



Peer-Reviewed Case Report

## Lactate Dehydrogenase Rising: Bleeding or Clotting?

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### Abstract

Modern continuous-flow ventricular assist devices (VADs) have greatly improved the survival of patients with end stage heart failure. However, they are associated with adverse effects, including cerebrovascular accidents (CVA), bleeding, infection, and device thrombosis. Definitive measures to evaluate for pump thrombosis can be challenging; hence, multiple laboratory and imaging modalities have been studied to help guide decision making. Lactate dehydrogenase (LDH) has proven to be a reliable test when used in the appropriate clinical settings to help diagnose pump thrombosis. When a patient presents with both signs of life-threatening cerebral hemorrhage and VAD thrombosis, the clinical picture can be quite challenging. We present a case with intracerebral hemorrhage that was associated with a significant increase in LDH and created a clinical dilemma since anticoagulation had to be completely reversed in the setting of the bleed. The fact that brain injury (in particular hemorrhage) leads to elevation of LDH is highlighted. Importantly, not all that raises LDH in a ventricular assist patient is thrombosis of the device.

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## Background

Modern continuous-flow ventricular assist devices (VADs) have greatly improved the survival of patients with end stage heart failure. However, they are associated with adverse effects, including cerebrovascular accidents (CVA), bleeding, infection, and device thrombosis. Definitive measures to evaluate for pump thrombosis can be challenging; hence multiple laboratory and imaging modalities have been studied to help guide decision making. Lactate dehydrogenase (LDH) has proven to be a reliable test when used in the appropriate clinical settings to help diagnose pump thrombosis. When a patient presents with both signs of life-threatening cerebral hemorrhage and VAD thrombosis, the clinical picture can be quite challenging.

## Case Report

A 62-year-old male received a HeartMate II VAD (Abbott) four years prior to admission and was currently listed for a heart transplant. He presented to the emergency department following the acute onset of slurred speech. Computed tomography (CT) of the head showed a 1.4 cm left frontal lobe hemorrhage with subarachnoid extension. Laboratory data on arrival are listed in Table 1. Of note, LDH was 2.2 times the upper limit of the normal range.

**Table 1. Admission laboratory values**

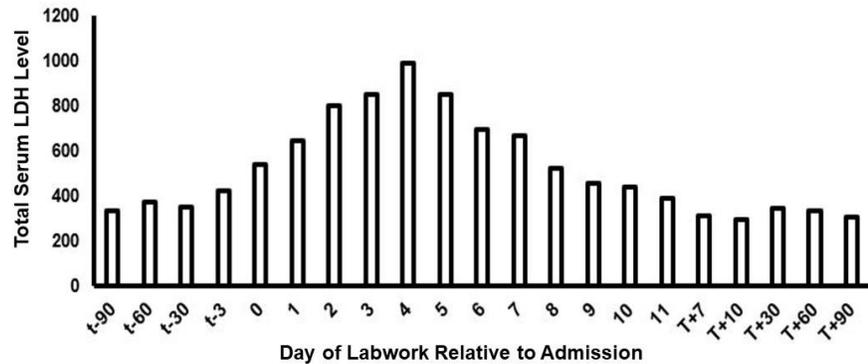
Hemoglobin	11.1 g/dL
Platelets	106 K/ $\mu$ L
Plasma-free hemoglobin	4.5 mg/dL (normal range: 0-4.9 mg/dl)
International normalized ratio	3.5
<i>Lactate dehydrogenase</i>	<i>426 U/L, (normal range 98-192)</i>
Creatinine	1.2 mg/dL
Total bilirubin	0.8 mg/dL

Neurosurgery recommended the immediate reversal of warfarin and, in the short term, no further anticoagulant. The patient's dysarthria improved, and he was admitted to the neurology intensive care unit for ongoing monitoring. An echocardiogram demonstrated appropriate VAD function with a closed aortic valve and normal VAD inflow velocities.

The following day, a repeat head CT demonstrated expansion of the left frontal lobe bleed to 2.2 cm despite the reversal of anticoagulation and cessation of antiplatelet agents. LDH levels sharply climbed along with other markers of VAD thrombosis (Figure 1). The plasma free hemoglobin rose from 4.5 mg/dL to 42 mg/dL, and haptoglobin was undetectable. LDH isoenzyme fractionation was obtained on a peak value of 936 (upper limit of normal 224, 4.2 times upper limit): **LDH-1:** 35 % [17-32%], **LDH- 2:** 35% [25-40%], **LDH-3:** 19 % [17-27%], **LDH-4:** 5% [5-13%], **LDH-5:** 6 % [4-20].



**Figure 1.** Total serum lactase dehydrogenase levels throughout the hospital stay.



Given the acute hemorrhagic CVA, the patient was not a candidate for an urgent transplant nor VAD pump exchange. The team was concerned that the patient had evolving VAD thrombosis, and if so, we needed to counsel the patient that this was likely a terminal event. After reviewing the LDH fractionation, we realized that the LDH could have been driven by his cerebral bleed, and we were able to watch without anticoagulation despite multiple indices pointing towards VAD thrombosis.

The VAD parameters remained normal, and the patient remained asymptomatic. On hospital day 5, warfarin therapy was re-initiated with a lower target international normalized ratio of 1.5-2, and the patient was monitored closely. He remained hemodynamically stable and was successfully discharged to home on hospital day 11. On the day of discharge, his LDH was 442 U/L, but the remainder of his labs continued to be within a normal range. Two weeks later, a repeat head CT scan showed interval improvement in the size of his hemorrhagic foci without evidence of extension.

## Discussion

LDH has a tetrameric structure, with subunits most commonly made up of LDH-H and LDH-M proteins, which can, in turn, form five possible pentamers or isoenzymes of LDH with different concentrations in different tissues.<sup>1</sup> Of these, LDH-1 is localized primarily in the brain, the heart, and in red blood cells. LDH-2, the predominant form in the serum, is localized primarily to the reticuloendothelial system. LDH-3 is localized in the lungs. LDH-4 localizes in the pancreas and renal system, and LDH-5 is found in striated muscle and the liver.<sup>1</sup> Little has been previously reported on the kinetics of LDH-1 within the neuron. One previous *in vitro* study on human LDH-1 isoenzyme reported an average half-life of approximately 110 hours in the absence of other physiological stressors.<sup>1</sup>

In patients with acute ischemic or hemorrhagic strokes and no evidence of concurrent cardiac lesions, serum LDH has been previously shown to rise in



proportion with the cardiac-specific enzymes aspartate aminotransferase (AST) and creatine phosphokinase myocardial band (CPK-MB); where the sharpest increases in LDH, AST, and CPK-MB were seen in patients with hemorrhagic CVA.<sup>2</sup> Further, all three proteins follow similar expression profiles, with peaks at approximately post-stroke day 4, suggesting the concurrent existence of acute myocardial dysfunction in some patients with acute intracranial hemorrhage (ICH).<sup>2</sup>

Changes in serum LDH levels have been correlated previously with intravascular hemolysis and pump thrombosis in patients with continuous-flow LVAD support.<sup>3,4</sup> In appropriate clinical settings, studies have shown a rise of 2.5 times or greater from total baseline LDH is indicative of pump thrombosis.<sup>3,4</sup>

The current case illustrates that intracranial bleeding may lead to marked elevations of serum LDH, which may confound the clinical picture for patients on VAD support who have frequent monitoring of LDH.

In patients with acute hemorrhagic CVAs, an increased total serum LDH level may serve as an independent and reliable predictor of hematoma expansion.<sup>5-7</sup> In conjunction with imaging to evaluate for ICH, the changes in serum LDH levels may have significant predictive value in guiding the decision of when to resume anticoagulation in a patient with an acute CVA as well as a VAD, as was seen in this case.<sup>5-7</sup>

The current case illustrates a patient with dramatic elevations of VAD thrombosis markers with a HeartMate II VAD, and yet the patient never required a pump exchange. The brain bleed was the likely culprit for the blood test abnormalities, and the correct course of action was patience and supportive care.

Since both brain and red blood cell damage affect LDH-1, the value of fractionating the LDH is to exclude other causes such as lung (LDH-3) or skeletal muscle (LDH-5). In the case of a patient unfortunate enough to have a brain injury and a VAD thrombosis, the LDH-1 would be elevated, and clinical judgment and hemodynamic/echocardiographic data would guide diagnosis and management. On the other hand, a patient with severe pneumonia, or high CPK with rhabdomyolysis could also have a very high LDH and yet have no issues with their VAD. As cardiologists, we tend to focus on the risk of VAD thrombosis when noting a high serum LDH. However, it is important to know the other origins of these enzyme elevations, and fractionation can help establish the source.

In summary, this report highlights the fact that intracranial pathology can lead to marked elevations of serum LDH and mimic incipient VAD thrombosis. Fractionation of LDH can be helpful, but ultimately, clinical judgment is the best way to decide if rising enzymes signify a damaged pump, damaged brain, or both.



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