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STATE-OF-THE-ART PAPER

Treatment of Obstructive Thrombosed Prosthetic Heart Valve

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Obstructive thrombosed prosthetic heart valve (OTPHV) is a serious complication of heart valve replacement. There are no generally accepted criteria for management of these patients. Therefore, in September 2012, a literature survey of studies published after 1995 was performed to analyze the data regarding clinical outcomes of patients with OTPHV treated with thrombolytic agents and with surgery since 1996. The search yielded appropriate and relevant studies, which included 17 studies comprising 756 patients who had received thrombolytic therapy and 13 studies comprising 662 patients who had received surgery. The data on these 2 groups was analyzed in detail relating to frequency of use of the diagnostic studies, baseline patient data, and on the rate of complete success, outcomes, and complications of the therapy they had received, and the limitations of the studies. We have then developed a strategy for therapy of OTPHV. (J Am Coll Cardiol 2013;62:1731–6) © 2013 by the American College of Cardiology Foundation

Obstructive thrombosed prosthetic heart valve (OTPHV) is an uncommon complication of prosthetic heart valve (PHV). However, when it occurs, it is associated with significant mortality and morbidity. The American College of Cardiology/American Heart Association and the American College of Chest Physicians guidelines do not have any Class I or Class III recommendations for treatment of OTPHV (1,2). The 2006 American College of Cardiology/American Heart Association guidelines provide Class II recommendations in which the level of evidence was "C" in all 3 of the IIa recommendations and in 2 of the 4 IIb recommendations. The recent 2012 European Society of Cardiology and the European Association for Cardio-Thoracic Surgery guidelines gave a Class I recommendation for surgery in "critically" ill patients who have an obstructive thrombosed PHV; the Level of Evidence was C (3). "Critically" was not defined. However, these guidelines have now made an essential and important distinction between obstructive thrombus and nonobstructive thrombus, which needs to be emphasized (3). The European Society of Cardiology/European Association of Cardio-Thoracic Surgery guidelines recommend, if surgery is not immediately available for OTPHV, that the patient should receive thrombolytic therapy. All the guidelines cite a very small number of references to single studies for the management of these patients. These recommendations indicated to us that a study of clinical outcomes of therapy from a comprehensive analysis of data of all published studies would be useful, valuable, and would also be of help for inclusion in the next revised guidelines.

There are 2 forms of therapy, thrombolytic therapy and surgical replacement of the OTPHV. Our goal was to determine the clinical outcomes of the use of these 2 forms of therapy. Outcome of treatment has been generally categorized into "complete success," "partial success," or "ineffective." Complete success is complete resolution of the thrombus and the obstruction. The remainder are considered a "failure" and include partial success, which is incomplete resolution of the thrombus and/or obstruction, and ineffective, which is no discernible change in the thrombus and the obstruction. For use of thrombolytic agents, 2 reviews were published in the 1990s (4,5), which included data up to 1995. There are no randomized trials except for 1 (6) in 2009 that compared an accelerated dose versus a conventional dose of streptokinase for the treatment of OTPHV and showed no differences in outcomes.

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Abbreviations and Acronyms

CVA = cardiovascular accident(s)

NYHA = New York Heart Association

OTPHV = obstructive thrombosed prosthetic heart valve

PHV = prosthetic heart valve

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

Therefore, in September 2012, we undertook a literature survey of studies published after 1995 to analyze the data that would be focused on and would critically evaluate clinical outcomes of patients with OTPHV treated with thrombolytic agents and with surgery since 1996.

Literature Survey

In September 2012, encompassing a 17-year time period, a PubMed literature survey was performed using the terms "prosthetic heart valve" and "thrombosis" for all English language articles published from 1996 to September 2012. The search returned 1,667 articles, of which 65 were identified that were related to PHV thrombus. From the 65 articles, topics unrelated to PHV thrombosis were excluded. Also excluded were articles that related to PHV thrombus, transcatheter aortic valves, pregnancy, case reports, studies with <5 patients, editorials, and reviews. When there were multiple studies from the same medical center(s) and similar authors, only the most recent study was included. A few studies had compared data on thrombolytic agents and surgery; however, in these studies: 1) the therapies were not given as part of randomized trials or in a systematic predetermined protocol; 2) the baseline characteristics of the patients in the 2 groups were not adequately described and/or were not similar; and 3) the number of patients in each group were too small and/or were not comparable. Therefore, the findings in the 2 groups were included with the rest of the studies on thrombolytic agents and on surgery, respectively. To ensure that no studies were missed, the cited references in the relevant studies were also reviewed; some of the articles were finally retrieved through interlibrary loans by the University of Southern California Medical School Library. The search eventually yielded 17 studies, comprising 756 patients (6–22) (Online Table A), which were related to thrombolytic agents in OTPHV and 13 studies, comprising 662 patients (7,11,16,17,21–29) (Online Table B), which were related to surgery in OTPHV.

Findings

Diagnosis. The diagnosis of OTPHV was based on clinical assessment and imaging modalities including fluoroscopy and echocardiography. Of the available data in 22 studies (6–14,16–22,24–29), 59% of the studies utilized fluoroscopy, 86% of the studies utilized transthoracic echocardiography (TTE), and 77% of the studies utilized transesophageal echocardiography (TEE). Nine percent of the studies utilized only TTE, and 9% utilized only TEE. Forty-one percent utilized 2 imaging modalities (56% utilized both TTE and TEE, and 44% used a combination of fluoroscopy and echocardiography), and 41% utilized all 3 imaging modalities.

Pannus/thrombus. Ten studies presented data regarding findings of thrombus and/or pannus at the time of surgery for a total of 518 patients (7,11,16,17,22–27) (Table 1); 41% had thrombus only, 38% had pannus only, and 21% had both thrombus and pannus. Only 1 study (8) evaluated whether patients had pannus and/or thrombus at echocardiography in 87 patients; 24% had thrombus only, 31% had pannus alone, and 45% had both thrombus and pannus. Thus, pannus was present in 59% to 76% of patients.

Previous anticoagulation. Eighteen studies provided information regarding anticoagulation status of patients at time of diagnosis of OTPHV (7–15,17,20–22,24–28). Of 1,005 patients, 61% had stated anticoagulation levels as adequate in the cited studies, and 39% had stated anticoagulation levels as inadequate in the cited studies (Table 2).

Right-sided OTPHV. ISOLATED THROMBOSIS OF THE TRICUSPID VALVE. Nine studies, comprising 48 patients (7,9,12,14,18,20–22,29), reported clinical outcomes for isolated thrombosed tricuspid valve. Of 43 who had received thrombolysis, 42 had a mechanical valve and 1 had a bioprosthesis. Complete success was achieved in 38 (88%) patients, partial success was achieved in 1 patient, and was ineffective in 4 patients. These 4 patients also needed surgical tricuspid valve replacement of the OTPHV. There were 4 additional studies (13,23,28,29) for a total of 8 patients with isolated tricuspid OTPHV, for which outcome of therapy was not stated.

Left-sided OTPHV. LEFT-SIDED OTPHV TREATED WITH THROMBOLYSIS. Seventeen studies (6–22) presented characteristics and clinical outcomes of 756 patients who received thrombolytic agents for treatment of 801 episodes of OTPHV (Online Table A). The findings are summarized in Table 3. The majority of the patients were female (59%); the patients' ages ranged from 32 to 61 years, and only 3 patients had received a bioprosthetic PHV. Of the data that were available in 665 patients, 35% presented in

Table 1 Pannus and/or Thrombus in OTPHV Diagnosed at Surgery

First Author (Ref. #)	Thrombus	Pannus	Thrombus + Pannus
Aoyagi et al. (7)	16	4	
Lengyel et al. (11)	11	8	1
Durrleman et al. (16)	13	5	20
Renzulli et al. (17)	78	93	42
Keeulers et al. (22)	10		9
Rizzoli et al. (23)	25	33	13
Bollag et al. (24)	11		5
Ozkokeli et al. (25)	25	5	
Lafci et al. (26)	6	5	7
Toker et al. (27)	18	45	
Total (n = 518)	213 (41%)	198 (38%)	107 (21%)

Values n or n (%).
OTPHV = obstructive thrombosed prosthetic heart valve.

Table 2 Anticoagulation Status at Time of Clinical Presentation

First Author (Ref. #)	Adequate	Inadequate
Aoyagi et al. (7)	14	6
Vitale et al. (8)	75	12
Manteiga et al. (9)	6	13
Gupta et al. (10)	62	48
Lengyel et al. (11)	70	15
Lopez et al. (12)	7	8
Teshima et al. (13)	16	11
Ramos et al. (14)	6	11
Roudaut et al. (15)	57	53
Renzulli et al. (17)	191	48
Caceres-Loriga et al. (20)	17	51
Ermis et al. (21)	10	23
Keuleers et al. (22)	16	15
Bollag et al. (24)	2	11
Ozkokeli et al. (25)	15	15
Lafci et al. (26)	5	13
Toker et al. (27)	35	28
Ahn et al. (28)	6	14
Total (n = 1,005)	610 (61%)	395 (39%)

Values are n or n (%).

Table 3 Summary of Pooled Data of Thrombolysis in 756 Patients for 801 Episodes of Left Heart OTPHV

Mean age, yrs*	32–61
Sex†	
Female	410 (59%)
Male	286 (41%)
Location of valve‡§	
Mitral	481 (68%)
Aortic	151 (21%)
NYHA functional class	
I/II‖	235 (35%)
III/IV‖	430 (65%)
Recurrence	106 (13%)
CVA/emboli	111 (14%)
Complete success	558 (70%)
Failures¶	243 (30%)
Partial success	85 (35%)
Subsequent surgery	38
No follow-up data	47
Ineffective	158 (65%)
Subsequent surgery	85
Died before surgery	15
No follow-up data	58
30-day mortality	61/756 (8%)
Complete success subgroup	45/558 (8%)
Failure subgroups with known follow-up	16/138 (12%)

Values are range, n (%), or n. *4 studies did not provide data for age. †5 studies did not provide data for sex. ‡10 studies included a small number of patients with tricuspid OTPHV. §3 studies did not provide information on location of OTPHV. ‖5 studies did not provide data for NYHA functional class. ¶Failure includes 85 with partial success and 158 with no success.

CVA/emboli = cerebrovascular accident (emboli/bleeding) and/emboli to other vascular sites. NYHA = New York Heart Association; OTPHV = obstructive thrombosed prosthetic heart valve.

New York Heart Association (NYHA) functional classes I/II and 65% presented in NYHA functional classes III/IV. Six studies provided data regarding complete success according to NYHA functional class on presentation (6,10,11,15,18,20) (Table 4). Complete success was achieved in 81% of patients presenting in NYHA functional classes I/II and 74% of patients presenting in NYHA functional classes III/IV. Streptokinase was used in 12 of the 17 studies. The recurrence rate was 13%. The rate of cerebrovascular accident (CVA) or embolic phenomenon to other arterial sites was 14%. Some studies included tricuspid OTPHV; excluding these, 481 involved the mitral PHV, and 151 involved the aortic PHV.

The rate of complete success was 70%; we have labeled the rest as failures of therapy. Of the failures, 85 (35%) had partial success and 158 (65%) were ineffective with thrombolytic agents. Of the partial successes, 1 patient died, 38 had surgery, and follow-up was not provided in 47. Of the complete failures, 85 patients had surgery, 15 died before surgery could be performed, and follow-up was not provided in 58.

The overall 30-day mortality was 8%. The 30-day mortality in the complete success subgroup was 8% and in the failure subgroup was 12%. However, follow-up data were not presented in 105 in the failure group.

LEFT-SIDED OTPHV TREATED WITH SURGERY AND PHV RE-REPLACEMENT. Thirteen studies (7,11,16,17,21–29) presented baseline patient characteristics and clinical outcomes in 662 patients with OTPHV who were treated surgically (Online Table B); the findings are summarized in Table 5. In 10 studies (8,12,17,18,22,23,25,28–30), of 543 patients, 490 (91%) had surgery as the initial therapy of OTPHV. In other words, in these 10 studies, 9% of the patients had surgery following failure of thrombolytic therapy. The majority of the patients were female (66%); the patients' ages ranged from 36 to 59 years. All patients had received a mechanical PHV. Time from initial PHV implantation to OTPHV ranged from 4 months to 14 years. Eighty-one percent of patients with OTPHV were in NYHA functional classes III/IV. Occurrence of CVA or emboli was 6%. The initial success can be considered to be complete because the obstructed valves were replaced and any remaining thrombus was removed; 3 studies (17,22,29) had reported a recurrence. In these 3 studies, of a pooled total of 367 patients, 21 (6%) patients had a recurrence of OTPHV. Some studies included tricuspid OTPHV; excluding these, of the 620 patients, 483 had mitral OTPHV, and 137 patients had aortic OTPHV. The 30-day mortality was 15%.

Limitations of these data. There are a large number of patients in the pooled data from the cited studies which is an advantage. However:

1. The details of the patients both at baseline and on follow-up that were included in the publications were variable;
2. A total of 12 studies with left-sided OTPHV also had an occasional patient with tricuspid OTPHV. However, this was not a serious problem relating to the analysis of this review because the data on isolated

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Table 4 Patients Who Had Complete Success With Thrombolysis for OTPHV Based on NYHA FC at Baseline

	NYHA Functional Class I/II		NYHA Functional Class III/IV	
First Author (Ref. #)	Patients	CS	Patients	CS
Karthikeyan et al. (6)	82	61	37	9
Gupta et al. (10)	25	20	85	69
Lengyel et al. (11)	6	5	26	22
Roudaut et al. (15)	37	30	90	60
Tong et al. (18)	39	35	68	58
Caceres-Loriga et al. (20)	4	4	64	54
Total	193	156 (81%)	370	272 (74%)

Values are n or n (%).
CS = complete success; NYHA = New York Heart Association; OTPHV = obstructive thrombosed prosthetic heart valve.

Table 5 Summary of Pooled Data With Surgical Treatment for Left Heart OTPHV

n	662
Mean age, yrs*	36–59
Sex†	
Female	211 (66%)
Male	111 (34%)
Location of valve‡	
Mitral	483 (73%)
Aortic	137 (21%)
NYHA functional class	
I/II§	48 (19%)
III/IV§	199 (81%)
Initial therapy with surgery	490 (91%)
Surgery after failed thrombolysis‖	53 (9%)
Complete success	662 (100%)
Recurrence¶	21 (6%)
CVA/emboli	37 (6%)
30-day mortality	98 (15%)

Values are n, range, or n (%). *Three studies did not provide data for age. †4 studies did not provide data for sex. ‡6 studies included a small number of patients with tricuspid OTPHV. §4 studies did not provide data for NYHA FC. ||3 studies did not provide data for preceding failed thrombolysis. ¶3 studies provided data on recurrence.
Abbreviations as in Table 3.

tricuspid OTPHV reviewed in the preceding text showed 88% of patients had complete success with thrombolysis and had no serious complications. Thus, the data on left-sided OTPHV appear valid for left-sided OTPHV;

3. The studies on left-sided OTPHV included thrombosed aortic and mitral PHV. The stated number of patients in each location of PHV tended to be very small in several studies and outcomes in each location of PHV had been frequently combined;
4. The reviewed studies mostly do not provide reasons for the choice of thrombolysis or of surgery as initial therapy; and
5. The outcomes of patients who had failure with thrombolytic agents (partial success and ineffective) are not completely described. The follow-up outcomes in 105 episodes who remained in these 2 subgroups of failures were not described. It is clinically likely that at least some of them died, and the reported 30-day mortality of 61 (8%) is most likely an underestimate of the total mortality with thrombolytic agents.

Summary. Nevertheless, the data provided by the review in the preceding text has provided important clinical information that is valuable and are summarized as follows:

1. Fluoroscopy and 2-dimensional echocardiography (TTE and TEE) were the main techniques that were utilized. It is possible that in the future, 3-dimensional echocardiography, computed tomography, and magnetic resonance imaging will document in multiple studies the accuracy, especially for the diagnosis and assessment of the extent of associated pannus formation. Importantly, their relationship to clinical outcome also has to be documented. Fluoroscopy alone for the diagnosis and assessment of thrombus and/or obstruction may be of limited value.
2. Thirty-nine percent of the patients had subtherapeutic anticoagulation at the time of clinical presentation. These data should be interpreted with caution. It is known that "rapid" changes in the intensity of anticoagulation status leads to thrombus formation (30,31). Thus, the subtherapeutic and therapeutic status at clinical presentation may not be representative of anticoagulation status at the time of start of thrombus formation, that is in the weeks/months before the diagnosis of OTPHV.
3. Tricuspid OTPHV: thrombolytic therapy was successful in 88% of the patients; surgery can be reserved for those in whom thrombolysis is not adequate.
4. Left-sided OTPHV:
   a. Fifty-nine percent to 66% of the episodes occurred in women. All but 3 valves were mechanical valves. The mitral valve was affected in about two-thirds to three-fourths of the patients.
   b. A comparatively small amount of thrombus at the hinges of a mechanical valve can result in OTPHV and be associated with severe symptoms. One can postulate this accounts for rapid complete success of thrombolytic agents in at least some of the patients who were in NYHA functional classes III/IV.
   c. Of patients who were treated with thrombolytic agents, 35% were in NYHA functional classes I/II. Complete success was achieved in 81%. The incidence of NYHA functional classes III/IV was 65%, and complete success was achieved in 74%. The incidence of CVA/emboli and of recurrence was 14% and 13%, respectively. Emboli may occur in peripheral arteries and coronary arteries. Patients with complete success of OTPHV had a mortality of 8%. They may have died of complications such as CVA (embolic/bleeding) and systemic and

Table 6 Suggested Therapeutic Strategies for OTPHV*

Right-sided OTPHV
Thrombolytic therapy is first choice
Surgery if thrombolysis is unsuccessful
Left-sided OTPHV
Thrombolysis is first choice for:
Patients in NYHA functional class I/II
Those with very severe comorbid conditions that would be associated with a very high surgical operative mortality
If surgery is not a viable option
Patient refuses surgery
"Small thrombus" (area <0.8 cm^2) with or without previous stroke
Surgery is first choice for:
Prosthesis replacement that is necessary or appropriate
Those in whom the coronary blood flow is potentially or actually compromised
Contraindications to thrombolytic therapy
Pannus is a significant contributor to the obstruction
Surgery that may be needed urgently in those with unsuccessful thrombolysis
Surgery may be the preferred therapy initially for:
Patients in NYHA functional class III/IV
Large thrombus (area ≥ 0.8 cm^2)

*For limitations of these strategies, see text.
Abbreviations as in Table 3.

coronary emboli. The mortality in those who had failure of thrombolytic agents was at least 12%.

d. Of patients who were treated with surgery, 81% were in NYHA functional classes III/IV, and complete success was achieved in all. The incidences of CVA/emboli and of recurrence in those who had surgery was 6% and 6%, respectively. The mortality with surgery was 15%, which may be partly related to a high incidence (81%) of NYHA functional classes III/IV at clinical presentation.

5. Because both therapies are associated with complications and mortality, routine initial thrombolytic therapy followed by surgery can be considered to constitute a form of "double jeopardy," because thrombolytic therapy might delay the initiation of surgical therapy if it becomes necessary. In the series we reviewed, 15 patients died while awaiting surgery after failure of thrombolytic agents. Streptokinase was used in 12 of the 17 studies of thrombolysis, and the suggested time lag for performing surgery after using streptokinase is 24 h after discontinuation of the fibrinolytic infusion or 2 h after fibrinolytic activity has been neutralized via protease inhibition, that is, aprotinin (32). In addition, 15 patients died while awaiting surgery after failure of thrombolytic agents. Surgery in these clinical situations should be considered "emergent" or "urgent," depending on the clinical status of the patient. Also, the mortality in the failure group is higher. These issues must be considered in making the choice of initial therapy, which should also be carefully explained to the patient before initiating therapy.
6. One study (18) indicated that use of thrombolytic agents in those with thrombus size area ≥ 0.8 cm^2 was associated with a very high complication rate (41%) and higher mortality (12.9%) in those in NYHA functional classes III to IV. The method of measuring thrombus area was not described. Additional studies are needed. Rarely, thrombi can be very large and are obviously not suitable for therapy with thrombolytic agents (33).

Conclusions

For tricuspid valve OTPHV, thrombolytic therapy is the optimal initial therapy. For left-sided OTPHV, thrombolytic therapy is easier to administer than is surgery but is associated with complication rates and of recurrence of 14% and 13%, respectively. Complete success of thrombolysis is achieved in 70% but is associated with serious complications and a mortality of 8%. In the 30% who have failure of thrombolytic therapy, surgery is necessary, frequently urgently; their mortality is at least 12%, the outcome in this subgroup may have been much worse, additional studies with complete follow-up information are needed. Surgery is associated with a higher mortality of 15%, but 81% of these patients were in NYHA functional classes III/IV. It was associated with lower complication and recurrence rates of 6%. Complete success of thrombosis can be assumed to be 100% because the thrombosed PHV and residual thrombus were removed.

Suggested therapeutic strategies for OTPHV. We have developed suggested strategies for treatment of OTPHV (Table 6). The data related to the strategies were not included or were not complete in the studies that were included in our review. Therefore, the suggestions are partly based on our detailed and critical analysis of the 27 studies cited in this review, also on our clinical experience over many decades and judgment, but they are partly difficult to quantitate at the present time.

LIMITATIONS OF SUGGESTED STRATEGIES.

1. Thrombus area data are based on 1 study (18). Moreover, that study did not describe the method for the measurement/calculation of thrombus area;
2. The "very high" surgical operative mortality is difficult to quantitate because: 1) it is partly related to surgical experience at each medical center; and 2) OTPHV is potentially a lethal disorder, and thus, even a very high operative mortality, say 40% to 50%, may be considered appropriate in selected cases;
3. Surgery not being a viable option is difficult to define, but examples include patients in remote rural areas and inadequately insured patients who may have difficulty in accessing surgery 24 h, 7 days/week; and
4. Subvalvular pannus is an important factor that was present in 59% of patients at surgery (Table 1). It would be suspected of contributing to obstruction in patients who underwent valve replacement in the

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remote past (8 to 10 years) and especially in patients with obstruction who have well-documented adequate anticoagulation. Also, underlying pannus leading to thrombotic obstruction may be preceded by gradual increase in transprosthetic pressure gradients.

Strategy after successful thrombolysis. This information was also not uniformly presented in the reviewed studies. However, from the 1960s, patients have received adequate anticoagulation with warfarin and more recently have had additional clopidogrel or aspirin. They have been given intravenous unfractionated heparin during the interim period as a bridging procedure till therapeutic anticoagulation is achieved.

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APPENDIX

For supplemental tables and additional references, please see the online version of this article.