ESC European Society of Cardiology

European Heart Journal - Case Reports (2024) **8**, 1–6
https://doi.org/10.1093/ehjcr/ytae001

CASE SERIES
Heart failure

A low-dose thrombolytic infusion protocol for safe and successful treatment of left ventricular assist device thrombosis: a case series

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Received 27 February 2023; revised 4 December 2023; accepted 2 January 2024; online publish-ahead-of-print 3 January 2024

Background Pump thrombosis is a serious complication of continuous-flow left ventricular assist device (CF-LVAD) therapy. In this study, we aim to report a novel protocol of an intermittent, low-dose, and slow infusion of tissue plasminogen activator (alteplase).

Case summary We treated seven LVAD pump thrombosis events (HeartMate® II and HeartWare) in four patients with a median age of 52 years (31–63), and all were female. The protocol was applied from January 2015 to December 2018, and it consisted of an intermittent, low-dose, and slow infusion of systemic thrombolytic therapy in the intensive care unit. This therapy resulted in successful resolution of pump thrombosis in six out of seven events. Bleeding complication occurred in one patient, which included a ruptured haemorrhagic ovarian cyst and a small cerebellar intra-parenchymal haemorrhage. All patients were discharged home in a stable condition, except one patient who died during hospitalization because of severe sepsis, pump thrombosis with subsequent pump exchange, and multi-organ failure.

Discussion A low-dose, prolonged, and systemic thrombolytic infusion protocol is an effective and relatively safe treatment that can lead to a sustained resolution of pump thrombosis with low bleeding complications and failure rates.

Keywords LVAD thrombosis • Case series • Thrombolytic • Complications

ESC curriculum 6.5 Cardiomyopathy • 6.2 Heart failure with reduced ejection fraction

Learning points

- A low-dose, prolonged, and systemic thrombolytic infusion protocol is an effective and relatively safe treatment.
- This protocol leads to a sustained resolution of left ventricular assist device pump thrombosis with low bleeding complications and failure rates.

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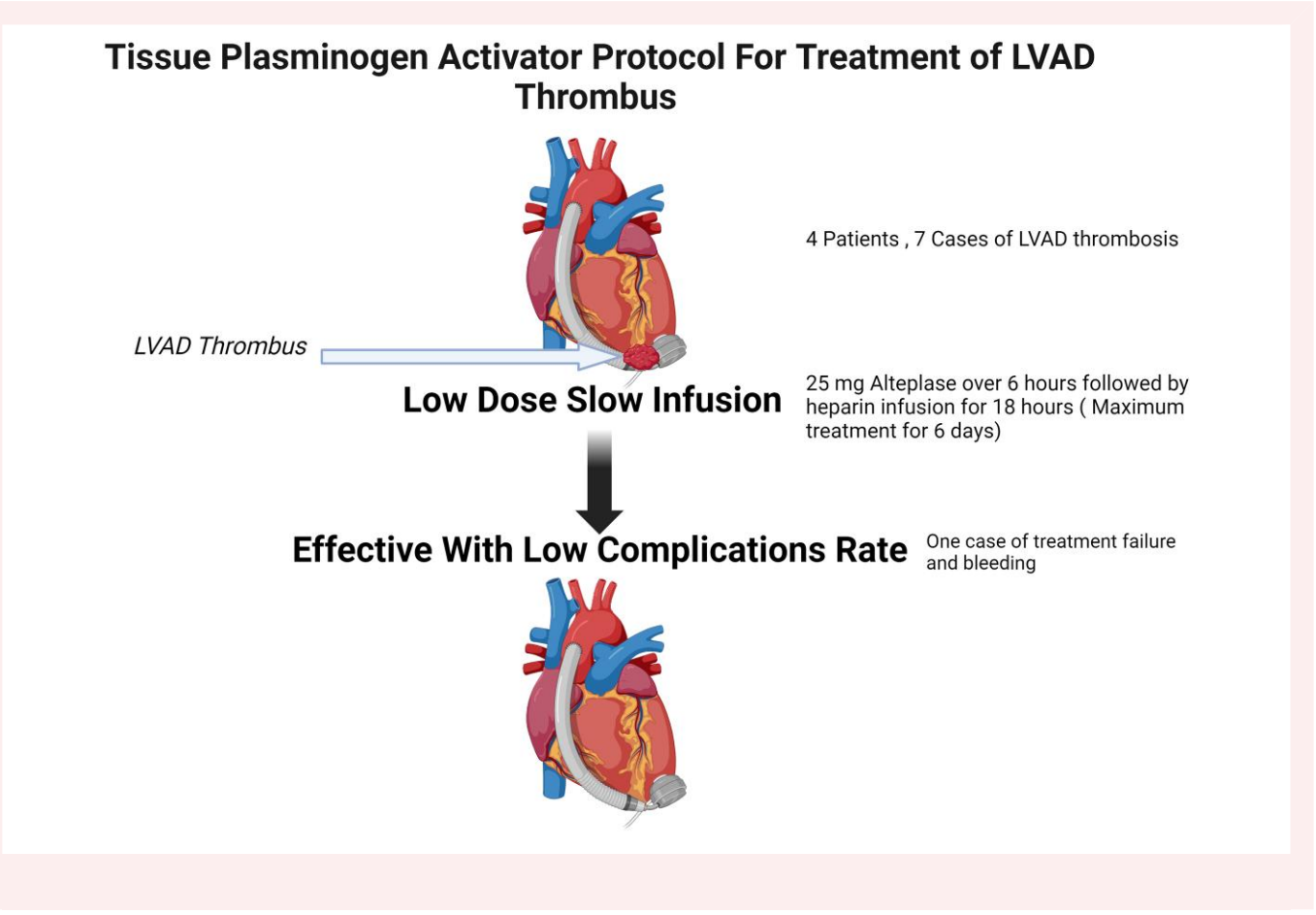
Handling Editor: Christophe Vandenbriele
Peer-reviewers: Waqas Akhtar; Ana Filipa Cardoso
Compliance Editor: Ralph Mark Louis Neijenhuis

Introduction

Continuous-flow left ventricular assist device (CF-LVAD) therapy has revolutionized the treatment of patients with advanced heart failure by improving the quality of life, functional capacity, and survival rates.[1] However, LVAD implantation can result in serious complications such as bleeding, stroke, infection, and pump thrombosis.[2] Although initial trials of the HeartMate® II CF-LVAD reported low rates of pump thrombosis, later reports have shown an increased incidence of thrombosis at around 7–11% at 6–12 months.[2,3] With regard to the HeartWare® (Medtronic) continuous-flow Ventricular Assist Device (HVAD®), the 12-month rate of incidence of pump thrombosis has been reported to be up to 8%.[4] Advancements in bioengineering have led to the introduction of HeartMate III™ (Abbott) Chicago, IL, USA, which is a fully magnetically levitated intra-pericardial centrifugal flow pump. Although these advancements have minimized the incidence of pump thrombosis and stroke,[5] they have not eliminated it completely. In the final report of the MOMENTUM 3 multi-centre study, the 2-year rate of incidence of suspected or confirmed pump thrombosis was found to be 1.4%, the incidence rate of stroke was 9.9%, and the incidence rate of transient ischemic attack was 3.1%.[6] Also, a Medtronic press release revealed that the company will stop selling HeartWare, which will lead to the shifting of future patients to HeartMate III. However, according to current estimates, there are still around 8100 patients with HeartMate II and 4000 patients with HeartWare HVAD systems. This makes the problem of pump thrombosis in patients with these devices an ongoing concern. Moreover, cases of late HeartMate III pump thrombosis were recently reported.[7,8]

Society guidelines and randomized clinical trials addressing the management of pump thrombosis are lacking. Therefore, different centres have established different approaches to manage this morbid complication, with variable success rates. Heart transplant or pump exchange is the treatment of choice for pump thrombosis. However, for patients who are not candidates for these surgical options, a safe and efficacious alternative is needed. Herein, we report a novel protocol with an intermittent, low-dose, and slow infusion of tissue plasminogen activator (alteplase).

Summary figure



Case summary

We treated seven LVAD pump thrombosis events in four patients, from January 2015 to December 2018, with an intermittent, low-dose, and slow infusion of systemic thrombolytic therapy. As outlined in *Table 1*, the protocol consisted of daily infusion of 25 mg of alteplase over 6 h, followed by heparin infusion for 18 h, for a total of 6 days of treatment (maximum alteplase dose of 150 mg). The patients did not have any surgically correctable problems such as inflow cannula malposition or outflow graft obstruction on chest imaging and were considered high-risk surgical candidates for pump exchange. Pump thrombosis was diagnosed in these patients based on a combination of clinical history and physical examination, device alarms, a significant

rise in the laboratory indices of haemolysis such as lactate dehydrogenase (LDH), plasma-free haemoglobin, and a fall in haptoglobin, echocardiography, and invasive haemodynamic assessment through right heart catheterization. An escalation of anticoagulation therapies failed to resolve the pump thrombosis. Therefore, we decided to proceed with thrombolytic therapy.

Patient 1

A 29-year-old with peripartum cardiomyopathy with systolic heart failure requiring Heartmate II placement and implantable cardioverter defibrillator (ICD) was admitted to our hospital due to ICD shock and drive line infection. Laboratory investigations revealed a subtherapeutic international normalized ratio (INR) of 1.5 with elevated LDH that continued to rise despite an escalation of anticoagulation therapies. She continued to have LVAD alarms, haemolysis, and a worsening kidney function. Therefore, slow infusion low-dose alteplase was started, as shown in the protocol (*Table 1*). The patient received a total of 150 mg of alteplase, resulting in thrombus resolution with no complications.

A year later, she was admitted for incision and drainage of chronic drive line infection. A few days later, she started showing signs of right ventricular (RV) failure with elevated LDH suggestive of an LVAD thrombus. After failed attempts to optimize RV function with inotropes, she was started on alteplase per protocol with a total dose of 125 mg, resulting in thrombus resolution with no complications. The patient died 1 year later.

Patient 2

A 56-year-old female with non-ischaemic cardiomyopathy requiring a placement of Heartmate II was admitted due to increased shortness of breath with abnormal LVAD parameters and driveline infection. Laboratory evaluation revealed elevated LDH, elevated plasma haemoglobin level, and INR 1.7 suggestive of LVAD thrombosis. Therefore, the alteplase protocol was initiated, and she received a total dose of 112.5 mg, resulting in a resolution of the thrombus without complications and improvement in laboratory values, LVAD parameters, and clinical status. (*Table 2* shows admission INR, total dose of alteplase, and trends in serum LDH during treatment for all events.)

The patient was admitted a year later with respiratory failure requiring intubation due to bi-ventricular failure and pneumonia. She was successfully weaned from respiratory support. However, due to low blood pressure, RV failure, and LVAD alarms with elevated haemolysis laboratory values, an LVAD thrombus was diagnosed. She received a total of 120 mg of alteplase with no complications.

Four months later, she presented to the clinic with tea-coloured urine and LVAD alarms with admission INR 1.5 and elevated LDH and plasma haemoglobin. She was treated with a total of 150 mg of alteplase with a resolution of the LVAD thrombus and no complications. Unfortunately, the patient died 21 months after discharge.

Patient 3

Our third patient was 44-year-old female with a medical history of non-ischaemic cardiomyopathy requiring a placement of Heartmate II and a history of LVAD exchange due to prior thrombosis. She also had a history of traumatic subdural haematoma with craniotomy 1 year before presentation. She was admitted due to elevated LDH and intermittent high flow and high power on LVAD parameters. Due to her history of subdural haematoma, she was given half dose of alteplase (12.5 mg) every day with a total dose of 50 mg. Despite this reduced dose, she developed a ruptured haemorrhagic ovarian cyst with small-volume pelvic haemoperitoneum and a small cerebellar intra-parenchymal haemorrhage. All anticoagulation medications were held for 48 h, thereafter serial brain imaging showed stable bleeding size. Systemic heparin therapy was restarted after 48 h but with a lower activated partial thromboplastin time (aPTT) goal. Of note, her admission INR was 2.1, and she was found to have bacteraemia, which was successfully treated with IV antibiotics. She continued to do well with conservative medical management, her indices of haemolysis had returned to baseline, and she was eventually discharged home on warfarin. However, the patient died 4 months after discharge.

Table 1 A low-dose, prolonged tissue plasminogen activator (alteplase) protocol used for the treatment of appropriate patients who developed an left ventricular assist device pump thrombus complication

(1)	LVAD patient maintained on a heparin drip weight-based protocol, except during alteplase infusion.
(2)	Stop the heparin drip 30 min prior to planned alteplase infusion and follow partial thromboplastin time (PTT) every 30 min until <50 s.
(3)	Start alteplase 25 mg intravenous infusion once PTT < 50 s and infuse for over 6 h.
(4)	Obtain neuro checks every 1 h while alteplase is infused and every 4 h after completion of the infusion.
(5)	Immediately restart the heparin drip at the previous rate on completion of alteplase infusion.
(6)	Maintain the patient on the heparin drip weight-based protocol with a goal PTT of 60–90 s for the next 18 h.
(7)	Alteplase infusion will be given as 25 mg daily, iv piggyback over 6 h, with the total not exceeding 150 mg (6 days of dosing).
(8)	Criteria to stop alteplase: • Change in neurologic status • Active uncontrolled bleeding, a significant drop in haemoglobin <7.0 mg/dL • Suspicion of gastrointestinal bleeding, for example, melena • Unstable haemodynamics • Lactate dehydrogenase stable below <800 U/L for 3 consecutive readings performed every 12 h (ideal level 400–700 U/L) • Total dose of 150 mg of alteplase has been reached

Patient 4

This patient was a 63-year-old female with ischaemic cardiomyopathy requiring a placement of HeartWare HVAD. She was admitted due to abdominal pain with increased LVAD alarms with a suspicion of RV failure and LVAD thrombosis. Her admission INR was 1.6, and LDH and plasma haemoglobin were elevated. She was started on alteplase with a total dose of 112.5 mg. Two days later, she developed headache with visual changes, and a head computed tomography showed acute ischaemic stroke with haemorrhagic conversion. Anticoagulation was interrupted, and her LVAD parameters suggested thrombosis, following which she underwent pump exchange. Thereafter, she had a prolonged hospital course that was complicated by severe sepsis, multi-organ failure, and subsequent death.

Discussion

We reported a novel therapeutic approach for LVAD pump thrombosis with a high rate of success and low risk of complications. In this case series of seven pump thrombosis events in four patients, treated with a low-dose, prolonged thrombolytic therapy protocol, we noted

Table 2 Admission INR, total dose of t-PA, and trends in serum lactate dehydrogenase (LDH) levels in patients who developed left ventricular assist device pump thrombosis and treated with a thrombolytic therapy protocol

Events	Patients	INR on admission	LDH level at baseline[a]	LDH level at admission	Peak LDH level during hospitalization	LDH level at discharge	LDH level at 3–6 months after discharge	Total T-PA dose
Event 1	1	1.5	500–600	967	3779	515	461	150
Event 2	1	2.6	500–600	598	2959	774	580	150
Event 3	2	1.7	600–700	1543	2074	619	666	112.5
Event 4	2	1.9	600–700	2071	>6450	639	656	120
Event 5	2	1.5	600–700	746	2392	651	735	150
Event 6	3	2.1	600–700	3886	5289	731	613	50
Event 7	4	1.6	700–800	1314	>6450	[b]	[b]	112.5

[a]Lactate dehydrogenase levels in Units/Litre, reference range 300–600 U/L.
[b]Patient died during hospitalization because of sepsis with multi-organ failure.

an 86% acute resolution of pump thrombosis and only one case of persistent pump thrombosis and acute ischaemic stroke with haemorrhagic conversion (14%).

Our protocol was derived from Özkan *et al*. who successfully applied it for prosthetic heart valve thrombosis in 24 pregnant patients with a very low rate of complications.[9] In comparison with other reports of systemic thrombolytic therapy for pump thrombosis, the distinguishing feature of this protocol is that it allows for the thrombolytic drug, alteplase, to be given intermittently at a low dose and in a slow and prolonged manner over multiple days.

Therefore, exposing the pump thrombus to a thrombolytic drug for a longer duration heightens the chances of its resolution, while allowing dose reduction and thereby reducing the chances of major bleeding.

The definitive therapy of pump thrombosis has been perfomred with explanation of thrombosed pump or cardiac transplantation. However, this option can be impractical due to limited donor availability. In addition, pump exchange has its own inherent risks of bleeding, infection, RV failure, and alloimmunization due to repeated blood transfusions.

Escalation of anticoagulation has been shown to have only modest benefits with high rates of recurrence and mortality.[1,10] This holds true in our experience with a failed escalation of anticoagulant and/or antiplatelet therapy to resolve the abnormal laboratory indices of intravascular haemolysis. Hasin *et al*. reported initial success in managing pump thrombosis with intravenous heparin and clopidogrel. However, they found that six out of eight patients suffered from recurrence within 7 months.[10] In one of the largest published reports of 72 confirmed cases of pump thrombosis in HeartMate® II LVAD, Starling *et al*. reported 38 patients who were managed medically with an augmentation of anticoagulation and antiplatelet therapy. The rate of mortality in these patients was reported to be high, reaching around 48% at 6 months.[2]

The experience of using thrombolytic drug therapy (both intraventricular and intravenous) to manage pump thrombosis has been reported in a few case reports and case series. Ertugay *et al*. published a case series of 21 pump thrombosis events in which thrombolytic therapy was used to treat seven pump thrombosis events (intraventricular in five events and systemically in two events). A dose of 30–50 mg of t-PA (tenecteplase or alteplase) was infused over 3–5 min, and a second dose was infused if the patient's pump parameters did not return to normal within 30 min after the initial dose. This protocol was successful in resolving pump thrombosis in four out of the seven events (57% success rate).[11]

Schlendorf *et al*. reported a series of eight patients with LVAD pump thrombosis treated with intraventricular thrombolytic drug therapy. Alteplase was infused via a pig tail catheter positioned near the LVAD inflow cannula in the left ventricular apex, at 1 mg/min over 30–50 min with concomitant unfractionated heparin to achieve an activated clotting time >200 s. Thrombolytic therapy led to a successful dissolution of the pump thrombus in three out of eight patients (37% success rate).[12] Although intraventricular administration can reduce the total dose of a thrombolytic drug, it is more invasive and carries a significant risk of complications such as catheter ingestion into the LVAD, debris embolization, and severe vascular access complications.[13] Raffa *et al*. discovered that intraventricular thrombolysis led to the rate of serious complications such as radial artery occlusion, groin haematomas, and femoral artery false aneurysm reaching as high as 56%.[13]

Muthaih *et al*. published a case series of 13 pump thrombosis events in five patients. Thrombolytic therapy was used to treat seven pump thrombosis events in four patients. Single bolus doses of tenecteplase or alteplase with a dose range of 12.5–50 mg were used. The success of thrombolytic therapy was not clearly documented in four pump thrombosis events that occurred in a single patient. Thrombolytic therapy was deemed successful in the resolution of the remaining three pump thrombosis events. However, two of these patients died within 48 h.[14]

Najjar *et al*. published a report of 382 patients who underwent implantation of the HVAD as a bridge to transplant. In the study, they found that 34 pump thrombosis events occurred in 31 patients. Most events (30 of 34) were treated with medical therapy first, which was successful in resolving the pump thrombus in 15 patients (50% success rate). Medical therapy consisted of heparin, glycoprotein IIb/IIIa antagonists, and tissue plasminogen activator, used individually or in combination. The tissue plasminogen activator was infused at doses that varied according to site (total dose range, 15–100 mg) and was administered either intravenously or intraventricularly. Of the 19 patients who received the tissue plasminogen activator (alone or in combination), a successful resolution of the thrombus was seen in 12 patients. The overall success rate of the tissue plasminogen activator was around 63%.[4]

In another study by Schrage *et al*., nine male patients with 16 HVAD thrombosis events caused by infection were successfully treated with low-dose t-PA with a median dose of 42 mg.[15] All patients in the study had therapeutic INR, and therefore, they did not receive heparin after t-PA but instead received a low total dose of t-PA. Two patients had bleeding events, and all patients had thrombus resolution.[15] Similarly in our study, all patients except one had thrombus resolution and one bleeding event. All our patients were female, three had HeartMate II, and one patient had HVAD. Recurrent thrombosis occurred in two patients 1 year after the first event and was associated with infection (drive line infection, pneumonia) and sub-therapeutic INR. The third thrombosis event occurred 4 months after the second

Table 3 A summary of selected studies reporting the use of thrombolytic therapy to treat left ventricular assist device pump thrombosis

	Number of pump thrombosis events	Number of pump thrombosis events treated with thrombolytic therapy	Number of times complete resolution of pump thrombosis (success rate) seen	Number of patients who needed urgent heart transplant or pump exchange due to failure of thrombolytic therapy	Incidence of bleeding complications in patients receiving thrombolytic therapy	Number of patients who had received thrombolytic therapy and died
Ertugay *et al.*[11]	21	7 5-intraventricular 2-systemic/intravenous	4 (57%)	2 (29%)	Not reported	3 (43%)
Schlendof *et al.*[12]	8	8 (all intraventricular)	3 (37%)	2 (25%)	None	3 (37%)
Muthiah *et al.*[14]	13	7 (all systemic)	Not clearly documented.	None	Not reported	2 (28%)
Najjar *et al.*[4]	34	19 (8-systemic/intravenous, 7-intraventricular, 4-route not specified)	12 (63%)	6 (31%)	Not reported	Not reported
Schrage *et al.*[15]	16	Systemic t-PA	100%	0(0%), two pump exchange not included in analyses	2	None
Our protocol	7	Systemic t-PA	6 (86%)	1 (14%)	1	1 (14%) sepsis and multi-organ failure}

event and was mainly due to sub-therapeutic INR = 1.5. Infection is a well-known risk factor for stimulating the coagulation cascade and subsequently increases the risk of pump thrombosis.[15,16] In a study by Schrage *et al.*[15], all three patients who had recurrent thrombosis had infection. *Table 3* summarizes all the above studies and includes the rates of success and failure of the various thrombolytic therapies used in the resolution of pump thrombosis, together with the rates of observed bleeding complications and mortality.

Limitations

This is a retrospective review that included only a few patients at a single medical centre. The protocol reported in this study needs further validation of its efficacy and safety in a larger number and variety of patients. Despite this, the initial safety and efficacy profile of this protocol is encouraging.

Conclusion

Pump thrombosis is a serious complication of LVAD therapy. Using an intermittent, low-dose, prolonged, and systemic thrombolytic infusion protocol is a safe and effective treatment alternative that can lead to a sustained resolution of pump thrombosis.

Lead author biography

Dr Khaled Chatila graduated from medical school at the American University of Beirut. He then joined as a postdoctoral research fellow in cardiovascular disease at Baylor College of Medicine, studying myocardial infarction in animals. He completed internal medicine residency at Good Samaritan Hospital in Baltimore.

Dr Chatila did general cardiology and advanced heart failure and transplant training at the University of Louisville, kentucky. He learned under the guidance of world-renowned experts in the field about the care and management of patients with end-stage heart failure, mechanical heart pumps (LVAD) and heart transplantation. He then joined the University of Texas Medical Branch (UTMB) Division of Cardiology.

Acknowledgements

None.

Consent: All patients consented for the treatment protocol, and this case series is approved by the Institutional Review Board (IRB # 23-0069). The authors confirm that witnessed verbal consent for submission and publication of this case report including images and associated text has been obtained from three of the patients' next of kin in line with COPE guidance. Despite the best efforts of the authors, they have been unable to contact the fourth patient's next of kin. This has been discussed with the Editors.

Conflict of interest: A.A., R.G., M.W.C., V.C., S.L., W.I. K., and K.C. declare no conflict of interest. 'All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.'

Funding: None.

Data availability

The data used to support the findings of this case series are included within this article.

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