Intravenous Thrombolytic Treatment of Mechanical Prosthetic Valve Thrombosis: A Study Using Serial Transesophageal Echocardiography

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OBJECTIVE	We analyzed the results of intravenous thrombolytic treatment under transesophageal echocardiographic (TEE) guidance in prosthetic valve thrombosis.
BACKGROUND	Thrombotic occlusion of prosthetic valves continues to be an uncommon but serious complication. Intravenous thrombolytic treatment has been proposed as an alternative to surgical intervention.
METHODS	In a four-year period, 32 symptomatic patients with prosthetic valve related thrombosis underwent 54 thrombolytic treatment sessions for the treatment of 36 distinct episodes. All patients had low international normalized ratio values at the presentation. Transesophageal echocardiography was performed at baseline and repeated after each thrombolytic treatment session (total 98 TEE examinations). Streptokinase was used as the initial agent with a repeat dose given within 24 h when necessary. Recurrent thrombosis was treated either with tissue plasminogen activator or urokinase.
RESULTS	The initial success after first dose was only 53% (17/32) but increased up to 88% (28/32) after repeated thrombolytic sessions upon documentation of suboptimal results on TEE examination (p < 0.01). In addition, four asymptomatic patients with large thrombi were also successfully treated with single infusion. The TEE characteristics of thrombus correlated with clinical presentation and response to lytics. Success was achieved with single lytic infusion in 40% of the obstructive thrombi as compared with 75% of the nonobstructive ones (p < 0.05). The success rates of lytic treatment were similar for mitral versus aortic valves, and for tilting disk versus bileaflet valves. Rapid (3 h) and slow (15 to 24 h) infusion of streptokinase resulted in similar success rates. However, major complications (three patients) occurred only in the rapid infusion group.
CONCLUSION	In patients with prosthetic valve thrombosis, intravenous slow infusion thrombolysis given in discrete, successive sessions guided by serial TEE and transthoracic echocardiography can be achieved with a low risk of complications and a high rate of success. (J Am Coll Cardiol 2000;35:1881–9) © 2000 by the American College of Cardiology

Thrombotic prosthetic valve occlusion is an uncommon but serious complication that has been reported to occur in 0.5% to 8% of the left-sided mechanical prosthetic valves and in up to 20% of tricuspid prostheses (1–3). Surgical thrombectomy and valve replacement have been used routinely for this condition, although the operative mortality was quite high in certain subsets (4,5). Intravenous lytic treatment for thrombosed prosthetic valves has been used as an alternative to surgical thrombectomy and valve replacement (6–31). In

recent years, transesophageal echocardiography (TEE) has greatly improved the detection of intracardiac thrombus and valve dysfunction (32–34). Likewise, several authors (35–38) have recommended the use of TEE in the management of thrombotic prosthetic valve occlusions. However, the indications and delivery methods for thrombolytic treatment in prosthetic valve thrombosis have not been well defined. Recently, new treatment algoritms have been proposed in two publications (29,30). The new American College of Cardiology/American Heart Association (ACC/AHA) guidelines on valvular disease (39) essentially adopted the approach proposed in these articles, with more emphasis on the potential side effects of thrombolysis. The knowledge base for the thrombolytic treatment of prosthetic

Abbreviations and Acronyms
ACC/AHA = American College of
            Cardiology/American Heart Association
CT   = computed tomography
INR   = international normalized ratio
NYHA   = New York Heart Association
SKZ   = streptokinase
TEE   = transesophageal echocardiography
tPA   = tissue plasminogen activator
TTE   = transthoracic echocardiography
UK   = urokinase

valve thrombosis is mostly derived from heterogeneous patient series and anecdotal evidence. Therefore, the questions remain regarding the selection of patients according to the thrombus characteristics, the duration and dose of the thrombolytic treatment, the proper monitoring method and the role of intensified anticoagulation as compared with early thrombolysis.

In the present study, we analyzed the results in a consecutive series of patients with prosthetic heart valves in whom the thrombolytic treatment was administered in discrete, successive treatment sessions guided by serial TEE. The success and the complication rates were analyzed according to the echocardiographic and clinical characteristics of the patients.

METHODS

The study group included 32 consecutive symptomatic patients with mechanical heart valves (13 male, 19 female; average age, 36 ± 12 years) who underwent 54 intravenous thrombolytic treatment sessions in the same, single institution between May 1993 and June 1997 for the treatment of 36 distinct valvular thrombotic events (one involving two valves in the same patient). In 6 of these 32 patients, an additional left atrial mural thrombus was also present. These events involved either hemodynamically significant thrombotic valvular obstruction or large valvular thrombus formation with embolic events despite normal valve function (Table 1). In addition, 4 asymptomatic patients (2 male, 2 female) with mechanical heart valves and large (>10 mm in diameter) thrombi were analyzed separately, thus bringing the total number of patients to 36.

The TEE was performed using 5-MHz multiplane transducer connected to a system (Vingmed CFM 800) after oropharyngeal anesthesia (10% lidocaine) and conscious sedation (intravenous midazolam, 1 to 3 mg). Transthoracic echocardiography (TTE) to supplement gradient and valve area calculations was performed using the same system with 3.25-MHz transducers. All echocardiographic examinations were performed at baseline and repeated after each thrombolytic treatment session (total 98 TEE examinations). Each recording was initially evaluated by two echocardio-

graphers independently and the consensus by both reviewers was achieved in a subsequent session. The protocol was approved by the Institutional Review Board. Written informed consent was obtained from each patient before entry into the study.

Echocardiographic criteria. The echocardiographic data used in this study were as follows: prosthetic valve thrombus was recognized as soft and homogeneous, mobile or fixed echo densities located at the valve occluder and/or valve struts. The largest diameter of the thrombus as well as the length of the mobile portion, if present, were measured. A diagnosis of pannus formation was made when fixed, bright echodense structures, sometimes containing focal calcific deposits, were present primarily along the valve ring with extension into the valve orifice. Patients with valve dysfunction due to pannus formation were not included in this series (four patients in the same time period, all confirmed at surgery).

Although different makes of mechanical valves will have different "normal gradient" ranges, we arbitrarily selected the cutoff points for valvular obstruction. These limits were largely based on the previously published values (40). Since we did not have a baseline recording for each valve, more specific cutoff points could not be determined. The limitation of the occluder movement was evaluated subjectively. A significant narrowing of the prosthesis was diagnosed when the Doppler mitral valve area was ≤1.5 cm^2 and the mitral valve mean gradient was ≥10 mm Hg, or when the aortic mean gradient was ≥40 mm Hg.

Thrombolytic treatment. Patients with obstructive thrombus, and those with nonobstructive thrombus, who either had a history of embolization or had a large thrombus mass (≥10 mm base diameter and/or ≥5 mm mobile segment length) were accepted as candidates for thrombolysis. Patients with large thrombus were not excluded. Thrombolytic treatment was contraindicated in patients with bleeding tendency and in those with expanding or hemorrhagic cerebral infarcts.

Streptokinase (SK) was the initial agent infused in all patients. No loading dose of SK was used. In the early experience (15 patients), a total of 1.5 million units of SK was administered in 3 h. In subsequent patients, a slow infusion of 60,000 to 100,000 U/h for a total of 15 to 24 h was given (Table 2). When the persistence of thrombus was documented by repeated TEE, another infusion of 1.5 million units of SK was given. Urokinase (UK) or tissue plasminogen activator (tPA) (depending on the availability) was chosen for recurrent thrombus or in the case of failure of two subsequent SK sessions. The tPA dose was 100 mg (10-mg bolus followed by the infusion of the remaining amount in 5 h). The UK dose for each session was 1.5 million units given as a 15-h continuous infusion (100,000 U/h).

Table 1. Summary of 36 Patients With Prosthetic Valve Thrombosis

No	Age (yr), Gender	Valve Type	Thrombus Type	NYHA Class	Presenting Symptoms	Agent	Protocol	Efficacy	Overall Complications
1.	31, F	Mi, SO ML	FO	IV	Dyspnea	SKZ	Slow	S	No
2.	30, M	Ao, MT ML	MNO	II	C. embolism	SKZ	Slow	S	No
3.	37, F	Mi, SJ BL	MNO	II	C. embolism	SKZ	Rapid	S	No
4.	30, M	Mi, SO ML	FO	III	Dyspnea	SKZ x2+rt-PA	Rapid	F	No
5.	52, F	Mi, CM BL	FO	IV	Dyspnea	SKZ x2	Rapid	S	No
6.	47, F	Mi, SO BL	MNO	III	Dyspnea	SKZ	Slow	S	No
7.	55, M	Mi, SO ML	FO	IV	Dyspnea	SKZ x2	Rapid	S	No
8.	41, M	Mi, SJ BL	MNO	I	C. embolism	SKZ	Rapid	S	No
9.	25, M	Mi, SJ BL	FO	IV	Dyspnea	SKZ	Rapid	S	Epistaxis
10.	49, M	Ao, BS ML	FO	II	Fever	SKZ	Rapid	S	No
11.	46, F	Mi, BS ML	MNO	I	C. embolism	SKZ	Rapid	S	No
12.	40, F	Ao, SJ BL	FO	II	C. embolism	SKZ	Rapid	S	AMI
13.	20, F	Mi, UL ML	MO	III	TIA	SKZ x2	Slow	S	No
14.	68, F	Ao, DM BL	MNO	I	C. embolism	SKZ	Slow	S	No
15.	28, M	Ao, MT ML	FO	III	P. embolism	SKZ x2	Rapid	S	No
16.	25, M	Ao, MT ML	FO	II	Dyspnea	SKZ x2	Slow	F	No
17.	34, F	Mi, UL ML	FO	III	Loss of VS	SKZ	Slow	S	Vaginal hemorrhage
		1st ReTHR	FO	III	Dyspnea	rt-PA		S	
		2nd ReTHR	FO	II	Dyspnea	rt-PA x2		S	
18.	41, F	Mi, UL ML	FO	III	Loss of VS	SKZ x2	Slow	S	No
19.	28, M	Mi, SO ML	MNO	I	TIA	SKZ	Rapid	S	No
20.	48, F	Mi, SO ML	FO	III	Dyspnea	SKZ	Rapid	S	C. embolism
21.	44, M	Mi, SJ BL	MNO	II	TIA	SKZ x2	Rapid	F	No
22.	25, M	Mi, CM BL	FO	III	Loss of VS, Dsypnea	SKZ x2	Rapid	S	No
		Ao, CM BL	MO		Dyspnea				
23.	31, F	Mi, SO ML	FO	III	P. embolism	SKZ	Slow	S	Epistaxis
24.	31, F	Mi, SJ BL	MO	III	Dyspnea	SKZ x2	Slow	S	No
		Re THR	MNO	II	Dyspnea	UK x2		S	
25.	36, F	Mi, MT ML	MNO	II	C. embolism	SKZ x2	Slow	S	No
		ReTHR	MNO	II	Dyspnea	rt-Pa		S	
26.	31, F	Ao, MT ML	FO	III	Dyspnea	SKZ	Slow	S	No
27.	30, F	Mi, SJ BL	FO	II	Dyspnea	SKZ x2	Slow	S	No
28.	36, F	Mi, ATS BL	FO	II	Dyspnea	SKZ	Slow	S	No
29.	37, M	Mi, SJ BL	MNO	I	C. embolism	SKZ	Slow	S	No
30.	23, F	Mi, UL ML	MO	IV	Dyspnea	SKZ x2	Rapid	F	Death
31.	51, M	Mi, UL ML	FO	III	Dyspnea	SKZ x2	Slow	S	No
32.	38, F	Tri, SJ BL	FO	II	Loss of VS	rt-Pa x2		S	No
33.	27, M	Mi, SO ML	MNO	I	Asympt.	SKZ	Rapid	S	No
34.	64, M	Mi, SO BL	FNO	I	Asympt.	SKZ	Slow	S	No
35.	55, F	Mi, SO BL	MNO	I	Asympt.	SKZ	Slow	S	No
36.	69, F	Mi, SO BL	FNO	I	Asympt.	SKZ	Slow	S	No

Abbreviations: F = female; M = male; Mi = mitral; Ao = aortic; Tri = tricuspid valve; ML = monoleaflet; BL = bileaflet; SO = Sorin; MT = Medtronic-Hall; SJ = St. Jude; DM = Duromedics; BS = Björk-Shiley; UL = Ultracor; CM = Carbomedics; F = fixed; O = mobile; NO = nonobstructive; SKZ = streptokinase; rt-PA = recombinant tissue type plasminogen activator; UK = urokinase; lytic agent name x2 indicates that two successive doses were administered; S = success; F = failure; ReTHR = rethrombosis; VS = valve sound; Asympt. = asymptomatic; C = cerebral; P = peripheral; TIA = transient ischemic attack; AMI = acute myocardial infarction.

Definition of thrombolytic success. The response to thrombolytic treatment was defined as a complete success when significant narrowing of the valve (based on hemodynamic measurements mentioned above) was no longer present and a ≥75% reduction in largest diameter of the thrombus mass was achieved. For nonobstructive thrombi, a reduction by ≥75% in thrombus diameter or complete lysis of the mobile portion of the thrombus was required as criteria for complete success. The positive responses that were less than "completely successful" were accepted as partial success.

Heparin and warfarin treatment was started in patients with complete and partial success and heparin therapy was continued until an international normalized ratio (INR) of ≥2.5 was achieved.

Table 2. Hemodynamic Measurements at Baseline and Following Final Thrombolysis Session

Case No.	Mean Gradient (mm Hg)		Mitral Valve Area (cm^2)		Valve	Thrombus Type
	Before	Final	Before	Final		
1.	12	5	1.3	2.7	Mitral	FO
2.	22	22	—	—	Aortic	MNO
3.	3.8	3.6	2.6	2.6	Mitral	MNO
4.	12	10	1.3	1.4	Mitral	FO
5.	10.2	4	1	1.8	Mitral	FO
6.	6	5.4	2.6	2.6	Mitral	MNO
7.	13	3.5	0.8	2.4	Mitral	FO
8.	3	2.9	2.5	2.5	Mitral	MNO
9.	26	5.5	0.7	2.5	Mitral	FO
10.	42	17	—	—	Aortic	FO
11.	5.2	5	2.2	2.2	Mitral	MNO
12.	65	14	—	—	Aortic	FO
13.	10	4	1.5	2.5	Mitral	MO
14.	17	15	—	—	Aortic	MNO
15.	48	22	—	—	Aortic	FO
16.	47	41	—	—	Aortic	FO
17.	25	2.3	0.7	2.8	Mitral	FO
rethromb.	23	2.5	0.8	3		FO
rethromb.	15	2.1	1	3.1		FO
18.	17	2	0.85	2.5	Mitral	FO
19.	6	5.5	3	3.1	Mitral	MNO
20.	19	2.8	1.02	3	Mitral	FO
21.	2	2	2.8	2.8	Mitral	MNO
22.	24	4	1.4	2.8	Mitral	FO
22.	47	19	—	—	Aortic	MO
23.	13	2.5	1.4	3.5	Mitral	FO
24.	9	3.4	0.9	1.9	Mitral	MO
rethromb.	3	3	1.8	1.8		MNO
25.	5	4.3	2.4	2.7	Mitral	MNO
rethromb.	3	3.2	2.6	2.6		MNO
26.	52	18	—	—	Aortic	FO
27.	17	3	1	2.9	Mitral	FO
28.	30	3.2	0.8	2.5	Mitral	FO
29.	3.2	3.2	3.2	3.2	Mitral	MNO
30.	10	6	1.4	1.8	Mitral	MO
31.	18	4.5	1	2.7	Mitral	FO
32.	7.5	2.1	1*	3.2*	Tricuspid	FO
33.	3.5	3.7	2.5	2.5	Mitral	MNO
34.	3	3	2.8	2.8	Mitral	FNO
35.	5	3.5	2.8	2.9	Mitral	MNO
36.	3.5	3	2.8	2.8	Mitral	FNO

Patients are listed in the same order as in Table 1. Abbreviations are same as in Table 1. (*) tricuspid valve area. Rethromb. = Hemodynamic values recorded at the time of rethrombosis for the same patient.

Statistical analysis. Chi-square test and Student's t test were utilized for the comparison of discrete and continuous variables, respectively. A p value of <0.05 was accepted as significant.

RESULTS

The types of the prosthetic valves and clinical status at presentation were summarized in Table 1. Of the 32 symptomatic patients, 23 had mitral, 7 had aortic and 1 had tricuspid valve prostheses. In one patient thrombus complicated both aortic and mitral prostheses. The etiology of valve disease was rheumatic in all patients. The types of prosthetic valves were 13 tilting disks and 11 bileaflet valves in mitral position, and 5 tilting disks and 3 bileaflet valves in aortic position. The only tricuspid prosthesis in this series was a bileaflet design. The average interval between valve replacement and presentation was 133 ± 132 weeks (1 to

Table 3. Comparison of Thrombolytic Success for the Initial and Subsequent Doses of Thrombolytics According to Valve Type and Location

	Initial Thrombolytic Success (%)	Subsequent Thrombolytic Success (%)	Overall Success (%)
Primary			
Mitral	12/24 (50%)	9/12 (75%)	21/24 (87.5%)
Aortic	5/8 (62.5%)	2/3 (66.6%)	7/8 (87.5%)
Total	17/32 (53%)	11/15 (73.3%)	28/32 (87.5%)
Rethrombosis			
Mitral	2/4 (50%)	2/2 (100%)	4/4 (100%)
Tricuspid	0/1	1/1 (100%)	1/1 (100%)
Total	2/5 (40%)	3/3 (100%)	5/5 (100%)
Overall	19/37 (51%)	14/18 (78%)	33/37 (89%)

624 weeks; median, 103 weeks). In 4 of 32 patients (12.5%), recurrent thrombus was documented 20 ± 6 weeks (median, 20 weeks) after initially successful thrombolysis. One of these four patients had a third recurrence 22 weeks after the last one. Of note, all patients had subtherapeutic INR values at the presentation (1.3 ± 0.3). Recurrent thrombotic events were also associated with low INR values. Atrial fibrillation was present in 19 of 36 patients (53%).

The symptoms at presentation (Table 1) of 36 distinct clinical episodes in 32 patients were mainly dyspnea (58%) and embolic events or transient ischemic attacks (36%). Interestingly, four patients reported muffling or cessation of their prosthetic valve sounds. The New York Heart Association (NYHA) functional class was III or greater in 50% of the episodes.

The number and the type of treatment sessions are also shown in Table 1. In the mitral position, 41 thrombolytic sessions (including 4 recurrent thrombus) were performed in 27 episodes in 23 patients. In aortic position 9 thrombolytic sessions were given for 7 episodes in 7 valves. The patient with both aortic and mitral valve thrombi was given SK in two successive sessions. The patient with tricuspid prosthesis previously had SK infusion at another institution and was presented with recurrence (14). Doppler hemodynamic measurements before and after the final session of thrombolytic treatment were listed in Table 2.

The outcome of thrombolytic treatment. According to the study definitions, four episodes resulted in partial success (Table 3). These were included in the complete success group for their small numbers. The initial rate of success after the first dose of SK in primary valvular thrombosis was only 53% (17/32), but increased up to 87.5% (28/32) after repeated thrombolytic sessions upon documentation of suboptimal results on TEE examination ($p < 0.01$). One additional thrombolytic session was administered in 17 episodes. A total of three thrombolytic sessions were necessary in only one patient, who had an unsuccessful result. In four patients with five episodes of recurrent thrombosis, a single dose was successful in two and two successive treatments were necessary in the remain-

ing three. Of the three patients with no response to lytics, two were maintained on regimens of higher-dose oral anticoagulants and the third one underwent surgery.

The initial and overall success rates of thrombolytic treatment in mitral and aortic valves were 50% and 63%, and 87.5% and 87.5%, respectively ($p = $ NS). The overall success rates in tilting disk and bileaflet valves were 86% and 94%, respectively ($p = $ NS). The success rates for thrombolysis were 89%, 92% and 80% in patients with NYHA class $\leq$II, III and IV symptoms, respectively ($p = $ NS). There was no difference in success rate for rapid as compared with slow infusion of SK (Table 4).

Echocardiographic thrombus characteristics and thrombolytic response. Baseline TEE results for each valve in the symptomatic initial (n = 32) and recurrent (n = 5) thrombotic episodes were analyzed together (total 37 valve-episodes) (Table 5). Interobserver agreement was achieved in 96 of 98 TEE recordings (98%) regarding the diagnosis of thrombus and definition of its characteristics. Thrombus characteristics were correlated with clinical presentation. A fixed thrombus mass measuring at least 10 mm at its base was documented in 21 episodes (57%) of which all were associated with hemodynamically significant valvular obstruction. In contrast, a mobile thrombus with significant motion of the thrombus mass (average length, 12.1 ± 5.5 mm; 5 to 22 mm), regardless of the size, was found in 16 episodes (43%), and it was associated with valvular obstruction in only 4 (25%, $p < 0.001$). However, mobile thrombi were found in 10 of 13 discrete episodes that were presented with embolic events (77%), while only 6 of 24 (25%) episodes without embolism were associated with mobile thrombi ($p < 0.05$). Nonobstructive thrombi were smaller (8.6 ± 5.3 mm vs. 17.6 ± 7.6 mm, $p < 0.001$) and they were less likely to be associated with class III or greater symptoms at presentation as compared with the obstructive thrombi (8% vs. 71%, $p < 0.001$).

After the initial thrombolytic dose, complete success was achieved in 10 of the 25 (40%) obstructive thrombi. In nine more instances, thrombus was lysed enough to become nonobstructive and in the remaining six, it continued to be

Table 4. Patient Characteristics in Rapid and Slow Streptokinase Infusion Groups

| | SKZ Infusion | | |
	Rapid	Slow	p Value
Age (yr)	36 ± 10.5	40.5 ± 14	NS
Gender (F/M)	(6/9)	(12/4)	NS
Bileaflet valve	7/15 (47%)	6/16 (37.5%)	NS
Obstructive THR	10/15 (67%)	11/16 (69%)	NS
THR diameter (mm)	13.8 ± 8.4	15.2 ± 6.8	NS
NYHA ≥III symptoms	8/15 (53.3%)	9/16 (56.3%)	NS
Initial TT success	8/15 (53.3%)	9/16 (56.3%)	NS
Subsequent TT success	4/7 (57.1%)	6/7 (85.7%)	NS
Overall success	12/15 (80%)	15/16 (93.7%)	NS

Abbreviations as in Table 1; TT = thrombolytic therapy; THR = thrombus.

obstructive despite some (n = 4) or no (n = 2) change in appearance. Complete success was confirmed in 12 of these 15 episodes after repeated administration of thrombolytics, bringing the total success rate to 88% (22/25). Among the 12 nonobstructive thrombi, however, complete success was achieved in 9 (75%) at the initial thrombolysis attempt (p < 0.05, as compared with obstructive thrombi). The remaining three patients with nonobstructive thrombi were given a second dose of thrombolytics with success in two, thus bringing the overall success in this subset to 91.6%. The overall success rates in fixed (90.5%) and mobile (87.5%) thrombi were not statistically different.

Thrombolytic treatment in asymptomatic patients. There were two male and two female patients with mitral valve prostheses (three bileaflet, one tilting disk) who underwent successful thrombolysis for large, nonobstructive left atrial thrombi detected on routine examination (Table 1). The thrombi were mobile in two and fixed type in the remaining two. A single SK infusion session was successful in all four patients.

Left atrial mural thrombus associated with thrombosis of the mitral valve prosthesis. The left atrial mural thrombus persisted in six patients despite successful lysis of the thrombus associated with the prothesis itself. No systemic embolization was noted in this group.

Table 5. Comparison of Thrombolytic Success Rates According to Transesophageal Echocardiography Characteristics of Thrombus

	Obstructive	Nonobstructive
Initial thrombolysis success*	10/25 (40%)	9/12 (75%)
Subsequent thrombolysis success	12/15 (80%)	2/3 (66.6%)
Overall success	22/25 (88%)	11/12 (91.6%)
Average no. of thrombolytic sessions per episode†	1.64	1.25

*p < 0.05; †p = 0.04.

Complications of thrombolytic treatment. The symptomatic and asymptomatic groups of patients combined for the analysis of complications. The complications of thrombolytic treatment were seen in 15% of the 40 total thrombotic episodes in 36 patients (Table 1). Major complications included death in one patient (2.8%), coronary embolization in one patient (2.8%) and cerebral embolization in one patient (2.8%). Both patients with embolization had large, fixed, obstructive thrombi on TEE. Death was due to cerebral bleeding in a patient with 10-day-old brain embolism with no evidence of hemorrhagic infarct on baseline computed tomographic (CT) scan. Minor bleeding was noted in three (8.3%) of the episodes. Of interest, all major complications occurred in the group that received the rapid infusion of SK as initial treatment. No complications occurred in four asymptomatic patients. No complications occurred as a result of TEE examinations.

DISCUSSION

Our study showed that intravenous thrombolysis can be achieved with a high success rate in all echocardiographic subsets of prosthetic valve thrombosis by administering thrombolytics in successive episodes. In slightly more than half of the events, a single infusion of thrombolytic was successful, and one additional infusion ensured a successful result in about three-fourths of the remaining. Additional infusions were required more often in patients with obstructive as compared with nonobstructive thrombus. The relief of hemodynamic obstruction by thrombolysis can be monitored simply by transthoracic Doppler echocardiography. Fluoroscopy may also be useful by detecting the return of valve occluder motion to normal range (22). In addition to its fundamental value in detecting nonobstructive thrombus, TEE may still provide additional valuable information in other subsets of prosthetic valve thrombosis that may be important in the treatment of individual patients. Although the changes in thrombus mass generally mirrored the hemodynamic changes in patients with obstructive thrombi, in 4 of these 25 patients, initial thrombolysis caused

reduction in the thrombus mass with no change in hemodynamic obstruction. These four patients received additional thrombolytic infusions with relief of obstruction. In three patients with no initial change in thrombus configuration by TEE after the first thrombolytic dose, subsequent doses also failed. Potentially, TEE may be useful in identifying these "resistant" cases. Nevertheless these are observations in small groups and the potential impact of serial TEE in this context deserves to be investigated in larger series.

Obstructive versus nonobstructive thrombus. Although the hemodynamic benefit of lysing an obstructive thrombus is obvious, the issue with nonobstructive prosthetic valve thrombus is somewhat controversial. Recently published guidelines by Lengyel et al. (30) proposed intensive anticoagulation, rather than thrombolysis, in patients with nonobstructive thrombi. Valvular thrombi without hemodynamic obstruction can be detected with higher accuracy by TEE (35) and may be seen in 15% to 18% of the patients in the early postoperative period following valve replacement (41). Despite the absence of hemodynamic embarrassment, nonobstructive prosthetic thrombi may not be totally benign. We and others showed that nonobstructive mobile prosthetic valve thrombi carried an increased risk of systemic embolization (35,41). In the current study, the thrombolytic treatment was not associated with increased embolic complications in this subset despite the more frequent initial presentation with embolic events. Similarly, a more recent study, again by Lengyel et al. (42), reported that the anticoagulant treatment failed in half of the patients with nonobstructive thrombi, while there was no failure or complication in the group treated with thrombolysis. Together these results bring strong support to extending the indications for thrombolytic treatment to patients with nonobstructive thrombi. Transesophageal echocardiography may show persistent residual thrombus (with embolic potential) following initial thrombolysis, even if the relief of hemodynamic obstruction is detected by other means. In our series, 9 of 25 (32%) obstructive thrombi were transformed into nonobstructive but large thrombi (4 of them gaining mobility) after the first SK dose and were treated successfully with additional infusion of the thrombolytic in all but one.

Thrombolysis results according to the valve type and location. Roudaut et al. (20) reported higher thrombolytic success rates for aortic than mitral prosthetic valves. Some authors suggested that the bileaflet valve thrombotic occlusions were more responsive to thrombolysis (20,23). An explanation for this was the potential for the flow obstruction by a smaller thrombus occupying the critical pivot point in a bileaflet valve as compared with a single disk valve. Our series, in contrast, did indicate similar success rates in both valve locations and valve types. This was true even when the success rates for each valve location and type were further

stratified according to fixed or mobile, and obstructive or nonobstructive thrombus characteristics.

Thrombolysis results according to the clinical status. The thrombolytic success was achieved in equal proportion of patients who were in class II or less as compared with those who were in class III or greater. Hurrell et al. (29) recommended direct surgical treatment rather than thrombolytics for patients with class IV symptoms, because of a high medical mortality reported in some series. The ACC/AHA valve disease guidelines (39) also recommended surgical treatment in class IV patients except those who are nonsurgical candidates. Unfortunately, the surgical mortality is also highest in this group of patients (4,5). Recently published thrombolytic therapy guidelines (30) proposed the thrombolytic treatment as the treatment of choice for the "critically ill" patients in functional class III or IV, although the definition of "critically ill" may be quite variable. We believe that an individual approach based on the expected surgical mortality rate is necessary in patients with class IV symptoms. We suggest that, in the absence of cardiogenic shock, these patients may be treated in the intensive care unit by TEE-guided thrombolysis.

Systemic embolization and other complications. Due to the lack of a generally accepted standard regimen, various infusion protocols and thrombolytic doses were used in the previous studies (6–31), making a direct comparison of the results difficult. The rate of major events and minor bleeding in our study was within the previously reported range. The embolization rate of 5.7% (two patients) in our series compares favorably with previously reported single institution series (Table 6). Both embolic complications occurred in patients with fixed, obstructive thrombi who were given rapid thrombolytic infusions. In the recent thrombolytic treatment guidelines article (31), the presence of a large thrombus on the prosthetic valve or in the left atrium has been included in the relative contraindications based on one case report of embolism following a rapid (3-h) infusion of tPA (26). In a recent study by Manteiga et al. (31) 3 instances of embolization (33%) occurred in 10 patients with large left atrial thrombi who were given rapid infusion of SK (1.5 million units in 90 min). It appears that rapid thrombolytic infusion, especially in the presence of large thrombus, may increase the risk of embolization. Understanding the predictors of systemic embolism is important because this complication seems to be the Achille's heel of the thrombolytic treatment of prosthetic valve thrombosis. There are little data available on this subject. Reddy et al. (24) published the series with lowest embolization rate and suggested that advanced age and atrial fibrillation may be the risk factors for embolic complications. Roudaut et al. (20), however, found that class IV clinical status was the only predictor of embolic complications (and death). It is not known whether this was secondary to larger amounts of thrombi in these patients.

The only mortality in our series was the result of cerebral

Table 6. Risk of Embolization After Thrombolytic Treatment of Left-Sided Prosthetic Heart Valves (Single Center Series With ≥8 Patients)

Author	Year	N	Average Age (yr)	A, Fib (%)	Protocol	Embolization (%)
Witchitz	1980	12	51	NR	SK, 100 K U/h, for ≤96 h (n = 7)	1 (8.3%)
					UK, 150 K U/h, for ≤96 h (n = 4)	
Ledain	1986	26	56	NR	SK, 200 K U/h for 10 h (n = 14)	5 (19%)
					UK, 4,500 U/kg/h for 12 h (n = 12)	
Roudault	1992	63*	55	NR	tPA, 10 mg bolus, 90 mg in 90 min (n = 10)	11 (17.5%)
					UK, 2,000–4,500 U/kg/h for 12–24 h (n = 27)	
					SK, 500 K U bolus, 150 K U/h for 10 h	
Vasan	1992	16	41	25%	SK, 250 K U bolus, 100 K U/h ≤72	4 (12.5%)
Silber	1993	10*	67	NR	SK, 250 K U bolus, 100 K U/h for 72 h	1 (10%)
					UK, 4,400 U/kg bolus, 4,400 U/kg/h	
Vitale	1994	8	47	63%	tPA, 10 mg bolus, 50 mg + 20 mg + 20 mg in 3 h	1 (12.5%)
Reddy	1994	38	32	13%	SK, 250 K U bolus, 100 K U/h ≤75 h	1 (2.6%)
Manteiga	1998	16*	49	NR	SK, 1.5 million U in 90 min	3 (18.8%)
Current study		35*	36	53%	See text	2 (5.7%)

*Includes patients with right-sided valves.
A Fib = atrial fibrillation; NR = not recorded; SK = streptokinase; UK = urokinase; tPA = tissue plasminogen activator.

bleeding in a patient with a 10-day-old cerebral embolism. Although the baseline CT scan had not shown bleeding, a repeated CT before second thrombolytic application might have been important in this case. As a precaution, probably no patient with cerebral embolism within 10 days should be given thrombolytics and each patient should be carefully assessed individually for the risk of hemorrhagic transformation of cerebral infarct.

CONCLUSIONS

In this series, intravenous thrombolysis for prosthetic valve thrombosis was achieved with a low risk of complications and a high rate of success in both obstructive and nonobstructive prosthetic valve thrombosis. Thrombolytic treatment was equally effective in both mitral and aortic valve thrombi, and in both bileaflet and single disk valve designs. We believe that the slow administration of intravenous thrombolytics in discrete, successive sessions guided by serial TEE and TTE information is a safe and effective method that may expand the indications for nonsurgical treatment of prosthetic valve thrombosis.

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REFERENCES

1. Edmunds LH. Thromboembolic complications of current cardiac valvular prosthesis. Ann Thorac Surg 1982;34:96–106.
2. Kontos GH, Schaff HV, Orszulak TA, et al. Thrombotic obstruction of disc valves: clinical recognition and surgical management. Ann Thorac Surg 1989;48:60–5.
3. Thorburn CW, Morgan JJ, Shanahan MX, Chang VP. Long-term results of tricuspid valve replacement and the problem of prosthetic valve thrombosis. Am J Cardiol 1983;51:1128–32.
4. Husebye DC, Pluth N, Piehler JM, et al. Reoperation of prosthetic heart valves: analysis of risk factors in 552 patients. J Thorac Cardiovasc Surg 1983;4:543–52.
5. Deviri E, Sareli P, Wisenbaugh T, Cronje SL. Obstruction of mechanical heart valve prostheses: clinical aspects and surgical management. J Am Coll Cardiol 1991;17:646–50.
6. Luluaga IT, Carrera D, D'oliveria J, et al. Successful thrombolytic therapy after acute tricuspid valve obstruction (letter). Lancet 1971; 1067–8.
7. Baille Y, Choffel J, Sicard MP, et al. Traitment thrombolytique des thromboses de prothese valvulaire (letter). Nouv Press Med 1974;3: 1233.
8. Witchitz S, Veyrat C, Moisson P, et al. Fibrinolytic treatment of thrombus on prosthetic heart valves. Br Heart J 1980;44:545–54.
9. Olson GW, Copeland RB. Emergency fibrinolytic treatment of thrombosed prosthetic heart valves (letter). Lancet 1982;1:1122.
10. Gagnon RM, Beaudet R, Lemire J, et al. Streptokinase thrombolysis of a chronically thrombosed mitral prosthetic valve. Cathet Cardiovasc Diagn 1984;10:5–10.
11. Czer LS, Weiss M, Bateman TM, et al. Fibrinolytic therapy of St. Jude valve thrombosis under guidance of digital cinefluoroscopy. J Am Coll Cardiol 1985;5:1244–9.
12. Ledain LD, Ohayon JP, Colle JP, et al. Acute thrombotic obstruction with disc prostheses: diagnostic considerations and fibrinolytic treatment. J Am Coll Cardiol 1986;7:743–51.
13. Kurzrok S, Singh AK, Most A, William DO. Thrombolytic therapy for prosthetic cardiac valve thrombosis. J Am Coll Cardiol 1987;9: 592–8.
14. Enar R, Ersanli M, Kucukoglu S, et al. Thrombolytic therapy of prosthetic valve thrombosis in a pregnant woman. Arch Turk Soc Cardiol 1994;22:338–42.
15. Zoghbi WA, Desir RM, Rosen L, et al. Doppler echocardiography: application to the assessment of successful thrombolysis of prosthetic valve thrombosis. J Am Soc Echocardgr 1989;2:98–101.
16. Fyfe DA, Taylor AB, Kline CH, et al. Doppler echocardiographic evaluation of streptokinase lysis of thrombosed right-sided St. Jude Medical valves in patients with congenital heart defects. Am Heart J 1991;121:1156–60.
17. Marti V, Subirana MT, Ballester M, et al. Successful thrombolytic therapy for prosthetic pulmonary valve thrombosis evaluated by Doppler echocardiography. Am Heart J 1992;123:1065–7.
18. Mehan VK, Dalvi BV, Kale PA. Streptokinase treatment of a thrombosed Björk-Shiley prosthesis in the aortic position. Br Heart J 1992;67:498–9.
19. Vasan RS, Kaul U, Sangvi S, et al. Thrombolytic therapy for prosthetic valve thrombosis: a study based on serial Doppler echocardiographic evaluation. Am Heart J 1992;123:1575–80.
20. Roudaut R, Labbe T, Lorient-Roudaut MF, et al. Mechanical cardiac

valve thrombosis: is fibrinolysis justified? Circulation 1992;86 suppl 2:II8–15.

21. Koska J, Kunichika ET, Pepine CJ, Wagman AJ. Successful use of low-dose tissue plasminogen activator for treatment of thrombosed prosthetic valve in a 22-month-old child. Am Heart J 1992;124:783–5.

22. Aoyagi S, Higa Y, Matsuzoe S, Nishi Y, et al. Obstruction of St. Jude mechanical valve—diagnostic and therapeutic values of cineradiography. Thorac Cardiovasc Surg 1993;41:357–63.

23. Silber H, Khan SS, Matloff JM, Chaux A, De Robertis M, Gray R. The St. Jude valve: thrombolysis as the first line of therapy for cardiac valve thrombosis. Circulation 1993;87:30–7.

24. Reddy NK, Padmanabhan TN, Singh S, et al. Thrombolysis in the left-sided prosthetic valve occlusion: immediate and follow-up results. Ann Thorac Surg 1994;58:462–70.

25. Ramamurthy S, Talwar KK, Saxena A, et al. Prosthetic mitral valve thrombosis in pregnancy successfully treated with streptokinase. Am Heart J 1994;127:446–8.

26. Pape LA, Love DG, Gore JM. Massive thromboembolic stroke and death after fibrinolytic therapy of St. Jude prosthetic mitral valve thrombosis: documentation by transthoracic Doppler echocardiography. Am Heart J 1994;128:406–9.

27. Glotzer TV, Tunick PA, Kloth H, et al. Thrombosis of a Starr-Edwards tricuspid prosthesis: diagnosis by Doppler echocardiography and treatment with thrombolysis. Am Heart J 1994;127:705–8.

28. Vitale N, Renzulli A, Cerasuolo F, et al. Prosthetic valve obstruction: thrombolysis versus operation. Ann Thorac Surg 1994;57:365–70.

29. Hurrell G, Schaff HV, Tajik J. Thrombolytic therapy for obstruction of mechanical prosthetic valves. Mayo Clin Proc 1996;71:605–13.

30. Lengyel M, Fuster V, Keltai M, et al. Guidelines for management of left sided prosthetic valve thrombosis: a role for thrombolytic therapy. J Am Coll Cardiol 1997;30:1521–6.

31. Manteiga R, Souto JC, Altes A, et al. Short-course thrombolysis as the first line of therapy for cardiac valve thrombosis. J Thorac Cardiovasc Surg 1998;115:780–4.

32. Nanda NC, Cooper JW, Mahan EF, Fan P. Echocardiographic assessment of prosthetic valves. Circulation 1991;84 suppl:1228–39.

33. Daniel WG, Mügge A, Grote J, et al. Comparison of transthoracic and transesophageal echocardiography for detection of abnormalities of prosthetic and bioprosthetic valves in the mitral and aortic position. Am J Cardiol 1993;71:210–5.

34. Dzavik V, Cohen G, Chan KL. Role of transesophageal echocardiography in the diagnosis and management of prosthetic valve thrombosis. J Am Coll Cardiol 1991;18:1829–33.

35. Gueret P, Vignon P, Fournier P, et al. Transesophageal echocardiography for the diagnosis and management of nonobstructive thrombosis of mechanical mitral valve prostheses. Circulation 1995;91:103–10.

36. Om A, Sperry R, Paulsen W. Transesophageal echocardiography for evaluation of thrombosed mitral valve prosthesis during thrombolytic therapy. Am Heart J 1992;124:781–3.

37. Young E, Shapiro SM, French WJ, Ginzton LE. Use of transesophageal echocardiography during thrombolysis with tissue plasminogen activator of a thrombosed prosthetic mitral valve. J Am Soc Echocardiogr 1992;5:153–8.

38. Currie P, Sutherland GR, Starkey IR. Thrombolysis as an emergency treatment for a thrombosed prosthetic mitral valve diagnosed by transesophageal echocardiography. Br Heart J 1993;70:198–200.

39. Bonow RO, Carabello B, de Leon AC, et al. ACC/AHA guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (committee on management of patients with valvular heart disease). J Am Coll Cardiol 1998;32:1486–1582.

40. Weyman AE. Principles and Practice of Echocardiography, 2nd ed. Lea and Febiger, 1994; 1210.

41. Özkan M, Kaymaz C, Kirma C, Pektas O. Diagnostic approach of mitral and aortic prosthetic valves thrombosis with transesophageal echocardiography in relation to embolic events (abstr). Eur Heart J 1997;18 suppl:P1810;325.

42. Lengyel M, Temesvari A, Nagy A, et al. The role of thrombolysis in obstructive and nonobstructive mitral prosthetic valve thrombosis diagnosed by multiplane TEE. Echocardiography 1997;14:50.