Accelerated LVAD Pump Thrombosis in COVID-19 Patient: Case report and Mini review

Ishaq Wadiwala J[1], Pankaj Garg[1], Mohammad Alomari[1], Mohamed Elawady S[1], Emad Alamouti-Fard[1], Lekhya Raavi[1], Nargis Mateen[1], Fazal Khan[1], Md Walid Akram Hussain[1], Si Pham[1], and Samuel Jacob[1]

[1]Mayo Clinic in Florida

September 30, 2022

Abstract

Coronavirus (COVID-19) infection exposes patients with heart failure to a higher risk of morbidity and mortality. In LVAD patients, one of the key problems that can lead to life-threatening low-flow or pump malfunction due to thrombus development in the inflow cannula, device body, or outflow graft, implicating hemodynamic instability, hemolysis, renal or hepatic failure, or cerebral or peripheral thromboembolism. [Endothelial protein C receptor and thrombomodulin levels are elevated along with procoagulants such as factor VIII, P-selectin, and von Willebrand factor and downregulated along with thrombomodulin as a result of the cytokine storm released by endothelial and immune cells. In general ,](#ref-0013) LVAD thrombosis has been found to occur in 2–13% of adult patients who use current continuous-flow devices. However, LVAD thrombosis due to COVID-19 is underreported and a few cases presented. We present a case of accelerated LVAD outflow thrombosis in the setting of COVID-19 infection with multiorgan failure.

Introduction

Coronavirus (COVID-19) infection exposes patients with heart failure to a higher risk of morbidity and mortality.[1] Asymptomatic or mildly symptomatic COVID-19 respiratory virus infections can include fever, coughing, tiredness, dyspnea, diarrhea, headaches, and myalgia. Respiratory rate >30 bpm, arterial oxygen saturation less than 93% at rest, development of acute respiratory distress syndrome, septic shock, metabolic acidosis, and coagulopathy, including disseminated intravascular coagulation, are characteristics of severe cases. [2] In addition, patients infected with the COVID-19 virus have an increased risk of developing both venous and arterial thrombosis [3-6]

Thrombocytopenia and an increase in D-dimer are the hemostatic changes caused by COVID-19 that are most frequently observed, and they are linked to a greater need for mechanical ventilation, admission to intensive care, and death. It has been noticed that patients who are older and have comorbid conditions are more likely to have a high mortality rate, [7] which is believed to be greatly influenced by blood vessel dysfunction and clot formation, as indicated by elevated D-dimer levels brought on by blood clots.[8] Despite the that VAD thrombosis is a common complication, LVAD thrombosis due to COVID -19 is underreported and few cases are presented in the literature. Here we present a case of accelerated LVAD outflow thrombosis in the setting of COVID-19 infection with multiorgan failure.

Case report

A 53 year - old African American with class 1 obesity , hypertension (HTN), diabetes mellitus DM2, gout with chronic systolic (congestive) heart failure secondary to nonischemic cardiomyopathy who underwent initial implantation of a Left ventricular Assist device HeartMate III (LVAD) on 3/17/2017

The patient had been quite active running his company until October 2016 when he presented with progressively worsening dyspnea on exertion, lower extremity edema, and orthopnea. He was diagnosed with heart failure and his ejection fraction (EF) of $< 10\%$. He underwent cardiac catheterization on 8/3/2016 which demonstrated near-normal coronary arteries, right dominant system, Left ventricular end-diastolic Pressure (LVEDP) of 18, and normal pulmonary pressures. He was optimized with medical therapy but failed to respond. He underwent automatic implantable cardioverter defibrillator (AICD) placement for primary prevention after failing to respond to medical therapies. He subsequently had multiple readmissions for heart failure despite complete compliance with medication. During one of his hospitalizations, Right heart catheterization pressures (RHC) demonstrated the following right atrium (RA) 21, right ventricle (RV) 64/42, Pulmonary capillary wedge pressure (PCWP)35, cardiac output (CO)4.9, Cardiac Index (CI) 2.2, pulmonary pressure (PA)55%. He had been on inotropes since 1/2017. He presented on 2/28/2017 with cardiogenic shock and required an intra-aortic balloon pump.

On 3/17/2017 He underwent Heartmate III LVAD placement and needed chest tube 2 days later after developing acute anemia during epicardial lead removal. Chest exploration was remarkable for many clots along the diaphragmatic surface of the heart extending around the lateral wall presumed to be related to the previously removed pacing wire. His postoperative course was remarkable for RV failure needing prolonged milrinone and fever of unknown origin. Work-up for infection was unrevealing except for nonspecific mediastinal and retroperitoneal lymphadenopathy. He was commenced on aspirin and warfarin

Three years later, on 7/20/2021, our patient presented to the emergency department (ED) with dyspnea. He was found to be COVID positive (he was unvaccinated) with a heart rate of 100, respiratory rate of 29, SPO2 87 %, and MAP of 63 mmHg. He was admitted to the ICU for acute hypoxic respiratory failure. Zosyn and Azithromycin, dexamethasone, Remdesivir, and Tocilizumab were incited. His respiratory requirements increased, requiring BiPAP

During the night of 7/22, his LVAD alarmed, and it was found that the flow had decreased to 0.5 L/min. CT Cardiac Angiogram with IV Contrast showing LV Complete distal thrombosis of the outflow conduit from LVAD (Figure 1), diffuse ground-glass disease of lungs due to edema versus infection/inflammation, and laboratory changes (Table 1). Our patient was not a surgical candidate as he was too unstable with multiple organ failures including heart, liver, kidney, and lung. As an obstructive clot in the LVAD would be fatal, it was decided to start tPA to try to dissolve the clot. After tPA was started, he had increased bleeding from a central venous catheter (CVC) and began to have melena. His LVAD flow did not significantly increase despite tPA, and on the morning of 7/24, it was 0.4 L/min. After discussion with the family, he was transitioned to comfort care. His LVAD was turned off, and later that morning he stopped breathing and became pulseless.

Discussion

It was noticed recently, that COVID-19 causes significant alterations in blood cells, including morphological and mechanical abnormalities like enlarged sizes, sometimes lasting for months after hospital discharge.[9] Through a variety of mechanisms, including tissue factor release, endothelial damage brought on by inflammation and hypoxia, and platelet activation, COVID-19 has a major impact on the etiology of coagulopathy.[10] Endothelial protein C receptor and thrombomodulin levels are elevated along with procoagulates such as factor VIII, P-selectin, and von Willebrand factor and downregulated along with thrombomodulin as a result of the cytokine storm released by endothelial and immune cells.[11]

It is also known that patients with left ventricular assist devices (LVAD) are at a greater risk of pump thrombosis if having any concurrent infections.[12]

One of the key problems that can lead to life-threatening low-flow or pump malfunction is LVAD thrombus development in the inflow cannula, device body, or outflow graft, implicating hemodynamic instability, hemolysis, renal or hepatic failure, or cerebral or peripheral thromboembolism.[13] LVAD thrombosis has been found to occur in 2–13% of adult LVAD patients who use current continuous-flow devices.[14]

The clinical picture of pump thrombosis shows a wide range of variability.[15, 16]

Our patient had pump thrombosis three years after HMIII insertion which was considered the longest period compared to other case reports which presented mostly during the first 2 years in COVID and none COVID patients (Tables 2, 3). symptoms like other COVID reported cases (Table 3) . Reviewing the literature regarding to LVAD thrombosis, indicated that patient had COVID-19 had higher morbidity and mortality as indicated in table 2 no-COVID and table 3 COVID patients.

CTA showed complete outflow graft thrombosis with low flow of 0.5 L/M.

Our patient had supratherapeutic INR measuring 6.1, and 9.0 on 0 at day 2 and day 3, respectively. Following that tPA was stopped. That signifies the importance of anticoagulation balance in VAD patients with COVID infection.

LVAD thrombosis has very high mortality and the pathophysiology of LVAD thrombosis is complicated, and it is mainly due to emboli secondary to sluggish blood flow in the left ventricle's endocardium, clots formed in the left atrial appendage, or in ventricular debris from prior surgery, inadequate anticoagulation, and inflow cannula malposition.[17]

In the clinical situation of advancing heart failure symptoms, LVAD low-flow alert, abnormal test results for hemoglobin, free-hemoglobin, and LDH, and symptoms refractory to fluid infusion, making LVAD thrombosis highly suspicious..[16] TTE and CTA are helpful diagnostic methods for LVAD thrombus detection, and a positive thrombus diagnosis may lead to timely alterations in patient management.[18]

The most conclusive forms of treatment for suspected thrombosis are immediate heart transplantation or surgical device exchange.[19] Initiating medical management to deal with pump thrombosis is crucial for transplant candidates or individuals who cannot endure surgery. Heparin monotherapy is the first instituted along with inotropic/diuretic depending on heart failure symptoms.[20] Additional medications including direct thrombin inhibitors, thrombolytics, and glycoprotein IIb/IIIa inhibitors may be used in the dissolution of pump thrombosis.[14] t-PA can be administered along with heparin to accelerate the dissolution of the LVAD thrombus and successful outcomes have been reported in some cases.[21, 22] Furthermore, there are no specific guidelines available for the dose and treatment of t-PA administration in patients with LVAD thrombosis. As a result, since there is no acknowledged method for addressing t-PA, administration depends on personal experience and the favored tactic in each facility.[16] A substantial risk of hemorrhage does exist with t-PA therapy which was also seen in our patient as bleeding from CVC and melena.[14] Although transplant and LVAD exchange are definitive forms of treatment, our patient's persistent multiorgan failure prohibited him from being a good surgical candidate.

Conclusion

Significant morbidity and mortality are attributed to LVAD thrombosis, which are exasperated by prothrombotic conditions manifested in COVID-19 infections. LVAD thrombosis due to COVID -19 is underreported .For the best clinical outcomes, a high level of clinical suspicion must be present to diagnose and treat this problem effectively and efficiently.

Author contributions

SJ and IJM designed the research study and performed the critical revision, PG, LR, NM, SMP, MA, EAF, MSE and MWAH, performed the research and wrote up the script. MWAH, designed the figure and tables. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Acknowledgments

We would like to express our gratitude to all those who helped us during the writing of this manuscript. Thanks to all peer reviewers for their opinion and suggestions.

References

1-Chatrath, N., et al., The effect of concomitant COVID-19 infection on outcomes in patients hospitalized with heart failure. ESC heart failure, 2020. **7** (6): p. 4443-4447.

2 Varghese, G.M., et al., Clinical management of COVID-19. The Indian journal of medical research, 2020. **151** (5): p. 401-410.

3-Cheruiyot, I., et al., Arterial Thrombosis in Coronavirus Disease 2019 Patients: A Rapid Systematic Review. Annals of vascular surgery, 2021.**70** : p. 273-281.

4-McBane, R.D., 2nd, Arterial Thrombosis and Coronavirus Disease 2019. Mayo Clinic proceedings, 2021. **96** (2): p. 274-276.

5-Burn, E., et al., Venous or arterial thrombosis and deaths among COVID-19 cases: a European network cohort study. Lancet Infect Dis, 2022.

6-Gold, D.D., R. Kurd, and S. Einav, Don't forget arterial thrombosis in patients with COVID-19: A case series. Thrombosis Update, 2021.**5** : p. 100065.

7-Levi, M., et al., Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol, 2020. **7** (6): p. e438-e440.

8-Abou-Ismail, M.Y., et al., The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. Thrombosis research, 2020.**194** : p. 101-115.

9-Kubánková, M., et al., Physical phenotype of blood cells is altered in COVID-19. Biophysical journal, 2021. **120** (14): p. 2838-2847.

10-Whyte, C.S., et al., Fibrinolytic abnormalities in acute respiratory distress syndrome (ARDS) and versatility of thrombolytic drugs to treat COVID-19. J Thromb Haemost, 2020. **18** (7): p. 1548-1555.

11-Roberts, K.A., et al., Vascular Manifestations of COVID-19 - Thromboembolism and Microvascular Dysfunction. Frontiers in cardiovascular medicine, 2020. **7** : p. 598400-598400.

12-Whitson, B.A., et al., Hemolysis, pump thrombus, and neurologic events in continuous-flow left ventricular assist device recipients. Ann Thorac Surg, 2014. **97** (6): p. 2097-103.

13-Fatullayev, J., et al., Continuous-Flow Left Ventricular Assist Device Thrombosis: A Danger Foreseen is a Danger Avoided. Medical science monitor basic research, 2015. **21** : p. 141-144.

14-Dang, G., et al., Medical Management of Pump-Related Thrombosis in Patients with Continuous-Flow Left Ventricular Assist Devices: A Systematic Review and Meta-Analysis. Asaio j, 2017. **63** (4): p. 373-385.

15-Upshaw, J.N., et al., Incidence, Management, and Outcome of Suspected Continuous-Flow Left Ventricular Assist Device Thrombosis. Asaio j, 2016. **62** (1): p. 33-9.

16-Gyoten, T., et al., Identification of characteristics, risk factors, and predictors of recurrent LVAD thrombosis: conditions in HeartWare devices. J Artif Organs, 2021. **24** (2): p. 173-181.

17-Gyoten, T., et al., Identification of characteristics, risk factors, and predictors of recurrent LVAD thrombosis: conditions in HeartWare devices. Journal of artificial organs : the official journal of the Japanese Society for Artificial Organs, 2021. **24** (2): p. 173-181.

18-Tchantchaleishvili, V., et al., Evaluation and treatment of pump thrombosis and hemolysis. Annals of cardiothoracic surgery, 2014.**3** (5): p. 490-495.

19-Jennings, D.L. and P.A. Weeks, Thrombosis in continuous-flow left ventricular assist devices: pathophysiology, prevention, and pharmacologic management. Pharmacotherapy, 2015. **35** (1): p. 79-98.

20-Goldstein, D.J., et al., Algorithm for the diagnosis and management of suspected pump thrombus. J Heart Lung Transplant, 2013.**32** (7): p. 667-70.

21-Webber, B.T., A.L. Panos, and Y.F. Rodriguez-Blanco, Intravenous thrombolytic therapy for patients with ventricular assist device thrombosis: An attempt to avoid reoperation. Annals of cardiac anaesthesia, 2016. **19** (1): p. 192-196.

22-Nair, N., et al., Thrombolytics in VAD management - A single-center experience. International journal of cardiology. Heart & vasculature, 2016. **11** : p. 49-54.

23-Alkhunaizi MA, Ali B. Left Ventricular Assist Device Pump Thrombosis in a Patient Treated with Apixaban. Am J Case Rep. 2021 Dec 9;22:e934787. doi: 10.12659/AJCR.934787. PMID: 34880201; PMCID: PMC8669518.

24-Pendyal A, Chien CV, Mudd JO, Gelow JM. Minimally Invasive LVAD Deactivation in a 65-Year-Old Man with Recurrent Pump Thrombosis and Left Ventricular Recovery. Tex Heart Inst J. 2017 Feb 1;44(1):70-72. doi: 10.14503/THIJ-16-5787. PMID: 28265218; PMCID: PMC5317366.

25-Hubbert, L. , Forssell, C. , Baranowski, J. , Lindgren, B. , Holm, J. & Ahn, H. (2017). Endovascular Stenting of a LVAD Outflow Graft Thrombosis. ASAIO Journal, 63 (1), e3-e5. doi: 10.1097/MAT.0000000000000371.

26-Rajapreyar, I. , Acharya, D. , Tallaj, J. , Hornbuckle, L. , Sharpton, J. , Joly, J. & Pamboukian, S. (2019). Left Ventricular Assist Device Thrombosis—Amiodarone-Induced Hyperthyroidism: Causal Link?. ASAIO Journal, 65 (2), e18-e20. doi: 10.1097/MAT.0000000000000773.

27-Rajapreyar, I. , Acharya, D. , Tallaj, J. , Hornbuckle, L. , Sharpton, J. , Joly, J. & Pamboukian, S. (2019). Left Ventricular Assist Device Thrombosis—Amiodarone-Induced Hyperthyroidism: Causal Link?. ASAIO Journal, 65 (2), e18-e20. doi: 10.1097/MAT.0000000000000773.

28-Dobner S, Gräni C, Hugi-Mayr B, Mihalj M, Rhyner D, Wieser M, Martinelli M, Hunziker L, Reineke D. Pump thrombosis and dynamic outflow graft compression: complications in left ventricular assist device therapy. ESC Heart Fail. 2021 Apr;8(2):1631-1636. doi: 10.1002/ehf2.13244. Epub 2021 Feb 10. PMID: 33566444; PMCID: PMC8006604.

29-Sivathasan C, Tan TE, Sim D, Kerk KL. "Burnt out" dilated hypertrophic cardiomyopathy causing acute LVAD thrombosis. Clin Case Rep. 2015 Jun;3(6):376-8. doi: 10.1002/ccr3.237. Epub 2015 Apr 9. PMID: 26185632; PMCID: PMC4498846.

30-Bunge, Jeroen J. H.*,+; den Uil, Corstiaan A.*,+; Constantinescu, Alina C.*; Budde, Ricardo P. J.++; Maat, Alexander P. W. M.SS; Caliskan, Kadir* Acute Pump Thrombosis in the Early Postoperative Period After HeartMate 3 Implantation, ASAIO Journal: September/October 2019 - Volume 65 - Issue 7 - p e72-e74 doi: 10.1097/MAT.0000000000000932

31-Frick WH, et al. Unusual Case of Pump Thrombosis in LVAD Patient with COVID-19. The VAD Journal. 2020; 6(2):e2020622.https://doi.org/ 10.11589/vad/e2020622.

32-Jarrett SA, et al. Left Ventricular Assist Device Thrombosis Treated with Intravenous Tissue Plasminogen Activator in a patient with COVID-19 Infection. The VAD Journal. 2021; 7(1):e2021716. https://doi.org/10.11589/vad/e 2021716

33-Hodges K, Mubashir M, Insler J, et al. Successful management of COVID-19 and associated coagulopathy in a patient with durable left ventricular assist device. J Card Surg. 2020;35(11):3202-3204. doi:10.1111/jocs.14937.

34- Maharaj V, Steiner M, Boyle B, Kazmirczak F, Markowitz J, Alexy T, Shaffer A, John R, Martin CM, Cogswell R, Kamdar F. Rapidly Progressive Left Ventricular Assist Device Outflow Graft Thrombosis Associated With COVID-19 Infection. Circ Heart Fail. 2021 Dec;14(12):e008334. doi: 10.1161/CIRCHEARTFAILURE.121.008334. Epub 2021 Nov 15. PMID: 34775782.

35-Zakrzewski J, Coyle L, Aicher T, Chickerillo K, Gallagher C, Kuper K, Sciamanna C, Chau VQ, Tatooles A. Impact of COVID-19 on Patients Supported with a Left Ventricular Assist Device. ASAIO J. 2021 Nov 1;67(11):1189-1195. doi: 10.1097/MAT.0000000000001578. PMID: 34475334; PMCID: PMC8555883.

36- Birati, Edo Y et al. "Characteristics and Outcomes of COVID-19 in Patients on Left Ventricular Assist Device Support." Circulation. Heart failure vol. 14,4 (2021): e007957. doi:10.1161/CIRCHEARTFAILURE.120.007957

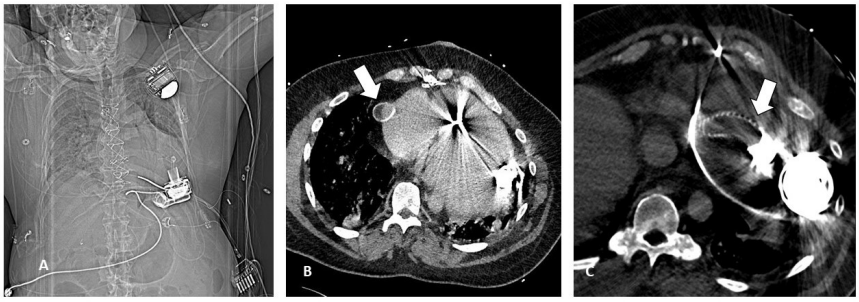

Figure 1 CT angiogram post VAD thrombosis A, sagittal view showing the position of the VAD and AICD. B, Transfer section of the out flow showing complete blockage . C, longitudinal section of the outflow graft showing the cut off the contract in the graft

Table (1) shows the laboratory finding of our patient

Laboratory values	Days after admission	Days after admission	Day 0	Day 1	Day 2	Day 3	Day 4
		Lactate Dehydro-genase U/L	867	1035	1122	932	751
		D-Dimer ng/mL	1221	1252		1163	
		Ferritin (mcg/L)	3096	3946		3955	
		Fibrinogen (mg/dL)	570		668	519	
		PT Pro-thrombin time (second)	35.6	42.7	68.5	102.9	121.1
		INR	3.2	3.8	6.1	9.0	10.6
		APTT	36	43	>300		
	CBC	Hemoglobin (mg/dl)	10.6	10.6	10.2	9.4	7.6
		White cell count (x1000 /mcL)	6.1	7.5	7.4	10.9	12.3
		Platelets (x 1000 /mcL)	91	85	90	109	120
	RFT	BUN (mg/dL)	78	83	85	85	83

Laboratory values	Days after admission	Days after admission	Day 0	Day 1	Day 2	Day 3	Day 4
		Creatinine (mg/dL)	3.18	2.75	2.81	2.55	3.21
	LFT	Aspartate Amino-trans-ferase (AST) U/L	153	202	219	176	
		Alanine Amino-trans-ferase (ALT) U/L	40	47	73	79	
		Bilirubin mg/dL	0.5	1.2	1.4	1.3	
	ABG	Respiratory rate	18	20	25	33	28
		PH	7.4	7.4	7.4	7.4	7.4
		Po2 (mm Hg)	68.8	58.2	40.6	61.2	95.3
		Pco2 (mm Hg)	35.8	35.1	32.9	33	33.7
		Hco3 (mmol/L)	22.1	20.6	21.3	20.9	23.2
		O2 Saturation %	91.7	89.7	75.3	88.8	96.5

Table 2; LVAD thrombosis cases in patient had no COVID infection

Case	Device	Date of thrombosis after device insertion
Mansour A. Alkhunaizi(23)	HVAD 2	2 years after insertion
Pendyal A (24)	HM II	3 years later with previous 3 episodes of thrombosis
Hubbert, L. (25)	HM II	
Rajapreyar (26)	HeartWare LVAD	1 year after
Rajapreyar (27)	HeartWare LVAD	2 years after
Dobner S (28)	HVAD 2	5 recurrent pump thrombosis at 4,6,12,13,14 months respond to medical t
(28)	HM III	6 months after
Sivathasan (29)	HM II	4 months later
Bunge, Jeroen J. H (30)	HM III	3 days after insertion

Table 3; LVAD thrombosis cases in patient had COVID infection

Case	Device	Date of thrombosis after device insertion	Complain	Diagnostic tool	Covid-19	Treatment	outcome
Frick WH (31)	HM III	"Two episodes of pump	during routine laboratory check high LDH was found and 1 week later she developed fever, mild cough, myalgias, fatigue and tested positive for COVID-19	CTA and TEE	yes	combination of cangrelor and heparin	survived
Jarrett SA (32)	HM II	thrombosis at 23 months and 55 months post-implantation"	fatigue, malaise, and dark, red-colored urine for one week	TTE and CTA	yes	IV UF heparin then tPA	Discharged 14 days later from hospital
Hodges K (33)	HM III	18 months after	flu-like symptoms, intermittent fevers and worsening dyspnea on exertion	Thrombosis diagnostic tool	yes	heparin with continuation of antiplatelet therapy	discharged 11 days later
Maharaj(34)	HM III	2 years after insertion	Covid pneumonia	CT chest	yes	unfractionated heparin, bivalirudin infusion, dipyridamole +aspirin	died
Tatooles(35)	HM II	866 days (median)	classic signs of pump thrombosis	Labs CT angio of the chest	yes	systemic heparin and intravenous fluid	discharged

Case	Device	Date of thrombosis after device insertion	Complain	Diagnostic tool	Covid-19	Treatment	outcome
Tatooles(35)	HVAD	777 days (median)	Cardiogenic shock	Labs highly suggestive of Pump thrombosis	yes	Multiorgan failure???	died within 48 hours of presentation
Genuardi(36)	HM III	16 months (median)	Covid symptomatic	?????	yes	medically managed	Discharged 14 days (mean)
Genuardi(36)	HM III	16 months (median)	abdominal pain and fatigue with reduced LVAD flows	CT scan partial outflow graft obstruction	yes	percutaneous stenting	Discharged 14 days (mean)