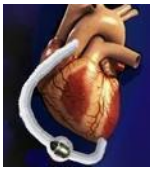

***The VAD Journal:*** *The journal of mechanical assisted circulation and heart failure*

**Peer-reviewed Case Report**

# Unusual Case of Pump Thrombosis in LVAD Patient with COVID-19 — Diagnostic Challenges

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## Abstract

We present the first reported case of left ventricular assist device (LVAD) pump thrombosis in the setting of the coronavirus pandemic. We describe the clinical features of the case which helped to differentiate coronavirus disease 19 (COVID-19) from LVAD pump thrombosis. The patient is 56-year-old female supported by destination LVAD therapy. She was originally implanted with a HeartMate II device in 2015 and underwent two pump exchanges in 2017 and 2019 for pump thrombosis, despite medication adherence. Shortly after routine lab work revealed near doubling of her lactate dehydrogenase (LDH) levels, she tested positive for COVID-19. She then developed power spikes and symptomatic heart failure, which prompted hospital admission. An initial computed tomography (CT) scan showed bilateral ground glass opacities, but repeat testing was negative for COVID-19. Her LVAD pump thrombosis was treated with aspirin, unfractionated heparin, and cangrelor, which was guided by thromboelastogram. Over several weeks, her LDH returned to baseline, and she was transitioned from cangrelor to ticagrelor and from heparin to warfarin. A repeat CT scan after several days of IV diuresis showed resolution of the ground glass opacities.

## Background

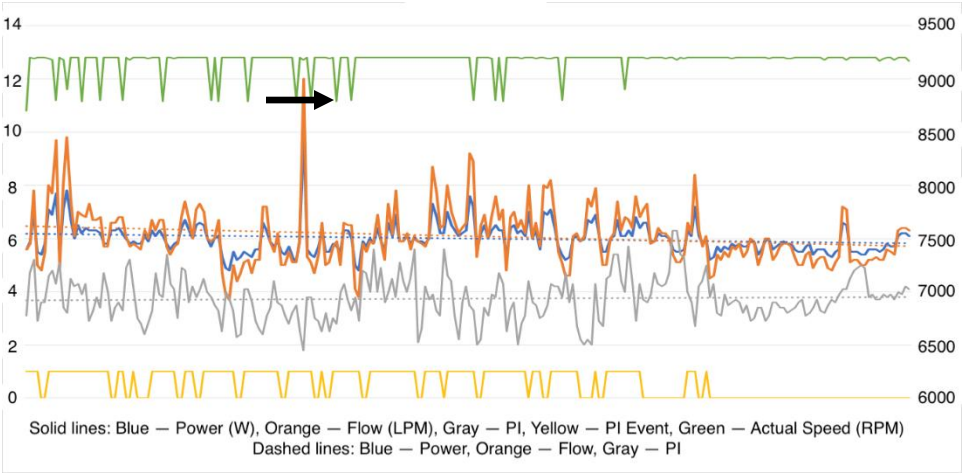
The coronavirus disease 2019 (COVID-19) pandemic creates unique challenges, as it complicates the diagnosis of common medical problems. In general, infection is known to frequently precede pump thrombosis in patients on left ventricular assist device (LVAD) support,[1] but the potential role of coronavirus in precipitating pump thrombosis is unknown. We present the case of pump thrombosis in a patient with COVID-19 infection.

## Case Series Description

A 56-year-old female with history of ischemic cardiomyopathy and morbid obesity received a HeartMate II (HMII) device (Abbott Laboratories, Abbott Park, IL) in 2015 as destination therapy. Her course was complicated by two episodes of pump thrombosis at 23 months and 55 months post-implantation. Each episode required a pump exchange.

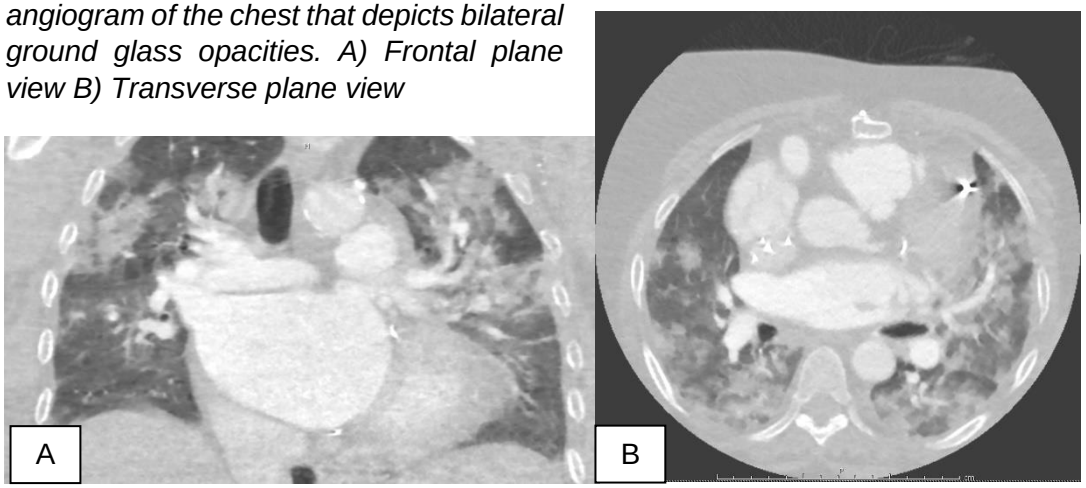
During a routine laboratory check in 2020, it was noted that her lactate dehydrogenase (LDH) increased to 1727 Units/Liter (baseline LDH in 800-900s U/L). Since she had no other symptoms, the test was repeated 2 days later, and her LDH returned to baseline level of 802 U/L at that time. Within a week, she developed a fever, mild cough, myalgias, fatigue and tested positive for COVID-19. Since her symptoms were mild, she was advised to self-quarantine at home without any additional medications. During this time, the patient's international normalized ratio (INR) remained within therapeutic range (2-3). After 14 days of quarantine, the patients LDH showed a persistent elevation at 1722 U/L. Analysis of the LVAD's log file captured a single elevated power of 10 W about 10 days after patient was symptomatic with COVID-19 infection (Figure 1). At this point she was transferred to our center for further evaluation.

***Figure 1.*** *The log file of the left ventricular assist device recorded a single power spike (arrow).*



Upon admission, the physical exam was significant for a multi-tonal hum on auscultation, instead of the monotonic hum of HMII. The patient was afebrile, an oxygenation saturation of 94% on room air, a mean arterial pressure of 70 mmHg and a heart rate of 80 beats per minute. The following day, the patient became progressively more dyspneic with activity, had crackles on auscultation, and was hypoxic requiring oxygen. She was tested for COVID-19 by nasopharyngeal/oropharyngeal swab upon admission and again a few days later, both tests returned negative. The differential diagnosis at this point was pump thrombosis with heart failure versus worsening of the COVID-19 infection. The computed tomography (CT) angiography of the chest revealed patchy bilateral ground glass opacities throughout both lungs in a pattern concerning for COVID-19 (Figures 2) or acute pulmonary edema. There was no thrombus in the inflow and outflow cannulas, raising concern for thrombosis in the pump itself. An echocardiogram showed a dilated left ventricle with end diastolic diameter of 5.8 cm and a dilated hypokinetic right ventricle.

***Figure 2.*** *Computed tomography (CT) angiogram of the chest that depicts bilateral ground glass opacities. A) Frontal plane view B) Transverse plane view*




She was started on diuretics, milrinone, and heparin. Her dual antiplatelet regimen of aspirin (81 mg daily) and dipyridamole (75 mg three times daily) was continued. Thromboelastography (TEG) was suggestive of inadequate inhibition of platelets; hence, dipyridamole therapy was discontinued and cangrelor was initiated at a dose of 0.75 mcg/kg/min.

With the combination of cangrelor and heparin, both the patient's LDH and free hemoglobin trended down (Table 1). There was marked clinical improvement, and she was able to be weaned off diuretics and inotropic therapy by post-admission days 7 and 10, respectively. As clinical improvement was seen along with an improving LDH, cangrelor was transitioned to ticagrelor. A loading dose of ticagrelor was administered just prior to discontinuation of the cangrelor drip,

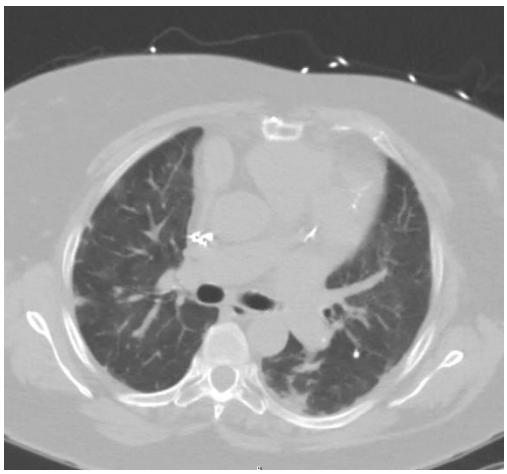
**Table 1: Laboratory values collected over the hospital stay, including thromboelastagraphy and platelet mapping, are depicted alongside the summary of pharmacological therapy.**

| Hospital Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Therapies** | | | | | | | | | | | | | | |
| Heparin | activated partial thromboplastin time was kept at goal during the entire hospitalization | | | | | | | | | | | | | |
| Cangrelor | | | | | 0.75 mcg/kg/min | | | | | | | | | |
| Warfarin | | | | | | | INR within range 2-3 | | | | | | | |
| Dipyridamole | 75 mg three times per day | | | | | | | | | | | | | |
| Ticagrelor | | | | | | | Initial 180 mg load then 90 mg twice per day | | | | | | | |
| **Laboratory Values** | | | | | | | | | | | | | | |
| Prothrombin Time (sec) | 51.1 | 52.1 | 47.1 | 57.9 | 39.4 | 27.2 | 24.6 | 21.5 | 16.7 | 17.1 | 18.4 | 22 | 24.1 | 32.7 |
| International Normalized Ratio | 4.45 | 4.5 | 4.07 | 5.04 | 3.44 | 2.37 | 2.14 | 1.87 | 1.46 | 1.49 | 1.61 | 1.82 | 2.1 | 2.84 |
| Lactate Dehydrogenase (U/L) | | 1060 | 1602 | 1959 | 2287 | 1442 | 1111 | 1093 | 898 | 808 | 904 | 850 | 685 | 607 |
| Hemoglobin Free (mg/dL) | 26 | | 13 | 21 | 13 | | 4 | 6 | 6 | 6 | 8 | 6 | 5 | 2 |
| **Thromboelastography** | | | | | | | | | | | | | | |
| R value | 5.2 | | | 6.8 | | 6.2 | 5.2 | | 5.5 | | 4.5 | | | |
| K value | 0.9 | | | 1.1 | | 1.0 | 0.8 | | 0.8 | | 0.8 | | | |
| Angle | 77.6 | | | 74.0 | | 77.2 | 78.4 | | 78.5 | | 78.5 | | | |
| Maximum Amplitude | 77.7 | | | 79.0 | | 80.4 | 82 | | 79.6 | | 80.1 | | | |
| LY30 | 0.1 | | | 0.0 | | 1.3 | 0.1 | | 0.0 | | 0.0 | | | |
| Coagulation Index | 3.8 | | | 2.6 | | 3.5 | 4.5 | | 4.0 | | 4.7 | | | |
| **Platelet Mapping** | | | | | | | | | | | | | | |
| ADP % Inhibition | 16.7 | | | 43.3 | | 87.7 | 64.7 | | 73.3 | | 40.8 | | | |
| ADP % Aggregation | 83.3 | | | 56.7 | | 12.3 | 35.3 | | 26.7 | | 59.2 | | | |
| MA ADP | 70.9 | | | 54.8 | | 39.9 | 49.4 | | 45.3 | | 58.8 | | | |
| AA % Inhibition | 29.9 | | | 75.8 | | 100 | 89.6 | | 87.2 | | 78.5 | | | |
| AA % Aggregation | 70.1 | | | 24.2 | | 0.0 | 10.4 | | 12.8 | | 21.5 | | | |
| MA AA | 64.2 | | | 36.3 | | 32.5 | 38.1 | | 38.8 | | 39.1 | | | |

***ADP - adenosine phosphate; MA - maximal amplitude; AA - arachidonic acid; LY30 - lysis at 30 minutes***

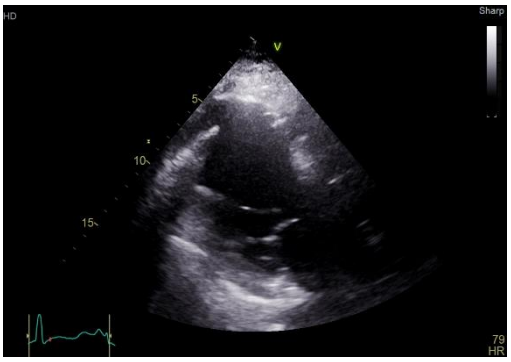
followed by standard dosing of 90mg twice daily, replacing dipyridamole therapy. Warfarin was reinitiated at this time with the heparin drip continuing until the INR reached a target goal of 2.5-3.5.

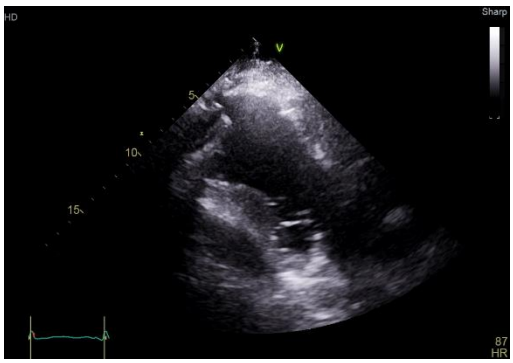
***Figure 3.*** *Transverse plane computed tomography angiogram chest after several days of diuresis showing near resolution of ground glass opacities*



Her condition improved, and she was ambulating well on room air. A repeat CT scan of the chest showed marked improvement of the patient's bilateral ground glass opacities (Figure 3). The repeat echocardiogram showed a left ventricular end diastolic diameter of 4.9 cm and improved right heart function (Figure 4). A right heart catheterization was performed after hemodynamic stabilization showed a right atrial pressure of 6/3 mmHg and a mean pulmonary capillary wedge pressure of 6 mmHg. Prior to discharge, the LDH was at baseline (607 U/L), free hemoglobin was 2 mg/dL, and LVAD function was stable. TEG values while on the cangrelor infusion showed a more inhibited adenosine diphosphate arm compared to the TEG on admission. The patient was discharged home on warfarin (INR goals remained at 2.5-3.5), ticagrelor (90 mg twice daily), and aspirin (81 mg daily).

***Figure 4.*** *Echocardiogram upon presentation with LV dilatation. (Left panel). The echocardiogram after treatment of pump thrombosis (right panel). Both are in the parasternal long axis.*





## Discussion

Pump thrombosis is a complication of LVAD implantation, affecting approximately 5% of patients.[2] It can present with clinically significant hemolysis, device alarms, left heart failure, and cardiogenic shock. Our patient had symptoms of fatigue, shortness of breath, hypoxia, dry cough, elevated LDH, and bilateral ground glass opacities in the setting of a recently positive COVID-19 test. All of these symptoms could be seen in both pump thrombosis and COVID-19 infection. T Ai et al. reported on a series of patients with an initially negative PCR test showed signs with COVID-19 on CT and subsequently became PCR positive.[3] Thus, the negative PCR test upon admission did not rule out the possibility of an active COVID-19 infection.

An LDH elevation is common in patients with COVID-19, and multiple retrospective analyses have shown a correlation between the degree of LDH elevation and outcome.[4,5] Zhou et al. found that survivors of COVID-19 had a modest elevation of LDH, with an average value of 253 U/L, whereas non-survivors had an average of 521 U/L, ranging as high as 669 U/L.[5] In a case series of 1099 patients, Guan et al. reported that among patients with LDH levels of greater than 250 U/L, 70.5% met the primary endpoint, which was a composite of intensive care unit (ICU) admission, mechanical ventilation, or death, compared to 39% of patients with a lower LDH.[5] At the same time, LDH is the principal laboratory marker used to diagnose LVAD thrombosis. Pump thrombosis is generally suspected in HMII patients when the LDH level is greater than 600 U/L.

The presence of ground glass opacities is another non-specific symptom. However, ground glass opacities have been reported to be among the most common radiologic findings in COVID-19, occurring in about half of patients;[1,4-6] they are also commonly seen in pulmonary edema. Cell-free hemoglobin elevations have also been shown to occur and predict poor outcomes in sepsis in non-LVAD patients.[7]

In general, infection is an inflammatory event that can lead to a systemic hypercoagulable state, increasing the incidence of LVAD pump thrombosis. Many studies have shown that infection increases the risk of thrombotic complications of LVAD.[1,8] This risk is seen within six weeks of a major infection.[8] Our patient had a prior history of pump thrombosis; however, we suspected the current episode was triggered by the preceding COVID-19 infection. In retrospect, the COVID-19 infection had likely resolved by the time she was hospitalized for the thrombotic event.

Coagulopathy is a widely reported phenomenon in COVID-19, with high rates of venous and arterial thrombus formation.[9,10] Klok et al. reviewed 184 ICU patients with COVID-19 and found that 35% of them had pulmonary embolism and 3.8% had arterial thrombotic events.[9] Similarly, Merkler et al. reported a stroke rate of 1.6% in COVID-19 patients presenting to the ED.[11] There are emerging case reports of patients in their 30s with COVID-19-induced strokes.[12] Indeed, our patient's LDH nearly doubled eight days prior to the COVID-19 diagnosis,

suggesting the virus may have exacerbated or even precipitated the pump thrombus.

In our analysis, the most helpful clinical clues to the eventual diagnosis of pump thrombosis in the setting of recent COVID-19 diagnosis were the degree of LDH elevation and the power spikes. LDH is rarely reported in excess of 600 U/L, even in high mortality cases from COVID-19. Given the acute surge in this patient to a peak value of 2287 U/L, we felt this was better explained by pump thrombosis, and that her COVID-19 had likely resolved by this point. Resolution of the ground glass opacities after diuresis (Figure 3) further supported pump thrombosis and not ongoing COVID-19.

Medical management of pump thrombosis typically includes heparin monotherapy, direct thrombin inhibitors, thrombolytic agents, and/or glycoprotein IIb/IIIa inhibitors. The use of escalated therapies has been more successful than heparin alone in a number of cases; however, there is also a higher rate of bleeding seen with these agents.[13] Cangrelor is a reversible P2Y12 inhibitor that is structurally and functionally similar to the more commonly used oral P2Y12 inhibitor, ticagrelor. Cangrelor rapidly blocks adenosine diphosphoate-mediated platelet aggregation and has a very quick onset of action with a short half-life. Our center has utilized cangrelor in combination with heparin for suspected pump thrombosis and have reported successful outcomes in at least two patients.[14] In combination with other markers (i.e., LDH, pump parameters), our center has utilized TEG-directed decision making to guide antiplatelet therapies for our LVAD patients. Although use of cangrelor at our center is rare and has not been directly compared to alternative agents, it has shown potential over previously described strategies in lowering LDH in suspected pump thrombosis while possibly providing a lower bleeding risk.

In summary, this is the first case of pump thrombosis reported in a LVAD patient after COVID-19 infection. Our case is also unique in that we were able to medically manage the thrombosis with the combination of cangrelor and heparin. Earlier, Singh et al. proposed a registry of COVID-19 infection in LVAD population.[15] We agree that such registry is needed for defining the cardiovascular effects in this special LVAD patient population.

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