

An unusual thrombolytic therapy decision in prosthetic valve thrombosis during early pregnancy

Erken dönem gebelikte protez kapak trombozuna yönelik sıradışı trombolitik tedavi kararı

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Summary–Pregnancy is among the risk factors for mechanical valve thrombosis, and even though thrombolytic therapy is contraindicated during pregnancy, it may be used in the treatment of this life-threatening complication. This case report describes a pregnant patient, whose echocardiogram showed evident gradient increase on her mechanical prosthetic mitral valve, and who was treated successfully with tissue plasminogen activator for mechanical valve thrombosis.

Özet– Mekanik kapak trombozu hayatı tehdit eden bir komplikasyon olup, gebelik de bu durum için bir risk faktörü olmaktadır. Trombolitik tedavi gebelik döneminde kontrendike kabul edilse de, hayatı tehdit eden bu durumda kullanılabilir. Bu yazıda, ekokardiyografi incelemesinde protez kapağında tromboza bağlı yüksek basınç farkı ölçülen ve daha sonra trombolitik tedaviyle başarılı şekilde tedavi edilen bir gebe sunuldu.

Pregnant patients with a mechanical prosthetic heart valve have a high risk of valve thrombosis.^[1] Previous studies in pregnant patients with a mechanical prosthetic heart valve have shown that patients who use warfarin during their pregnancy have a thromboembolism incidence of 3.9% and a maternal death rate of 2%, whereas patients who use unfractionated heparin (UFH) during their 1st trimester followed by warfarin during their 2nd and 3rd trimesters, have a thromboembolism incidence of 9.2% and a maternal death rate of 4%. The majority of these deaths are related to prosthetic valve thrombosis (PVT),^[2] the treatment of which is still a topic of debate.

This case report presents a 29-year-old patient in her 6th week of pregnancy. A mechanical mitral valve thrombus could not be observed, but it was highly

suspected due to an evident gradient increase. The patient was given a prolonged infusion of low-dose tissue plasminogen activator (tPA) and was eventually treated successfully.

CASE REPORT

A 29-year-old pregnant patient presented at our clinic with a 3-day history of dyspnea and weakness. She was evaluated as a New York Heart Association (NYHA) Class II, and had undergone mitral valve replacement (MVR) surgery (with a St. Jude bileaflet mechanical prosthetic valve) due to rheumatic valve disease 4 years prior to this admission. She was on her first pregnancy and was using warfarin, alternating daily between 2.5 mg and 5 mg. Her international normalized ratio (INR) value had been checked 1 month prior to admission and was then 2.5. During physical examination, the patient was found to have bilateral basal lung crackles, a mitral mechanical valve sound and apical grade 2 diastolic murmur. Her blood pressure was 105/55 mmHg and her pulse

Abbreviations:

INR	International normalized ratio
NYHA	New York Heart Association
PVT	Prosthetic valve thrombosis
TEE	Transesophageal echocardiography
tPA	Tissue plasminogen activator
TT	Thrombolytic therapy
TTE	Transthoracic echocardiography
UFH	Unfractionated heparin

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was rhythmic, at 113/min. Her axillary temperature was 36.5 °C and her INR value was found to be 1.42. Complete blood count and biochemical tests were within normal range. The patient underwent trans-thoracic echocardiography (TTE) and restricted mobility of the anterior leaflet of the mechanical mitral valve and an increased pressure gradient on the same valve was detected. In addition, transesophageal echocardiography (TEE) showed the anterior leaflet of the mechanical mitral valve failing to open properly during diastole. Mean transmitral gradient was 28 mmHg and mitral valve area was found to be 0.8 cm². No clear image of a thrombus could be detected (Figure 1a, b, Video file 1*). Because the patient was pregnant, a fluoroscopy could not be performed. The patient's most recent TEE had been 2 months prior

to admission and had detected a functional mechanical prosthetic mitral valve with a mean mitral gradient of 6 mmHg. Based on her symptoms, the presence of a state susceptible to thrombosis—pregnancy—and her subtherapeutic INR values, the patient was thought to have a pathological mechanical valve thrombosis, leading to restricted mobility of the valve. With the exception of pregnancy, the patient had no other contraindications for thrombolytic therapy, and was started on a 6-hour-long 25 mg tPA infusion. Following this, and with no change found in the transmitral gradient on a second TTE, the patient was given another 6-hour 25 mg tPA infusion. This was followed by a third TTE, again showing no change in the transmitral gradient, so a third 6-hour 25 mg tPA infusion was administered.

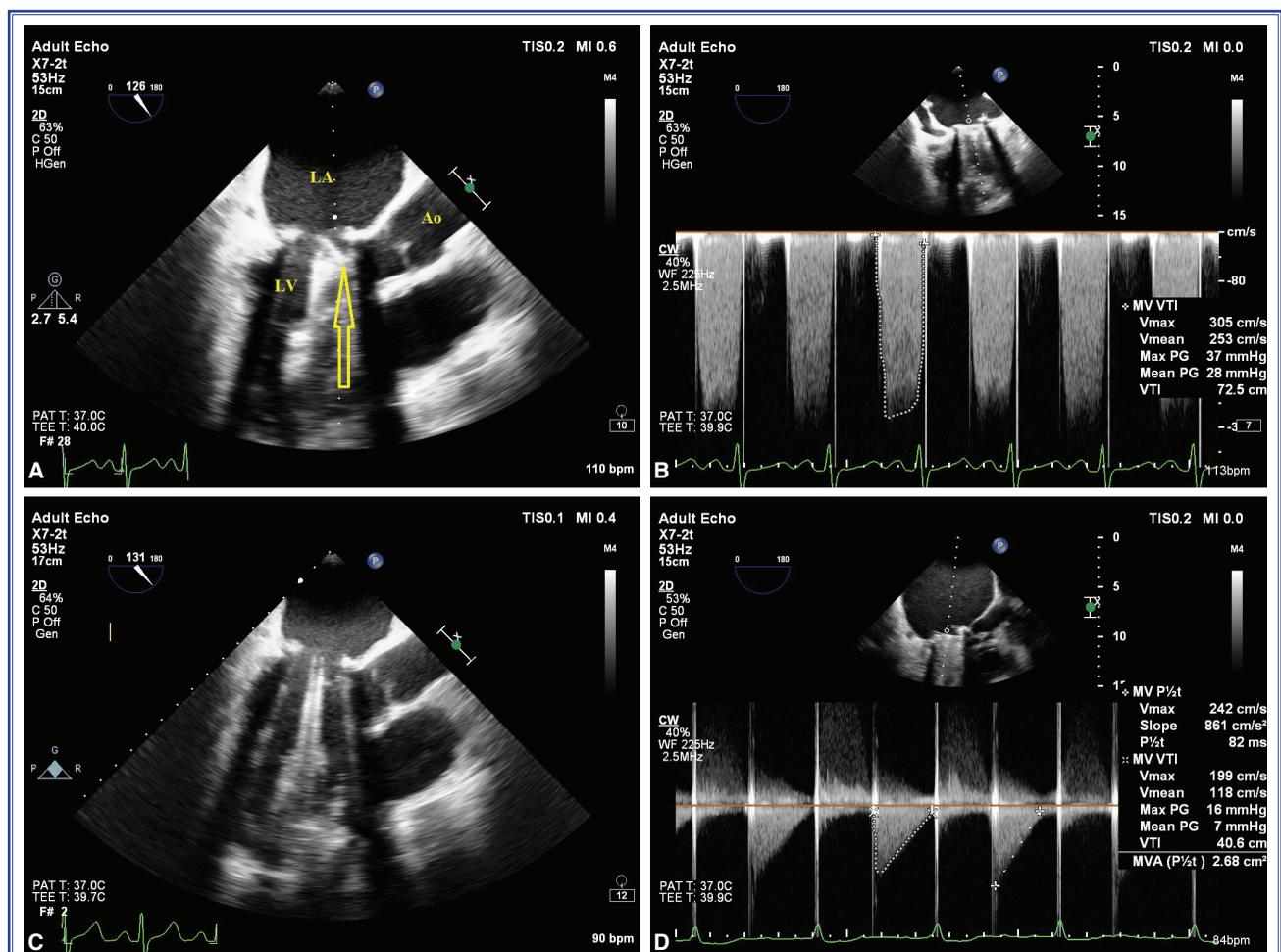


Figure 1. (A, B) The arrow shows that expansion of anterior leaflet of the mitral valve prosthesis is limited in diastole in transesophageal echocardiography and increased in transmitral gradient is observed. (C, D) In transesophageal echocardiography, after tissue plasminogen activator (tPA), expansion of anterior leaflet of the mitral valve prosthesis is normal in diastole and transmitral gradient and mitral valve area is within normal limits.

At the end of this third infusion a TTE and a TEE were performed and the movement of the patient's anterior mitral leaflet was found normal. Mean trans-mitral gradient was 7 mmHg and mitral valve area 2.7 cm² (Figure 1c, d, Video file 2*). The bilateral basal lung crackles disappeared without diuretic usage. In order to raise her activated partial thromboplastin time (aPTT) levels to 2–3 times the normal value, the patient was given UFH and a dose of 5 mg/day of warfarin. When her INR value reached 3.2, the UFH was stopped. Throughout her pregnancy, the patient was followed up with a maximum dose of 5 mg/day of warfarin and regular monitoring of her therapeutic INR values. Warfarin usage was stopped 1 week prior to delivery and UFH was started. The patient had a vaginal delivery of a healthy child with no congenital defects detected in the newborn. On the evening of her delivery day, warfarin was added to the UFH usage. Upon reaching therapeutic INR levels, UFH usage was stopped.

DISCUSSION

PVT is a rare but highly fatal complication. Although the most frequent cause of thrombus formation is insufficient usage of anticoagulants, it is also influenced by factors such as surgery technique, localization of the prosthetic valve, valve type, pannus formation around the valve and patient hemodynamic state. Atrial fibrillation, pregnancy, left atrial enlargement and ventricular dysfunction are additional factors that may lead to thrombus formation.^[3]

In their study, Lengyel et al. showed that 82% of PVT patients have an inadequate usage of anticoagulants.^[4] It is believed that pregnancy-related changes exaggerate blood coagulation reaction in mothers, leaving them more vulnerable to thrombosis. Hereby, in pregnant women with mechanical valves, adequate anticoagulation becomes even more critical. Therefore, stricter control of anticoagulation therapy is necessary for those patients who have used a mechanical valve. Despite using the same doses of warfarin, our patient's INR values had dropped from 2.5 to 1.4. We tend to think that pregnancy, among other factors, could have altered her INR value.

As this report shows, patients with PVT present themselves with new and worsening symptoms. Clinical presentation may vary from dyspnea, embolic events, and symptoms of cardiac insufficiency, to car-

diogenic shock and pulmonary edema.

In diagnosing PVT, TTE results may provide valuable guidance, but TEE is the gold standard procedure for diagnosis confirmation, measurement of thrombus size and mobility, evaluation of thrombus presence in the left atrial and/or left atrial appendage, evaluation of pannus or thrombus formation. TEE should be performed before therapy initiation. In particular, real-time 3-dimensional (3D) TEE, provides extremely useful information on the settlement and size of the prosthetic valve thrombosis, and in follow-up after TPA. In our patient we detected restricted mobility of the anterior leaflet of the prosthetic mitral valve and a gradient increase, but could not detect a thrombus formation. Also in our case, directing the treatment would be more accurate using real-time 3D TEE evaluation of the thrombus and prosthetic valve between TPA infusions.

As in our case, prior TTE results can lead the way to diagnosis in patients with elevated gradient values on prosthetic valves. The results of a TTE performed 1 month prior to admission, showed normal valve mobility, no gradient increase and no signs of valve incompatibility. The newly performed TTE and TEE showed no signs of vegetation or dehiscence on the valve. The patient's symptoms were new, her INR value was subtherapeutic and she was pregnant, a condition well-known for leading to thrombus susceptibility. Taking into account these factors, the patient was thought to have a PVT, even though no thrombus could be detected on her prosthetic valve. We thought that thrombus seems to occurred approximately 1–2 months based on previous TEE images and INR values.

In the guidelines, there is no consensus on the treatment of patients with PVT. Surgical treatment is recommended in ESC guidelines^[5] and thrombolytic therapy (TT) is recommended in The Society of Heart Valve Disease guidelines.^[6] Also, AHA/ACC Valvular Heart Disease guidelines^[7] that were published in March 2014, recommend TT for patients with a thrombosed left-sided prosthetic heart valve, recent onset (<14 days) of NYHA class I to II symptoms, and a small thrombus <0.8 cm².

The risks of TT during pregnancy have never been evaluated with randomized trials. The best level of evidence comes from case reports or case series. Although TT in these reports was performed with a

different drug, a different protocol and various indications, the overall complication rates of TT in these patients are not worse than the complication rates in the large randomized TT trials on stroke, myocardial infarction, and pulmonary embolism.^[8] PVT during pregnancy is uncommon but requires urgent therapy. The low-dose, slow infusion (25 mg/6 hour) tPA therapy performed by Özkan et al. on 24 pregnant patients has shown very promising results.^[9] In this study, the TEE-guided, low-dose, slow-infusion tPA protocol was associated with 100% thrombolytic success with no maternal mortality. Fetal mortality was 20%. In general, TT for the treatment of PVT in non-pregnant patients is successful in ≈85% of patients.^[10]

Pregnant patients with a mechanical heart valve need to be followed-up closely. A diagnosis of valve thrombosis should come to mind for those patients who show an evident gradient increase on their metallic valves during an echocardiographic follow-up. Pregnant patients with prosthetic valve thrombosis can be treated with prolonged infusions of low-dose tPA. Low-dose, long tPA may be given repeated doses.

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***Supplementary video files associated with this article can be found in the online version of the journal.**

REFERENCES

1. Elkayam U, Singh H, Irani A, Akhter MW. Anticoagulation in pregnant women with prosthetic heart valves. *J Cardiovasc Pharmacol Ther* 2004;9:107–15.
2. Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. *Arch Intern Med* 2000;160:191–6.
3. Roudaut R, Serri K, Lafitte S. Thrombosis of prosthetic heart valves: diagnosis and therapeutic considerations. *Heart* 2007;93:137–42.
4. Lengyel M, Vándor L. The role of thrombolysis in the management of left-sided prosthetic valve thrombosis: a study of 85 cases diagnosed by transesophageal echocardiography. *J Heart Valve Dis* 2001;10:636–49.
5. Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, 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.
6. Lengyel M, Horstkotte D, Völler H, Mistiaen WP; Working Group Infection, Thrombosis, Embolism and Bleeding of the Society for Heart Valve Disease. Recommendations for the management of prosthetic valve thrombosis. *J Heart Valve Dis* 2005;14:567–75.
7. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al. 2014 AHA/ACC guideline 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 Thorac Cardiovasc Surg* 2014;148:1–32.
8. Ahearn GS, Hadjiliadis D, Govert JA, Tapson VF. Massive pulmonary embolism during pregnancy successfully treated with recombinant tissue plasminogen activator: a case report and review of treatment options. *Arch Intern Med* 2002;162:1221–7.
9. Özkan M, Çakal B, Karakoyun S, Gürsoy OM, Çevik C, Kalçık M, et al. Thrombolytic therapy for the treatment of prosthetic heart valve thrombosis in pregnancy with low-dose, slow infusion of tissue-type plasminogen activator. *Circulation* 2013;128:532–40.
10. Ozkan M, Kaymaz C, Kirma C, Sönmez K, Ozdemir N, Balkanay M, et al. Intravenous thrombolytic treatment of mechanical prosthetic valve thrombosis: a study using serial transesophageal echocardiography. *J Am Coll Cardiol* 2000;35:1881–9.

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