


Received: 2021.09.14
Accepted: 2021.10.18
Available online: 2021.11.03
Published: 2021.12.09

Left Ventricular Assist Device Pump Thrombosis in a Patient Treated with Apixaban

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF **Mansour A. Alkhunaizi** 
E **Basim Ali**

Department of Internal Medicine, Internal Medicine Residency Program, Baylor College of Medicine, Houston, TX, USA

Corresponding Author: Mansour A. Alkhunaizi, e-mail: Mansour.alkhunaizi@gmail.com, Mansour.alkhunaizi@bcm.edu
Financial support: None declared
Conflict of interest: None declared

Patient: Female, 56-year-old
Final Diagnosis: LVAD pump thrombosis
Symptoms: Fatigue • hematuria
Medication: —
Clinical Procedure: —
Specialty: Cardiology • Hematology

Objective: Unusual or unexpected effect of treatment





Background: Direct oral anticoagulants (DOAC) are currently the preferred agents for long-term anticoagulation in the appropriate patient with venous thromboembolism, non-valvular atrial fibrillation, and left ventricular thrombi because of their ease of use, fixed dosing, lack of need for routine monitoring, and limited dietary and drug interactions. However, warfarin is still the agent of choice for preventing thromboembolic events in patients with left ventricular assist devices (LVAD). In this case report, we explore the outcome of using apixaban in a patient with an LVAD.

Case Report: A 56-year-old woman with morbid obesity and stage D congestive heart failure status after HeartWare ventricular assist device (HVAD) placement 2 years prior, who was on long-term anticoagulation with apixaban after failure of warfarin therapy, presented to the Emergency Department with 2 months of worsening fatigue, dark urine, and 1 day of low-flow alarms from her HVAD. Laboratory and radiographic data were consistent with a diagnosis of pump thrombosis. She underwent pump exchange and was started on a heparin drip. Genetic testing for warfarin resistance was negative. Detailed history-taking revealed that the failure to maintain a therapeutic international normalized ratio (INR) was likely due to dietary factors. She was re-challenged with warfarin, and a therapeutic INR level was reached shortly after initiation. She was later discharged on a stable dose of warfarin and remained in a good clinical state without any major adverse events at the 1-year follow-up.

Conclusions: Apixaban can be associated with an increased risk of thrombosis in patients with HVADs and should be used with caution and only in select patients.

Keywords: Apixaban • Heart Failure • Heart-Assist Devices

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/934787>

 1386  —  —  17



Background

Anticoagulation is essential for maintaining functional left ventricular assist devices (LVAD) and preventing thromboembolic events. The 2013 International Society of Heart and Lung Transplantation Guidelines issued a level B evidence recommendation for the use of vitamin K antagonists (VKA) as the agents of choice for anticoagulation, with a goal international normalized ratio (INR) individualized to each device manufacturer [1]. One of the main challenges with VKA is maintaining therapeutic INR, and failure to do so can predispose patients to bleeding and thromboembolic complications. One meta-analysis of 5 studies showed that patients with continuous-flow LVADs had a time in therapeutic range (TTR) of only 46.6% [2]. The many challenges with VKA led to an interest in using direct oral anticoagulants (DOAC) as an alternative option because of their ease of use and limited dietary interactions, despite the lack of solid safety data in LVAD patients [3]. Here, we present a case of a patient who developed an LVAD pump thrombosis while taking apixaban.

Case Report

A 56-year-old woman with stage D congestive heart failure status after HeartWare ventricular assist device (HVAD) placement 2 years prior, presented to the Emergency Department with 2 months of worsening fatigue, dark cola-colored urine, and 1 day of low-flow alarms from her HVAD. Her past medical history was significant for class III obesity (weighing 144 kg with a body mass index [BMI] of 44 kg/m²), non-insulin-dependent diabetes mellitus, chronic kidney disease (CKD) stage IIIb with an estimated glomerular filtration rate (eGFR) of 44, obstructive sleep apnea, and stage 1B endometrial cancer status after total abdominal hysterectomy with no evidence of active disease. Since the HVAD placement, she was maintained on a daily high-dose aspirin 325 mg and warfarin with a goal INR between 2.0 and 3.0. At first, she maintained consistently therapeutic INR levels with a stable warfarin dose of 15 mg daily. Five months after warfarin initiation, she was prescribed a course of nitrofurantoin for a urinary tract infection (UTI), resulting in a supra-therapeutic INR level of 8 that required temporary discontinuation of warfarin. After successful treatment of the UTI, she was re-started on her prior maintenance dose of 15 mg, but her INR level remained subtherapeutic despite adherence to warfarin and no medication changes. Antithrombin III level was low at 62 (range: 80-120), while protein C and S levels were not checked. Two months after up-titration of warfarin to doses as high as 25 mg daily without achieving goal INR, a decision was made to switch her anticoagulation to apixaban 5 mg twice daily because of inadequate TTR and presumed warfarin resistance. The patient was maintained on apixaban for over 1 year without any serious adverse events except for a minor episode of upper

gastrointestinal bleeding secondary to erosive gastropathy requiring cessation of anticoagulation for 2 days. Two months prior to the current encounter, she noticed intermittent cola-colored urine and worsening fatigue. She denied chest pain, palpitations, new pedal edema, or dyspnea. One day prior to the encounter, she noticed low-flow alarms from her HVAD, which prompted her to present to the Emergency Department. Her workup was significant for a greater than 50% rise in lactate dehydrogenase up to 606 (range: 140-280) and plasma-free hemoglobin of 30 (range: 5-15) while serum creatinine remained at baseline. Apixaban was held, and the patient was started on bivalirudin drip. HVAD interrogation showed a reduced average flow of 0.5 L/min, and power of 2.3 Watts at a speed of 2500 rpm. Computed tomography (CT) imaging of the chest was negative for pulmonary embolism and did not show definitive outflow cannula thrombosis or significant stenosis. Due to high clinical suspicion of thrombosis, a transesophageal echocardiogram was performed, which showed a lack of Doppler flow through the HVAD, confirming a diagnosis of pump thrombosis. The patient underwent pump exchange with excellent post-exchange flow rates, and was started on a heparin drip. Genetic testing for warfarin resistance gene mutation (VKORC1) was negative. The difficulty in achieving and maintaining therapeutic INR with warfarin in the past was attributed to consuming a diet rich in vitamin K; therefore, a decision was made to re-challenge with warfarin while bridging with heparin. Therapeutic INR was achieved within 3 days of starting warfarin, and she was discharged after extensive counseling on dietary restrictions and drug-drug interactions. One month following discharge, a repeat echocardiogram and device interrogation showed an adequately functioning HVAD with a stable and therapeutic INR. No major complications occurred at 1-year follow-up.

Discussion

Durable mechanical circulatory support (MCS) devices such as LVADs have been shown to improve heart failure outcomes when used as destination therapy compared to medical therapy alone in severe refractory disease [4]. Long-term anticoagulation is used to mitigate the increased risk of thrombotic events associated with the implantation of these devices, including that of ischemic stroke and device thrombosis. The current evidence suggests that VKA offers the best outcomes and the lowest risk of thromboembolic events in this patient population [5]. On this basis, the International Society of Heart and Lung Transplantation issued a level B evidence recommendation for the use of VKA as the method of choice for anticoagulation in their 2013 guidelines, with a goal INR individualized to each device manufacturer [1].

HeartWare, the manufacturer for this patient's ventricular assist device, specifically recommend aspirin 325 mg daily and

warfarin with a goal INR of 2.0 to 3.0 for long-term anticoagulation [6]. Sufficient safety data for the use of DOACs is still lacking; therefore, they are not recommended for primary anticoagulation in patients with HVADs [3]. The presumed superiority of vitamin K antagonists may be explained by the underlying mechanism responsible for thrombus formation in this setting. In contrast to atrial fibrillation, where thrombi are formed mainly due to stasis and endothelial dysfunction in the left atrial appendage, the trigger for thrombosis in patients with ventricular assist devices is related to direct blood contact with the artificial surface of the device. This direct contact, in turn, leads to activation of the contact pathway (factors VII, IX, X, and II), all of which are inhibited by VKA [7,8]. To the best of our knowledge, this is the first reported case of HVAD pump thrombosis associated with apixaban after failing warfarin therapy.

As described by Loebstein et al., Warfarin resistance is defined as a dose requirement of >80 mg/week to maintain therapeutic INR [9]. A number of different gene mutations have been shown to influence the response to warfarin, specifically, mutations in VKORC1, which can be associated with up to 30% variance in warfarin dosing [9-11]. Our patient had the wild-type variant and this finding prompted a more in-depth exploration of external potentiating factors such as diet and over-the-counter medication use, which eventually led to the decision to re-challenge her with warfarin. The patient's history of endometrial cancer was taken into account before restarting warfarin. VKAs are considered inferior to low molecular weight heparin and DOACs in the treatment of venous

thromboembolic disease in patients with cancer [12]. Because our patient's cancer was localized and completely resected, it was not thought to have played a role in this thrombotic event; therefore, warfarin remained our preferred agent.

When analyzing the unfavorable outcome our patient had while on apixaban, it is essential to consider patient-specific risk factors that predisposed to thrombosis; specifically, her weight of 144 kg (BMI of 44 kg/m²). In 2016, the International Society of Hemostasis and Thrombosis recommended against the use of direct oral anticoagulants in patients with BMI >40 or a weight >120 kg due to the lack of solid supportive clinical data [13]. Since then, a few studies have shown apixaban to be safe in patients with such extremes of weight without any dose adjustments [14,15], while others advocated for the use of drug-specific peak and trough levels [16]. However, there has not been any revision of the guidelines as of yet.

Conclusions

This case serves as a reminder that apixaban can be associated with an increased risk of thrombosis in patients with HVADs, despite the few case series supporting its use in patients with warfarin resistance. Until more convincing data is available, apixaban should be used with caution and selectively in patients with HVADs and preferably avoided in those at extremes of body weight (BMI >40), with poor renal function (eGFR <30), and who are taking drugs known to interact with DOACs [17].

References:

- Feldman D, Pamboukian SV, Teuteberg JJ, et al. The 2013 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support: Executive summary. *J Heart Lung Transplant*. 2013;32(2):157-87
- Martinez BK, Yik B, Tran R, et al. Meta-analysis of time in therapeutic range in continuous-flow left ventricular assist device patients receiving warfarin. *Artif Organs*. 2018;42(7):700-4
- Loyaga-Rendon RY, Kazui T, Acharya D. Antiplatelet and anticoagulation strategies for left ventricular assist devices. *Ann Transl Med*. 2021;9(6):521
- Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. *New Engl J Med*. 2009;361(23):2241-51
- Rossi M, Serraino GF, Jiritano F, Renzulli A. What is the optimal anticoagulation in patients with a left ventricular assist device? *Interact Cardiovasc Thorac Surg*. 2012;15(4):733-40
- HeartWare HVAD System: Instructions for Use. (n.d.). Retrieved October 14, 2021, from https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100047S090D.pdf
- Andreas M, Moayedifar R, Wieselthaler G, et al. Increased thromboembolic events with dabigatran compared with vitamin K antagonism in left ventricular assist device patients. *Circ Heart Fail*. 2017;10(5):e003709
- den Exter PL, Beeres SLMA, Eikenboom J, et al. Anticoagulant treatment and bleeding complications in patients with left ventricular assist devices. *Expert Rev Cardiovasc Ther*. 2020;18(6):363-72
- Loebstein R, Dvoskin I, Halkin H, et al. A coding VKORC1 ASP36TYR polymorphism predisposes to warfarin resistance. *Blood*. 2006;109(6):2477-80
- Tan GM, Wu E, Lam YY, Yan BP. Role of warfarin pharmacogenetic testing in clinical practice. *Pharmacogenomics*. 2010;11(3):439-48
- Rost S, Fregin A, Ivaskevicius V, et al. Mutations in VKORC1 cause warfarin resistance and multiple coagulation factor deficiency type 2. *Nature*. 2004;427(6974):537-41
- Key NS, Bohlke K, Falanga A. Venous thromboembolism prophylaxis and treatment in patients with cancer: Asco clinical practice guideline update summary. *Journal of Oncology Practice*. 2019;15(12):661-64
- Martin K, Beyer-Westendorf J, Davidson BL, et al. Use of the direct oral anticoagulants in obese patients: Guidance from the SSC OF THE ISTH. *Journal of Thrombosis and Haemostasis*. 2016;14(6):1308-13
- Anusim N, Ionescu F, Jindal V, et al. Outcome of morbidly obese patients with acute venous thromboembolism managed with direct oral anticoagulants. *Blood*. 2019;134(Suppl.1):4973
- Lachant DJ, Bach C, Fe A, White RJ, Lachant NA. Direct oral anticoagulant therapy in patients with morbid obesity after intermediate- or high-risk pulmonary emboli. *ERJ Open Res*. 2020;7(1):00554-2020
- Covert K, Branam DL. Direct-acting oral anticoagulant use at extremes of body weight: Literature review and recommendations. *Am J Health Syst Pharm*. 2020;77(11):865-76
- Chen A, Stecker E, Warden B. Direct oral anticoagulant use: A practical guide to common clinical challenges. *Journal of the American Heart Association*. 2020;9(13):e017559