Management of prosthetic valve thrombosis

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Fibrinolysis and surgery with either valvular re-replacement or thrombectomy are both established therapies for prosthetic valve thrombosis. In both treatment strategies, the complication rate depends to a similar degree on pre-interventional clinical and haemodynamic status. Fibrinolysis serves to avoid a second operation, but the incidence of recurrent thrombosis is higher. Before deciding in favour of thrombolytic therapy, structural defects of the prosthetic valve or tissue in-growth, which increase the risk of rethrombosis, should be ruled out by transoesophageal echocardiography. Apart from those cases in which there are contraindications to either treatment, we recommend surgery in cases of underlying prosthetic valve dysfunction or recurrent thrombosis.

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Introduction

Valvular re-replacement is the traditional therapy for prosthetic valve thrombosis[1–7]. Systemic fibrinolysis, leaving the valve substitute in place, and thrombectomy have been suggested as alternative therapeutic options. In order to weigh the risks against the benefits of surgical versus thrombolytic treatment, we performed a meta-analysis of data from 23 major studies reported since 1980 in the English language literature (11 large single-centre series with eight or more patients treated with fibrinolysis, and 12 series with five or more patients treated with either valve re-replacement or thrombectomy)[1–23]. Case reports of left-sided prosthetic valve thrombosis were not included. Because published experience with thrombolysis of tricuspid prostheses comprise only case reports or studies of few patients, we extended a meta-analysis of 26 cases presented by Horstkotte and Burckhardt[24] to include nine additional cases that were reported later[3,7,10,12]. With respect to surgical treatment of tricuspid valve thrombosis, only two small series[25,26] have been reported during the past 2 decades, and therefore we did not include those data in the meta-analysis.

Although differing definitions of procedural success and complications make direct comparisons difficult, pooled data may allow an estimate of the specific risks and benefits of the treatment options currently available (Tables 1 and 2).

Univariate statistical analysis using Chi-square test was restricted to the unambiguous end-points of hospital mortality, recurrent thrombosis and crossover to valve surgery in patients undergoing fibrinolysis. P < 0.05 was considered statistically significant.

Operative treatment of prosthetic valve thrombosis

The replacement of an obstructed valve offers the advantage that structural dysfunction of the prosthesis or fibrous tissue in-growth can be reliably identified. Apart from additional patient-related factors, those two factors are the principal reasons for thrombus formation[8,9,16,19,24]. Variation in peri-operative mortality between reported series reflects differences in clinical condition at the time of surgery, priority of operation (elective versus emergent) and year of operation[6,7,16,18,19,24,27–30]. The lowest perioperative mortality (4.7%) was reported by Deviri et al.[19] for 43 patients in New York Heart Association (NYHA) functional class I–III. Average, risk-unadjusted perioperative mortality in our meta-analysis of seven studies amounts to 14% (Table 1). Fifteen of the 17 deaths (88%) reported in four of those studies, classifying patients according to the NYHA scale, occurred in patients in functional class III or IV[8,15,19,22]. The perioperative mortality of patients in a stable clinical condition might presumably be almost equivalent to that of elective prosthetic valve reoperation[19,30].

Mechanical de-clotting was introduced in 1973 by Björk and Henze to reduce the total cardiopulmonary bypass
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Hospital mortality and recurrent thrombosis rate for three different treatment strategies for left-sided prosthetic valve thrombosis. The meta-analysis is based on seven studies of valve replacement\cite{8,15,16,18–20,22}, 11 studies with thrombectomy\cite{13–23} and 11 studies with thrombolysis\cite{1–11} published since 1980. Thromboembolic complications have not been recorded systematically in operated patients. No major surgical series of patients with right-sided prosthetic valve thrombosis has been presented during the past 2 decades. Follow-up information was not available for three studies that included patients treated with valve replacement or thrombectomy.

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<tr>
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<th>Valve replacement</th>
<th>Thrombectomy</th>
<th>Thrombolysis</th>
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<tbody>
<tr>
<td>Number included</td>
<td>162</td>
<td>124</td>
<td>365</td>
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<tr>
<td>Hospital mortality (%)</td>
<td>14</td>
<td>10*</td>
<td>8†</td>
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<tr>
<td>Recurrent thrombosis (%)</td>
<td>3 (2/63)</td>
<td>8 (7/88)*</td>
<td>20‡</td>
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†Not significant, versus valve replacement. *Not significant, versus thrombectomy and valve replacement. ‡P < 0.01, versus valve replacement; ‡P < 0.05, versus thrombectomy.

Comparison between success and complication rates of thrombolytic therapy for left-sided\cite{1–11} versus tricuspid\cite{3,7,10,12,24} prosthetic valve thrombosis. The classification of partial success is included in a minority of studies. Thromboembolic complications were defined as severe if they led to permanent sequelae or operative treatment was necessary. Severe haemorrhagic complications required blood transfusion or operative treatment. *P < 0.0001, versus left heart thrombolysis; †not significant, versus left heart thrombolysis. A=aortic valve; M=mitral valve.

Fibrinolytic treatment of prosthetic valve thrombosis

Fibrinolysis was first described by Luluaga et al. in 1971\cite{32}, and a wide variety of fibrinolytic substances and dosages have been used since that time\cite{1–11}. In a summary of the results of a consensus conference, streptokinese (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) was recommended\cite{33}. In addition, recombinant tissue-type plasminogen activator (rt-PA) at a dosage of 100 mg given over a period of 2–5 h has been employed successfully\cite{3,7–10}.

Dissolution of thrombotic material should be monitored by conventional and Doppler echocardiography, with determination of transprosthetic pressure gradient (every 3–6 h) as well as transoesophageal echocardiography performed once daily as long as thrombotic material remains visible\cite{33}. Thrombolysis is stopped when the transprosthetic gradient has more or less normalized and the
thrombotic material has completely dissolved. If there is no improvement within 24 h, fibrinolysis should be stopped and surgery performed 24 h later or after 2 h if the fibrinolytic therapy has been neutralized by protease inhibitors[1,2,5,33]. At any rate, fibrinolysis must be discontinued after 72 h, even if it has not been entirely successful[5,33,34].

Pre-treatment with oral anticoagulants should be stopped before thrombolytic agents are administered. Fibrinolytic activity should be monitored every 6 h by determining the fibrinogen concentration and fibrinogen breakdown products[24]. After successful thrombolysis, heparin infusion is started and activated partial thromboplastin time is maintained at twofold baseline values, followed by conversion to oral anticoagulation combined with aspirin (100 mg·day−1)[33,34]. International Normalized Ratio is adjusted to 3–4 for aortic and 3.5–4.5 for mitral prostheses[34]. If thrombolysis does not completely dissolve the clot and the patient remains stable, subcutaneous heparin may be combined with oral anticoagulation for about 3 months (International Normalized ratio 2.5–3.5)[33,34].

Fibrinolysis has gained general acceptance for treatment of patients with right-sided prosthetic valve thrombosis and critically ill patients with left-sided prosthetic valve thrombosis, who are assumed to carry high operative risk[9,12,33,34]. Use of thrombolysis in NYHA class I or II patients is still controversial because of the danger of embolic complications[3,9,33,35,36]. In our meta-analysis of 11 studies including 365 patients with left-sided prosthetic valve thrombosis, 5% of the patients suffered severe embolic complications and the overall hospital mortality of 8% was comparable to that after surgery (Table 2). Similar to the surgical series, 28 out of 31 deaths (90%) and 7 out of 10 major embolic events recorded in 10 studies (70%; one study could not be analyzed because of sparse clinical data) occurred in patients in NYHA class III or IV. Therefore, fibrinolysis in NYHA class I or II patients appears to be a safe, but not superior therapeutic option in comparison with operative treatment. For the subgroup of patients with non-obstructive valve thrombosis, Lengyel et al.[33,34] suggested intravenous heparin infusion for 48 h as an alternative, followed by a combination of subcutaneous heparin and oral anticoagulants for up to 3 months on an outpatient basis. Overall success rates are inferior to those with conventional thrombolysis, however[35].

Overall, fibrinolysis resulted in complete clinical and haemodynamic recovery in approximately 76% of patients with left-sided and 71% of those with tricuspid prosthetic valve thrombosis (Table 2). Success rates were slightly higher in aortic than in mitral valve prostheses, probably because of the greater degree of thrombotic burden necessary to cause significant obstruction in mitral valve prostheses[36] and an increased predisposition to thrombosis in low pressure sections of the circulation[12,24]. Partial success was achieved in approximately 10% of the patients, and was usually followed by either conservative or operative treatment. Non-responders mostly underwent immediate surgery.
Complications of fibrinolytic treatment

Minor bleeding complications may be treated with local haemostatic measures. In cases of major bleedings, fibrinolytic activity can be reversed by the infusion of fresh frozen plasma or the injection of prothrombin complex concentrates or protease inhibitors [33]. If peripheral embolic events occur, continuation of thrombolysis is recommended. Embolectomy is necessary if clinical manifestations are not entirely reversible. If clinical signs of transitory ischaemic attack or stroke develop, thrombolytic therapy should be discontinued immediately and a computed tomography or magnetic resonance imaging scan performed to exclude intracranial haemorrhage.

In recent years, several studies have examined the role of fibrinolysis during the early stages of an ischaemic stroke. A beneficial effect of streptokinase has yet to be demonstrated, and clinical trials with rt-PA have produced inconsistent results [39,40]. Specific indicators for thrombolytic therapy in acute ischaemic stroke remain to be defined, and at present discontinuation of thrombolytic therapy is strongly recommended. Heparin therapy can be administered (activated partial thromboplastin time no more than 1.5–2 times the control value) and operation performed within 72 h after onset of symptoms, if haemorrhagic transformation has been excluded in a second computed tomography or magnetic resonance imaging scan immediately before surgery [33,41].

Contraindications to fibrinolytic treatment

Thrombolytic therapy for prosthetic valve thrombosis has the same contraindications as fibrinolysis for other indications. Early (<2 weeks) after valve replacement, reoperation or heparin therapy in stable patients with non-obstructive mechanical valve thrombosis is preferable. Because large atrial thrombi increase the risk for major embolic events and significantly decrease the overall success rate, they must be excluded by transoesophageal echocardiography before commencing with thrombolysis [33,34]. Pregnancy is considered a relative contraindication [33].

Conclusion

Thrombolysis and reoperation (valvular re-replacement or de-clotting) are widely accepted options for treatment of prosthetic valvular thrombosis. Immediate success rate, major adverse events and peri-procedural mortality are comparable. In haemodynamically unstable patients, the risk for major complications increases to the same extent for both procedures. Reoperation constitutes a more definitive treatment, with complete and thorough removal of thrombotic material. It also allows close inspection of the thrombosed valve, which enables identification of the valve-related factors that may predispose to recurrent thrombosis. Thrombolysis serves to avoid a second operation, although this may still be necessary if thrombolysis fails. Until randomized clinical trials are performed, there is no evidence that either of the two treatment options offers any substantial advantage over the other. It is therefore advisable to tailor therapy according to the preferences of the individual patient and the experience of the managing physicians. Thrombolysis is certainly more cost-effective than reoperation; this is an important consideration in developing countries, where a substantial number of patients cannot afford a second operation [7,11]. Treatment with intravenous heparin for 48 h, followed by a combination of subcutaneous heparin and oral anticoagulation on an outpatient basis, should be restricted to patients with non-obstructive thrombosis and a stable clinical condition (NYHA class I or II). Close clinical surveillance is mandatory.

Therapeutic decision making must take into account the circumstances specific to the individual patient (Table 3).
References


