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Michael Todt PharmD; and Bryan Statz PharmD

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# Bivalirudin Anticoagulation Dosing Protocol for Extracorporeal Membrane Oxygenation: A Retrospective Review

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**Abstract:** Anticoagulation with unfractionated heparin during extracorporeal membrane oxygenation (ECMO) is common, but alternative agents are being evaluated for safety and efficacy. The objective of this analysis was to assess if a comprehensive bivalirudin dosing and monitoring protocol effectively guides dose adjustments and monitoring of bivalirudin in patients during ECMO. Our analysis included 11 patients who received bivalirudin during ECMO therapy and had dosing managed using our hospital derived protocol. Patients treated over a 1-year period were included in this retrospective analysis. Clinical characteristics and changes in activated partial thromboplastin time (aPTT) were evaluated from medical records to determine the efficacy of the dosing protocol. ECMO was initiated for acute respiratory distress syndrome in eight (72.7%) patients and for cardiac arrest in three (27.3%) patients. A total of 178 protocol guided dose adjustments were made during the study. Among the dose

adjustments, 56 (31.5%) attained the protocol predicted aPTT level change, 96 (53.9%) of the measured aPTT changes were less than predicted, and 26 (14.6%) of the measured aPTT changes were more than predicted. On average, patients were within their defined therapeutic aPTT target range 66.3% of the time. All patients reached their designated aPTT target range within the first 24 hours of therapy. Significant bleeding was documented in eight (72.7%) patients. No clinically evident thromboembolic events were identified in vivo while cannulated. This analysis suggests that bivalirudin can be managed using a dosing protocol to provide anticoagulation therapy to patients during ECMO and can provide foundational guidance for dose adjustment and monitoring for other institutions.

**Keywords:** extracorporeal membrane oxygenation, blood, anticoagulation, bivalirudin, pharmacology. *J Extra Corpor Technol. 2018;50:161–6*

Extracorporeal membrane oxygenation (ECMO) is a life support system that provides pulmonary and/or circulatory support for patients experiencing a variety of disease states, such as hypoxemic or hypercapnic respiratory failure, cardiac arrest, cardiogenic shock, and cardiopulmonary distress (1–2). During ECMO, patients are at risk for thromboembolic events due to the blood's exposure to the foreign surfaces of the system circuit which necessitates the use of anticoagulants. Patients are often anticoagulated using a continuous intravenous infusion of heparin which places them at a concomitant increased risk of bleeding (3–5).

The prevalence of thromboembolic events reported in previous studies has been variable, ranging from 8.7 to 46.1% (5–7). Systemic anticoagulation is commonly used to reduce the risk of thromboembolic events from occurring in the patient and/or the machine's circuit. Monitoring of anticoagulation is necessary to evaluate efficacy of therapy and to maintain patient safety and hemodynamic stability (8–11). Unfractionated heparin is the primary anticoagulant mentioned in guidelines published by the extracorporeal life support organization and is frequently used during ECMO (12).

Newer anticoagulants, such as direct thrombin inhibitors, are being used as an alternative to unfractionated heparin (13–15). Direct thrombin inhibitors directly bind to active sites on thrombin, providing a more predictable pharmacokinetic profile and a greater reduction in thrombin compared with unfractionated heparin (16). Direct thrombin inhibitors are short-acting which allows for rapid titration to achieve desired anticoagulation (17). Heparin-induced thrombocytopenia or other immune mediated

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thrombocytopenias are not seen with direct thrombin inhibitors (18). Only two intravenous direct thrombin inhibitors are commercially available: argatroban and bivalirudin. Need for dose adjustment in patients with hepatic impairment, false elevation of prothrombin time and international normalized ratio, and cost are obstacles for the use of argatroban. There has been preliminary data regarding the use of bivalirudin as an anticoagulant during ECMO; however, there is limited published data or protocols about bivalirudin dosing and monitoring in ECMO.

The objective of this analysis was to assess if a hospital derived comprehensive bivalirudin dosing and monitoring protocol could safely and effectively guide dose adjustments and monitoring of bivalirudin in patients during ECMO.

## MATERIALS AND METHODS

This descriptive retrospective analysis was conducted at a single center community hospital in Fort Wayne, Indiana,

following the implementation of a bivalirudin based anti-coagulation protocol for patients on ECMO.

All patients who were placed on ECMO during a 1-year period were evaluated. Patients were evaluated to be included in the study if they were placed on ECMO following the protocol's implementation (Figure 1). This analysis excluded patients who were not candidates for anti-coagulation therapy during ECMO and patients who did not have at least one protocol-based dose adjustment during therapy.

The following data were collected for each eligible patient: basic demographic information (age, gender, height, weight), indication for ECMO therapy, bivalirudin dosing information (weight used for initial dose calculation, renal function, infusion rate adjustments, and bolus dosing information), baseline and subsequent activated partial thromboplastin time (aPTT) values (measured 2 hours after infusion initiation, 1 hour after a bolus given, 2 hours after non-bolus dose adjustments, and every 4 hours if within target range), highest and lowest complete blood count levels during therapy, continuous renal replacement

### BIVALIRUDIN DOSING AND MONITORING DURING ECMO PROTOCOL

#### 1. Initial dosing

- Initial bivalirudin infusion rate 2.5 mcg/kg/min for all patients
- Check aPTT 2 hours after initiating bivalirudin, then every 4 hours scheduled

#### 2. The physician will have the option of changing between one of three aPTT goal ranges:

- 40 – 60 sec
- 50 – 70 sec
- 60 – 80 sec
- Default initial aPTT goal range if not specified: 50 - 70 seconds

#### 3. Dosage adjustments for CrCl > 30 ml/min

To increase aPTT 1 – 5 sec	Increase infusion rate by 10% (multiply rate by 1.1)
To increase aPTT 6 – 10 sec	Increase infusion rate by 15% (multiply rate by 1.15)
To increase aPTT 11–15 sec	Increase infusion rate by 25% (multiply rate by 1.25)
To increase aPTT 16–20 sec	Give 0.03 mg/kg IV bolus and increase infusion rate by 35% (multiply rate by 1.35)
To increase aPTT 20–30 sec	Give 0.04 mg/kg IV bolus and increase infusion rate by 50% (multiply rate by 1.5)
To increase aPTT > 30 sec	Give 0.05 mg/kg IV bolus and increase infusion rate by 50% (multiply rate by 1.5)

Check aPTT 1 hour after any IV bolus (including IV bolus + drip rate change) and 2 hours after a change in infusion rate (no bolus); otherwise, continue routine aPTT checks q 4 hours

To decrease aPTT 1–5 sec	Reduce infusion rate by 10% (multiply rate by 0.9)
To decrease aPTT 6–10 sec	Reduce infusion rate by 15% (multiply rate by 0.85)
To decrease aPTT 11–20 sec	Reduce infusion rate by 20% (multiply rate by 0.8)
To decrease aPTT 21–30 sec	Reduce infusion rate by 30% (multiply rate by 0.7)
To decrease aPTT 31–40 sec	Reduce infusion rate by 40% (multiply rate by 0.6)
To decrease aPTT > 40 sec, or if aPTT > 110 sec	Hold for 30 minutes and reduce infusion rate by 50% (multiply rate by 0.5)

Check aPTT 2 hours after any reduction in infusion rate. (do not check after 30 minute hold; instead check 2 hours after re-start); Otherwise, continue routine aPTT checks q 4 hours

#### 4. Dosage adjustments for CrCl 10–29 ml/min OR if patient on CRRT

Same as CrCl > 30 ml/min with the following exception:

To decrease aPTT > 40 sec, or if aPTT > 110 sec	Hold for 60 minutes and reduce infusion rate by 50% (multiply rate by 0.5)
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If CRRT paused, held, or discontinued, reduce IV bivalirudin to last therapeutic IV infusion rate prior to initiating CRRT and adjust dose per ordered protocol. If not available, reduce IV bivalirudin rate by 70% (multiply rate by 0.3) and adjust dose per ordered protocol. If CRRT subsequently re-started, resume IV bivalirudin at last previous therapeutic IV infusion rate used with active CRRT and adjust dose per ordered protocol.

Check aPTT 1 hour after any IV bolus and 2 hours after any change in infusion rate (no bolus); Do not check after 60 minute hold; instead check 2 hours after re-start; Otherwise, continue routine aPTT checks q 4 hours

#### 5. Dosage adjustments for CrCl < 10 ml/min OR for intermittent hemodialysis

To increase aPTT 1 – 5 sec	Increase infusion rate by 10% (multiply rate by 1.1)
To increase aPTT 6 – 15 sec	Give 0.01 mg/kg IV bolus and increase infusion rate by 10% (multiply rate by 1.1)
To increase aPTT 16–20 sec	Give 0.015 mg/kg IV bolus and increase infusion rate by 15% (multiply rate by 1.15)
To increase aPTT > 20 sec	Give 0.02 mg/kg IV bolus and increase infusion rate by 15% (multiply rate by 1.15)

Check aPTT 1 hour after any IV bolus (including IV bolus + drip rate change) and 2 hours after a change in infusion rate (no bolus); otherwise, continue routine aPTT checks q 4 hours

To decrease aPTT 1–5 sec	Reduce infusion rate by 10% (multiple rate by 0.9)
To decrease aPTT 6–10 sec	Reduce infusion rate by 15% (multiple rate by 0.85)
To decrease aPTT 11–15 sec	Reduce infusion rate by 25% (multiple rate by 0.75)
To decrease aPTT 16–20 sec	Reduce infusion rate by 35% (multiple rate by 0.65)
To decrease aPTT 21–30 sec	Reduce infusion rate by 50% (multiple rate by 0.5)
To decrease aPTT > 30 sec, or if aPTT > 110 sec	Hold for 2 hours and reduce infusion rate by 50% (multiple rate by 0.5)

Check aPTT 2 hours after any change (including hold or re-start) in infusion rate; otherwise, continue routine aPTT checks q 4 hours

**Figure 1.** Bivalirudin dosing and monitoring during ECMO protocol.

(CRRT) therapy usage, and thromboembolic or significant bleeding events if they occurred. Significant thromboembolic events were defined as events requiring ECMO therapy to be suspended to allow for replacement of oxygenator and/or tubing if there was a sufficient decrease in flow or thromboembolic events identified in vivo by a computerized tomography scan. Significant bleeding was defined as any bleeding event that warranted treatment including, but not limited to, blood transfusions, surgical interventions, or use of hemostatic agents, and any need to adjust the infusion rate of bivalirudin to target the lower aPTT range.

This analysis had two co-primary outcomes. The first co-primary outcome was the percentage of time patients were maintained within the defined aPTT target range to achieve a targeted anticoagulated state. The second co-primary outcome was to determine the accuracy of dose adjustments by comparing the predicted aPTT change utilizing the protocol and the actual change in aPTT values following the dose adjustments. The primary safety outcomes for this analysis were the occurrence of significant bleeding and thromboembolic events. In some cases of significant bleeding, anticoagulation was continued if the patient-specific details deemed it clinically necessary. If anticoagulation was continued, the need for a lower aPTT target range was assessed and per protocol, the infusion could be held if desiring a decrease in aPTT by more than 40 seconds. Secondary outcomes included percentage of time aPTT was within the upper half of target range, percentage of time the aPTT was within the lower half of the target range, percentage of aPTT levels lower and higher than the target range, time to achieve therapeutic aPTT, length and outcome of ECMO treatment, and mortality rates.

Patients were originally assigned a goal aPTT range for anticoagulation therapy as determined to be appropriate by the physician initiating ECMO therapy. Physicians could initiate goal therapy to target an aPTT monitoring goal of 40–60 seconds, 50–70 seconds, or 60–80 seconds. All

patients were started on the same initial dose and no initial bolus dose was given per protocol. Following the initiation of therapy, aPTT was checked after 2 hours and then every 4 hours thereafter. After a follow-up aPTT level had been collected, the patient's goal range could be increased or decreased dependent on the physician's clinical discretion. New aPTT target ranges did not have to be limited to the original predefined ranges and physicians could also indicate targeting toward the higher or lower end of the target range dependent on the clinical situation. Details of the dosing and monitoring protocol can be found in the supplemental information. No additional anticoagulation was provided to the patient through sample ports or pigtailed to reduce areas of stasis.

Descriptive and frequency statistics were used to analyze the data. All data management and statistics were performed using Excel 2010 (Microsoft Corp., Redmond, WA).

## RESULTS

A total of 15 patients were treated with ECMO during the analysis period. After eligibility screening, four patients were excluded: two did not receive anticoagulation therapy during ECMO and two did not have at least one protocol-directed dose adjustment for bivalirudin therapy.

Of the 11 patients included in this analysis, eight (72.7%) patients had an indication of acute respiratory distress syndrome (ARDS), and three (27.3%) patients had an indication of cardiac arrest for ECMO. Four patients underwent veno-arterial ECMO, six patients underwent veno-venous ECMO, and one patient was started on veno-venous ECMO and later transitioned to veno-arterial ECMO. Additional demographic information can be found in Table 1.

On average, patients spent 66.3% of time within their defined therapeutic aPTT target range. The lowest percentage of time within therapeutic range was 30.0%, and

**Table 1.** Baseline patient demographics and outcomes.

Case	Age (years)	Weight (kg)	Indication	ECMO LOT	Hospital LOS	CRRT	Platelet Range (th/ $\mu$ L)	Hemoglobin Range (g/dL)	Outcome
1	41	57.1	AMI	4	4	No	20–199	8.1–12.1	Weaned and expired
2	60	70.4	ARDS	7	19	No	203–391	7–11.8	Survived
3	22	72.5	ARDS	4	11	No	57–313	7.6–18.4	Survived
4	60	114.1	ARDS	6	30	Yes	61–279	7.5–13.8	Survived
5	47	89.4	AMI	4	4	No	39–529	6.8–17.5	Weaned and expired
6	61	62.7	ARDS	22	50	Yes	44–344	6.6–11.2	Survived
7	56	127.7	ARDS	21	29	No	48–276	8.6–14.9	Weaned and expired
8	61	84.1	ARDS	12	19	Yes	29–273	7.2–15.5	Weaned and expired
9	16	80.7	ARDS	17	39	No	85–292	8.2–16.6	Survived
10	69	97.9	ARDS	4	9	No	30–115	6–11.5	Survived
11	74	105.0	AMI	8	9	Yes	63–437	7.7–16.8	Weaned and expired

AMI, acute myocardial infarction; LOS, length of stay; LOT, length of therapy.

the highest time within therapeutic range was 90.0%. The most common therapeutic goal range selected as an original target by physicians was 50–70 seconds. Only two (18.2%) patients did not have their target aPTT goal adjusted during ECMO treatment.

A total of 178 protocol guided dose adjustments were made during the analysis period. Of the dose adjustments, 56 (31.5%) attained the protocol predicted aPTT level change. Most commonly, the aPTT level change following protocol guided dose adjustments was less than what was predicted by the protocol. Among the dose adjustments, 96 (53.9%) were less than what the protocol predicted and 26 (14.6%) were greater than what the protocol predicted. Adjustments made at lower infusion rates were more likely to be less than what the protocol predicted compared with adjustments made at higher infusions rates. Additional data for time within designated therapeutic ranges can be found in Table 2.

In addition to changing the aPTT target range, physicians could also specify to target the lower end or higher end of the target range. Targeting the lower end of the target range was commonly performed if the patient had significant bleeding or clinical discretion that the patient may be likely to bleed at higher aPTT levels. Targeting the higher end of the target range was commonly performed if clots or fibrin strands were seen in the oxygenator or circuit. For aPTT levels that were within the patients' predefined target range, 47.3% of levels were specific to the lower half of the target range and 52.7% of levels were specific to the higher end of the target range.

Patient time to therapeutic goal varied. There were three (27.7%) patients who reached goal from the initial bivalirudin infusion dose, 2.5 mcg/kg/min, as indicated by the first aPTT level drawn after the start of the infusion. The other eight patients had a supratherapeutic aPTT after the start of the infusion and required dose adjustments to get them into their defined therapeutic range. By 14 hours after the start of the infusion, eight patients (72.7%) reached their target goal range. All patients reached their target aPTT goal range within the first 24 hours of therapy.

Significant bleeding was documented in eight (72.7%) patients. The most common documented bleeding event was from cannulation sites of the ECMO circuit. Bleeding was also noted from other tubing sites. One patient had documented bleeding from a pulmonary source identified via their endotracheal tube and another patient had a gastrointestinal bleed identified via their orogastric tube. Neither patient required intervention to stop or prevent additional bleeding. One patient was admitted with open sores in the mouth before ECMO therapy. During treatment, the oral sores began to bleed and the patient required packing with fibrin sealant to stop the bleeding.

All patients included in our analysis had documented clotting within the oxygenator and/or fibrin strand formation pre-oxygenator. Clots and fibrin strands were monitored routinely with every shift change and aPTT laboratory draw. No patients required ECMO therapy to be stopped because of significant obstruction of flow in the tubing or oxygenator. Two patients were identified as having thromboembolic events, but both occurred after decannulation and discharge from the hospital. One patient was readmitted 1 week later for superior vena cava thrombus and one patient was readmitted 2 months later for bilateral lower extremity deep vein thromboses.

The average length of ECMO was 9.9 days ( $\pm$ SD 6.6) with an average length of hospitalization of 20.3 days ( $\pm$ 14.4). Death occurred in five (45.5%) patients during their admission. All deaths occurred in the hospital following the decision for patients to be terminally weaned from ventilator support and other supportive care, including ECMO therapy. All six of the patients discharged from the hospital were still living 90 days after the discharge date.

## DISCUSSION

This analysis found that changes in aPTT levels could be predicted using pre-specified adjustment rates for bivalirudin. These results suggest that anticoagulation

**Table 2.** Protocol efficacy per patient case.

Case	No. aPTT Collected	No. aPTT in Target Range (% of time in range)	No. aPTT Higher than Target Range (% of time in range)	No. aPTT Lower than Target Range (% of time in range)
1	10	9 (90.0)	1 (10.0)	0 (0.0)
2	47	35 (74.5)	7 (14.9)	5 (10.6)
3	20	6 (30.0)	7 (35.0)	7 (35.0)
4	39	26 (66.7)	9 (23.1)	4 (10.2)
5	23	11 (47.8)	11 (47.8)	1 (4.4)
6	133	106 (79.7)	17 (12.8)	10 (7.5)
7	125	86 (68.8)	19 (15.1)	20 (16.1)
8	90	61 (67.8)	20 (22.2)	9 (10.0)
9	93	78 (83.9)	14 (15.1)	1 (1.0)
10	27	15 (55.6)	5 (18.5)	7 (25.9)
11	53	34 (64.2)	7 (13.2)	12 (22.6)

needs during ECMO therapy can be accomplished with bivalirudin using a protocol to guide dose adjustments and monitoring.

Our findings serve to expand on the limited data available for the use and management of bivalirudin as anticoagulation therapy during ECMO therapy. Anticoagulation therapy during ECMO has traditionally been managed with intravenous heparin infusions. Although some data have been published about the use of bivalirudin as an anticoagulant in ECMO, the data has been limited. Additional data on how to manage and adjust bivalirudin when it is used in anticoagulation therapy has yet to be published.

In our institution, we designed a protocol to manage the dose adjustment of bivalirudin to reduce possible confounding factors that may occur if dose adjustment occurred on a patient to patient basis; thus, all patients were managed in the same fashion allowing for homogenous data to assess how effective our protocol was and if it could effectively manage bivalirudin. All patients were assigned a target aPTT range before starting anticoagulation therapy. Our analysis included patients for both ARDS and cardiac arrest. Patient demographics were also widely varied allowing the protocol to be used in a fairly heterogeneous population. Despite our small analysis population, having a varied patient population allows for the application and generalizability of a bivalirudin dose adjustment protocol that may be applied to larger populations.

Our analysis has some limitations. First, the sample size was small during the approximate year of observation for the protocol after it was implemented. Our analysis also excluded two patients who did not receive anticoagulation therapy during ECMO therapy. One patient transferred from the hospital before having anticoagulation therapy initiated. The second patient had anticoagulation therapy withheld because of preexisting pancytopenia that predisposed the patient to a high bleeding risk. Two other patients who received bivalirudin were excluded because they did not have at least one protocol-managed dose adjustment. For one patient, care was withdrawn before having a dose adjustment completed. The other patient was started on bivalirudin, however, following the first aPTT, the value was supratherapeutic and elevated beyond being detectable by the laboratory. Follow-up aPTT laboratory draws were completed on a scheduled basis for 32 hours, then the patient was weaned and withdrawn from supportive care. Despite a small patient population, we felt the sample size reported was significant considering the limited amount of data available on the subject. Our findings are introductory and need to be confirmed in a larger patient population.

Secondly, the reported number of times an adjustment in the infusion rate achieved a predicted change in aPTT was only 31.5%. During analysis of the data, it was

discovered that at lower infusion rates, the dose adjustments made were less accurate than dose adjustments made when the infusion rate was higher. Because our dose adjustments were percentage based, lower infusion rates would have a smaller adjustment in the dose compared with higher infusion rates where the dose changes would be more significant. It was found that changes in the aPTT were most commonly less than what was predicted by the protocol. At the time our hospital's bivalirudin dosing protocol was created and implemented there was limited data available for dosing bivalirudin in ECMO patients and it was felt that more conservative dose adjustments where the actual change was less than the predicted was preferable so we were not over-anticoagulating our patients. Following any dose adjustments of bivalirudin, the aPTT was rechecked in 2 hours, and doses could be re-adjusted again if out of range. Thus, patients were not out of their goal range for long periods of time if a dose adjustment did not achieve its desired or predicted change.

Third, the reported amount of time patients were maintained in their designated aPTT therapeutic range was 66.3% of the time. This may be construed to mean that patients were ineffectively managed 33.7% of the time, however, our protocol did allow for clinical discretion to override the need for dose adjustment if the patient was only slightly out of range. For the purpose of our analysis, we used hard set ranges to determine the time within therapeutic range; however, it should be noted that patients were at times maintained at an aPTT that was either subtherapeutic or supratherapeutic if it was clinically perceived to be beneficial to the patient. One example was for a patient with a target aPTT range of 50–70. The patient had clotting in the ECMO machine circuit and one aPTT resulted at 71.2 seconds. Despite the aPTT being elevated higher than the goal range, the patient was continued at the same infusion rate to reduce the risk of further clot formation. During the analysis period, patients were maintained at either a subtherapeutic level or supratherapeutic level as directed a total of 28 times.

Last, our health system used aPTT levels to guide dose adjustment of bivalirudin. There is little information for direct correlation between the anticoagulation effect of bivalirudin and reported aPTT levels. Other health systems may use different laboratory values to measure the effects of parenteral direct thrombin inhibitors such as activated clotting time, ecarin chromogenic assay, dilute thrombin time test, or prothrombinase-induced clotting time test. Activated clotting time laboratory draws are not commonly used on the patient floors at our institution and the other laboratory assessment tools are not available at our health system. This may decrease the generalizability of our protocol to other institutions that use these other laboratory values and not aPTT levels.

In conclusion, we demonstrated that bivalirudin can be managed using a dose adjustment protocol during ECMO therapy to provide anticoagulation therapy with minimal bleeding events and no clinically evident thromboembolic complications in vivo while cannulated. Although our dose adjustment only resulted in the predicted aPTT change 31.5% of the time, we believe the conservativeness of our dose adjustment prevented over anticoagulation while still not placing the patient at risk of clinically evident thromboembolic complications. Our data helps expand on the limited data available for dosing and adjusting bivalirudin in ECMO patients and may help provide a foundational protocol for other health systems looking to modify or create a bivalirudin anticoagulation dosing policy for ECMO patients.

## REFERENCES

1. Squiers JJ, Lima B, Dimaio JM. Contemporary ECMO therapy in adults: Fundamental principles and systematic review of the evidence. *J Thorac Cardiovasc Surg.* 2016;152:20–32.
2. Bartlett RH, Gattinoni L. Current status of extracorporeal life support (ECMO) for cardiopulmonary failure. *Minerva Anesthesiol.* 2010;76:534–40.
3. Bakhtiary F, Keller H, Dogan S, et al. Venoarterial extracorporeal membrane oxygenation for treatment of cardiogenic shock: Clinical experiences in 45 adult patients. *J Thorac Cardiovasc Surg.* 2008;135:382–8.
4. Rastan AJ, Dege A, Mohr M, et al. Early and late outcomes of 517 consecutive adult patients treated with ECMO for refractory post-cardiotomy cardiogenic shock. *J Thorac Cardiovasc Surg.* 2010;139:302–11, 311.e1.
5. Beiras-fernandez A, Deutsch MA, Kainzinger S, et al. ECMO in 108 patients with low cardiac output—a single-center experience. *Int J Artif Organs.* 2011;34:365–73.
6. Trudzinski FC, Minko P, Rapp D, et al. Runtime and aPTT predict venous thrombosis and thromboembolism in patients on ECMO: A retrospective analysis. *Ann Intensive Care.* 2016;6:66.
7. Rastan AJ, Lachmann N, Walther T, et al. Autopsy findings in patients on postcardiotomy extracorporeal membrane oxygenation (ECMO). *Int J Artif Organs.* 2006;29:1121–31.
8. Esper SA, Levy JH, Waters JH, et al. Extracorporeal membrane oxygenation in the adult: A review of anticoagulation monitoring and transfusion. *Anesth Analg.* 2014;118:731–43.
9. Oliver WC. Anticoagulation and coagulation management for ECMO. *Semin Cardiothorac Vasc Anesth.* 2009;13:154–75.
10. Bembea MM, Schwartz JM, Shah N, et al. Anticoagulation monitoring during pediatric extracorporeal membrane oxygenation. *ASAIO J.* 2013;59:63–8.
11. Sulkowski JP, Preston TJ, Cooper JN, et al. Comparison of routine laboratory measures of heparin anticoagulation for neonates on extracorporeal membrane oxygenation. *J Extra Corpor Technol.* 2014;46:69–76.
12. Buck ML. Control of coagulation during extracorporeal membrane oxygenation. *J Pediatr Pharmacol Ther.* 2005;10:26–35.
13. Ranucci M, Ballotta A, Kandil H, et al. Bivalirudin-based versus conventional heparin anticoagulation for postcardiotomy extracorporeal membrane oxygenation. *Crit Care.* 2011;15:R275.
14. Jyoti A, Maheshwari A, Daniel E, et al. Bivalirudin in venovenous extracorporeal membrane oxygenation. *J Extra Corpor Technol.* 2014;46(1):94–7.
15. Pieri M, Agracheva N, Bonaveglia E, et al. Bivalirudin versus heparin as an anticoagulant during extracorporeal membrane oxygenation: A case-control study. *J Cardiothorac Vasc Anesth.* 2013;27:30–4.
16. Bates SM, Weitz JJ. The mechanism of action of thrombin inhibitors. *J Invasive Cardiol.* 2000;12(Suppl F):27F–32.
17. Di nizio M, Middeldorp S, Büller HR. Direct thrombin inhibitors. *N Engl J Med.* 2005;353:1028–40.
18. Lee CJ, Ansell JE. Direct thrombin inhibitors. *Br J Clin Pharmacol.* 2011;72:581–92.