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CASE REPORT

# Successful intra-arterial thrombolytic therapy for a right middle cerebral artery stroke in a 2-year-old supported by a ventricular assist device

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**Conflicts of Interest**
The authors have declared no conflict of interest.

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## Summary

Embolic stroke is a common complication in patients on ventricular assist devices in both adults and children. The reported incidence of strokes in children supported by VAD's varies from 7 to 38%. The rapid increase in recent years in the availability of both adult and pediatric VADs will likely add to the overall prevalence of strokes in patients being bridged to heart transplant. Strokes in this population can be lethal as they frequently necessitate withdrawal of the extracorporeal device support and withdrawal from the organ transplant waiting list. We present a case of a fully anti-coagulated 29-month-old supported on a Berlin EXCOR LVAD (Berlin, Germany) with embolic stroke which was treated successfully with direct thrombolysis with recombinant tissue plasminogen activator. This is the first report which uses intra-arterial thrombolytics while on a ventricular assist device in a pediatric patient.

## Case report

A 29-month-old girl was admitted with a 2-week history of cough followed by complaints of abdominal pain, vomiting, anorexia and easy fatigability. On examination, she was noted to be tachypneic and have hepatomegaly. Chest X-ray revealed cardiomegaly and echocardiogram showed dilated left ventricle with severely reduced function and significant mitral valve regurgitation. She was transferred to our institution with an initial diagnosis of acute myocarditis, which was confirmed subsequently on cardiac biopsy and was attributed to be because of parvovirus infection. Initial medical management, which included diuresis and afterload reduction failed to improve her symptoms, and 38 days postadmission a decision to place a Berlin EXCOR LVAD (25 ml pump, 9 mm apical cannula, and 5 mm aortic cannula) was made. Postoperative transesophogeal echocardiogram demonstrated decompression of the left ventricle and no evidence of intracardiac thrombus.

Post-LVAD placement, the patient did well and was successfully extubated, advanced to full enteral diet and an aggressive rehabilitation program was initiated. Anticoagulation management of the LVAD was accomplished with twice daily enoxaparin (anti-factor Xa level was 1 on the day of stroke with levels maintained 0.6–1.1 during the previous 2 weeks), two-times-per-day aspirin and four-times-per-day dipyridamole (100% inhibition of

arachidonic acid (AA) receptors and ADP net-G of 7 on the day of the stroke by thromboelastography-based platelet mapping and 61–100% AA inhibition and net-G of 0–7.5 during the previous 2 weeks).

On LVAD day 95, the patient developed acute mental status changes, anisocoria and left sided hemiplegia. A fibrin deposit that had been stable over the last 17 days along the outflow limb of the LVAD was no longer present. A computed tomogram with angiogram performed within 75 min after the onset of symptoms revealed thromboembolic occlusion of the right internal carotid artery (ICA) which extended from the supraclinoid portion to the M1 portion of the middle cerebral artery (MCA). This arterial occlusion was associated with right cerebral hemisphere hypoperfusion and focal areas of attenuation in the right putamen compatible with an acute infarct (Fig. 1). After multi-disciplinary discussion, a decision for direct intra-arterial thrombolytic therapy and possible revascularization was made.

In the interventional radiology laboratory, angiograms were obtained and confirmed the imaging findings and revealed an extensive thrombus in the cavernous portion of the right ICA, and nonfilling of the right anterior and MCA. A 0.018-inch guidewire and coaxial microcatheter was advanced through the right ICA thrombus and 1.3 mg of alteplase (0.1 mg/kg) was applied directly to the thrombus under angiographic guidance 216 min following recognition of the stroke (Fig. 2). Postintervention angiogram through the left ICA (Fig. 3) showed improved flow to the right MCA, via the anterior communicating artery and no extravasation of contrast from the arteries. A filling defect in the right ICA artery remained at the end of the procedure. The patient returned to the cardiovascular intensive care unit where she was started on a continuous infusion of 0.1 mg/kg of recombinant tissue plasminogen activator administered over the next 24 h. Mechanical ventricular assist device support and anti-coagulation regimen consisting of dypyridamole, aspirin, and unfractionated heparin was continued. She required a change of her left ventricular assist device 3 days after the stroke for formation of a large clot within the chamber. Unfractionated heparin was later transitioned to low molecular weight heparin until her orthotopic heart transplantation 46 days later.

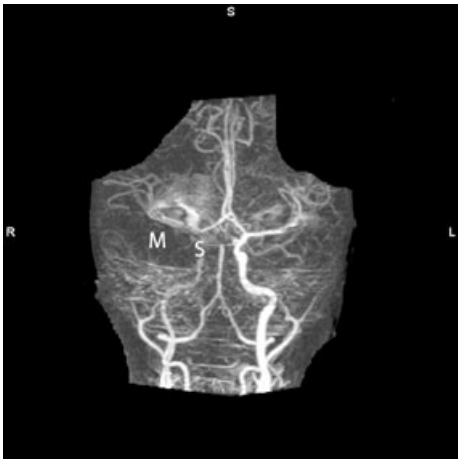


**Figure 1** Three-dimensional reconstruction of computed tomogram angiogram of the head 75 min after clinical change noted. Decreased flow in the right internal carotid artery from the cavernous portion (C). Filling defect is depicted from the supraclinoid portion of the right internal carotid artery (S) with extension of thrombus into the M1 portion of the right middle cerebral artery (M).

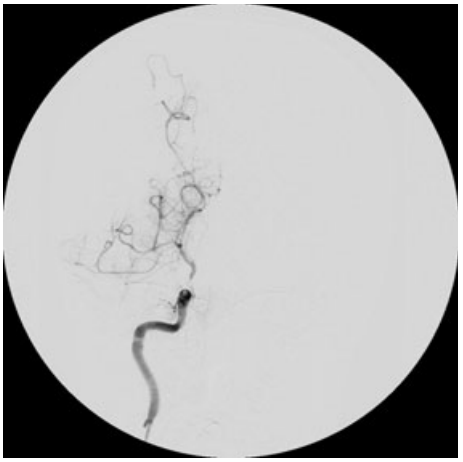

**Figure 2** Selective angiogram of the right internal carotid artery demonstrates near complete occlusion of the vessel and no flow into the right middle cerebral artery distal to the occlusion.

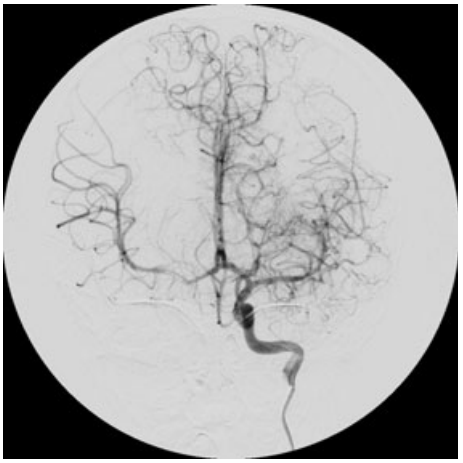

**Figure 3** Selective angiogram into the left internal carotid artery demonstrates unobstructed flow of contrast material into the right middle cerebral artery via the anterior communicating artery.

On follow-up 12 months after intervention, she remains with a modified Rankin score of 1 with mild left hemiparesis and ambulates with the assistance of braces as she continues to receive physical, occupational, and speech therapies. At present, she has tolerated her transplanted heart.

## Discussion

We report the first use of intra-arterial alteplase in a pediatric patient being supported with a ventricular assist device. There is only one report of an adult patient with a LVAD having received intra-arterial alteplase [1]. Patients supported on VAD's are at an increased risk of thromboembolic events because of complex interaction between the non-biologic surfaces and blood which activates the coagulation cascade [2–5]. Despite systemic anticoagulation with a combination of vitamin K antagonists, unfractionated heparin, low molecular weight heparin, and anti-platelet agents, fibrin sheaths and thrombi form frequently within the pump which become a nidus for embolic stroke. Treatment options include altered anticoagulation regimens, anti-inflammatory therapies, or device change [2,6].

The role of thrombolytic agents to establish arterial recanalization within a therapeutic window of 4.5 h is associated with improved neurological outcomes in adult patients [7]. The low incidence of strokes in all children, delay in recognition, and the limited availability of a structured, rapid response to include neuro-interventional specialists in pediatric centers, makes its use in pediatrics extremely limited [8]. The evidence for the dose and method of administration is scant and small trials are underway to begin to answer these questions [8,9]. In addition, the risk of hemorrhagic transformation in the infarcted area associated with the use of alteplase needs to be weighed in any discussion on its use.

Further work to tailor anticoagulation regimen for children on ventricular-assist device based on their genomics, physiologic, and developmental state will be critical to decrease the incidence of stroke in this population. A large degree of pharmacogenetic variability is recognized in aspirin and persantine, the standard antiplatelet agents for ventricular assist devices; however, the clinical relevance of this variability remains uncertain at present [10,11]. Other extracorporeal devices used during cardiopulmonary bypass and for use in extracorporeal membrane oxygenation have seen significant advancements in design to decrease the thrombogenesis of the circuit [12]. Similar modifications have been made in the Berlin EXCOR device also, but further research is needed to continue to decrease the thrombogenecity of VAD's.

## Authorship

All authors have read and approved the submitted manuscript; the manuscript has not been submitted elsewhere nor published elsewhere in whole or in part.

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## References

1. Moazami N, Smedira NG, McCarthy PM, *et al.* Safety and efficacy of intraarterial thrombolysis for perioperative stroke after cardiac operation. *Ann Thorac Surg* 2001; **72**: 1933.
2. John R, Panch S, Hrabe J, *et al.* Activation of endothelial and coagulation systems in left ventricular assist device recipients. *Ann Thorac Surg* 2009; **88**: 1171.
3. Grunkemeier JM, Tsai WB, McFarland CD, *et al.* The effect of adsorbed fibrinogen, fibronectin, von Willebrand factor and vitronectin on the procoagulant state of adherent platelets. *Biomaterials* 2000; **21**: 2243.
4. Keuren JF, Wielders SJ, Willems GM, *et al.* Fibrinogen adsorption, platelet adhesion and thrombin generation at heparinized surfaces exposed to flowing blood. *Thromb Haemost* 2002; **87**: 742.
5. Linneweber J, Dohmen PM, Kertzscher U, *et al.* The effect of surface roughness on activation of the coagulation system and platelet adhesion in rotary blood pumps. *Artif Organs* 2007; **31**: 345.
6. Malaisrie SC, Pelletier MP, Yun JJ, *et al.* Pneumatic paracorporeal ventricular assist device in infants and children: initial Stanford experience. *J Heart Lung Transplant* 2008; **27**: 173.
7. Lees KR, Bluhmki E, von Kummer R, *et al.* Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet* 2010; **375**: 1695.
8. Amlie-Lefond C, deVeber G, Chan AK, *et al.* Use of alteplase in childhood arterial ischaemic stroke: a multicentre, observational, cohort study. *Lancet Neurol* 2009; **8**: 530.
9. Thrombolysis in acute childhood stroke: design and challenges of the thrombolysis in pediatric stroke clinical trial.
10. Goodman T, Ferro A, Sharma P. Pharmacogenetics of aspirin resistance:a comprehensive systematic review. *Br J Clin Pharmacol* 2008; **66**: 222.
11. Nakagawa T, Kishino S, Itoh S, *et al.* Differential binding of disopyramide and warfarin enantiomers to human alpha(1)-acid glycoprotein variants. *Br J Clin Pharmacol* 2003; **56**: 664.
12. Svenmarker S, Haggmark S, Jansson E, *et al.* Use of heparin-bonded circuits in cardiopulmonary bypass improves clinical outcome. *Scand Cardiovasc J* 2002; **36**: 241.