Thrombolytic therapy for prosthetic valve thrombosis in children: Two case reports and review of the literature

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Thrombotic occlusion of a mechanical valve prosthesis can be life threatening and requires urgent evaluation and treatment. Traditionally, the treatment for mechanical valve thrombosis has been urgent reoperation with attempted declotting of the valve or valve rereplacement. Unfortunately, this is associated with a high mortality, and efforts have been made to pursue nonoperative treatment with thrombolytics. There are many reports of the successful use of thrombolytics in adults, but very little data are reported in the pediatric population. We review the literature, report 2 cases of successful treatment of mechanical mitral valve thrombotic occlusion with thrombolytic therapy in children, and summarize the major reports of thrombolytic use for prosthetic valve occlusion in the pediatric population.

Clinical Summary

PATIENT 1. The patient was born with a complete atrioventricular canal and coarctation in June 1999. Shortly after birth, she underwent coarctation repair along with palliative pulmonary artery banding. She subsequently had a definitive repair of her atrioventricular canal. This was complicated by mitral regurgitation and heart block requiring pacemaker insertion. Her mitral regurgitation progressively worsened, and she required mitral valve replacement in 2002 with a 17-mm St Jude Medical (St Jude Medical, Inc, St Paul, Minn) mechanical prosthesis. At this time, her family moved to Atlanta, and she was referred to Egleston Hospital, Children's Healthcare of Atlanta, for further care. In January 2003, a routine echocardiogram and subsequent cardiac catheterization revealed mitral valve stenosis with a mean gradient of 11 mm Hg across the valve, increased pulmonary artery pressures, and calcification with posterior leaflet fixation of her mechanical prosthesis. She was taken to the operating room for rereplacement of her mitral valve with a 21-mm St Jude Medical mechanical prosthesis. Over the next 3 months, she required multiple operative interventions for pacemaker revisions-replacements, with each requiring interruption of her anticoagulant regimen. During one of her admissions in March, an echocardiogram revealed a worsening gradient of 10

mm Hg across the mitral valve compared with that seen in previous studies. Valve fluoroscopy demonstrated an anterior leaflet with one half the normal motion and a fixed posterior leaflet. She was started on tissue plasminogen activator (TPA) infusion at $0.1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, and this was gradually increased to $0.4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ over 24 hours. Repeat valve fluoroscopy was unchanged at 24 hours but showed normal function, with full leaflet excursion at 36 hours. At this point, her TPA infusion was discontinued. She was started on a heparin drip and warfarin sodium (Coumadin). Her heparin was discontinued when her warfarin level was therapeutic. She was discharged from the hospital without a repeat operation for valve thrombosis. Echocardiography in May confirmed normal valve function without a significant gradient.

PATIENT 2. The patient was born with an unbalanced atrioventricular canal, multilevel pulmonary stenosis, and a borderline but adequate mitral valve annulus in June 2002. In March 2003, she underwent a 2-ventricle repair of her atrioventricular canal with pulmonary valve commissurotomy and pulmonary artery patch angioplasty. Her initial postoperative course was unremarkable, but she returned in May with increased work of breathing and lethargy. An echocardiogram at that time revealed an increased mitral valve velocity with a peak gradient of 29 mm Hg and a mean gradient of 17 mm Hg across the valve. She was taken back to the operating room, where she underwent mitral valve replacement with a 17-mm St Jude Medical mechanical prosthesis. Several days after the operation, her postoperative course was complicated by bleeding after removal of a right atrial intracardiac line. Control of the bleeding required interruption of her anticoagulant regimen, exploration, and suture closure of the right atrium. Despite restarting her anticoagulation after this episode, a routine echocardiogram a week later revealed moderate prosthetic mitral valve stenosis. Only one leaflet was moving, and the gradient across the valve had increased from that seen on the immediate postoperative echocardiogram. Valve fluoroscopy confirmed poor anterior leaflet mobility and an immobile posterior leaflet. She was given a streptokinase bolus of 2000 U/kg and started on a streptokinase infusion of $2000 \text{ U} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, but the results of repeat valve fluoroscopy 24 hours later was unchanged. Her streptokinase was discontinued, and she was started on a TPA infusion at $0.05 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, which was gradually increased to $0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ over 24 hours. Valve fluoroscopy 24 hours later showed no resolution. She was subsequently transported to the operating room for mitral valve thrombectomy-rereplacement; however, her preoperative transesophageal echocardiogram demonstrated normal valve function with a normal gradient across the valve. Both leaflets were freely mobile and without evidence of thrombus. She was returned to the cardiac intensive care unit, where her TPA was discontinued. She was started on a heparin drip and warfarin. Her heparin was discontinued when her warfarin level was therapeutic. She was discharged from the hospital without a repeat operation

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for valve thrombosis, and an echocardiogram 1 month later confirmed normal valve function without significant gradient.

Discussion

Because the options for mitral valve replacement are limited in young children, valve repair is indicated if at all possible. With mild or moderate symptoms, surgical intervention is delayed so that if valve replacement is required, an adult-sized prosthesis can be used.¹ Because bioprosthetic valves degenerate rapidly in infants and children, mechanical prostheses are typically used for these patients so long as there are no contraindications to anticoagulation.

Unfortunately, there are many complications associated with mechanical valve replacement. These include thromboembolism, acute thrombotic occlusion, complications of long-term anticoagulation, prosthetic valve endocarditis, periprosthetic leakage, chronic hemolysis, and reoperation. The incidence of acute thrombotic occlusion of a mechanical replacement device is 0.03% to 8% per patient-year.²⁻⁵ This complication occurs primarily in patients with suboptimal anticoagulant therapy, which usually results when therapy is stopped or interrupted for a surgical procedure. The only other risk factor that has been identified is female sex.¹

The presentation of these patients ranges from asymptomatic thrombotic occlusion detected by means of routine echocardiography to cardiogenic shock. The most common symptoms include those of pulmonary venous hypertension: dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. Other signs and symptoms include a decrease in the intensity of the prosthetic heart valve sounds, systemic thromboembolism, or the signs and symptoms of congestive heart failure. Cardiac examination reveals a prominent apical middiastolic murmur of mitral stenosis. Electrocardiography shows a tracing consistent with left atrial hypertrophy, and chest radiography shows left atrial enlargement.

Confirmation is usually achieved with a fluoroscopic valve examination or echocardiography. These modalities play complementary roles, with fluoroscopy providing information solely about restriction of leaflet motion and echocardiography providing hemodynamic information about pressure gradients and valve areas.⁴ Cardiac catheterization is rarely indicated for confirmation of the diagnosis.¹

Thrombosis of a prosthetic valve can be a catastrophic event. Traditional therapy for this condition is emergency thrombectomy, with valve rereplacement as needed. When patients are taken to the operating room, valve thrombectomy is attempted first. However, there are times when thrombectomy is not feasible and valve rereplacement is required. Most commonly, this results from organization and fibrosis of the thrombotic material or when the thrombus is located on the ventricular side of the valve and cannot be extracted without removing the prosthesis. Risks of operation include all of the risks of an initial valve operation, along with the risk of reoperation. Reoperation mortality is dependent on age, function of the heart, whether the procedure is performed on an elective or emergency basis, and whether the prosthesis is infected. Reoperation for a failed valve has a mortality of 5% to 20%,^{4,6,7} with mortality statistics becoming increasingly worse with each subsequent reoperation.

Several factors have prompted the nonoperative treatment of valve thrombosis with thrombolytic therapy. First, the morbidity and mortality of valve reoperation is significant. Second, the risk of acute thrombotic occlusion is not linear. The likelihood of acute thrombotic occlusion has a peak early after the operation and then decreases to a low level several years after the operation. Finally, the majority of patients do not have a problem intrinsic to the prosthetic valve, but the complication has developed from inadequate anticoagulation. Thrombolysis provides an opportunity to treat the valve thrombosis, avoid surgical intervention and save the prosthetic valve, and achieve a good long-term result.

Recently, thrombolytic agents, such as TPA, streptokinase, and urokinase, have allowed nonoperative treatment of some prosthetic valve thromboses. Patient selection is a crucial factor in successful nonoperative treatment. Patients with organized fibrosis are less likely to achieve success with thrombolytic therapy and benefit from primary surgical intervention. Also, thrombolytics should only be used in patients without signs of cardiogenic shock. Patients with contraindications to thrombolytic therapy or those in low-output states should undergo emergency operations.

Results, primarily from adult series, appear to be very promising.³⁻¹⁰ The general efficacy is approximately 70% to 75%. There is increased efficacy of thrombolytics for occlusion of prosthetic valves in the aortic position compared with in the mitral position. Most studies used single-agent regimens, and there was no difference in efficacy between TPA and streptokinase. Some studies showed even higher success rates with combined agents in those patients in whom single-agent therapy failed. There was no difference in the efficacy according to valve type or for episodes of recurrent thrombosis. Complications occurred in approximately 25% of patients. These included major bleeding episodes, systemic thromboembolism, failure resulting in reoperation, or death. Mortality was 0% to 10%.

Thrombolytic therapy is also emerging as a suitable alternative to reoperation in children with prosthetic valve occlusion. There are only limited data in the pediatric population because of the infrequent nature of this problem. Table 1^{6,7,11-16} summarizes the major reports of thrombolytic use for prosthetic valve occlusion in the pediatric population. The combination of our 2 patients with those from 9 other studies total 26 patients less than 18 years of age. These patients had a total of 32 occurrences of prosthetic valve thrombosis, of which 31 were treated with thrombolytics. The overall success rate of thrombolytic treatment for valve thrombosis was 87% (27/31).

The state of anticoagulation was known at the time of valve thrombosis in 24 occurrences. Of these, 75% (18/24) of occurrences involved either interruption of the anticoagulation regimen for surgical intervention, cessation of the regimen because of noncompliance, or inadequate levels of anticoagulation. According to valve type, 20 occurrences involved a St Jude Medical valve with a success rate of 80% (16/20), 8 occurrences involved a Carbomedics (Sulzer Carbomedics, Inc, Austin, Tex) valve with a success rate of 75% (6/8), and 3 occurrences involved other valves or were unknown. According to thrombolytic regimen, 17 occurrences were treated with TPA only with a success rate of 88% (15/17), 10 occurrences were treated with streptokinase only with a success rate of 90% (9/10), and 4 occurrences were treated with another agent or a combined regimen. Interestingly, our patient

TABLE 1. Summary of major reports of thrombolytics in prosthetic valve occlusion in children less than 18 years of age

Study (no. of patients <18 y)	Age	No. of occurrences	Therapeutic anticoagulation (warfarin)	Valve position- type	Thrombolytic agent	Outcome (success, failure, rethrombosis, operation, death)
Bolz and associates, 2000 ¹¹ (1)	17 y	1	No	Tr-SJM	TPA	Success
(Current report, 2003) (2)	3 y	1	No	Mi-SJM	TPA	Success
	1 y	1	No	Mi-SJM	SK/TPA	Success
Fyfe and associates, 1991 ¹² (2)	8 y	2	No	Tr-SJM	SK	Success with subsequent rethrombosis; subsequent valve replacement without attempted rethrombolysis
			Yes			
Joyce and associates, 1983 ¹³ (1)	11 y	1	No	Pu-SJM	SK	Success
	16 mo	1	No	Tr-SJM	UK	Success
Koska and associates, 1992 ¹⁴ (1)	22 mo	1	Yes	Tr-SJM	TPA	Success
Kothari and Wasim, 1993 ¹⁵ (1)	5 y	1	Yes	Ao-Björk-Shiley	SK	Success
Munclinger and associates, 1998 ⁶ (5)	13 y	1	No	Mi-SJM	TPA	Success
	16 y	1	Yes	Mi-SJM	TPA	Success
	11 y	1	No	Ao, Mi-SJM	TPA	Success, death several weeks later with nontherapeutic anticoagulation
	16 y	2	Yes	Mi-SJM	TPA	Success with subsequent rethrombosis
			Yes		TPA	Repeat success with rethrombolysis
Reddy and associates, 1994 ⁷ (8)	13 y	1	No	Mi-SJM	TPA	Failure leading to valve replacement
	15 y	1	No	Mi-Carbomedics	SK	Success
	17 y	1	No	Mi-Carbomedics	SK/UK	Failure in patient who arrived moribund in cardiogenic shock
	17 y	1	No	Mi-Carbomedics	SK	Success complicated by retroperitoneal bleed
	13 y	1	No	Mi-Carbomedics	SK	Success
	16 y	2	No	Mi-Carbomedics	SK	Success with subsequent rethrombosis
			No		SK	Repeat success with rethrombolysis
	15 y	1	No	Mi-Carbomedics	SK	Failure in patient who arrived moribund in cardiogenic shock
Ries and associates, 1994 ¹⁶ (2)	14 y	1	No	Mi-Carbomedics	SK	Success
	18 y	1	No	Mi-SJM	UK	Success
	3 y	1		Mi	TPA	Success
Serpi and associates, 2001 ¹⁷ (3)	12 y	1		Tr	TPA	Success
	4 mo	1		A-V-SJM	TPA	Success
	10 mo	4		A-V-SJM	TPA	Success with subsequent rethrombolysis
					TPA	Repeat success with rethrombolysis
					TPA	Repeat success with rethrombolysis
					TPA	Failure leading to valve replacement
	18 mo	1		A-V-SJM	TPA	Success

Tr, Tricuspid; TPA, tissue plasminogen activator; SJM, St Jude Medical; Mi, mitral; SK, streptokinase; Pu, pulmonary; Ao, aortic; A-V atrioventricular; UK, urokinase.

was converted from streptokinase to TPA after 24 hours, and subsequently her thrombosis resolved. Overall, there did not appear to be a difference in the results according to the valve type or thrombolytic regimen. The complications of thrombolytic therapy in this population included failure to alleviate the obstruction, initial success with subsequent rethrombosis, hemorrhage, need for reoperation, and death. There were only 4 (13%) occurrences of valve thrombosis in which thrombolytic therapy failed. There were 3 failures at the initial occurrence, resulting in 2 deaths and 1 reoperation, and 1 failure at a subsequent occurrence, after which the patient underwent reoperation. There were 6 episodes of initial successful thrombolysis, followed by subsequent rethrombosis. One patient was taken to the operating room for valve rereplacement without a repeat attempt at thrombolysis. Of the 5 patients who were treated with repeat thrombolytics, the success rate was 80% (4/5), with the patient in whom there was a failure also proceeding to the operating room. There were no embolic complications reported and only one hemorrhagic complication consisting of a retroperitoneal bleed. Of the total number of attempts at thrombolytic therapy, only 10% (3/31) resulted in death. One death occurred several weeks after successful thrombolysis in a patient found to be inadequately anticoagulated. It was not known whether the death was due to rethrombosis of the valve. The other 2 deaths occurred in patients who arrived to the hospital moribund in cardiogenic shock, where thrombolytics were used as a last effort as salvage therapy.

Although it seems quite promising, the literature is difficult to interpret. Overall, there are relatively few patients with prosthetic valve thrombosis. Some of these patients are taken directly to the operating room without attempted thrombolysis because of contraindications to thrombolytic therapy, refusal of thrombolytic therapy, or physician preference. On the other hand, some of these patients might be deemed too sick for surgical intervention and are offered thrombolytic therapy as a last-resort treatment option. Also, unsuccessful attempts at thrombolysis followed by an operation are not necessarily reported.

Conclusion

The results of thrombolytic therapy for prosthetic valve thrombosis are encouraging. Given the significant risks associated with emergency valve thrombectomy-rereplacement, fibrinolytic therapy might prove to be a safer alternative for this difficult problem in the pediatric population.

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