Original Article

Coagulation Monitoring During Extracorporeal Membrane Oxygenation: The Role of Thrombelastography

Alfred H. Stammers, MSA, CCP; Lynne Willett, MD; Lance Fristoe, BS, CCP; Jonathan Merrill, BS, RN, CCP; Todd Stover, BSRT, CCP; Allen Hunt, BS, RN, CCP; John Morrow, BS, CCP; Jamie Newberry, BS, CCP

Division of Clinical Perfusion Education, School of Allied Health Professions, University of Nebraska Medical Center, Omaha, NE

Keywords: thrombelastography, ECMO, bleeding, coagulation monitoring

ABSTRACT

Patients undergoing extracorporeal membrane oxygenation (ECMO) are at an increased risk for developing coagulopathies due to the adverse effects of extracorporeal circulation on the hemostatic mechanism. Methods of determining causative factors of bleeding diathesis are often inconsistent and non-specific. ECMO patients require aggressive transfusion therapy with autogenic blood products to stabilize and maintain hemostasis. The present study evaluated the coagulation status of newborn patients undergoing ECMO therapy, using a viscoelastic monitor (Thrombelastograph -TEG) that measures functional aspects of clot development and stabilization.

Seventeen neonatal patients undergoing ECMO for severe respiratory dysfunction were entered into this study. Serial blood samples were obtained and routine coagulation assessment including fibrinogen concentration, platelet count and ionized calcium was performed. In addition, fibrin (ogen) degradation products (FDP), d-Dimers, antithrombin III and plasma free hemoglobin were measured. Transfusion indicators were established and total transfusion requirements recorded. TEG profiles were determined with the use of heparinase, an enzyme that degrades heparin but has little effect on other coagulation factors.

The most commonly encountered complication was hemorrhaging which was diagnosed by laboratory and clinical assessment in 11 of 17 patients. Transfusion requirements (measured in ml/kg/ECMO hour) were the following: packed red blood cells - 1.34 ± 0.5; platelets - 0.71 ± 0.57; fresh frozen plasma - 0.09 ± 0.12; cryoprecipitate 0.05 ± 0.05. Thrombelastograph profiles reflected hemostatic conditions that ranged from severe coagulopathies (DIC) to hypercoagulability. Interpretation of TEG profiles identified hemostatic abnormalities in 57 of 101 profiles (46.5%), with the most common etiology related to platelet dysfunction. In the non-hemorrhagic group the TEG profiles were normal in 30 of 41 (73.2%) instances, while the hemorrhagic group had 24 of 60 (40%) profiles in the normal range ($p<.001$). d-Dimers and FDP were elevated in all patients during ECMO despite maintenance of activated clotting times greater than 180 seconds.

During ECMO coagulation assessment with the TEG provides useful information for the rapid diagnosis of hemorrhagic conditions, which may help guide transfusion therapy.

Address correspondence to:
Alfred H. Stammers, MSA, CCP
Division of Clinical Perfusion Education
University of Nebraska Medical Center
600 South 42nd Street
Swanson Hall, Room 3019
Omaha, NE 68198-5155

INTRODUCTION

Extracorporeal circulation profoundly influences various hemostatic mechanisms which increases the risk for both hemorrhagic and thrombotic complications (1,2). These events are elicited when blood is exposed to foreign non-endothelialized surfaces, abundantly present within the extracorporeal circuit. Both cellular and acellular systems are activated, causing the release of various intermediate products into the systemic circulation (3). Systemic anticoagulation is necessary to inhibit thrombin activation which further exacerbates alterations of hemostasis. In addition, the abnormal circulatory patterns created in the extracorporeal devices generate both areas of stasis and excessive shear stresses, which increase red cell fragility and activate coagulation factors (4). These processes are directly related to both the total area of surface activation and to the length of time of exposure (5).

The process of extracorporeal membrane oxygenation (ECMO) for the treatment of neonates with respiratory dysfunction, induces numerous changes in the hemostatic mechanism, which include quantitative and qualitative platelet defects, enhanced coagulation factor consumption, and hyperfibrinolysis (6,7). These patients are also at an increased risk of developing coaguloapthies, such as Disseminated Intravascular Coagulation (DIC), because of the underlying lesions. In addition, patients are also susceptible to thrombotic complications which develop both in the extracorporeal circuit and in the systemic circulation.(8) Recently investigators have identified two distinct periods of blood coagulation activation which involve contact activation and complement stimulation in the first phase, and hyperfibrinolysis and clotting in the second (9). Each phase has specific pathognomonic indicators that can be detected by laboratory examinations that identify coagulopathic conditions. Unfortunately, the majority of these tests require significant time to complete, require additional blood samples, and are costly.

Routine methods for determining the etiology of ECMO related bleeding diathesis are often inconsistent and non-specific, with patient treatment mainly facilitated by aggressive transfusion with autogeneic blood products. Transfusion criteria are often poorly defined and are often based upon end-point coagulation tests, and rarely on quantitative measures of specific coagulation elements. Rarely are coagulation functional analyses performed. Theoretically, such tests have the distinct advantage of studying the cumulative attributes of the various elements of hemostasis *in toto*. The coagulation monitor called the Thrombelastograph (TEG) is a device which measures the viscoelastic properties of blood, as blood changes from a liquid to a gel (coagulum) state (10). This device has successfully been used to assess coagulation disturbances in several clinical situations including hepatic transplantation (11), cardiac and vascular surgery (12), and obstetrics (13). The present study was designed to evaluate the efficacy of the TEG to evaluate the coagulation status of newborn patients undergoing ECMO, and to compare these results with those obtained from routine coagulation assays.

MATERIALS AND METHODS

Seventeen neonatal patients undergoing ECMO therapy for severe respiratory dysfunction were entered into this study. Patients underwent standard ECMO treatment which included both arterial-venous (n=12) and veno-venous ECMO (n=5). The ECMO circuit was similar to that described elsewhere (14) and consisted of gravity drainage from a venous cannula, blood gas exchange with a coiled silicone membrane oxygenator[a] and a stainless steel heat exchanger[a]. Flow rates ranged from 100 to 125 ml/min/kg during total support and decreased during timed discontinuation from ECMO. Patients were initially anticoagulated with a 100 IU/kg loading dose of bovine lung heparin just prior to cannulation. Once on ECMO, activated clotting times (ACT) were monitored hourly and maintained between 180 and 220 seconds by a continuous infusion of heparin.

Patients received concentrated single donor platelet transfusions to maintain platelet (PLT) counts greater than 100,000/mm^3. Fresh frozen plasma and cryoprecipitate were administered to maintain fibrinogen levels greater than 100 mg/dL, or when excessive bleeding was noted at the cannulation sites. Packed red blood cells were transfused to maintain the patient's hematocrit greater than 40%.

Coagulation Monitoring

Serial blood samples were drawn at regular intervals for the assessment of coagulation. Platelet counts were performed every 4 hours while fibrinogen and ionized calcium levels were drawn every twelve hours. Additional samples were drawn prior to initiation of ECMO, 10 minutes post initiation, once per day while on ECMO (at 8 a.m.), and 1 hour post separation from ECMO. The following assays were performed: fibrin (ogen) degradation products (FDP), d-Dimers, antithrombin III and plasma free hemoglobin. At these same times, a one ml sample of blood was placed in a vial containing a known quantity of heparinase[b], an enzyme used to degrade heparin in quantities up to 5 USP units per ml (15). 360 uL of deheparinized blood was then placed on the TEG which produced a corresponding coagulation profile. The TEG monitor was calibrated at the onset of each case according to the '2 point' method described by the manufacturer[b], and thereafter checked for alignment on a daily basis.

Thrombelastography

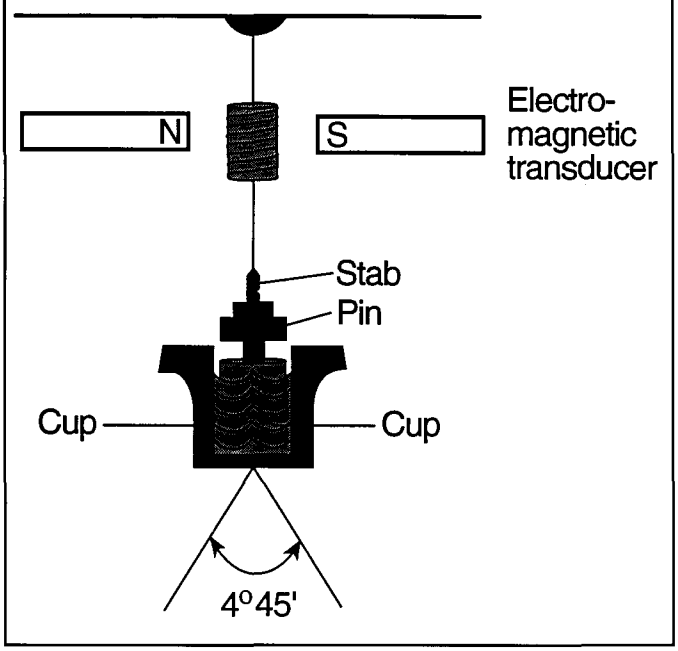
The TEG is a whole blood coagulation monitor that measures the viscoelastic properties of blood, reflecting the interac-

a AVECOR, Plymouth, MN 55440
b Haemoscope Corporation, Skokie, IL 60077

tion of cellular and plasmatic components of coagulation (16,17). A sample of non-anticoagulated blood (360 uL) is placed in a cup which rotates at a slight angle (4°) over a specified time period (4.5 seconds) (Figure 1). This creates a mechanical shear modulus between the sample and the rotating cup which is detected by an electromagnetic transducer, which converts the mechanical signal into an electrical one. This signal is sent to a microprocessor which displays it as a graphical profile. As blood changes phases from a liquid to a gelatinous mass, the shear modulus changes, reflecting the interaction of platelets with the fibrin mass. This interaction is displayed in a graphic format as a profile from which measurable parameters are determined (Figure 2). These parameters have been identified and are listed below:

Reaction Time - (R) - Correlates with the Whole Blood Clotting Time. Marks the beginning of coagulation and occurs when the amplitude of the trace is equal to 2 mm.

Figure 1: Mechanical operation schematic for the thrombelastograph



Clot Growth Kinetics - (K) and Alpha Angle - The rate of clot growth is depicted as the time in between initial clot formation (R time) and a 20 mm deflection in amplitude. Alpha angle and K time describe the polymerization of the structural elements involved in clotting. This is the rate of clot growh and is related to platelet function and plasma components residing on the platelet surface.

Clot Strength - Maximum Amplitude (MA) - The strength of the clot is the ability of the clot to form hemostasis. This is a direct result of the function of platelets and plasma factors (fibrinogen), and their interaction.

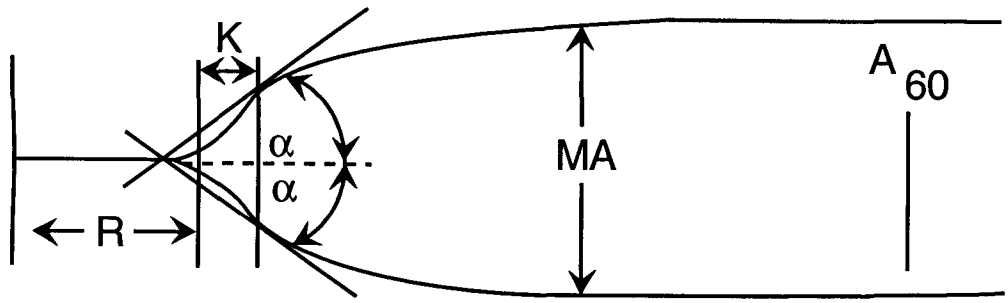
Clot Stability - Amplitude at 60 minutes (A 60) - Refers to the potential of the clot to redissolve as a result of circulating fibrinolytic activators which activate the plasminogen incorporated in the clot. A steady or abrupt reduction in the MA over time represents clot dissolution and the presence of fibrinolysis. Both DIC and fibrinolysis can be identified this way.

Coagulative interpretation of the results obtained from a TEG profile are based upon laboratory experimentation and clinical experiences. Algorithms for the coagulative state, which relate the measured parameters to coagulative function, have been determined (18). The algorithm utilized by our institution is listed below.

Abnormal values and their most likely clinical meaning:

TEG Values	Clinical Cause
Prolonged R and K, and low alpha	Heparin
Decreased MA and normal R	Reduced platelet function
Decreased MA and extended R	Reduced platelet and clotting factors
Prolonged K and low alpha	Decreased platelet function, low plasma factors (fibrinogen), anticoagulants
Increased MA and short R	Hypercoagulable
Normal or reduced MA with reduced A 60	Clot fibrinolysis (Hyperfibrinolysis, DIC)

Figure 2: Geometrical pattern analysis for a thrombelastograph coagulation profile.



a - Alpha Angle; A 60 - Amplitude at 60 minutes after maximum amplitude; MA - Maximum Amplitude; R - Reaction Time; RK - Kinetic Time

Statistics

When appropriate, intergroup comparison was made through one way analysis of variance, and significant difference accepted at $p<.05$ level, or lower. All data is reported as mean ± standard deviation of the mean.

Table 1: Patient data on 17 children on ECMO.

Patient	Gender	Weight (kg)	Gestational age (weeks)	Indication	ECMO Type	Age at ECMO (hours)	Duration of ECMO (hours)
1	M	3.2	38	CDH	A-V	45	289
2	M	2.6	35	PNEUM/SEPSIS - GBS	A-V	162	273
3	M	3.2	36	PNEUM/SEPSIS - GBS	A-V	25	50
4	F	2.9	41	MAS	A-V	22	137
5	F	2.9	40	MAS	V-V	11	142
6	M	3.5	41	MAS	A-V	10	188
7	F	2.7	41	MAS	V-V *	13	180
8	F	2.9	39	PPHN	A-V	24	37
9	M	3.4	38	PNEUMONIA	V-V *	39	22
10	M	4.1	41	PNEUM/SEPSIS - E. Coli	A-V	61	141
11	M	3.2	43	MAS	A-V	32	104
12	F	3.6	42	MAS	A-V	11	91
13	M	3.2	38	MAS	V-V	3	104
14	M	3.9	40	PNEUM/SEPSIS - Ent.viral	A-V	264	216
15	F	2.6	40	PPHN	A-V	33	152
16	M	3.1	38	RDS	A-V	74	92
17	M	3.0	30	PNEUMONIA	V-V	10 weeks	236

***Patients began on V-V ECMO but were changed to A-V ECMO due to ensuing cardiac dysfunction.**

A-V - Arterio-Venous ECMO; CDH - Congenital Diaphragmatic Hernia; GBS - Group B Streptococcus; MAS - Meconium Aspiration; PPHN - Persistent Pulmonary Hypertension in the Newborn; RDS - Respiratory Distress Syndrome; V-V - Veno-Venous ECMO

Table 2: ECMO complications and outcomes.

Patient	ECMO RELATED COMPLICATIONS	OUTCOME
1	None	Late Death
2	Clots in circuit	Alive
3	Cerebral hemorrhage, thrombus	Alive
4	Cerebral hemorrhage, hemolysis	Alive
5	Hemorrhage, hemolysis	Alive
6	Clots in circuit, hemorrhage	Alive
7	Hemolysis	Early Death
8	Cerebral hemorrhage	Alive
9	Cerebral hemorrhage, hemolysis	Early Death
10	None	Alive
11	Cerebral hemorrhage	Alive
12	Cerebral hemorrhage	Alive
13	Hemolysis	Alive
14	Hemorrhage	Alive
15	Clots in circuit	Late Death
16	Hemolysis, myocardial stun	Alive
17	Hemolysis	Alive

RESULTS

Table 1 lists the patient demographics and the indications for extracorporeal support. The mean length of ECMO support was 144.4 ± 78 hours, and all but one patient was successfully weaned from support. There were 2 early deaths caused by multiorgan failure and 2 late deaths; one resulting from gross sepsis and the other of unknown causes. The most common complications were either thrombosis or hemorrhage, which occurred in 11 of 17 patients (Table 2). Significant clots were observed in the circuits of 3 patients, with 2 patients undergoing circuit change-out.

Indices of fibrin(ogen)-olysis and the breakdown product of cross linked fibrin (d-Dimers) were elevated at all times during ECMO, despite maintenance of ACT values between 180 and 220 seconds. Prothrombin and partial thromboplastin times were determined on a routine basis and found to have no relationship to the degree of clinical bleeding or hemorrhagic complication. Transfusion requirements while on ECMO are shown on Table 3.

Patients were separated into two groups depending upon the quantity of red blood cell transfusion required during ECMO. This classification differs from the diagnosis of hemorrhage identified by the complication list in Table 2, with the latter based upon several factors including isolated component therapy, surgical bleeding and individual clinician assessment. Patients with greater than 1.0 mL/kg/ECMO hour were placed in the hemorrhagic group (n=12) and compared to the non-hemorrhagic group (n=5). Using this classification of bleeding, patients in the hemorrhagic group required greater transfusions than patients in the non-hemorrhagic group, but the only significant values were found in red blood cell transfusion.

Thrombelastograph coagulation profiles reflected hemostatic conditions that ranged from severe coagulopathies (DIC) to hypercoagulability. In the non-hemorrhagic group the TEG profiles were normal in 30 of 41 (73.2%) instances, while the hemorrhagic group had 24 of 60 (40%) profiles in the normal range ($p<.001$). Figures 3a-d are a summarization of profiles obtained from a patient who had a 150 hour ECMO procedure

and experienced significant hemorrhage as evidenced by transfusion requirements and abnormal coagulation parameters. Figures 4a-d represent the TEG profiles of a patient who had a 141 hour ECMO procedure with minimal clinical bleeding, and belonged to the non-hemorrhagic group.

DISCUSSION

Extracorporeal circulation induces profound effects on the hemostatic mechanism which predisposes patients to an increased risk of hemorrhage (1-3). During ECMO, clinicians attempt to maintain a delicate balance between procoagulant and anticoagulant factors to reduce both the risk of thromboembolic complications and of excessive bleeding. Despite these efforts coagulopathies remain one of the primary complications of long term extracorporeal suport, and the morbidity associated with these conditions may predispose the patient to early separation from support, before the therapeutic effects of ECMO have been achieved (6-8). Results from the autopsies of 44 children undergoing ECMO at Children's Hospital of Pittsburgh have shown that cerebral hemorrhagic lesions were present in 52% of patients, and focal cerebral infarcts and necrosis were equally distributed (19). In our study, 6 of 17 patients (35%) were diagnosed with intracerebral hemorrhage via cranial ultrasound. This diagnosis necessitated a hastened separation from extracorporeal support, and undoubtedly, underestimated the degree of cerebral hemorrhage as compared to autopsy examinations.

Unfortunately, complications of ECMO are common (8,20). Nagaraj reported 96 complications in 67 patients undergoing neonatal ECMO over a 6 year period, with the most frequent complication being bleeding (20). In the present study there were 21 complications in 17 patients with bleeding being the most common event. Nargaraj and colleagues state in their conclusions that better control of coagulation would result in a decrease in ECMO related complications. In a recent study by Hirthler and colleagues, the authors state that the presence of intracranial hemorrhage was preempted by instability in the maintenance of either ACT or platelet counts, and concluded that such variation is a valuable indicator for an intracranial event (21).

Methods for monitoring the coagulative status of patients undergoing ECMO are seriously limited. The most frequently used assessment of coagulation is the ACT which simply reflects fibrin development as an end-point analysis (22,23). Despite the limitations of the ACT, it is widely utilized as the primary test for anticoagulation during ECMO. Unfortunately, the ACT is affected by numerous additional circumstances including temperature, hemodilution and interpersonnel technique, all of which influence coagulation in lieu of heparinization (24). Therefore, the ACT should not be utilized to gauge the stability of patient hemostatsis, and should be used only as an approximate guide to monitor heparin therapy (25). The platelet count is also regularly measured during ECMO with transfusion criteria established to maintain some minimal circulating number (IE:100,000/mm^3). Unfortunately the platelet count does not address the more important characteristic of platelet function which has been shown to decrease with prolonged extracorporeal exposure (5). Other coagulation tests that are based upon plasmatic assays (prothrombin, thrombin and partial thromboplastin times) are devoid of platelet interactions rendering them of questionable utility during extracorporeal circulation (26). Coagulation tests that would be useful in diagnosing specific hemostatic defects include both platelet aggregation studies and isolated factor analysis, but are substantially more expensive and require significant time to complete.

The TEG is a monitor that measures whole blood coagulation and develops a kinetic profile of the interaction of coagulation elements over time. To our knowledge, it has not heretofore been applied to ECMO patients because of its extreme sensitivity to heparin. The incorporation of heparinase has increased the application of the TEG in clinical situations where heparin contamination precluded its use (15,27). The heparinase enzyme degrades heparin removing it from blood prior to beginning thrombelastography. Heparinase has been shown to have a minimal effect on the TEG coagulation profile and does not significantly alter the results from a non-heparinized sample (27).

In the present study the inadequacies of routine coagulation screens in assessing patient coagulative status became readily apparent. Even when strict adherence to accepted anticoagulation protocols was maintained, and transfusion 'triggers' closely fol-

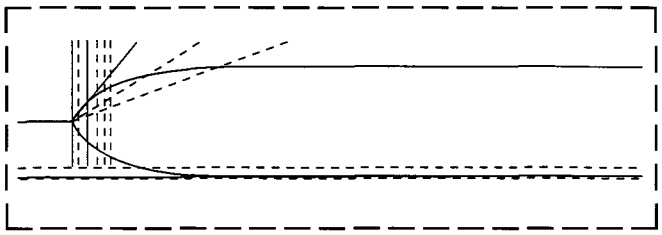
Table 3: Transfusion requirements during ECMO.

Parameter	Total Volume	mL/kg/ECMO Hour	p value vs. non-hem.	
	All Patients (n=17)			
PRBC	585±352 mL	1.34±0.50		
PLATELET	287±229 mL	0.71±0.57		
FFP	44.4±51 mL	0.09±0.12		
CRYO	17.4±13.6 mL	0.05±0.05		
	Hemorrhagic* Patients (n=12)			
PRBC	682±361 mL	1.58±0.30	.04	.0001
PLATELET	336±255 mL	0.84±0.63	.18	.14
FFP	54.5±55 mL	0.12±0.13	.20	.22
CRYO	19.6±13.6 mL	0.06±0.06	.30	.18
	Non-Hemorrhagic Patients (n=5)			
PRBC	351±199 mL	0.77±0.10		
PLATELET	170±85 mL	0.40±0.10		
FFP	20.0±31 mL	0.04±0.05		
CRYO	12.0±19.0 mL	0.02±0.03		

CRYO - Cryoprecipitate; FFP - Fresh Frozen Plasma; Platelet concentrate from random donor; PRBC - Packed Red Blood Cells. All data mean ± STDEV

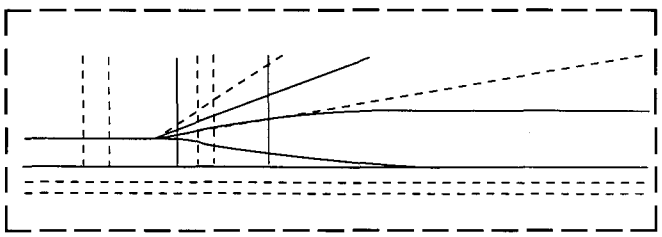
Figures 3a through 3d: Thrombelastograph profiles for a hemorrhagic patient. Each profile was completed at the hour on ECMO indicated and the corresponding laboratory values are included. CRYO - Cryoprecipitate; FFP - Fresh Frozen Plasma; PLT - Platelets; RBC - Packed Red Blood Cell; PLT-C - Platelet count; FIB - Fibrinogen; FSP - Fibrin Split Products

Figure 3a: PRE-ECMO



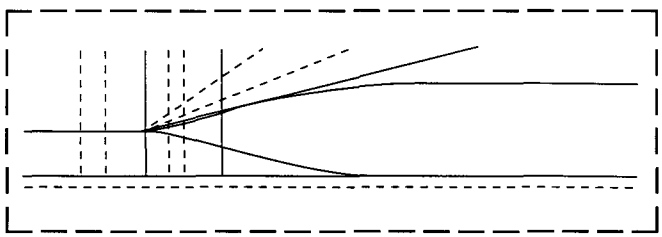
R TIME - 18mm K TIME - 5mm MA - 58mm A ANGLE - 61°

14 hour Transfusion RBC - 136 PLT - 27 FFP - 27 CRYO - 50
ECMO HR 14 PLT-C - 169 FIB - 45 ACT - 336 FSP - >40



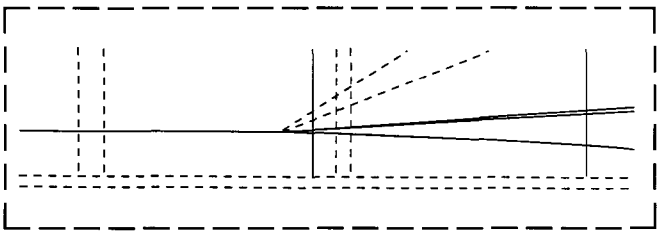
R TIME - 51mm K TIME - 32mm MA - 31mm A ANGLE - 14°

Figure 3b: 24 hour transfusion RBC - 194 PLT - 36 FFP - 57 CRYO - 2
ECMO HR 39 PLT-C - 167 FIB - 170 ACT - 218 FSP - >40 PFHB - 98



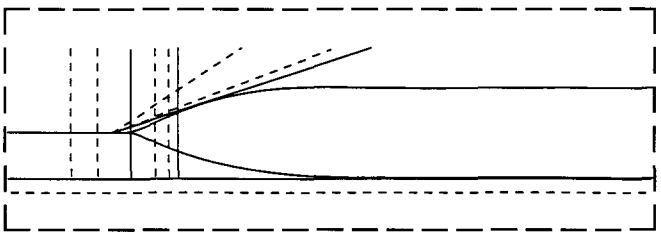
R TIME - 42mm K TIME - 27mm MA - 48mm A ANGLE - 20°

24 hour transfusion RBC - 100 PLT - 11 FFP - 0 CRYO - 0
ECMO HR 63 PLT-C - 77 FIB - 155 ACT - 202 FSP - >40



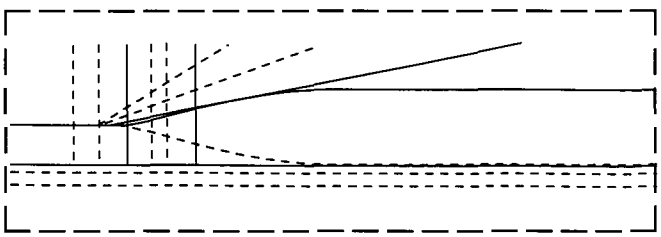
R TIME - 100mm K TIME - 95mm MA - 18mm A ANGLE - 4°

Figure 3c: 24 hour transfusion RBC - 114 PLT - 70 FFP - 0 CRYO - 0
ECMO HR 87 PLT-C - 133 FIB - 140 ACT - 180 FSP - >40



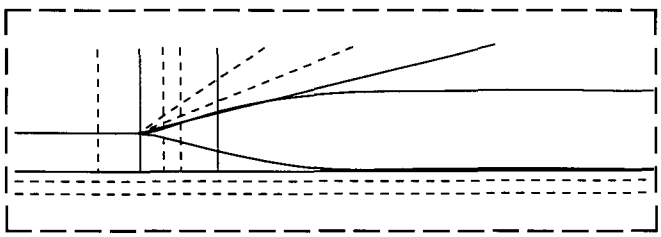
R TIME - 39mm K TIME - 16mm MA - 48mm A ANGLE - 26°

63 hour transfusion RBC - 215 PLT - 198 FFP - 74 CRYO - 7
ECMO HR 150 PLT-C - 82 FIB - 103 ACT - 191 FSP - >40



R TIME - 38mm K TIME - 23mm MA - 39 mm A ANGLE - 17°

Figure 3d: 40 hour transfusion RBC - 138 PLT - 93 FFP - 27 CRYO - 12
POST-ECMO PLT-C - 101 FIB - 125



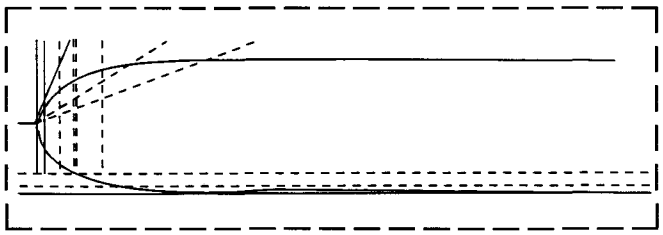
R TIME - 43mm K TIME - 26mm MA - 39mm A ANGLE - 19°

lowed, a significant number of patients experienced coagulopathic morbidity. This is most likely a combined result of both the inherent immature coagulation mechanism of the newborn patient and surface activation phenomena resulting from blood exposure to extracorporeal circuitry.

Coagulation factors in the newborn are substantially underdeveloped in the perinatal period, with the only factors approaching mature levels at birth being V, VII, XIII and fibrinogen (28,29). Vitamin K dependent factors do not reach pediatric or adult levels until between the third and twelfth month of life (28).

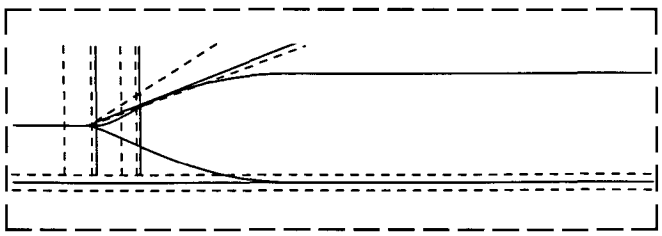
Figures 4a through 4d: Thrombelastograph profiles for a non-hemorrhagic patient. Each profile was completed at the hour on ECMO indicated and the corresponding laboratory values are included. CRYO - Cryoprecipitate; FFP - Fresh Frozen Plasma; PLT - Platelets; RBC - Packed Red Blood Cell; PLT-C - Platelet count; FIB - Fibrinogen; FSP - Fibrin Split Products

Figure 4a: PRE-ECMO PLT - 194 FIB - 375



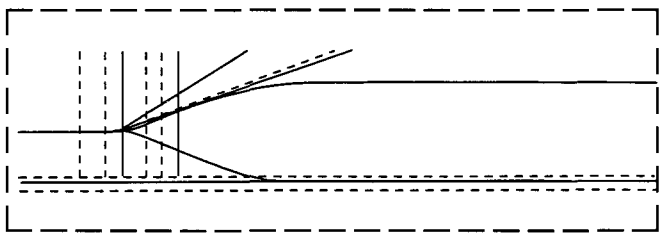
R TIME - 5.5mm K TIME - 2.5mm MA - 68mm A ANGLE - 74°

16 hour transfusion RBC - 82 PLT - 50 FFP - 0 CRYO - 0
ECMO HR 16 PLT-C - 114 FIB - 255 ACT - 222 FSP - >40
D-DIMER - <250 PFHB - 42



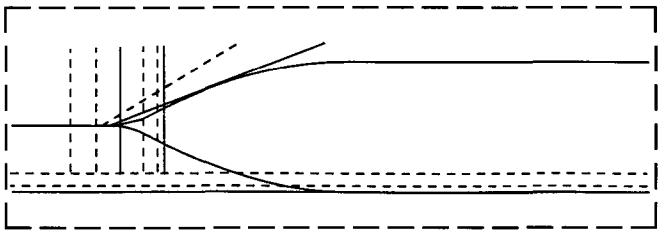
R TIME - 38mm K TIME - 14mm MA - 54mm A ANGLE - 31°

Figure 4b: 24 hour transfusion RBC - 123 PLT - 36 FFP - 0 CRYO - 0
ECMO HR 41 PLT-C - 97 FIB - 240 ACT - 214 FSP - >40
D-DIMER - 500-1000 PFHB - 30



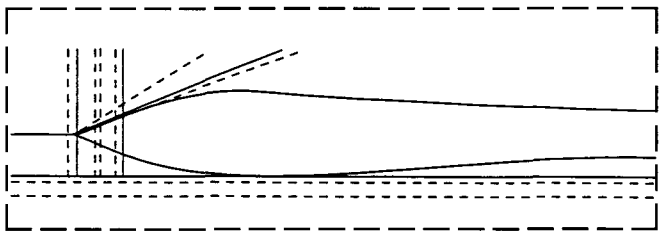
R TIME - 35mm K TIME - 19mm MA - 52mm A ANGLE - 28°

24 hour transfusion RBC - 41 PLT - 34 FFP - 0 CRYO - 0
ECMO HR 65 PLT-C - 121 FIB - 315 ACT - 211 FSP - >10<40
D-DIMER - <250 PFHB - 37



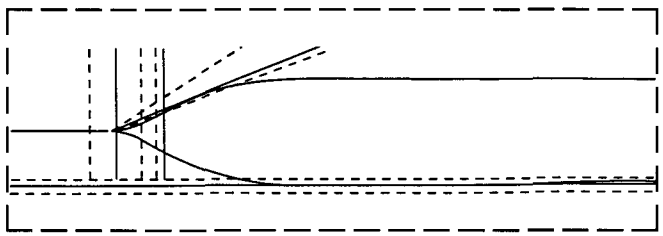
R TIME - 37mm K TIME - 15mm MA - 68mm A ANGLE - 29°

Figure 4c: 24 hour transfusion RBC - 82 PLT - 0 FFP - 0 CRYO - 0
ECMO HR 90 PLT-C - 90 FIB - 380 ACT - 221 FSP - >40
D-DIMER - >1000 PFBH - 38



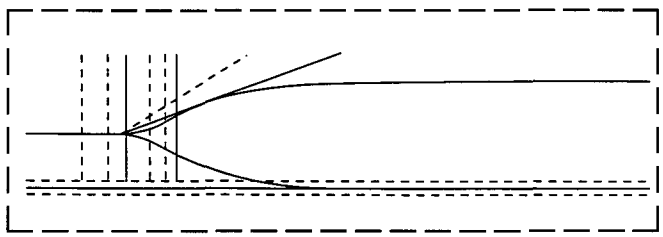
R TIME - 22mm K TIME - 15mm MA - 44mm A ANGLE - 32°

24 hour transfusion RBC - 82 PLT - 25 FFP - 0 CRYO - 0
ECMO HR 113 PLT-C - 124 FIB - 335 ACT - 192 FSP - >40
D-DIMER - >1000 PFHB - 62



R TIME - 37mm K TIME - 15mm MA - 53mm A ANGLE - 31°

Figure 4d: 24 hour transfusion RBC - 82 PLT - 18 FFP - 0 CRYO - 0
POST-ECMO PLT-C - 118 FIB - 340



R TIME - 35mm K TIME - 17mm MA - 55mm A ANGLE - 29°

Platelet counts are normal in the newborn but overall platelet function, assessed by various aggregation and adhesion stimuli, is below that of the adult (30). Fibrinolytic activity is generally increased in the term infant but rapidly adjusts to adult potentialwithin 6 hours of birth (31). Newborn patients in respiratory distress are at an increased risk of developing microvasculature thrombosis and consumptive coagulopathies (DIC) resulting from numerous predisposing stimuli, which include hypotension, sepsis, anoxia, and acidemia (28).

Many investigators have shown that large quantities of non-endothelialized surfaces within the ECMO circuit elicit profound changes in protein and cellular elements of blood (9,32,33). Plotz

and colleagues have identified two distinct phases for blood activation during neonatal ECMO (9,32). In the first phase, contact activation stimulates both the intrinsic limb of the coagulation cascade and complement mediated proteins, leading to the formation of thrombin-antithrombin III complexes and factor XIIa-C1 esterase inhibitor complexes. Fibrin(ogen) degradation products were also elevated during this phase which lasted approximately 24 hours. During the second phase, which occurred 72 hours after the start of ECMO, there was increased clotting and fibrinolytic activity, but little complement intermediate release (9,32). The majority of platelet consumption occurred within the contact phase of activation. The importance of identifying these specific periods of coagulation lies in the timing of pharmacologic and transfusion therapy to stave off further derangements which may precipitate a bleeding diathesis.

In our study, intermediates of complement activation were not measured. However, careful attention was made in recording the timing of all blood products. We were unable to show that there were any discernible differences in the consumption of coagulation factors or platelets over the phases described by Plotz and colleagues, despite having similar transfusion criteria and heparin maintenance protocols (9). We were also unable to detect an increased trend towards fibrinolysis at any time during ECMO with the TEG (minor fibrinolysis was detected in 2 of 101 coagulation profiles). This was unexpected since the TEG is an extremely sensitive monitor for detecting fibrinolytic conditions (15,17). However, measurements of D-dimers, a breakdown product of cross linked fibrin, were elevated at all times during ECMO. Plotz measured FDP and found that they began ro rise at approximately 48 hours of ECMO and peaked at 96 hours. We likewise measured FDP but found no correlation to the length of time on ECMO. Only one out of 17 patients experienced an increase in FDP after the first 48 hours of ECMO.

The intent of this investigation was not to prescribe therapeutic interventions from the results of the TEG. It was solely to record coagulation profiles of patients at specific time periods, or events, and correlate those with the clinical situation at hand. To this charge, the TEG served as an effective means of assessing a patient's hemostatic state, and identifying a bleeding diathesis that resulted from coagulation disorders, as well as those of surgical or mechanical origin.

It is important to note that the TEG has specific characteristics that must be heeded in applying the interpretation of the profiles to clinical situations. First, it is a device that measures whole blood coagulation, and therefore, will not correlate with routine plasmatic coagulation tests such as the prothrombin and partial thromboplastin times. Secondly, it will not differentiate between quantitative and qualitative platelet disorders, and therefore, may not correlate with platelet count when qualitative platelet dysfunction is seen concomitantly. Thirdly, the TEG profile develops over 60 to 90 minutes, and although initial results can be obtained in as short as 15 minutes, the entire assessment takes significant time.

Future studies involving the TEG and extracorporeal life support include identifying individuals who are at an increased thromboembolic risk resulting from a state of hypercoagulatbility. A promising area of research presently underway is the development of assays that contain a high degree of specificity in identifying specific coagulopathic conditions. TEG profiles, determined by adding hypocoagulable blood to vials containing either premeasured lyophilized platelet concentrate, fibrinogen (plasma, cryoprecipitate) or pharmacologic agents (epsilon aminocaproic acid), could be used to direct strategies for intervention. Perhaps most importantly, the TEG can be used to determine the appropriateness of laboratory assays for guiding transfusion decisions, while at the same time, validating the efficacy of such treatment.

The results of this study have shown that the thrombelastograph is a useful tool in providing supplemental information for the clinical management of patients undergoing long-term extracorporeal support. Furthermore, the device provides useful information for the diagnosis of both thromboembolic condition and hemorrhagic states, and can facilitate prompt intervention and guide therapy.

REFERENCES

1 Turner-Gomes SO, Mitchell L, Williams WG, Andrew A. Thrombin regulation in congenital heart disease after cardiopulmonary bypass operations. J Thorac Cardiovasc Surg. 1994; 107: 562-8.

2 Rinder CS, Gaal D, Student LA, Smith BR. Platelet-leukocyte activation and modulation of adhesion receptors in pediatric patients with congenital heart disease undergoing cardiopulmonary bypass. J Thorac Cardiovasc Surg. 1994; 107: 280-8.

3 Kirklin JW. The postperfusion syndrome: inflammation and the damaging effects of cardiopulmonary bypass. In: Tinker J, ed. Cardiopulmonary Bypass: Current Concepts and Controversies. Philadelphia: WB Saunders, 1989; 131-46.

4 Greeley WJ, Kern FH. Anesthesia for pediatric cardiac surgery. In: Miller RE, ed. Anesthesia. New York: Churchill Livingstone, 1990; 1653-91.

5 Harker LA. Bleeding after cardiopulmonary bypass. N Eng J Med 1986; 22: 1446-8.

6 Plotz FB, Wildevuur WR, Wildevuur CRH, et al. Platelet consumption during neonatal extracorporeal life support (ECLS). Perfusion 1992; 7: 27-33.

7 Sell LL, Cullen ML, Whittlesey GC, et al. Hemorrhagic complications during extracorporeal membrane oxygenation: prevention and treatment. J Pediatr Surg 1986; 21: 1087-91.

8 Faulkner SC, Chipmen CW, Baker LL. Troubleshooting the extracorporeal membrane oxygenator circuit and patient. J Extra Corpor Technol 1994; 24:120-29.

9 Plotz FB, van Oeveren W, Bartlett RH, Wildevuur CRH. Blood activation during neonatal extracorporeal life sup-

port. J Thorac Cardiovasc Surg 1993;105:823-32.
10 Mallett SV, Cox JA. Thrombelastography. Br J Anesthesia 1992;69:307-13.
11 Kang YG, Martin DJ, Marquez J, et al. Intraoperative changes in blood coagulation and thrombelastographic monitoring in liver transplantation. Anesth Analg 1985;64:888-96.
12 Martin P, Horkay, F, Rajah, SM, et al. Monitoring of coagulation status using thrombelastography during pediatric open heart surgery. Int J Clin Monit 1991;8:183-7.
13 Fisch IR, Freedman SH. Oral contraceptives, ABO blood groups and in vitro fibrin formation. Obstet Gynecol 1975;45:473-9.
14 Arensman RM, Cornish JD. Extracorporeal Life Support. Boston: Blackwell Scientific Publication, 1993;156-74.
15 Forst CF, Chapin JW, Forst SH, Stammers AH, Galbraith TA. Coagulation monitoring with heparinase during cardiopulmonary bypass. J Extra Corpor Technol 1994;26:129-34.
16 Riley JB, Stammers AH. A technique to give clinical relevance to parameters from the thrombelastograph. J Extra Corpor Technol 1992;23:112-24.
17 Stammers AH, Rasmussen CA, Kratz JM. Hemorrhagic effects of post-cardiopulmonary bypass fibrinolysis. J Extra Corpor Technol 1993;25:122-32.
18 Spiess BD, Ivankovich AD. Thrombelastography. A coagulation monitoring technique applied to cardiopulmonary bypass. In: Ellison N, Jobes DR. eds. Effective Hemostasis in Cardiac Surgery. Philadelphia: WB Saunders, 1988;163-81.
19 Jarjour IT, Ahdab-Barmada M. Cerebrovascular lesions in infants and children dying after extracorporeal membrane oxygenation. Pediatr Neurol 1994;10:13-9.
20 Nagaraj HS, Mitchell KA, Fallat ME, Groff DB, Cook LN. Surgical complications and procedures in neonates on extracorporeal membrane oxygenation. J Pediatr Surg 1992;27:1106-9.
21 Hirthler MA, Blackwell E, Abbe D, et al. Coagulation parameter instability as an early predictor of intracranial hemorrhage during extracorporeal membrane oxygenation. J Pediatr Surg 1991;27:40-3.
22 Seay RE, Uden DL, Kriesmer PJ, Payne NR. Predictive performance of three methods of activated clotting time measurement in neonatal ECMO patients. ASAIO 1993;39;39-42.
23 Peverini RL, Sale M, Rhine WD, Fagan, LM, Lenerte LA. Anticoagulation therapy advisor: A decision support system for heparin therapy during ECMO. Proc Annu Symp Comput Appl Med Care 1992;567-71.
24 Uden DL, Payne NR, Kriesmer P, Cipolle RJ. Procedural variables which affect activated clotting time test results during extra-corporeal membrane oxygenation therapy. Crit Care Med 1989;17:1048-51.
25 Green TP, Isham-Schopf B, Steinhorn RH, Smith C, Irmiter RH. Whole blood activated clotting time in infants during extracorporeal membrane oxygenation. Crit Care Med 1990;18:494-8.
26 Gravlee GP, Arora S, Lavender SW, et al. Predictive value of blood clotting tests in cardiac surgical patients. Ann Thorac Surg 1994;58:216-21.
27 Tuman KJ, McCarthy RJ, Djuric M. Rizzo V, Ivankovich AD. Evaluation of coagulation during cardiopulmonary bypass with a heparinase-modified thrombelastographic assay. J Cardiothorac Vasc Anesth 1994;8:144-9.
28 Oski, FA, Naiman, JL. Blood coagulation and its disorders in the newborn. In: Hematologic Problems in the Newborn. Philadelphia: WB Saunders;1982;137-74.
29 Andrew M, Paes P, Milner R, et al. Development of the human coagulation system in the full term infant. Blood 1987;70:165-72.
30 Ware JA, Reaves WH, Hoard JA, et al. Defective platelet aggregation in patients undergoing surgical repair of cyanotic congenital heart disease. Ann Thorac Surg 1983;36:289-94.
31 Ekelund AR, Hedner V, Nilsson IM. Fibrinolysis in newborns. Acta Paediatr Scand 1970; 59:33-38.
32 Plotz FB, Wildevuur WR, Wildevuur CRH, Delius RE, Bartlett RH. Platelet consumption during neonatal extracorporeal life support. Perfusion 1992;7:27-33.
33 Webb AR, Mythen MG, Jacobson D, Mackie IJ. Maintaining blood flow in the extracorporeal circuit: haemostasis and anticoagulation. Int Care Med 1995;21:84-93.