Case Series

Thrombolytic Therapy for Right-Sided Mechanical Pulmonic and Tricuspid Valves:

The Largest Survival Analysis to Date

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Data regarding thrombolytic treatment of right-sided mechanical valve thrombosis are almost nonexistent, and all current guidelines arise from very small case series. We retrospectively studied the in-hospital and long-term outcome data of a larger series of patients who had received, from September 2005 through June 2012, thrombolytic therapy for right-sided mechanical pulmonary valve or tricuspid valve thrombosis.

We identified 16 patients aged 8–67 years who had undergone thrombolytic therapy for definite thrombotic mechanical valve obstruction in the tricuspid or pulmonary valve position (8 in each position). All study patients except one had subtherapeutic international normalized ratios. The 8 patients with pulmonary mechanical valve thrombosis had a 100% response rate to thrombolytic therapy, and their in-hospital survival rate was also 100%. The 8 patients with tricuspid mechanical valve thrombosis had a 75% response rate to thrombolytic therapy, with an in-hospital survival rate of 87.5%. The one-year survival rate for mechanical valve thrombosis treated with thrombolytic therapy (whether pulmonary or tricuspid) was 87.5%.

On the basis of our data, we recommend that thrombolytic therapy remain the first-line therapy for right-sided mechanical valve thrombosis in adults or children—including children with complex congenital heart disease and patients with mechanical pulmonary valve thrombosis. Surgery should be reserved for patients in whom this treatment fails. ***(Tex Heart Inst J 2015;42(6):543-7)***

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Thrombosis is a serious sequela of prosthetic-valve (predominantly mechanical-valve) implantation, for it carries substantial morbidity and mortality rates.[1,2] Depending on the type of valve used, the incidence of left-sided prosthetic-valve thrombosis ranges from 0.1% to 5.7% per patient-year.[2] Thrombosis is still more prevalent in the right-sided position. In 71 patients who underwent implantation of a mechanical tricuspid valve (TV), 20% of the tilting-disc valves developed thrombosis, in comparison with 4% of the Starr-Edwards valves. Because of this, some surgeons use a bioprosthesis as the valve of choice for right-sided valve replacement.[3,4]

The most common cause of prosthetic-valve thrombosis is interrupted or inadequate warfarin therapy.[5,6] There are 3 options for treating acute valve thrombosis: immediate surgery, thrombolytic therapy, and intensified anticoagulation.[7] However, a meaningful recommendation for the treatment of right-sided prosthetic-valve thrombosis has to date been rendered problematic by minimal outcome data.

Indeed treatment data on the use of thrombolytic therapy or surgery for right-sided mechanical valve thrombosis are almost nonexistent: all the guidelines have arisen from very small case series. A detailed literature search with the help of PubMed and Google Scholar revealed that the largest report on thrombolytic therapy for mechanical TV thrombosis included only 6 patients.[8] More specifically, data on the treatment of mechanical pulmonary valve (PV) thrombosis are virtually nonexistent. A small study of 22 patients reported the incidence of mechanical PV thrombosis to be 12%,[9] but failed to mention any treatment response. The largest case series in the literature on thrombolytic therapy of mechanical PV thrombosis included only 3 patients, with a failure rate of 33%.[10]

In order to generate more data regarding the success rates of thrombolytic therapy in patients with right-sided mechanical valve thrombosis, we performed a retrospective survival analysis of 16 patients—both in the short and long terms—who had received thrombolytic therapy for right-sided mechanical valve thrombosis. Half of these patients had PV thrombosis, and the other half had TV thrombosis. This present analysis, we believe, is the largest case series now reported in the literature and includes some young patients with complex congenital heart disease.

Patients and Methods

We retrospectively studied the in-hospital and long-term outcome data of 16 patients who had received thrombolytic therapy for right-sided mechanical PV or TV thrombosis from September 2005 through June 2012. All study patients were drawn from 2 large teaching hospitals (Loghman Hakim and Shahid Modarres), both of which are affiliated with Shahid Beheshti University in Tehran. Both have large coronary care units and cardiology wards. Modarres Hospital also has a cardiac surgery department. All transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and fluoroscopy had been performed by consulting cardiologists.

Study patients were identified by their admission diagnoses and by careful review of their charts. The diagnosis of prosthetic-valve thrombosis was made on the basis of clinical presentation, physical examination, and imaging results (via TTE, fluoroscopy, and TEE). All patients suspected to have prosthetic-valve thrombosis had undergone initial TTE and fluoroscopic examination and, if needed in the judgment of the treating cardiologist, TEE.

Sixteen patients had a confirmed diagnosis, arising from clinical judgment and from published guidelines,[11] of right-sided mechanical valve thrombosis without contraindications for thrombolytic therapy. On the basis of drug availability and at the discretion of the treating cardiologist, 10 patients were treated with alteplase and 6 with streptokinase. Because of the known high prevalence of anti-streptococcal antibodies in children, all patients younger than 18 years of age were given alteplase. In patients who weighed less than 30 kg, alteplase was given without a loading dose, in a median dose of 0.3 mg/kg/hr for a median duration of 12 hours. Others received alteplase as a 15-mg loading dose given over 10 minutes, followed by 35 mg given in 30 minutes and 50 mg given over 1 hour. In the case of streptokinase, 200,000 units were given as a bolus over 30 minutes followed by 100,000 units/hr for at least 6 hours up to 72 hours, as a continuous infusion.

The duration of therapy was grounded on recommendations in the literature for thrombolytic treatment of all mechanical valves, and at the discretion of the treating clinicians. Hemodynamic response was defined as normalization of the mean gradient and pressure half-time, with normalization of valve motion. No definite contraindications were identified in any patients who received thrombolytic therapy. During thrombolytic therapy, patients were evaluated by means of serial TTE and fluoroscopy. All patients were registered in the cardiovascular research center of Modarres Hospital and were monitored for 2 years after hospital discharge. The data were evaluated by a committee consisting of independent cardiologists and cardiothoracic surgeons. This study was approved by the institutional review board of both hospitals. Figure 1 is a flow-chart that illustrates our patient-selection process.

Results

During the study period, 16 patients (11 female) with definite thrombotic mechanical valve obstruction in the TV or PV position were identified. At the time of diagnosis, only 2 of these patients were not taking warfarin. However, all patients but one had a subtherapeutic international normalized ratio (INR) of <2 at the time of presentation. The median time from prior surgery was 18.25 months (range, 8–36 mo). Other risk factors for mechanical right-sided valve thrombosis were right atrial enlargement in 11 of the patients and right ventricular failure in 10. None of the patients had thrombocytosis or evidence of a hypercoagulable state.

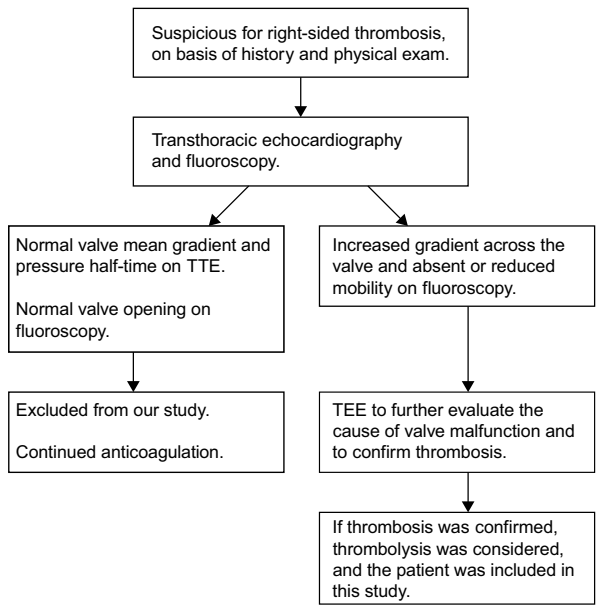

Fig. 1 *Flow chart shows our patient-selection method during the study period.*

TEE = transesophageal echocardiography; TTE = transthoracic echocardiography

These patients (8 with thrombus in the PV position and 8 in the TV) were between the ages of 8 and 67 years at the time of thrombolytic therapy. Ten were given alteplase and 6 were given streptokinase. Their baseline characteristics and the results of their treatment are summarized in Table I. All 8 patients with mechanical PV thrombosis had a 100% response to thrombolytic therapy, as indicated by hemodynamic data and fluoroscopy. The in-hospital survival rate of these 8 patients treated with alteplase was 100%. The 1-year survival rate of patients successfully treated for mechanical PV thrombosis was 87.5% (7/8). Complete hemodynamic TV response was seen in 75% of patients (6/8) whose mechanical TV thrombosis was treated with thrombolytic therapy. Incomplete response was seen in one patient and failure to respond in another. The in-hospital and 1-year survival rate for mechanical TV thrombosis treated with thrombolytic therapy was 87.5%.

No major complications related to thrombolytic therapy (such as major bleeding, death, or significant pulmonary embolism) occurred. Minor complications included fever in 2 (12.5%), nausea and vomiting in 1 (6.3%), and mild gingival bleeding in 1 (6.3%). All patients who were given alteplase, as well as all children, had complete responses.

Deaths

There were 3 deaths, none as a consequence of thrombolytic therapy.

Patient 11. The only in-hospital death (after 1 month) occurred in Patient 11, who had no response to streptokinase therapy and was not deemed a candidate for repeat TV surgery.

Patient 14. This patient had an incomplete response to streptokinase, but had experienced clinical improvement in edema, decreased gradient across the TV, and reduction in right ventricular size. However, her TV gradient had remained above normal, and under fluoroscopy one leaflet had shown reduced mobility. Because this patient had a history of mitral, aortic, and tricuspid valve replacement 6 years earlier, together with an ongoing history of poor renal and liver function, she was not considered a surgical candidate. One year after her partial response to streptokinase, she was readmitted to the hospital for increasing leg edema and ascites due to the recurrence of TV thrombosis. Although the

TABLE I. Summary of Patients with Right-Sided Mechanical Valve Thrombosis Treated with Use of Thrombolytic Therapy

Pt. No.	Age (yr), Sex	Underlying Condition	AF Rhythm	Warfarin Stopped	Subtherapeutic INR	Thrombolytic Agent	Response	Recurrence	Outcome
1	8, F	TOF	No	No	Yes	t-PA	Complete	No	Lived
2	9, F	PS	No	Yes	Yes	t-PA	Complete	No	Lived
3	14, M	TOF	No	No	Yes	t-PA	Complete	No	Lived
4	16, F	Rastelli (MPV)	No	No	No	t-PA	Complete	Yes	Died
5	18, F	TOF	No	No	Yes	t-PA	Complete	No	Lived
6	39, F	PS	No	No	Yes	STK	Complete	Yes	Lived
7	48, M	RHD	Yes	No	Yes	t-PA	Complete	No	Lived
8	49, M	RHD	Yes	No	Yes	t-PA	Complete	No	Lived
9	50, F	RHD	Yes	No	Yes	t-PA	Complete	No	Lived
10	55, M	PS	No	No	Yes	t-PA	Complete	No	Lived
11	56, F	Ebstein (MTV)	Yes	Yes	Yes	STK	Failure	No	Died
12	56, M	RHD	No	No	Yes	t-PA	Complete	No	Lived
13	62, F	RHD	Yes	No	Yes	STK	Complete	No	Lived
14	64, F	RHD (MTV)	Yes	No	Yes	STK	Partial	Yes	Died
15	65, F	RHD	No	No	Yes	STK	Complete	No	Lived
16	67, F	RHD	Yes	No	Yes	STK	Complete	No	Lived

AF = atrial fibrillation; INR = international normalized ratio; MPV = mechanical pulmonic valve; MTV = mechanical tricuspid valve; PS = pulmonary stenosis; Pt. = patient; RHD = rheumatic heart disease; STK = streptokinase; TOF = tetralogy of Fallot; t-PA = recombinant tissue plasminogen activator

patient at that time underwent successful repeat TV replacement with a bioprosthesis, she died of liver failure 3 months later.

Patient 4. A 3rd death, caused by endocarditis after repeat PV surgery, occurred more than one year after the patient's hospital discharge. This girl, 16 years old at the time of her thrombolytic therapy, had at age 14 undergone treatment for transposition of the great vessels, with the Rastelli procedure and mechanical PV implantation. When she presented at our hospital, she had cyanosis and dyspnea caused by PV thrombosis. Her response to alteplase was complete, with an apparent full recovery. After 8 months, she developed recurrent thrombosis, which was again treated with alteplase, for a 2nd "complete response." After she presented with a 3rd thrombosis a few months later, repeat surgery was performed, this time by implanting a bioprosthetic valve. However, the patient died 3 months later, of prosthetic-valve endocarditis.

Discussion

Prosthetic-valve obstruction has various causes, such as thrombus, pannus formation, and the growth of vegetations. Making a distinction between pannus and thrombus can be difficult. However, patients with thrombosis have acute onset of symptoms, usually accompanied by a subtherapeutic INR. In cases of suspected endocarditis, a history, a physical examination, and blood cultures are helpful in excluding this entity.[12,13] The risk of thrombosis is dependent upon anticoagulation status, valve type, valve position, atrial fibrillation, and ventricular function.[14] Thrombosis of mechanical valves is more common in right-sided valves (especially in the tricuspid position) than in left-sided, because of the lower pressures and velocity of blood flow. The risk of thrombosis is the lowest for bioprosthetic valves, which have in the past been the valves of choice for TV replacements; however, their durability is a concern. Several studies have shown that, if adequate anticoagulation is maintained, mechanical prosthetic valves are as safe and effective in the right-sided position as are bioprosthetic valves, yet with better durability. Furthermore, patients with right-sided prosthetic valves are usually at high risk of complications when undergoing repeat surgery because of their history of multiple valve replacements or complex congenital heart surgeries. This has led to increased use of mechanical valve prostheses in the right-sided heart position.[15-17] In a series of 28 PV implantations, the 30-day mortality rate was only 3.6%, and no patient needed reoperation at one year.[15]

Data on right-sided mechanical valve thrombosis treated with thrombolytic agents are still minimal, however. As we said above, our detailed literature search found that the largest case series included only 6 patients[8] for the treatment of mechanical TV thrombosis and 3 patients for the treatment of PV thrombosis.[10] Thrombolytic therapy seems to be safe and effective in treating right-sided mechanical valve thrombosis. Mild pulmonary embolization after thrombolysis is usually well tolerated and is less serious than embolization into the systemic circulation.[18] Our study, to the best of our knowledge, is the largest case series confirming the positive effect of thrombolytic therapy for right-sided prosthetic-valve endocarditis. It reveals a very high success rate of thrombolytic therapy for mechanical right-sided valve thrombosis: 100% success in the PV position and 75% in the TV position, with superior in-hospital and one-year survival rates. Our success rate and safety data are comparable with those of other reported cases that included very few patients.[8,10,18,19]

Limitations

Our study was not a randomized trial but a retrospective case series that involved a small number of patients, which limits the application of our results. Furthermore, the very elderly and those with a higher risk for intracranial bleeding were not present in our case series, which limits our data to children and somewhat younger adults. Because the types and doses of thrombolytic therapy varied between cases, simple dosing recommendations for specific thrombolytic therapies are rendered difficult. However, alteplase in our case series showed a 100% success rate in children. Bearing in mind the known presence of high antibody titers against streptococci in children, we believe that alteplase should be the first-line thrombolytic choice in this population.

Conclusions

On the basis of our data and review of the literature, we recommend that thrombolytic therapy remain the first-line therapy for right-sided mechanical valve thrombosis in adults or children (including patients with complex congenital heart disease). Surgery should be reserved for patients who fail thrombolytic therapy. In our case series, all patients (including all children) who were treated with alteplase had a complete response. The importance of maintaining adequate long-term anticoagulation therapy can be seen in our patients, as well as in patients whose results have been reported elsewhere. All but one of our patients had a subtherapeutic INR, which suggests that most right-sided mechanical valve thrombosis is preventable. Therefore, education, in conjunction with improved access to healthcare, can dramatically reduce this potentially deadly complication. According to the 2014 American Heart Association/American College of Cardiology valvular guidelines,[11] fibrinolytic therapy is reasonable for right-sided prosthetic-heart-valve thrombosis as a class IIa indication, with B as the level of evidence. Our study strengthens this recommendation, by showing the excellent results of thrombolytic therapy as a first-line choice in these patients.

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