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Prosthetic Valve Thrmbosis: Literature Review

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Introduction

Valvular heart disease represents a high cardiovascular burden with more than 100 million persons worldwide affected, and related morbidity and mortality are still significant [1].

Surgical valve replacement still is a corner stone for severe valvular disease in patients at low and intermediate risk for surgery [2]. Meanwhile, the last decade witnessed the emergence of transcatheter alternatives meanly for high surgical risk patients with aortic stenosis [2].

Prosthetic heart valves can be divided to 2 types: mechanical or biological [3].

While Mechanical prosthetic heart valve are durable, it comes with a price of thrombogenic risk, yet that risk has been reduced the bileaflets models .Biological prosthetic Heart Valves (BHVs) are less thrombogenic but with less durability [3].

The transcatheter aortic valve is considered as biological, while being mounted on an expandable metallic armature [4].

Prosthetic Valve Thrombosis (PVT) is a rare but may be a fatal complication of valve replacement, with an incidence varying between 0.5%-8% in mechanical valves in the mitral and aortic positions, with contrast of a relatively low incidence rate of 0.03% in bioprosthetic valves [2,5].

Often the diagnosis can be challenging, considering the variable clinical presentations and the severity of valvular obstruction. So differentiating a prosthetic valve thrombosis from valvular pannus, PV degeneration or endocarditis is crucial as it will determine the appropriate management [6].

Albeit surgical treatment is usually the preferred treatment for preferred obstructive PVT, optimal treatment remains controversial. Different alternatives are available for PVT (heparin treatment, fibrinolysis, surgery) depending on presence of obstruction, thrombus size and clinical status [1].

The aim of this article is to review the pathogenesis, diagnosis and treatment modalities and strategies for PVT.

Pathogenesis and aetiologies

All external devices (including valve prosthesis) implanted in the human cardiovascular system are thrombogenic, which imply the necessity for a form of anticoagulation or antiplatelet therapy to prevent thrombus formation, which can lead to systemic emboli or dramatic consequences. PV thrombosis is characterized by thrombus formation on the surface or near to the prosthetic structures, responsible for PV dysfunction [1].

The formation of thrombosis is mainly related to the Virchow's triad which includes: stasis or hemodynamic flow, endo-

thelial injury or surface and hypercoagulability or haemostatic parameters [7].

- **Stasis or hemodynamic flow:** Transprosthetic blood flow is often a turbulent flow that may result in an increase in shear stress whereas stasis increases blood coagulability, the resulted turbulence may contribute also a delay endothelialization which is prothrombotic. Conjointly a low flow state whether related to low cardiac input or to anatomic position of the PV is a well known risk factor for thrombosis , therefore for instance tricuspid prosthetic valve are nearly 20 times more thrombogenic than left sided chambers valves [8].

- **Endothelial injury or surface:** foreign surfaces promote thrombosis through a multiple mechanisms mediated mainly by proteinadsorption especially fibrinogen and activation of XII factors which promote platelets adhesion and clot formation [9].

- **Hypercoagulability or hemostatic parameters:** mostly related to patient's characteristics and co morbidities as : obesity , chronic kidney disease , lupus , pregnancy , COPD , smoking , malignancy ; Besides , lack of adherence with therapeutic anticoagulation increases significantly the risk of PV thrombosis [1].

Diagnosis and clinical presentation

The clinical presentation of thrombosis of prosthetic valve is variable and depends on the degree of obstruction.

Whilst obstructive thrombosis is often linked to a dramatic presentation with hemodynamic compromise, acute heart failure, cardiogenic shock with reduced cardiac output; clinical symptoms on the other hand might range from dyspnea on exertion to orthopnea and pulmonary edema, or systemic emboli whether cerebral, on peripheral limbs or even coronary embolism [10].

On contrast, non-obstructive valve thrombosis is more insidious and could be found in asymptomatic patient on routine echocardiography or identified as part of the work up in case of a stroke.

It is crucial to search for thrombosis risk factors as poor anticoagulation adherence, sub therapeutic anticoagulation verified by INR in the last three months, besides it's important to consider other differential diagnosis as endocarditis, in which a history of prolonged fever would redirect the diagnosis.

Physical examination is generally poor apart from the disappearance of the prosthetic sound in case of mechanical valves, or sometimes the presence of a new heart murmur.

Imaging modalities

Trans-Thoracic Echocardiography (TTE) is often the first imaging modality to be performed [11], it allows in addition to the measurement of the cardiac chambers, the mass of the LV, the study of the systolic and diastolic functions of the LV, allows the study of leaflet mobility, permits the visualization of the thrombus which appears as an added echostructure, but the TTE has, like any test, some limitations due in particular to the artefacts of mechanical prostheses.

The ultrasound study includes continuous pulse and color Doppler measurements; the study of severity of the obstruction, the flow velocity study of the PVT is the same as for the measurement of stenoses on native valves [12]. Measurements

should be taken at 100 mm/s and preferably in a patient at optimal cardiac frequency of 65-85 ppm. In patients with Atrial Fibrillation (AF) the measurements should be averaged over at least 5 cycles [11, 12].

For valves in the aortic position, the Doppler measurements needed are peak velocity, mean gradient, velocity time integral, Doppler velocity index, and effective orifice area by the continuity equation, whereas the measurements needed in the mitral and tricuspid positions are peak velocity, mean pressure gradient, velocity time integral, and pressure half-time [11]. It should be noted that high trans-valvular gradients do not necessarily mean PVT, other conditions should be considered such as tachycardia, anemia, and arteriovenous fistula, and measurements should always be compared with a baseline measurement (Figure 1) [13].
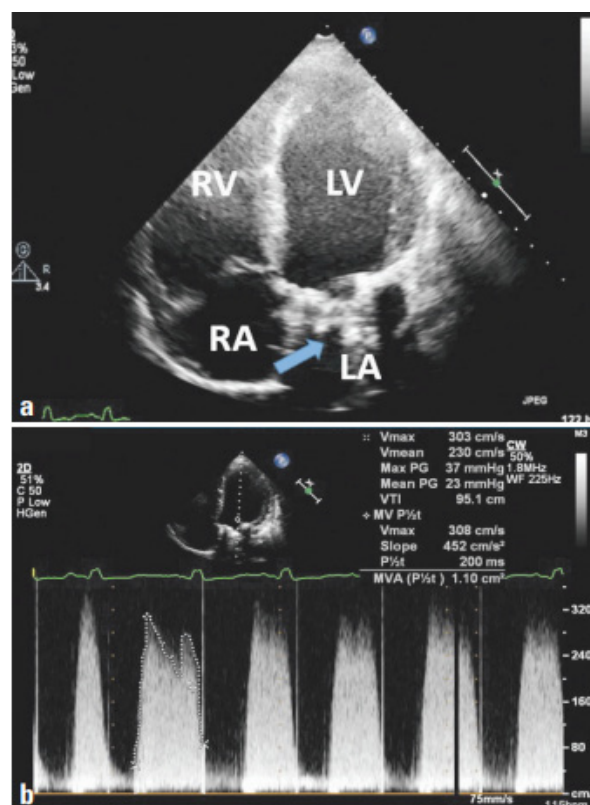
Figure 1: Two-dimensional transthoracic echocardiographic imaging of mitral prosthetic valve thrombosis (arrow) in four-chamber view **(a)** and increased transvalvular gradients and reduced mitral valve area, as demonstrated by Doppler imaging **(b)**.

LA - left atrium; LV - left ventricle; RA - right atrium; RV -right ventricle.

Trans-Oesophageal Echocardiography (TEE) allows a better resolution, due to the proximity of the oesophagus to the heart and the absence of interference with the lungs and ribs [14]. It should always be performed if the transthoracic echocardiography is technically suboptimal, if the findings are not definitive, or if there is strong clinical suspicion of PVT.

Furthermore TOE has some limitations: Aortic prostheses are more difficult to evaluate than mitral prostheses, and the ventricular side of a mitral prosthesis is more difficult to evaluate than the atrial side. It is also important to differentiate small thrombi from strands or sutures.

A thrombus was defined as soft and homogeneous, with mobile or fixed echodensity, similar to myocardium, located at the valve occluder, hinges, and/or valve struts [15,16]. The

thrombus burden usually contributes to the severity of trans-valvular gradients. Larger thrombi are more likely to cause hemodynamic compromise and may result in thromboembolic complications. The thrombus size visualized by TEE is important in deciding on the optimal treatment strategy. PRO-TEE trial has reported that a thrombus area < 0.8 cm² confers a lower risk for embolism or death associated with TT in left-sided obstructive PVT. Therefore, they showed that TEE could predict a low-risk group for thrombolytic therapy [17].

Cinefluoroscopy (CF) is a low-cost, noninvasive imaging technique, which is readily available in most centers and can be performed rapidly, particularly in unstable patients, for detecting stuck valves [18,19]. In the case of bileaflet valves, the disks can be directly visualized, and opening and closing angles measured using a tangential view [20,21,22]. Although the role of CF has declined since the introduction of TEE, it still serves as a complementary method to echocardiography in evaluation of prosthetic valve obstruction [21]. It may be particularly utilized as an easily repeatable modality to follow stable patients for evaluation of valve motions during TT. CF has also limitations; it is not useful in distinguishing pannus from thrombus since neither pannus nor thrombus can be identified fluoroscopically. Therefore, TEE should be performed to confirm the findings obtained by CF (Figure 2).
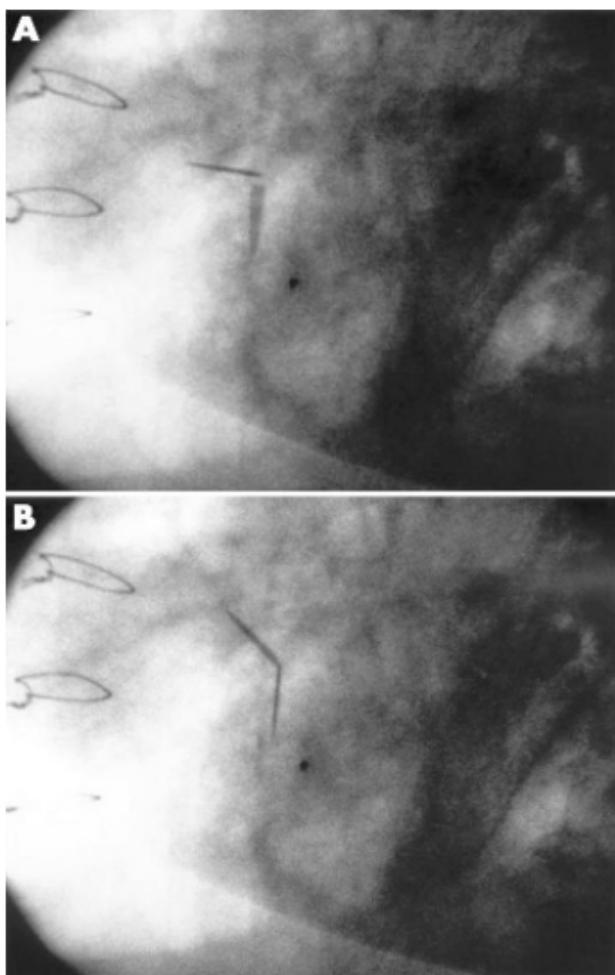
Figure 2: Cinefluoroscopy showing impaired motion of the two leaflets of a mechanical mitral valve.

Management

Prosthesis thrombosis is a life-threatening condition and its management must be urgent. Treatment options include surgery, firinolysis and anticoagulant therapy [23]. The 2014 ACC/AHA guidelines recommend thrombolytic therapy for right-sided PV thrombosis if clots persist despite intravenous heparin [2], The approach to left-sided PV thrombosis treatment involves clinical and imaging evaluation of the thrombus burden.

Until the 1990s surgery was the only treatment option, since then thrombolysis has gradually taken its place in the treatment algorithm.

Surgery

Replacement of a thrombosed prosthesis allows the identification of the exact causes related to the prosthesis itself apart from patient-related factors, i.e. structural dysfunction of the prosthesis or fibrous tissue growth [24]. Mortality rates between series vary greatly depending on the clinical status of the patient including the NYHA class, momentum of the surgery (urgent or elective) and the year of surgery [25-28]. The lowest perioperative mortality (4-7%) was reported by Deviri et al [29].

The in-hospital mortality of mechanical deobstruction introduced by BjOrk and Henze in 1973 is not significantly lower than that of conventional valve replacement [25,29]. The incidence of recurrent thrombosis appears to be higher, although this is largely influenced by the adverse long-term experiences of Martinell et al [30], while other investigators have reported a very low rate of rethrombosis during follow-up [31-33]. It has been suggested that thrombectomy should be combined with rotation of the valve housing to reduce the risk of rethrombosis triggered by abnormal transprosthetic flow patterns [32]. In cases of primary prosthetic valve dysfunction or extensive pannus formation, prosthesis replacement is mandatory [34]. In all other cases, the two techniques appear to be essentially equivalent, and the decision to replace or debride the thrombotic valve should be made by the surgeon based on personal experience and morphological findings.

Fibrinolysis

Fibrinolysis was first described by Luluaga et al. in 1971 [35], and a wide variety of fibrinolytic substances and assays have been used since then [36-46]. In a summary of the results of a consensus conference, streptokinase (starting with a bolus of 250,000 IU over 30 min, followed by an infusion of 100,000 IU. h - 1) or urokinase (with the same protocol used in patients with acute pulmonary embolism) were recommended [47]. In addition, recombinant tissue plasminogen activator (rt-PA) at a dose of 100 mg administered over a period of 2-5 h has been used successfully [34,39,45, 48-50]. Monitoring of the thrombus and trans-prosthetic gradients should be done by TTE every 3-6h and TEE should be done once a day as long as the thrombus remains visible. Thrombolysis is stopped when the transprosthetic gradient has more or less normalised and the thrombotic material has completely dissolved. If there is no improvement within 24 hours, fibrinolysis should be stopped and surgery performed 24 hours later or after 2 hours if the fibrinolytic treatment has been neutralised by protease inhibitors [51]. In any case, fibrinolysis should be discontinued after 72 h, even if it has not been fully successful [51]. Pre-treatment with oral anticoagulants should be stopped before administration of thrombolytic agents. Fibrinolytic activity should be monitored every 6 hours by determining fibrinogen concentration and fibrinogen degradation products [52]. After successful thrombolysis, a heparin infusion is started and the activated partial thromboplastin time is maintained at twice the baseline values, followed by conversion to oral anticoagulation with aspirin (100 mg. day-1) [51]. The International Normalized Ratio is adjusted to 3-4 for aortic

prostheses and 3.5-4.5 for mitral prostheses [49]. If thrombolysis does not completely dissolve the thrombus and the patient remains stable, subcutaneous heparin can be combined with oral anticoagulation for about 3 months (International Normalized Ratio 2.5-3.5) [48,49]. Fibrinolysis has been generally accepted for the treatment of patients with right prosthetic valve thrombosis and patients with left prosthetic valve thrombosis who are thought to be at high operative risk [41,48,49]. The use of thrombolysis in NYHA class I or II patients remains controversial due to the risk of embolic complications [50,51]. As in the surgical series, 28 of 31 deaths (90%) and 7 of 10 major embolic events in 10 studies (70%; one study could not be analysed due to insufficient clinical data) occurred in NYHA class III or IV patients. Therefore, fibrinolysis in NYHA class I or II patients appears to be a safe treatment option, but not superior to surgical treatment. For the subgroup of patients with non-obstructive valve thrombosis, Lengyel et al [48,49] proposed a 48-hour intravenous heparin infusion as an alternative, followed by a combination of subcutaneous heparin and oral anticoagulants for up to 3 months on an outpatient basis. However, the overall success rates are lower than for conventional thrombolysis [50]. Overall, fibrinolysis resulted in complete clinical and haemodynamic recovery in approximately 76% of patients with left prosthetic valve thrombosis and 71% of those with tricuspid prosthetic valve thrombosis. Success rates were slightly higher for aortic than for mitral valve prostheses, probably due to the higher degree of thrombotic load required to cause significant obstruction in mitral valve prostheses and an increased susceptibility to thrombosis in low-pressure sections of the circulation [51-53]. Partial success was achieved in about 10% of patients, and was usually followed by conservative or operative treatment. Non-responders mostly underwent immediate surgical intervention.

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