

Management of Prosthetic Valve Thrombosis

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Prosthetic valve thrombosis (PVT) is a life-threatening disease, the treatment strategies for which remain controversial. Transesophageal echocardiography (TEE) is the diagnostic technique of choice. Prosthetic valve obstruction is defined as limited leaflet motion; obstructive and non-obstructive PVT are separated by abnormal or normal leaflet motion. TEE is limited in differentiating thrombus from pannus ('tissue ingrowth'), and sterile thrombi from infected vegetations. Clinical aspects are helpful. The estimated incidence of PVT is 2-4% per year based on autopsy and surgical findings. The true incidence should be higher, as TEE reveals almost as many obstructive as non-obstructive PVT, of which 50% are asymptomatic. The prevalence of asymptomatic non-obstructive PVT in the early postoperative period may reach 10%. Three therapeutic approaches are available for PVT. Surgical mortality may reach 69%, depending on NYHA class and need for emergency surgery. Thrombolysis represents an alternative to surgery, with 84% success and low complication rates (stroke 9%, mortality 5%). In non-obstructive PVT patients in NYHA class I or II,

Prosthetic valve thrombosis (PVT) is a life-threatening disease for which treatment strategies remain controversial (1,2). Before discussing and comparing the different therapeutic approaches that are available for this condition, it may be important to review the definitions, diagnostic tools and their limitations, and the epidemiology of PVT.

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thrombolysis success was higher (92%), without severe complications. No other clinical predictor of success could be confirmed. Besides classical contraindications there are no absolute contraindications (large thrombi, pregnancy, early postoperative period) for thrombolysis. Long-term streptokinase protocols have been used with regular TEE monitoring. Heparin may be an initial treatment for non-obstructive PVT, but thrombolysis is superior in this subset. If thrombi are >5 mm in size, heparin therapy is unsuccessful and unsafe. TEE monitoring is mandatory during heparin treatment, as thrombi may increase in size and become obstructive. Thrombolysis is recommended as first-line treatment if there are no contraindications. Heparin may be used initially for small non-obstructive thrombi, particularly if thrombolysis is contraindicated. Surgery should be reserved for patients in whom thrombolysis is either contraindicated or has been ineffective, independent of NYHA class.

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Definitions

Mechanical prosthetic valves are thrombogenic, and may result in obstruction and/or thromboembolic events. There is no general agreement regarding these complications, and the epidemiology, prognosis and treatment are relatively unclear. An explanation of these uncertainties is the use of different diagnostic approaches such as autopsy or surgery on the one hand, and non-invasive imaging utilizing either transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE) and cinefluoroscopy (CF) on the other hand. The definitions of PVT as "any obstruction of a prosthesis by non-infective thrombotic material" (3) or "valve-related clotting impairing the function of the valve diagnosed at operation or autopsy" (4) neglect non-obstructive PVT

(5,6), while “prosthetic valve obstruction” as a specific entity (7) covers different pathologies (thrombus, pannus, and infected vegetations). The use of TEE as the technique of choice allows the following differentiation to be made:

Prosthetic valve obstruction: limited leaflet motion
PVT obstructive: limited leaflet motion + thrombus
PVT non-obstructive: thrombus + normal leaflet motion

Diagnosis

Clinical presentation

Obstructive PVT presents as progressive heart failure, pulmonary edema or cardiogenic shock and/or systemic embolism. On auscultation, the occluder clicks are typically muffled or absent, stenotic or regurgitant murmurs may be heard (8). Non-obstructive PVT may cause stroke or peripheral embolism, but may be asymptomatic in almost 50% of cases (6,8).

Diagnostic techniques

Obstruction in hemodynamic terms is assessed using Doppler echocardiography. Increased transvalvular gradients however may be caused by paravalvular regurgitation or prosthesis-patient mismatch (9). Obstruction occurring as restricted occluder motion may be diagnosed by CF (10-12), though this cannot contribute to etiological differentiation. In addition to the demonstration of limited leaflet motion, TEE allows the detection of any obstructive mass, of any absence or increase in normal central regurgitation (8), and the visualization of coexistent left atrial thrombi. Non-obstructive PVT can be diagnosed by multiplane TEE only (13), while multislice computed tomography (CT) may, in time, be used as another sensitive imaging technique.

Limitations of TEE

Although TEE has been accepted unanimously as the imaging technique of choice for the diagnosis of PVT

(14), there are three potential limitations: the aortic location; the need to differentiate between thrombus and pannus formation; or infective vegetations. In the aortic position, limited leaflet motion and thrombus may not be visualized reliably by TEE in all cases (15). Therefore, CF should be used in addition in cases with uncertain or negative TEE findings for both the initial diagnosis and for monitoring thrombolytic therapy (10-12). Severe intraprosthetic aortic regurgitation, when demonstrated by TTE, is a valuable indication of restricted occluder motion.

It may be important to differentiate between thrombus and pannus in order to choose the optimal treatment strategy. In obstructive PVT, both conditions may have similar morphologies, and may result in similar functional abnormalities. They coexist in the majority of cases (16), but thrombus formation is more likely in patients with inadequate anticoagulation (3), or thromboembolic risk factors (mitral position, left ventricular dysfunction, atrial fibrillation, older valve types, hypercoagulable states as pregnancy) (17), early post-operatively (18), and in the presence of larger and less echogenic masses on TEE (19). Successful lysis is another proof of thrombus versus pannus. Intermittent obstruction is more likely to be caused by tissue ingrowth (20). The absence of a mass in obstructive PVT suggests pannus, but a thrombus within the valve orifice may also be invisible.

There are further similarities between thrombus and infective vegetation in obstructive and non-obstructive cases. Vegetation is more likely in febrile patients and in the presence of symptoms and clinical signs of infective endocarditis, but also in the presence of perivalvular destruction, leak or abscess formation.

Epidemiology

The incidence of thromboembolism in orally anticoagulated patients with prosthetic valves has been estimated at between 1 and 4% per year: the lowest values were reported for St. Jude Medical prostheses in the

Table I: Comparison of treatment results.

Treatment/ Condition	No. of patients	NYHA class IV	Success (%)	Complications (%)	Death (%)
Lysis					
Obstructive	33	22	85	12	6
Non-obstructive	11	0	91	9	0
Heparin					
Obstructive	4	3	0	0	25
Non-obstructive	18	0	50	33	0
Surgery					
Obstructive	19	13	-	10	36
Non-obstructive	2	0	-	0	0

aortic position, and the highest for Björk-Shiley prostheses in the mitral position (21).

The true incidence of PVT however is unknown, as much of the data are based on biased autopsy and surgical findings which do not include the large number of non-obstructive PVT cases. In our experience, as reported earlier, 40% of all PVT cases were non-obstructive, and 45% of these were diagnosed by TEE in asymptomatic patients (8). Indications for TEE in these cases were inadequate anticoagulation, slightly elevated transvalvular gradients, or early postoperative screening (5,6). A literature search for the period 1992 to 1999 revealed an average 10% prevalence of PVT with routine postoperative screening in about 1,000 patients (2,5,6,22-24). The difficulties of early postoperative anticoagulation and the management of such complications are clearly reflected in these reports, and some authors concluded by strongly recommending that TEE be performed routinely before discharge (22).

Treatment strategies in PVT

Surgery

For many years, the standard treatment of PVT has been reoperation. However, the surgical mortality may be as high as 60%, depending on the patients' NYHA functional class and the urgency of operation (3,7,25). According to Deviri et al., mortality is 4.7% even in NYHA class I-II patients (16).

Thrombolysis

Thrombolysis was first used to treat PVT in 1974 (26). One reason to favor thrombolysis for the left-sided prosthetic valve is the high operative mortality, particularly among critically ill subjects. Arguments against thrombolysis include the risk of systemic embolism and the relatively high recurrence rate. A review of the English literature highlighted more than 50 reports, presenting a total of over 500 cases (8), the large majority of which were case reports with, in the largest series, 110 (27), 64 (2) and 43 (8) cases being included. The results can be summarized as an overall success rate of 84% and a recurrence rate of 16%. Among complications reported, systemic embolism was noted in 9% of cases, but only 15% of the complications resulted in disability or fatal stroke. All of the severe complications reported occurred among patients in NYHA class III-IV, with major bleeding in 3% and an overall mortality of 5%. Most reports did not distinguish obstructive from non-obstructive PVT, but the success rates in NYHA class I-II patients were higher (92%) than in class IV (81%), with zero versus 7% mortality ($p = 0.04$). In recurrent PVT, where a second thrombolysis was performed, the success rate was

75%. In recurrent unsuccessful cases, pannus was a frequent intraoperative finding (8).

Treatment protocols

In most of the reported studies, streptokinase (SK) was used at the traditional dosage to treat pulmonary embolism; namely, a loading dose of 250,000 U over 30 min, followed by 100,000 U/h for 72 h until the occluded motion had normalized, the fibrinogen level had fallen to zero, or any severe complication (bleeding or stroke) had occurred. Short-course, high-dose SK treatment (1,500,000 U over 90 min) was reported in 16 left-sided PVT cases (28). Urokinase has been used mostly after previous treatment with SK as the loading dose of 4,400 U/kg in 30 min, followed by 4400 U/kg per hour. Tissue plasminogen activator (tPA) was used very rarely, and mostly in critically ill patients as an accelerated protocol, with a bolus of 15 mg and an 85-mg infusion for 90 min (20,29,30). For other, more frequent complications (e.g. acute pulmonary embolism or acute myocardial infarction), SK is no longer recommended as a thrombolytic agent. Long-term thrombolytic treatment in obstructive PVT requires frequent TTE monitoring (every 2-5 h), and daily TEE monitoring is recommended for all cases.

Predictors of success with thrombolysis

As indicated previously, NYHA class I-III and non-obstructive thrombosis predict a better outcome than NYHA class IV or obstructive PVT (2,8,13,31).

The supposed less than 14 days duration of PVT was considered by some to increase the success rate (31,32), but others did not find any relationship between the onset of symptoms and the time at which thrombolysis was started (8,33). The longest duration with successful PVT lysis was 180 days (33). Valve type and the time since valve implantation had no influence on the success rate of thrombolysis (33), but success rates were higher if the thrombus was visualized (8). The choice of thrombolytic agent did not affect the results, but there were more embolic complications with the use of tPA (30,34-36). The efficacy and safety of short-term high-dose SK administration is controversial (28,34,37). Some authors consider the success rate to be higher (but not significantly so) in the aortic than in the mitral position (7,38,39), but others have been unable to confirm this suggestion (27).

Contraindications to thrombolysis

In order to minimize embolic risk, recent guidelines (14,40) and one large review (7) have recommended that thrombolysis be carried out only in the absence of large thrombi at the atrial aspect of the mitral valve. However, the size of obstructive thrombi is difficult to measure, as they are sessile and may be located within

the valve orifice. Successful thrombolysis of mobile thrombi up to 20 mm in size without subsequent embolism has been reported (8).

Only one case has been reported of a large mobile atrial thrombus treated by slow thrombolysis, without embolic complications (41). Lysis of mural thrombi or thrombi attached to left atrial appendages have been reported with and without embolic complications (28,31,34,37).

Other relative contraindications may be pregnancy, early postoperative period or previous non-hemorrhagic stroke.

Seven patients have been reported who were treated successfully with thrombolysis for PVT during pregnancy (2,26,36,42,43). Among these, one patient received thrombolysis during the first trimester without any complications, and subsequently had a normal delivery after nine months' gestation (44).

Early postoperative thrombolysis has been reported as soon as four days after valve replacement (22,28,31,45), without complications. Twenty cases of non-hemorrhagic stroke or transient ischemic attack have been treated with thrombolysis, with only one hemorrhagic transformation (8,29,34,37,46,47).

Children may also be treated successfully with thrombolysis for PVT (48).

One potential problem of thrombolysis is the risk of delayed surgery if lysis fails, or if only a partial success can be achieved. In critically ill patients, it is possible to perform surgery only 2 h after fibrinolytic therapy has been neutralized by protease inhibitors (46). In most cases however, the partial relief of obstruction leads to patient stabilization and hence a better surgical outcome (33).

Comparison of thrombolysis and surgery

Thrombolysis and surgical treatment were compared in three studies. In eight cases of non-obstructive PVT there was complete success without complications following tPA treatment, compared with one death among 20 surgical cases who were in NYHA class III-IV (31).

In an intention-to-treat analysis of obstructive PVT, there was no mortality among 19 patients treated with thrombolysis, while five of 11 surgical patients died (49). In our own experience, an intention-to-treat analysis of mostly symptomatic patients with obstructive PVT and NYHA class IV, mortality was 13% after thrombolysis and 33% after surgery (8). By comparison, an on-treatment analysis showed mortality after thrombolysis to be 5%, and after surgery to be 30%. In reviewing the existing literature, the overall mortality among 89 patients in NYHA class IV in five studies was 7% after thrombolysis, and ranged from 17 to 54% after surgery (3,16,18,25). By comparison, among patients in NYHA class I-III, mortality was approxi-

mately 5% with both treatment modalities (1,2,31,34,35,38).

Heparin or oral anticoagulant treatment in PVT?

In obstructive PVT, anticoagulant treatment failed in all reports, with an overall mortality rate of 10%. Although in non-obstructive PVT the success rate was 60%, the mortality rate was 9%, and rates of 7% for stroke and 17% for newly developing valve obstruction were also reported (5,6,24,27,47).

Non-obstructive PVT is a unique subset in which the patients are stable, and the goal of treatment is the prevention of embolism. In addition, almost half of these patients present after stroke (8), in which case thrombolysis is generally contraindicated. Therefore initial anticoagulant treatment is justified (24,40). The success and complication rates appear to be related to thrombus size; for thrombi of <5 mm the success rate was 82%, and stroke and TIA rates 4% and 8% respectively, with no deaths. By contrast, for thrombi \geq 5 mm the reported success rate was 61%, while the stroke rate was 23% with similar TIA frequency and 38% mortality (5,24). This study was the first to compare all three treatment modalities (Table I), and thrombolysis was shown to be clearly superior to heparin treatment, even in non-obstructive PVT (8).

At present, it is unclear as to how long heparin or oral anticoagulant treatments should be given. It seems reasonable to start heparin treatment in non-obstructive PVT if the thrombus size is <5 mm on baseline TEE. Subsequently, if TEE at 48 h does not show any increase in thrombus size or obstruction, then heparin may be continued and TEE repeated every two to three days for a period of seven to 10 days. If there is progression of PVT, then any further strategy would depend on the patient's cerebral status: those who had suffered a stroke (as indicated by positive CT scanning) should undergo surgery, while those who had not had a stroke can be switched to thrombolysis. There is most likely an intermediate group in which the ischemic brain infarct is small or decreasing, and these patients can be treated for a longer period with anticoagulants and switched to thrombolysis if necessary after six to eight weeks.

Recommendations

Transesophageal echocardiography is the diagnostic technique of choice for PVT, both at baseline and for treatment monitoring, while CF is complementary and required mostly when the obstruction is in the aortic location. Doppler echocardiography has a role in raising the suspicion of obstructive PVT and in the monitoring of thrombolysis in these patients.

Previous guidelines for the treatment of PVT remain controversial (14,40), the main point under question

being which should be first-line therapy in obstructive and non-obstructive PVT. These guidelines recommend surgery in the severely ill (NYHA classes III and IV) and in those who have large clots, while thrombolysis remains the preferred alternative in patients with a high surgical risk or any contraindication to surgery. In patients with mild to moderate symptoms (NYHA classes I and II), heparin was suggested as the first choice.

However, more recent data have shown thrombolysis to be superior to surgery in obstructive PVT (particularly in the critically ill), and to heparin in non-obstructive PVT. Thrombolytic therapy should now be considered first-line treatment in all patients with obstructive PVT, independently of NYHA class, if there are no contraindications. Heparin treatment may be initiated in small non-obstructive PVT and either continued or switched to thrombolysis or surgery depending on the results of TEE and brain CT scans. Surgery should be reserved for those patients in whom thrombolysis is contraindicated, or has failed. Thrombolysis and surgery may be complementary therapies as the surgical risk is significantly reduced in patients with partial success of thrombolysis because of hemodynamic improvement.

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