

Prosthetic Valve Obstruction - Surgery is the Preferred Option

Ganesan Karthikeyan, MD, DM, MSc, *New Delhi, India*

Left-sided prosthetic valve thrombosis (PVT) is commonly encountered in our country. Although there are no prospective studies from which a reliable assessment of its incidence can be made, there is evidence to suggest that it occurs much more frequently here than in developed countries. A retrospective study found that over 6% of patients developed valve thrombosis over a 6-month period (1). Likewise, estimates derived from a trial of treatment of PVT also suggested an annual rate of 10% (2).

The treatment of choice for left-sided PVT in our country is the administration of fibrinolytic agents, mainly streptokinase (3–6). Fibrinolytic therapy (FT) for PVT is associated with a high risk of major bleeding and embolic complications (2,7), but continues to be used for all patients, perhaps because it is presumed to be cheaper than urgent surgery. In this article I will discuss the reasons behind the continued, extensive use of FT for PVT and the arguments in favor of considering urgent surgery for most patients.

Efficacy of Fibrinolytic Therapy for Left-sided PVT is Overestimated

One of the most important reasons why physicians continue to advocate FT for PVT is because of the impression that it is very effective. Several guideline

committees and investigators have consequently recommended that it should be the first-line therapy for all patients with PVT (8,9). The assumption of high efficacy of FT is beset by two major problems with the data on which it is based.

Small-study effect

First, most of the data that has gone into derivation of the estimates of efficacy are from case reports and very small case series (8). The influential review by Lenyel and colleagues estimated that the success of FT for the treatment of PVT was over 80%. They did not perform a systematic review, but included “at least 200” reports of PVT treated with FT. The largest study in this review included only 68 patients and the five largest studies included a mere 179 patients. The vast majority of studies included less than 8 patients each (8). Estimates of efficacy derived from case reports and small case series are likely overestimates because of positive reporting and publication biases; unsuccessful FT and complications occurring due to FT are less likely to be reported and published. A more recent systematic review attempted to reduce this bias by excluding studies with less than three patients (7). The estimate of efficacy in this review dropped to about 75%.

Retrospective data collection and poor outcome definition

The second problem with the literature on the efficacy of FT is that the vast majority of studies involved retrospective data collection. Consequently, most of these studies neither prespecified nor applied standard outcome definitions. Application of different definitions of success will, for instance, result in differing estimates of a successful outcome with FT. This is illustrated by the fact that estimates of “clinical success” (i.e., successful valve opening without major complications)

From: Department of Cardiology, Cardiothoracic Sciences Centre, All India Institute of Medical Sciences, New Delhi, India (G.K.)

Corresponding Author: Dr. G. Karthikeyan, MD, DM, MSc
Additional Professor of Cardiology
Cardiothoracic Sciences Centre
All India Institute of Medical Sciences
Ansari Nagar, New Delhi - 110029, INDIA.
Ph: +91-011-26593322; Fax: +91-011-26488641
Email: karthik2010@gmail.com

are consistently about 7–10% less than estimates of “hemodynamic success” (i.e., successful valve opening irrespective of the occurrence of major complications). A large retrospective study found that FT resulted in hemodynamic success in about 82% of patients, while the clinical success rate was only about 73% (3). Similarly in another series, the success rate fell from 68% to about 61% when a clinical definition of success was applied (6). More recently, we showed in the largest prospective series using prespecified, standardized definitions that clinical success rates with FT were only about 60% (2).

Surgery for Left-sided PVT Is Safer and More Efficacious

Efficacy of urgent surgery compared to FT

Two large studies have reported the experience with urgent surgery for the treatment of left-sided PVT (10,11). These two studies included a total of 502 episodes of PVT, 349 of which were treated with surgery. Urgent surgery was successful in restoring valve function in 88% of episodes compared to 68% with FT. The odds of successful restoration of valve function was four times higher with surgery when compared to FT (random effects OR 4.32, 95% CI 2.54–7.35, $p < 0.0001$, $I^2 = 0\%$).

Safety of urgent surgery compared to FT

Risk of mortality with surgery is a significant deterrent to the referral of patients with PVT for urgent surgery. Of the patients who underwent surgery 11.7% died (10,11). The high mortality rate should be seen in light of the fact that most of the mortality appeared to be confined to patients presenting in NYHA class IV (10 of 14 deaths in the study by Roudaut and colleagues) (11). Moreover, patients presenting in poor functional class have poor outcomes irrespective of the treatment they receive. The mortality for patients who received FT in these two studies was similar at 9.8%. We have also shown recently that nearly a quarter of the patients in NYHA class III or IV have a major adverse event (death, major bleeding or systemic embolism) with FT (2).

All other complications associated with the treatment of PVT occur much more often with FT than with urgent surgery. The rate of thromboembolism and stroke is estimated to be about 12–14% with FT (7,8), while it was very rare with surgery (3/349) (10,11). Similarly,

major bleeding occurs about 5% of the time with FT, while it rarely occurs with surgery (1/136) (11). Finally, recurrent PVT occurs in up to 18% of patients receiving FT (7,8) and may be less frequently seen after urgent surgery (approximately 10%) (10, 11). Recurrent PVT is associated with poorer outcomes with treatment than a first episode of PVT (6).

Some clinicians believe that complications due to FT may be minimized by administering the fibrinolytic agent over a shorter period of time (either at a high-dose or as part of an accelerated regimen). We did not find any support for this belief in a randomized trial involving 120 patients (2). Moreover, complications due to FT were unpredictable and tended to occur early (within 12 hours) rather than late after initiating FT (12).

Why Surgery Should be the Preferred Treatment for Left-sided PVT

The available data suggests that urgent surgery may be more efficacious and may be associated with fewer complications compared to FT. If 100 patients with PVT were treated with surgery rather than FT, about 20 *more* patients are likely to have a successful outcome and practically all the 10 or so major complications of treatment which would occur with FT are likely to be avoided. There are, however, two caveats to this interpretation of the available data. First, all the data comparing surgery with FT is observational and is likely to be subject to several biases and the estimate of relative efficacy can at best serve as a rough guide. Second, surgery consumes more resources than administering FT. But when seen in the context of the superior outcomes and the major adverse events avoided, it may ultimately provide better value for money (e.g., lower cost per adverse event avoided). This trade-off is similar to the one we make when treating acute ST elevation myocardial infarction with primary angioplasty rather than with FT. Nevertheless, there is a need to generate data from adequately powered randomized trials to estimate more precisely the benefits and costs of a strategy of treating patients with urgent surgery rather than FT. We are undertaking one such study (clinicaltrials.gov registration number NCT01641549), which will hopefully provide some definitive answers to these questions. In the meantime, I believe that patients with left-sided PVT should preferably undergo surgery.

References

1. Talwar S, Kapoor CK, Velayoudam D, Kumar AS. Anticoagulation protocol and early prosthetic valve thrombosis. *Indian Heart J.* 2004; 56:225–8.
2. Karthikeyan G, Math RS, Mathew N, Shankar B, Kalaivani M, Singh S, Bahl VK, Hirsh J, Eikelboom JW. Accelerated infusion of streptokinase for the treatment of left-sided prosthetic valve thrombosis: a randomized controlled trial. *Circulation.* 2009; 120:1108–14.
3. Gupta D, Kothari SS, Bahl VK, Goswami KC, Talwar KK, Manchanda SC, Venugopal P. Thrombolytic therapy for prosthetic valve thrombosis: short- and long-term results. *Am Heart J.* 2000; 140:906–16.
4. Rajasekhar D, Balakrishnan KG, Venkitachalam CG, Tharakan JA, Titus T, Pillai VR, Kumar VK, Bhat A. Thrombolytic therapy for prosthetic cardiac valve thrombosis. *Indian Heart J.* 1994; 46:101–5.
5. Reddy NK, Padmanabhan TN, Singh S, Kumar DN, Raju PR, Satyanarayana PV, Rao DP, Rajagopal P, Raju BS. Thrombolysis in left-sided prosthetic valve occlusion: immediate and follow-up results. *Ann Thorac Surg.* 1994; 58:462–70; discussion 70-1.
6. Balasundaram RP, Karthikeyan G, Kothari SS, Talwar KK, Venugopal P. Fibrinolytic treatment for recurrent left sided prosthetic valve thrombosis. *Heart.* 2005; 91:821–2.
7. Reyes-Cerezo E, Jerjes-Sanchez C, Archondo-Arce T, García-Sosa A, Garza-Ruiz A, Ramírez-Rivera A, Ibarra-Pérez C. Fibrinolytic therapy in left side-prosthetic valve acute thrombosis. In depth systematic review. *Arch Cardiol Mex.* 2008; 78:309–17.
8. Lengyel M, Fuster V, Keltai M, Roudaut R, Schulte HD, Seward JB, Chesebro JH, Turpie AG. Guidelines for management of left-sided prosthetic valve thrombosis: a role for thrombolytic therapy. Consensus Conference on Prosthetic Valve Thrombosis. *J Am Coll Cardiol.* 1997; 30:1521–6.
9. Lengyel M, Horstkotte D, Voller H, Mistiaen WP. Recommendations for the management of prosthetic valve thrombosis. *J Heart Valve Dis.* 2005; 14:567–75.
10. Renzulli A, Onorati F, De Feo M, Vitale N, Esposito S, Agozzino L, Santarpino G, Mastroberto P, Marchese AR, De Luca L, Scardone M, Cotrufo M. Mechanical valve thrombosis: a tailored approach for a multiplex disease. *J Heart Valve Dis.* 2004; 13 (Suppl 1):S37–42.
11. Roudaut R, Lafitte S, Roudaut MF, Reant P, Pillois X, Durrieu-Jaïs C, Coste P, Deville C, Roques X. Management of prosthetic heart valve obstruction: fibrinolysis versus surgery. Early results and long-term follow-up in a single-centre study of 263 cases. *Arch Cardiovasc Dis.* 2009; 102:269–77.
12. Karthikeyan G, Mathew N, Math RS, Devasenapathy N, Kothari SS, Bahl VK. Timing of adverse events during fibrinolytic therapy with streptokinase for left-sided prosthetic valve thrombosis. *J Thromb Thrombolysis.* 2011; 32:146–9.