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New under the sun: ClotPro's ECA-test detects hyperfibrinolysis in a higher number of patients, more frequently and 9 min earlier

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Liver diseases result in a re-balanced state of the haemostatic system with decreased haemostatic reserves. Increased fibrinolytic activity is commonly seen during liver transplants. The aim of this study was to assess whether ClotPro's ECA-test is able to detect hyperfibrinolysis earlier and with higher frequency than ClotPro's conventional viscoelastic assays for the intrinsic and the extrinsic coagulation pathway.

From 25 liver transplant recipients, systemic blood samples were collected during surgery. Viscoelastic haemostatic assays with ClotPro's IN-test, EX-test and ECA-test were performed simultaneously from each blood sample. Hyperfibrinolysis was defined on the basis of the manufacturer's prespecified threshold value (maximal lysis >15%). The incidence of hyperfibrinolysis detected with each test was compared with the McNemar test. For each assay, lysis detection time (LDT) was calculated and analysed with the nonparametric Kruskal–Wallis test. A total of 125 tests were performed simultaneously. Compared with the IN-test and the EX-test, the ECA-test detected hyperfibrinolysis in significantly ($P<0.001$) higher number of patients (9; 11; 14, respectively) and in more measurement points (14; 18; 28, respectively). The analysis of LDT values revealed significant superiority of the ECA-test to the IN-test ($P=0.046$) and to the EX-test ($P=0.035$), indicating the profibrinolytic state of the haemostasis 8.9 ± 0.65 and 8.7 ± 0.17 min earlier, respectively. These are preliminary results of the study NCT0424637.

ClotPro's ECA-test appeared to detect fibrinolysis in a higher number of patients, more frequently, and the mean time of detection was 9 min earlier than that of the IN-test and the EX-test. *Blood Coagul Fibrinolysis* **34:99–104**

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Introduction

Haemostasis has two functions playing antagonistic roles in relation to each other. Firstly, a blood clot must be formed at the site of an injury, and later on, secondly, the resolution of the blood clot is mandatory. Both functions depend on the regulation of the haemostatic processes exerted by activating and inhibiting factors. Liver diseases are defined by a re-balanced state of the haemostatic processes with decreased reserves [1]. Hyperfibrinolytic activity may arise in any phase of liver transplantation; however, due to the absence of hepatic tPA-clearance, it is typically observed in the anhepatic [2] and in the neohepatic phases [3]. During surgery, fibrinolytic activity might further be aggravated by acidosis, shortage of fibrinoge, and the administration of synthetic colloid solutions [4,5]. Viscoelastic assays for the evaluation of haemostasis, such as TEG, ROTEM and ClotPro, play a crucial role in the early diagnosis of hyperfibrinolysis [6,7]. Indeed, ClotPro's EX-test, IN-test and FIB-test are similar to the assays of ROTEM, and furthermore, both devices were developed by the same team. On the contrary, with ClotPro, novel testing facilities have been introduced such as the RVV-test, ECA-test and TPA-test. In this research, the applicability of these novel tests in the liver transplant setting was evaluated.

ClotPro's ECA-test initiates blood coagulation immediately at the step when prothrombin is converted to meizothrombin. The aim of this study was to assess whether the ECA-test of ClotPro is able to detect hyperfibrinolysis earlier and with higher frequency in the blood samples compared to ClotPro's conventional viscoelastic assays for the analysis of the intrinsic and the extrinsic coagulation pathway (IN-test and EX-test).

Patients and methods

The authors are disclosing preliminary results of the prospective study being conducted at the Department of Transplantation and Surgery at Semmelweis University, Budapest, Hungary. Prior to its initiation, a positive opinion of the Hungarian Ethics Committee Medical Research Council was obtained (20325-2/2019/EKU), and the study was registered at ClinicalTrials.gov (Identifier: NCT0424637).

Twenty-five adults were included in the study who underwent cadaveric liver transplantation. The study

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complied with the provisions of the Declaration of Helsinki. Exclusion criteria were age under 18 years, acute liver failure, multiorgan transplantation, liver re-transplantation procedure, and the situation if the patient did not consent to the study in writing.

Blood samples were collected from a cannula introduced into the external jugular vein, which was solely dedicated for the purposes of blood sampling throughout the surgery so that haemodilution and interference with the effects of heparin sodium could be avoided. For each test, blood samples were collected in 3.5 ml Vacuette 3.2% sodium citrate blood collection tubes (Greiner Bio-One International GmbH, Kremsmünster, Austria). During the surgery, five blood sample collection was performed from each patient: prior to the surgery (S1), 10 min before the anhepatic phase during hepatectomy (S2), in the anhepatic phase when the anastomosis of the portal vein was formed (S3), 15 min after the reperfusion of the portal vein in the neohepatic phase (S4) and at the end of the surgery (S5).

Viscoelastometric testing was conducted with ClotPro (enicor GmbH, München, Germany) analyser equipment, using IN-test, EX-test and ECA-test.

The ellagic acid in the IN-test, after recalcification, initiates the intrinsic pathway of coagulation. The EX-test is re-calcified with calcium chloride. After its activation with recombinant tissue factor, the EX-test allows the assessment of the extrinsic coagulation pathway. The ECA-test contains ecarin, which substance is extracted from the venom of the viper species Echis carinatus, and does not contain any calcium chloride. The ecarin converts prothrombin to meizothrombin, which is an active intermediate and cleaves fibrinogen to fibrin in the blood. The ECA-test has been designed for the monitoring of the action of thrombin inhibitor drugs. Thrombin inhibitors (e.g. dabigatran) in the blood sample exert their effect through inactivating meizothrombin, thus giving rise to a delay in the initiation of the coagulation process [8].

The duration of each testing process was 60 min. Hyperfibrinolysis was defined on the basis of the manufacturer's prespecified threshold value. Maximal lysis (ML) was determined as 15%, whenever the maximal clot firmness (MCF) decreased by at least 15% during the testing process. The ML values were collected for analysis from each test report. A so-called lysis detection time (LDT) was created for the purposes of this study by measuring the time that had elapsed from the start of the testing process until the MCF had decreased by 15%, and so the LDT was regarded as an indicator of the rapidness of the evolution of lysis. The impairment of the tPA-clearance is proportionate to the severity of the liver disease. Hence, the peak value of hyperfibrinolytic activity develops in the anhepatic phase of liver transplant surgery in which tPA-clearance is completely missing, and corresponds to the duration of the anhepatic phase.

A decrease in the size of the MCF below the 15% value is known as clot retraction, which can be attributed to the activation and shape change of the thrombocytes, and also to the interaction between the fibrin mesh and the Gp IIb/IIIa receptor on the surface of the thrombocytes.

Continuous variables were analysed with descriptive statistical tools. Shapiro-Wilk test was applied to assess whether the results show normal distribution, while the homogeneity of variance was assessed using Levene's test.

Due to insufficient fulfilment of conditions for the parametric analysis of variance (ANOVA) test, differences between viscoelastometric tests were analyzed using the Kruskal–Wallis (ANOVA) test. Paired nominal data were assessed using a contingency table and McNemar's test. Results were regarded as significant if P value less than 0.05. Data analysis was conducted using the software IBM SPSS Statistics 28.0 for Windows (SPSS Inc. Chicago, Illinois, USA).

Results

Twenty-five patients were included in the study, their average age was 50 ± 12 years, with a slight predominance of male patients (64%). In the studied population, the two most common indications for liver transplantation were alcohol-associated liver disease and biliary cirrhosis (32 and 28%, respectively). Three-quarters proportion of the patients had disease severity of Child-Turcotte-Pugh B or C. The median MELD-Na score was 16 ± 5 points. In 80% of the surgeries, the cross-clamp technique was applied. Demographic features of the patients and surgery data are described in Table 1.

As increased fibrinolytic activity might emerge in any phase during the course of liver transplant surgery and might be persistent as well, it was possible that hyperfibrinolysis was detected in multiple blood samples of a patient during the intervention. A total of 125 tests were performed, of which 1 ClotPro assay had been excluded from evaluation due to technical error. Notably, such a scenario did not occur in any settings of the measurement pairs when ECA-test failed to indicate increased fibrinolysis while the others, that is IN-test, EX-test, did (Table 2).

On the basis of the cut-off value for hyperfibrinolysis prespecified by the manufacturer, increased fibrinolytic activity was observed in 14 samples of nine patients with IN-test (11.2 and 36%, respectively); in 18 samples of 11 patients with EX-test (14.6 and 44%, respectively); and in 26 samples of 14 patients with ECA-test (20.96 and 56%, respectively). These data are presented in Fig. 1. In all relations, the ECA-test detected a profibrinolytic state in significantly more measurement points when compared with the other tests (ECA-test vs. IN-test $P < 0.001$; ECA-test vs. EX-test $P < 0.001$).

Table 1 Demographics of patients and surgery data

	Patient number ($n = 25$)
Age (years)	50 ± 12
Sex – male	16 (64%)
Cause of ESLD (%)	
Viral hepatitis	3 (12%)
Biliary cirrhosis	7 (28%)
Autoimmune hepatitis	2 (8%)
Alcoholic liver disease	8 (32%)
Other (tumour, PCLD, BCS, NAFLD)	5 (20%)
Severity of ESLD (%)	
CTP – A	6 (24%)
CTP – B	15 (60%)
CTP – C	4 (16%)
MELD-score (median)	14 ± 5
MELD-Na score (median)	16 ± 4.7
Data of surgery	
Length of operation (min)	241 ± 57
Hepatectomy (min)	69 ± 29
Anhepatic phase (min)	60 ± 17
CIT (min)	459 ± 122
WIT (min)	44 ± 16
Cross clamp/piggy back	20 / 5 (80% / 20%)

The time periods from the start of a ClotPro testing process to the detection of a 15% decrease in the MCF, which were previously defined as the lysis detection times (LDT-s), were analysed using the Kruskal–Wallis test. The analysis revealed a significant advantage of the ECA-test in terms of the timing of fibrinolysis detection. This means that ECA-test indicated fibrinolysis 8.9 ± 0.65 min earlier when compared with IN-test, and 8.7 ± 0.17 min earlier when compared with EX-test ($P = 0.046$ and $P = 0.035$, respectively). The results are shown in Figs. 2 and 3.

Discussion

Fibrinolysis, the result of several complex and well regulated processes, constitutes an integral part of normal haemostasis. In chronic liver disease, the synthetic and metabolic functions of the liver are disturbed with inherently decreased capacity, contributing to alterations in the haemostasis and leading to a re-balanced state of the system with decreased reserves [1]. Any shift in this frail balance might trigger serious clinical consequences [9]. Furthermore, increased fibrinolytic activity has been shown to correlate with the severity of the liver failure [10,11]. Although hyperfibrinolysis may arise in any phase of liver transplantation, it is typically observed in the anhepatic and neohepatic stages of the intervention and might even be persistent in the early postoperative period if the graft occurs to be dysfunctional [12–15]. Thus, early diagnosis is of paramount importance. Viscoelastic haemostatic assays display different sensitivity and timing in terms of fibrinolysis detection [12,16,17], and, additionally, there are differences in the applied parameters for lysis detection between the types of equipment as well.

The sensitivity of these assays is not sufficiently high to enable the diagnosis of hyperfibrinolysis, neither can their specificity be determined in the absence of confirmatory tests. At present, there is no recognized 'gold standard' method for the diagnosis of increased fibrinolytic activity [18].

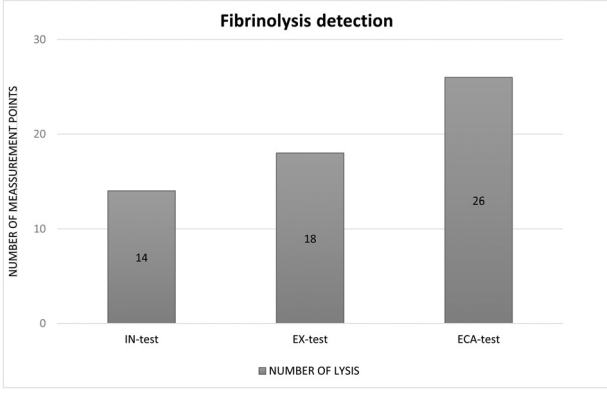
This study demonstrated that ClotPro was able to detect increased fibrinolytic activity in higher number of patients, in more measurement points, and in a shorter

Table 2 Maximal lysis values (ML %) in 25 patients measured in each phase of the liver transplantation

	preoperative (S1)			hepatectomy (S2)			anhepatic phase (S3)			neophepatic phase (S4)			end of operation (S5)		
	EX-test	IN-test	ECA-test	EX-test	IN-test	ECA-test	EX-test	IN-test	ECA-test	EX-test	IN-test	ECA-test	EX-test	IN-test	ECA-test
P1	5	3	1	21	13	60	1	0	11	1	0	1	1	0	0
P2	6	4	0	6	4	10	98	72	97	0	1	69	0	0	0
P3	9	5	0	8	8	1	5	4	1	9	4	0	0	5	0
P4	6	5	0	70	33	97	96	95	94	88	54	94	0	0	0
P5	3	0	17	96	95	94	95	93	90	5	0	95	0	0	0
P6	12	6	0	97	96	97	80	53	97	13	6	0	11	6	0
P7	4	3	0	23	33	96	23	20	95	2	1	0	3	2	0
P8	6	5	0	3	2	0	6	5	0	4	3	0	3	3	0
P9	13	10	0	0	0	0	3	2	1	4	2	0	2	0	0
P10	8	5	0	8	5	5	8	5	1	6	3	0	3	4	0
P11	12	12	0	14	9	7	90	71	97	7	7	4	4	3	0
P12	8	6	8	5	3	27	4	3	2	4	0	0	8	7	0
P13	3	4	0	0	2	0	1	1	0	1	2	0	2	3	0
P14	10	8	0	3	2	0	6	5	0	5	4	0	4	4	0
P15	4	2	0	3	2	4	29	28	97	2	2	84	0	0	0
P16	2	3	0	0	1	0	0	0	0	0	1	0	0	0	0
P17	12	7	0	14	11	29	20	13	61	12	8	0	10	6	0
P18	3	7	0	97	68	97	70	23	97	ND	ND	ND	30	12	97
P19	9	6	0	12	7	25	4	3	6	4	2	0	5	3	0
P20	6	3	0	6	2	0	5	3	0	3	2	0	3	2	0
P21	6	6	0	2	3	0	3	0	0	5	6	0	5	5	0
P22	3	3	0	3	3	5	18	6	58	1	1	0	1	1	0
P23	13	14	0	13	12	0	12	11	0	11	10	0	11	10	0
P24	6	4	0	7	5	13	8	3	42	3	2	0	0	0	0
P25	4	6	0	0	0	0	6	7	0	1	4	0	0	2	0

ND, no data due to technical error.

Fig. 1



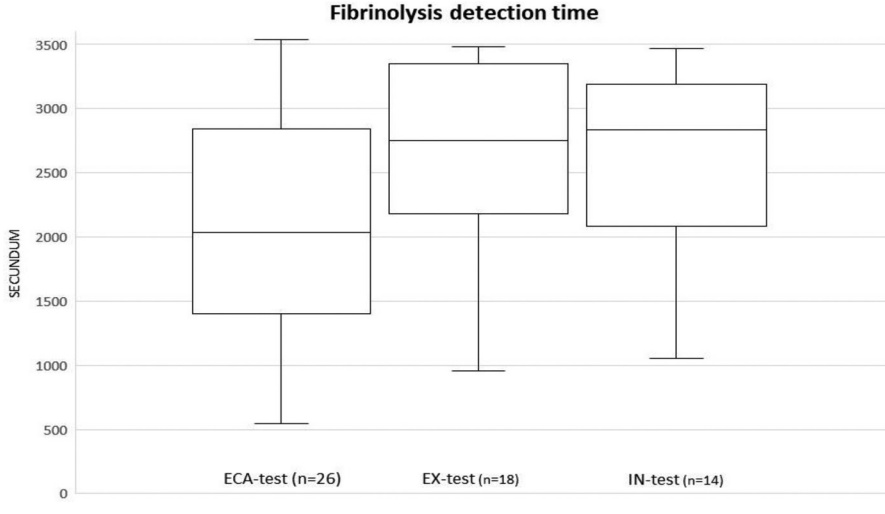
Incidence of hyperfibrinolysis detected with particular tests.

time. This finding might be explained by two underlying causes. Firstly, ecarin acts directly on prothrombin by converting it to meizthrombin. Meizothrombin is able to cleave fibrinogen [19]. Consequently, the clot is formed in a shorter time, which enables fibrinolytic activity to become apparent earlier. Secondly, the ECA-test does not contain calcium, leading to a weaker activation of calcium-dependent reactions such as the activation of factor XIII, a stabilizing agent for fibrin [20], and the activation of thrombin-activated fibrinolysis inhibitor (TAFI) [21,22]. Thus, the clot that was formed in the blood sample is more susceptible to profibrinolytic effects, which susceptibility facilitates dynamic detection of fibrinolytic tendencies in a higher number of patients. According to literature data ECATEM, an ecarin-based test developed for ROTEM equipment contains calcium [17], and for this reason, the activity of FXIII and TAFI is preserved during the testing process. To the authors' knowledge, no comparison between ECATEM and ECA-test has been performed so far, but certainly, a study on these two reagents would be able to provide evidence for the decisive role of calcium if ECA-test would be superior in terms of proportion and time of fibrinolysis detection. Apart from this, the scopes of ClotPro's TPA and ECA test might be considered as each other's complementary in practice. To be more precise, the presence of recombinant tissue plasminogen activator (rtPA) in the TPA-test helps to highlight the failure of clot resolution by indicating increased antifibrinolysis, also known as fibrinolysis resistance or fibrinolysis shut down [23]. On the contrary, the failing of the antifibrinolytic reactions in the calcium-free medium of the ECA-test is indicative of over-active clot clearance.

According to international data, the incidence of hyperfibrinolysis lies in a wide range (6.7–84.1%), depending on the testing method and the criteria for its definition applied. In this study, criterion for fibrinolysis was adopted from the prespecified value given by the manufacturer. Depending on the test applied for respective blood samples, hyperfibrinolysis was detected in 36, 44 and 56% of patients. Considering the total number of testing processes in this study, the incidence of hyperfibrinolysis detected with IN-test was 11.2%, and interestingly, with ECA-test, the incidence was twice as many, 20.96%.

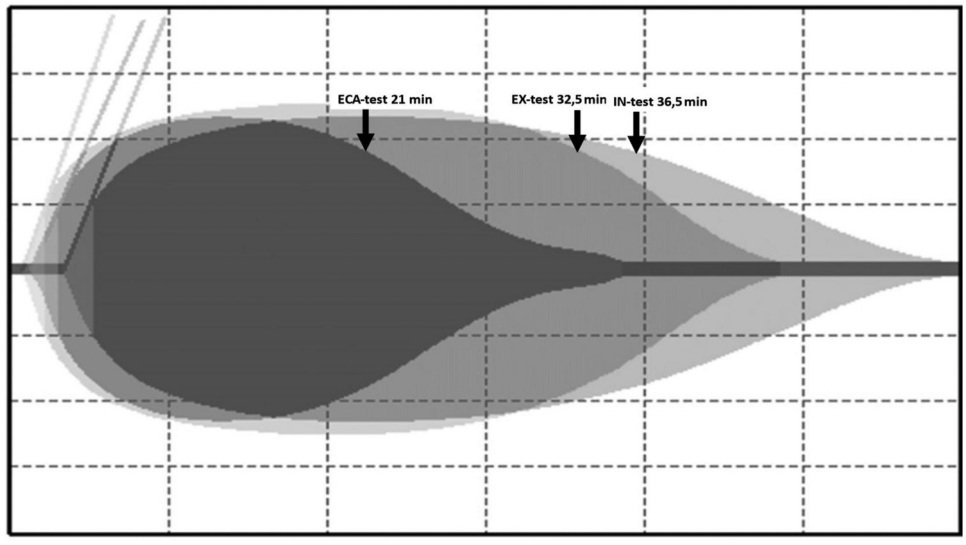
Abuelkasem *et al.* [24] have conducted a comparison study on kaolin-TEG and ROTEM EXTEM in adult liver transplant recipients. Their findings have

Fig. 2



Comparison of lysis detection time values.

Fig. 3



Three different types of ClotPro tests ran on the same blood sample.

demonstrated twice as high sensitivity of the EXTEM test, in which the reaction is activated by tissue factor, compared with the scenario when the activation is initiated by the negatively charged surface. Our findings seem to correspond to these results, with the addition that the thrombin-activated ECA-test enabled more frequent detection of increased fibrinolytic tendency, allowing earlier intervention if clinically justified.

The creation of the novel parameter, LDT, which was defined as the time period that had elapsed from the start of the testing process to the time point when a 15% decrease in the MCF was detected, allowed to assess the timing of fibrinolysis detection of each ClotPro test and also to make a comparison between them. Notably, the ecarin-initiated coagulation pathway was able to detect profibrinolytic tendency in a significantly shorter time in comparison to IN-test and EX-test (8.9 ± 0.65 min for ECA vs. IN, $P = 0.046$; 8.7 ± 0.17 min for ECA vs. EX, $P = 0.035$).

In the past, the majority of liver transplant centres used to have a preventive approach to antifibrinolytic therapy [25]. This concept has recently been replaced by the therapeutic application of antifibrinolytic agents. The availability of viscoelastic haemostatic assays may provide further supportive background for this approach by enabling earlier and more specific hyperfibrinolysis detection. Literature data and the findings of the present study suggest differences in sensitivity between particular tests [24]. In this study, ECA-test provided hyperfibrinolysis detection in the highest number of patients and in the shortest time. These findings support the suggestion that the ECA-test is likely to allow early diagnosis and treatment of hyperfibrinolysis, thus contributing to Pillar Two of patient blood management (PBM) [26].

In the anhepatic and reperfusion phases of liver transplant surgery, hyperfibrinolysis is self-limiting and is not related to increased mortality. Moreover, in the absence of major bleeding, it does not require specific treatment. Obviously, repeated testing is reasonable, and if the results refer to persistent hyperfibrinolysis, intervention might be necessary [17].

Apart from this, ECA-test seems to be beneficial not only in liver transplantation but also in various scenarios of medical care when overactivation of the fibrinolytic system can be suspected, for instance, in cases of polytrauma patients or in postpartum haemorrhage situations [27,28].

One limitation to these conclusions is the observational nature of this study, another is that the original goal of the investigation was not hyperfibrinolysis detection, and for this reason, hyperfibrinolysis in this study was not verified with AP-test, nor were the results assessed against the severity of the bleeding and transfusion needs. Furthermore, the tests were carried out on a small, selected and homogenous patient population.

In conclusion, the ECA-test detected increased fibrinolytic activity in a higher number of patients and in more measurement points; furthermore, indicated fibrinolysis nearly 9 min earlier than the IN-test and the EX-test. This finding might be interpreted as ECA-test enables

earlier treatment initialization when intervention is required. The authors hypothesize calcium to impair the effects of FXIII and TAFI, which presumption could be confirmed with simultaneous testing of blood samples with ECATEM and ECA-test. Testing of a larger patient population would be desirable to be able to determine if ECA-test potentially carries additional information on monitoring of antifibrinolytic therapy, compared to ClotPro's TPA-test.

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Conflicts of interest

There are no conflicts of interest to disclose.

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