Case Report: Successful Use of Two Thrombolytic Drugs in Prosthetic Mitral and Aortic Valve Thrombosis

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ABSTRACT

Introduction: Prosthetic valve thrombosis is a rare and severe complication of valve replacement, most often encountered with a mechanical prosthesis. The significant morbidity and mortality associated with this condition warrant rapid diagnostic evaluation. Although surgery is the first-line therapy in symptomatic obstructive mechanical valve thrombosis, thrombolytic therapy has been used as an alternative.

Case Description: In this case report, we describe a 46-year-old man with a history of the mitral valve and aortic valve replacement 2 years ago. In echocardiography, we detected a mobile mass on the atrial side of the mitral valve prosthesis and a fixed one on the leaflet of the mechanical aortic valve with a high gradient. To save his life, we used double thrombolytic therapy considering the patient's hemodynamic situation and the risk of bleeding. Although a routine dose of reteplase and streptokinase was considered, we administered these two thrombolytic drugs together within 72 hours.

Conclusion: Ultimately we succeeded with this method without any significant or life-threatening adverse effects, and the patient was discharged after an optimal anticoagulation therapy.

Introduction

The incidence of prosthetic valve thrombosis varies according to the efficacy of anticoagulation, type, and location of the implanted prosthesis, and the presence of atrial fibrillation [1]. Based on the patient's clinical status, the decision for acute thrombolytic treatment versus immediate valve surgery was made in agreement with our cardiac surgeons. The patient's informed consent was obtained. Since there was not enough information on whether to continue thrombolytic therapy or do surgery considering the patient's outcome, the best procedure is dependent on the patient's hemodynamic condition. Therefore, this case report has a vital role in the management of this medical crisis.

Case Description

A 46-year-old man presented to our emergency room with a complaint of progressively worsening shortness of breath in the last 3 days. Two prosthetic valves had been inserted in the mitral and aortic positions 2 years ago. Physical examination showed function class III, sinus

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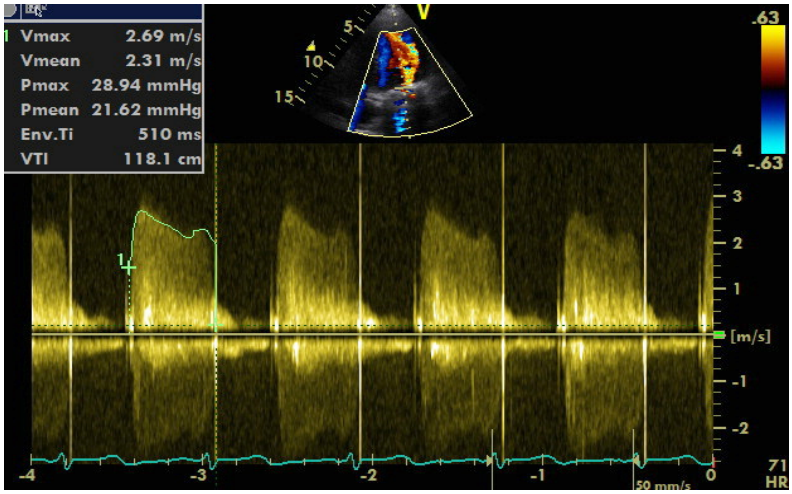

Figure 1. Transesophageal echocardiography of mitral valve showed mean gradient of 21.62 mmHg

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tachycardia on electrocardiogram with a heart rate of 100 beats per minute and systolic blood pressure of 110.70 mmHg. He did not regularly take his medications for the last 10 days, and his international normalized ratio was 1.6 (target range: 2.5-3.5). Transesophageal Echocardiography (TEE) showed moderate transvalvular regurgitation in Mitral Valve (MV) and a mobile mass on the atrial side of the prosthesis, both leaflets of Atrial Valve (AV) and MV were fixed and the mean gradients in AV and MV were 36.77 and 21.62 mmHg, respectively. Also, TEE showed D-shaped Left Ventricle (LV) with moderate to severe systolic dysfunction (left ventricular ejection fraction: 30-35%), mildly dilated ascending aorta (3.6 cm) (Figures 1, 2). Fluoroscopy showed malfunction of AV and MV prosthetic (multiple mobile masses >0.8 cm^2).

Surgeons refused the operation, so thrombolytic therapy was prescribed to rescue the patient's life. Reteplase (r-tPA) was administered at a dose of 36 mg continuous infusion for 18 h. To evaluate the treatment, TEE repeated and showed improvement of AV, however in one of the mitral leaflets, the thrombotic lesion was still fixed. Since the patient's condition had not been changed, another dose of r-tPA was repeated as 36 mg continuous infusion for 24 h. Fluoroscopy showed a well-functioning aortic valve prosthesis, but the malfunction of MV persisted. Because of the malfunctioning of MV, we decided to administer another thrombolytic agent due to low bleeding risk. However, more research is needed in this regard. Streptokinase vial was infused as 200000 IU intravenous bolus and then 100000 IU/h for 12 h. In the next TEE, we found significant improvement in the excursion of the antero-

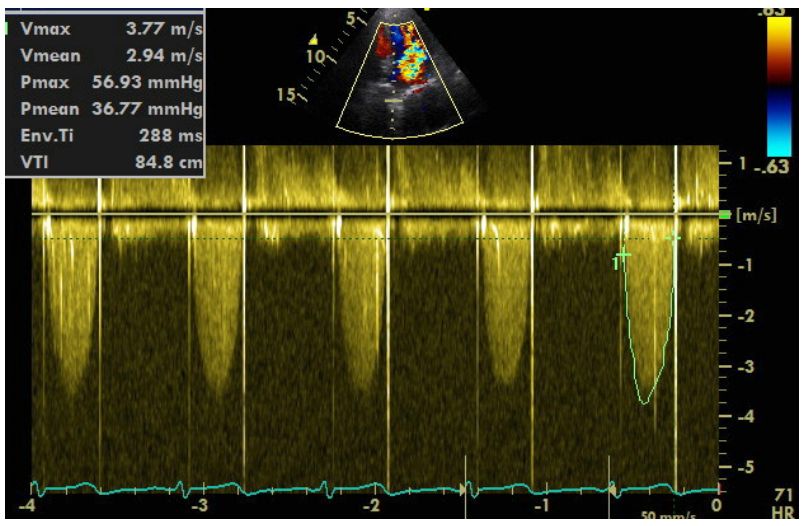

Figure 2. Transesophageal echocardiography of aortic valve showed mean gradient of 36.77 mm Hg

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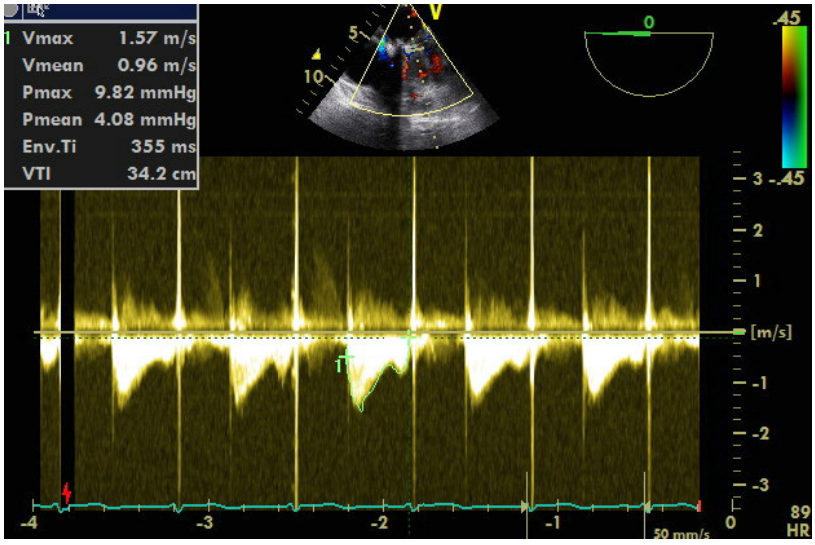

Figure 3. TEE showed well-functioning of AV and reduction of valve gradient

lateral leaflet and no paravalvular regurgitation in AV and MV (Figures 3, 4). No evidence of embolic complications or bleeding (according to Wells score and TIMI bleeding) was found in the patient. After optimal anticoagulation therapy, the patient was discharged.

Discussion

These data, for the first time, demonstrate the massive increase in cardiac output and excellent blood flow in the patients with prosthetic valve thrombosis by the administration of double thrombolytic drugs.

Prosthetic heart valve thrombosis is a serious and urgent complication and related to the type and position of the valve [2]. Valve thrombosis can be classified according to its timing as early (less than 3 months), late (3 months to 1 year), or very late (more than 1 year). The definitive diagnosis of prosthesis thrombosis can be established with clinical, imaging (computed tomography or echocardiography), or pathological criteria [3]. Superiority of surgery or thrombolytic therapy is related to the patient's hemodynamic condition. Currently, there are no randomized controlled trials favoring surgery over thrombolytic therapy. Operation is associated with a high risk of mortality, but thrombolytic therapy for left-sided prosthetic valve thrombosis is associated with bleeding, cerebral embolization, and recurrent thrombosis of the prosthetic valve [4-6].

The treatment of choice in right-sided obstructive prosthetic valve thrombosis is thrombolytic therapy, and fibrinolytic agents have been associated with a high success rate and a low complication rate. Surgery should be reserved for cases with a pannus, thrombolytic failure, and contraindication to thrombolysis. In the most recent European and American guidelines, surgery is recommended for patients in the New York Heart Association

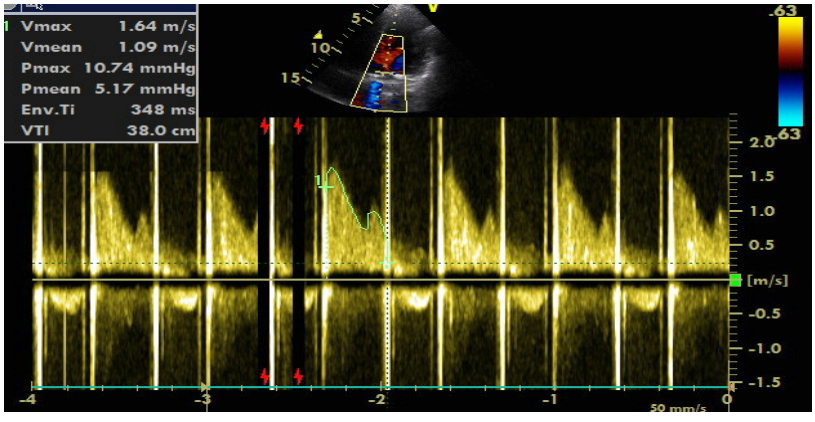

Figure 4. TEE showed well-functioning of MV and reduction of valve gradient.

(NYHA) functional classes III and IV unless surgery is high risk (class IIA). Thrombolysis is given a class IIA indication in patients with right-sided valve thrombosis and a class IIB indication in patients with a left-sided but small thrombus.

The European Society of Cardiology guidelines also emphasize surgery for critically-ill patients and restrict thrombolysis to patients with high surgical risk and or right-sided valve thrombosis. However, the results of more recent studies have reported better outcomes with thrombolytic therapy compared with the previous reports and suggested that thrombolytic therapy would be the treatment of choice in all cases except for patients with contraindications to these agents [7, 8]. The approach to left-sided prosthetic valve thrombosis treatment involves clinical and imaging evaluation of the thrombus burden [3].

We used thrombolytic therapy in our case with function class III and malfunction AV and MV. According to ACC/AHA 2017, low-dose, slow-infusion fibrinolytic therapy for mechanical valve thrombosis is recommended as an initial approach, comparable to surgery class I [9]. In the case of hemodynamic instability, guidelines recommend t-PA 10 mg bolus and then 90 mg intravenous infusion in 90 min with Unfractionated Heparin (UFH) or streptokinase 1.5 million units in 60 min without UFH. However, clear guidelines for dosing and duration of therapy to reach maximum therapeutic effect should be investigated in future studies. For this reason, we used r-tPA continuous infusion at first, and then we decided to administer streptokinase after r-tPA based on the patient's condition. The half-life of streptokinase is biphasic. Initially, it is 18 min (from antibody action) and then extends to 83 min. The anticoagulant effect may persist for 12 to 24 h after the infusion is discontinued.

As with other thrombolytic agents, bleeding is the most common adverse event seen in reteplase recipients. No significant differences in the overall risk of bleeding are observed between reteplase and either accelerated alteplase or standard streptokinase treatment in clinical trials. The risk of stroke in reteplase recipients appears to be similar to that of other thrombolytic agents. The initial half-life (t1/2α) of reteplase activity or antigen ranged from 11 to 19 min in healthy volunteers or patients with AMI [10]. The complete success rate of thrombolysis has been reported from 71% to 91%. The duration of thrombosis is variable. Some authors reported thrombosis in 10 days related to the heparin-induced thrombocytopenia [11, 12], while some authors reported very late, and as long as 32 years after the metallic valve replacement [13]. Owing to chronic thrombosis or the presence of pannus, fibrinolysis is less likely to be successful in the mitral prosthesis [3].

The complications related to thrombolytic treatment are common. Death rates have been reported between 2.8% and 11.8% and stroke ranged from 4.4% to 6.7% [14-19]. However, Ermis reported that complete resolve, in ischemic and hemorrhagic stroke rates with thrombolysis or surgery, were similar [20]. They concluded that thrombolytic therapy is more effective and safer than surgery for specific patient groups who belonged to the functional class 3/4. Ultraslow (25 h) infusion of low-dose (25 mg) t-PA without bolus is associated with quite low mortality in patients with prosthetic valve thrombosis, except for those with NYHA class IV, without compromising effectiveness [21]. Comparing different thrombolytic regimens for prosthetic valve thrombosis (these regimens chronologically included rapid (group I), slow (group II) streptokinase, high-dose (100 mg) tissue plasminogen activator (t-PA) (group III), a half-dose (50 mg) and slow infusion (6 h) of t-PA without bolus (group IV), and a low dose (25 mg) and slow infusion (6 h) of t-PA without bolus (group V)) showed the overall success rate as 83.2%. This rate did not differ significantly among groups [22].

In our case, double thrombolytic treatment was successful and prosthesis valve echocardiography parameters improved. The study results showed that double thrombolytic administration could be prescribed based on the patient's hemodynamic characteristics and relative response to the first drug. We decided to use it in a slow infusion rate rather than a bolus to reduce the risk of breaking up the thrombus into large emboli and the risk of cerebral bleeding.

The use of thrombolytic drugs has increased over the last decades due to the incompliance of patients for drugs and the prevalence of valve stenosis. The condition should be considered in all patients taking warfarin and presenting with acute shortness of breath due to valve stenosis. The patient's adherence to the anticoagulation therapy, routine checking of blood parameters, and echocardiographic investigations can detect the malfunction of leaflets early. We presented a rare case of mitral and aortic prosthetic valve thrombosis, who was successfully treated with double thrombolytic therapy. This combination therapy has been proved to be beneficial with no additional risk to the patient.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles were considered in this article.

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Authors' contributions

All authors contributed equally in preparing all parts of the research.

Conflict of interest

The authors declared no conflict of interest.

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