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Case Study and Review: Treatment of Tricuspid Prosthetic Valve Thrombosis

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Abstract

Prosthetic valve thrombosis (PVT) is a severe and life-threatening complication of heart valve replacement. Conventional therapy is surgical thrombectomy or valve replacement. Medical thrombolysis is another emerging option. We report the case of a 57 year old woman with a history of Ebstein anomaly who underwent successful treatment of a tricuspid prosthetic valve thrombosis with intra-atrial infusion of very low dose recombinant tissue plasminogen activator (tPA). We review the presentation, etiology, diagnosis, and treatment of the tricuspid PVT emphasizing a modified medical option as a safe, minimally invasive alternative to surgical intervention or conventional medical therapy for tricuspid valve thrombosis.

INTRODUCTION

Prosthetic valves have been used in humans since 1952 [1]. Improvements of valve design and materials have reduced morbidity and mortality after heart valve replacement. However, thrombosis is still a severe complication of prosthetic heart valves, especially those deployed in the left heart chambers. Inadequate anticoagulation is the most common cause of thrombus formation on valves. The overall incidence of prosthetic valve thrombosis is reported to range from 0.1 to 5.7 percent per patient year [2]. Even with adequate anticoagulation, prosthetic valve thrombosis occurs with a 11-year probability of 1-2% for patients with either a bioprosthetic or mechanical valve in either the aortic or mitral valve position [3]. Prosthetic valve thrombosis can be as high as a 4% per patient year incidence in the tricuspid position [4].

Surgical intervention has been the conventional way to treat prosthetic valve thrombosis, especially those on the left side of the heart, although it is associated with mortality rates as high as 69%, depending on the patient's cardiac functional class [5]. Using thrombolytic therapy, as an alternative therapy, has been controversial due to its adverse effects of bleeding and cerebral embolism as well as the uncertainty of success or time to success,

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particularly when there is hemodynamic decompensation. However, right-sided valve thrombosis may be a more acceptable condition for thrombolysis due to a more commonly stable clinical state and lower risk of a cerebrovascular accident, unless there is an interatrial communication. Major bleeding is still a concern in this situation. We present a case report involving tricuspid PVT and review the subject describing tricuspid valve thrombolysis with a low dose, short duration and direct atrial infusion of tPA. This approach is an important consideration, as it should significantly decrease the risk of major bleeding.

CASE REPORT

A 29 year-old woman was diagnosed with Ebstein anomaly at the National Institutes of Health (NIH), and she received a 33 mm bovine prosthetic valve replacement of the tricuspid valve, suture closure of a patent foramen ovale, and partial excision of the right atrium in 1981. Also, due to persistent complete heart block with a nodal escape rhythm after surgery, she underwent permanent epicardial pacemaker placement during that hospitalization. Previously, the patient had cyanotic spells, dyspnea and chest pain, but had relief of all symptoms postoperatively. She has had atrial tachycardia and atrial flutter/fibrillation since 1989, which has been treated with warfarin and digoxin. In 2006, at the age of 54, because of increasing symptoms of fatigue and an echocardiogram showing increasing tricuspid prosthetic valve stenosis, she underwent right and left heart catheterization. She had a 10 mm Hg mean gradient across her prosthetic valve, mild mitral valve regurgitation, moderate global LV dysfunction with an LVEF of 35%, and normal coronaries.

In April, 2007, the patient underwent tricuspid valve replacement surgery with a 31 mm St. Jude Masters Series mechanical valve (St. Jude, St. Paul, MN) and also replacement of her VVI pacemaker generator (Medtronic, Minneapolis, MN). Her excised bioprosthetic valve was noted to be partially partially calcified as well as fibrosed. After discharge, she became much more active, and walked for at least one hour every day. Since her surgery, the patient has been on warfarin and international normalized ratios (INR) have been followed up by her private cardiologist. Her INRs have ranged from 2.5 to 3.0. However, there has sometimes been a lapse as long as 3 months between INR checks.

In January 2009, the patient had a probable syncopal episode and fractured her hip. It is not known how her anticoagulation was handled during this incident and throughout her subsequent hip surgery. After surgery and rehabilitation, the patient resumed walking for one hour, three to four times per week. She had her pacemaker interrogated and it was reported that there was no evidence of an arrhythmia causing the syncopal episode. At a routine visit in September 2009, she had no cardiovascular symptoms. On examination, prosthetic heart sounds were absent and heart sounds were distant and she had petechiae over both shins. Her INR was 4.04 and her warfarin was held for one day. Transthoracic echocardiogram (TTE) revealed normal left ventricular function, a severely dilated right ventricle with evidence of dysfunction, and moderate tricuspid regurgitation. Her mean tricuspid valvular gradient was 9 mm Hg and had increased significantly from her prior study in March 2008. In addition, her valve leaflets could not be well seen. A follow-up transesophageal echocardiogram (TEE) demonstrated the mechanical valve leaflets to appear thickened and immobile. The same day, a cardiac CT demonstrated minimal mobility of the mechanical valve leaflets with the opening angle being 70 degrees and the closing angle being 83 degrees (Fig. 1). A diagnosis of either thrombus or pannus formation was considered. Initial discussions involving her cardiologist and cardiothoracic surgeon as well as a hematologist and interventional radiologist resulted in the decision to use empiric thrombolytic treatment for mechanical tricuspid valve obstruction. If this failed, either surgery or continued medical follow up would be considered.

In November, 2009, the patient was admitted to NIH Clinical Center for planned thrombolysis therapy. Her warfarin was discontinued one day prior to admission (INR was 1.72 on admission). She was started on a heparin infusion immediately after admission to maintain the activated partial thromboplastin time (aPTT) between 50-75 seconds during the hospitalization. On day 1 of treatment, a 4 French catheter with end and side holes was positioned in the right atrium via the right internal jugular vein and a 2 mg bolus of alteplase (tPA) was injected into the right atrium just above the tricuspid valve prosthesis. The catheter was exchanged for a 4 French double-lumen Arrow central catheter, using one lumen to infuse 6 mg tPA in 50 ml normal saline over 6 hours and the second lumen to infuse the heparin needed for anticoagulation. Serial blood counts were monitored every 8-12 hours. The left arm peripheral veins were used for peripheral blood sample collection. Heart sounds and TTE were monitored before, during and after t-PA administration. Serum D-dimer, fibrinogen, tPA, plasminogen, alpha-2 antiplasmin, and plasminogen activator inhibitor-1 (PAI-1) levels were obtained at serial points before, during, and after the infusion of tPA. Day 2 infusion was 8 mg tPA without a bolus in 50 ml of normal saline through the central catheter over 6 hours. Opening and closing sounds of the mechanical valve could be heard clearly on day 1. Her TTE showed progressive improvement of mechanical leaflet mobility and the valve gradient was reduced (mean gradient 9 mm Hg at baseline, 4 mm Hg at the end of day 1, 2 mm Hg at the end of day 2). The day 3 cardiac CT angiogram demonstrated complete restoration of prosthetic leaflet motion with the opening and closing angles within the normal limits according to the manufacturer's specifications (Fig. 1). The opening angle was 13 degrees (normal 10-13 degrees), and the closing angle was 129 degrees (normal 120-127 degrees).

During the hospitalization, her platelet count dropped from 137,000 per ul to as low as 94,000 per ul, but then increased to 100,000 per ul at the time of discharge. She had a low-grade fever after the t-PA infusion on day 1, temperature 38.0 to 38.8 degree Celsius without any symptoms except fatigue. Two sets of blood cultures were negative. Chest X-ray and urine culture did not support any evidence of infection. An infectious disease consultant considered the fever to be secondary to thrombolysis.

After the cardiac CT on day 3, the heparin was discontinued and the central catheter was removed. The patient was discharged to home on the same day with enoxaparin bridging therapy (1 mg/kg subcutaneously twice a day) and oral warfarin (12 mg daily). The new INR target was 3.0 to 3.5. She was also started on 81 mg aspirin daily orally. Follow up after discharge revealed no bleeding complications. However, she continued to complain of intermittent low grade fever and fatigue which slowly improved over the ensuing week. Repeat echocardiography one, five and eleven months post discharge revealed a normally functioning prosthetic tricuspid valve with a mean tricuspid valve gradient of 2.0 mm Hg.

PRESENTATION

A typical presentation of tricuspid PVT would be a change in physical examination such as was seen in our patient. It might be noted that there is an absence or muffling of prosthetic sounds. A new holosystolic murmur located at the left lower sternal border or in the subxiphoid region that may increase with inspiration or maneuvers that increase venous return and represents tricuspid regurgitation may be present. On the other hand, a new murmur that is low in frequency, diastolic, located at the lower left sterna border or infraxiphoid area, and increases with inspiration and other maneuvers that increase tricuspid flow velocity and represents tricuspid stenosis may be heard. A combination of murmurs that characterize both these conditions may be auscultated. Sometimes mid-diastolic and/or pan-systolic murmurs can be heard in the tricuspid area. Also present may be signs or symptoms of right heart failure secondary to either tricuspid valve obstruction and/or

regurgitation. These may include fatigue, syncope, jugular vein distention, and signs of low cardiac output and/or fluid retention. However, the onset of tricuspid valve symptoms is usually insidious, in contrast to the acute presentation of mitral or aortic PVT. Finally, a pulmonary embolus or left sided embolic event, if an interatrial communication is present, may be the presenting manifestation of tricuspid PVT.

ETIOLOGY

The pathogenesis of prosthetic valve thrombosis is caused by complex mechanisms. In general, those factors include the interaction at the molecular level between prosthetic valve surface and plasma components, hemodynamics of blood flow through the prosthetic valve, and inadequate anticoagulation. However, the presence of a hypercoagulable state and loss of effective atrial contraction should also be considered as possible etiologies [6].

Deviri et al. studied 112 obstructed valves in all positions with confirmed surgical findings, demonstrating the underlying cause as pannus (10.7%), pannus combined with thrombus (11.6%), and the remainder thrombus alone (77.7%) [7]. Relative to timing, Deviri et al. reported that thrombus can be formed at any time, while pannus typically develops at a minimum of 12 months and commonly 5 years from the date of surgery [7]. In the study by Deviri et al, there were 41 bileaflet valves (St. Jude Medical). Among them, 30 patients (73.2%) had thrombus at the hinge site, impairing motion of both leaflets [7].

DIAGNOSIS

Suspicion of tricuspid PVT may be raised by physical findings, symptoms of heart failure, or the diagnosis of embolization. Cinefluoroscopy is a simple and rapid test to detect diminished motion of leaflets, but it does not assess the presence and size of thrombus or pannus [8]. Echocardiography, especially transesophageal echocardiography (TEE), is the procedure of choice since it is more sensitive and specific. Kaul et al. proposed the following criteria as confirmation by TTE: 1) high transvalvular gradients – mean of 6 mm Hg or higher, and peak of 15 mm Hg or higher 2) transvalvular gradients 50% or higher than observed before 3) visible thrombus on the prosthetic valve 4) inability to demonstrate two different mobile echoes representing the valve leaflets in a high quality image [9].

MRI has a limited role and is best used to demonstrate the presence of regurgitation which can also be demonstrated by echocardiography. The role of cardiac catheterization is also limited because TEE and cinefluoroscopy can provide adequate data for decision making [8]. However, cardiac CT can provide sharp images to characterize quantitatively the reduced mobility of prosthetic leaflets or even directly visualize the thrombus or pannus if possible [10].

In our case report, a thrombus or pannus on the obstructed prosthetic tricuspid valve was not visible although the leaflets were felt to be possibly thickened on a TEE. It is often difficult to differentiate pannus from thrombus, but Barbetseas et al. report clinical and echocardiographic (TTE and TEE) parameters to help make the differential diagnosis with aortic and mitral valve prostheses [11]. However, in our case, these parameters were not useful, since there was no visible tissue on the prosthesis and no definite symptoms. Barbetseas indicates that the ability of TEE to identify an etiology for abnormal valve motion was usually due to a small mass, usually pannus, encroaching on the hinges of the valve [11]. The lack of mobility of both discs simultaneously in our case which was relieved with thrombolysis suggests that a small thrombus affected the hinges of her St. Jude prosthetic valve.

TREATMENT

The choice of treatment is among watchful waiting with maintenance of adequate anticoagulation versus surgical or thrombolytic pharmacologic intervention. The conservative continued anticoagulation approach would only be appropriate if there is no significant hemodynamic compromise or a contraindication to either surgery or pharmacologic intervention is present. There is one description of a combination of pharmacologic and mechanical intervention using thrombolysis and pacemaker induced increases in heart rate perturbations [12]. In the past, surgery was less attractive as a primary choice because of its relatively high mortality [13]. However, with present day techniques, it can be performed with good results [14, 15] and is sometimes necessary when a large thrombus or pannus formation is responsible for tricuspid prosthetic valve malfunction.

Although thrombolysis of a thrombosed prosthetic tricuspid valve creates a risk of thromboembolism to the lungs, such a risk is quite low and relatively less serious than that of a cerebrovascular accident from left-sided valve thrombolysis. For the patient with a PFO or atrial septal defect, the danger of an embolic stroke with prosthetic tricuspid valve thrombolysis is a concern, and the relative benefit versus risk must be weighed with this approach. Otherwise, thrombolysis should be the treatment of choice for mechanical tricuspid valve thrombus, as long as the patient is relatively stable hemodynamically and there is no major contraindication. If thrombolysis fails, a large thrombus or pannus should be considered, which requires surgical intervention including thrombectomy or valve replacement.

The use of thrombolysis has been described in a few case reports or small series, and almost all the studies were attempted on mitral or aortic prosthetic valves. These are summarized in recent recommendations [16], a review [17], and 2 large single center reports [18,19]. Hurrell et al. considered a large (>5 mm) left sided thrombus as a contraindication for thrombolysis [20]. Lengyel et al. listed a large thrombus as a relative contraindication in their guideline, but no cut-off size was given [21]. Shapira et al. proposed in 2000 that all stuck valves should undergo thrombolysis, unless a large thrombus (>5 mm) is visualized. They also pointed out that visualization of the thrombus is not an essential prerequisite for establishing diagnosis of prosthetic valve thrombosis [22]. Another recent study by Montorsi et al. described a treatment strategy for thrombosed mitral bileaflet prostheses. They proposed that leaflet mobility and duration of prosthetic valve symptoms were important factors in determining successful thrombolysis [5]. They used 21 days as cut-off for the interval between onset of symptoms and diagnosis of prosthetic valve thrombosis. In our case, the patient did not have any symptoms and the time from presumed diagnosis to thrombolysis was outside the 21 day limit. By these criteria, however, the hypomobility of one leaflet of the mechanical valve would have improved the chances of success for at least that one leaflet. It is unclear why long-standing PVT may be susceptible to thrombolysis. One hypothesis was that the amount of thrombus that led to the stuck valve could be minimal, thereby improving the chance of successful thrombolysis [5].

Our approach to thrombolytic therapy in this patient was based on extensive experience with treatment of deep vein thrombosis with low doses of tPA.[23-25]. Although prolonged continuous infusions of thrombolytic agent, often lasting 24 -48 hours, have been commonly used in treatment of thrombosis, animal research indicates that thrombolysis continues long after discontinuation of tPA [26], and bleeding risk should be lower with shorter infusions of tPA [27]. This is based on specific binding of tPA to fibrin clot rather than fibrinogen, and the enhanced efficiency of local plasmin generation by tPA bound to fibrin clot. PAI-1 is consumed by pharmacologic doses of tPA as long as the infusion is maintained, but once the tPA infusion is terminated, PAI-1 recovers and often rebounds to levels higher than baseline

within hours. At the same time, tPA is rapidly cleared due to its short half-life (~5 minutes). In essence, shorter infusions of tPA reduce the time of elevated tPA levels (and risk of remote bleeding complications), but are effective if an adequate amount of tPA is delivered locally to the clot.

We therefore restrict the duration of tPA infusions to a maximum of 6-8 hours a day using doses of ~1mg tPA/ per hour. This is much less tPA than is used in most reports on use of tPA for heart valve thrombosis or for acute myocardial infarction (typically 100-120 mg). Besides the case reported here, we have been successful in clearance of mural thrombi in the SVC, RA, and IVC after 2-3 episodes of daily treatment without bleeding complications, even in high risk patients. Since tPA binds more specifically to fibrin than other agents, it is associated with less postoperative blood requirement, if surgery has to be performed within 24 hours of tPA infusion [22].

At high doses of tPA, serum fibrinogen level will be decreased despite its specificity for fibrin. However, we did not observe the decreased fibrinogen level, which is consistent with a previous report [28] and stands to reason in view of the large fibrinogen pool. The fibrin degradation product, D-dimer will be increased with any dose of tPA as a consequence of clot dissolution, and D-dimer levels rose in our patient (Figure 2) on both day one and day two, as expected.

Data from previous thrombolytic studies using tPA were used to help determine the dosage and route of tPA infusion and are summarized in Table 1. To our knowledge, this is the third report using direct intra-atrial infusion for prosthetic valve thrombolysis [29, 30], and it is the first time it was used for a thrombosed tricuspid mechanical valve. In addition, it is the first report to use such low dosage (16 mg tPA total) of the agent via direct intra-atrial infusion. The pharmacokinetic studies in this report demonstrate that the serum concentration of tPA peaked at 3 hours after each day's tPA infusion, while the greatest inhibition of PAI-1 occurred at the same time (Fig. 3). We also measured the plasminogen and alpha-2 antiplasmin level, which did not change.

A critical decision we had to make was how long to continue thrombolytic therapy based on hematological lab results and/or clinical findings. We decided to stop thrombolysis after the second day based on the complete restoration of prosthetic bileaflet function as well as the concern for the risk of major bleeding with further tPA therapy. However, it was our original intention that, if there had been no improvement in valve function with the low initial dose of tPA, we would have doubled our dose of tPA in subsequent treatment days and continued to monitor hematologic parameters, prosthetic valve function, and clinical effects. The higher dosing would have remained within the range of thrombolytic therapy of prosthetic valve thrombosis of previously published studies (Table 1).

There is a paucity of randomized studies examining the effectiveness of unfractionated heparin versus low molecular weight heparin for bridging therapy until the INR returns to the therapeutic range [33,34]. We chose to use unfractionated heparin during tPA infusion because of the increased experience with it, but used low molecular weight heparin as a bridge to warfarin because it provided a more practical approach, and allowed us to discharge the patient from the hospital.

Guidelines do not provide a recommended INR for prostheses in the tricuspid position [33,34]. For bileaflet prosthetic valves in the mitral position, a range of 2.5 – 3.5 is recommended, 2.0 – 3.0 in the aortic position for patients without additional risk factors for thromboembolism [34]. In order to try to prevent future thrombotic complications of her prosthetic valve, we increased the therapeutic range for her INR from 2.5 – 3.5 to 3.0 – 3.5 and added 81 mg. of aspirin to her program. Although there is very little data regarding the

addition of aspirin to warfarin to prevent thrombotic events for prostheses in the tricuspid position, there is evidence for a reduction in such events without an excessive increase in the bleeding risk for prosthetic mitral and aortic valves as well as multiple prosthetic valve replacement [33,34].

SUMMARY

We have reviewed the mechanism, presentation, diagnosis, and treatment of prosthetic valve thrombosis, emphasizing the use of thrombolytic therapy. We describe a case with successful thrombolytic therapy for the presumed remote onset of prosthetic tricuspid valve thrombosis. This is the first report of the use of such a low dose and the direct atrial infusion of tPA in PVT treatment. This treatment provides a safe, low risk thrombolytic therapeutic option to conventional surgical intervention or continued observation for tricuspid PVT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors of this manuscripts have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [35].

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Closing Angle**Opening Angle****Pre-Lytics** **Post-Lytics**

FIGURE 1.

A. Initial cardiac CT of the heart before thrombolytic therapy, demonstrating minimally mobile leaflets of the mechanical tricuspid valve. B. Follow-up cardiac CT of the heart post t-PA infusion therapy showing restoration of the mobility of the mechanical tricuspid leaflets, with opening and closing angles.

FIGURE 2.

The pharmacokinetic profile of serum fibrinogen and D-dimer during the t-PA infusion. The t-PA infusions were initiated at 0 and 24 hours, and ran for 6 hours each day. The patient's serum was collected at the times indicated. The two parameters were measured by the Hematology Laboratory at the NIH.

FIGURE 3.

The pharmacokinetic profile of serum t-PA and PAI-1 during the t-PA infusion. The t-PA infusions were initiated at 0 and 24 hours, and ran for 6 hours each day. The patient's serum was collected at the times indicated. The two parameters were measured by the Hematology Laboratory at the NIH.

Table 1

Literature review of tPA thrombolytic therapy for prosthetic valve thrombosis (PVT).

Type of prosthetic valve	Dosage of thrombolytic therapy	Indication	Number of patients	Confirmed by
Prosthetic mitral valves [5]	Each patient was treated with 100 mg recombinant tPA as a 10-mg IV bolus followed by 90 additional mg over 3-hour continuous infusion.	Research.	Series: 17 patients	Fluoroscopy and TTE
Prosthetic mitral valves [22]	Recombinant tPA was usually administered as a 10-mg bolus followed by 90 additional mg in a continuous 3-hour drip.	Research.	Series (8 patients)	TTE
Prosthetic mitral valve [29]	Recombinant tPA was infused directly into the left atrium via the pigtail catheter at a rate of 0.5 mg/hr. Over the course of the next 70 hours, the patient was maintained on both a continuous tPA and heparin infusion.	Not surgical candidate.	Case report	Fluoroscopy
Prosthetic mitral valve [30]	Direct atrial administration of recombinant tPA, along with heparin, was given at 0.4 mg/kg/hr for 2 hours until bleeding at the femoral catheter site, as with 3 previous attempts of IV infusions.	Not surgical candidate.	Case report	Fluoroscopy and TEE
Native tricuspid valve vegetation in a 12 day neonatal girl [31]	Recombinant tPA was administered thru central line at a dose of 0.5mg/kg during 10 minutes, followed by a continuous infusion of 0.2mg/kg/hr for a total of 72 hours.	Acute deteriorating clinical condition.	Case report	Echo.
Prosthetic tricuspid valve [9]	100 mg of recombinant tPA was given intravenously as a continuous 3 hour infusion.	Failed heparin and oral warfarin for 1 week.	Case report	T EE
Different prosthetic valves (mitral, tricuspid, aortic) [18]	Recombinant tPA - high dose (100 mg): loading dose 10 mg, followed by 90 mg for 90 minutes or for 3 hours without heparin. Low dose (50 mg): loading dose 20 mg then 10 mg/h for 3 hours without heparin.	Research.	Series (110 patients)	Fluoroscopy; TTE or TEE
Different prosthetic valves (mitral, tricuspid, pulmonary) [32]	Recombinant t-PA, with 10 mg loading dose IV followed by 90 mg for 90 minutes.	Research.	Series (4 patients)	TTE