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Quantitative Measurement of Heparin in Comparison With Conventional Anticoagulation Monitoring and the Risk of Thrombotic Events in Adults on Extracorporeal Membrane Oxygenation

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Dear Editor

The activated clotting time (ACT) is the most commonly used test to assess anticoagulation during extracorporeal membrane oxygenation (ECMO). Unlike the ACT or the activated partial thromboplastin time (aPTT), anti-factor Xa (antiXa) is a direct measure of heparin activity (1). ACT is poorly correlated to heparin dose and to aPTT in adults and in children antiXa levels track better with heparin dose, but the ideal monitoring strategy for anticoagulation during ECMO is unknown (2, 3). We sought to determine whether ACT, aPTT, or antiXa levels were associated with bleeding requiring transfusion or clotting events in adults on ECMO.

The study was approved by our Institutional Review Board (IRB #023013). We included 22 adults (n = 330 total measurements for ACT, aPTT, and antiXa). Hourly ACT goals were monitored based on the ACT level when the antiXa level was within range (0.3-0.7 U/mL). If the ACT fell out of range, this prompted a blood draw for the measurement of aPTT and antiXa. Heparin dose was modified in response to antiXa levels only. The first five simultaneous measurements were analyzed. Generalized mixed modeling was used to assess

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the relationship between ACT, aPTT, and antiXa levels and bleeding or thrombotic events, respectively.

Most patients (15/22, 68%) were supported with veno-venous ECMO for a median of 6 days (range 1 – 14). There were 6 bleeding episodes at the cannula site requiring transfusion and 4 deep venous thromboses (DVT). The majority (59%) had no events related to bleeding or clotting. There were no changes in circuit components required. Survival to decannulation was 86%, and survival to hospital discharge was 77%. ACT was poorly correlated ($r = 0.50$ for all) and aPTT was modestly correlated ($r = 0.51 - 0.67$) with antiXa levels. Lower levels of antiXa were associated with DVT (0.33 U/mL, 95% CI 0.27 – 0.39, $p = 0.0031$) such that for every unit decrease in antiXa there was a 7-fold increase in the odds of DVT (OR 7.28, 95% CI 1.61 – 32.94, $p = 0.011$) (Table 1). There were no relationships between antiXa and bleeding and ACT or aPTT and outcomes.

Robust data linking the use of antiXa levels for heparin titration with outcomes are lacking. In hospitalized patients who required heparin for cardiovascular indications, aPTT and antiXa levels were discordant the majority of the time; high aPTT/in-range antiXa discordance predicted major bleeding and mortality (4). In pediatric ECMO patients, lower antiXa levels (but not ACT or aPTT levels) were associated with circuit thrombosis, although hemostatic changes that occur during early life makes it difficult to generalize this observation to adults (5).

Surrogate assays such as ACT and aPTT are at best modestly correlated with antiXa, a direct heparin assay, and lower antiXa levels predict DVT in adult ECMO patients. Heparin dosing titrated to antiXa levels may have an important role in reducing morbidity, but the optimal target range for this assay is unknown. Larger prospective studies are needed to determine the best approach to anticoagulation during extracorporeal support.

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Table 1
Associations between ACT, aPTT, and antiXa levels and risk of thrombosis

Variable	Outcome*	OR for clinical event per 1 unit change in assay	95% CI	P value
ACT	Thrombosis vs. no event	1.01	0.99 – 1.03	0.335
	Thrombosis vs. any event	1.01	0.99 – 1.03	0.257
aPTT	Thrombosis vs. no event	1.01	0.99 – 1.03	0.351
	Thrombosis vs. any event	1.01	0.99 – 1.03	0.269
AntiXa	Thrombosis vs. no event	7.28	1.61 – 32.94	0.011
	Thrombosis vs. any event	6.45	1.77 – 23.53	0.006

* Any event includes bleeding or no events.

ACT=activated clotting time; aPTT= activated partial thromboplastin time; AntiXa=anti factor Xa level; OR=odds ratio; CI=confidence interval