

Review

Case study and review: Treatment of tricuspid prosthetic valve thrombosis

David Yi Zhang^a, Jay Lozier^b, Richard Chang^c, Vandana Sachdev^d, Marcus Y. Chen^d, Jennifer L. Audibert^d, Keith A. Horvath^e, Douglas R. Rosing^{d,*}

^a Division of Internal Medicine, University of Miami Miller School of Medicine, Miami, FL, United States

^b Hematology Service, National Institutes of Health Clinical Center, Bethesda, MD, United States

^c Diagnostic Radiology Department, National Institutes of Health Clinical Center, Bethesda, MD, United States

^d Cardiovascular and Pulmonary Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, United States

^e Office of the Director, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, United States

ARTICLE INFO

Article history:

Received 25 March 2011

Received in revised form 8 August 2011

Accepted 17 September 2011

Available online 14 October 2011

Keywords:

Tricuspid valve

Prosthetic valve

Thrombosis, thrombolysis, fibrinolysis

Ebstein anomaly

Recombinant tissue plasminogen activator

(tPA)

Pannus

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 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 tricuspid PVT emphasizing a modified medical option as a safe, minimally invasive alternative to surgical intervention or conventional medical therapy for tricuspid valve thrombosis.

Published by Elsevier Ireland Ltd.

1. 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% per patient year [2]. Even with adequate anticoagulation, prosthetic valve thrombosis occurs with an 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, 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.

2. 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 November 2005, at the age of 53, because of symptoms of fatigue and an echocardiogram showing increasing tricuspid prosthetic valve stenosis with a mean gradient of 8 mm Hg, mild to moderate tricuspid regurgitation, and thickened cusps, 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. It was recommended that she undergo repeat tricuspid valve replacement, but due to the choice of the patient and her description of limiting, but stable symptoms, she delayed surgery.

* Corresponding author at: Building 10, CRC 5-3330, National Institutes of Health, Bethesda, MD 20892-1454, United States. Tel.: +1 301 451 8018; fax: +1 301 451 7093.

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), which was the patient's choice upon discussion with the surgeon, and also replacement of her VVI pacemaker generator (Medtronic, Minneapolis, MN). Her valve was noted to be partially calcified as well as fibrosed. After discharge, she became much more active, and walked for at least 1 h every day. Since her surgery, the patient had been on warfarin and international normalized ratios (INR) had been followed up by her private cardiologist. Her INRs had ranged from 2.5 to 3.0. However, there had 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 1 h, 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° and the closing angle being 83° (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 and 75 s 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 h and the second lumen to infuse the heparin needed for anticoagulation. Serial blood counts were monitored every 8–12 h. 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 h. 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° (normal 10–13°), and the closing angle was 129° (normal 120–127°).

During the hospitalization, her platelet count dropped from 137,000 per μ l to as low as 94,000/ μ l, but then increased to 100,000/ μ l 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 °C 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 consult 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, eleven, and eighteen months post discharge revealed a normally functioning prosthetic tricuspid valve with a mean tricuspid valve gradient of 2.0 mm Hg.

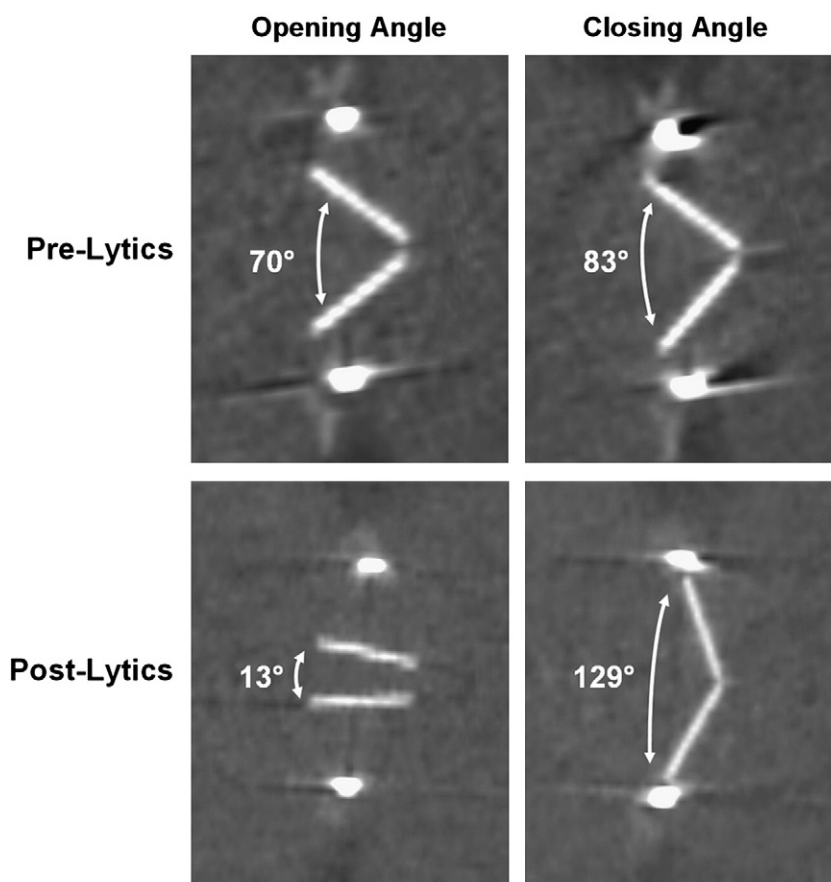


Fig. 1. A. Initial cardiac CT of the heart before thrombolytic therapy, demonstrating minimally mobile leaflets of the mechanical tricuspid valve. B. Follow-up cardiac CT of the heart post t-PA infusion therapy showing restoration of the mobility of the mechanical tricuspid leaflets, with opening and closing angles.

3. 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 sub-xiphoid 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 sternal 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.

4. 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, they 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. In the study, 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.

5. Diagnosis

Suspicion of tricuspid PVT may be raised by physical findings, symptoms of heart failure, or the diagnosis of embolization. Cine-fluoroscopy 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 inability 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.

6. 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, particularly since the clot burden is typically quite small, compared for instance to that from a deep vein thrombosis of the lower extremity. 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, the presence of 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 the 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

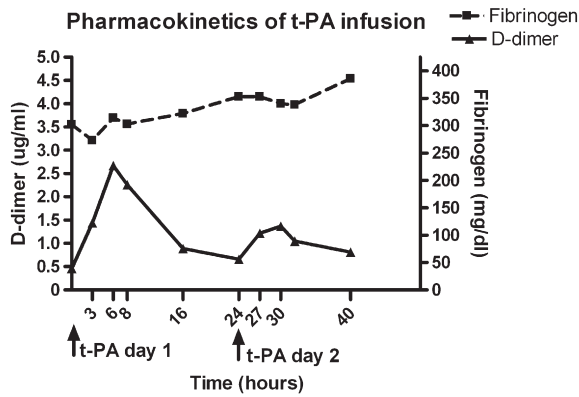


Fig. 2. The pharmacokinetic profile of serum fibrinogen and D-dimer during the t-PA infusion. The t-PA infusions were initiated at 0 and 24 h, and ran for 6 h each day. The patient's serum was collected at the times indicated. The four parameters were measured by the Hematology Laboratory at the NIH.

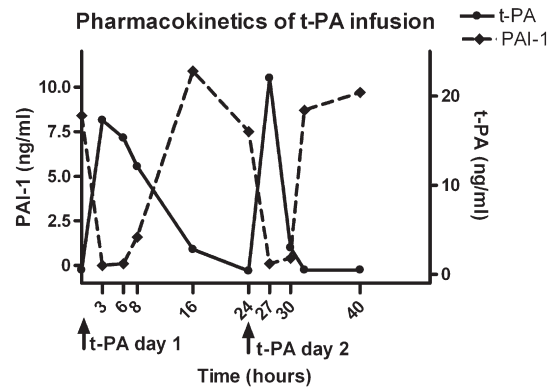


Fig. 3. The pharmacokinetic profile of serum t-PA and PAI-1 during the t-PA infusion. The t-PA infusions were initiated at 0 and 24 h, and ran for 6 h each day. The patient's serum was collected at the times indicated. The four parameters were measured by the Hematology Laboratory at the NIH.

PVT may be susceptible to thrombolysis. One hypothesis was that the amount of thrombus that led to the stuck valve was 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 a thrombolytic agent, often lasting 24–48 h, 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 min). 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 h a day using doses of ~1 mg tPA/h. 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 h 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 (Fig. 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

Table 1

Literature review of tPA thrombolytic therapy for native and 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/h. Over the course of the next 70 h, 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/h for 2 h 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 0.5 mg/kg during 10 min, followed by a continuous infusion of 0.2 mg/kg/h for a total of 72 h.	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 min or for 3 h without heparin. Low dose (50 mg): loading dose 20 mg then 10 mg/h for 3 h 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 min.	Research	Series (4 patients)	TTE

studies in this report demonstrate that the serum concentration of tPA peaked at 3 h 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].

7. 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.

Acknowledgment

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology (Shewan and Coats 2010;144:1–2).

Supported by the Intramural Research Programs of the National Heart, Lung, and Blood Institute (NHLBI) and Clinical Center (CC) of the National Institutes of Health.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.ijcard.2011.09.081.

References

- [1] DeWall RA, Qasim N, Carr L. Evolution of mechanical heart valves. *Ann Thorac Surg* 2000;69:1612–21.

- [2] Vongpatanasin W, Hillis LD, Lange RA. Prosthetic heart valves. *N Engl J Med* 1996;335:407–16.
- [3] Hammermeister KE, Sethi GK, Henderson WG, Oprian C, Kim T, Rahimtoola S. A comparison of outcomes in men 11 years after heart-valve replacement with a mechanical valve or bioprosthesis. Veterans Affairs Cooperative Study on Valvular Heart Disease. *N Engl J Med* 1993;328:1289–96.
- [4] 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.
- [5] Montorsi P, Cavoretto D, Alimento M, Muratori M, Pepi M. Prosthetic mitral valve thrombosis: can fluoroscopy predict the efficacy of thrombolytic treatment? *Circulation* 2003;108(Suppl. 1):II79–84.
- [6] Caceres-Loriga FM, Perez-Lopez H, Santos-Gracia J, Morlans-Hernandez K. Prosthetic heart valve thrombosis: pathogenesis, diagnosis and management. *Int J Cardiol* 2006;110:1–6.
- [7] 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.
- [8] Tsiouris N, Ahmad M. Prosthetic valve thrombosis and thrombolysis: a case report and review of the literature. *Am J Med Sci* 2001;322:229–32.
- [9] Kaul P, Adluri K, Javangula K, Baig W. Successful management of multiple permanent pacemaker complications-infection, 13 year old silent lead perforation and exteriorisation following failed percutaneous extraction, superior vena cava obstruction, tricuspid valve endocarditis, pulmonary embolism and prosthetic tricuspid valve thrombosis. *J Cardiothorac Surg* 2009;4:12.
- [10] LaBounty TM, Agarwal PP, Chughtai A, et al. Hemodynamic and functional assessment of mechanical aortic valves using combined echocardiography and multidetector computed tomography. *J Cardiovasc Comput Tomogr* 2009;3:161–7.
- [11] Barbetseas J, Nagueh SF, Pitsavos C, Toutouzas PK, Quinones MA, Zoghbi WA. Differentiating thrombus from pannus formation in obstructed mechanical prosthetic valves: an evaluation of clinical, transthoracic and transesophageal echocardiographic parameters. *J Am Coll Cardiol* 1998;32:1410–7.
- [12] Aoyagi S, Fukunaga S, Teshima H. Treatment for mechanical valve thrombosis in the right heart: combined pharmacological and mechanical thrombolysis. *Artif Organs* 2010;34:E238–41.
- [13] Jones JM, O'Kane H, Gladstone DJ, et al. Repeat heart valve surgery: risk factors for operative mortality. *J Thorac Cardiovasc Surg* 2001;122:913–8.
- [14] Guenther T, Noebauer C, Mazzitelli D, Busch R, Tassani-Prell P, Lange R. Tricuspid valve surgery: a thirty-year assessment of early and late outcome. *Eur J Cardiothorac Surg* 2008;34:402–9.
- [15] Kao CL, Lu MS, Chang JP, Yang TY, Cheng HW. Thrombotic obstruction of a mechanical prosthetic valve in tricuspid position. *Tex Heart Inst J* 2009;36:261–3.
- [16] Vahanian A, Baumgartner H, Bax J, et al. Guidelines on the management of valvular heart disease: the task force on the management of valvular heart disease of the European society of cardiology. *Eur Heart J* 2007;28:230–68.
- [17] Sun JC, Davidson MJ, Lamy A, Eikelboom JW. Antithrombotic management of patients with prosthetic heart valves: current evidence and future trends. *Lancet* 2009;374:565–76.
- [18] Roudaut R, Lafitte S, Roudaut MF, et al. Fibrinolysis of mechanical prosthetic valve thrombosis: a single-center study of 127 cases. *J Am Coll Cardiol* 2003;41:653–8.
- [19] Caceres-Loriga FM, Perez-Lopez H, Morlans-Hernandez K, et al. Thrombolysis as first choice therapy in prosthetic heart valve thrombosis. A study of 68 patients. *J Thromb Thrombolysis* 2006;21:185–90.
- [20] Hurrell DG, Schaff HV, Tajik A. Thrombolytic therapy for obstruction of mechanical prosthetic valves. *Mayo Clin Proc* 1996;71:605–13.
- [21] Lengyel M, Fuster V, Keltai M, et al. Guidelines for management of left-sided prosthetic valve thrombosis: a role for thrombolytic therapy. Consensus conference on prosthetic valve thrombosis. *J Am Coll Cardiol* 1997;30:1521–6.
- [22] Shapira Y, Herz I, Vaturi M, et al. Thrombolysis is an effective and safe therapy in stuck bileaflet mitral valves in the absence of high-risk thrombi. *J Am Coll Cardiol* 2000;35:1874–80.
- [23] Chang R, Chen CC, Kam A, Mao E, Shawker TH, Horne III MK. Deep vein thrombosis of lower extremity: direct intraclot injection of alteplase once daily with systemic anticoagulation – results of pilot study. *Radiology* 2008;246:619–29.
- [24] Lozier J, Chang R. Clinical safety, efficacy & pharmacokinetics of intra-clot tPA for lower extremity DVT. *J Thromb Haemost* 2009;7(Suppl. 2):7.
- [25] Chang R, Horne III MK, Shawker TH, et al. Low-dose, once-daily, intraclot injections of alteplase for treatment of acute deep venous thrombosis. *J Vasc Interv Radiol* 2011;22(8):1107–16.
- [26] Agnelli G, Buchanan MR, Fernandez F, Van Ryn J, Hirsh J. Sustained thrombolysis with DNA recombinant type tissue plasminogen activator in rabbits. *Blood* 1985;66:399–401.
- [27] Agnelli G. Rationale for bolus t-PA therapy to improve efficacy and safety. *Chest* 1990;97(4 Suppl):161S–7S.
- [28] Muhl D, Furedi R, Gecse K, et al. Time course of platelet aggregation during thrombolytic treatment of massive pulmonary embolism. *Blood Coagul Fibrinolysis* 2007;18:661–7.
- [29] Desai S, Kavinsky C. Localized left atrial administration of tPA for the treatment of mechanical mitral valve thrombosis. *Catheter Cardiovasc Interv* 2008;72:151–5.
- [30] Seltzer SM, Reed MD, Siwik ES. Intra-atrial tissue plasminogen activator infusion for prosthetic valve thrombosis. *Catheter Cardiovasc Interv* 2006;67:139–41.
- [31] Van Overmeire B, Van Reempts PJ, Van Acker KJ. Intracardiac thrombus formation with rapidly progressive heart failure in the neonate: treatment with tissue type plasminogen activator. *Arch Dis Child* 1992;67:443–5.

- [32] Manteiga R, Carlos Souto J, 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.
- [33] Bonow RO, Carabello BA, Chatterjee K, et al. focused update incorporated into the ACC/AHA 2006 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. *J Am Coll Cardiol* 2008;52:e1–142.
- [34] Salem DN, O'Gara PT, Madias C, et al. Valvular and structural heart disease: American College of Chest Physicians evidence-based clinical practice guidelines (8th ed). *Chest* 2008;133:593S–629S.