Journal of Cardiothoracic and Vascular Anesthesia 000 (2023) 1–2

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Editorial

Pulmonary Embolism: HITT the Nail on the Head

THE AUTHORS READ WITH great interest the recent article by Kawaji et al. in the *Journal of Cardiothoracic and Vascular Anesthesia*.[1] In this work, the authors described the case of a patient with known malignancy treated surgically, who developed a massive pulmonary embolism postoperatively in the setting of heparin-induced thrombocytopenia (HIT). The patient underwent venoarterial extracorporeal membrane oxygenation (VA ECMO) support with bivalirudin anticoagulation after a lack of improvement with anticoagulation and multiple thrombolysis attempts. This report raised several interesting discussion points, including the efficacy of thrombolytics in pulmonary embolism due to HIT, the risks of VA ECMO cannulation after thrombolysis, the use of echocardiography to locate the mixing point in VA ECMO with a femoral arterial cannula, heparin coating in ECMO circuits, and the process of weaning VA ECMO support.

There is a paucity of literature regarding the use of thrombolytic therapy in patients diagnosed with HIT.[2,3] Systemic thrombolysis is the treatment of choice in massive pulmonary embolism (unless contraindicated), and has been shown to decrease all-cause mortality.[4] However, it may be the case that thrombolytics have variable efficacy in pulmonary embolism in the setting of HIT. Indeed, *in vitro* HIT-associated thromboses are notable for altered fibrin microstructure with increased platelet activation compared to non−HIT-associated thromboses.[5] As a result of this altered structure, HIT-associated clots are commonly 'denser' than regular clots and may be more resistant to thrombolytic therapy.[6,7]

The use of thrombolytics prior to VA ECMO cannulation also raises multiple important points of discussion. Although VA ECMO has shown no survival advantage in acute pulmonary embolism compared to standard care, it is being used increasingly in this setting, often as salvage therapy and in the presence of thrombolytics.[8] In general, TPA administration increases bleeding risk (more specifically, intracranial hemorrhage).[9] Bleeding is the most common complication reported in patients supported with VA ECMO, including access site bleeding, gastrointestinal bleeding, surgical sites, the airway, and, more rarely, intracranial hemorrhage.[10] This is due to multiple factors, such as exposure of the blood to the mechanical circulatory support surface, consumptive coagulopathy, systemic inflammation, and anticoagulation. Considering these risks and the paucity of data to guide therapeutic decision-making, many inquiries arise regarding the optimal management of these patients after TPA administration. For example, consider the following: (1) Should the cannulation strategy be modified (percutaneous versus open/cutdown), (2) should systemic anticoagulation initiation be delayed, and (3) is there a role for early surveillance brain imaging in patients too unstable for an awakening trial? These are all questions that will require further investigation to forward the use of VA ECMO in this patient population.

In this article, the authors used point-of-care ultrasound (echocardiography) to locate the mixing point between ECMO and cardiac flows. Although it requires additional validation, this novel method could be used as an efficient surveillance method for Harlequin Syndrome, and could help monitor cardiac recovery. Given that the mixing point can be affected by multiple factors in addition to cardiac recovery, including ECMO flows, inotrope dosing, hypovolemia and/or hemorrhage, and venting strategy, further studies could help measure how ultrasound and pulse-wave doppler could be used to assess recovery with these factors taken into consideration.

Another point that warrants discussion is the use of heparin-coated circuits in ECMO patients with HIT. In an attempt to reduce the coagulation response elicited by contact of the blood with the circuit surface, ECMO circuit components (eg, oxygenators) are often heparin-coated. It is well-documented in the literature that any exposure to heparin could predispose a patient to develop HIT (eg, intravenous heparin flushes).[11] It is still unclear if patients supported by VA ECMO develop HIT more than the general population exposed to heparin and what role the circuit plays in triggering HIT. As an alternative to heparin, multiple other chemical coatings have been developed and used (ie, phosphorylcholine, poly-2-methoxylacrylate, synthetic albumin), and circuits may be changed to non−heparin-coated circuits in these patients.[11]

Due to its relative infrequency, the body of literature on HIT in patients supported by ECMO is lacking in evidence-based guidelines. As a result, practice, including the method of

DOI of original article: http://dx.doi.org/10.1053/j.jvca.2022.11.004.

https://doi.org/10.1053/j.jvca.2023.01.013

assessing for the likelihood of diagnosis, will significantly vary by institution.[12,13] Indeed, one literature search from 2019 described a total of 28 patients with confirmed HIT supported by extracorporeal life support (15 VA ECMO and 13 venovenous ECMO) but not necessarily with thrombotic complications.[13] In summary, patients supported with VA ECMO had a lower minimum platelet count than patients supported with VV ECMO (26 *v* 45), were more likely to experience arterial thromboembolism, and most patients (22 of 28) were treated with argatroban.[13] Interestingly, a retrospective study of ECMO patients diagnosed with HIT was notable for the resolution of thrombocytopenia 14 days after the discontinuation of systemic anticoagulation, with no change in heparin-coated ECMO circuit components (eg, the oxygenator).[14] Additionally, changing to a non−heparin-coated circuit did not significantly affect survival. If future studies confirm those findings, it may be possible to avoid exposing a patient to a potentially hazardous procedure (eg, ECMO circuit exchange) and limit the risk of iatrogenic complications.

Another important point to discuss is VA ECMO weaning. In this article, the authors described decreasing the flows and trialing the patient with a sweep of 0 L/min, as this could help ensure that the patient would tolerate decannulation. Caution should be taken when clamping the sweep in patients supported with VA ECMO in order to avoid a large shunt from the venous system to the arterial system. As such, the sweep only should be clamped for short time intervals after the ECMO machine is first set to allow retrograde flow (from the arterial to the venous system) to avoid the shunting of venous blood.[15]

To conclude, the authors described an extremely complex case of HIT-induced pulmonary embolism successfully treated with thrombolytics and VA ECMO. The paucity of literature on HIT in patients supported by ECMO warrants further research, which, given the rarity of this patient population, likely will include case reports and case series. Investigations of large databases, such as the Extracorporeal Life Support Organization Registry, would be very enlightening and assist in informing practice in this very challenging patient population.

Conflict of Interest

None.

Carl Geahchan, MD*
Nicole Ruopp, MD†
Jamel Ortoleva, MD*,[1]
*Department of Anesthesiology and Perioperative Medicine, Tufts Medical Center, Boston, MA
†Division of Pulmonary, Critical Care and Sleep Medicine, Tufts Medical Center and Tufts University School of Medicine, Boston, MA

References

1 Kawaji Q, Rostami S, Whitman GJR, et al. Bivalirudin and venoarterial extracorporeal membrane oxygenation for treatment of massive pulmonary embolism from heparin-induced thrombocytopenia with thrombosis [e-pub ahead of print]. J Cardiothorac Vasc Anesth. doi: 10.1053/j.jvca.2022.11.004. Accessed January 7, 2023.
2 Assaad M, Ataya S, Ha L. Abstract 567: A successful use of tissue plasminogen activator and Argatroban for acute therapy of a submassive pulmonary embolism caused by heparin-induced thrombocytopenia. Arteriorscler Thromb Vasc Biol 2014;34:A567.
3 Martinez LA, Burnett AE. Catheter-directed thrombolysis with alteplase and bivalirudin in a patient with heparin-induced thrombocytopenia. Am J Health Syst Pharm 2015;72:707–10.
4 Jaff MR, McMurty MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension. Circulation 2011;123:1788–830.
5 Thomas BR, Hambly RJ, Weisel JW, et al. Abnormal clot microstructure formed in blood containing hit-like antibodies. Thromb Res 2020;193:25–30.
6 Weisel JW, Litvinov RI. Mechanisms of fibrin polymerization and clinical implications. Blood 2013;121:1712–9.
7 Collet JP, Park D, Lesty C, et al. Influence of fibrin network conformation and fibrin fiber diameter on fibrinolysis speed: Dynamic and structural approaches by confocal microscopy. Arterioscler Thromb Vasc Biol 2000;20:1354–61.
8 Karami M, Mandigers L, Miranda DD, et al. Survival of patients with acute pulmonary embolism treated with venoarterial extracorporeal membrane oxygenation: A systematic review and meta-analysis. J Crit Care 2021;64:245–54.
9 Chatterjee S, Chakraborty A, Weinberg I. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: A meta-analysis. J Vasc Surg 2014;60:1094.
10 Lo Coco V, Lorusso R, Raffa GM, et al. Clinical complications during veno-arterial extracorporeal membrane oxigenation in post-cardiotomy and non post-cardiotomy shock: Still the achille's heel. J Thorac Dis 2018;10:6993–7004.
11 Kadidal VV, Mayo DJ, Horne MK. Heparin-induced thrombocytopenia (HIT) due to heparin flushes: A report of three cases. J Intern Med 1999;246:325–9.
12 Renou A, Neuschwander A, Kimmoun A, et al. Modified 4T score for heparin-induced thrombocytopenia diagnosis in VA-ECMO patients. Intensive Care Med 2020;46:1481–3.
13 Choi JH, Luc JGY, Weber MP, et al. Heparin-induced thrombocytopenia during extracorporeal life support: Incidence, management and outcomes. Ann Cardiothorac Surg 2019;8:19–31.
14 Pabst D, Boone JB, Soleimani B. Heparin-induced thrombocytopenia in patients on extracorporeal membrane oxygenation and the role of a heparin-bonded circuit. Perfusion 2019;34:584–9.
15 Lorusso R, Shekar K, MacLaren G, et al. ELSO Interim guidelines for venoarterial extracorporeal membrane oxygenation in adult cardiac patients. ASAIO J 2021;67:827–44.