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Rotation thromboelastometry detects thrombocytopenia and hypofibrinogenaemia during orthotopic liver transplantation

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Background. Orthotopic liver transplantation can be associated with haemorrhage, particularly in patients with severe liver dysfunction. We assessed the value of rotation thromboelastometry (ROTEM®) to monitor coagulation in the operating theatre, its correlation with routine laboratory findings, and its ability to guide platelet (Plt) and fibrinogen (Fg) transfusion.

Methods. Twenty-three patients were included in this prospective observational study. Laboratory tests and ROTEM® tests (EXTEM, INTEM, FIBTEM, and APTEM) were performed six times during the procedure. Correlations between laboratory findings and ROTEM® parameters were sought. Thresholds for ROTEM® parameters were determined with receiver-operating characteristic (ROC) curve analysis according to Plt count and Fg levels.

Results. Clot amplitude at 10 min (A10) of EXTEM was well correlated with Plt count and Fg levels (R^2=0.46 and 0.52, respectively, $P<0.0001$). FIBTEM A10 was correlated with Fg (R^2=0.55, $P<0.0001$). ROC analysis showed that EXTEM A10 with a threshold of 29 mm predicted thrombocytopenia with a sensitivity of 79% and a specificity of 60%, and a threshold of 26 mm predicted hypofibrinogenaemia with a sensitivity of 83% and a specificity of 75%.

Conclusions. ROTEM® is useful for the global assessment of coagulation in the operating theatre. EXTEM was the most informative for assessing the whole coagulation process and A10 showed value in guiding Plt and Fg transfusion.

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Although orthotopic liver transplantation (OLT) is associated with haemorrhage, preoperative coagulation tests are not predictive of perioperative bleeding and transfusion requirements.[1 2] Cirrhotic coagulopathy results from various factors such as quantitative and qualitative defects in pro- and anticoagulant proteins, diminished clearance of activated factors, quantitative and qualitative platelet (Plt) defects, and hyperfibrinolysis.[3] Bleeding occurs commonly with dissection of native liver, graft recirculation, and vascular anastomosis. Diffuse bleeding can occur at any time, including during the postoperative period. Standard monitoring of coagulation disorders includes haemoglobin (Hb), haematocrit (Ht), Plt count, prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen (Fg). Fibrinolysis parameters such as D-dimer, euglobulin lysis time (ELT), and plasminogen activator inhibitor (PAI-1) concentration can also be measured. All these tests are done on plasma after blood centrifugation. While awaiting the results of these tests, the clinical situation can worsen and require rapid transfusion in the absence of timely information regarding the patient's coagulation status.

Rotation thromboelastometry ROTEM® (Pentapharm GmbH, Munich, Germany) is a point-of-care device that assesses the viscoelastic properties of blood samples under low shear conditions and enables evaluation of the process of clot initiation, formation and stability using whole blood.[2 4 5] Several studies have shown the usefulness of

coagulation monitoring with thromboelastography, making it possible to decrease both transfusion volumes and the number of patients undergoing transfusion.[6 7] With regard to OLT, consensus is lacking about the value of thromboelastography or ROTEM® for decreasing transfusion requirements.[8–10]

The present study aimed to assess the correlation between laboratory findings and ROTEM® parameters during OLT, and to determine whether ROTEM® could be a useful guide for perioperative transfusion.

Methods

This prospective observational study was carried out between April 2008 and March 2009 in the liver transplantation unit of our university hospital (CHU). The study protocol was approved by the institutional review board (IRB) of the CHU de Bordeaux. Patients were informed of the study protocol. All patients undergoing OLT during the study period were included. Exclusion criteria were innate or acquired coagulopathy, irrespective of haemostatic disturbances due to liver disease.

Patients were called as soon as the transplantation staff knew there was an available hepatic graft and they arrived at hospital a few hours before surgery. Anaesthesia protocol, haemodynamic monitoring, antibiotic therapy, and immunosuppressive protocols were similar for all patients. The surgical technique used by the four experienced surgeons was the 'piggy-back' technique.

Six measurement times were defined: T0 after induction of general anaesthesia, T1 during hepatectomy, T2 at the anhepatic stage, T3 30–60 min after graft revascularization, T4 at the end of surgery, and T5 24 h after surgery. If postoperative acute bleeding of more than 200 ml h^{-1} occurred, an additional measurement was made. Laboratory coagulation tests, ROTEM® tests, and arterial blood gases were performed at T0–T5. ROTEM® tests were performed according to the manufacturer's instructions using equipment and test reagents provided by Pentapharm GmbH. The ROTEM® was placed in the operating theatre and tests were done by the anaesthesiologists treating the patients. ROTEM® tests were EXTEM, INTEM, FIBTEM, and APTEM. Coagulation was activated either by tissue factor from rabbit brain (EXTEM test) or by ellagic acid (INTEM test). In the FIBTEM test, the contribution of Plts to whole blood coagulation is inhibited by the Plt neutralizing reagent cytochalasin D. In the APTEM test, aprotinin is added to inhibit fibrinolysis.

Perioperative bleeding was recorded, and blood products transfused during OLT and the first 24 postoperative hours. Blood samples for ROTEM® analysis were collected in a 3.5 ml test tube containing sodium citrate (BD Vacutainer®). Plasma was centrifuged twice at 3000*g* for 15 min, aliquoted, and rapidly frozen at −70°C, except for routine parameters which were immediately analysed. Laboratory coagulation tests were performed on ACL Top automates (Instrumentation Laboratory, Lexington, MA, USA) using deficient plasma from Stago (Asnières, France) for determination of factors II, V, X, and VIII, and Liquid Antithrombin® from Instrumentation Laboratory. Blood cell counts were performed on an Abbott CELL-DYN 3700 or Sapphire™ counter (Abbott Park, IL, USA). Total activity of plasminogen activators was evaluated by euglobulin clot lysis time (ELT expressed in minutes) as described by Kluft and colleagues.[11] PAI-1 activity was determined by an indirect method using a chromogenic substrate (Spectrolyse® PAI, Biopool).

In previous studies, the correlation coefficient between maximum clot amplitude of FIBTEM and Fg was 0.75–0.82.[8 12] With four measurements for 20 patients, that is, 80 measurements, we expected a correlation coefficient of 0.80 with a 95% confidence interval (CI) of (0.76–0.82). Results are expressed as median [inter-quartile range (IQR)], mean (SD), or % (95% CI). The Mann–Whitney *U*-test was used for continuous variables. The χ^2 test or Fisher's exact test was used for qualitative variables when appropriate. For multiple comparisons, the Kruskal–Wallis test with Bonferroni's correction was used. Pearson's correlation coefficients were determined between laboratory and ROTEM® tests. A two-tailed *P*-value of <0.05 was considered significant. Prediction models for clot amplitude at 10 min of EXTEM and FIBTEM were determined using a stepwise multiple linear regression. Receiver-operating characteristic (ROC) curves were calculated for ROTEM® parameters (EXTEM) to predict coagulation parameters leading to transfusion of Plt units or Fg. Sensitivity, specificity, and positive and negative predictive values were calculated for the best cut-off value. All statistical tests were performed using commercially available statistical software (XLSTAT 2009, Addinsoft, Paris, France).

Results

Twenty-three patients were included in the study protocol. Owing to technical problems, 104 of the expected 138 measurements were performed.

Patient characteristics are presented in Table 1. Haematological and coagulation variables determined at T0, T3, and T5 are shown in Table 2. One patient had a heterozygotic mutation of factor V Leiden, one had a heterozygotic mutation of factor II, and one had anti-β2 antibodies. All were asymptomatic.

Perioperative blood loss was 5.0 (2.0–8.5) litre. Peroperative crystalloid infusion was 8 ml kg^{-1} h^{-1} and colloid fluid administration consisted of 0.5 (0.3–1.0) litre of hetastarch (HES) 130/0.4 and 4.0 (2.5–4.8) litre of albumin 4%. During OLT and until the 24th postoperative hour, patients received 5 (3–11) packs of red blood cells, 4 (0–10) units of fresh-frozen plasma, 0 (0–2) concentrate of Plts, and 0.0 (0.0–1.5) g of Fg. One patient received 1 million IU of aprotinin.

Evolution of clot amplitude at 10 min (A10) of EXTEM is shown in Figure 1. EXTEM A10 correlated with Plt count and Fg concentration (Fig. 2). FIBTEM A10 correlated with Fg concentration (Fig. 2). Multiple linear regression showed that EXTEM A10 was well predicted (R^2=0.78) by a model including Hb, Plts, Fg, antithrombin III, D-dimers, factor X, and ELT (Fig. 3). ROC analysis showed that EXTEM A10 was highly predictive of thrombocytopenia $<50\,000$ mm^{-3} and hypofibrinogenaemia <1 g litre^{-1}, whereas FIBTEM A10 poorly predicted hypofibrinogenaemia (Fig. 4 and Table 3). Linear regression for FIBTEM showed that FIBTEM A10 was predicted by a model including Fg, with an R^2 of 0.37. For samples with EXTEM A10 >29 mm (n=50), FIBTEM A10 was predicted by a model including Ht, Fg, and D-dimers (R^2=0.34). For samples with EXTEM A10 ≤ 29 mm (n=45), FIBTEM A10 was not predicted by any coagulation test.

Table 1 Patient characteristics (n=23). Data are expressed as median (IQR) or number as appropriate. HCV, hepatitis C virus; HBV, hepatitis B virus; IGS2, index of gravity score; MELD, model for end-stage liver disease

Characteristics	
Age (yr)	54 (47–60)
Height (cm)	174 (168–178)
Weight (kg)	84 (67–90)
Body mass index (kg m^{-2})	25.8 (23.8–29.7)
Gender M/F (n)	21/2
Liver disease	
Alcoholic cirrhosis (n)	11
HCV cirrhosis (n)	7
HBV cirrhosis (n)	2
Amyloidosis neuropathy (n)	1
Retransplantation (n)	1
Steato-hepatitis (n)	1
MELD score	12 (7–17)
IGS2	34 (28–41)
Death at day 7	2
Death at day 28	3

Two patients had typical ROTEM® tracings of hyperfibrinolysis in EXTEM, INTEM, and FIBTEM, corrected by the addition of aprotinin in APTEM (Fig. 5). At these times, they had an ELT of 0 min and a PAI level at 0 IU ml^{-1}. ELT and ROTEM® parameters were poorly correlated overall, with significant although low coefficient correlation with amplitudes observed with EXTEM and INTEM (R^2=0.12 and 0.21 for A30, respectively; P=0.001 and 0.0001, respectively). However, among the 23 patients included in the study, 18 presented an ELT ≤ 50 min at some point of time. This severely shortened ELT was encountered mostly at T1 and T2 (9 and 15 samples, respectively), while it was noted at T0, T3, and T4 in one, six, and one sample, respectively. Severely shortened ELT corresponded to a dramatic decrease in PAI-1 which was 0 (0–1) IU ml^{-1} in the 28 samples with ELT ≤ 50 min, whereas PAI-1 was 26 (10–126) IU ml^{-1} in the samples with an ELT >50 min ($P<0.0001$). Most of the patients exhibited a dramatic decrease in ELT during hepatectomy, whereas four exhibited a decrease at T2. Only five of 23 patients maintained an almost stable ELT throughout the procedure (ELT >135 min at all measure times), while all patients but one recovered ELT values >50 min at T4 and normal ELT values 24 h after surgery. In fact, few ROTEM® parameters reflect deterioration in fibrinolysis. Apart from the two patients with the typical lyre-shaped ROTEM® graph that corresponds to total lysis occurring rapidly after clot formation as shown in Figure 5, severely altered ELTs remained compatible with subnormal ROTEM® graphs when Fg concentration and Plt count remained above threshold values (respectively, >1 g litre^{-1} and $>30\,000$ µl^{-1}).

Twenty-three out of the 104 blood samples were obtained from patients with a tendency to diffuse bleeding. In this subgroup, thrombocytopenia was more severe [54 (43–91) *vs* 68 (57–100) $\times 10^9$ litre^{-1}, P=0.049] and

Table 2 Haematological and coagulation values at T0 (before induction of general anaesthesia), T3 (after graft revascularization), and T5 (24 h after surgery). Data are expressed as median (IQR). aPTT, activated partial thromboplastin time; PAI, plasminogen activator inhibitor. Prothrombin rate is the PT expressed as activity percentage. To express the percentage of PT activity, a saline dilution curve is constructed with normal pool plasma and the patient's result is expressed as the percentage of normal plasma yielding the same PT in seconds

Laboratory data	T0	T3	T5
Haemoglobin (g dl^{-1})	10.7 (9.2–12.5)	10.0 (9.4–11.2)	10.4 (9.6–11.7)
Haematocrit (%)	31.7 (26.7–36.7)	30.1 (27.2–32.2)	30.0 (27.2–34.9)
Platelets (10^9 litre^{-1})	73.0 (56.5–95.5)	79.0 (60.0–89.0)	68.0 (47.0–78.0)
Prothrombin rate (%)	50 (41–61)	28 (20–39)	41 (38–51)
aPTT (s)	38 (34–43)	77 (55–117)	39 (35–45)
Fibrinogen (g litre^{-1})	1.89 (1.40–2.50)	0.95 (0.71–1.32)	2.24 (1.87–2.70)
Factor II (%)	39 (31–54)	23 (15–34)	33 (26–38)
Factor V (%)	53 (40–74)	23 (15–31)	50 (34–70)
Factor X (%)	49 (39–60)	22 (16–34)	29 (22–37)
Factor VIII (%)	154 (133–179)	—	—
D-dimers (µg litre^{-1})	842 (434–2220)	3333 (2074–5388)	1826 (1604–4580)
Euglobulin lysis time (min)	285 (210–300)	275 (73–300)	300 (300–300)
PAI (IU ml^{-1})	12 (2–21)	19 (4–30)	101 (45–146)
Antithrombin III (%)	37 (28–47)	26 (17–30)	31 (24–35)
Protein S activity (%)	72 (54–77)	—	—
Protein C activity (%)	23 (19–32)	—	—

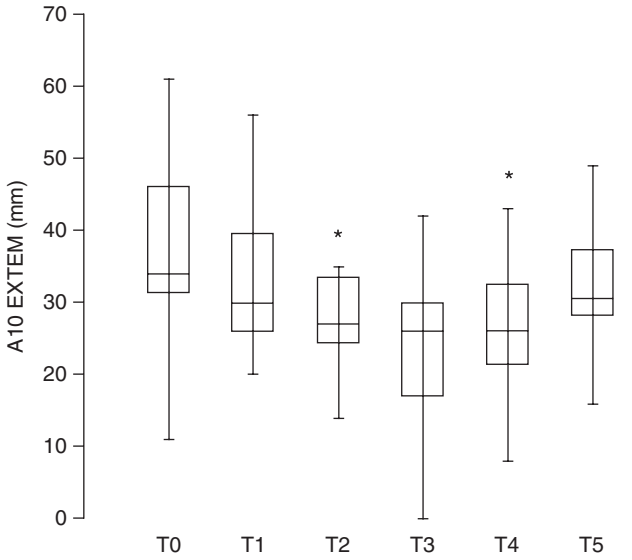

Fig 1 Evolution of clot amplitude at 10 min (A10) of EXTEM during the OLT. *$P<0.004$ *vs* T0. Data are shown as box plots with median represented by horizontal line with the 75th percentile at the top and the 25th at the bottom. The 10th and 90th percentiles are shown as whiskers. T0, after induction of general anaesthesia; T1, during hepatectomy; T2, anhepatic stage; T3, 30–60 min after graft revascularization; T4, end of surgery; T5, 24 h after surgery.

EXTEM A10 was significantly lower [26 (9–30) *vs* 30 (26–40) mm, $P<0.006$]. Nevertheless, no further significant correlation was found between ROTEM® parameters and laboratory tests for this subgroup of bleeding patients.

Discussion

In 23 patients who received OLT, EXTEM A10 correlated well with Plt count and Fg concentration. This parameter was an efficient surrogate of the whole coagulation process in predicting thrombocytopenia or hypofibrinogenaemia.

Rugeri and colleagues[13] found a good correlation between ROTEM® results and standard coagulation parameters in trauma patients including between FIBTEM A10 and Fg concentration comparable with the correlation found in our study. They also found that a 5 mm cut-off for FIBTEM A10 had a good sensitivity and specificity to detect Fg <1 g litre^{-1}, with an AUC of the ROC curve of 0.96. In our study, EXTEM A10 was a better predictor of hypofibrinogenaemia than FIBTEM A10. In multiple linear regression, Fg was the first variable included in the model predicting EXTEM A10. These slightly conflicting results might arise from differences in baseline haemostasis observed, since trauma patients are not expected *a priori* to have impaired baseline coagulation. In our study, patients had disturbances of both pro- and anticoagulant systems (Table 2). In cirrhotic patients, thrombin generation has been shown to be normal in the presence of thrombomodulin despite abnormal conventional coagulation tests, which likely explains why most patients have no spontaneous bleeding.[3] Patients with liver disease also

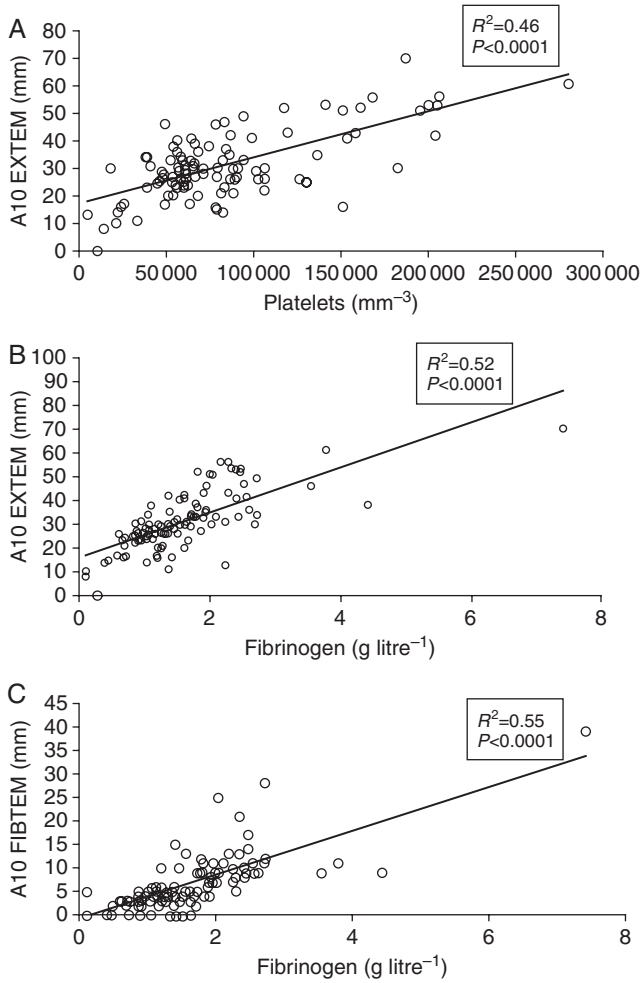

Fig 2 Correlation between (A) clot amplitude at 10 min (A10) of EXTEM and platelet count, (B) A10 of EXTEM and Fg concentration, and (C) A10 of FIBTEM and Fg concentration.

have portal hypertension, modifications of endothelial function, and high plasma levels of von Willebrand factor that support Plt adhesion.[14] In liver disease, coagulation and haemostasis are influenced by multiple and often discrepant alterations. Assessment of coagulation based on conventional laboratory tests does not represent the whole coagulation process and the use of global functional tools such as ROTEM® should be considered.[14]

In our study, Fg was primarily (88 out of 95 measures) determined by the Clauss method (the activity method), according to our decision tree that triggers the Clauss method as soon as the derived method gives a result lower than 3.5 g litre^{-1}. Large amounts of colloids during the surgical procedure can lead to an overestimation of Fg using the Clauss method.[15 16] This was unlikely in our study, however, where patients received a median of 0.5 litre of hetastarch at the beginning of the procedure, and no colloid other than human albumin thereafter.

We did not find any correlation between ROTEM® results and hyperfibrinolysis defined as an ELT <90 or <50 min, a result at odds with the findings of Levrat and

colleagues[17] in trauma patients. Although there was a major change in fibrinolysis with a dramatic decrease in ELT due to a decline in PAI-1 in more than 75% of patients, only two patients out of 23 had a typical ROTEM® hyperfibrinolysis tracing. This clearly illustrates the overall significance of ROTEM® tracings, which primarily reflect Fg and Plt levels and also Plt–fibrin interactions. In one *in vitro* haemodilution model, EXTEM α-angle, A10, maximum clot firmness, clotting time, and clot formation time were improved by addition of Fg in a concentration-dependent manner.[18] On the other hand, hyperfibrinolysis is revealed only when accompanying factors are also altered. In the patient whose tracings are shown in Figure 5, Fg was 1.39 g litre^{-1} and Plts were expected to be dramatically decreased because they were 20 000 μl^{-1} 15 min after this sampling time (exact Plt count at T1 withdrawal time was not available). No other patient presented the same combination of very low Plt count with hyperfibrinolysis due to total PAI-1 disappearance.

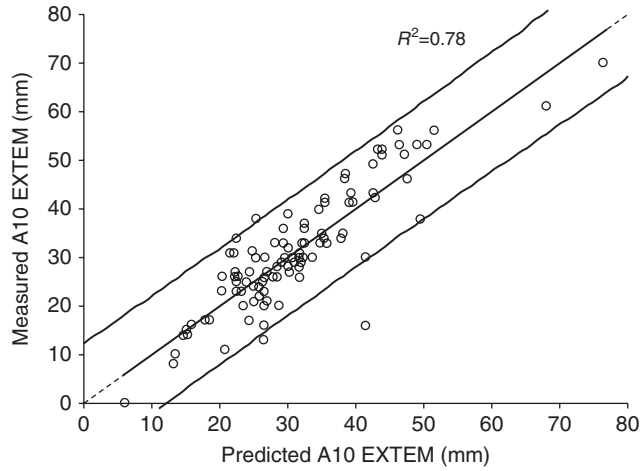

Fig 3 Multiple linear regression for EXTEM A10. A10, clot amplitude at 10 min. Predicted EXTEM A10=17.53−0.83×Hb+1.323E−04×Plt+6.16×Fg−0.14×ATIII−5.75E−04×DD+0.15×FX+1.19E−02×ELT. Hb, haemoglobin (g dl^{-1}); Plt, platelets (mm^{-3}); Fg, fibrinogen (g litre^{-1}); ATIII, antithrombin III (%); DD, D-dimers (μg litre^{-1}); FX, factor X (%); ELT, euglobulin lysis time (min).

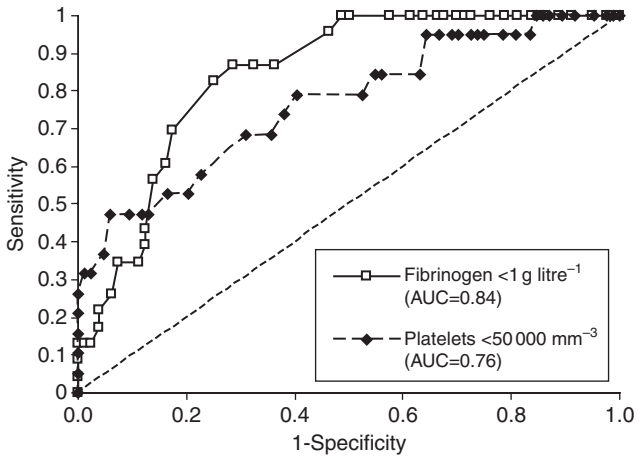

Fig 4 ROC curves of EXTEM A10 for predicting thrombocytopenia under 50 000 mm^{-3} and Fg concentration under 1 g litre^{-1}.

We found that EXTEM A10 could be a guide for transfusion of Plts and Fg during OLT. In cardiac surgery, transfusion and surgical re-exploration can be minimized by using a transfusion algorithm based on thromboelastography.[6 7] During cardiopulmonary bypass, ROTEM® can be used to monitor perioperative changes in haemostasis and postoperative bleeding risk.[19 20]

Thromboelastography has been demonstrated to be a reliable tool for monitoring OLT patients and for helping to decrease transfusion of red blood cells and fresh-frozen plasma, although at the price of an increase in Plt transfusion.[10] Coakley and colleagues[8] showed that transfusion practice in OLT was likely to differ according to the method of coagulation monitoring used. Whatever the method used, any tool helping to guide and limit Plt transfusion during OLT is useful, as Plt transfusion appears to be an important risk factor of mortality after OLT.[21 22] In our study, we found that EXTEM was the best predictor of hypofibrinogenaemia and thrombocytopenia. However, during OLT, anaesthesiologists have to choose between Plt concentrates and Fg-rich products in the case of bleeding. Our results show that it could be useful to perform an EXTEM test in the case of bleeding. If EXTEM A10 was $<$29 mm, patients would benefit from Plt concentrates and Fg-rich products. If EXTEM A10 was $>$29 mm, the FIBTEM A10 would help to guide transfusion, because in this case, the linear regression found a prediction model including Fg and also Ht and D-dimers. Nevertheless, this algorithm has to be confirmed by other studies before its use can be recommended. It seems that Fg deficiency is the primary problem associated with haemodilution, although thrombocytopenia exacerbates the fibrinolytic tendency.[18] Linear regression for EXTEM A10 and

Table 3 ROC curve analysis for the diagnosis of thrombocytopenia and hypofibrinogenaemia with ROTEM® EXTEM and FIBTEM. Values are presented with 95% CI in parentheses. A10, clot amplitude at 10 min; PPV, positive predictive value; NPV, negative predictive value; AUC, area under curve

Variables	Sensitivity	Specificity	PPV	NPV	AUC
Platelets $<$50 000 mm^{-3}					
EXTEM A10: $\leq$29 mm	0.79 (0.56–0.92)	0.56 (0.49–0.69)	0.31	0.93	0.76 (0.64–0.89)
Fibrinogen $<$1g litre^{-1}					
EXTEM A10: $\leq$26 mm	0.83 (0.62–0.93)	0.75 (0.64–0.83)	0.49	0.94	0.84 (0.74–0.95)
FIBTEM A10: $\leq$8 mm	0.83 (0.62–0.93)	0.35 (0.25–0.46)	0.27	0.87	0.61 (0.47–0.74)

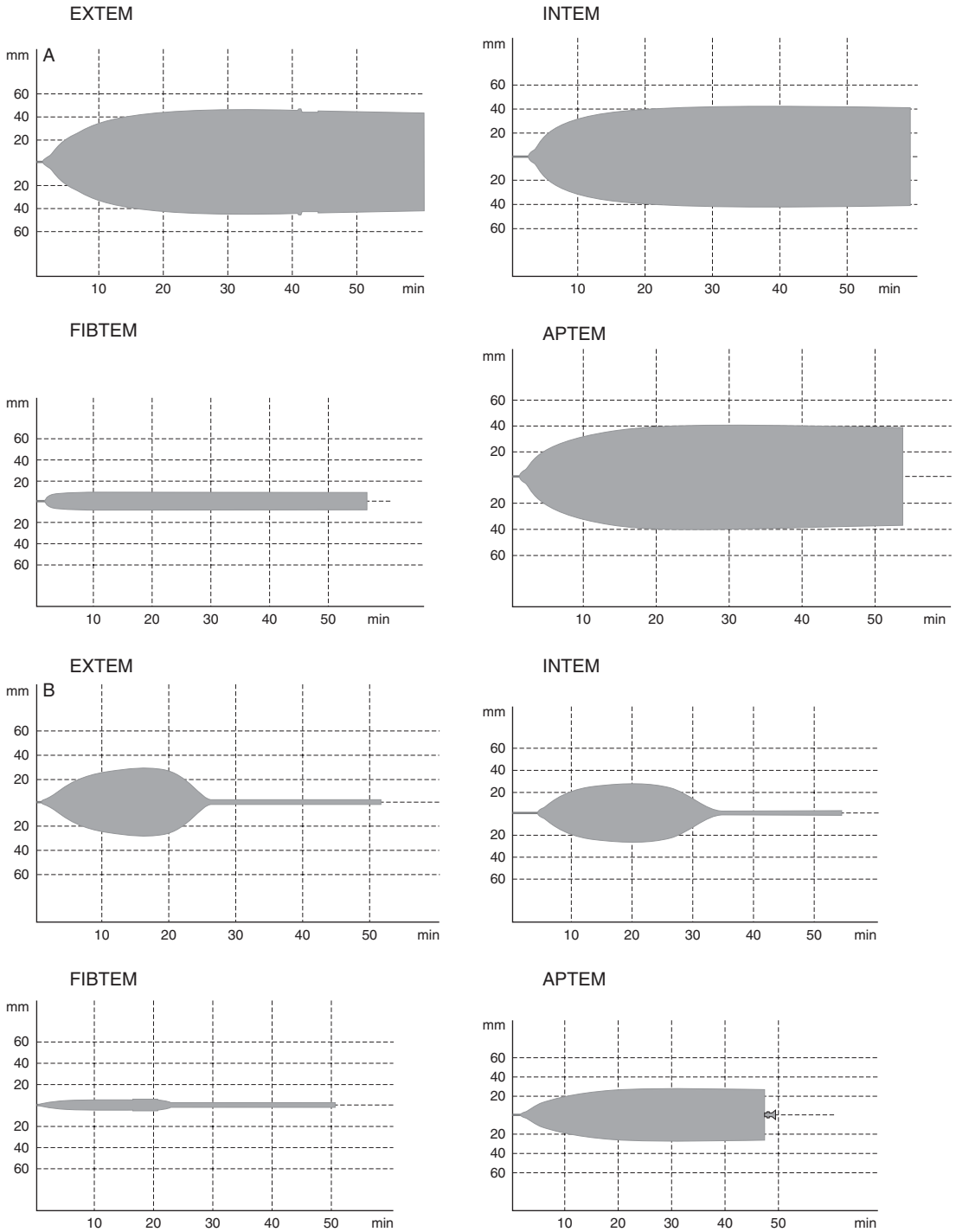

Fig 5 (A) Normal ROTEM® tracing. (B) ROTEM® tracing depicting severe coagulation abnormalities with hyperfibrinolysis corrected by the addition of aprotinin (APTEM).

FIBTEM A10 highlights the role of erythrocytes in the clot formation process, consistent with older studies on Ht and bleeding time.[23–25]

This study was observational. We did not assess the potential changes in transfusion management that could have been made after ROTEM® findings. While mastering ROTEM® involves a learning curve, the step-by-step procedure is user-friendly and helps to avoid technical errors. A limitation of ROTEM® is that, while it evaluates the whole coagulation process, vascular disorders and endothelial cell function are not assessed. When looking for fibrinolysis, systemic fibrinolysis should be evident on ROTEM® tracings, but localized fibrinolysis may not be detected, which can contribute to late bleeding.

In conclusion, ROTEM® findings obtained during OLT correlated with Plt count and Fg level, which could help to

optimize transfusion. Further studies are warranted to confirm these results, to position ROTEM® tests within the perioperative setting of OLT, and to assess the clinical relevance of the tracings and their interpretation in follow-up.

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