

Prosthetic valve thrombosis: literature review and two case reports

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SOUHRN

Trombóza umělé srdeční chlopně představuje jednu z nejzávažnějších komplikací implantace této chlopně. Zabránit vzniku této komplikace pomáhá řádné monitorování a péče o tyto pacienty. V případě trombózy je pro zhodnocení funkce umělé chlopně měřením úhlů otvírání a zavírání chlopně výhodné fluoroskopické vyšetření. Popisujeme dva případy trombózy mechanické aortální chlopně s různými mechanismy vzniku trombu. První případ se týkal 48leté ženy hospitalizované pro dušnost při minimální námaze a významně snížené toleranci zátěže. Vzhledem k přítomnosti revmatické choroby srdeční byly pacientce implantovány umělé aortální a mitrální chlopeň s podáváním warfarinu v terapeutických dávkách. Echokardiografické vyšetření prokázalo obstrukci mechanické aortální chlopně a těžkou regurgitaci trojicípe chlopně. U pacientky byla indikována operace aortálního kořene a implantace umělé trojicípe chlopně. Druhému pacientovi byla rovněž implantována mechanická aortální chlopeň pro těžkou aortální stenózu v důsledku revmatické choroby srdeční; ten se k lékaři dostavil s organizující pneumonií a progredujícím respiračním selháním jako komplikacemi onemocnění covid-19 a byl hospitalizován s dyspnoe, kašlem a celkovou slabostí. Přes optimální léčbu a terapeutickou hodnotu INR byla u pacienta stanovena diagnóza trombózy umělé aortální chlopně.

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ABSTRACT

Prosthetic heart valve thrombosis is one of the most dangerous prosthetic valve complications. Proper monitoring and management of these patients help to prevent this complication. Fluoroscopy is advantageous in cases of thrombosis to assess the function of the prosthetic valve by measuring opening and closing angles. We describe two cases of aortic mechanical valve thrombosis with different mechanisms of thrombus formation. The first case was a 48-year-old woman admitted to the hospital because of shortness of breath during minimal exertion and significantly reduced exercise tolerance. Due to rheumatic heart disease the patient underwent aortic and mitral mechanical prosthesis and has been using warfarin in therapeutic norms. During echocardiography aortic prosthesis obstruction and severe tricuspid valve regurgitation were observed. The patient was scheduled for aortic root and TV prosthesis surgery. The second patient also had aortic mechanical valve due to severe aortic stenosis caused by rheumatism and presented with organizing pneumonia and progressing respiratory failure as complications of the COVID-19 infection and was admitted with dyspnea, cough, and weakness. Aortic prosthetic valve thrombosis was diagnosed despite optimal treatment and therapeutic INR.

Keywords:

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Introduction

Prosthetic heart valve thrombosis (PVT) is an uncommon but usually life-threatening condition. PVT is a cause of valve prosthesis dysfunction and a complication of valve replacement surgery, occurring in any part of the heart valve prosthesis.¹ The exact rate of valve thrombosis is not known, but some authors estimate that incidence ranges from 0.5% to 6% per patient per year in the aortic and mitral position and up to 20% in the tricuspid position.² The main factors influencing the development of PVT are inappropriate treatment by anticoagulants, thrombogenicity of the valve and hemodynamics of the transprosthetic blood flow.³ Although thrombus formation is less frequent with new surgical techniques, the hemodynamic and physical properties of mechanical valves remain thrombogenic.⁴ The purpose of this article is to review the epidemiology, clinical features, diagnosis and updated management according to current guidelines of PVT.

Indications for aortic valve replacement, prosthetic valve thrombosis etiology, and risk factors

In Europe alone more than 13 million people are diagnosed with valvular heart disease (VHD) each year and 100 million worldwide.⁵ Aortic valve (AV) disease is the most common among valvular conditions (44.3% of all VHD)⁶ and surgical aortic valve replacement (SAVR) or transcatheter aortic valve implantation (TAVI) are the main treatment for this condition.⁷ Worldwide the number of AV replacement in 2003 was 290,000 and by 2050 is predicted to be 850,000.⁸ According to the latest ESC/EACTS guidelines, indications for AV replacement are severe symptomatic aortic regurgitation or asymptomatic aortic regurgitation in patients with left ventricular end-systolic diameter (LVESD) >50 mm or LVESD >25 mm/m² body surface area (BSA) in patients with small body size or resting left ventricular ejection fraction (LVEF) ≤50%. In case of aortic root or tubular ascending aortic aneurysm surgery is indicated in patients with Marfan syndrome who have aortic root disease with a maximal ascending aortic diameter ≥ 50mm or aortic dilation, if performed in experienced centers and durable results are expected. In addition to, AV replacement is recommended in symptomatic patients with severe, high-gradient aortic stenosis or in symptomatic severe low-flow, low-gradient aortic stenosis with LVEF <50% and evidence of flow (contractile) reserve.⁹ Each surgery has its own risks and one of the most common complications in valve replacement is PVT. Prosthetic valve dysfunction depends on the valve that has been implanted and on the procedure (SAVR or TAVI). Usually the suitable valve is selected based on the following risk factors: anticoagulant-related bleeding and valve deterioration. Antithrombotic therapy slows down but does not eliminate the risk of PVT, which also depends on the patient's lifestyle, metabolic profile or inflammatory status, especially in the case of TAVI.¹⁰ Predisposing factors for thrombosis include a high body mass index, male sex, bicuspid AV and a large aortic root requiring a large sized prosthesis.¹¹ There are several de-

scribed mechanisms causing PVT, one of them is surface-induced thrombosis, which is well described in mechanical valves and other medical devices. The exposure of valve prostheses to blood leads to a thrombogenic process that results in formation of thrombin, platelet activation, and the formation of platelet-fibrin networks on the surface of the prosthesis. Transcatheter aortic valves are also associated with pathological processes – thromboembolic events commonly found in the first 3 months after the procedure. One hypothesis is that, because the original valve is not removed during TAVI but left in place, the leaflets of native valves still contain high levels of tissue factor, which enhances platelet activation.¹²

Mechanical aortic valve thrombosis

Mechanical AV replacement is recommended for patients who are younger than 60 years and have no contraindications to long-term anticoagulation.¹³ Mechanical AV prostheses are characterized by their robust structure and a long service life. Monoleaflet valves are composed of a single disc with an opening angle relative to the valve annulus ranging from 60° to 80°, resulting in 2 different sized orifices. Bileaflet valves consist of 2 semilunar discs, the opening angle of the discs varies from 75° to 90° and the open valve consists of 3 orifices.¹⁴ When a mechanical valve is implanted, patients are at a high risk of stroke and valve thrombosis and require long-term anticoagulant treatment. The risk of PVT is higher for mechanical mitral valves (0.9% of cases per year) than for mechanical AV (0.5% of cases per year). Long-term anticoagulation reduces the annual risk of PVT from 1.8% to 0.4%.¹⁵ PVT is a serious complication occurring in 0.5–8% of mechanical mitral and AV prosthesis.¹⁶ Thrombus formation is more frequently observed in the mechanical valve than in the bioprosthetic, presumably due to inadequate anticoagulant use, and is associated with atrial fibrillation (AFib) and poor cardiac function.¹⁷ However, Maribas et al. reported that valve thrombosis is similarly frequent in patients with bioprosthetic valves and in those with mechanical valves who are consuming adequate anticoagulant therapy.¹⁸

Biological aortic valve thrombosis

The incidence of biological prostheses in middle-aged patients has increased in the last decade due to the improved durability of newer generation prosthesis, the reduced risk of reoperation for a degenerated aortic biological prosthesis, and emerging data on the unsuccessful outcome of TAVI in high-risk patients.¹⁹ Although biological prostheses do not require anticoagulant therapy, they are subject to structural valve degeneration, resulting in limited durability, which lasts between 10–15 years and exposes the patient to the risk of reintervention.²⁰ Surgical biological AV prostheses are made of biological tissue and can be xenogenic or allogenic as well as stented or stentless.²¹ Meta-analysis of aortic bioprosthesis estimates the incidence of PTV at 0.03 per 100 patients per year.²² Due to similar transvalvular flow gradients mechanical

and transcatheter valves are homogeneous in terms of thrombogenic potential while bioprosthesis remains the least thrombogenic prosthetic valve.²³

Transcatheter aortic valve thrombosis

Since first TAVI was performed in 2002, the rate of this procedure has raised enormously, with more than 50 000 having been performed worldwide, the vast majority of them in Europe.²⁴ In cases of severe aortic stenosis and appropriate heart anatomy, TAVI is the best treatment option.²⁵ Although current literature declares that SAVR is more likely to cause bleeding complications, acute kidney insufficiency and new arrhythmias,²⁶ TAVI is associated with higher rates of permanent pacemaker implantation, paravalvular regurgitation and vascular complications.²⁷

During the TAVI procedure, the tissue valve is implanted by balloon dilation or self-expansion. They are inserted percutaneously, using a transfemoral access in 90%²⁸ of cases, and the aortoventricular angle during the procedure must be $> 60^\circ$.²⁹ PVT after TAVI is rare, with an estimated incidence of approximately 0.61–2.8% based on echocardiography or cardiac CT angiography.³⁰ Risk factors for PVT include balloon-expandable valves, large valve prosthesis size, inappropriate valve expansion, patient-prosthesis mismatch and valve-in-valve TAVI.³¹ Researchers are currently attempting to prove that stasis in the neosinus between the native AV leaflets and the TAVI leaflets may be a major contributor to the formation of PVT, and quantification of stasis using patient-specific in vitro modeling has shown that it correlates with the extent of thrombosis.³² Bioprosthetic valves, both surgical and transcatheter, have better hemodynamic properties than mechanical valves, therefore the antithrombotic therapy is needed during the endothelialization process in the first 3–6 months after surgery. Although oral anticoagulants have been shown to reduce the incidence of leaflet thrombosis, the routine use of an oral anticoagulant after TAVI leads to excessive bleeding, and studies are currently underway to investigate whether the use of anticoagulants therapy will be demanded after TAVI in the future.³³

Indications for mitral valve replacement and risk factors

Based on 2020 ACC/AHA guidelines for the management of patients with VHD, mitral valve (MV) surgery is indicated for symptomatic severe primary mitral regurgitation (MR) when LVEF is above 30% and asymptomatic severe primary MR in patients with severe, chronic disease and left ventricular dysfunction with LVEF of 30% to 60%, or LVESD of at least 40 mm. For secondary MR valve replacement is indicated when patients do not have severe ventricular dysfunction and are symptomatic despite optimal medical therapy or while undergoing concomitant coronary artery bypass grafting.²⁰ Myllykangas' study in Finland that included 3684 patients shows that the annual prevalence rates of mitral surgery during the study period was 3.9/100 000. 62.4% of these procedures were

MV repairs and 37.6% were MV replacements. The mean age of MV surgery patients is 66.0 years and 33.4% of the patients were women.³⁴ The ideal time for MV surgery is when the patient's left ventricle approaches but has not yet reached the parameters that indicate systolic dysfunction (LVEF $\leq 60\%$ or LVESD ≥ 40 mm).³⁵ MV replacement is recommended for patients with moderate to severe mitral stenosis (mitral valve area ≤ 1.5 cm²) who have NYHA class III or IV symptoms, are not at high risk for surgery, and have an MV not amenable to either percutaneous mitral balloon commissurotomy or open commissurotomy/repair.²⁰ The opening and closing angles determined by 64-slice multidetector CT were 10.9 ± 0.6 and 131.1 ± 3.2 for the MV.³⁶ Main factors for development of mitral PVT are hemodynamic (local blood flow turbulences, relatively slow blood flow in case of AFib, atrial dilation or low LV output), hemostatic (tissue injury), surface (leaflet injury, prosthesis malposition, incomplete prosthesis endothelialization).³⁷

Mechanical mitral valve

Mitral PVT is two- to threetimes more common than aortic prosthetic thrombosis. The annual rate of PVT ranges from 0.1% to 5.7%, with higher rates in the early perioperative period and in association with subtherapeutic anticoagulation.³⁸ For patients undergoing prosthetic MV replacement surgery, the decision regarding the choice of prosthesis mechanical or bioprosthetic is based on the need for anticoagulation with mechanical valves, the belief of improved durability with current bioprostheses, and patient risks for reoperation.³⁹ Mortality rates of patients who receive a mechanical valve are equal to those of patients who receive a bioprosthetic valve. Mechanical prosthetic valves (MPV) are associated with lower risk of reoperation but increased risk of bleeding and stroke.⁴⁰ Lifelong anticoagulation using oral vitamin K antagonists (VKA) is required for all currently available mechanical MV prostheses. Newer anticoagulants have not shown to be safe or effective in patients with MPV. Anticoagulation with a VKA might be reached with an acceptable risk in most patients younger than 50 years, particularly if there is appropriate monitoring of INR levels. Mechanical valve in patients < 50 years of age is chosen more frequently due to more favorable balance between valve durability and risk of bleeding and thromboembolic events, unless anticoagulation is not desired, cannot be monitored, or is contraindicated.²⁰ The intensity of anticoagulation depends on the characteristics of prosthetic valve, e.g., bileaflet or tilting disc, and patient factors such as a history of thromboembolism, AFib, left atrial enlargement, left ventricular dysfunction with the target INR of 3.0 for modern bileaflet mechanical MV prostheses.⁴¹

Biological mitral valve

Biological heart valves should be chosen in patients with shorter anticipated survival or comorbidities that may lead to reoperations, and those who are at increased risk for bleeding. Bioprostheses are recommended for pati-

ents >70 years of age or those in whom life expectancy is shorter than the expected bioprosthetic valve durability. Thromboembolic complications are less frequent in pregnant women with biological bioprostheses than mechanical.⁴² Butnaru's case reported an incidence of 6% mitral bioprosthetic valve thrombosis out of 149 MV replacement surgeries over 10-year period, two thirds of whom showed resolution of symptoms.⁴³ A significant amount of implanted mitral bioprosthesis degenerate over time and need further treatment due to clinically significant prosthetic stenosis or regurgitation.⁴⁴ Between 60–70% of patients who undergo MV replacement surgery receive a bioprosthetic valve.³⁹ It was reported that patients between 40 to 69 years of age who receive a bioprosthetic MV have significantly higher 15-year mortality rates compared with those who received a mechanical MV.⁴⁵

Transcatheter mitral valve replacement

Together with developing transcatheter MV repair, investigators are improving methods for transcatheter MV replacement (TMVR).⁴⁶ Compared with transcatheter AV replacement, TMVR has been more challenging because of the size, location and anatomy of the MV, and the risk of left ventricular outflow tract obstruction.⁴⁷ TMVR for patients who have severe primary MR is a safe alternative when there are contraindications for surgery or operative risk is high.⁴⁸ As patients are carefully selected to avoid the failure of intervention, rejection rates for TMVR have been about 60% to 70%. Recent developments demonstrate the promise of increasing the population that could be treated, for example, using a transeptal or transapical approach. Procedure success rate was high but has some limitations due to intracardiac maneuverability and sheath sizes.⁴⁹ Advancing the development of TMVR is critical, as MR is the most common valvular lesion in the world, and substantial advances in treatment of heart failure (HF) has led to an aging population with MR who may be at either high or prohibitive risk for open surgery.⁵⁰

Mechanical tricuspid valve

According to 2020 ACC/AHA guidelines surgical treatment for tricuspid valve (TV) is an option for patients with tricuspid regurgitation (TR) at the time of surgery for left-sided valve lesions to treat symptomatic or asymptomatic severe regurgitation or to prevent further development of severe regurgitation. Surgical intervention should also be considered for selected patients with isolated TR in the absence of pulmonary hypertension (PH) or dilated cardiomyopathy. MPV are rarely implanted in the right heart, mainly because of their important thrombogenicity. TV replacement is needed when repair is unfeasible because of the marked leaflet tethering, complex primary TR with tricuspid annulus diameter >40 mm, or severe tricuspid stenosis with valve area ≤ 1.0 cm² with the manifesting symptoms of right ventricular malfunction, such as peripheral edema and ascites.⁵¹ The mean age of the surgery is 52.3 \pm 8.8 years and 66.7% are females.⁵²

Thrombosis is the most important and common complication of the prosthetic TV and is 20 times more likely in the tricuspid position (the reason is the lower pressure of the right system, the right ventricular morphology, and the low prostacyclin concentration of venous blood) during the first post-operative year compared with the AV and MV.⁵³ Mechanical valves have desirable hemodynamic properties, low gradients, low disturbances in flow, and long durability. The normal range of the opening angle is 60–80° for tilting disc valves and 73–90° for bileaflet valves.⁵⁴ MPV are preferred in younger age groups as well as patients with another mechanical valve.⁵⁵

Biological tricuspid valve

The advantage of the bioprosthetic valves is that they do not require long life anticoagulation in contrast to the mechanical valves and cause a higher risk for thromboembolism and hemorrhage.⁵⁶ Because of the lower risk of thromboembolism, many surgeons favor bioprosthetic valves but the choice of the type of prosthesis should be individual, considering the patient's age, condition, and concomitant cardiac or non-cardiac diseases.⁵⁷ Low pressure and stress in the right heart provides higher durability for the bioprosthesis compared to the left sided prosthetic valves and requires less reoperations compared with mechanic valve as well.⁵⁸ The average time for failure of tricuspid bioprosthesis is 7 years.⁵⁹ There are no differences between the mechanical and tissue valves in survival rate. Patients who receive bioprostheses must be carefully evaluated with periodic echocardiograms, especially after 7 to 10 years, for detecting clinical and subclinical signs of structural valve degeneration.⁶⁰

Clinical presentation and diagnosis

The clinical presence of PVT varies depending on whether there is an obstruction. Severe obstructive PVT (OPVT) is usually associated with HF, while a non-obstructive PVT (NOPVT) is often an accidental finding or presents as an embolic episode. When obstruction is partial it results in dyspnea, systemic embolism or fever. In the presence of fever diagnostic blood cultures should be performed to prevent or to diagnose infectious endocarditis early. Concentrations of D-dimers may be affected and increased. A detail physical examination should be performed, examining for the suppression or disappearance of prosthetic sounds and the occurrence of new regurgitating or obstructive murmurs, especially if PVT is suspected for the first time. The initial diagnostic tests are transthoracic echocardiogram (TTE) and cinefluoroscopy.⁶¹ Echocardiographic features that might help to suspect PVT are an acute increase in valve gradient of more than 50% over 5 years, thickening of the valve leaflet (>2 mm) downstream of the valve, decreased or limited leaflet mobility, and regress of echocardiographic abnormalities within 1–3 months of anticoagulant therapy. Cinefluoroscopy helps to assess the movement of the leaflets in mechanical valves. Nevertheless, for cinefluoroscopy a suitable patient position is required and this examination is time

consuming. Conversely, the valve can be reoriented in any CT plane. CT offers optimal visualization of valve profiles and it does not depend on valve position, neither patient physical characteristics. CT complements TTE and cinefluoroscopy by performing a functional and morphological evaluation of the mechanical valve as it combines the measured values of the opening and closing angles with other information like the size of the valve or the presence of a thrombus or pannus.⁶²

Thrombosis of prosthetic heart valves: treatment

Main therapeutic modalities considered when PVT is diagnosed: surgery, fibrinolysis, heparin treatment or optimization of anticoagulant and antiplatelet therapy. Treatment depends on the presence of obstruction and prosthesis location but prosthesis type does not have an importance in choosing a treatment.

Right-sided obstructive and non-obstructive PVT

Right-sided thrombosis is much more frequent than left-side. Although there are no formal prospective studies evaluating different treatment modalities, intensified anticoagulation should be the first choice of treatment in patients with right-sided NOPVT. Patients with obstructive TV thrombosis usually present with signs of right HF, such as peripheral edema and ascites, and the prosthetic valve click may be inaudible during the auscultation. TTE and transesophageal echocardiography (TEE) can reveal the increased echogenicity on the prosthesis, decreased movement of the disc, and an elevated prosthetic valve gradient. The treatment of choice in right-sided OPVT is thrombolytic therapy, fibrinolytic agents are associated with a high success rate and a low complication rate. Surgery should be reserved for cases of thrombolytic failure, and contraindication to thrombolysis. Replacement of the mechanical TV with a bioprosthesis can be considered in patients with failed thrombolysis, recurrent thrombosis, evidence of pannus or contraindications to thrombolytic therapy.⁶³

Non-obstructive left-sided PVT

Management can be divided according to the size of thrombus. Fibrinolysis has been performed with success for small non-obstructive thrombi, but also with a significant risk of systemic embolism. The prognosis is favorable with medical therapy by optimization of anticoagulant treatment (short-term intravenous unfractionated heparin followed by warfarin adjustment and aspirin addition) for small asymptomatic thrombi (length <10 mm). If thrombus size is increased or is complicated by embolism, thrombolytic therapy or surgery should be considered.⁶⁴ In all cases of PVT, anticoagulant treatment has to be optimally adjusted. Surgery is recommended for large (≥ 10 mm) NOPVT complicated by embolism or which persists

despite optimal anticoagulation.⁶⁵ Fibrinolysis should also be considered if surgery is at high risk.

Left-sided obstructive PVT

The treatment includes surgery (thrombectomy or valve replacement), thrombolytic therapy, and heparin. After a diagnosis has been made, heparin treatment should be started immediately. Surgery is recommended for patients in NYHA functional classes III–IV, unless it is at high risk. Surgery is also indicated for critically ill patients and restrict thrombolysis to patients with high surgical risk (thrombus area [2D TEE] >0.8 cm² and thrombus diameter 1.0 cm is associated with increased embolic risk and the rate of complications increases 2.4 times per 1.0 cm² increase in size, which makes surgery a better option.⁶⁶ Outcomes have been better with thrombolytic therapy, therefore it is suggested that thrombolytic therapy would be the treatment of choice in all cases except for patients with contraindications to these agents.

In hemodynamically unstable patients fibrinolysis should consist of recombinant tissue plasminogen activator (rtPA) 10 mg bolus + 90 mg in 90 min, or streptokinase 1 500 000 U in 60 min without heparin. While in hemodynamically stable patients: urokinase 4500 U/kg/h over a 12 h period, or 2000 U/kg/h + heparin over 24 h, streptokinase 500 000 IU in 20 min followed by 1 500 000 IU for 10 h without heparin or rtPA 10 mg bolus, 50 mg during the first hour, 20 mg during the second hour and 20 mg during the third hour.⁶¹

Prevention

Long-term anticoagulation is required to prevent thromboembolism after mechanical heart valve replacement, its value in patients receiving bioprostheses is uncertain.⁶⁷ Moderate-intensity anticoagulant therapy (INR of 1.5 to 2.0) was reported to be safe and feasible for preventing thromboembolic complications in high-risk surgical patients who are receiving long-term oral anticoagulant therapy. The study included 18% patients with a mechanical valve.⁶⁸ Patients with mechanical or bioprosthetic valves should receive antibiotic prophylaxis before some dental and surgical procedures to prevent endocarditis.⁶⁹ Nowadays, new generation of smart heart devices is capable of auto-detecting valve status and able to measure specific markers in plasma that could predict prosthetic HF. For bioprostheses, several markers have been identified as predictors of structural valve degeneration: the ratio apoB/apoA-I (apoB/apoA-I); lipoprotein-associated phospholipase A2 (Lp-PLA); the ratio of oxidized low-density lipoprotein and high-density lipoprotein (OxLDL/HDL); proprotein convertase subtilisin/kexin 9 (PCSK9) levels.⁷⁰ In addition, to solve geometry issues like patient-prosthesis mismatch latest technologies use stereolithographic 3D printing models based on X-ray CT scans of native valves.⁷¹ Using this technology it becomes possible to produce a tailor-made prosthetic valve, made of tissues or polymers that would mimic the native valve with a minimal error. In patients with suspected bioprosthetic

valve thrombosis who are hemodynamically stable, a trial of anticoagulation should be considered. It is also crucial to recognize the difference between structural valve degeneration and bioprosthetic valve thrombosis as a cause of prosthetic valve dysfunction as the treatment differ. Thrombolysis or secondary surgical intervention could be suggested in patients who do not respond to anticoagulation therapy or are hemodynamically unstable.⁷²

Case 1

A 48-year-old woman was referred to Lithuanian University of Health Sciences (LUHS) Kaunas Clinics, Department of Cardiology suffering shortness of breath during minimal exertion, significantly reduced exercise tolerance, swelling of the legs and recurrence of rhythm disorders. The patient has been suffering from the above complaints for the past year, shortness of breath and HF symptoms progressing during the last months. In 1999, the patient was diagnosed with a mixed rheumatic defect and underwent mechanical AV and MV prosthesis, since then she has been using warfarin in therapeutic norms. The patient had recurrent atrial flutter (AF) episodes since 2016 and had undergone radiofrequency catheter ablation 4 times but no positive effect was observed. VVI mode cardiac pacing was implanted in 2019, followed by recurrence of atypical AF episodes which was reversed with cordarone. During TTE severe TR was observed. For further investigation in the function of the mechanical prostheses, treatment of TR and clarification of the diagnosis, a decision to hospitalize the patient was obtained. Patient denied other chronic and infectious diseases. For outpatient treatment she has been using warfarin, cordarone, β -blockers, trimetazidine and diuretics.

Upon arrival in the cardiology department, clinical findings included: heart rate (HR) 83 b.p.m., blood pressure (BP) 120/70 mmHg, pulse oximetry 96%, normal mechanical valve clicks, and a II° systolic murmur at the apex of the heart, AV and Erb's point. Laboratory tests showed slightly elevated NT-proBNP (344.9 ng/l) and anticoagulation studies revealed an INR of 3.1, an aPTT of 45.1 s and a PT of 80.6 s. ECG showed normal cardiac pacing activity. 2D TTE showed impaired LVEF – 50%, elevated transprosthetic aortic Doppler peak velocity – 3.2 m/s, elevated peak transprosthetic gradient – 40.96 mmHg, I° intraprosthetic regurgitation. Signs of rheumatic damage to the TV were also observed, such as copulating leaflets, accelerated tricuspid peak velocity – 1.7 m/s, III–IV° TR. Chest x-ray showed mild pulmonary vascular congestion. Invasive hemodynamic tests were performed to differentiate possible causes of dyspnea and severe post-capillary PH with reduced cardiac output were found. TTE was repeated to monitor the dynamics – AV prosthesis peak velocity 3.8–4 m/s was recorded from the adaptive positions and assessed as prosthesis dysfunction (Fig. 1).

Patient's status worsened and the "heart team" consensus recommended reoperation of the AV and TV prosthesis surgery. In the department of cardiology lansoprazole and heparin, with dose titration according to aPPT, were added to the previous treatment. The patient was transferred to the cardiac surgery unit for further surgi-

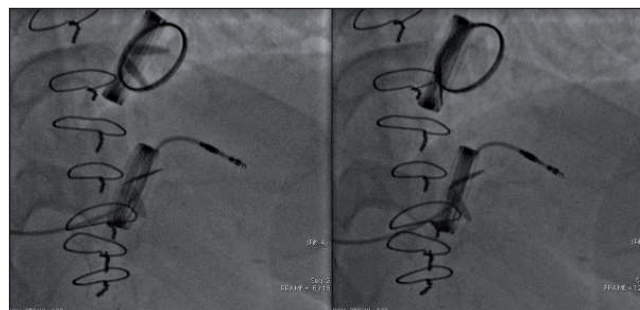


Fig. 1 – Fluoroscopic view of the mechanical prosthetic aortic valve thrombosis.

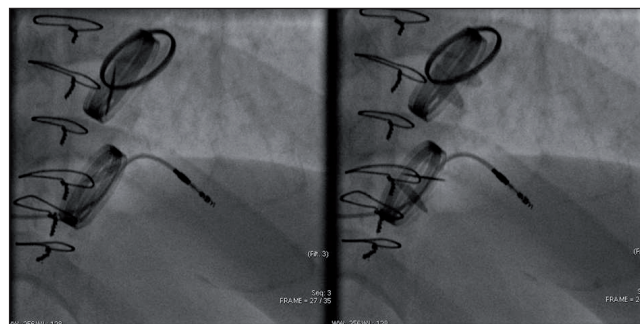


Fig. 2 – Fluoroscopic view of the prosthetic aortic valve replacement due to valve thrombosis and tricuspid valve prosthesis.

cal treatment – aortic root and TV prosthesis surgery in case of dysfunction of the mechanical AV prosthesis and severe TV regurgitation (Fig. 2).

PVT can still occur despite adequate anticoagulation and optimal INR values, so it is important to monitor patients at risk and identify complications as soon as possible.

Case 2

A 60-year-old man was referred to the LUHS Kaunas Clinics, Department of Cardiology with progressive dyspnea on minimal exertion and at rest, cough that produces hemoptysis and weakness. The previous medical history of the patient was a surgical closure of patent ductus arteriosus at the age of 8 and rheumatism in childhood. There is family history of rheumatism. A mechanical AV for severe aortic stenosis was implanted 15 years ago and the patient has been treated with acenocoumarol since then. Complaints lasted for a month, especially it has been intensifying during the last 2 weeks. In the regional hospital patient was treated for organizing pneumonia and progressing respiratory failure that were recognized as complications of the Covid-19 infection. He was treated with dexamethasone and cefuroxime but it was unsuccessful. There is past history of left middle cerebral artery infarct that was diagnosed in 2016, patient lost eyesight in one eye. Patient was admitted taking beta-blockers, angiotensin receptor-neprilysin inhibitors (ARNi), and loop diuretics due to HF, hypertension and permanent AFib. Hospitalization was required for the further investigation of progressing respiratory and HF.

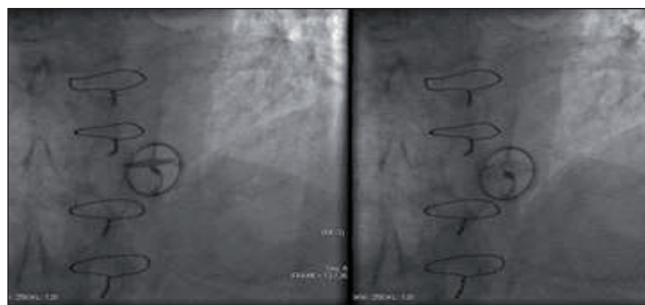


Fig. 3 – Fluoroscopic view of the mechanical prosthetic aortic valve leaflet with a 15° opening angle secondary to thrombus formation.

Upon arrival in the cardiology department, clinical findings included: HR 94 b.p.m., BP 116/54 mmHg, pulse oximetry 92% with 6 L/min oxygen mask, irregular heartbeats, both diastolic and systolic III° murmurs at the projection of the aortic, tricuspid valves, apex and Erb's point.

Laboratory results showed electrolytes in normal range, normal liver function and impaired renal function (creatinine 150.8 $\mu\text{mol/L}$, urea 20.7 mmol/L). Troponin I was 82 ng/L ($n < 14$ ng/L), NT-proBNP 18000 ng/L ($n < 300$ ng/L), D-dimers 2400 $\mu\text{g/L}$ ($n < 350$ $\mu\text{g/L}$). Abnormal coagulation test was observed with INR 2.7, PT 67.1 s, aPTT 41 s, ECG – AFib.

2D TTE showed reduced mobility of the one-leaflet mechanical aortic prosthesis with an image suggestive of thrombus ($V_{\text{max}} - 4.6$ m/s, $G_{\text{max}} - 73.96$ m/s, the mean transprosthetic gradient – 29 mmHg, effective orifice area – 0.97 cm^2) and reduced LVEF (44%) in the setting of AFib. Dilated left ventricle, moderate (II–III°) MV insufficiency, signs of severe PH – right ventricle systolic pressure – 89 mmHg.

Chest X-ray showed large bilateral non-homogenous infiltrations. The AV opening angle measured by the thoracic CT-scan was 15° (Fig. 3). Coronary artery angiography was performed to differentiate the cause of dyspnea but coronary artery stenoses were excluded and it confirmed the dysfunction of AV.

Despite the adequate treatment of HF, anticoagulation therapy, patient's condition was worsening due to venous congestion and hypotension, therefore urgent surgical treatment was recommended. Intravenous dopamine was given to the patient but cardiogenic shock was progressing and patient was transferred to the intensive care unit. Mechanical aortic prosthesis was surgically removed and changed with bioprosthetic valve. During the postoperative period patient's condition continued to worsen due to progressing respiratory failure, cardiogenic shock, acute renal failure, liver failure, urinary tract infection and metabolic acidosis. Patient vital functions were supported with veno-arterial extracorporeal membrane oxygenation, renal replacement therapy, mechanical ventilation, antibiotics were added to the treatment. On the 8th postoperative day patient died. Histopathological examination of AV showed thrombotic mass with the features of degeneration on the valve. Even though further investigations are needed because of the unclear mechanisms but it is suspected that the pro-inflammatory and pro-coagulant states of SARS-CoV-2 virus are related

to the risk of PVT despite therapeutic INR and optimal treatment.

Discussion

Prosthetic valve obstruction by pannus, thrombus, or both is one of the most life-threatening complications of mechanical prostheses.⁷³ Clinical presentation of the patient may vary from mild dyspnea to severe respiratory failure and rapid worsening of HF. Sudden increases in transvalvular gradients from baseline during TTE are indicative of valvular obstruction.⁷⁴ It is crucial to be aware of a possible acute decline in a clinical status and alert in case of an emergency intervention. Fibrinolytic therapy and surgical intervention remain main options in PVT management, even though it is still controversial and the choice is based on the clinical manifestations. The choice of the PVT treatment is reliant on the features of mechanical valve thrombosis.⁹ High-risk left-sided PVT features (NYHA functional class III to IV, mobility of the thrombus and the size > 0.8 cm^2) are in favor of surgical approach.

Thrombosis may present with acute manifestations while the pannus usually presents with chronic evolution, over several weeks or months. Prosthetic valve dysfunction at AV position is often caused by pannus formation which is an uncommon, but serious complication. Its incidence varies between 1.8% in tilting discs to 0.73% in bileaflet valves.⁷⁵ All types of available prosthetic valves can be affected by pannus formation. Pannus formation is a biological reaction to valve prostheses associated with factors such as surgical technique, thrombus formation due to inadequate anticoagulation and infection.⁷³

Rheumatic heart disease patients are usually treated with mechanical valve replacement surgery, owing to their durability and lower reoperation rates. However, these patients require lifelong oral anticoagulation therapy to prevent thromboembolic complications. Chronic anticoagulation has the risk of bleeding which necessitates close monitoring of INR. This complicates the lives of patients with mechanical prosthesis, thus inadequate anticoagulation therapy is the main reason for the development of PVT. A large meta-analysis of 1005 patients showed that up to 61% of patients with PVT had adequate anticoagulation so the cause of PVT in them remains unclear.⁷⁶ However, the INR can be falsely elevated in certain cases. Falsely elevated INR have been recorded in patients with lupus anticoagulant antibodies or dysfibrinogenemia and in those undergoing conversion from direct thrombin inhibitors.⁷⁷ Though the increase of INR may also result from the coagulation factors deficiency, liver dysfunction or vitamin K deficiency.⁷⁸ In our first case, the patient had sufficient anticoagulation but still developed prosthetic valve dysfunction. In this case, we need to remain alert and suspect other conditions that may be responsible for the high INR values.

Cardiac rheumatism may have played a role in our cases, especially considering that our first patient also developed TV rheumatic regurgitation. It is important to note that most of the previously reported cases of pannus formation at AV position were females as well as our first case. Differential diagnosis between thrombus

and pannus is made based on clinical, echocardiographic and morphopathological criteria and is essential because therapeutic approaches are different. If in thrombotic obstruction, thrombolysis can be considered, this is contraindicated in the case of pannus, where the only valid treatment is surgery – valve replacement or pannus removal.⁷⁹ In our case, chronic evolution and effective anticoagulation resembles the clinical picture of pannus formation rather than thrombosis. Since a TV prosthesis surgery was required, it was decided that the dysfunction of the AV prosthesis would be corrected during the same surgery.

Recently it was discovered that the pro-coagulant effect of the SARS-CoV-2 virus does not always protect patients from the risk of thrombosis, even under effective anticoagulation like it was observed in the second clinical case. In patients with mechanical valves receiving VKA treatment, high risk of thrombus formation remains.⁸⁰ The treatment is based on thrombolysis by therapeutic anticoagulation, fibrinolysis, or surgery and is selected depending on the size, composition of thrombus, and clinical status. In our case, due to the manifestation of organizing pneumonia as a late-phase Covid-19 infection complication and the rapidly worsening condition of the patient, the surgical treatment was required. Allione's study shows that the monitoring of D-dimer levels associated with the inflammation parameters (CRP and IL-6) might be useful for early recognition of prothrombotic pattern associated with SARS-CoV-2, despite therapeutic values of INR during warfarin treatment.⁸¹

Conclusions

Despite PVT being rare, it is a highly lethal condition that requires rapid diagnostic assessment. Diagnosis is based on the findings of the clinical examination, cinefluoroscopy and echocardiography. The role of TTE is fundamental, not only for accurate diagnosis but also to provide optimal treatment. Treatment depends on the presence of obstruction and prosthesis location and might be chosen as one of the following: surgery, fibrinolysis, heparin treatment or optimization of anticoagulant and antiplatelet therapy. Adequate anticoagulation remains the most important factor in the prevention of PVT in mechanical prosthesis.

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