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ORIGINAL ARTICLE

Earlier detection of coagulopathy with thromboelastometry during pediatric cardiac surgery: a prospective observational study

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Keywords
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Summary

Objective: Earlier detection of coagulopathy in pediatric cardiac surgery patients.
Aim: To determine whether thromboelastometry (TEM) analysis before weaning from cardiopulmonary bypass (CPB) and hemoconcentration is predictive of post-CPB results and whether analysis of clot firmness already after 10 min yields reliable results.
Background: Cardiac surgery with CPB induces a coagulopathy that may contribute to postoperative complications. Earlier detection increases the possibility of initiating countermeasures.
Methods/Material: Fifty-six pediatric cardiac surgery patients were included in a prospective observational study. HEPTEM and FIBTEM clotting time (CT), clot formation time (CFT), and clot firmness after 10 min (A10) and at maximum (MCF) were analyzed during CPB and after CPB and ultrafiltration with modified rotational thromboelastometry (ROTEM®). The analyses were compared, and correlations and differences were calculated.
Results: Hemoconcentration with modified ultrafiltration increased hematocrit from 28 ± 3 to 37 ± 4% ($P < 0.001$). Correlation coefficients of the TEM variables during and after CPB ranged from 0.61 to 0.82 (all $P < 0.001$). HEPTEM-CT and HEPTEM-MCF differed significantly but the differences were marginal. Both HEPTEM and FIBTEM A10 measurements during CPB were significantly less than MCF ($P < 0.001$ for both), but the correlations were highly significant (HEPTEM: $r = 0.95$, $P < 0.001$; FIBTEM: $r = 0.96$, $P < 0.001$), and the differences were predictable, with narrow confidence intervals (HEPTEM: −8.2 mm (−8.9 to −7.5); FIBTEM: −0.5 mm (−0.7 to −0.3).
Conclusion: The results suggest that intraoperative TEM analyses can be accelerated by analyzing HEPTEM/FIBTEM on CPB before hemoconcentration and by analyzing clot firmness already after 10 min.

Introduction

Excessive bleeding during and after cardiac surgery increases morbidity and mortality. The bleeding may be due to surgical causes and/or impaired hemostasis. Cardiac surgery with cardiopulmonary bypass (CPB) induces a coagulopathy, which, if severe, may contribute to perioperative bleeding complications (1,2). Early

detection and characterization of the coagulopathy increases the possibility of initiating countermeasures to minimize perioperative blood loss and transfusion requirements. The perioperative coagulopathy can be detected with thromboelastometry/thromboelastography (TEM/TEG) (3–8), and routine use of intraoperative TEM/TEG has been demonstrated to reduce transfusion requirements in both adult and pediatric cardiac surgery (9,10).

Thromboelastometry/thromboelastography analysis during CPB would allow earlier detection of the coagulopathy. However, the inevitable hemodilution and systemic heparinization during CPB might influence the measurements. TEM/TEG can be performed with heparinase to adjust for the heparin effects, but little is known about the influence of hemodilution on TEM/TEG variables during pediatric cardiac surgery. Furthermore, a complete TEM/TEG analysis takes approximately 30 min. The total time is solely dependent on the time it takes to analyze maximum clot firmness (MCF). If clot firmness could be determined faster, the coagulopathy would be detected earlier.

We hypothesized that TEM analyses in pediatric cardiac surgery can be accelerated by analyzing TEM on CPB before weaning and hemoconcentration instead of immediately after CPB, and by analyzing clot firmness at 10 min instead of at maximum firmness. To test this hypothesis, we designed a prospective observational study.

Methods

Patients

Fifty-six pediatric cardiac patients undergoing surgery with CPB were included in this prospective observational study. Twenty-three patients (41%) had a bodyweight <5 kg. The group underwent surgery between March 2008 and May 2011. The study was approved by the Regional Medical Research Ethics Committee and conducted in accordance with the Declaration of Helsinki. Written informed consent was signed by all parents. All patients were operated on and anesthetized by the same group of surgeons and anesthesiologists. Patients with a known coagulation defect or severe renal or hepatic disorder were excluded. Patient characteristics and types of congenital heart defects are given in Table 1.

Table 1 Patient characteristics, diagnoses, and intraoperative variables. Mean ± SD, median (range), or number (percentage)

Age, months	
Mean ± SD	21 ± 33
Median (range)	5.8 (0.1–124)
Weight, kg	
Mean ± SD	9.5 ± 8.0
Median (range)	5.8 (2.3–42)
Girls, *n* (%)	21 (38%)
Diagnoses, *n* (%)	
ASD	3 (5%)
VSD	13 (23%)
AS	3 (5%)
AVSD	9 (16%)
CoA	2 (4%)
Fallot	4 (7%)
HLHS	7 (13%)
TGA	4 (7%)
Others	11 (20%)
CPB time, min	132 ± 72
Aortic clamp time, min	66 ± 45

ASD, atrial septal defect; AS, aortic stenosis; AVSD, atrial ventricular septal defect; Coa, coarctation; CPB, cardiopulmonary bypass; HLHS, hypoplastic left heart syndrome; TGA, transposition of the great arteries; VSD, ventricular septal defect.

Anesthesia

Midazolam and ketamine was used for induction of anesthesia. Maintenance of anesthesia included isoflurane fentanyl (25–75 $\mu g \cdot kg^{-1}$), midazolam (0.1–0.3 $mg \cdot kg^{-1}$), and atracurium (0.5–0.7 $mg \cdot kg^{-1}$), supplemented with propofol if indicated during CPB. The anesthesia procedure was unchanged during the study period.

Anti-coagulation and reversal

An initial i.v. bolus of unfractioned heparin (Leo Pharma A/S, Ballerup, Danmark), 400 $U \cdot kg^{-1}$ bodyweight, was administered before CPB cannulation. The level of anti-coagulation was repeatedly controlled during bypass with activated clotting time (ACT) (Hemocron Jr II; ITC, Edison, NY, USA). Reversal of heparinization was achieved with protamine (Leo Pharma A/S), 1 mg per 100 U of the total heparin dose.

Bypass technique

Cardiopulmonary bypass was conducted with a hard-shell reservoir and a patient size-adapted membrane oxygenator (Terumo, Tokyo, Japan). Target rectal temperature (28–36°C) was decided by the surgeon depending on the type of surgery. The total pump prime volume ranged from 350 to 700 ml, depending on the tubing and the oxygenator. The priming solution consisted of crystalloid fluid and allogenic blood, mannitol (5 $ml \cdot kg^{-1}$), and 100 ml Tribonat® (Fresenius Kabi AB, Uppsala, Sweden) and heparin. During bypass, heparin was administered whenever ACT was less than 480 s. Myocardial protection was achieved with cold intermittent blood cardioplegia. Modified

ultrafiltration was performed after weaning from CPB with cannulas in place, aiming at a hematocrit of 35–40%.

Surgical technique

The diagnoses of the children are reported in Table 1. Atrial septal defects (ASD) were closed with either direct suture or patch and ventricular septal defects (VSD) were closed with a patch. Aortic stenosis was operated with commissurotomy or Ross procedure. Patients with transposition of the great arteries (TGA) were operated with arterial switch. Coarctation (CoA) of aorta was operated with resection or extended resection and end-to-end anastomosis. Atrial ventricular septal defects (AVSD) were repaired with two patch technique. Fallot's tetralogy was repaired with closure of VSD with patch, resection of right ventricular outflow tract obstruction, commissurotomy or if needed transannular patch. Patients with hypoplastic left heart syndrome were operated with Norwood palliation. The temperature during CPB ranged from 28°C to normothermia. Fifteen patients were operated at 28–30°C, 25 at 32–34°C and 16 in normothermia. No patient was operated in circulatory arrest.

Study protocol

Hemoglobin (Hb), hematocrit, and platelet counts were analyzed with routine methods before surgery, immediately after surgery, and on the first postoperative morning (Table 2). Prothrombin time was analyzed before surgery. We determined hematocrit, TEM with HEPTEM clotting time (CT), HEPTEM clot formation time (CFT), HEPTEM clot firmness after 10 min (A10) and at maximum (MCF), and FIBTEM clot firmness after 10 min and at maximum at five clinical intervals: (i) after induction of anesthesia, (ii) at the end of CPB, after rewarming, (iii) after modified ultrafiltration (after weaning from bypass but before protamine administration), (iv) after surgery had been completed, and (v) on the first postoperative day. Measurements of TEM variables before and after weaning and ultrafiltration were compared. In addition, HEPTEM and FIBTEM clot firmness after 10 min and at maximum firmness were compared. All intraoperative samples were collected from an arterial line. An accredited university hospital laboratory performed all analyses, except TEM.

Modified rotational thromboelastometry

Whole-blood coagulation was analyzed by modified rotational thromboelastometry (ROTEM®; Pentapharm, Munich, Germany). Technical details and evaluation of the method have been reported elsewhere (6,11). Nine hundred microliters of whole blood was obtained from the nonheparinized arterial line and collected in a tube containing citrate (Minicollect; Greiner Bio-One GmbH, Badhaller, Austria). Samples of 300 μl each were analyzed at 37°C using HEPTEM (with heparinase added for heparin-insensitive analysis) and FIBTEM (with cytochalasin D added to discern fibrin polymerization from the effects of platelets). A heparin-inhibiting agent was also included in the FIBTEM analysis. Clotting time (CT), clot formation time (CFT), and maximum clot firmness (MCF) were measured in the HEPTEM

Table 2 Selected modified thromboelastometry variables and hemoglobin, hematocrit, and platelet counts before, during, and after CPB. Mean and SD

	Before surgery	On CPB	After CPB and hemoconcentration	After surgery	Day 1 after surgery
HEPTEM					
CT, s	173 ± 34	278 ± 91	306 ± 126*	246 ± 100	190 ± 41
CFT, s	73 ± 24	255 ± 145	229 ± 104	189 ± 115	115 ± 41
A10, mm	55 ± 7	34 ± 43	36 ± 7	39 ± 9	48 ± 7
MCF, mm	60 ± 5	43 ± 8	44 ± 7*,###	48 ± 7	54 ± 6
FIBTEM					
A10, mm	11.4 ± 4.4	4.5 ± 2.3	4.7 ± 2.7	5.9 ± 2.8	9.3 ± 4.2
MCF, mm	12.1 ± 4.6	5.0 ± 2.4	5.2 ± 2.9###	6.3 ± 2.9	10.2 ± 4.8
Hemoglobin (g l^{-1})	130 ± 20	NA	NA	122 ± 18	122 ± 17
Hematocrit (%)	39 ± 6	28 ± 3	37 ± 4	37 ± 5	38 ± 5
Platelet count ($\times 10^9$ per l)	358 ± 140	142 ± 49	151 ± 55	165 ± 67	197 ± 117
Prothrombin time (INR)	1.3 ± 0.2	NA	NA	NA	NA

A10, clot firmness after 10 min; CFT, clot formation time; CPB, cardiopulmonary bypass; CT, clotting time; INR, international normalized ratio; MCF, maximum clot firmness; NA, not analyzed.

*$P < 0.05$ vs on CPB.

###$P < 0.001$ vs A10 at the same time point.

analysis. The importance of fibrin polymerization for the MCF was evaluated in the FIBTEM analysis.

Statistical analysis

The study is observational and explorative, and the analyses have mainly a descriptive purpose. No formal sample size calculation was performed. The number of study subjects is based on previous publications on the subject and practical reasons. The results are presented as mean and standard deviation (SD) or mean and 95% confidence interval. Paired *t*-test was used to compare continuous variables before and after ultrafiltration, and clot firmness after 10 min and at maximum firmness. Correlation was calculated with Pearson's test. Any *P*-value of <0.05 was considered statistically significant. Statistical analysis was carried out using SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Clinical course

All 56 children completed the study protocol. There was no perioperative mortality.

TEM variables before and after hemoconcentration

Modified ultrafiltration with hemoconcentration increased hematocrit from 28±3% to 37 ± 4%, $P < 0.001$. There were limited differences when absolute values of TEM variables were compared before and after hemoconcentration (Tables 2 and 3). Only the differences in HEPTEM-CT and HEPTEM-MCF were statistically significant ($P = 0.036$ and $P = 0.038$, respectively). The correlation coefficients between all variables on CPB and after modified ultrafiltration were statistically significant ($r = 0.61$–0.82, all $P < 0.001$) (Table 2).

Table 3 Correlations and absolute and relative differences between thromboelastometric measurements during CPB and after weaning and hemoconcentration

	Correlation coefficient	*P*-value (correlation)	Absolute difference (95% CI)
HEPTEM			
CT, s	0.61	<0.001	29 (2 to 57)
CFT, s	0.73	<0.001	−26 (−53 to 1)
A10, mm	0.74	<0.001	1.2 (−0.3 to 2.7)
MCF, mm	0.77	<0.001	1.5 (0.1 to 2.9)
FIBTEM			
A10, mm	0.79	<0.001	0.2 (−0.2 to 0.7)
MCF, mm	0.82	<0.001	0.2 (−0.3 to 0.6)

A10, clot firmness after 10 min; CFT, clot formation time; CI, confidence interval; CT, clotting time; MCF, maximum clot firmness.

Clot firmness after 10 min and at maximum

Clot firmness after 10 min for both HEPTEM and FIBTEM was significantly less than maximum clot firmness during and after CPB. However, there were excellent correlations between HEPTEM A10 and MCF before surgery ($r = 0.94$), during CPB ($r = 0.95$), after weaning and hemoconcentration ($r = 0.93$), after surgery ($r = 0.93$), and on postoperative day 1 ($r = 0.91$) (all $P < 0.001$). In FIBTEM also, the correlations between A10 and MCF were excellent ($r = 0.98$ before surgery, $r = 0.96$ on CPB, $r = 0.95$ after weaning and hemoconcentration, $r = 0.95$ after surgery, and $r = 0.97$ on postoperative day 1 (all $P < 0.001$).

The differences between A10 and MCF during surgery were highly predictable both during CPB (with narrow confidence intervals: HEPTEM −8.2 mm (−8.9 to −7.5) and FIBTEM −0.5 mm (−0.7 to −0.3)) (Figure 1), and after weaning and hemoconcentration (HEPTEM −8.5 mm (−9.2 to −7.8) and FIBTEM −0.5 mm (−0.8 to −0.3).

Discussion

The main findings of the present study were as follows: The correlations between TEM variables before and after weaning CPB and hemoconcentration were statistically significant, and maximum clot firmness could be predicted with great accuracy already after 10 min. The results therefore suggest that intraoperative TEM analyses can be accelerated by analyzing HEPTEM/FIBTEM during CPB before weaning and hemoconcentration and by analyzing clot firmness after 10 min.

Cardiopulmonary bypass induces a coagulopathy that may increase the risk of bleeding complications and transfusion requirements in both adult and pediatric cardiac surgery (1,2). In pediatric cardiac surgery, the risk of bleeding complications is further aggravated due to complex surgery in low-weight patients with an immature coagulation system (12,13). Early detection and characterization of the coagulopathy with TEM/TEG will increase the opportunity for early treatment of hemostatic disturbances if bleeding occurs. Pediatric cardiac surgery studies with TEM/TEG have shown that patients with congenital heart disease have impaired clot formation, which is most pronounced in children with cyanotic heart disease (12,14). An association between TEG variables and postoperative bleeding has also been shown

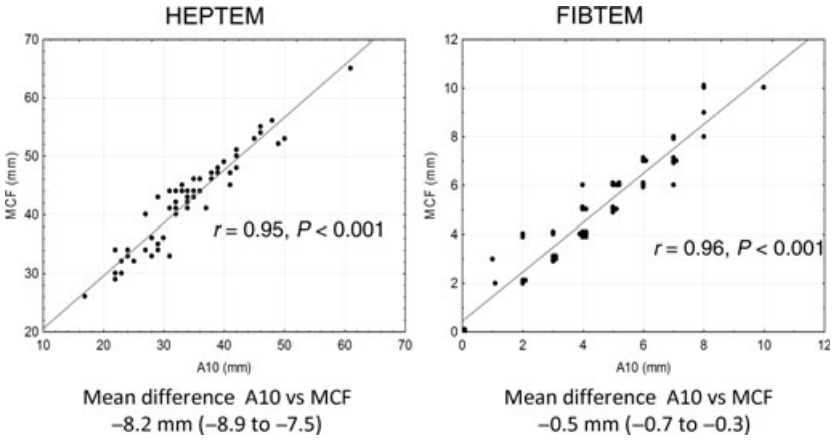

Figure 1 Correlation between HEPTEM and FIBTEM A10 and maximum clot firmness during cardiopulmonary bypass.

(4,7,8,15). The results were recently confirmed by Moganasundram *et al*. (16), who concluded that TEG may be a useful tool to predict and guide treatment of bleeding in pediatric cardiac surgery. Our group has shown that routine use of intraoperative TEM is associated with reduced transfusion requirements in pediatric cardiac surgery (10). Similar results have also been reported in adult cardiac surgery (9). This is important, since blood transfusions are associated with side effects including infections, transfusion-related acute lung injury, immunomodulation, and—in infants undergoing cardiac surgery—also prolonged mechanical ventilation and prolonged hospital stay (17,18).

In the present study, TEM measurements were performed before, during, and after CPB. According to the literature, preoperative measurements have no or limited prognostic value (3,8). In contrast, measurements performed immediately after CPB seem to predict postoperative-bleeding volumes and transfusion requirements (4,7,8,15,16). In the present study, we investigated whether there was any correlation between measurements performed during CPB, and measurements performed after weaning CPB and hemoconcentration. A systematic difference between the two measurements would indicate that it is necessary to wait until after weaning and hemoconcentration to perform the analysis. However, we could not detect any clear systematic variation. The correlations between the two measurements were statistically significant (*r*-values between 0.61 and 0.82), and in the only two variables where absolute values differed significantly (HEPTEM-CT and HEPTEM-MCF), the differences were small (29 s in CT and 1.5 mm in MCF). The results therefore suggest that TEM analyses with heparinase allow measurements during CPB after rewarming. However, in some patients, the differences were greater. As a method, rotational thromboelastometry analysis has acceptable repeatability, with an intra-assay coefficient of variation for FIBTEM MCF of 6–13% and of <5% for EXTEM MCF (19) Thus, the present results suggest that there are individual differences in alterations of hemostasis in response to hemoconcentration.

Our results also suggest that hemoconcentration has no significant systematic influence on thromboelastometry variables. However, hemoconcentration is still an important tool to reduce transfusion requirements. Modified ultrafiltration has previously been associated with reduced transfusions, improved platelet function, and increased platelet concentration (20–23).

Our second aim was to determine whether the assessment of intraoperative coagulation could be evaluated already after 10 min instead of at maximum firmness, which normally takes about 30 min. We found that the correlation between A10 and MCF was excellent (Figure 1), but the difference was statistically significant. The confidence interval was, however, narrow, and it is possible to directly predict the MCF intraoperatively from the A10 values by adding 8 mm to the HEPTEM analysis and 0.5 mm to the FIBTEM analysis. The close association between A10 and MCF has been found before in liver transplant and trauma patients (24,25), but not in children undergoing cardiac surgery.

One limitation of the present study was the number of study subjects. The size of our material does not allow subgroup analysis or calculation of associations with clinical variables such as bleeding volumes and transfusions.

In conclusion, hemoconcentration and weaning from CPB had no or limited effect on TEM results. Measurements of clot firmness after 10 min were highly predictable of maximum clot firmness. The results suggest that intraoperative TEM analysis can be accelerated by analyzing HEPTEM/FIBTEM on CPB before hemoconcentration and by determining clot firmness already after 10 min.

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Conflict of interest

No conflicts of interest declared.

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