in any skin biopsy specimen and were never present in more than one muscle biopsy specimen from each patient. Conclusions: The prevalence of cholesterol embolization in patients with acute myocardial infarction treated with thrombolytic therapy is not significantly higher than in those treated without thrombolytic therapy. The cholesterol embolization seen in 12% of our patients was mostly subclinical and was probably spontaneous and/or catheterization induced. Isolated case reports of severe cholesterol embolization temporally associated with thrombolytic therapy do not represent a phenomenon that has widespread subclinical occurrence.

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Key words: thrombolytic therapy; cholesterol embolization; complications

Nineteen case reports have attributed multiple cholesterol embolization to thrombolytic therapy for acute myocardial infarction or deep venous thrombosis. However, several large trials of thrombolytic therapy have not reported cholesterol embolization as a complication, and reviews of thrombolytic complications have largely ignored it. To our knowledge, no studies have prospectively assessed the incidence of cholesterol embolization after thrombolytic therapy. In the present study, we prospectively took biopsy specimens from patients after acute myocardial infarction treated with or without thrombolytic therapy to determine if cholesterol embolization is more prevalent in patients treated with thrombolytic therapy.

Methods

Study Patients

Patients were considered for inclusion in this study if they had been admitted to the hospital with acute or recent (within 1 week)

myocardial infarction and had undergone coronary artery bypass surgery within 1 month. Patients were excluded if they had a history of cholesterol embolization, emergent bypass surgery, or had cardiac catheterization and saphenous veins harvested from the same leg. The study was approved by the Geisinger Medical Center Institutional Research Review Board. All patients gave informed consent.

Clinical Features

Patients were interviewed and examined an average of 5 days after cardiac catheterization and again an average of 6 days after bypass surgery. Patients were interviewed for a history of previous thromboembolic events, symptoms of peripheral vascular disease, the presence of concomitant systemic disease, and recent use of anticoagulants. Examination before and after surgery identified vascular bruits, peripheral pulses, and signs of cholesterol embolization, including livido reticularis and distal extremity gangrene. Surgical complications, serum creatinine levels, and eosinophil counts were recorded.

Patients in the thrombolytic group were routinely treated with 100 mg of intravenous tissue plasminogen activator and heparin. Heparin therapy was routinely continued until the time of catheterization.

Tissue Analysis

At the time of surgery, one skin and two muscle biopsy specimens were obtained. Each muscle biopsy specimen measured about 5×10×3 mm. Biopsy specimens were taken from the quadriceps and gastrocnemius muscles if saphenous veins were harvested from the upper and lower leg (50% of patients). Oth-
erwise, two muscle biopsy specimens were obtained from the muscle underlying the incision in the upper (13%) or lower leg (37%). A 5×10-mm full-thickness skin biopsy specimen was taken from the margin of the skin excision. Each specimen was divided; one half was snap frozen and the other half was fixed, processed, and embedded in paraffin. Ten frozen sections were cut from each snap-frozen tissue sample and examined under polarized light for the presence of birefringent cholesterol crystals. Twelve sections were cut from each paraffin block, stained with hematoxylin-eosin, and examined for the presence of cholesterol emboli.

Statistical Analysis

Patient data are reported as the mean ± 1SD. Thrombolytic and nonthrombolytic patient groups were compared using unpaired two-tailed t tests and \( \chi^2 \) analysis. Biopsy-positive and biopsy-negative groups were compared using Fisher’s exact test when expected frequencies were less than 5. A p value of <0.05 was considered statistically significant.

RESULTS

Clinical Characteristics

Patients receiving thrombolytic therapy had higher creatine kinase values (2,441 IU/L vs 981 IU/L, \( p=0.002 \)) and were more likely to have Q-wave infarction (52% vs 19%, \( p=0.02 \)) compared with the nonlytic group (Table 1). (Review of records of nonlytic group patients confirmed that the most common reason for withholding thrombolytic therapy was lack of definite electrocardiographic criteria for acute myocardial infarction. These patients evolved fewer electrocardiographic abnormalities such as Q-waves.) Other characteristics, including age, gender distribution, presence of peripheral vascular disease, extent of coronary disease and revascularization, and complications of bypass surgery were similar between the thrombolytic and nonthrombolytic groups.

Cholesterol Embolization

Clinical evidence of cholesterol embolization (slight toe discoloration) was observed in one patient (Fig 1). Follow-up several months later revealed no permanent sequelae.

Cholesterol embolization was not found in any skin biopsy specimen (Table 2). Muscle biopsy specimens revealed cholesterol embolization in four patients in the thrombolytic therapy group and three patients in the nonthrombolytic therapy group (14% vs 10%, \( p=NS \)). In all seven patients in whom biopsy evidence of cholesterol embolization was found, emboli

![FIGURE 1. Blue discoloration of the fifth toe in patient 27, secondary to cholesterol embolization.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21710/)
were present in only one of the two muscle biopsy specimens. Four of the seven patients had emboli demonstrated in frozen sections (Fig 2), and six of the seven patients had emboli observed in paraffin block sections (Fig 3). When emboli were present in a specimen, they were not observed in all sections from the specimen. Emboli were found in an average of 60% of frozen sections and in 70% of paraffin block sections from positive specimens.

Biopsy-positive and biopsy-negative patients were compared with respect to clinical characteristics, serum creatinine values, and eosinophil counts (Table 3). There were no differences in clinical characteristics or eosinophil counts, but biopsy-positive patients more frequently had abnormal initial creatinine values (57% vs 15%, p=0.025). There were no significant differences between biopsy-positive and biopsy-negative patients in the incidence of creatinine level rise during hospital admission (43% vs 19%, p=0.17) or in the incidence of a concomitant rise in eosinophil count and creatinine level during hospital admission (14% vs 8%, p=NS).

**DISCUSSION**

The major finding of this study is that peripheral cholesterol embolization does not occur frequently after thrombolytic therapy. While peripheral cholesterol embolization may occur occasionally after thrombolytic therapy with clinically evident results, there is not a corresponding subclinical or clinically unrecognized embolic process that occurs routinely as a result of thrombolytic therapy. The overall 12% prevalence of cholesterol embolization in our patients was more likely due to cardiac catheterization and underlying aortic atherosclerosis than to thrombolytic therapy.

This study also provides the first prospective survey of the prevalence of peripheral cholesterol embolization in patients undergoing cardiac catheterization. The 12% prevalence found in this study is intermediate between 25% prevalence found at autopsy of previously catheterized patients and the 1% prevalence observed in consecutive renal biopsy specimens.

**Etiology of Cholesterol Embolism**

Cholesterol embolism occurs in patients with diffuse atherosclerosis, but mechanisms that precipitate discrete episodes of embolism are unclear. Any event that exposes the soft lipid core of an atherosclerotic plaque to the systemic circulation can potentially cause cholesterol embolism. Nineteen patients have been described with cholesterol embolization temporally related to thrombolytic therapy (Table 4). The proposed cause in these patients is dissolution by the lytic agent of thrombus overlying ruptured atherosclerotic plaque, thereby exposing the inner lipid pool to the systemic circulation. However, neither this mechanism nor a causal relationship between thrombolytic therapy and cholesterol embolization has been proved. Several large thrombolytic trials have not reported any patients with cholesterol embolization. To our knowledge, no previous study has prospectively assessed cholesterol embolization in patients undergoing thrombolytic therapy.
Cardiac catheterization has been associated with cholesterol embolization in individual case reports.\textsuperscript{25-38} The proposed mechanism in these cases is mechanical disruption of atherosclerotic plaques by a guidewire or catheter, exposing the soft inner lipid pool to the systemic circulation. To our knowledge, no study has assessed the prevalence of cholesterol embolization in patients surviving cardiac catheterization. Ramirez et al\textsuperscript{23} identified cholesterol embolization at autopsy in 25% of patients with recent catheterization, compared with 2 to 10% in other series of unselected autopsies.\textsuperscript{39-42}

Our study found cholesterol embolization in 14% of patients treated with thrombolytic therapy and in 10% of patients without thrombolytic therapy (\(p=\text{NS}\)). This does not suggest a relationship between cholesterol embolization and thrombolytic therapy. The overall prevalence of cholesterol embolization of 12% in this study was less than the 25% observed in the autopsy study by Ramirez et al\textsuperscript{23} of patients who had undergone cardiac catheterization. The lower prevalence in our patients may reflect a lesser degree of atherosclerosis and prior cholesterol embolization than that which led to the ultimate death of the patients of Ramirez et al.

Clinical Course of Patients With Cholesterol Embolization

Cholesterol embolization, when it produces a clinical picture clear enough to be diagnosed, is often fatal. The mortality rate for patients with clinically evident cholesterol embolization is 58% when it follows cardiac catheterization\textsuperscript{25-38} and 38% when it follows thrombolytic therapy (Table 4). However, Rosman et al\textsuperscript{45} reported a benign clinical course without death or renal failure in 5 of 13 patients following cholesterol embolization. Our findings confirm their observation that cholesterol embolization may occur without severe clinical complications. All seven of our patients with biopsy specimen-proved cholesterol embolization followed a benign course without renal failure, death, gangrene, or severe skin complications. The high prevalence of baseline renal insufficiency in biopsy-positive patients in this study probably reflects a shared etiology of severe peripheral atherosclerotic disease.

Diagnosis of Cholesterol Embolization

Cholesterol embolization is notoriously hard to diagnose because of its nonspecific manifestations. One autopsy study identified 25 cases of widespread cholesterol embolization, none of which was identified clinically premortem.\textsuperscript{39} Cholesterol embolization was suspected in only 31% of 221 patients with autopsy evidence of it in a later series.\textsuperscript{43} Our prospective study confirms these retrospective findings. Although we examined and followed up patients specifically for this complication, clinical findings of cholesterol embolization were found in only one of seven (14%) patients with positive biopsy specimens.

Limitations of the Study

Our study has several limitations.

Tissue Sampling: The incidence of cholesterol embolization in this study (12%) is less than would be expected from the autopsy data of Ramirez et al.\textsuperscript{23} Our patients may have had less severe, diffuse, or chronic vascular disease than that which led to the death of patients in autopsy series. Alternatively, the lower incidence observed in our study may reflect more limited tissue sampling in live patients compared with that available at autopsy. However, we obtained biopsy specimens of the same size as in studies reporting that lower extremity muscle is the most sensitive biopsy site for cholesterol emboli. Maurizi et al\textsuperscript{42} found that biopsy of the vastus lateralis or peroneus longus was 100% sensitive, much more sensitive than biopsy of any other single organ for cholesterol embolus. Anderson and Richards\textsuperscript{41} reported that biopsy of the quadriceps or gastrocne-
### Table 4—Summary of 19 Cases of Multiple Cholesterol Embolization Following Thrombolytic Therapy Reported in the Literature *

<table>
<thead>
<tr>
<th>Source</th>
<th>Clinical Problem</th>
<th>Thrombolytic Drug</th>
<th>Time From Lytic Drug to Presentation</th>
<th>Clinical Manifestations</th>
<th>Outcome</th>
<th>Biopsy Confirmation of CE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stafford et al1</td>
<td>Acute MI</td>
<td>APSAC</td>
<td>48 h</td>
<td>Mottled leg, leg pain</td>
<td>Recovery</td>
<td>-</td>
</tr>
<tr>
<td>Case 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Stafford et al1</td>
<td>Acute MI</td>
<td>APSAC</td>
<td>12 h</td>
<td>Abdominal pain, renal failure, discolored skin</td>
<td>Death</td>
<td>-</td>
</tr>
<tr>
<td>Case 4</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Stafford et al1</td>
<td>Acute MI</td>
<td>APSAC</td>
<td>18 min</td>
<td>Leg pain, renal failure</td>
<td>Recovery</td>
<td>-</td>
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<tr>
<td>Case 5</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Beutler et al2</td>
<td>Acute MI</td>
<td>APSAC</td>
<td>20 h</td>
<td>Myalgias, livido reticularis</td>
<td>Recovery</td>
<td>+</td>
</tr>
<tr>
<td>Shapiro3</td>
<td>Acute MI</td>
<td>tPA</td>
<td>1 wk</td>
<td>Abdominal pain, mottled skin, hypertension, testicular pain</td>
<td>Recovery</td>
<td>+</td>
</tr>
<tr>
<td>Bhardwaj et al4</td>
<td>Acute MI</td>
<td>tPA</td>
<td>24 h</td>
<td>Leg myalgias, livido reticularis, renal failure</td>
<td>Recovery</td>
<td>+</td>
</tr>
<tr>
<td>Queen et al5</td>
<td>Acute MI</td>
<td>SK</td>
<td>1 h</td>
<td>Ecchymosis, acute renal failure, livido reticularis</td>
<td>Death</td>
<td>+</td>
</tr>
<tr>
<td>Glassock et al6</td>
<td>DVT, pulmonary embolus</td>
<td>SK</td>
<td>&lt;24 h</td>
<td>Levido reticularis, skin lesions, gangrenous toes, hypertension, renal failure</td>
<td>Death</td>
<td>+</td>
</tr>
<tr>
<td>Rieben et al7</td>
<td>?</td>
<td>SK</td>
<td>2 d</td>
<td>Livido reticularis, renal failure, gangrenous foot</td>
<td>Death</td>
<td>+</td>
</tr>
<tr>
<td>Ridker and Michel8</td>
<td>DVT</td>
<td>SK</td>
<td>?</td>
<td>Livido reticularis, gangrenous toes</td>
<td>Recovery</td>
<td>+</td>
</tr>
<tr>
<td>Pirson et al9</td>
<td>Acute MI</td>
<td>SK</td>
<td>&lt;24 h</td>
<td>Renal insufficiency</td>
<td>Recovery</td>
<td>+</td>
</tr>
<tr>
<td>King et al10</td>
<td>Acute MI</td>
<td>SK</td>
<td>6 d</td>
<td>Painful toe, livido reticularis, renal failure</td>
<td>Recovery</td>
<td>+</td>
</tr>
<tr>
<td>Pochmalicki et al11</td>
<td>Acute MI</td>
<td>SK</td>
<td>7 h</td>
<td>Livido reticularis, gangrenous toes, renal failure</td>
<td>Recovery</td>
<td>+</td>
</tr>
<tr>
<td>Matturi et al12</td>
<td>Acute MI</td>
<td>SK</td>
<td>8 h</td>
<td>Abdominal pain</td>
<td>Death</td>
<td>+</td>
</tr>
<tr>
<td>Blankenship13</td>
<td></td>
<td>tPA</td>
<td>72 h</td>
<td>Back pain, spinal cord infarct</td>
<td>Death</td>
<td>+</td>
</tr>
<tr>
<td>Case 1</td>
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<tr>
<td>Blankenship13</td>
<td>Acute MI</td>
<td>tPA SK</td>
<td>24 h</td>
<td>Livido reticularis, leg pain</td>
<td>Recovery</td>
<td>+</td>
</tr>
<tr>
<td>Case 2</td>
<td></td>
<td></td>
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<tr>
<td>Schwartz and McDonald14</td>
<td>Acute MI</td>
<td>SK</td>
<td>36 h</td>
<td>Gangrenous toes, renal insufficiency</td>
<td>Recovery</td>
<td>+</td>
</tr>
<tr>
<td>Case 1</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Schwartz and McDonald14</td>
<td>Acute MI</td>
<td>SK</td>
<td>24 d</td>
<td>Painful toes, mottled skin, hypertension, renal failure, bowel infarction</td>
<td>Death</td>
<td>+</td>
</tr>
<tr>
<td>Case 2</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Mendia et al15</td>
<td>Acute MI</td>
<td>SK</td>
<td>30 d</td>
<td>Acute renal failure, cyanotic toes, livido reticularis</td>
<td>Recovery</td>
<td>+</td>
</tr>
</tbody>
</table>

*DVT=deep venous thrombosis; MI=myocardial infarction; SK=streptokinase; tPA=tissue plasminogen activator; CE=cholesterol embolization; APSAC=anisoylated plasminogen streptokinase activator complex.

**mius muscle was 95% sensitive for cholesterol embolization and was the most sensitive biopsy site. Fine et al43 found in their retrospective review that muscle and skin were the organs most often yielding biopsy evidence of cholesterol embolization. These data from other investigators would suggest that we adequately sampled the tissues that are most sensitive for cholesterol embolization. The lack of sensitivity of skin biopsy specimens in this study is not surprising. Maurizi et al42 found skin biopsy specimens to be 41% sensitive, compared with 100% sensitivity for muscle biopsy specimens.**
**Thrombolytic Drug:** Some case reports describing cholesterol embolization after thrombolytic therapy involved streptokinase\(^5\)\(^\text{-}^\text{12}\)\(^\text{14}\)\(^\text{15}\) or anisoylated plasminogen streptokinase activator complex\(^1\)\(^\text{-}^\text{2}\) rather than tissue plasminogen activator\(^3\)\(^\text{-}^\text{4}\)\(^\text{13}\). The results of this study with tissue plasminogen activator cannot be generalized to other thrombolytic drugs.

**Type II Error:** While our study does not support the hypothesis that thrombolytic therapy predisposes to cholesterol embolization, larger studies would be needed to exclude the possibility of a type II error (failure to detect a true difference between the groups). Assuming a 10% baseline prevalence of cholesterol embolization in our nonthrombolytic patients, retrospective power calculations suggest that our study population would have been large enough to detect a 40% prevalence of cholesterol embolization in the thrombolytic group (power=0.8, p=0.05, two-tailed test). Retrospective power calculations, assuming that the difference we observed between the groups (10% vs 14%) was real, suggest that 685 patients would need to be enrolled in each arm to demonstrate statistical significance (power=0.80, p=0.05, two-tailed test). Even if a larger study associated cholesterol embolization with thrombolytic therapy, the benign course of our patients suggests that clinically it would rarely be important.

**Conclusions**

To our knowledge, this is the first prospective study to assess the prevalence of cholesterol embolization in coronary disease survivors who have undergone catheterization. The prevalence in our patients (12%) is intermediate between the 1 to 10% seen in unselected autopsy series and the 25% observed in patients who died after catheterization.

This study does not demonstrate a significantly higher prevalence of cholesterol embolization in patients receiving thrombolytic therapy than in patients treated conservatively. A weak relationship between thrombolytic therapy and cholesterol embolization cannot be excluded, but our finding that most cholesterol embolization is subclinical suggests that any such relationship would be of very limited clinical significance. Isolated case reports of severe cholesterol embolization temporally associated with thrombolytic therapy do not represent a phenomenon that has widespread subclinical occurrence.

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**References**

28 Jay ME. Severe abdominal pain after cardiac catheterization. Choices Cardiol 1990; 4:239-40
42 Maurizi CP, Barker AE, Truehart RE. Atheromatous emboli: a postmortem study with special reference to the lower extremities. Arch Pathol 1968; 86:528-34