Successful Fibrinolytic Therapy in a Challenging Obstructive Prosthetic Mitral Valve Thrombosis

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Abstract
Prosthetic valve thrombosis is a rare and severe complication of the mechanical prosthetic valve. Management can be challenging due to varying clinical presentation, overlapping features of differential diagnosis, and lack of randomized controlled trials on the therapeutic options. In this article, we report the case of a patient with a mechanical prosthetic mitral valve presented with symptoms of heart failure, and an echocardiography showing increased mean pressure gradient across the prosthesis along with a fixed posterior leaflet and a partially restricted anterior leaflet with no visible mass. That raised the concern for an obstructed prosthesis. After multimodality imaging and multidisciplinary team discussions, prosthetic valve thrombosis diagnosis was favored over other differential diagnoses that included but not limited to pannus ingrowth. Fibrinolytic therapy was administered, and the patient was discharged on optimal anticoagulation. Repeated echocardiography a month later showed normal mean gradient and normal functioning prosthetic mitral valve without the need for repeat mitral valve surgery.

Keywords
heart valve prosthesis, mitral valve, thrombolytic therapy, heart valve diseases, thrombosis

Introduction
Prosthetic valve thrombosis (PVT) has an incidence of 0.1% to 5.7% in prosthetic mechanical valves with higher rates in the early preoperative period, mitral position, and with suboptimal anticoagulation.\(^1\) It can be either obstructive or non-obstructive with subsequent clinical or subclinical symptoms. That adds to the challenge of diagnosis of PVT, as some cases of PVT can be undetected.

Case Report
A 65-year-old female with a history of rheumatic mitral valve disease, treated with a mechanical St. Jude 25-mm bileaflet prosthetic valve 18 months ago, presented with a 2-week history of progressively worsening dyspnea on exertion and orthopnea. She was on warfarin for anticoagulation without aspirin because of aspirin hypersensitivity. On presentation, vital signs revealed a temperature of 98.1°F, blood pressure of 92/61 mm Hg, regular heart rhythm with a heart rate of 120 beats per minute, respiratory rate of 30 breaths per minute, and oxygen saturation of 92% on room air. She was alert but in acute distress. Physical examination revealed jugular venous distension at 10 to 12 cm, basal rales bilaterally on lungs auscultation, and a trace lower limb edema. Initial electrocardiogram showed sinus tachycardia with nonspecific ST-T-wave changes. Chest X-ray showed bilateral diffuse interstitial prominence with bilateral pleural effusion. International normalized ratio (INR) was 3.8. Otherwise her laboratory workup was unremarkable. Transthoracic echocardiogram (TTE) showed ejection fraction of 60% to 65% and not well-visualized prosthetic mitral valve with no visible mass with a mean gradient of 20 mm Hg, peak E wave velocity was 2.9 m/s. Mitral valve Doppler Velocity Index was 3.85, and a pressure half-time was 254 ms (Figure 1). Blood culture was negative for 3 times for any infection. Further evaluation with a transesophageal echocardiogram (TEE) showed a fixed posterior leaflet and a partially restricted anterior leaflet of the prosthetic mitral valve with no visible mass and a mean gradient of 42 mm Hg at a heart rate of 87 beats per minute (Figure 2). We then proceeded with computed tomography (CT) scan to better assess

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Figure 1. The initial transthoracic echocardiogram on presentation showing a mean pressure gradient of 20 mm Hg across mitral valve prosthesis along with fixed posterior leaflet and partially restricted anterior leaflet with no visible mass.

Figure 2. Repeat transesophageal echocardiogram after 2 rounds of fibrinolytic therapy showing improvement in the mean pressure gradient across the prosthetic mitral valve at 8 mm Hg along with a normal movement of the anterior leaflet and persistent fixed posterior leaflet.
the mitral valve leaflet motion, which showed severely restricted movement of both prosthetic mitral valve leaflets with streak artifact near the valve ring limits evaluation for pannus. The patient was started on a heparin drip for the possible thrombotic mitral valve, and then underwent repeat TEE the next day, which showed no clear thrombus or mass on the prosthetic mitral valve, but persistent restricted prosthetic motion with elevated mean gradient at 27 mm Hg. We elected to proceed with fibrinolytic therapy for suspected prosthetic mitral valve thrombosis and started the Mayo Clinic protocol of alteplase 20 mg bolus followed by 30 mg infusion drip over 3 hours. TEE after the first round of fibrinolytic therapy showed improved mean gradient across the prosthetic mitral valve from 27 mm Hg to 18 mm Hg; however, it showed persistent fixed posterior leaflet. With the partial improvement of the mean gradient across the valve after the first course of fibrinolytic therapy, we repeated the same protocol for another course with continuous heparin drip in between the 2 courses. Repeat TTE following the second course showed further improvement in the mean gradient across the prosthetic mitral valve from 18 mm Hg to 8 mm Hg, normal movement of the anterior leaflet, and persistent fixed posterior leaflet (Figure 3). Afterward, she was started on warfarin plus clopidogrel, with intravenous unfractionated heparin bridging with a higher INR target of 3.5 to 4. Subsequently, she was discharged home in a stable state with the plan to reevaluate for repeat mitral valve surgery. Follow-up TEE 1-month postdischarge showed a completely normal mean pressure gradient across the mitral valve prosthetic with a properly functioning anterior and posterior valve leaflets. Subsequent 6-month follow-up TTE showed properly functioning mitral valve prosthetic with normal pressure gradient across the prosthetic.

Discussion

Prosthetic valve thrombosis and/or obstruction diagnosis demands a high clinical suspicious for proper management and should be suspected in patients with prosthetic valve presented with clinical symptoms and/or signs related to heart failure, new valvular heart disease, thromboembolic (TE) event, or an increase in the mean gradient across the prosthetic valve compared with the baseline. The first step in the management is to determine the underlying cause that includes thrombus formation, pannus ingrowth, and a combination of both or vegetations. Also, prosthesis-patient mismatch should be considered in the differentials, and it can increase the pressure gradient across the normally functioning prosthetic valve. Urgent evaluation with multimodality imaging is indicated once PVT is suspected. TTE can assess the valve hemodynamics and function. TEE is superior to TTE in evaluating prosthetic valve dysfunction as a clear visualization of the underlying cause of the prosthetic dysfunction can be limited with TTE. Fluoroscopy can be used to assess mechanical PV mobility and opening angles. Moreover, CT can assess PV structure, especially if a mass is visible on
the TEE (lower attenuation levels with thrombus).4,5 Pannus ingrowth favoring features on echocardiography include no mass with normal leaflet motion or mass. High attenuation levels of the mass or extension along the valve ring on CT is suggestive of pannus ingrowth. On the other hand, low echogenicity mass or mass with low attenuation levels, irregular shape, or attachment to valve structure on CT would favor thrombus.6 The imaging features can overlap, and they usually favor one diagnosis over another; however, the final diagnosis should be considered in a clinical context.

In our case, the symptoms and signs of heart failure with a history of prosthetic valve raised the suspicion of prosthetic dysfunction. The echocardiogram findings including elevated pressure gradient across the prosthesis along with elevated velocity, Doppler Velocity Index, and pressure halftime raised the concern for prosthetic valve obstruction. Our main differential diagnoses were pannus ingrowth and PVT. The absence of infection signs and negative blood cultures made underlying infective endocarditis less likely. Multimodality imaging did not show a visible mass and was inconclusive to the most part, which made the discrimination between 2 entities challenging. However, in a clinical context of restricted valve motion, no visible mass, and not being on Aspirin initially, the diagnosis of PVT was favored after a multidisciplinary team discussion.

The presumptive underlying etiology of prosthetic valve obstruction plays a critical role in determining the treatment. PVT has the treatment options of anticoagulation, fibrinolytic therapy, or surgery. However, deciding on optimal treatment is challenging especially with no randomized controlled trials. Current guidelines are based on observational studies and expert opinions. On the other side, surgery is the only option for pannus ingrowth.4 Anticoagulation therapy using unfractionated heparin plus warfarin with or without aspirin has been reported to be successful, at least partial resolution of the thrombus, in patients with asymptomatic, small (<10 mm) left-sided PVT.7 Although anticoagulation with heparin should be started immediately once the diagnosis of PVT has been made, however, definitive therapy with either fibrinolytic therapy or surgery should be considered. Fibrinolytic therapy is an effective treatment option for PVT; however, there is no head to head comparison between different regimens, with most studies limited to a single-center study. In TROIA (Comparison of Different Transesophageal Echocardiography Guided thrombolytic Regimens for prosthetic valve Thrombosis) study, 220 PVT episodes were included comparing 5 different fibrinolysis therapy regimens. A low-dose, slow-infusion regimen of tissue plasminogen activator (t-PA; low-dose [25 mg], slow infusion [6 hours] of t-PA repeated as needed without a bolus) was associated with no mortality and showed lower overall complications (10.5% vs 24.4 to 37.5% in other regimens).8 A subgroup of comparison from the TROIA trial showed a 100% success rate in 24 pregnant women with 28 PVT episodes that were treated with low-dose, slow-infusion regimen.9

In the Ultra-slow PROMETE (PROsthetic MEchanical valve Thrombosis and the prEdictors of outcome) trial that included 120 episodes of PVT, an ultraslow regimen of alteplase (alteplase 25 mg infusion over 25 hours with no bolus, which was repeated based on TTE/TEE findings up to 8 times up to a total of 200 mg) was successful in 90% of the patients with a low mortality rate (0.8%) and overall complications (6.7%).10

Overall, there has been a significant change in the outcomes of fibrinolytic therapy after the introduction of the protocols using echocardiogram-guided slow or ultraslow infusion rate and small dose fibrinolytic. These new protocols compared with the ones using high doses and rapid infusion had a success rate as high as 90% versus 75%, TE rate of <2% versus 13%, and major bleeding rate of <2% versus 6%.4

The clinical outcomes in patients with PVT treated with surgery versus fibrinolysis have been reported in 2 systematic reviews and meta-analyses, and surgery was not superior to fibrinolysis with higher mortality, 13.5% to 18.1% compared with 6.6% to 9.5% in the thrombolysis groups.5,11 Most studies included in these reports used standard thrombolytic dose and not slow-infusion, low-dose fibrinolytic therapy. It is important to note that in 2017 new focused update of the 2014 American Heart Association/American College of Cardiology guidelines has a significant update with Class I-B recommendation for urgent initial treatment with either slow-infusion low-dose fibrinolytic therapy or emergency surgery in the patient with a left-sided mechanical PVT presenting with symptoms of valve obstruction.4 Also, it emphasizes on individualizing the treatment choice based on different clinical and institutional factors that include the patient’s choice. The definitive treatment option should be supported by the initial clinical response to the initial chosen therapy. After mechanical PVT or TE event, optimizing anticoagulation should be initiated based on the site of the mechanical prosthetic valve and risk factors for TE plus aspirin 75 to 100 mg daily. Intensification of the INR goal should be the next step for patients who were on optimum anticoagulation goal plus Aspirin.4

Our patient was placed on heparin therapy once PVT was suspected, and later on, when the decision was made for definitive treatment with fibrinolytic therapy, we initiated Mayo Clinic protocol with alteplase 20 mg bolus followed by 30 mg infusion drip over 3 hours.12 With the significant improvement in symptoms and the pressure gradient across the prosthetic valve after the first dose, we opted to administer the second dose with further improvement in the pressure gradient and eventually back to normal along with normal motion of valve leaflets. Since our patient presented with PVT on therapeutic anticoagulation, her INR target was intensified to be 3.5 to 4 along with adding clopidogrel as she was allergic to Aspirin.

Conclusion

Prosthetic valve thrombosis management can be very challenging due to the overlapping features of different diagnoses, along with lacking randomized controlled trials between different therapeutic modalities. High suspicion is required
in the presence of suggestive signs and symptoms along with multimodality imaging, which is critical to evaluate and diagnose the prosthetic valve dysfunction. Slow regimens of fibrinolytic therapy can be lifesaving and a critical management option to avoid high-risk repeated surgery.

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