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Comparison of Routine Laboratory Measures of Heparin Anticoagulation for Neonates on Extracorporeal Membrane Oxygenation

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Abstract: Our objective was to determine the best measure of heparin anticoagulation in neonatal patients on extracorporeal membrane oxygenation. Activated clotting time (ACT), activated partial thromboplastin time (aPTT), and antifactor Xa levels, along with corresponding heparin infusion rates and heparin bolus volumes, were collected from neonates receiving ECMO at our institution from 2008 to 2013. After natural log transformation of antifactor Xa, ACT, and aPTT, overall correlations between antifactor Xa levels and either ACT or aPTT and correlations between these tests and heparin infusion rates were evaluated using linear mixed models that accounted for both within- and between-patient correlations. Twenty-six neonates with an average weight of 3.4 kg (standard deviation .7) had a total of 27 separate ECMO runs during the study period. Within each patient, ACT (r = .40, p < .0001) and aPTT (r = .48, p < .0001) were both directly correlated with antifactor Xa levels. In contrast, between patients, only aPTT maintained a direct correlation with antifactor Xa (r = .61, p = .07), whereas ACT showed a statistically significant inverse correlation with antifactor Xa (r = –.48, p = .04). Compared with ACT, aPTT is more consistently reflective of the anticoagulation status both within each patient on ECMO and between patients treated with ECMO. Future efforts to develop standardized heparin infusion algorithms for patients on ECMO should consider using aPTT levels to monitor anticoagulation. **Keywords:** ECMO, partial thromboplastin time, heparin, activated clotting time. *JECT. 2014;46:69–76*

During extracorporeal membrane oxygenation (ECMO), anticoagulation administration is necessary to prevent thrombotic complications that occur with exposure of blood to the artificial surfaces of the ECMO circuit (1). This is most commonly accomplished by continuous administration of unfractionated heparin, which binds to and increases the activity of antithrombin III leading to inhibition of the intrinsic and common coagulation pathways (2,3).

Careful monitoring of anticoagulation during neonatal ECMO is necessary to prevent both thrombotic and hemorrhagic complications that can have morbid and sometimes fatal outcomes (1). Activated clotting time (ACT) assesses the ability of the intrinsic coagulation pathway to form a clot by adding an activator to whole blood and then measuring the time to clot formation (4). The test can be performed quickly and inexpensively at the bedside, which has contributed to its broad use for patients on ECMO. Across all patient populations and indications, the most commonly used test for measuring heparin activity is the activated partial thromboplastin time (aPTT), which assesses the function of both coagulation pathways (4). Until the recent development of bedside assays, this test required blood samples be sent to a central laboratory for processing, making it suboptimal for adjusting heparin

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infusions in real time (3). Although more costly and less commonly available, the antifactor Xa assay is considered the best overall measure of heparin activity because it is a more specific indicator of heparin's availability for anticoagulation (5).

In a recent international survey of certified ECMO programs, ACT was the parameter of choice to measure anticoagulation for 97% of respondents (2). However, without any widely accepted protocols for administering or monitoring anticoagulation during ECMO, heparin dosing and monitoring strategies varied widely between institutions. The objective of this study was to evaluate how well ACT and aPTT levels reflect heparin anticoagulation as determined by antifactor Xa levels for neonatal patients on ECMO.

METHODS

Study Design

The Institutional Review Board at Nationwide Children's Hospital approved this retrospective review of neonates placed on ECMO at less than 1 month of age between March 2008 and February 2013. Basic demographic information, clinical outcomes, laboratory values, heparin infusion rates at the time of each sample collection, and the timing and amount of heparin boluses were extracted from the medical records of eligible patients.

Extracorporeal Membrane Oxygenation and Anticoagulation

All patients were supported on a Quadrox series oxygenator (Maquet, Wayne, NJ) and Carmeda BioActive Surface circuitry (Medtronic, Minneapolis, MN), the latter of which is coated with a material that has been shown to be significantly less thrombogenic (6). The cannulas inserted were not heparin-coated. A loading dose of 200 International units (IU)/kg was administered at the time of cannulation and approximately 1 IU of heparin per milliliter was contained within the blood products and fluids used to prime the circuit. Continuous heparin infusion was initiated only when the ACT dropped below 240 seconds, after which heparin was initiated at 20 IU/kg/h and titrated according to the algorithm outlined in Figure 1.

Laboratory Tests

A standardized monitoring protocol is followed whereby antifactor Xa levels were collected twice daily, aPTT was collected every 4 hours, and ACT was collected every 1–3 hours or as clinically indicated. Antifactor Xa levels were drawn at least 3 hours after a change in heparin dose to ensure steady-state conditions. The

Anti-Xa (0.3-0.8 u/ml)	aPTT (60-90 seconds)	ACT (180-220 seconds)	Response
normal	↑	↑	Repeat antifactor Xa, aPTT, ACT Consider fibrin degradation/split products to rule out DIC Check patient temperature Rule out hemodilution If at upper end of antifactor Xa range, consider **decreasing** UFH drip rate by 5-10%.
normal	↓	↓	Consider checking ATIII and Fibrinogen level Administer FFP 20ml/Kg or ATIII, then repeat antifactor Xa level **Increase** UFH drip rate by 10%
normal	↑	↓	Consider checking ATIII level Repeat antifactor Xa, aPTT and ACT at this time If at upper end of antifactor Xa range, consider **decreasing** UFH drip rate by 5-10%.
↑	↑	↑	**Decrease** UFH drip rate by 10%
↑	↓	↓	Consider checking ATIII level Administer FFP/ATIII (preferably ATIII) **Decrease** UFH drip rate by 5-10%
↓	↓	↓	Consider UFH bolus **Increase** UFH drip rate by 10%
↓	↑	↑	Consider UFH bolus Consider fibrin degradation/split products to rule out DIC **Increase** UFH drip rate by 5%

Figure 1. Anticoagulation algorithm. ACT, activated clotting time; aPTT, activated partial thromboplastin time; ATIII, antithrombin; anti-Xa, unfractionated antifactor Xa; DIC, disseminated intravascular coagulopathy; FFP, fresh-frozen plasma; UFH, unfractionated heparin.

antifactor Xa and aPTT samples were collected in citrated tubes and required approximately 15 minutes centrifugation before analysis; the assays were performed with the STA-R Evolution device (Diagnostica Stago, Parsippany, NJ). Antifactor Xa levels were tested using the chromogenic method without adding exogenous antithrombin. Before December 2010, the measurement of ACT, performed with whole blood, was carried out on the Hemochron Junior Signature Elite (Junior) (ITC, Edison, NJ) with the ACT+ cuvette and a target range of 160–200 seconds. Subsequent to December 2010, our institution has been using the Hemochron Response (Response) (ITC) with a target range of 180–220 seconds. Correlations of ACT and antifactor Xa with either the Response or the Junior were qualitatively and statistically similar.

Statistical Analysis

Each patient's ECMO course was divided into 1-hour time periods, and each heparin infusion rate and laboratory value was placed into its corresponding time period for analyses. To ensure that patients with the longest ECMO courses did not have undue influence on the results, only the first 272 hours of each patient's ECMO course were included in analyses. This cutoff was chosen because only two patients had ECMO courses longer than 272 hours, whereas three patients had ECMO courses between 253 and 272 hours. The 272-hour cutoff limited the undue influence of the two patients with very long ECMO courses (>330 hours) while minimizing data loss and allowing convergence of the mixed models used to estimate between- and within-patient correlations. Descriptive statistics were used to examine patient characteristics with medians and interquartile ranges used for continuous variables. For measures of anticoagulation, the reported values are the median of each patient's median value and interquartile range; these values were determined by first identifying the median and interquartile range (IQR) of each measure for each patient and then identifying and reporting the median and IQR of these values for each measure. Bivariate linear mixed models were used to model within-patient and between-patient correlations among coagulation markers and heparin infusion rates. The within-patient correlation describes the association between changes in the measures within each patient over time on ECMO. The between-patient correlation measures across patients if high values of one factor are associated with high values of the other factor over the course of their ECMO run. Ninety-five percent confidence intervals and p values for each of these correlation coefficients were calculated using bootstrapping with 5000 replications (7). Similar models were used to calculate these correlation coefficients during periods of nonsteady state (defined as the first 4 hours on ECMO, within 4 hours of a heparin drip change, or within 3 hours of a heparin bolus) and steady state (all other time points). As a result of their skewed distributions, ACT, aPTT, and antifactor Xa were log-transformed before all analyses to meet the normality assumption of linear mixed models with the exception of the analyses used to produce the figures showing trends in each factor over time. Probability values of <.05 were considered statistically significant. Correlation coefficients between steady state and nonsteady state were compared after using a Bonferroni correction to adjust p values for multiple testing (α = .05/14). Statistical analyses were performed using SAS (Statistical Analysis Software Version 9.3, Cary, NC).

RESULTS

Population Characteristics

Twenty-six neonates underwent 27 total ECMO runs for a median duration of 93.1 hours (IQR, 61.1–177.7) (Table 1). There were 14 males (53.8%) and the most common indications for ECMO cannulation were congenital diaphragmatic hernia (11 [42.3%]) and persistent pulmonary hypertension of the newborn (seven [26.9%]). Most patients survived to decannulation (22 [84.6%]) and to discharge (18 [69.2%]).

The median dose of heparin administered in this population over the course of their ECMO runs was 28.5 IU/kg/h (IQR, 24.0–33.0). The median ACT, aPTT, and antifactor Xa levels in this population over the course of their ECMO runs were all within our targeted ranges (Table 1).

Changes in Measures of Anticoagulation Over Time

Figure 2 shows the changes in anticoagulation measures and heparin infusion rates over time on ECMO. Over the

Table 1. Population characteristics.

Characteristic	
Male, no. (%)	14 (53.8%)
Weight, mean (standard deviation)	3.4 (±.7) kg
Primary diagnosis, no. (%)	
Congenital diaphragmatic hernia	11 (42.3%)
Primary pulmonary hypertension	7 (26.9%)
Meconium aspiration	5 (19.2%)
Sepsis	2 (7.7%)
Cardiomyopathy	1 (3.8%)
ECMO duration in hours, median (IQR)	93.1 (61.1–177.7)
Anticoagulation, median (IQR)	
Heparin dose (units/kg/h)	28.5 (24–33)
ACT (seconds)	196 (159–219)
aPTT (seconds)	88 (73.8–104.3)
Antifactor Xa (IU/mL)	.5 (.4–.6)
Survival, no. (%)	
To decannulation	22 (84.6%)
To discharge	18 (69.2%)

ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; ACT, activated clotting time; aPTT, activated partial thromboplastin time.

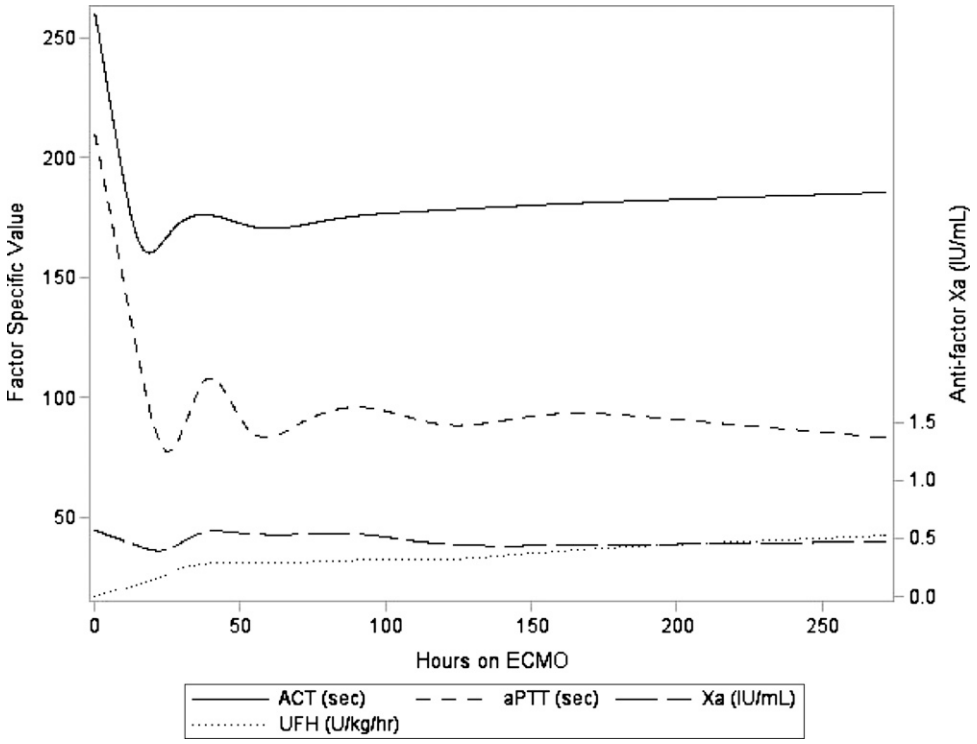

Figure 2. Changes in coagulation markers over time on ECMO. These curves were estimated by averaging patient-specific changes in anticoagulation measures and heparin infusion rates over time on ECMO across all patients. Over the entire ECMO run for all patients, there was an average increase in the heparin infusion rate of .19 units/kg/h (95% confidence interval, .11–.26) with aPTT and ACT decreasing by .48 seconds (.18–.78 seconds) and .12 seconds (.02–.22 seconds) each hour, respectively ($p < .05$). Most of these changes occurred within the first 48 hours. After 48 hours, ACT had a significant increase over time (.14 seconds, .00–.27 seconds, $p = .047$), whereas aPTT had no significant change. There was no significant change in the antifactor Xa levels over the duration of ECMO ($p = .76$). ECMO, extracorporeal membrane oxygenation; ACT, activated clotting time; aPTT, activated partial thromboplastin time; Xa, antifactor Xa level; UFH, unfractionated heparin.

entire ECMO run for all patients, there was an average increase in the heparin infusion rate of .19 units/kg/h (95% confidence interval [CI], .11–.26), whereas aPTT and ACT decreased by .48% (95% CI, .18–.78) and .12% (95% CI, .02–.22) each hour, respectively ($p < .05$). The largest changes in each of these factors occurred within the first 48 hours on ECMO. After 48 hours, ACT showed an average increase of .14 percent per hour (95% CI, .00–.27, $p = .047$), whereas aPTT showed no significant linear change over time. There was no significant change in the antifactor Xa levels over the duration of ECMO ($p = .43$).

Measures of Anticoagulation: Within-Patient Correlations

Following natural log transformation of data, within-patient correlations were first evaluated. Changes in ACT and aPTT both reflected similar changes in antifactor Xa levels, as shown by the statistically significant within-patient correlations detected between both ACT and antifactor Xa ($r = .40$; 95% CI, .21–.58; $p < .0001$) (Figure 3A) and aPTT and antifactor Xa ($r = .48$; 95% CI, .13–.62; $p < .0001$) (Figure 3B). No significant within-patient correlations were seen between ACT or aPTT and the heparin infusion rate. Within individual patients, an increased heparin infusion rate was associated with an increased antifactor Xa level, as demonstrated by the positive within-patient correlation between heparin infusion rate and antifactor Xa level ($r = .26$; 95% CI, .06–.48; $p = .009$).

Measures of Anticoagulation: Between-Patient Correlations

Again using natural log-transformed data, between-patient correlations were determined to see if overall average values of ACT or aPTT correlated with average antifactor Xa levels. On average, patients with higher ACT measures over the course of their ECMO run did not have higher antifactor Xa levels over the course of their ECMO run. In fact, the between-patient correlation was significantly negative for ACT and antifactor Xa ($r = –.48$; 95% CI, –.81 to –.14; $p = .04$) (Figure 3C). However, patients with higher aPTT measures over the course of their ECMO run did have higher antifactor Xa levels over the course of their ECMO run, as demonstrated by the positive between-patient correlation between aPTT and antifactor Xa ($r = .61$; 95% CI, –.29 to .92; $p = .07$) (Figure 3D). No significant between-patient correlations were seen between ACT or aPTT and the heparin infusion rate. Heparin infusion rates were positively correlated with antifactor Xa levels between patients ($r = .56$; 95% CI, –.15 to 1.00; $p = .07$), demonstrating that, on average, patients with higher heparin infusion rates over the course of their ECMO run had higher antifactor Xa levels.

Sensitivity Analyses

Analyses were compared before and after the change in ACT machines and no significant differences were found in within- or between-patient correlations during the time

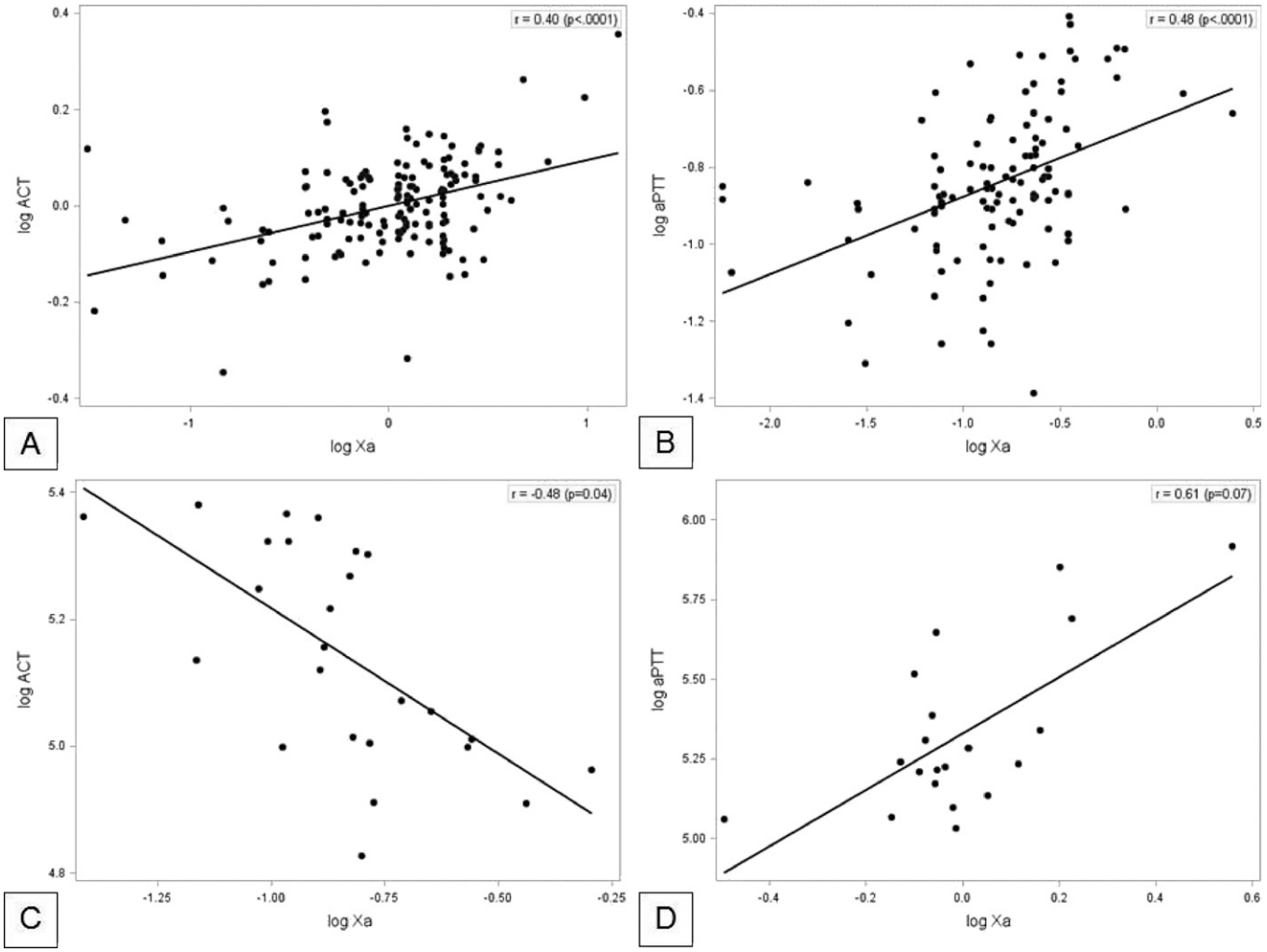

Figure 3. Correlations between measures of anticoagulation in neonatal patients on ECMO receiving heparin. Within-patient correlations between ACT (**A**) or aPTT (**B**) and antifactor Xa are displayed in **A** and **B**; these within-patient correlations describe the association between changes in these factors over time in each patient during their ECMO run. In an individual patient, changes in ACT and aPTT both reflect similar changes in antifactor Xa levels. Between-patient correlations between ACT (**C**) or aPTT (**D**) and antifactor Xa are displayed in **C** and **D**; the between-patient correlations measure whether high values of one factor are reflective of high values of the other factor across patients on EMCO. Across patients on ECMO, higher ACT measures do not reflect higher antifactor Xa levels, whereas for aPTT, higher aPTT levels are reflective of higher antifactor Xa levels. ECMO, extracorporeal membrane oxygenation; ACT, activated clotting time; aPTT, activated partial thromboplastin time.

periods when the different ACT machines were used (p = .12 for both). In addition, separate correlations were estimated during "steady state." After correcting for multiple comparisons, no significant differences were found in any of the investigated correlations between the steady-state and nonsteady-state periods.

DISCUSSION

In this study of neonatal patients on ECMO, we demonstrated significant differences in how ACT and aPTT levels reflect heparin anticoagulation, as measured by antifactor Xa levels. Within each patient, changes in both their ACT and aPTT levels directly correlated with changes in their antifactor Xa levels; therefore, as the ACT and aPTT levels increased, the antifactor Xa level also increased in each patient. However, when comparing measures of anticoagulation across patients, we found that aPTT continued to be directly correlated with antifactor Xa levels but ACT now had a significant inverse correlation with antifactor Xa levels. Therefore, when comparing levels across patients, higher aPTT levels were reflective of higher antifactor Xa levels for each patient, but higher ACT levels were reflective of lower antifactor Xa levels. Consequently, within a given patient,

a change in either ACT or aPTT is associated with a similar change in antifactor Xa levels. However, across different patients, a specific aPTT value reflects similar levels of anticoagulation, whereas a specific ACT level does not necessarily reflect similar levels of anticoagulation across patients.

Because the first reports suggested that serial ACT monitoring during cardiopulmonary bypass resulted in improved outcomes, it has been widely adopted for routine anticoagulation monitoring in patients on mechanical circulatory support including ECMO (2,8,9). However, multiple studies in several different patient populations receiving anticoagulation for a wide variety of indications have yielded mixed results about the utility of ACT as a measure of heparin activity (10,11). In addition, several studies examining patients on ECMO in particular have suggested that ACT is not an ideal measure for serial anticoagulation monitoring. A recent report from our institution found no significant correlation between ACT levels and either heparin infusion rate or antifactor Xa levels (12). In a study of over 600 pediatric patients on ECMO, Baird et al. (13) demonstrated a positive correlation between ACT levels and heparin infusion rate; however, they were only able to identify a relationship between heparin infusion rates and mortality with inadequate heparin dosing associated with higher mortality. Maul et al. examined ACT, bedside aPTT, and laboratory aPTT in 47 pediatric patients on ECMO. They demonstrated a greater correlation between aPTT and heparin infusion rate compared with ACT with the laboratory-based aPTT assay being superior to the bedside aPTT assay (14). Neither of these studies included antifactor Xa levels in their analyses. In 34 pediatric patients on ECMO, Bembea et al. found no significant correlation between ACT and antifactor Xa levels and only a weak correlation between aPTT and antifactor Xa levels (15). Our study confirms the results of these studies that have raised concerns over using ACT alone to titrate heparin infusions in neonates on ECMO. Potential reasons for this unreliability include differences within the endogenous coagulation system, varying disease states between populations, use of coated versus uncoated ECMO circuits, and use of different ACT devices or activators (16,17).

Although there were direct correlations between heparin infusion rate and antifactor Xa levels both within and between patients, heparin infusion rate alone is not an adequate measure of a neonate's anticoagulation status. Neonates on ECMO have ongoing physiologic derangements secondary to sepsis, repeated blood product transfusion, and the inflammatory response to the ECMO circuit. In addition, their levels of endogenous coagulation factors are unpredictable because of age-dependent variations in factor levels and consumption of factors secondary to both their underlying disease and the ECMO circuit, both of which must be considered along with concurrent transfusion of variable amounts of blood products. In addition, variability in heparin clearance between patients and the unknown role the circuit components play in sequestering heparin further limit the use of heparin infusion rates as measures of anticoagulation between patients. Multiple measures of heparin anticoagulation are now available; however, antifactor Xa is widely seen as the gold standard measure of heparin activity against which other measures are compared (18). For this reason we have focused our current analysis of measures of anticoagulation on the correlations between ACT and aPTT with antifactor Xa.

To best avoid thrombotic or hemorrhagic complications in patients treated with ECMO, rapid assays are needed to obtain interpretable and actionable results. Antifactor Xa levels would be preferable if they were less expensive, could be obtained more rapidly, and were more widely available. Instead, ACT and aPTT are currently the best available options for routine anticoagulation monitoring. Based on our findings in the neonatal patient on ECMO, on initiating heparin therapy, initial levels of anticoagulation should be measured using aPTT or antifactor Xa levels. Subsequently, either ACT or aPTT can be relied on to make dosing adjustments in heparin infusions based on the trend leading up to their present result, although changes in aPTT are slightly more reflective of changes in antifactor Xa levels. However, other laboratory measures should also be considered when trying to determine a patient's current coagulation status, including levels of antithrombin III and fibrin split products. In addition, another potentially valuable laboratory measure available for point-of-care testing not used in this study is thromboelastography (TEG; Haemonetics, Braintree, MA) or the similar assay rotational thromboelastometry (ROTEM; Tem Innovations GmbH, Munich, Germany). TEG and ROTEM provide information about anticoagulation, thrombosis, platelet function, and fibrinolysis and can assist in decision-making with respect to both heparin infusion rate and administration of blood products or coagulation factors. This assay is poorly studied in the ECMO population and rarely used with nearly 60% of ECMO programs reporting that they never obtain TEG in their patients (2,19). However, TEG and ROTEM may be useful adjuncts for managing anticoagulation in patients in ECMO and warrant further investigation.

Our study focused on heparin anticoagulation as measured by ACT, aPTT, and antifactor Xa levels. However, achieving adequate anticoagulation in patients on ECMO is a complex process that needs to account for multiple factors within the coagulation pathways including heparin, antifactor Xa, thrombin, antithrombin III, platelets, fibrinogen, and fibrin degradation products. It is likely

that the correlations between ACT and aPTT with antifactor Xa do not follow simple linear relationships either within patient or between patients because of the complex interplay of the factors outlined previously. For example, depletion of antithrombin may lead to heparin resistance, whereas depletion of fibrinogen may lead to an accentuated heparin effect. Although we use ACT and aPTT levels to manage heparin infusions in our neonatal patients on ECMO, we favor a multimodal approach to anticoagulation including monitoring of several measures of anticoagulation and using heparin and targeted blood product transfusion to achieve anticoagulation. Currently, we monitor and adjust our anticoagulation based on levels of several measures using the algorithm outline in Figure 1.

This study has a number of important limitations. The small sample size limited our power to detect significant between-patient correlations. Similarly antifactor Xa levels were drawn only one to two times per day, which limited the number of data points available for analyses. Also, using the chromogenic method to measure antifactor Xa levels may have led to some of the lack of correlation between the measures of anticoagulation because it determines the antifactor Xa levels at the patient's own antithrombin level rather than adding exogenous antithrombin. This and other complexities of the coagulation system and the dynamic physiology of patients treated with ECMO limit the generalizability of our results. In addition, the changes in ACT machines that occurred during the study period may also have affected our results; however, sensitivity analyses comparing results before and after these changes did not demonstrate any significant differences. Therefore, both ACT machines used in this study had similar issues with ACT levels not accurately reflecting antifactor Xa levels across patients. One strength of this study was our use of mixed models to separately estimate both within-patient and between-patient correlations, which in most cases were quite different. Simple Pearson correlation may be inappropriate for longitudinal data because it is a weighted average of the between- and within-patient correlations and thus may not be interpretable for longitudinal data when within- and between-patient correlations are different, as demonstrated by the correlations presented here.

CONCLUSIONS

Understanding how different measures of anticoagulation compare is critical for developing standardized guidelines for heparin administration in neonatal patients on ECMO. In this study, we detected a positive correlation of both ACT and aPTT with antifactor Xa levels when looking at changes within patients over time. However, the between-patient correlations were only positive between aPTT and antifactor Xa, suggesting that aPTT may be the more appropriate measure to use for developing anticoagulation algorithms to be used across different patient populations and institutions. On initiating heparin therapy in an individual patient, initial levels of anticoagulation should be measured using aPTT or antifactor Xa levels. Once adequate anticoagulation has been achieved, then either aPTT or ACT are acceptable measures for making further adjustments, although aPTT may be more reflective of antifactor Xa levels. A multimodal approach to anticoagulation in patients on ECMO including monitoring of several measures of anticoagulation and using heparin and targeted blood product transfusion to achieve anticoagulation is warranted.

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