The technological advances of current medicine have allowed the population greater longevity. Specifically in regard to heart valve diseases, the increased life expectancy has allowed the patients to undergo repeated surgical interventions, with an increasing indication for implantation of metallic valvular prostheses. Prosthetic valve thrombosis is a rare, highly lethal complication1-3, and cardiac emergency teams have little experience in managing prosthetic valve thrombolysis. Therefore, this updating report aimed at reviewing the major alternatives for treating an episode of thrombosis, presenting, in a practical way, the thrombolytic treatment as a feasible and effective alternative, when properly indicated.

Prosthetic valve thrombosis: a diagnostic and therapeutic challenge – The incidence of prosthetic valve thrombosis varies according to the following variables: efficacy of anticoagulation; type and location of the implanted prosthesis; and presence of atrial fibrillation1-4. In a meta-analysis published in 19942,5 with 13,000 patients with metallic prosthesis, the annual incidence of thrombosis was 0.2%, with thromboembolic events occurring at a rate of 1.8% per year. These incidences were much greater in patients receiving only antiplatelet agents (thrombosis in 1.6%, and thromboembolism in 8.2%). According to that study, in regard to location, patients with mitral prosthesis had a 2-fold greater risk for thrombosis than those with aortic prosthesis, and the metallic prosthesis in the tricuspid position had the greatest thrombogenicity. In addition, the caged metallic prostheses was the most thrombogenic.

Obstruction of the prosthesis is more frequent during the first postoperative year. The clinical findings vary from lack of symptoms to extreme cases of cardiogenic shock. The most common symptoms are progressive dyspnea on exertion, lipothymia, and syncope. Systemic embolism and acute pulmonary edema may be the first manifestations of the disease.

The physical examination reveals new murmurs or a change in the pattern of the old murmur2,4. The best complementary examination to refine the diagnosis of thrombosis is transesophageal echocardiography, which allows elucidation of the obstructive mass, leading to a more accurate diagnosis6-8. Reoperation, in such cases, increases the risk, with mortality rates ranging from 10% to 15% in some case series3,4,9,10. This surgical risk may be increased when the patient’s clinical conditions are unfavorable, such as in hemodynamic instability. Then, thrombolysis appears as an alternative treatment.

Prosthetic valve thrombolysis: history – In 1971, Luuaga et al11 were the first to use the thrombolytic therapy in prosthetic valve thrombosis. Streptokinase was used for treating thrombosis of the tricuspid valve prosthesis. Three years later, Baille et al12 reported the use of that thrombolytic agent in the aortic valve prosthesis. Since then, several cases of prosthetic valve thrombolysis have been reported, with varied rates of success and complication.

A review of approximately 200 reports on left-sided prosthetic valve thrombolysis4 has shown the following: an initial success rate of 82%; thromboembolic events in 12% of the cases; stroke in 5 to 10% of the cases; mortality rate of 6%; greater bleedings in 5% of the cases; and recurrence of thrombosis in 11%. Table I shows a summary of such reports.

In 2000, Gupta et al1 reported a series of 110 patients with thrombosis of the mitral (96 patients) and aortic (14 patients) prostheses undergoing thrombolysis, 108 of whom received streptokinase, and 2 received urokinase. The infusion dosage of streptokinase was a bolus of 250,000 U in 30 minutes, followed by 100,000 U/h. Doppler echocardiography was used to monitor the time of infusion of the thrombolytic agent and to assess its efficacy. The criteria for interrupting infusion were as follows: hemodynamic improvement, assessed on echocardiography; occurrence of major bleedings or hemorrhagic stroke; and infusion time of 72 hours. The clinical characteristics of these patients before thrombolysis varied greatly. Of the 110 patients, 3.6% were in functional class I (New York Heart Association), 19.1% in functional class II, 46.4% in functional class III; 24.5% in functional class IV; and 6.4% had cardiogenic shock or acute pulmonary edema. Atrial fibrillation was observed in 31.8%. The mean time of prosthesis implantation was 24 months, and the mean time of symptom onset was 14 days. Complete hemodynamic improvement was observed in 81.8% of the patients, partial improvement in 10%, and treatment failure in 8.2%. An embolic event occurred in 19.1% of the patients during treatment. The success of thrombolysis was not influenced by the age of the patients, the time of symptom onset, the time of surgery, and the type or position of the valve prosthesis. Atrial fibrillation was a predictor of embolic events.

In the literature, the experience with thrombolysis in tricuspid and pulmonary valve prostheses is smaller, but has shown that the procedure is safe and a good treatment option in patients with those conditions13,14. High rates of success and low rates of complication have been reported in thrombolysis of the mechanical prosthesis in the tricuspid position.

Prosthetic valve thrombolysis: indication - In 1998, the American consensus on valvular heart diseases was published15.
Thrombolytic Therapy in Prosthetic Valve Thrombosis

Although the consensus did not contraindicate valvular thrombolysis, the recommendations were limited, and the indications were restricted to a small number of patients. The selection of candidates for thrombolysis is frequently complicated, and significant elements to predict success or complications of the procedure lack.

In this context, more recent studies\textsuperscript{3,16,17} have aimed at a better selection of candidates for thrombolysis. Echocardiography, particularly transesophageal echocardiography, has proved to be very important for the diagnostic and therapeutic decision\textsuperscript{3,6,7,8}.

The largest study analyzing the role of echocardiography in prosthetic valve thrombolysis was recently published (2004)\textsuperscript{4}. Considering that transesophageal echocardiography is the best examination to assess metallic prosthetic valves, allowing the detection and characterization of thrombi, the objective of this study was to determine the capacity of transesophageal echocardiography to predict the safety and efficacy of prosthetic valve thrombolysis and to establish the characteristics of the thrombi that increase the risk for thrombolysis.

An international multicenter registry of patients, involving the United States and carried out from 1985 to 2001, has been analyzed. In that registry, patients with prosthetic valve thrombosis underwent thrombolysis, and all of them had undergone transesophageal echocardiography before therapy. The registry comprised 107 patients, 79 of whom had mitral impairment, 13 had aortic impairment, and 15 had tricuspid impairment.

The agents used for fibrinolysis were streptokinase (54.7%), urokinase (17%), and rt-PA (28.9%). All fibrinolytic agents were administered for a longer period of time, and streptokinase was even used for 120 hours. The rt-PA dosage was a 10-mg bolus, followed by 90 mg in 2 to 6 hours.

All patients undergoing thrombolysis were submitted to transesophageal echocardiography before the procedure. Thrombi were visualized in 86% of the cases, and, in the rest of the patients, the inclusion criterion was valvular obstruction detected on Doppler. The thrombi were strictly assessed, and their area was calculated.

Thrombolysis was successfully performed in 85% of the cases. Complications were observed in 17.8% (19) of the patients, and death in 5.6%. Of the patients with complications, 18 had mitral valve impairment, and one had aortic valve impairment. No complications were observed in patients with tricuspid valve thrombosis (tab. II).

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Clinical and echocardiographic criteria were analyzed as predictors of complication after thrombolysis. Antecedent of stroke and size of the thrombus observed on the echocardiogram were independent predictors of complication related to the procedure. For each 1-cm\textsuperscript{2} increase in the area of the thrombus, a 2.4-fold increase was observed in the rate of complications. The antecedent of stroke increased the risk of adverse events by 4.5 times.

The statistical analysis allowed the establishment of a 0.8 cm\textsuperscript{2} cutpoint for the size of the thrombus, ie, patients with a thrombus area smaller than that value had a successful thrombolysis with no important adverse effects. The presence of a thrombus area >0.8 cm\textsuperscript{2} was a predictor of complication, with sensitivity of 79% and specificity of 68%. Thrombus size <0.8 cm\textsuperscript{2} was a predictor of success, independently of the patient’s functional class. Figure 1 shows the relation between the dimensions of the thrombus and the rate of complications.

The correlation between the dimensions of the thrombus and the rate of adverse events is very important for the patient’s management. The indication for thrombolysis has always taken into consideration the patient’s functional class and the characteristics of the thrombus\textsuperscript{4,15}. However, based on the results of this study, it is evident that the most important element for the therapeutic decision is the thrombus itself, allowing a broader selection of the candidates to thrombolysis, encompassing patients in all functional classes.

**Prosthetic valve thrombolysis: the rationale** - As already stated, prosthetic valve thrombolysis can be treated clinically, with

\[ \text{Fig. 1 - Adapted from Tong et al\textsuperscript{3}, PRO-TEE Registry, J Am Coll Cardiol. 2004; 43:1.} \]
thrombolysis, or surgically, the physician in charge being respon-
sible for this decision. When the thrombosis involves the tricuspid
valve, and, more rarely, the pulmonary valve, thrombolysis is the
therapy of choice. The studies have reported low complication
rates in that group of patients11,13,14,18, independently of the clinical
findings (asymptomatic, oligosymptomatic, or fully manifested heart
failure). When thrombosis involves the left-sided valves (mitral
and aortic), some aspects should be considered to choose the best
treatment. All patients should undergo transesophageal echocardi-
ography before definitive treatment10. The characteristics of the
thrombus should be assessed. A thrombus <0.8 cm² predicts
success of the thrombolysis³. Therefore, for patients in such con-
ditions, independently of the functional class, ie, from asymptomatic
to cardiogenic shock, and independently of the time of thrombosis
installation, the thrombolytic therapy can be considered the top
choice. This consideration is not valid if the patient has the ante-
cedent of stroke or atrial fibrillation, because the risk of compli-
cations is greater. When the thrombus is >0.8 cm², surgery should
be considered the top choice, unless the clinical conditions are
unfavorable, such as cardiogenic shock, posing high surgical risk.
In such conditions, thrombolysis, although potentially complicated,
is justified. Also when cardiac surgery is not available, thrombolysis
may be an option, mainly when clinical severity is extreme, and
expectant management is not recommended.

Once thrombolysis is chosen, the greater experience with
fibrinolytic agents makes streptokinase the first choice. Its
doage should be a bolus of 250,000 U in 30 minutes, followed by
100,000 U/h. Doppler echocardiography should be used to
monitor the time of infusion of the thrombolytic agent and to
assess its efficacy. The thrombolytic agent should be interrupted
at the 24 th hour of treatment, if no hemodynamic improvement
(improvement in the gradient) occurs. It should be interrupted
after 72 hours, even if the improvement is partial, or should be
interrupted earlier, if the hemodynamic improvement is complete,
ie, the transvalvular gradient returns to baseline values admitted
as normal for mechanic prostheses. After thrombolysis, the patients
should undergo anticoagulation with warfarin so that an INR be-
 tween 3 and 4 could be reached for the aortic prosthesis, and
between 3.5 and 4.5 for the mitral prosthesis15.

References

1. Gupta D, Kothari SS, Bahl VK et al. Thrombolytic therapy for prosthetic valve
2. Klugherz BD, Herrmann HC. Mechanical prosthetic valve thrombosis: case report
risk assessment of thrombolysis of prosthetic valve thrombosis: Results of the In-
4. Lenguy M, Fuster V, Kettai M et al. Guidelines for management of left-sided pros-
30:1521-6.
5. Cannegiefer SC, Rosendaal FR, Briet E. Fibrinolysis and bleeding complica-
tions in patients with mechanical heart valve prostheses. Circulation. 1994; 89:
635-41.
importância do ecocardiograma transesofágico no diagnóstico e acompanha-
formation in obstructed mechanical prosthetic valves: an evaluation of clinical,
transthoracic and transesophageal echocardiographic parameters. J Am Coll Cardi-
8. Rinaldi CA, Heppell RM, Chambers JB. Treatment of left-sided prosthetic valve
10. Shapira Y, Vaturi M, Hasdai D, Battler A, Sagie A. The safety and efficacy of repea-
ted courses of tissue-type plasminogen activator in patients with stuck mitral
valves who did not fully respond to the initial thrombolytic course. J Thromb
11. Luluaga IT, Carrera D, D’Oliveira J et al. Successful thrombolytic therapy after acu-
13. Hurrel DG, Schaff HV, Tajik A. Thrombolytic therapy for obstruction of mechanical
14. Lopez HP, Loriga FMC, Hernandez KM et al. Thrombolytic therapy with recombi-
16. Ozkan M, Kaymaz C, Kimra C et al. Intravenous thrombolytic treatment of me-
chanical prosthetic valve thrombosis: a study using serial transesophageal echo-
17. Shapira Y, Herz I, Vaturi M et al. Thrombolysis is an effective and safe therapy in
stuck bileaflet mitral valves in the absence of high-risk thrombi. J Am Coll Cardiol.
valve prosthesis: clinical spectrum and the role of nonsurgical treatment. Am Heart