

Successful Use of Catheter-Directed Low Dose Alteplase Infusion for Mitral Valve Thrombus: A Case Report

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Prothetic valve thrombosis (PVT) is a rare but serious complication of valve replacement. PVT can cause obstructive and nonobstructive complications, and both have significant morbidity and mortality rates. The incidence of obstructive PVT for mechanical valves is 0.3–1.3% incidence per patient years.¹ Nonobstructive PVT is more common, with reported findings as high as 10% during the early post-operative period. Roudaut et al described the variation in the incidence of PVT, with the first post-operative year marked by a 24% incidence of thrombosis and a subsequent decrease of approximately 15% between the second and fourth years.¹ The diagnosis of PVT can be challenging, because patients can present with varying signs and symptoms. The different therapeutic modalities available for PVT include heparin, fibrinolysis, surgery, or optimization of anticoagulation. Surgical treatment is usually preferred in obstructive PVT but largely influenced by the presence of several factors, including valvular obstruction, valve location, thrombus size, and clinical status. Anticoagulation is necessary to minimize complications from subsequent thromboses, but the optimal treatment strategy remains controversial.¹

Alteplase, a recombinant tissue-type plasminogen activator (t-PA), is a thrombolytic agent that is FDA-approved for the treatment of acute ischemic strokes, pulmonary embolism, acute myocardial infarction, and catheter occlusion. Other indications include treatment of deep vein thrombosis, catheter-directed thrombolysis in the treatment of peripheral arterial occlusive disease, and treatment of prosthetic valve thrombosis.² Alteplase thrombolysis works by binding to fibrin in a thrombus, causing the conversion of plasminogen to plasmin. Alteplase has a high affinity for fibrin and will produce

Abstract

We describe a patient case of the successful use of catheter-directed alteplase 25 mg IV administered over 25 hours to treat a thrombosis in a mechanical mitral valve.

Mechanical prosthetic valve thrombosis (PVT) is a rare but serious complication of valve replacement. Optimal treatment is controversial and depends on the cause of the obstruction and the hemodynamic status of the patient. The therapeutic treatment options include systemic anticoagulation, thrombolysis, surgery, or optimization of current anticoagulation strategy. In this case, the patient presented with a nonobstructive mitral valve thrombus and was initiated on catheter-directed low dose alteplase infusion, 25 mg IV over 25 hours, and subsequent bridging with IV heparin infusion to warfarin long-term therapy. Systemic heparin was monitored by activated partial thromboplastin time (aPTT) with a goal range of 45–70 seconds for a total duration of 5 days. Repeat echocardiographic imaging was done and showed complete resolution of the clot. There were no bleeding complications from anticoagulation. On discharge, the patient's international normalized ratio (INR) goal was 2.5–3.5 and the patient continues to be followed at our institutional anticoagulation clinics.

limited conversion of plasminogen in the absence of fibrin.³

Case Report

A 47-year-old female was seen in clinic in October 2019 with a complaint of shortness of breath and dyspnea on exertion. The patient's past medical history included chronic warfarin therapy for mechanical mitral valve replacement (2011), atrial fibrillation, heart failure with reduced ejection fraction, rheumatic fever, nonischemic cardiomyopathy, and hyperlipidemia. Family history included hyperlipidemia in her father and cardiovascular disease in her mother. Her social history was unremarkable.

Per the patient's report, she intermittently took her warfarin therapy and eventually stopped taking it due to

social, financial, and location difficulties for proper management. At the time of presentation, she had been off warfarin therapy for at least four years, as reported by the patient. During the initial workup, providers ordered a chest x-ray, which showed mild pulmonary edema. She was taken for a transthoracic echocardiogram and was found to have severe left ventricular dysfunction (ejection fraction 25%) and improper function of her mitral valve (mean gradient 7.8 mmHg). A transesophageal echocardiogram was completed and a nonobstructive thrombus (1.7 cm x 1.2 cm) was found on the septal annulus adjacent to the medial disc. Her left ventricular ejection fraction (LVEF) was severely decreased from her previous exam (LVEF 65% from 2015). The clinic physician advised the patient to be admitted to the intensive care unit and

start thrombolysis. However, she refused any medical treatment, and left against medical advice. After further worsening of her symptoms, she then presented to our hospital for further care.

On admission, the patient was well compensated. Her systolic blood pressure ranged between 150 and 160 mmHg; her heart rate was 70 beats per minute; her respiratory rate was 14–18 breaths per minute; and she was afebrile. Her oxygen saturation was 98% on room air. Her INR was 1.1, which was expected, since her last reported warfarin dose was several years earlier. An EKG was ordered and showed the patient in sinus rhythm with 1st degree AV block.

Initially, the patient was started on IV heparin, but that was stopped on the same day and switched to alteplase catheter-directed infusion, 1 mg per hour for 25 hours with no initial bolus. The concentration of the alteplase infusion was alteplase 10 mg in sodium chloride 0.9% 250 mL (25 mL/hour). After the alteplase infusion, the patient was then re-initiated on IV heparin infusion (no initial bolus) 11 units/kg/hour and eventually titrated per institutional protocol to 15 units/kg/hour based on aPTT goal range of 45–70 seconds. During the heparin infusion, the patient was bridged to warfarin with an INR goal of 2.5–3.5. The patient remained on heparin infusion for 5 days with no bleeding complications noted. She denied any further symptoms such as shortness of breath, chest pain, or palpitations. No adverse effects were noted from the alteplase. Two days after the alteplase infusion, a repeat transesophageal echocardiogram was completed and showed complete clot resolution. The patient was discharged on warfarin with a therapeutic INR and continues to follow up with our institutional anticoagulation clinic.

Discussion

PVTs can present as an acute, subacute, or chronic thrombus, with the latter being more common. Thrombus formation is complex; they are typically formed of multiple clot layers with varying degrees of organization.¹ In relation to Virchow's triad, endothelial, hemodynamic, and hemostatic factors can predispose thrombus formation. With regard to the prosthetic valve, endothelial factors represent the interaction between the prosthesis and

suture zone. The hemodynamic factors include the cardiac hemodynamic status of the patient and the characteristics of the prosthesis. Hemostatic factors involve anticoagulation management, which is often a challenging balance, especially during the early post-operative period. The balance between excessive anticoagulation and hemorrhagic complications, versus suboptimal anticoagulation and thrombosis must be evaluated on a case-by-case basis.¹

According to the 2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease for acute mechanical prosthetic valve thrombosis presenting with symptoms of valve obstruction, urgent initial treatment with either slow-infusion low-dose fibrinolytic therapy or emergency surgery is recommended.⁴ The level of evidence was updated to Level B-NR, which includes moderate-quality evidence from one or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies. Slow-infusion fibrinolytic therapy has higher success rates and lower complication rates than historically used high-dose regimens, and is effective in patients previously thought to require urgent surgical intervention.⁵ The overall 30-day mortality rate with surgery is 10% to 15%, with an even lower mortality rate (<5%) in patients with New York Heart Association (NYHA) class I/II symptoms.^{4,5} Prior to 2013, studies that evaluated fibrinolytic therapy showed an overall 30-day mortality rate of 7% and hemodynamic success rate of 75%. Furthermore, thromboembolism rates were as high as 13%, major bleeding rates 6%, and intracerebral hemorrhage 3%.^{6,7} However, recent reports have suggested that slow-infusion low-dose fibrinolytic protocols have high success rates (>90%), with embolic event rates <2% and major bleed rates <2%.^{4,5,8} These fibrinolytic therapy regimens can be successful even in patients with advanced NYHA class and larger-sized thrombi. The decision for emergency surgery versus fibrinolytic therapy should be individualized, as there have not been randomized controlled trials comparing the two interventions.⁵

The best treatment strategies for prosthetic valve thrombosis remain controversial. The TROIA trial was conducted to find the safest and most

effective regimen among different thrombolytic treatment strategies.⁸ This was a single-center study from 1993 to 2003 that included 182 patients with 220 episodes of mechanical PVT. The trial compared five regimens: rapid streptokinase administration (1.5 million units over 3 hours, group I); slow streptokinase (1.5 million units over 24-hours, group II); high-dose 100 mg tissue plasminogen activator (t-PA) (group III); half-dose 50 mg and slow infusion (6 hours) of t-PA without bolus (group IV); and a low dose (25mg) and slow infusion (6 hours) of t-PA without bolus (group V).

This trial showed that t-PA 25 mg over 6 hours was as efficacious as the other treatment regimens but had lower complication rates in patients with PVT. Complication rates varied between groups I-IV but did not differ significantly (37.5%, 24.4%, 33.3%, and 29.6%; $p>0.05$ for each comparison) but was significantly lower in group V (10.5%, $p<0.05$ for each).⁸ Specifically, for this patient case, the low dose alteplase infusion strategy was chosen based on the PROMETEE trial. The PROMETEE trial was conducted to test whether further prolongation of the alteplase infusion time would reduce complication rates without reducing success rates.⁹ This was a single-center study from 2009 to 2013 that included 114 patients with PVT in 120 different episodes. Outcomes for the PROMETEE trial found a success rate of 20% after the first thrombolytic therapy session (25 mg over 25-hour infusion). More than one t-PA session was required in 93 episodes (77.5%) and there were two median thrombolytic sessions.

Ultimately, there was a 90% success rate after the eighth session (maximum alteplase dose of 200 mg). The presence of atrial fibrillation, NYHA class IV status, higher baseline thrombus area, and greater duration of suboptimal anticoagulation (DSA) were associated with a lower likelihood of success by univariate analyses.⁹ Of note, the majority of the study population was NYHA classes I and II, and only 35% were NYHA class III and IV. The median age was 49 years, and PVT was nonobstructive in 36% and obstructive in 64% of patients. Four patients had NYHA class IV, one underwent surgery due to unsuccessful thrombolytic therapy, one developed an

embolism, one died from heart failure, and another had an ischemic stroke. The authors surmised that the poor outcomes in this group might have been due to a limited time interval to achieve thrombolysis.⁹

Compared to those patients, our patient had a history of atrial fibrillation and NYHA class III. Another similar characteristic was the thrombus size; in the PROMETEE trial, the average mitral thrombus size was 1.5 cm, and this patient's was 1.7 cm, as noted by an echocardiogram.⁹ One major difference from this case report and the PROMETEE trial was the DSA. The trial included patients with an average DSA of 7 months, but this patient had a DSA at 48 months. The DSA reflects the elapsed time since a thrombus formation, and the PROMETEE trial predicted that an earlier thrombus might have a better response to thrombolytic therapy. In comparison, thrombolytic therapy to an organized thrombus (longer DSA) may have a higher likelihood of unsuccessful outcomes.⁹

Furthermore, increased thrombus area is another independent predictor of complications, and was associated with unsuccessful outcomes of thrombolytic therapy. This is attributed to more severe valvular obstruction and higher NYHA class in patients with greater thrombus area.⁹

Despite the longer DSA, this patient had successful thrombus resolution after one round of alteplase infusion (25 mg over 25 hours), followed by IV heparin and warfarin. In terms of complication rates from the PROMETEE trial, these were relatively low and were comparable to previous published studies.^{8,10} The rates of embolism and major and minor hemorrhage were 1.7%, 1.7%, and 2.5%. The rates of complications did increase with the number of thrombolytic therapy sessions, and 67% of complications were seen after completion of the second thrombolytic session.⁹ For our patient case, there were no documented complications, which is likely attributed to only one thrombolytic session being performed.

One limitation of this case report is that there was a lack of follow-up during the four years during which the patient reported she wasn't taking warfarin. Based on the information provided by the patient, it is unclear whether warfarin was taken intermittently or not at all. From a

pathophysiologic standpoint, the longer DSA suggests more fibrin cross-linking and a stronger thrombus, which would make alteplase less successful. We would expect this patient would require more thrombolytic sessions to completely resolve the thrombus, which further suggests the patient had been taking warfarin intermittently.

The outcome of this case report supports the findings from the PROMETEE trial, in that catheter-directed low dose alteplase infusion over 25 hours is a feasible option for a patient with a mechanical mitral valve thrombus.

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