

## Suspected Heparin-Induced Thrombocytopenia in Patients Receiving Extracorporeal Membrane Oxygenation

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**Abstract:** Heparin-induced thrombocytopenia (HIT) is an immune reaction usually secondary to unfractionated heparin. Anticoagulation management is critical in patients while on extracorporeal membrane oxygenation (ECMO) to prevent thromboembolism and for the optimal functioning of the circuit. We identified five patients with respiratory failure at

our hospital managed with ECMO in the last 2 years that were treated for HIT. A brief clinical course and their management are discussed. We also briefly review the literature for best evidence for management of such patients. **Keywords:** ECMO, HIT, anticoagulation, antibody. *J Extra Corpor Technol. 2017;49:54–8*

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Extracorporeal membrane oxygenation (ECMO) use for patients with refractory respiratory and cardiac failure is increasing (1). The ECMO circuit uses large bore drainage and return cannulas—in the range of 19–31 French for adults—placed to achieve two main configurations; venovenous (VV) for pulmonary or venoarterial (VA) for cardiopulmonary support. The blood flow is circulated with a pump through an oxygenator and then returned to the patient. Preventing circuit thrombosis is important to maintain optimal flow and gas exchange, and this is critically important in VA ECMO to prevent arterial thromboembolism. Guidelines suggest a continuous infusion of unfractionated heparin (UNFH) to achieve anticoagulation (1,2). In addition, heparin-coated circuits are frequently used although other coatings and non-coated circuits are available. Coating of the circuit is a recommended although mostly studied in the setting of a laboratory experiment or cardiopulmonary bypass (3). One risk of anticoagulation with heparin infusions and heparin-coated circuits is heparin-induced thrombocytopenia (HIT).

HIT is an uncommon immunologically mediated condition. Overall, the incidence of HIT is reported between 0.1% and 5% with a 20–30% mortality rates. In patients on ECMO, the reported incidence of HIT is less than 1% (4–6). There is paucity of data of HIT-related mortality in ECMO population. More than 5 days of UNFH use, post-surgical—particularly cardiac surgery—patients and female gender are risk factors for HIT (3,6,7).

We identified five patients with respiratory failure at our hospital managed with VV ECMO in the last 2 years that were treated for HIT. A brief clinical course, management, and their outcomes are discussed. Our facility is an Extracorporeal Life Support Organization (ELSO) center of excellence. Patients are managed by a multidisciplinary ECMO team. For VV ECMO, our preferred cannulation technique is using an AVALON ELITE® Bi-Caval Dual Lumen Catheter (Maquet, Germany) placed in the right internal jugular vein. All patients in this report were managed with a circuit using a ROTAFLOW pump (Maquet, Germany) and QUADROX oxygenator (Maquet, Germany). All coated circuits refer to the BIOLINE circuit (Maquet, Germany) and non-heparin-coated circuits used were the SOFTLINE circuits (Maquet, Germany). Anticoagulation management is individualized to patient and circuit health. Heparin is the anticoagulant of choice unless contraindicated when we chose between bivalirudin and argatroban depending on organ dysfunction. We check activated clotting time every hour until in the range and then decrease frequency to every 2 hours. Activated clotting

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time (ACT) goals are more aggressive for VA vs. VV ECMO but in general maintained between 160 and 220 second range. A full coagulation panel consisting of prothrombin time, international normalized ratio, fibrinogen, and d-dimer is checked every 12 hours. If there is a discordance between the ACT and the PTT, we use PTT for heparin dosing. Thromboelastograms (TEGs) are done daily. Antithrombin III level is checked daily and replaced if level is below 80% and there are signs of heparin resistance.

This study was approved by the Institutional Review Board at the University of Arizona.

## DESCRIPTION

### Case 1

A 59-year-old Caucasian man was admitted after a motor vehicle accident leading to tibial-fibular fracture. He underwent open reduction and fixation and after 2 days developed a deep venous thrombosis and pulmonary embolism. Intravenous heparin was initiated at that time. Platelet count at initiation of heparin was 182,000/ $\mu\text{L}$ . He was later transferred to the intensive care unit due to progressive respiratory failure, diagnosed with acute respiratory distress syndrome (ARDS) and required intubation and mechanical ventilation. The patient was pharmacologically paralyzed and placed on volume assist mode mechanical ventilation with tidal volumes of 6 mL/kg of ideal body weight, positive end expiratory pressure (PEEP) of 20 cm  $\text{H}_2\text{O}$ , and 90%  $\text{FiO}_2$  and 10 ppm of inhaled nitrous oxide. Oxygenation remained poor despite this with P:F ratio of around 60. A decision was made to place the patient on VV ECMO. A 27 F AVALON ELITE<sup>®</sup> Bi-Caval Dual Lumen Catheter was placed in the right internal jugular vein and connected to a BIOLINE circuit. Flow rates were maintained at 4 L/min. Platelet count during cannulation was 368,000/ $\mu\text{L}$ . Three days after cannulation, his platelet count fell abruptly to 93,000/ $\mu\text{L}$  and HIT was suspected. PF4 antibody test was positive, supporting the diagnosis. The circuit was changed to a non-heparin-coated circuit and the anticoagulation changed to argatroban infusion. Anticoagulation was monitored with ACT, PTT, and TEG. The serotonin release assay (SRA) test came back as positive on the third day. Platelet counts recovered within 3 days and remained above 200,000/ $\mu\text{L}$  for the rest of the hospital course. There were no bleeding complications during this time. Unfortunately, due to lack of any signs of improvement of his respiratory failure, care was withdrawn per family wishes after 22 days on ECMO.

### Case 2

A 41-year-old Hispanic man with known pulmonary arterial hypertension and remote history of lower extrem-

ity deep vein thrombosis who was no longer on anticoagulation was intubated at an outside facility for pneumonia and progressive respiratory failure. He required VV ECMO 3 days later for hypoxemia despite mechanical ventilation and aggressive pulmonary arterial hypertension therapy. He was cannulated with a 31 F AVALON ELITE<sup>®</sup> Bi-Caval Dual Lumen Catheter. Flow rates were maintained at 4–4.5 L/min. After 12 days of treatment there, he was transferred to our facility. Platelet count at admission was 129,000/ $\mu\text{L}$ . On day 14 of ECMO, he had an abrupt drop of platelets to 45,000/ $\mu\text{L}$  and HIT was suspected. His anticoagulation was immediately changed to bivalirudin and the circuit was changed to a non-heparin coated tubing the next day. HIT was confirmed by a positive PF4 and a SRA. His platelet counts recovered and he had no bleeding or thrombotic episodes. He received a total of 3 units of platelets during his course. He was successfully taken off ECMO after a total of 30 days, weaned off the mechanical ventilator and discharged to home.

### Case 3

A 26-year-old Hispanic woman with known systemic lupus erythematosus (SLE), hemodialysis dependent renal failure and history of HIT presented to an outside facility with complaints of fever, cough and shortness of breath. She was diagnosed with pneumonia. During her 3 days of stay at that facility she sequentially required increasing supplemental oxygen, non-invasive ventilation and then mechanical ventilation. For ventilatory support, she was paralyzed and placed on Airway Pressure Release Ventilation (APRV) at pressures of 38/5 with 100%  $\text{FiO}_2$ . She was then transferred to our facility for consideration of ECMO. Given high airway pressures and supplemental oxygen levels required to maintain oxygen saturation, a decision was made to place this patient on ECMO. Given the history of HIT, a non-heparin coated circuit was used. A 26 F AVALON ELITE<sup>®</sup> Bi-Caval Dual Lumen Catheter was placed in the right internal jugular vein and connected to the circuit. Flow rates were maintained at 3.5 L/min. Anticoagulation was maintained with bivalirudin. ACT, aPTT, and TEG were monitored for anticoagulation management. Platelets counts on admission were 76,000/ $\mu\text{L}$  and she received one unit of platelets at the time of cannulation. She was diagnosed with a *Moraxella* and *Klebsiella* pneumonia, successfully treated with antibiotics, renal replacement therapy and was weaned off ECMO in 9 days. Her platelet counts remained low normal, improving as her illness improved. Mechanical ventilation was successfully discontinued after 17 days. There were no complications related to bleeding or thrombosis during her management.

#### Case 4

A 41-year-old Hispanic man without any significant medical history was transferred to our facility after being treated for ARDS secondary to bacterial pneumonia with high PEEP ventilatory support, paralysis, and prone positioning. His stay there was complicated by bilateral pneumothoraces due to elevated pulmonary pressures, which resulted in a cardiac arrest. He was resuscitated, bilateral chest tubes were placed, and he was transferred to our facility. ECMO was started at arrival with cannulation in the right internal jugular vein with a 31 F AVALON ELITE® Bi-Caval Dual Lumen Catheter, a heparin-coated circuit and flows maintained at 4.5 L/min. Platelet count at the time of cannulation was 144,000/ $\mu$ L. Monitoring was done by PTT, TEG, and ACT. Ten days after initiation of therapy, there was a drop of platelet count to 77,000/ $\mu$ L. A diagnosis of HIT was presumed and anticoagulation changed to bivalirudin. The diagnosis was supported by a high PF4 optical density. After 2 days of bivalirudin (13 days on ECMO), he was decannulated. Platelet count recovered to 208,000/ $\mu$ L after decannulation and since the SRA was negative, heparin was re-introduced in DVT prophylaxis dose. However, his platelet counts again decreased to 64,000. Given the significant drop in platelets and a lower limb DVT, he was diagnosed with HIT and treatment started with Fondaparinux. He was then transferred back to the original hospital with a platelet count of 430,000/ $\mu$ L.

#### Case 5

A 32-year-old Hispanic woman was transferred to our hospital after 12 days of respiratory failure requiring mechanical ventilation complicated by pneumothorax due to elevated pulmonary pressures on the mechanical ventilator. She was diagnosed with H1N1 influenza. Platelets at the time of transfer were 128,000/ $\mu$ L. Management with ECMO was started at transfer with a 31 F AVALON ELITE® Bi-Caval Dual Lumen Catheter placed in the right internal jugular vein connected to a heparin-coated circuit. Flows were maintained at 4.5 L/min. Continuous heparin infusion was used for anticoagulation. After 3 days of ECMO, there was a drop of platelets to 98,000/ $\mu$ L along with extensive clotting on both sides of the oxygenator. The high degree of clotting raised a suspicion for heparin-induced thrombocytopenia with thrombosis (HITT). Anticoagulation was changed to bivalirudin, and the circuit was changed to a non-heparin-coated circuit. The PF4 antibody optical density was high. Despite this, she continued to have extensive arterial and venous thrombosis. SRA came back as negative 4 days later. Anticoagulation was monitored with PTT, TEG, and platelet function assay. After 50 days of ECMO, multiple complications, and failure to improve, care was withdrawn per family wishes.

#### COMMENTS

Thrombocytopenia in critically ill patients can be due to decreased production, consumption, or destruction. Patients requiring ECMO have various reasons for thrombocytopenia; sepsis, bleeding, medications, hemodilution, circuit-related effects and HIT, which is unique since it is an immunologic reaction secondary to heparin. Glick et al. recently conducted a retrospective analysis and concluded that HIT was uncommonly diagnosed in their cohort; however, acknowledged its significance given its crucial effect on change in therapy (6).

The ECMO circuit presents a large surface area for interaction between the patient's blood and artificial biomaterials leading to a pro-coagulant state in an already vulnerable critically ill patient. Intravascular devices such as ventricular assist devices have been shown to have an increased level of thrombocytopenia even in the absence of HIT which in turn has been associated with increased bleeding, length of hospital stay, weaning off support devices, and inpatient mortality (6–9). When coupled with the requirement to maximize circuit life and optimal function, management of anticoagulation becomes a critical part of therapy. The ELSO anticoagulation guidelines suggest that UNFH is the anticoagulant of choice for ECMO patients (2). UNFH-coated circuits are widely used as they may decrease the initial anticoagulation requirements, especially when bleeding is a concern such as in immediate post-operative states. A bolus dose is recommended at the time of cannulation followed by maintenance therapy usually based on an ACT range of 180–220 seconds. Other methods of anticoagulation monitoring are anti-factor Xa levels, PTT, TEG, and rotational thromboelastometry. Antithrombin replacement is variably done, maintaining antithrombin activity between 30% and 80%, especially when there is evidence of reduction in anticoagulation level as evidenced by a decreasing ACT (2).

The pathogenesis of HIT involves the production IgG antibodies against Platelet Factor 4 (PF4) in the presence heparin products, particularly UNFH. PF4 is released by the alpha granules of the platelets and form a poly-anion complex with heparin against which B-lymphocytes produce the antibodies (4,7,10).

The diagnosis of HIT/HITT is based on a high index of suspicion and predictability scores such as the HIT expert probability score, post-CPB score, and the commonly used 4T score (11–13). The 4T score, which has a high negative predictive value, uses a scoring system wherein a numerical score (0–8) is given with four parameters—degree of thrombocytopenia, timing, thrombosis, and other causes (of thrombocytopenia). A higher score is suggestive of a higher likelihood of the diagnosis, which can then be confirmed by laboratory analysis with

PF4 immunoassays and functional testing like the SRA. Unfortunately, there is no validated prediction score for use in ECMO patients and as Sokolovic reports, following platelet count trends in this patient population is unreliable (14). Although bleeding is uncommon, paradoxically, about half of these patients will also develop in situ thrombi (HIT with thrombosis—HITT) (5–7). Deep venous thrombi of the limbs and pulmonary emboli are the common manifestations with peripheral arterial emboli and stroke being less common (3,7,10).

In patients with high likelihood of HIT, immediate discontinuation of all forms of heparin (unfractionated and low molecular weight) including prophylactic doses, flushes, and heparin-coated circuit is recommended. Immediate therapeutic anticoagulation is advised with a non-heparin containing anticoagulants. Oral vitamin K antagonists should not be given immediately and or reversed as there is an increased risk of venous limb gangrene due to protein C and S depletion. In ECMO, the heparin-coated circuit is a source of heparin exposure to the patient and when possible should be changed. There is insufficient evidence that there is ever “endothelialization” of the heparin-coated circuit and decrease in the exposure to the heparin (15,16). The two approved anticoagulants are argatroban, which is a direct thrombin inhibitor and danaparoid, a factor Xa inhibitor (not available in United States). Fondaparinux, bivalirudin and newer oral anticoagulants are not yet US Food and Drug Administration (FDA) approved for use in HIT (3,10,17).

The best strategy for anticoagulation in ECMO patients with HIT especially given that, typically, the circuits are heparin coated, is not well defined. Argatroban is FDA approved for the treatment of HIT. It is a synthetic direct thrombin inhibitor, which binds with thrombin in a reversible manner, independent of antithrombin (AT), on both bound and free thrombin. Its half-life is about 45 minutes and a steady state is usually achieved within 1–3 hours. It is metabolized by the liver; therefore, it can be safely used in patients with renal dysfunction. The volume of infusion required for therapeutic argatroban can be a challenge in fluid management of a critically ill patient. Argatroban monitoring can be done with effects the ACT and PTT. There are reports that reagents used to monitor the PTT may have variable effects at similar concentration of the drug (18). Bivalirudin is approved for use in those undergoing percutaneous coronary interventions with known HIT and otherwise in HITT. It is also a synthetic, direct thrombin inhibitor active against free and bound thrombin independent of AT. It is proteolyzed by thrombin and renally excreted, therefore, the half-life increases in patients with renal dysfunction. Fondaparinux is not a recommended agent in HIT; however, its successful use is described in several case reports and a propensity matched retrospective analysis showed efficacy and

safety in HIT similar to argatroban (19). Plasmapheresis has been explored as a therapeutic option in HIT. The American College of Chest Physicians guidelines do not discuss it and the American Society of Apheresis has maintained a class 2C recommendation in their latest guidelines (20,21). Although there was conflicting initial data, platelet transfusion seems safe in patients with HITT but transfusion is only recommended in patients with clinical indications of bleeding or pending invasive procedures (20). Oral vitamin K antagonists may be initiated if there is evidence of macro-clots once the platelet count normalizes (3,7,10).

HIT may be more common in patients on ECMO than previously described, and we recommend the following strategy:

1. Suspicion index for HIT must remain high in these vulnerable patients.
2. With any significant drop in platelet counts when the prediction scores are not “low probability,” further exposure of patient to heparin must be stopped and alternative anticoagulation with argatroban or bivalirudin should be started.
3. If clinically feasible, consider circuit change to a non-heparin-coated circuit, otherwise we recommend close monitoring further decrease in platelet counts, thrombus formation, embolization, and ischemic changes.
4. Serosurveillance can be considered in critically ill thrombocytopenic patients at high risk.

Recognition of HIT in ECMO is critical, as it requires an immediate change in therapy. Approved and off-label use of non-heparin anticoagulants has been successfully described. Further investigation of anticoagulation management in HIT is required with and without extracorporeal circuits.

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