Prospective Observational Study of Hemostatic Alterations during Adult Extracorporeal Membrane Oxygenation (ECMO) Using Point-of-Care Thromboelastometry and Platelet Aggregometry

Priya Nair, MBBS, MD, FCICM,* † Dominik Johannes Hoechter, MD, ‡ Hergen Buscher, MBBS, DEAA, EDIC, FCICM,* †† Karthik Venkatesh, † Susan Whittam, * Joanne Joseph, MBBS, FRACP, †‡ and Paul Jansz, MBBS, FRACP, PhD†‖

Objectives: To characterize the longitudinal hemostatic profile during adult ECMO using point-of-care tests (POCT) for coagulation and to compare these parameters to standard laboratory tests. In addition, the clinicians’ responses during bleeding episodes using available information were compared to a POCT-based response.

Design: Prospective observational cohort study.

Setting: ECMO-referral center in a university teaching hospital.

Participants: Ten critically ill adult ECMO patients.

Interventions: Daily laboratory coagulation profile, transfusion history and near-daily thromboelastometry (ROTEM®) and platelet aggregometry (Multiplet®).

Main Results: Six male and four female patients, seven with VA- and three with VV-ECMO were studied over 110 days. Seventy-five thromboelastometry (TEM) and 36 platelet aggregometry (MEA) results were analyzed.

A majority of TEM values were within the normal range, except for FIBTEM (majority high), which remained consistent over long (>5 days) ECMO runs. In MEA there were low values, particularly in the adenosine diphosphate- and ristocetin-induced assay, implying possibly a vWF-factor or GpIb-receptor defect. There was correlation between laboratory and POCT as well as good correlation between the clot firmness after 10 minutes (A10) and the maximum clot firmness in ROTEM, suggesting that reliable information can be obtained within 15 minutes.

Twenty-two bleeding episodes were observed in five patients. When comparing the clinicians’ response to a transfusion algorithm based on POCT, there was a concordance in less than 20% of episodes.

Conclusions: POCT for coagulation can provide specific, reliable, and timely information during bleeding episodes and the use of targeted therapy algorithms could improve outcomes and reduce costs.

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KEYWORDS: coagulation abnormalities, coagulation monitoring, ROTEM, platelet aggregometry, ECMO
methods

Ten serial ECMO patients were studied prospectively at a tertiary referral adult ECMO center in Sydney, Australia over a five-month period. This center also houses the only heart, lung transplant, and mechanical circulatory support program for the state (population 7.3 million). Patients were excluded if they were less than 16 years of age, pregnant or had a known pre-existing coagulation disturbance. This study was approved by the local Human Research Ethics Committee and informed consent was obtained from the patient or their senior next-of-kin.

Demographic data including age, gender, ECMO configuration, indication for ECMO support, and severity of illness scores were recorded. Daily conventional coagulation tests and transfusion history were recorded. In addition, near-daily thromboelastometry and platelet aggregometry tests were performed serially. Outcome data, such as duration of ECMO support, intensive care unit (ICU) and hospital length of stay, and ICU and hospital outcome, were noted. Bleeding episodes during ECMO support, which were defined as those deemed significant enough by the treating clinician to utilize blood products (excluding packed red cells) or coagulation factors for control, were studied. This center does not utilize POCT for coagulation currently and results of the tests performed for this study were not available to treating clinicians, who continued their transfusion strategies based on routinely available laboratory coagulation tests (platelet count, aPTT, PT, and fibrinogen) and clinical judgment by the treating intensivist. There currently is no standardized algorithm to treat bleeding complications.

short ECMO runs were defined as those lasting for one to four days, whereas ECMO runs lasting five days or more were defined as long runs.

All ECMO circuits were comprised of a centrifugal blood pump (Jostra pump head, Maquet, Rastatt, Germany) driven circuit flow, and polymethylpentene low-resistance oxygenators (Quadrox D, Maquet, Rastatt, Germany). Circuits were heparin bonded and unless actively bleeding, patients received unfractionated heparin infusions through the ECMO circuit targeting aPTT range of 1.5 to 2 times normal. Vascular cannulae were inserted through a peripheral approach into either femoral, jugular or both vessels.

Conventional coagulation tests included platelet count, PT and international normalized ratio, aPTT, and fibrinogen level.

Thromboelastometry was performed on citrated blood using the ROTEM device (TEM, Munich, Germany). Thromboelastometry is a whole-blood assay performed to evaluate the viscoelastic properties during blood clot formation and lysis. The different parameters in thromboelastometry (TEM) are dependent on the activity of the plasma coagulation system, platelet function, fibrinolysis, and other factors that influence these interactions including drugs. ROTEM parameters assessed included time to clot initiation (clotting time [CT] in EXTEM and INTEM), clot strength (Maximum Clot Firmness [MCF] in EXTEM, and INTEM), fibrinogen activity (maximum clot firmness in FIBTEM), and fibrinolysis (Maximum Lysis [ML] in EXTEM and INTEM).

Platelet function was assessed with MEA using the Multiplate analyzer (Roche, Munich, Germany). This is based on the attachment of platelets on two platinum electrodes, resulting in an increase of electrical resistance between the electrodes. The change of resistance (called “impedance” as an alternating current is applied in order to prevent electrolysis) is continuously recorded. This is proportional to the number of platelets sticking to the electrodes. MEA uses four electrodes per test cell (adenosine diphosphate (ADP), TRAP-6, collagen, and ristocetin). MEA results were excluded from analysis if the platelet count was <$100 \times 10^9/L$.

Continuous variables were expressed as median and categoric variables as percentages or proportions. Conventional tests were compared to corresponding POCT variables using Pearson’s correlation. Sensitivity, specificity, positive and negative predictive values of tests were determined from the observation of true and false negative and positive tests.

results

One hundred ten ECMO days were studied in 10 serial ECMO patients. The median age was 41 (38-52) years and six patients were male. The majority of patients (seven) received veno-arterial ECMO support and five patients received ECMO for the management of primary graft dysfunction (cardiac or pulmonary). ICU and hospital lengths of stay were 23 (16-35) and 41 (27-39) days, respectively. Six patients survived to hospital discharge (Table 1).

Before starting ECMO, platelet numbers were within the normal range in 50% of the patients; in 37% the platelet numbers were below the normal range (<150 \times 10^9/L), PT was above normal range in 86%, aPTT was below the therapeutic range in 57%. Fibrinogen levels were above normal range in 75%. After the commencement of ECMO, platelet
levels dropped significantly; about 76% of platelet counts were below normal range (Figure 2). PT as well as APTT remained relatively stable throughout the course of ECMO runs. Fibri-nogen levels remained normal or high.

Six patients (60%) underwent long (> 5 days) ECMO runs. There were no significant changes in standard coagu-

<table>
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<th>Table 1. Demographic Data</th>
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<tr>
<td>Patients (n)</td>
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<tr>
<td>Age Median (IQR)</td>
</tr>
<tr>
<td>Male (%)</td>
</tr>
<tr>
<td>ECMO Configuration</td>
</tr>
<tr>
<td>Veno-venous</td>
</tr>
<tr>
<td>Veno-arterial</td>
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<tr>
<td>Veno-pulmonary artery</td>
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<td>*configuration change in same ECMO run</td>
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Diagnostic Groups
- Primary graft dysfunction (lung)  2
- Severe ARDS                   1
- Primary graft dysfunction (heart) 3
- Cardiogenic shock             2
- Postcardiomyotomy            2
- APACHE-II Median (IQR)        19 (16-24)
- SAPS-2 Median (IQR)           34 (27-50)
- ECMO duration in days, median (IQR) 10 (5-14)
- ICU Length of stay in days, median (IQR) 23 (16-35)
- Hospital Length of stay in days, median (IQR) 41 (27-59)
- ICU Mortality (%)             4 (40%)
- Hospital Mortality (%)        4 (40%)

Abbreviations: n = number, IQR = interquartile range, ARDS = Acute Respiratory Distress Syndrome, APACHE = Acute Physiology and Chronic Health Evaluation score, SAPS = Simple Acute Physiology Score, ICU = Intensive Care Unit.

levels dropped significantly; about 76% of platelet counts were below normal range (Figure 2). PT as well as APTT remained relatively stable throughout the course of ECMO runs. Fibri-nogen levels remained normal or high.

Six patients (60%) underwent long (> 5 days) ECMO runs. There were no significant changes in standard coagu-

clination parameters when comparing short vs. long ECMO runs.

Clotting time (EXTEM) was low in approximately half of the tests performed, indicating likely factor deficiency. Clot-
ting time (INTEM) was normal in the majority of tests, indicating minimal contribution of heparin to coagulopathy (Figure 1). This also was reiterated with 106 of 109 APTT tests being below and within the therapeutic range and only 3/109 above it.

MCF, reflecting clot quality, was in the normal range or high in the majority, but when low, was a useful predictor of bleeding (Figures 1 and 3). Seventy-five ROTEM and 36 MultiPlate tests were analyzed.

In MEA, platelet dysfunction commonly was seen (Figure 1). All four tests performed (ADP, TRAP-6, collagen, and ristocetin) were low in 50% to 72%. ADP-induced tests were low in 72%, Ristocetin-induced tests were low in 61%.

Reasonable correlation was observed between standard coagulation parameters and the corresponding thromboelastometry parameter, specifically PT versus A10-EXTEM, APTT versus CT-INTEM and fibrinogen versus A10-FIBTEM (Figure 4). Furthermore, there was good correlation between the MCF at 10 minutes (A10) and the MCF value finally obtained, suggesting that accurate information on clot firmness could be obtained rapidly (Figure 5).

Thromboelastometry MCF in the individual tests was highly specific, but not very sensitive in the prediction of bleeding (Figure 3).

During the study period, five patients (50%) required transfusions of blood products (other than packed red cells) on 22 days of the 110 ECMO days studied. Using a proposed algorithm (Figure 6), which was based on published algorithms
that have been used successfully in cardiac surgical patients incorporating thromboelastometry and platelet function assays, cryoprecipitate was used appropriately in 1/12 occasions (8%), fresh frozen plasma in 2/12 (16%) and platelet transfusion in 6/13 (43%). Overall, the response corresponded to the algorithm in <20% of transfusions, with transfusions administered being in excess of those recommended (Figure 7).

**DISCUSSION**

This study demonstrated that clot strength generally was normal and this was preserved for the duration of ECMO, but if reduced was a predictor of bleeding.

As seen in APTT and CT INTEM, heparinization often was subtherapeutic; although routine daily ultrasound examination for venous thrombosis were not performed except in cases of
clinical suspicion, thrombotic complications in the form of arterial or venous thrombosis or oxygenator failure were not clinically apparent. This suggested that lower levels of heparinization may be used without increasing the risk of thromboembolic events in situations of high bleeding risk. This was borne out in clinical studies,1,5 which showed a significant incidence of life-threatening hemorrhage in ECMO patients; however, clinically relevant thrombotic complications are rather rare.

Both quantitative and qualitative platelet abnormalities were common, particularly with the ristocetin- and ADP-stimulated assays. Impaired platelet activation in the ristocetin-induced assay may have indicated a von Willebrand factor abnormality. This finding was supported in previous studies in patients on ECMO13,28–30 in whom an acquired von Willebrand syndrome (AVWS), characterized by the loss of high-molecular-weight multimers of vWF as a result of high shear stress leading to impaired binding of vWF to platelets and the subendothelial matrix have been described. Heilmann et al13 found features of AVWS in 31 of 32 ECMO patients in their study of whom 22 suffered bleeding complications. From a therapeutic perspective, this high incidence of platelet abnormalities suggested that desmopressin (DDAVP) may have a role in managing bleeding episodes due to its ability to increase vWF and factor VIII concentrations,31 as well as platelet-platelet32 and platelet-subendothelial interactions33 via Gp IIb/IIIa and GpIb platelet receptors. Its benefit in improving platelet function was demonstrated in a small group of cardiac surgery patients, who were determined to have cardiopulmonary bypass-induced platelet dysfunction using MEA analysis.34

In this study, platelet malfunction may have been overcome by the frequently supranormal, fibrinogen response observed (possibly an acute phase reactant in critically ill patients) resulting in relatively infrequent bleeding episodes. This could relate to the role of fibrinogen in GpIIb/IIIa-mediated support of platelet aggregation.35 From a clinical perspective, this might imply the utility of fibrinogen concentrate therapy to overcome the frequently observed platelet dysfunction.36 Early fibrinolysis was not observed in this cohort, suggesting that antifibrinolytics in this context may not be useful.

There was good correlation between standard coagulation tests and the corresponding POCT parameters, suggesting that

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**Fig 3.** Bleeding and nonbleeding days. Percentage of low, normal, and high clot firmness values and sensitivity and specificity of individual parameters for bleeding. MCF = Maximum Clot Firmness.

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<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tr>
<td>MCF EXTEM</td>
<td>64 %</td>
<td>83 %</td>
</tr>
<tr>
<td>MCF INTEM</td>
<td>53 %</td>
<td>91 %</td>
</tr>
<tr>
<td>MCF FIBTEM</td>
<td>44 %</td>
<td>89 %</td>
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**Fig 4.** Correlation between routine laboratory values and thromboelastometry parameters. Abbreviations: PT = Prothrombin Time, APTT = Activated Partial Thromboplastin Time, A10 = Clot firmness at 10 minutes, CT = Clotting Time.
along with the additional information that is obtained, they also provide information comparable to traditionally used parameters. This also was observed in a study of early coagulation abnormalities in trauma patients using rotational thromboelastometry\textsuperscript{21} in whom a similar good correlation was found with standard laboratory parameters.

Furthermore, by correlating clot firmness after 10 minutes to the maximum clot firmness, the authors were able to show that reliable information from the POCT could be obtained as early as 10-to-15 minutes from the onset of the test, which could be performed at the bedside by clinicians involved in patient care. These findings replicated those described in a retrospective study.

**Fig 5.** Correlation between values obtained at 10 minutes (A10) and Maximum Clot Firmness (MCF). Pearson’s correlation coefficients for EXTEM, INTEM, and FIBTEM $R = 0.99$.

**Fig 6.** Example of proposed algorithm using POCT in bleeding ECMO patients. Abbreviations: TEMMPO = TEM and MultiPlate observational study, $CT_{IN}$ = clotting time with INTEM test, $CT_{HEP}$ = clotting time with HEPTEM test, $A10_{EX}$ = clot firmness at 10 minutes with FIBTEM test, $A10_{EX}$ = clot firmness at 10 minutes with EXTEM test, $AUC = $ area under curve, ASPI = arachnoid acid-induced assay for cyclooxygenase pathway, COL = collagen-induced aggregation, ADP = for detection of adenosine diphosphate-receptor antagonism, TRAP = thrombin-receptor activating peptide-6 used as an agonist to detect glycoprotein 2b-3a receptor pathway defects.
analysis of more than 14,000 ROTEM\textsuperscript{37} assays in noncardiac surgical patients in whom strong linear correlations were seen with A5 (r = 0.93-0.95), A10 (r = 0.96), and A15 (r = 0.98), with areas under the ROC curve of 0.96-0.98.

The present observations suggested that clinicians’ response to bleeding episodes rarely correspond with the response that would have been recommended by POCT-based algorithms. An international survey of anticoagulation practices in 187 pediatric ECMO centers revealed a wide variation in anticoagulation management practices among centers.\textsuperscript{10} Although 43% of centers reported the use of thromboelastography, goal ranges and interventions triggered by out-of-range variables were found to be highly variable. Protocols incorporating POCT in ECMO and studies assessing their utility in this clinical context have not been published. Oliver in 2009\textsuperscript{12} described the process of hemostatic activation in the presence of the ECMO circuit and explained how the addition of thromboelastography to standard coagulation tests might assist in recognizing the level of thrombin formation and improve care in ECMO patients and potentially prevent neurologic injury. Goerlinger et al in 2012\textsuperscript{22} recommended the use of POC TEM and platelet function analysis during mechanical circulatory support therapy to reduce the risk of bleeding and thromboembolic complications. They suggested that these tests should be performed repeatedly during mechanical circulatory support therapy since thrombin generation, clot firmness, and platelet response may change significantly over time with high inter- and intra-individual variability; however, these tests currently are not incorporated routinely into clinical practice while managing ECMO patients, despite this being a particularly challenging context with a high risk of complications.

The randomized controlled trials comparing POCT coagulation testing-based intervention with standard care were almost exclusively in the area of cardiac surgery.\textsuperscript{38–43} These studies generally found that therapy based on POCT reduced patient exposure to allogeneic blood products and provided improvement in clinical outcomes, such as duration of mechanical ventilation, length of ICU stay, adverse events rate, and cost of hemostatic therapy. Of these, only one was able to demonstrate a 6-month all-cause mortality benefit.\textsuperscript{23}

Schoechl et al,\textsuperscript{44} in a recent review article, presented a ROTEM-guided treatment algorithm for the management of trauma-induced coagulopathy. They suggested that compared with a previous ratio-based approach to the administration of blood products, individual coagulation management potentially could reduce the risk of both over- and undertransfusion. Similarly, in another review article in this Journal, Tanaka et al\textsuperscript{14} advocated the implementation of transfusion algorithms based on POCT for damage-control resuscitation in trauma as well as in an elective or urgent cardiac surgical setting.

In addition, there have been reports of the successful use of these POCT in the area of liver transplantation,\textsuperscript{45} aortic aneurysm surgery,\textsuperscript{46,47} obstetrics,\textsuperscript{48} and cancer care.\textsuperscript{49} These reports and the authors’ findings suggest, therefore, that further exploration of the utility of these POCT coagulation tests in the clinical care of ECMO patients would be worthwhile.

**Strengths and Limitations**

This was a small study in a heterogeneous group of ECMO patients with a variety of underlying conditions that could potentially affect their hemostatic profile. The small number resulted in fewer bleeding days that could be studied. The observations from this study can, therefore, only be considered as hypothesis generating and form a basis for further studies in this area. Furthermore, due to its observational nature, the effect of blood-product transfusion could not be accounted for in the results; however, it provided interesting information serially over a number of days on the coagulation profile in this clinical context, which has not been described previously. This study also demonstrated the feasibility of utilization of POCT by clinicians in an ICU setting. Observation of clinicians’ responses and the suggestion that utilization of these tests could rationalize blood product use and potentially improve clinical care and cost effectiveness in ECMO patients was a strength of the study. This study provided a basis for further

**Fig 7. Use of coagulation factors in relation to algorithm-based approach.**

Abbreviations: Cryo = cryoprecipitate, FFP = fresh frozen plasma, PLT = platelets, DDAVP = desmopressin.
interventional studies that are required to evaluate the utility and feasibility of POCT-based algorithms to direct therapeutic interventions in ECMO patients. These will determine the safety and efficacy of hemostatic control as well as the cost benefit of incorporating these strategies into clinical practice.

In conclusion, POCT for assessment of hemostasis in ECMO patients can provide detailed information easily and rapidly. Platelet dysfunction is common in these patients and parameters of clot quality can predict likelihood of bleeding. Lower heparinization targets may be safe.

As clinicians’ response currently does not correspond with the intervention recommended if POCT algorithms had been used, further studies into the feasibility, safety, and efficacy of using these in ECMO patients are required. These strategies also have the potential to result in significant cost savings.

ACKNOWLEDGEMENTS

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