OBJECTIVES

This study was designed to analyze the results of fibrinolytic treatment (FT) in a large single-center group of patients with prosthetic heart valve thrombosis (PHVT).

BACKGROUND

Fibrinolytic treatment of PHVT represents an alternative to surgery, but is still controversial because of the risk of embolism.

METHODS

A total of 110 consecutive patients presenting with 127 instances of PHVT received FT between 1978 and 2001. The diagnosis of PHVT was established mainly by fluoroscopy and/or echocardiography. The first fibrinolytic agent used was streptokinase (SK) in 49 cases, urokinase (UK) in 41 cases, and recombinant tissue-type plasminogen activator (rtPA) in 37 cases. A second FT was consecutively infused in 38 patients (30%) and a third FT in 11 others. The efficacy of FT was assessed from hemodynamic parameters derived from echographic examinations as well as on clinical grounds.

RESULTS

Complete resolution of hemodynamic abnormalities was seen in 90/127 patients, partial resolution in 22/127 patients, and no change in 15/127 patients after one or more consecutive fibrinolytic regimens. When SK or rtPA were used as the first fibrinolytic agent, they appeared significantly superior to UK in terms of valve reopening. Fifteen patients died. Severe hemorrhagic complications were observed in six patients. Nineteen documented embolic events occurred during FT. Finally, PHVT recurred in 24 patients, 17 of whom were retreated with lytic agents.

CONCLUSIONS

These results indicate that FT is effective in most cases of PHVT, regardless of prosthesis or site involved. However, embolism, hemorrhage, and death were not uncommon after lytic therapy of left-sided PHVT, limiting its application to patients at high risk with alternative treatment. (J Am Coll Cardiol 2003;41:653–8) © 2003 by the American College of Cardiology Foundation

Thromboembolic complications remain a frequent cause of morbidity and mortality in patients with a mechanical prosthetic heart valve. The reported incidence of such complications ranges from 0.03% to 4.3% patient-years, depending on the generation and the thrombocity of the prosthesis used, the location of the valve, and the quality of the anticoagulation (1–6).

Fibrinolysis of Mechanical Prosthetic Valve Thrombosis

A Single-Center Study of 127 Cases

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the study group. The mean age was 57 ± 17 years (range 2 to 86 years). The mean time between PHV implantation and the thrombotic episode was 4.3 ± 4.2 years (range 14 days to 18 years).

Thrombosed valves comprised 79 (62%) bileaflet valves (47 Saint Jude, 22 Duromedics, 10 Carbomedics) and 48 (38%) tilting disc prostheses (41 Bjoerk Shiley, 7 Kaster Omniscience). They included 79 mitral, 46 aortic, 1 tricuspid, and 1 mitral-tricuspid sites. Thrombosis was obstructive in 115 cases (91%) and nonobstructive in 12 cases (9%). Nearly half the patients (48%) were not receiving adequate anticoagulant therapy at the time of diagnosis of the thrombosis.

Clinical data. The main clinical signs at the time of thrombosis were dyspnea, congestive heart failure, and systemic embolism. In 49 cases (38.6%), massive obstruction of the prosthesis led to acute or subacute pulmonary edema and, in some cases, low cardiac output (New York Heart Association [NYHA] functional class IV). Forty-one patients (32.3%) were in NYHA functional class III and 37 (29.2%) in class II or I. Massive obstruction (NYHA functional class IV) was more frequent with the disc prostheses (26/48, 54%) than with the bileaflet prostheses (23/79, 29%) (p = 0.005). An early systemic embolic episode occurred in 28 cases (21%) before admission or FT.

Diagnostic procedures. The clinical suspicion of PHVT was confirmed by complementary investigations in all patients, except two who were critically ill. Seven patients were catheterized initially. Because poppets impervious to X-rays are used by manufacturers, cinefluoroscopy was generally employed (n = 100). Currently, Doppler transthoracic echocardiography (TTE) is usually performed in such situations (n = 115), sometimes backed up by TEE (n = 49).

Fibrinolytic regimens. In all cases, FT was chosen in agreement with the surgical team, particularly in those patients for whom surgery was contraindicated. Various fibrinolytic regimens were used, depending on the availability of the different agents.

STREPTOKINASE (SK) (STREPTASE, HOESCHT LABORATORIES, GERMANY). Classical regimen: loading dose 500,000 IU in 20 min followed by 1,500,000 IU for 10 h (children’s loading dose 2,000 IU/kg, then 1,200 IU/h for 48 h) without heparin. Accelerated protocol: loading dose 500,000 IU in 20 min, then 1,500,000 IU over 60 min without heparin. This recent option was rarely used in our series.

UROKINASE (UK) (UROKINASE, CHOAY LABORATORIES, FRANCE). High dose: 4,500 IU/kg/h for 12 h without heparin. Low dose: 2,000 IU/kg/h associated with heparin for 24 h.

RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR (rtPA) (BOERINGHER INGELHEIM, GERMANY). High dose (100 mg): loading dose 10 mg, followed by 90 mg for 90 min or for 3 h without heparin. Low dose (50 mg): loading dose 20 mg then 10 mg/h for 3 h without heparin.

A combination of two or more fibrinolytic agents was used in one-third of the patients, particularly with SK and UK, when the first course failed or results were incomplete (Table 1).

Heparin infusion was usually introduced after FT, when fibrinogen level was higher than 0.5 g/l. Heparin infusion to obtain a partial thromboplastin time at least equal to the control value was continued for one week and then replaced by warfarin treatment adjusted to obtain optimal prothrom-

Table 1. Fibrinolytic Regimen

<table>
<thead>
<tr>
<th></th>
<th>SK Group (n = 49)</th>
<th>UK Group (n = 41)</th>
<th>rtPA Group (n = 37)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single</td>
<td>34</td>
<td>24</td>
<td>30</td>
<td>88</td>
</tr>
<tr>
<td>Combined</td>
<td>15</td>
<td>17</td>
<td>7</td>
<td>39</td>
</tr>
</tbody>
</table>

rtPA = recombinant tissue-type plasminogen activator; SK = streptokinase; UK = urokinase.
bin time and international normalized ratio. Low molecular heparin was never used.

**Evaluation of efficacy.** Efficacy of FT was evaluated from the clinical data and the TTE and cinefluoroscopic findings. Although we usually observed a rapid improvement in clinical status, FT was continued until the TTE and/or cinefluoroscopic data became normal.

We defined success as:

1. Full: hemodynamic normalization confirmed by cinefluoroscopy (normal mobility of tilting disks) or TTE/TEE data (normalization of transprosthetic gradient and valve area, normal mobility of leaflet).
2. Incomplete: significant clinical improvement without complete recovery of disc or leaflet motion on fluoroscopy and/or TTE.
3. Failure: no clinical improvement, in many cases associated with death or complications.
4. In some cases, FT succeeded in hemodynamic terms, but failed because of severe complications. These patients were classified as success with complications.

**Statistical analysis.** The relations among the fibrinolytic agents, the valve type, and the efficacy of FT were compared using the Pearson chi-squared test (with Yates correction for small groups).

**RESULTS**

**Efficacy of thrombolytic treatment. OVERALL EFFICACY (FIG. 2).** Full success with one or more consecutive fibrinolytic regimens was obtained in 90 out of 127 cases (70.9%): 37/46 (80%) aortic valve, 52/80 (65%) mitral valve, and 2/2 tricuspid prostheses (100%). Fibrinolytic therapy was more efficient in aortic prosthetic thrombosis than in mitral prosthesis thrombosis ($p = 0.07$). Full success was obtained in 62 patients (48%) with a single fibrinolytic agent, and in 28 other patients using a second or a third fibrinolytic agent consecutively (combined therapy). Combined therapy appeared to be more effective on the aortic site (38/46 82.6%) than the mitral (52/80 65%) site ($p = 0.02$). Incomplete success was obtained in 22 patients (17.3%), usually necessitating surgery. Failure was noted in 15 patients (11.8%), usually leading to surgery.

**Efficacy according to fibrinolytic regimen (FIG. 3).** A single fibrinolytic regimen was used in 88 patients and combined therapy in 39 patients.

In the patients treated by SK as first agent (SK group), 28/49 (57%) had full success with a single agent; 14 other patients (29%) had full success using one or two other fibrinolytic agents (combined therapy). Incomplete success or failure was observed in only seven patients with SK (14%).

In the patients treated by UK as first agent (UK group), 15/41 (36.6%) had full success with the single agent, and 9 other patients (22%) had full success using combined

**Figure 2.** Efficacy of fibrinolysis of prosthetic valve thrombosis.

**Figure 3.** Efficacy according to fibrinolytic agent: on the left, after the first single fibrinolysis treatment (FT); on the right, after complementary FT (combined therapy). rtPA = recombinant tissue-type plasminogen activator; SK = streptokinase; UK = urokinase.
therapy. An incomplete success or a failure was observed in 17 patients (41.4%) treated with UK.

In the patients treated by rtPA as first agent (rtPA group), 21/37 (43%) had full success with a single agent, and 4 others had full success with combined therapy. An incomplete success or a failure was observed in 13 patients (33%) treated with rtPA.

As first fibrinolytic agent, SK or rtPA appeared significantly superior to UK in terms of valve reopening: SK = 57%, rtPA = 43%, UK = 36.6%. Combined therapy improved the results of FT in all groups; however, no significant difference was observed between the three groups.

Analysis of the global results in the three groups showed that full success was obtained in 42/49 (86%) of the cases in the SK group, in 24/41 (59%) in the UK group, and in 25/37 (68%) in the rtPA group. With respect to valve reopening, the SK group thus appeared to be more efficient than the rtPA group or UK group.

EFFICACY ACCORDING TO FUNCTIONAL CLASSES. Fibrinolytic therapy improved the clinical status in all functional classes, but full success was higher in patients in NYHA functional classes I and II than in patients in NYHA functional classes III and IV (25/90, 28%) than in patients in NYHA functional classes I and II (6/37, 16%).

Risk stratification using TEE. Forty-nine patients with PHVT benefited from TEE followed by fibrinolysis from 1989 to 2001. The majority of cases involved the mitral valve (37 mitral, 11 aortic, 1 mitral-tricuspid). Forty-one cases were obstructive and eight were nonobstructive. The overall hemodynamic success rate was 71%; complications occurred in eight patients (18%). There was no significant correlation between the size of the thrombus and the occurrence of embolic events, although a huge thrombus imaged by TEE was associated with failure of FT or complications (p = 0.03).

Subsequent treatment and outcome. SURGERY. Twenty-five patients underwent surgery after thrombolysis because of incomplete success or failure of FT in all cases but two (systematic surgery).

Recurrence. Recurrence was noted in 24 cases (18.9%) with a mean interval of 2.06 years (range 3 months to 7 years). In two pregnant women there were two recurrences. Sixteen patients were treated with FT with a full success rate of 75%, five underwent surgery, two were treated with heparin, and one died soon after admission to hospital.

DISCUSSION

Thrombosis is a serious complication of prosthetic heart valve replacement and incurs a high mortality. Early diagnosis of obstructive thrombosis is paramount in optimizing management.

We report here a single-center study of 127 instances of PHVT treated with fibrinolysis over a 22-year period. The efficacy of FT was assessed by well-established hemodynamic parameters derived from echographic and cinefluoroscopic examinations as well as by clinical evaluation. After one or several consecutive FT regimens, we observed complete resolution of hemodynamic abnormalities in 70.9% of the cases, partial resolution in 17.3%, and no change in 11.8%. Severe hemorrhagic complications were observed in 4.7% of the cases, with 19 (15%) documented embolic events. A number of patients died (11.8%), either from low cardiac output or from complications. In 18.9% of the cases, there was a recurrence.

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**Table 2. Efficacy According to the Prosthetic Valve Type**

<table>
<thead>
<tr>
<th>Valve Type</th>
<th>Tilting Disc (n = 48)</th>
<th>Bileaflet Valve (n = 79)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full success</td>
<td>77% (37)</td>
<td>67% (52)</td>
<td>0.23</td>
</tr>
<tr>
<td>Incomplete success</td>
<td>15% (7)</td>
<td>19% (15)</td>
<td>NS</td>
</tr>
<tr>
<td>Failure</td>
<td>8% (4)</td>
<td>14% (11)</td>
<td>0.34</td>
</tr>
</tbody>
</table>
Management of PHVT is Still Controversial.

Thrombectomy or valve replacement are the treatments of choice for PHVT (7). However, mortality rates are high, ranging from 8% to 20% for urgent cases and 37% to 54% for critically ill patients, depending on the clinical status. However, in a study of 100 patients undergoing surgical treatment for obstruction of various types of currently used mechanical valves, Deviri et al. (13) reported an early mortality rate of 12.3%. The perioperative mortality rate was 17.5% in patients in NYHA functional class IV, and only 4.7% in NYHA functional classes I to III.

Fibrinolysis treatment represents a very interesting alternative to surgery; it is easy to perform, but is still controversial because of the risk of embolism.

The recent review of Lengyel et al. (20) of 200 published reports of left-sided prosthetic heart valve thrombolysis showed an 82% initial success rate, an overall thromboembolism rate of 12%, and a mortality rate of 10%. This consensus conference indicates that FT of left-sided PVT is acceptable for critically ill patients in whom surgical intervention carries high risk or in patients with contraindications to operation. The reasoning against thrombolysis in patients in NYHA functional classes I or II is based on the relatively low surgical mortality in this group, as opposed to the embolic risk of 12% to 17% from thrombolysis.

Our experience is less encouraging than those reported recently by Lengyel and Vandor (21) from a compilation of 10 studies each reporting data from 16 to 110 patients (515 cases). The overall success rate was 84%, mortality 5%, major bleeding 3%, systemic embolism 9% (but only 1.5% of disabling or fatal stroke), and a recurrence rate of 16%.

However, our results are close to those of the recent study of Gupta et al. (22), who reported a single-center study of 110 consecutive patients. A complete hemodynamic response was seen in 81.8%, a partial response in 10%, and failure in 8.2%. There were 21 (19.1%) embolic episodes during therapy, including 6 strokes and 25 recurrences during the follow-up period.

Numerous fibrinolytic protocols have been used over the past 30 years (10,12,20,23–28). So far there is a lack of consensus on the optimal thrombolytic agent and treatment protocol for PHVT, although most experience has been accumulated with SK.

In this study, conventional long-course SK or UK protocols were generally employed as the first line of therapy, often in combination with a second FT. However, rtPA was used as the first agent in 37 cases. Our results suggested that long-course SK is more effective than UK. Recombinant tissue-type plasminogen activator also appears to be an effective fibrinolytic agent, although unlike Lengyel et al. (20), we did not find that rtPA increased embolic risk.

We believe that in critically ill patients, a high-dose, short-course protocol may be proposed for rapid hemodynamic improvement, although for patients in a stable condition conventional long-course fibrinolysis may be both effective and safe.

Although few reports of successful thrombolysis of left atrial clots have been published, we think that a large clot should be ruled out by TEE before instigating FT. Transesophageal echocardiography should be performed in hemodynamically stable patients if uncertainty remains about the mechanism and degree of the obstruction. We feel that FT may be proposed in subacute obstruction after elimination of a large thrombotic material by TEE (29).

Thrombolysis and surgical treatment have been directly compared in only one study (30): rtPA treatment was fully successful without complications in all eight cases of partial or nonobstruction (NYHA functional class II to III), and there was one death among 20 surgical patients in NYHA functional class III to IV. These authors concluded that thrombolysis was an appropriate treatment in selected cases.

Although evidence-based medicine cannot be used for this pathology, a general consensus may be reached based on literature reports (20,21).

**Treatment algorithm (Fig. 4).** A treatment algorithm is required to optimize treatment of PHVT. **Right-sided PHVT:** Fibrinolysis is the first line of therapy. **Left-sided PHVT:** Surgery is usually the treatment of choice of left-sided prosthetic valves (7), particularly in cases of chronic obstruction or in cases of early postoperative obstruction. However, fibrinolysis may be proposed in critically ill patients with acute obstruction if immediate surgery is not possible, or if there is a contraindication to surgery (low cardiac output, respiratory insufficiency, redo surgery). Fibrinolysis treatment may also be proposed to clinically stable patients after elimination by TEE of significant thrombotic material. Finally, Reddy et al. (25) has suggested that thrombolysis may represent a valuable alternative in developing countries with limited resources.

**Study limitations.** This report analyzes retrospectively our experience of 127 prosthetic heart valve thromboses, treated with fibrinolytic agents over the past 22 years. The patients were selected for FT on the basis of the clinical judgment of the physicians.

The choice of the fibrinolytic agent was arbitrary, and the selection criteria of patients for FT were modified as a result of progress in diagnostic procedures. It is difficult to compare agents even among themselves, as they correspond to different generations and periods of utilization. For
example, for the rtPA used since 1990 in cases of FT failure, we chose to operate rather than administer combination FT.

Unfortunately, it is not possible to carry out a prospective randomized trial comparing FT and surgery, as the number of cases of PHVT is too small in a single center, and many factors affect the final therapeutic decision (such as contraindications to either surgery or fibrinolysis).

CONCLUSIONS

Valve obstruction is one of the most serious complications of a mechanical prosthetic valve. Recent studies have pointed out the variety of anatomical lesions (thrombus, pannus) and the wide spectrum of clinical presentations. Furthermore, the advent of new and more accurate diagnostic procedures, particularly TEE, enabled us to better select therapeutic options.

Fibrinolytic therapy is effective in PHVT, and SK and rtPA appear to be more effective than UK. Fibrinolytic therapy seems less effective on mitral valves. Major complications include systemic emboli and death, which are more likely to occur in patients in NYHA functional class IV. Thrombosis recurrence is frequent, particularly on mitral valves.

According to American College of Cardiology/American Heart Association suggestions (7), surgery is the favored treatment of left-sided PHVT. However, FT may be justified in cases of tricuspid valve thrombosis and in selected cases of left-sided PHVT, such as critically ill patients if immediate surgery is not possible, or in cases where there are contraindications to surgery (low cardiac output, respiratory insufficiency, redo surgery).

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REFERENCES