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Early thromboelastometry variables predict maximum clot firmness in children undergoing cardiac and non-cardiac surgery

A. Perez-Ferrer[1], J. Vicente-Sanchez[1], M. D. Carceles-Baron[2], P. Van der Linden[3] and D. Faraoni[4,*]

[1]Department of Anaesthesiology, La Paz University Hospital, Madrid, Spain, [2]Department of Anaesthesiology, University Hospital Virgen de la Arrixaca, Murcia, Spain, [3]Department of Anaesthesiology, Centre Hospitalier Universitaire Brugmann – Queen Fabiola Children University Hospital, Free University of Brussels, Brussels, Belgium, and [4]Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital, Harvard Medical School, 300 Longwood Avenue, Boston, MA, USA

*Corresponding author. E-mail: david.faraoni@childrens.harvard.edu

Abstract

Background: Early clot amplitudes measured on thromboelastometry (ROTEM®) predict maximum clot firmness (MCF) in adults. In this multicentre, retrospective study, we aimed to confirm the suspected relationship between early ROTEM® variables and MCF, in children undergoing cardiac or non-cardiac surgery.

Methods: 4762 ROTEM® tests (e.g. EXTEM, INTEM, FIBTEM, APTEM, and HEPTEM) performed in children undergoing cardiac or non-cardiac surgery at three University hospitals between January 2011 and June 2014 were reviewed. To assess the correlation between clot amplitudes measured after 5, 10 and 15 min and MCF, each variable was compared with the corresponding MCF by calculating Spearman's correlation coefficient.

Results: For the EXTEM® test, we observed that amplitude measured after 5 min (A5: r=0.91, P<0.001), 10 min (A10: r=0.95, P<0.001) and 15 min (A15: r=0.96, P<0.001) were strongly correlated to MCF. The same correlations were observed for INTEM® test (A5: r=0.93, P<0.001; A10: r=0.97, P<0.001; A15: r=0.97, P<0.001), and FIBTEM® test (A5: r=0.93, P<0.001; A10: r=0.94, P<0.001; A15: r=0.96, P<0.001). In addition, the amplitudes measured after five, 10 and 15 min were also strongly correlated with MCF in the APTEM® and the HEPTEM® tests. Receiver operating characteristics (ROC) analysis confirmed that A5, A10, A15 strongly predicted decreased MCF on all ROTEM® tests.

Conclusions: This study confirmed that early values of clot amplitudes measured as soon as five, 10 or 15 min after clotting time could be used to predict maximum clot firmness in all ROTEM® tests.

Key words: blood transfusion; blood coagulation; children; measurement techniques; thromboelastometry; transfusion algorithm

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Editor's key points

- Point-of-care (POC) coagulation testing is increasingly used and several devices are commercially available.
- Maximum clot firmness (MCF) relates to early clot amplitudes measured using the ROTEM® device in adults but there are limited data in children.
- In this retrospective study, there were close correlations between clot amplitudes as early as 5 min and subsequent maximum clot firmness.
- Early availability of this information could aid the management of coagulopathy, but further data are needed.

Standard coagulation assays have been used for a long time for the diagnosis of congenital and acquired coagulopathies, and to guide the administration of anticoagulation both in adults and children.[1 2] Although considered as the 'gold standard', these tests were not designed to monitor perioperative coagulopathy, and to guide the administration of haemostatic agents in bleeding situations.[3] As it usually takes 30–45 min to obtain the results from standard coagulation assays, limited information are provided by these tests in the context of acute bleeding.[4] In addition, standard laboratory tests are performed on platelet poor plasma (PPP) and do not allow for a global assessment of coagulation, giving no information about clot firmness and clot lysis.[5]

Over the past decade, thromboelastometry (ROTEM®, TEM International GmbH, Munich, Germany) has been increasingly used in different clinical conditions, and is now integrated in all recent guidelines for bleeding management.[6 7] Different tests performed on whole blood are available, allowing for an assessment of the intrinsic coagulation pathway (INTEM: in-tem®, ellagic acid), the extrinsic pathway (EXTEM: ex-tem®, tissue factor), the fibrinogen function (FIBTEM: fib-tem®, tissue factor and cytochalasin D), the fibrinolysis (APTEM: ap-tem®, tissue factor and aprotinin), and the presence of residual heparin activity (HEPTEM: hep-tem®, ellagic acid and heparinase). In adults undergoing cardiac and non-cardiac surgeries, clot amplitudes measured 5–10 min after initiation of coagulation have been shown to predict maximum clot firmness (MCF), allowing for a rapid detection and management of decreased clot strength.[8–11] In children undergoing cardiac surgery, Romlin and colleagues[12] reported a good correlation between clot amplitude measured 10 min after clot initiation and MCF, both in HEPTEM (r=0.95, P<0.001) and FIBTEM (r=0.96, P<0.001). Comparable results were also reported in another cardiac study, showing that the clot amplitude measured as soon as 10 min after clot initiation, offered the same predicted value for postoperative bleeding, when compared with the amplitude measured after 20 min or MCF.[13]

In this multicentre, retrospective study, we aimed to confirm the suspected relationship between early ROTEM® variables and MCF in children undergoing cardiac or non-cardiac surgery.

Methods

This retrospective study was approved by the local ethics committee at La Paz University Hospital (Madrid, Spain), and the ethics committee waived the requirement for written informed consent, as only de-identified ROTEM® variables were collected from the ROTEM® databases (30/03/2015, HULP: PI-1998). The study and the decision made by the principal ethics committee was also reviewed and approved by the other ethics committees.

Three authors (APF, MDCL, and DF) respectively reviewed the ROTEM® databases, including all tests performed in children undergoing cardiac and non-cardiac surgeries (e.g. visceral surgery, liver transplantation, trauma, orthopaedic surgery) at La Paz University Hospital (Madrid, Spain), University Hospital Virgen de la Arrixaca (Murcia, Spain), and Queen Fabiola Children's University Hospital (Brussels, Belgium) between January 2009 and June 2014. Five different tests (e.g. EXTEM, INTEM, FIBTEM, APTEM, and HEPTEM) were reviewed for adequacy. Exclusion criteria were: tests performed in patients ≥18 yr, total runtime <35 or >90 min and signs of hyperfibrinolysis defined as a lysis index, measured after 30 min (LI30) <75%.

In all centres, ROTEM® assays were performed in the operating room by experimented doctors, and respecting the recommendations published by the manufacturer.[14] The following parameters were obtained from the different ROTEM® tests: clotting time (CT, s), clot formation time (CFT, s), alpha angle (α, degree), amplitudes measured after five, 10, 15 min (A5, A10, A15, mm) and the maximum clot firmness (MCF, mm).

Statistical analysis

Data were analysed separately for each ROTEM® assays. Distribution of data was tested for normality using the Kolmogorov-Smirnov test. Continuous variables are reported as mean and standard deviation (SD). To assess the correlation between CT, CFT, α angle, A5, A10, A15 and MCF, each variable was compared with the corresponding MCF by calculating Spearman's correlation coefficient. The Bland-Altman analyses were performed to calculate the mean difference (bias) and the standard deviation (SD) between A5, A10, A15 and MCF. Optimal thresholds for all tested variables to predict a subnormal MCF on EXTEM®, INTEM®, APTEM® (MCF <50 mm), and FIBTEM® (MCF <9 mm) were calculated, using receiver operating characteristics (ROC) analysis. These cut-offs were defined a priori using the 2.5th percentile of the normal paediatric reference ranges defined by Ostwald and colleagues[15] Results are expressed as area under the ROC curve, sensitivity and specificity, and their 95% confidence intervals (CIs).

A P-value <0.05 was considered statistically significant for all comparisons. Statistical analysis was performed using IBM SPSS Statistics (version 21.0, IBM, Armonk, NY).

Results

From the 4762 ROTEM® assays obtained from children who underwent cardiac or non-cardiac surgery in this multicentre retrospective analysis, data from 1580 EXTEM®, 1227 INTEM®, 1415 FIBTEM®, 428 HEPTEM® and 112 APTEM® were analysed (Supplementary data, Table 1).

For all assays, correlations between CT, CFT, alpha angle and MCF were significant, but associated with weak correlation coefficients (Fig. 1A–C). For the EXTEM® test, we observed that amplitude measured five min (A5) after the clotting time was strongly correlated with MCF (Fig. 1D: r=0.91, P<0.001). The same strong correlations were reported for the amplitudes measured after 10 min (Fig. 1E: r=0.95, P<0.001) and 15 min (Fig. 1F: r=0.96, P<0.001). Amplitudes measured after 5, 10 and 15 min were also strongly correlated with MCF in the INTEM®, APTEM® and the HEPTEM® tests (Table 1). For the FIBTEM® test, we observed that amplitude measured after 5 min (A5) was strongly correlated with MCF (Fig. 2A: r=0.93, P<0.001). The same strong correlations were reported for the amplitudes measured after 10 min (Fig. 2B: r=0.94, P<0.001) and 15 min (Fig. 2C: r=0.96, P<0.001). In addition,

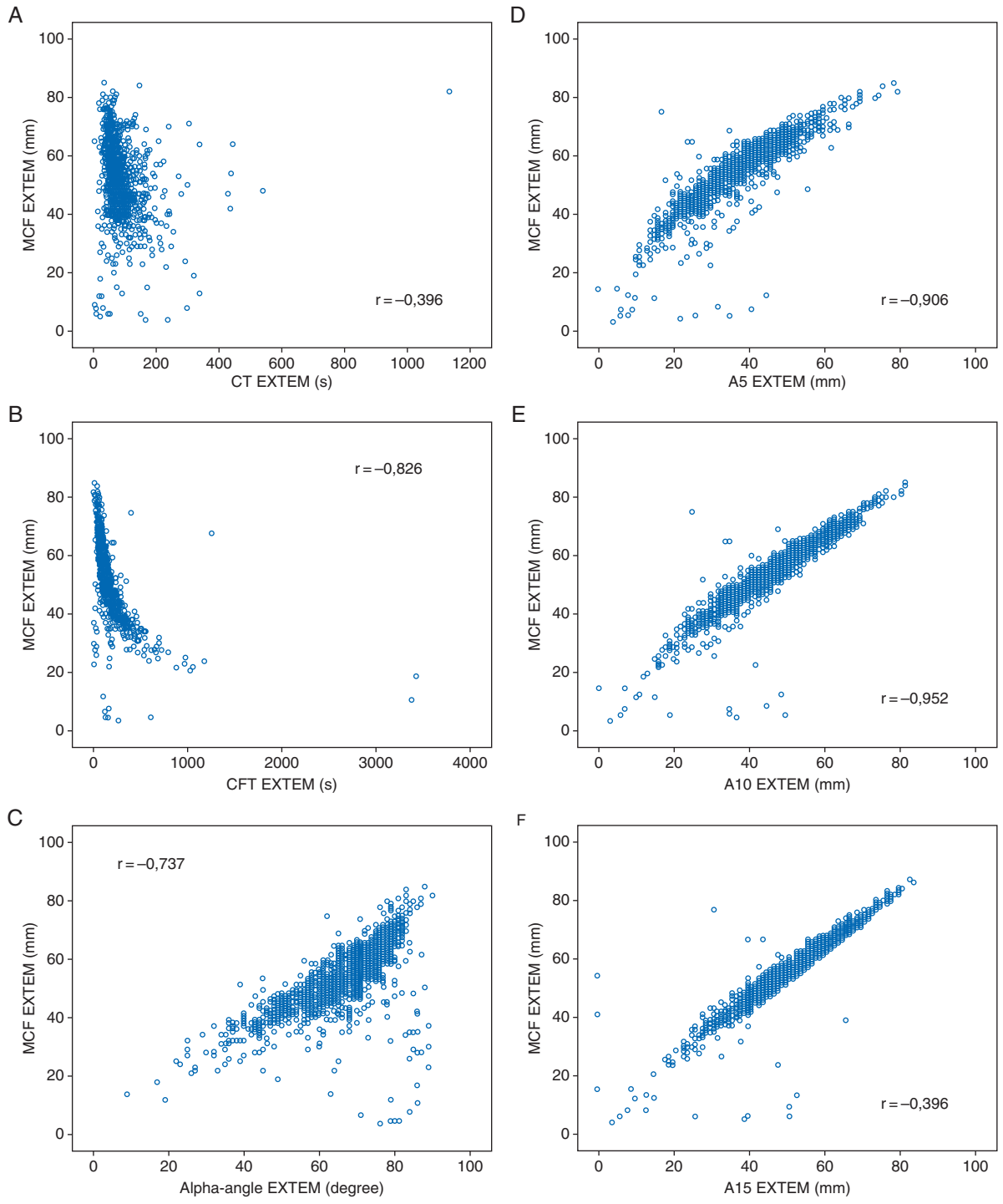

Fig 1 Graphs for the EXTEM® variables demonstrating correlation between clotting time (A), clot formation time (B), alpha angle (C), the amplitude measured after 5 min (D), 10 min (E), 15 min (F) and the maximum clot firmness (MCF). One outlier, in Fig. 1E, was not displayed but not excluded from the analysis.

specific bias obtained from the Bland-Altman analyses for A5, A10 and A15 values for the different ROTEM® tests are reported in Table 2 (online-only Supplementary Material 1). The bias for A10 values of EXTEM® and FIBTEM® in children presenting sub-normal (MCF<50 or <9 mm, respectively), normal (MCF 50–70 or 9–25 mm, respectively), and supra-normal MCF values (MCF>70 or >25 mm, respectively) and pooled data as obtained from the Bland-Altman analyses are presented in Table 3, and also the respective Spearman's coefficients ρ for linear regression. For all assays analysed, A5, A10, and A15 were excellent predictors for

Table 1 Spearman's correlation between variables and maximum clot firmness for each ROTEM® assays. Coef., coefficient regression; CT, clotting time; CFT, clot formation time; A, amplitudes

Assays	CT (s)	CFT (s)	Alpha (deg)	A5 (mm)	A10 (mm)	A15 (mm)
EXTEM®						
Coef.	−0.40	−0.83	0.74	0.91	0.95	0.96
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
N	1194	1183	1189	1004	1185	992
INTEM®						
Coef.	−0.42	−0.87	0.75	0.93	0.97	0.97
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
N	863	842	854	670	846	654
FIBTEM®						
Coef.	−0.50	−0.86	0.70	0.96	0.98	0.98
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
N	1141	189	580	970	1134	959
APTEM®						
Coef.	−0.29	−0.86	0.75	0.93	0.94	0.96
P-value	0.015	<0.001	<0.001	<0.001	<0.001	<0.001
N	70	67	68	70	69	69
HEPTEM®						
Coef.	−0.45	−0.92	0.84	0.90	0.95	0.94
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
N	313	307	309	125	311	124

decreased clot strength measured by the MCF (Table 4, online-only Supplementary Material 2).

Finally, we compared the correlation obtained between A5, A10 or A15 and MCF for EXTEM® and FIBTEM® between the three centres included. Although some statistically significant differences were observed between centres, the differences between Spearman's coefficients could not be considered as clinically relevant as coefficients were ≥0.888 for all comparisons (online-only Supplementary Material 3).

Discussion

This large, multicentre, retrospective study that analysed data from 4762 ROTEM® obtained in children who underwent cardiac or non-cardiac surgeries demonstrated a strong correlation between early values of clot amplitudes (e.g. A5, A10, A15) and maximum clot firmness (MCF). These results confirmed that the use of early thromboelastometry parameters (as soon as 5 min after clotting time) allows for an early goal-directed haemostatic therapy in bleeding children, which could improve bleeding management, and decrease blood product transfusion requirement, leading to better outcomes and reduced costs.

Our study confirmed the results reported by Görlinger and colleagues[8], in a large retrospective study that reviewed 14162 ROTEM assays, obtained from adults undergoing non-cardiac surgery. In this study, the authors observed that early values of clot firmness, measured as soon as five min after clotting time, were strongly correlated (r>0.9) with the maximum clot firmness (MCF). The authors also reported that these correlations were observed whatever the MCF values were in the normal, infra-normal or supra-normal ranges. In another study performed on 437 ROTEM® obtained from adults undergoing cardiac surgery with cardiopulmonary bypass, Dirkmann and colleagues[9] confirmed the strong correlations between A5, A10, A15 and MCF, both before and after protamine administration. Although the correlations were slightly decreased after cardiopulmonary bypass and protamine administration, correlation coefficients for EXTEM®, INTEM®, HEPTEM® and FIBTEM® were all >0.84, which was considered as a very good correlation.

Although ROTEM® is increasingly used in children undergoing cardiac and non-cardiac surgery to assess coagulopathy and guide haemostatic therapy,[13 16 17] and has been shown to be well correlated to standard coagulation assays,[18] only two studies,[12 13] performed in children undergoing cardiac surgery, have correlated early clot amplitude parameters with MCF. In 2013, Romlin and colleagues[12] reported a good correlation between A10 and MCF, both on HEPTEM® and FIBTEM® performed during cardiopulmonary bypass. Despite the good correlation, these results could not be extrapolated to other surgical settings, as the vast majority of ROTEM® values obtained during cardiopulmonary bypass were below the normal ranges. In another recent study that aimed to design a specific algorithm to guide haemostatic therapy in children undergoing cardiac surgery, the use of clot amplitudes measured after 10 min, both on EXTEM® and FIBTEM®, was used to predict postoperative bleeding, with the same area under the receiver operating characteristics curve than the amplitude measured after 20 min or at the MCF.[13] So far, no study has been performed in a large general paediatric population.

Early ROTEM® parameters could be used in transfusion algorithms to guide the administration of haemostatic agents in bleeding children. As reported by different authors,[16 17] this algorithm based on ROTEM® could significantly improve management of bleeding in children undergoing cardiac and non-cardiac surgery, leading to a significant reduction in blood product transfusion requirements. Based on our results, early clot amplitudes parameters (e.g. A5 or A10) could be used to predict decreased MCF. As mentioned by Görlinger and colleagues[8], the relationship between early clot amplitude parameter could be used to estimate the MCF, widely used in transfusion algorithms.[8] According to the data provided in Table 3, it seems appropriate to use A5 values by adding three mm or A10 values by adding one mm in FIBTEM®; or A5 values by adding 17 mm or A10 values by adding eight mm in EXTEM®, INTEM®, APTEM® and HEPTEM® to estimate MCF value.

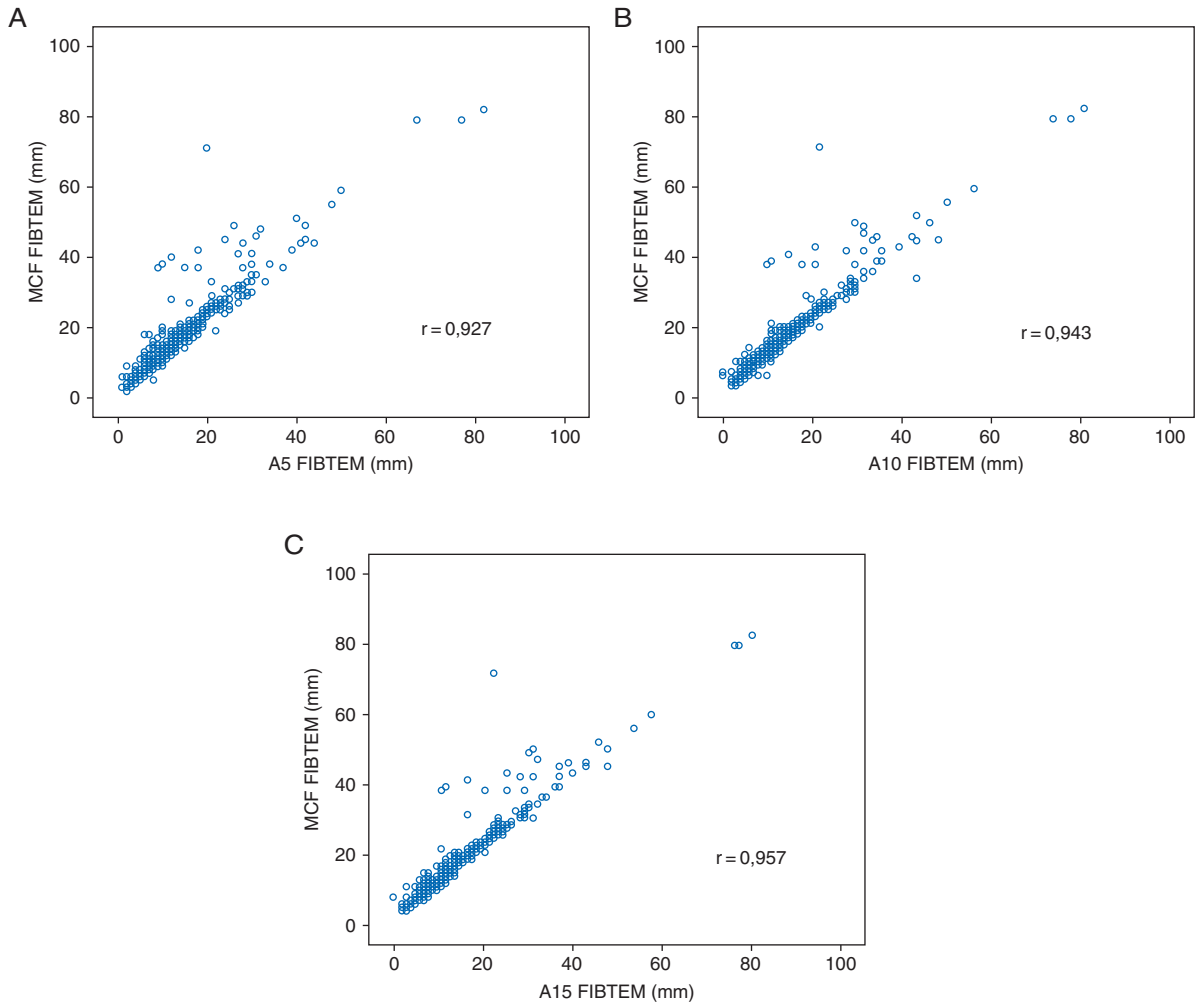

Fig 2 Graphs for the FIBTEM® variables demonstrating correlation between the amplitude measured after 5 min (A), 10 min (B), 15 min (C) and the maximum clot firmness (MCF).

Table 2 Specific bias obtained from the Bland-Altman analyses. Biases are presented as mean and standard deviation (SD)

Assays	A5 (mm)	A10 (mm)	A15 (mm)
EXTEM®			
Mean (SD)	11.13 (6.41)	7.82 (4.84)	3.57 (4.91)
N	1004	1184	992
INTEM®			
Mean (SD)	16.94 (5.70)	7.70 (3.87)	3.74 (3.78)
N	670	846	654
FIBTEM®			
Mean (SD)	2.67 (3.26)	1.35 (2.71)	0.93 (2.74)
N	970	1134	959
APTEM®			
Mean (SD)	16.26 (7.11)	7.52 (5.76)	3.48 (5.27)
N	70	69	69
HEPTEM®			
Mean (SD)	16.97 (6.69)	7.98 (4.63)	3.94 (4.73)
N	125	311	124

Table 3 Bias for A10 values of EXTEM and FIBTEM in paediatric patients with subnormal, normal, and supra-normal MCF and pooled data as obtained from the Bland-Altman analyses. Biases are presented as mean and standard deviation (SD). Spearman's coefficient ρ for each assay and range for linear regression

Assay	MCF range (mm)	A10 bias (mm)	ρ
EXTEM® (n=1184)	Overall	7.82 (4.84)	0.96
EXTEM® (n=440)	<50	8.20 (6.32)	0.91
EXTEM® (n=677)	50–70	7.77 (3.32)	0.89
EXTEM® (n=67)	>70	5.85 (5.95)	0.63
FIBTEM® (n=1134)	Overall	1.35 (2.71)	0.96
FIBTEM® (n=460)	<9	0.53 (0.99)	0.71
FIBTEM® (n=602)	9–25	1.5 (1.29)	0.90
FIBTEM® (n=72)	>25	5.38 (8.72)	0.86

The difference in bias in FIBTEM® and EXTEM® assays between patients with subnormal and normal MCF values (<1 and 0.4 mm respectively) was even smaller than those reported in the adult

Table 4 Results obtained for receiver operating characteristics analysis. AUC, Area Under the Receiver Operating Curve; PPV, Positive predictive value; NPV, Negative predictive value

Assay	Variables	AUC (95% CI)	Optimal cut-off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
INTEM®	CT (s)	0.721 (0.690–0.751)	>238	45 (39–52)	87 (84–90)	62 (59–64)	78 (75–79)
	CFT (s)	0.937 (0.919–0.953)	>142	89 (84–92)	92 (90–94)	83 (80–86)	95 (92–97)
	Alpha (deg)	0.871 (0.847–893)	< 65	93 (91–95)	76 (70–81)	90 (87–93)	82 (80–85)
	A5 (mm)	0.968 (0.951–0.980)	<30	97 (95–98)	83 (77–89)	95 (93–97)	91 (88–93)
	A10 (mm)	0.983 (0.972–0.991)	<41	96 (94–97)	91 (86–94)	96 (92–97)	91 (89–93)
	A15 (mm)	0.985 (0.972–0.993)	<44	99 (98–100)	85 (79–91)	96 (93–98)	96 (95–98)
EXTEM®	CT (s)	0.700 (0.672–0.725)	>101	41 (36–46)	88 (86–90)	65 (64–67)	74 (71–76)
	CFT (s)	0.789 (0.762–0.826)	>187	42 (37–47)	88 (86–90)	66 (63–68)	74 (70–77)
	Alpha (deg)	0.809 (0.766–0.824)	<78	37 (33–42)	90 (87–92)	66 (64–68)	73 (70–75)
	A5 (mm)	0.951 (0.935–0.963)	<30	96 (94–97)	79 (74–83)	91 (90–93)	90 (87–91)
	A10 (mm)	0.977 (0.967–0.985)	<41	95 (93–97)	90 (87–93)	95 (95–98)	91 (87–93)
	A15 (mm)	0.981 (0.971–0.989)	<46	95 (93–97)	93 (89–95)	97 (94–99)	89 (87–93)
APTEM®	CT (s)	0.652 (0.529–0.762)	>147	41 (24–61)	80 (65–91)	60 (58–63)	66 (64–69)
	CFT (s)	0.934 (0.846–0.980)	>180	77 (56–91)	98 (87–100)	95 (94–98)	87 (83–89)
	Alpha (deg)	0.868 (0.763–0.938)	<63	93 (80–98)	74 (54–89)	84 (83–86)	87 (84–99)
	A5 (mm)	0.961 (0.885–0.993)	<30	95 (83–99)	90 (73–98)	93 (90–95)	93 (90–95)
	A10 (mm)	0.969 (0.896–0.996)	<40	95 (83–99)	93 (77–99)	95 (93–98)	93 (90–95)
	A15 (mm)	0.974 (0.904–997)	<45	95 (83–99)	96 (82–100)	98 (95–99)	93 (91–96)
FIBTEM®	CT (s)	0.775 (0.749–0.799)	>93	49 (44–54)	85 (82–87)	64 (61–66)	76 (71–79)
	A5 (mm)	0.977 (0.966–0.986)	<7	85 (81–90)	96 (94–97)	88 (85–90)	95 (92–98)
	A10 (mm)	0.986 (0.978–0.992)	<8	82 (89–94)	96 (94–97)	92 (90–95)	96 (92–98)
	A15 (mm)	0.986 (0.976–0.992)	<9	97 (94–99)	94 (92–95)	85 (82–88)	99 (96–99)

study[8] and therefore, can be neglected for clinical decision-making. Although, these formulae could be used, the results obtained using ROC analyses confirmed that A5<7, A10<8 or A15<9 mm could certainly predict decreased MCF measured on FIBTEM, and A5<30, A10<40 or A15<45 mm on either INTEM®, EXTEM® or APTEM®. Although the correlation coefficient between A10 and MCF appeared to be lower (0.71) when FIBTEM MCF<9 mm, the positive and negative predictive values for a decreased A10<8 mm to predict MCF<9 mm were excellent, respectively 92 (95% CI: 90–95) and 96 (95% CI: 92–98). Dirkmann and colleagues[9] also reported the same decrease in correlation coefficient, when ROTEM decreased below the normal range after cardiopulmonary bypass.

Despite the strengths of our methodology and the consistency of our findings, this study presents some major limitations. On the one hand, we performed a large multicentre study and pooled ROTEM® data obtained from children undergoing different types of surgery, which does not allow us to evaluate the quality of the correlation between the different clinical situations. However, in view of the strong correlation we observed between early amplitude parameters and MCF, we consider that our results are generalizable for all clinical conditions, with the exception of situations where the diagnosis of fibrinolysis has to be considered. In our study, we excluded patients with excessive fibrinolysis, but as recently reported by Dirkmann and colleagues,[19] hyperfibrinolysis will be associated with reduced clot amplitudes as soon as 5 min after clot initiation. As a consequence, the correlation between decreased clot firmness and early measured ROTEM® parameters might be assessed in the specific context of hyperfibrinolysis.

In conclusion, this study confirmed that early values of clot amplitudes measured as soon as 5, 10 or 15 min after clotting time could be used to predict maximum clot firmness in all ROTEM® assays. Further studies are required to confirm whether this could be used to improve clinical management and outcomes.

Authors' contributions

Study design/planning: A.P.F., D.F.
Study conduct: A.P.F., M.D.C.B., D.F.
Data analysis: J.V.S.
Writing paper: A.P.F., J.V.S., M.D.C.B., P.V.d.L., D.F.
Revising paper: all authors

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Declaration of interest

None declared.

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