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CASE REPORT
Other

Thrombolytic therapy for mechanical aortic valve thrombosis in pregnancy: case report

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Background Mechanical heart valves require long-term anticoagulation strategies to prevent valve thrombosis. Pregnant women with mechanical heart valves are especially susceptible to valve thrombosis, given their procoagulant state and the complexity of anticoagulation strategies during pregnancy. We describe a case of prosthetic valve thrombosis in a pregnant woman treated successfully with low-dose slow infusion of thrombolytic therapy.

Case Summary A 23-year-old pregnant woman with a mechanical aortic valve on subcutaneous enoxaparin presented to the maternal cardiac clinic for a follow-up visit. Her physical exam was notable for a loud grade three crescendo decrescendo murmur and follow-up transthoracic echocardiography revealed peak and mean gradients of 87 and 58 mmHg, respectively. The Doppler velocity index (DVI) was 0.24 with an acceleration time of 130 ms. Fluoroscopy confirmed a stuck leaflet disk. Thrombolysis was performed using a low-dose ultra-slow infusion of thrombolytic therapy (1 mg/h of tissue-type plasminogen activator) with the restoration of normal valve function after 8 days. A repeat transthoracic echocardiography showed a decrease in the peak and mean gradients to 37 and 21 mmHg, respectively, with an improvement in the DVI to 0.53. Repeat fluoroscopy confirmed the opening of both leaflet disks.

Discussion Treatment options for mechanical aortic valve thrombosis are either slow-infusion, low-dose thrombolytic therapy or emergency surgery. The hypercoagulable state of pregnancy makes adequate anticoagulation, proper monitoring, and medication adherence even more critical to prevent valve thrombosis. Physicians should educate pregnant patients on anticoagulation strategies and participate in shared decision-making.

Keywords Prosthetic valve thrombosis • Pregnancy • Anticoagulation • Thrombolysis • Case report

ESC Curriculum 2.2 Echocardiography • 4.10 Prosthetic valves • 9.8 Pregnancy with cardiac symptoms or disease

Learning points

- Emphasize that thrombolytic therapy is a safe alternative to surgery and should be considered first line for treatment of prosthetic valve thrombosis in all patients, especially pregnant women.
- Highlight the importance of pre-conception counselling and meticulous anticoagulation management for female patients with mechanical heart valves.
- Understand the evaluation for prosthetic valve thrombosis and its implications for female patients during the peripregnancy period.

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Introduction

The annual rate of prosthetic valve thrombosis with mechanical heart valves ranges from 0.1 to 5.7%.[1] Prosthetic valve thrombosis (PVT) risk is higher in mechanical heart valves than with bioprosthetic heart valves, higher in the mitral position than the aortic position, and higher for the right heart than left heart position.[2] Surface, haemodynamic, and haemostatic factors contribute to prosthetic valve thrombosis. The hypercoagulable state of pregnancy presents a risk for women with mechanical valves, and contemporary data suggest that the rate of valve thrombosis during pregnancy is ~5%.[3]

Timeline

Dates	Event summary
Patient age 15	Developed streptococcus viridians endocarditis with severe aortic insufficiency presumed to be from dental cleaning in the setting of a bicuspid aortic valve and underwent a mechanical aortic valve replacement using a 21 mm St Jude valve. A mechanical valve was chosen given its longer durability in a young patient
Follow-ups	Counselled on the importance of avoiding unplanned pregnancies and avoidance of oestrogen-containing contraceptives due to the risk of valve thrombosis
Pregnancy discovery—patient age 23	Two days after discovering her unplanned pregnancy and despite being on warfarin, her anticoagulation regiment was switched from warfarin to subcutaneous enoxaparin
Clinic appointment—patient at 13 weeks and 3 days pregnancy—prior to hospitalization	23-year-old pregnant female patient found to have loud crescendo decrescendo murmur Neonatal ultrasound: Single living intrauterine pregnancy and normal first trimester anatomy Transthoracic echocardiogram (TTE): Left ventricular size and function is normal. Abnormal transvalvular gradients of the 21 mm St Jude valve mechanical aortic valve with peak/mean gradients being 87 and 58 mmHg, respectively. Doppler velocity index (DVI) is 0.24 and acceleration time is 130 ms. Trace expected aortic insufficiency Fluoroscopy: Shows one completely immobile leaflet and one partially mobile leaflet in the aortic position
Hospital Days 1–3: cardiac critical care unit	Low-dose slow-infusion thrombolytic protocol: Tissue plasminogen activator (tPA) at 1 mg/h (total of 25 mg over 25 h) Pause tPA for 6 h Place patient on unfractionated heparin Repeat the cycle up to 8 times if the thrombus is not dissolved Once PTT <50 s, restart 25 h infusion of tPA at 1 mg/h without bolus for another 25 h Two infusion sessions completed
Hospital Day 4: cardiac critical care unit	Repeat TTE: The peak and mean transvalvular gradients of the 21 mm St Jude mechanical aortic valve are 32.5 and 20.7 mmHg, respectively. The DVI is 0.43 Repeat fluoroscopy: Shows one fixed immobile leaflet and one leaflet that is still partially moving, similar to previous fluoroscopy Low-dose slow-infusion thrombolytic protocol restarted
Hospital Days 5–7: cardiac critical care unit	Low-dose slow-infusion thrombolytic protocol: total of five infusion sessions completed
Hospital Day 8: cardiac critical care unit	Repeat TTE: The peak and mean transvalvular gradients of the 21 mm St Jude mechanical aortic valve are 37 and 21 mmHg, respectively. The DVI is 0.53 Repeat fluoroscopy: Fluoroscopy in multiple angiographic projections reveals opening and closing of both mechanical leaflet disks
Hospital Days 9–14 (Discharge): intermediate care unit	Transition to warfarin with international normalized ratio goal 2.5–3.5 by bridging with unfractionated heparin. Discharged on warfarin 5 mg daily Patient agreed to start taking aspirin 81 mg daily Daily foetal Dopplers remain reassuring
Two-month follow-up visit—21 weeks pregnant	Transthoracic echo: The peak and mean transvalvular gradients are 30.7 and 17.8 mmHg, respectively. The DVI is 0.46 Foetal ultrasound (20–22 weeks): Single living intrauterine pregnancy with growth appropriate for gestational age. Normal foetal anatomic survey with no abnormalities identified
Planned delivery admission—37 weeks and 1 day pregnant	Planned admission for transition of warfarin to unfractionated heparin prior to labour Unfractionated heparin was continued until 6 h prior to her neuraxial anaesthesia Proceeded with uncomplicated primary low transverse Caesarean section given transverse foetal lie Patient was restarted on unfractionated heparin 6 h after epidural catheter removal and restarted on warfarin on postoperative Day 1

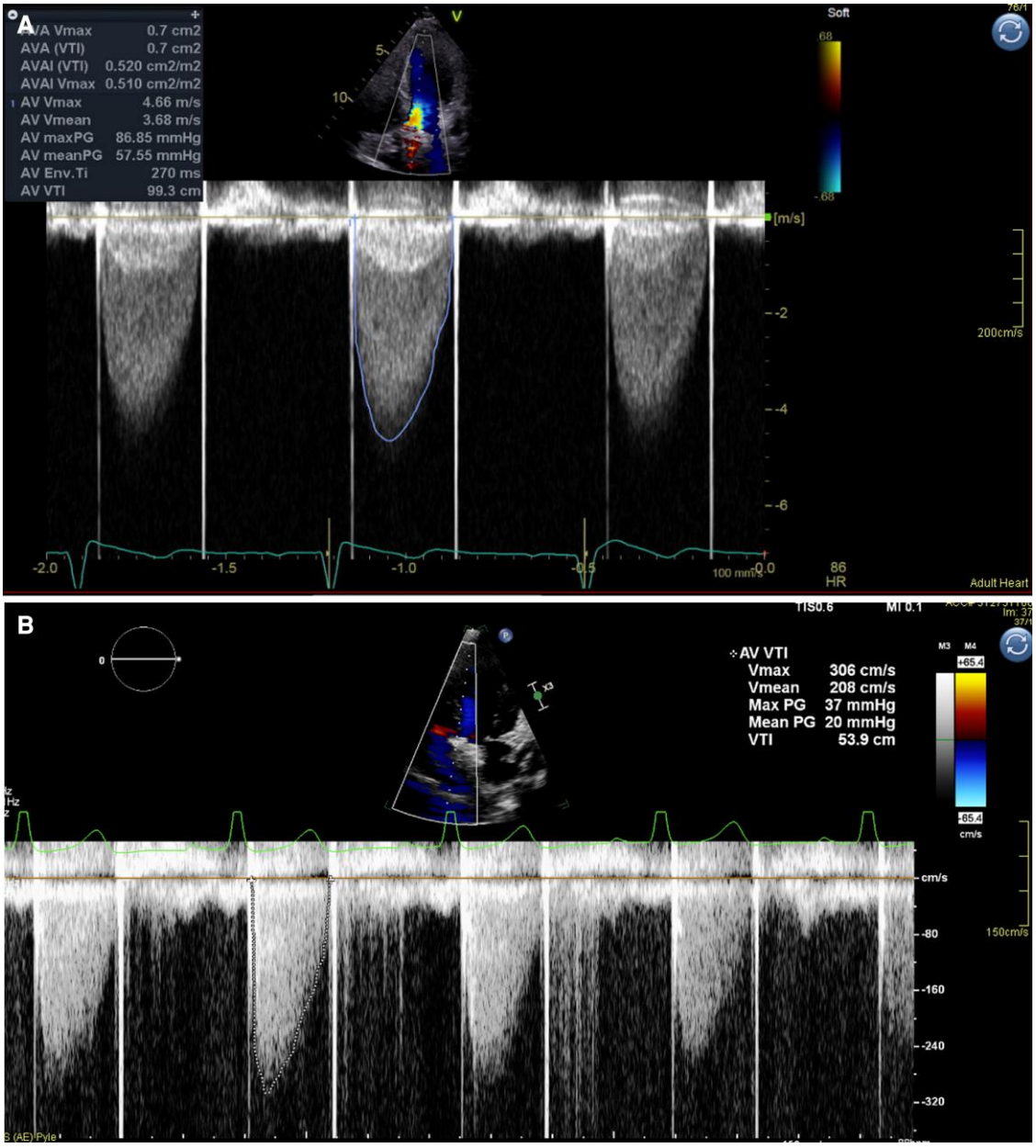

Figure 1 (*A*) Valve gradients on transthoracic echocardiography pre-thrombolytic therapy. Initial echo showing a peak and mean gradient of 87 and 58 mmHg, respectively, across the mechanical aortic valve in apical five-chamber view. (*B*) Valve gradients on transthoracic echocardiography post-thrombolytic therapy. Repeat echo after 5 sessions of low-dose ultra-slow infusion of tissue plasminogen activator showing decrease in the peak and mean gradients to 37 and 20 mmHg, respectively, across the mechanical aortic valve.

Case presentation

A 23-year-old white woman presented to the maternal cardiac programme at 13 weeks gestation. About 6 weeks prior, her anticoagulation clinic had stopped her warfarin 5 mg daily and placed her on subcutaneous enoxaparin without anti-Xa monitoring. At her current visit, she denied any cardiac symptoms. She had been compliant with enoxaparin but had opted not to take aspirin as recommended. Factor Xa level drawn during clinic was subtherapeutic at 0.8 (IU/mL). On her physical exam, she had a loud Grade 3 crescendo decrescendo murmur with preserved S2 and without a thrill or diastolic component, loudest at the right upper sternal border. She was promptly admitted for further work-up and management.

The patient's medical history was notable for bicuspid aortic valve endocarditis due to Streptococcus Viridians at age 15. As a result, she underwent surgical aortic valve replacement with a 21 mm St Jude valve and patent foramen ovale closure. Her international normalized ratio (INR) target for warfarin was 2.5 with a range between 2.0 and 3.0.

The differential diagnosis for an increasing intensity crescendo decrescendo murmur includes: (i) elevated flow from hyperdynamic state and/or expansion of blood volume in pregnancy and (ii) increased left

ventricular outflow tract flow from the new paravalvular leak, turbulence of flow due to pannus ingrowth, or obstructive mechanical disk motion from vegetation or thrombus.

On admission, a transthoracic echocardiogram (TTE) showed peak and mean gradients of 87 and 58 mmHg, respectively (*Figure 1A*). The Doppler velocity index (DVI) was 0.24 with an acceleration time of 130 ms. On the most recent echocardiogram 2 years prior to pregnancy, the peak and mean gradients were 24 and 15 mmHg. Fluoroscopy was used to confirm the diagnosis and demonstrated one immobile mechanical leaflet and one that was fixed (Supplementary material online, *Video S1*). Precautions were taken to position the foetus outside of the field of view, shield the foetus with lead, and limit fluoroscopy time to minimize exposure to scattered radiation.

The patient was admitted to the cardiovascular intensive care unit and started on a low-dose ultra-slow infusion of tissue-type plasminogen activator (tPA) without a bolus based on the PROMETEE trial.[4] One session consisted of tPA infusion at 1 mg/h for a total of 25 mg over 25 h. After each tPA infusion session, the patient was transitioned to an unfractionated heparin (UFH) infusion with a target activated partial thromboplastin time (aPTT) between 1.5 and 2.5 times the control for 6 h. During this UFH infusion period, serial TTE was performed to assess valve haemodynamics and mechanical disk motion for thrombosis resolution. Repeat tPA infusion was restarted, if needed, after holding the UFH infusion to achieve an aPTT <50 s. The patient was monitored every 2 h for signs and symptoms of major complications including ischaemic stroke, haemorrhage, embolic complications, and foetal loss.

After the fifth session and 125 mg of tPA over 8 days, the TTE showed a decrease in the peak and mean gradients to 37 and 21 mmHg, respectively, with an improvement in the DVI ratio to 0.53 (*Figure 1B*). To confirm the resolution of the thrombosis on the mechanical prosthesis, the patient underwent repeat fluoroscopy which demonstrated appropriate opening and closure of both mechanical leaflet disks (Supplementary material online, *Video S2*). The patient transitioned to daily warfarin (goal INR 2–3) with a heparin bridge and agreed to start aspirin 81 mg daily.

Discussion

The recent 2020 ACC/AHA Guidelines for Valvular Heart Disease gave a Class I recommendation for the evaluation of suspected mechanical PVT with TTE, transoesophageal echocardiogram (TEE), fluoroscopy, and/or multidetector computed tomography (CT) to assess valve function, leaflet motion, and presence and extent of the thrombus.[5] We opted to use TTE and fluoroscopy given our desire to avoid the haemodynamic consequences of sedation required for TEE and minimize the radiation exposure compared with CT.

Class I recommendation for treatment options of thrombosed left-sided mechanical PVT is either slow-infusion, low-dose fibrinolytic therapy or emergency surgery.[5,6] Cardiac surgery during pregnancy is considered extremely high risk, with high rates of maternal and foetal adverse outcomes, including foetal demise.[7] Therefore, thrombolysis therapy is an attractive alternative, especially in a haemodynamically stable patient. Low-dose ultra-slow infusion of tPA without a bolus has been found to be an effective thrombolytic regimen in the PROMETEE trial, which included seven patients all achieving successful thrombolysis.[8] Furthermore, a similar low-dose (25 mg), slow infusion (6 h) was proven to be safe and successful in a small series of pregnant women with prosthetic mitral valve thrombosis.[9] In this study, there were no maternal deaths and foetal mortality rate was 20%. The average dose of tPA per PVT episode was 48.7 ± 29.5 mg (range 20–100 mg) and all treatment sessions resulted in complete thrombolytic success. We extrapolated to our patient with prosthetic aortic valve thrombosis with similar success. As a result, thrombolytic therapy became our standard treatment protocol for all patients with PVT, including pregnant patients.

In pregnancy, the maternal and foetal risks of warfarin therapy must be balanced against the higher rate of valve thrombosis with low molecular weight heparin (LMWH), and the optimal anticoagulation strategy has yet to be defined.[10] When LMWH is used, strict monitoring of anti-Xa levels is recommended to optimize anticoagulation and prevent complications.[10] A recent meta-analysis showed that warfarin treatment throughout pregnancy was associated with the lowest risk of adverse maternal outcomes, whereas LMWH use throughout pregnancy was associated with the lowest risk of adverse foetal outcomes.[11] Warfarin teratogenicity is highest during the first trimester and further increased risk are seen in doses ≥5 mg/day.[11] This risk must be balanced against the higher rate of thrombotic complications with LMWH. Overall, no anticoagulation strategy has been proven to be superior for both the mother and the foetus; therefore, a shared decision-making process is optimal.

Conclusions

We present a case of prosthetic aortic valve thrombosis in a pregnant woman treated successfully and safely with thrombolytic therapy. Subtherapeutic anticoagulation and the hypercoagulable state of pregnancy were the likely culprits. In this case, we emphasize the importance of shared decision-making between physicians and patients regarding the prevention and treatment of valve thrombosis in pregnancy.

Lead author biography

Khoa Nguyen lives in Portland, Oregon, and he is completing his cardiovascular medicine fellowship at Oregon Health and Science University. His academic interests are in cardiac critical care, mechanical circulatory support, and cardiogenic shock. Outside of work, he enjoys travelling, hiking, surfing, and exploring the outdoors.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports*.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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