Chapter 8

Thrombolysis or Operation: That is the Question in Prosthetic Valve Thrombosis

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Additional information is available at the end of the chapter

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1. Introduction

The structural changes of mechanical prostheses over the last 3 decades have improved their haemodynamic features and prolonged their durability. Nowadays, they are preferable to bioprostheses in most cases (Figure 1). The risk of complications is still very high, among which thrombosis is the most dreaded. Its incidence varies in the literature between 4% [1] and 8.6% [2] within 5 years from implant. Despite various innovations, even today, prosthetic thrombosis is still associated with a high mortality, even if emergency medical or surgical treatment is promptly established [3, 4, 21]. The knowledge of factors that may determine prosthetic thrombosis is still limited. Numerous studies investigated this tragic complication: the most frequent risk factor as reported in the literature is inadequate or discontinued anticoagulant therapy. Other risk factors are related to previous endocarditis and the prosthetic model, since many authors found a major incidence of thrombosis in tilting disc valves [1, 5]. Predisposing factors are atrial fibrillation, atrial thrombosis, previous embolism, difficult left atrial emptying, low output and turbulence related to prosthetic model [6]. The size of the prosthetic valves does not seem significant, while the role of age greater than 60 years [7] and megaatrium [8] is still controversial. It is noteworthy that thrombosis is absent in young patients (under 20 years old) [9] and its incidence is increased during pregnancy [1].

Some authors investigated other interesting aspects such as the interval between implant and thrombosis and the hypothesis of a genetic predisposition to thrombosis [9]. A lower incidence of thrombosis is reported for the aortic prosthesis compared with mitral and tricuspid implants [1], All prosthetic valves are undoubtedly predisposed to thrombogenicity: they activate coagulation factors and platelets a degree dependent on their prosthetic valve type (material and design). Little attention has been given to the periprosthetic fibroblastic proliferation

which would be the primary event of thrombosis when it blocks the movement of the poppet [10]. In the past years, our research group analyzed possible statistically significant risk factors in patients who had undergone surgery for a preoperative diagnosis of thrombosis and the most important finding was the very high incidence of thrombosis in which the moving element of the prosthesis was gradually blocked to a complete arrest by an overgrowth of fibrous tissue that invaded the valve orifice. No bioprosthesis showed fibrous tissue ingrowth and therefore the phenomenon was defined as primary thrombosis: anticoagulant therapy would probably have been effective in preventing or limiting the obstruction while fibrinolytic therapy could resolve the acute obstruction. In our view, fibrous tissue cannot be an organized thrombus but more likely is a fibroblastic proliferation which for long periods remains limited to the periprosthetic endothelial connective tissue coating and may expand for unknown reasons and rapidly envelop the valve orifice [14] (Figure 2).

In a recent publication we reported the case of a patient with one blocked leaflet of a mechanical valve prosthesis on mitral position, that persisted for at least three months, without causing any secondary valve thrombosis. Intraoperatively, no thrombus and/or pannus was present. Despite an abnormal blood flow, the new phrostetic valves are resistant to secondary thrombosis [22].

Based on such data, analysis of our records identified risk factors that could affect this phenomenon: the incidence of obstruction was markedly lower for bioprostheses compared to mechanical valves and this is in agreement with the literature [3]. Obstruction of mechanical prostheses had an incidence at intermediate level as reported in the literature[3, 9], while mortality was high, even if immediate treatment was established. The obstruction was determined in most cases by the overgrowth of connective periprosthetic tissue which blocked the valve movement and 70% had adequate anticoagulant treatment. In the rest of cases with primary prosthetic thrombosis, anticoagulant therapy had been discontinued or was inadequate in a high percentage. No obstruction of tricuspid prostheses was observed and the incidence was markedly lower for aortic compared to mitral valves. Sex was not a significant risk factor while age between 40 and 50 turned to be a major risk. The importance of age has already been investigated in the literature [3]. Regarding the prosthetic design, the incidence of obstruction drops from tilting disc to bileaflet and to ball valves.

How this coating may affect fibroblastic proliferation and thrombogenesis in the context of obstruction of mechanical valves is not well established. Our experience confirms reports in the literature as far as the importance of the modality of transprosthetic flow in the origin of obstruction is concerned [5]. So the most important risk factors are large size, slow flow prostheses, tilting disc mitral valves with a small orifice oriented posteriorly where there is slow and turbulent flow, atrial fibrillation and a large left atrium. In addition the increased risk of thrombosis occurs in a period longer than 4 years after the implantation [3, 14] Primary importance has been attributed to the thrombogenic potential of available prosthetic valves and therefore to adequate anticoagulant therapy. No solution has yet been found for patients receiving adequate anticoagulation and for those receiving both coumadin and antiplatelet drugs who develop prosthetic thrombosis. The results of fibrinolytic therapy and prosthetic thrombectomy are not well documented. As far as the former is concerned, there is a high

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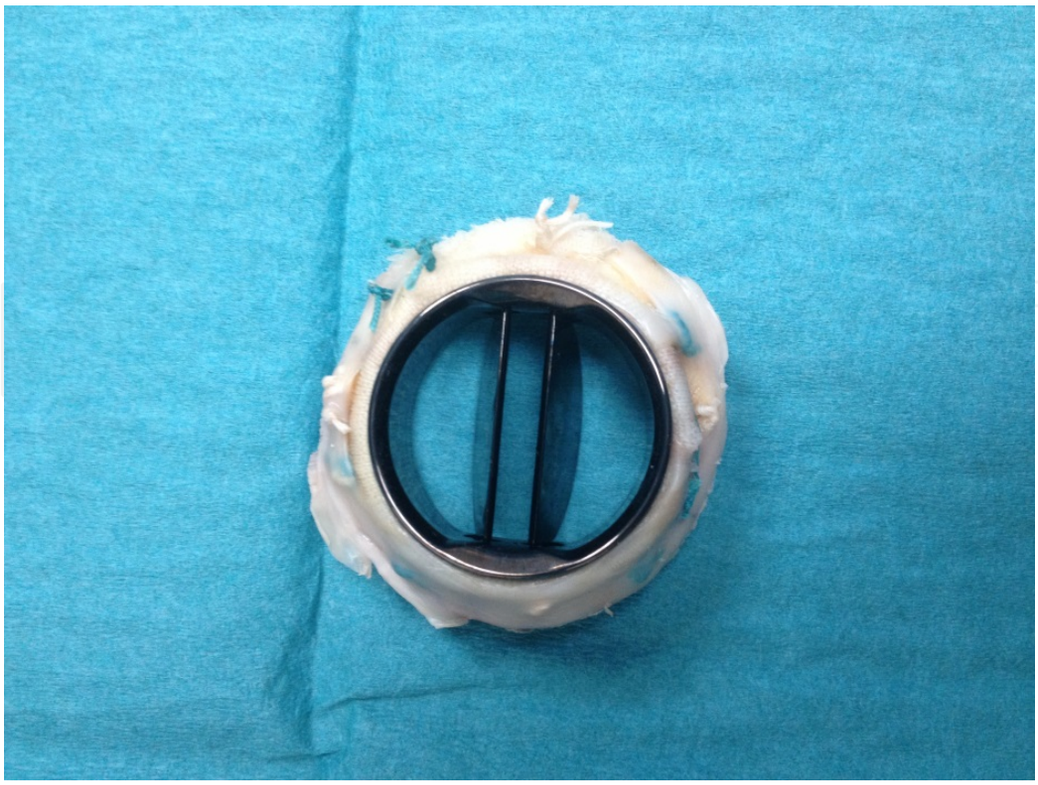

Figure 1. Last generation valve.

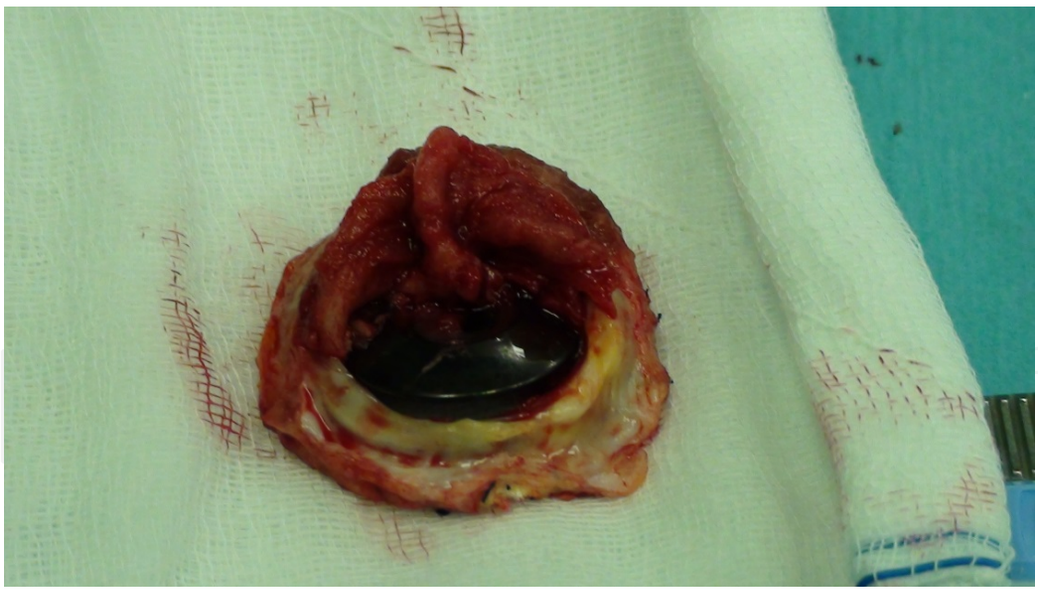

Figure 2. Thrombosis of a mechanical valve.

incidence of cases that do not benefit from this treatment with eventual fatal outcome or require second stage surgery. This incidence may vary from 25% to 38.46% [1]. As far as thrombectomy is concerned, there is a poorly documented high incidence of recurrent thrombosis [12]. A more appropriate subdivision of "biological obstruction" is:

A) primary thrombosis

B) secondary thrombosis

C) absence of thrombosis.

In the first case, thrombosis is determined by a thrombus that is the basic element of prosthetic malfunction; the anticoagulant prophylaxis may play a primary role and fibrinolytic treatment is indicated as confirmed by the almost complete success of this therapy in tricuspid valves where peri-prosthetic fibrous tissue is almost impossible to find. In these cases, thrombectomy may also give good results. In patients in groups B and C, prosthetic malfunction is not primarily determined by thrombosis, but by blockage of the moving element of the prosthesis due to overgrowth of peri-prosthetic fibrous tissue: thrombosis may follow this event (group B) or it may even be absent (group C). Fibrinolysis or thrombectomy may give only temporary and partial results or no result at all. Diagnostic procedures not always document precisely the type of obstruction and therefore the clinical picture and history of the patient, case by case, are more useful. Three different statistical evaluations allowed us to assess those risk factors that are important in determining prosthetic biological obstruction. Such factors are prosthetic design, pyrocarbon coating and valve orientation, time from the implant, local haemodynamic conditions and age. Other important risk factors might be pregnancy, endocarditis, bioprosthetic degeneration, composite conduits and individual predisposition [14]. Therefore, from what has been said before, it is clear that an acute obstruction is a life-threatening complication of mechanical valve prostheses, and is caused by the formation of fresh clot or fibrous tissue overgrowth, or both and the accurate selection of the most appropriate treatment for a particular patient is mandatory. Mechanical valve obstruction is currently the main reason for mechanical valve reoperations. Diagnosis of prosthetic obstruction is based on the presence of certain clinical, echocardiographic, fluoroscopic, and hemodynamic features. Symptoms are various: from palpitation to pulmonary edema or low output syndrome. Fluoroscopy examination can show a reduced or absent excursion of one or both prosthetic leaflets. It is very difficult to determine the morphologic process responsible for thrombosis preoperatively on the basis of the clinical, fluoroscopic, and hemodynamic features. In fact, fluoroscopic and hemodynamic investigations can only confirm the clinical diagnosis of prosthetic obstruction, but cannot give any further information concerning the nature of the obstruction. On the other hand, transesophageal echocardiography (TEE) is a very helpful diagnostic tool, when a prosthetic obstruction is suspected, especially for those obstructions due to primary thrombosis, as its resolution is superior to that of transthoracic echocardiography and it can better visualize thrombi on mechanical prosthetic valves and in cardiac chambers (Figure 3).

TEE has also proved useful for assessing thrombolysis results and for the long-term follow-up of patients after treatment for a thrombosed prosthesis. The TEE evidence of a thrombus seated, on a normal-functioning prosthesis or on the atrial walls is a further indication of thrombotic obstruction, improves the likelihood of successful thrombolysis in this setting (20). Cardiac catheterization may be useful to assess the coronary anatomy and plan the surgical strategy. The greater possibility of a successful treatment is time-dependent, because a thrombolytic agent is more effective on a fresh clot than on an organized one. For this reason, the 15-day

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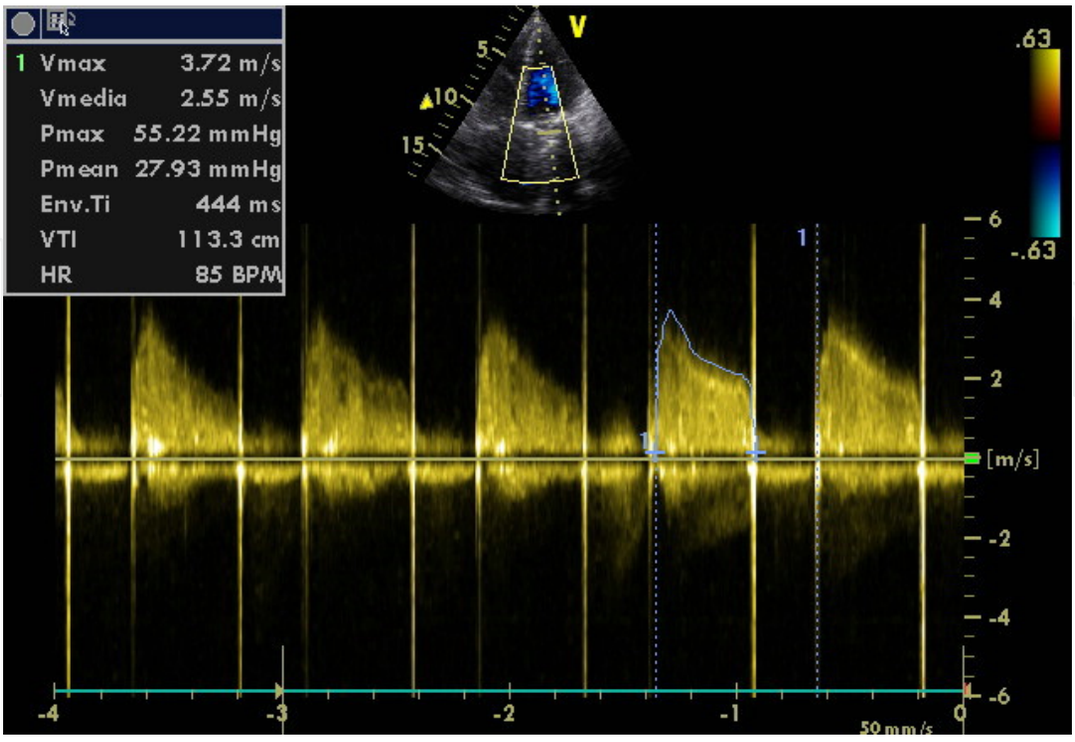

Figure 3. A transesophageal echocardiogram illustrating the presence of a thrombus in a mechanical valve.

cutoff has become the recommended period within which thrombolytic treatment should be initiated for pulmonary embolism [3, 14]. Many studies do not recommend the thrombolytic therapy in patients with left heart prostheses because of the high risk of precipitating cerebral or peripheral embolism. Our previous research found certain incidence of minor embolic complications in our series, and this has been noted by others too. On the other hand, the risk of permanent neurologic deficit or major peripheral embolism is not very high in these patients, as the embolism arises in patients already receiving fibrinolytic treatment. In this situation, if an embolism should occur, this indicates the need for a secondary form of fibrinolysis to reduce the risk of permanent damage. Nevertheless, more patients must be studied to adequately investigate the embolic risk in this setting [3, 14]

Our initial experience demonstrated the utility of thrombolysis in prosthetic valve obstruction. In fact in a previous study we enrolled 20 cases of prosthetic thrombosis treated with thrombolysis using recombinant tissue type plasminogen activator (rt-PA). Indication criteria for thrombolysis were: (i) recent onset of symptoms; (ii) transesophageal echocardiographic (TEE) evidence of clots on the valve or cardiac chambers; and (iii) a partially preserved disc excursion. All patients were fitted with mechanical valves on the left side. Symptoms of obstruction comprised cardiac failure in 11 cases and/or embolism in 10. After rt-PA infusion, normal prosthetic function was restored in all patients, though one underwent successful reoperation five days later. During infusion, five patients had a transient ischemic attack and one a minor transient peripheral embolism. Recurrence of thrombosis occurred in three patients during follow up; subsequent thrombolysis was successful in two, without any complication. A

deeper knowledge of mechanism of valve obstruction improved our understanding of the indications, benefits, and limitations of the surgical and fibrinolytic treatment [3, 14].

For this purpose we still consider the following criteria valid indications for thrombolysis: TEE evidence of clots on the valve and chambers, and slightly reduced disc excursion. Thrombolysis in tilting disc valves is reserved only for non-obstructive thrombosis, because obstructive thrombosis in this valve model is generally sustained by pannus [15]. On the other hand, bi-leaflet valves are more prone to primary thrombosis than fibrous tissue overgrowth and sometimes the obstruction affects only one leaflet [15]. Therefore thrombolysis can be considered also when a reduced leaflet excursion is noted [15, 17]. Multi-plane TEE is the best investigative tool for the diagnosis of valve obstruction [18]. It is also useful to monitor thrombolysis outcome [16, 18]. Although some TEE features have been identified to differentiate pannus from thrombus [19], they are not totally reliable and the distinction is still left to the expertise of the echocardiographer. Clinical history and presentation are also helpful. Recombinant tissue-type plasminogen activator was used as it requires only a short course of infusion. A 25% rate of transient embolic complications was observed during treatment. Although no permanent damage resulted because of a secondary fibrinolysis, we acknowledge that the complication rate is high. It can be speculated that while thrombotic material from the mitral valve remains in the left cardiac chambers long enough to be dissolved completely, clot debris from the aortic valve move into the bloodstream immediately after detachment and dissolve only during embolization. As a consequence thrombolysis for aortic valve thrombosis may carry a higher embolic risk. We never had any bleeding complications. No heparin, either in infusion or subcutaneously, was started after thrombolysis and warfarin is restarted the same evening after thrombolysis and dypiridamole is added. We do not agree with the policy of carrying out thrombolysis in patients hemodynamically too unstable to undergo operation [18]. In this subset of patients prosthetic valve replacement is the best option, because thrombolytic drugs take several hours to be effective, and the same refers to heparin (Figure 4); therefore the patient will deteriorate even further, dramatically increasing the risk of redo operation, if fibrinolysis fails. Also, results with replacement have improved over the years, as with any redo procedures. In conclusion, we consider thrombolysis a valid treatment for non-obstructive prosthetic thrombosis only. In the future we may witness an increase in the number of thrombolyses with a decrease of prosthetic valve replacements, as bi-leaflet valves are the most widely implanted valve prostheses. Any time a blocked disc is detected pannus should be suspected, and the patient referred for operation. Patients should also be well informed of the risks of thrombolysis, especially embolism.

Treatment failure is therefore not due to choosing the wrong thrombolytic drug but, instead, to an incorrect perioperative diagnosis. Successful treatment is related to the ability to distinguish patients with primary thrombosis from those with peri-prosthetic fibrous tissue overgrowth. TEE makes this selection possible. In the sub-group of patients with prosthetic fibrotic obstruction, the only effective treatment currently available is prosthetic valve replacement, because, if the patient is in an unstable condition, reoperation is still the best therapeutic option. On the other hand, thrombolysis for the management of primary prosthetic

thrombosis has a low incidence of severe complications and the morbidity and mortality related to the surgical procedure are avoided.

Regarding the valve thrombosis during pregnancy, the most suitable treatment seems to be the conservative approach, as confirmed by a single-center, prospective study including a large number of pregnant patients with a prosthetic valve thrombosis which demonstrated that low-dose, slow infusion of tPA is associated with successful thrombus lysis in all episodes, with lower incidence of maternal and fetal adverse events than surgery. So slow infusion of tPA with repeated doses as needed under TEE guidance seems to be effective and relatively safe for both mother and fetus, and the authors suggest that it should be used as first-line therapy for prosthetic valve thrombosis in pregnant women. [13]

2. Conclusions

Treatment failure is therefore not due to choosing the wrong thrombolytic drug but, instead, to an incorrect perioperative diagnosis. Successful treatment is related to the ability to distinguish patients with primary thrombosis from those with peri-prosthetic fibrous tissue overgrowth. TEE is helpful for the diagnosis. For the patients with prosthetic fibrotic obstruction, the only effective treatment currently available is the cardiac surgery with prosthetic valve replacement, because, if the patient is in an unstable condition, reoperation is still the best therapeutic option. On the other hand, thrombolysis for the management of primary prosthetic thrombosis has a low incidence of severe complications and the morbidity and mortality related to the surgical procedure are avoided.

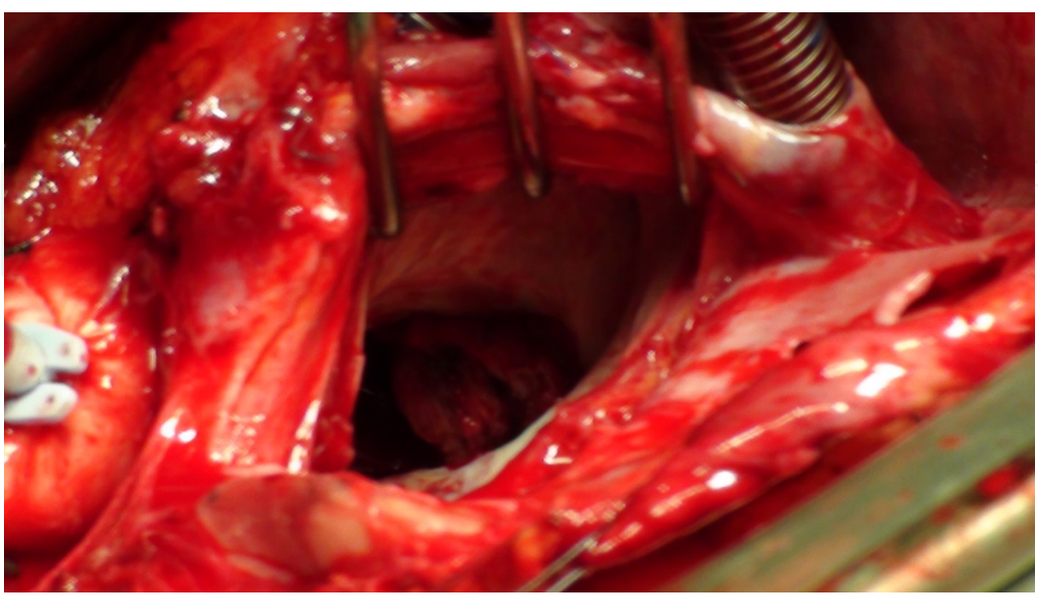

Figure 4. Surgery of mitral valve thrombosis.

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