

THROMBOELASTOGRAPHIC PROFILES AS A TOOL FOR THROMBOTIC RISK IN DIGESTIVE TRACT CANCER

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Background: Quantification of the magnitude of thrombotic risk associated with malignancy and with anti-cancer therapy is indispensable to use anticoagulant drugs which selectively interfere with haemostatic mechanisms protecting patients from venous thromboembolism (VTE) and probably from tumor progression. However, none of activation coagulation markers has any predictive value for the occurrence of the thrombotic events in one individual patient. Current clotting methods can't reveal the overall dynamic clot formation; in contrast thromboelastographic methods specifically assess overall coagulation kinetics and its strength in whole blood. **Aim:** Objective of study was to evaluate if the activation of coagulation as eventually revealed by ROTEM® thromboelastometry could assess an hypercoagulable state in surgical neoplastic patients. **Patients and Methods:** Fifty consecutive patients with carcinoma of the digestive tract in preoperative period (23 M, 27 F) aging 61.5 (45–79 years) and 147 healthy subjects (71 M, 76 F) were studied. A recent thromboelastometric method based on thromboelastography after Hartert was employed. Measurements were performed on ROTEM Coagulation Analyzer. The continuous coagulation data from 50 min course were transformed into dynamic velocity profiles of WB clot formation. **Results:** Standard parameters (CT, CFT, MCF) of cancer patients were similar to controls. CT (in cancer patients): females 50 s (38.3–58.7), males 50 s (42–71.2) vs 51 s (42–59), $p = 0.1210$ / 53 s (42–74.8), $p = 0.1975$ (in controls). CFT (in cancer patients): females 72 s (32–92.4), males 80 s (50.2–128.7) vs 78 s (62–100), $p = 0.0128$ / 80 s (59–124.4), $p = 0.9384$ (in controls). MCF (in cancer patients): females 70 mm (59.9–82.5), males 63 mm (56–73.7) vs 69 mm (59–95.8), $p = 0.9911$ / 69 mm (53.6–90), $p = 0.0135$ (in controls). Females showed a higher MaxVel when compared to males. The MaxVel was increased in cancer patients: females 19 mm / 100 s (14.3–49.5) males 18 mm / 100 s (11–27) vs 15 mm / 100 s (11.8–22), $p < 0.001$ / 13 mm / 100 s (10–21.8), $p < 0.001$ in controls. The t-MaxVel was shortened in cancer patients: females 65 s (48.6–112.8), males 81 s (50.1–135.9) vs 115 s (56.8–166), $p < 0.001$ / 115 s (59.8–180.8), $p = 0.0002$ in controls. The AUC was increased in cancer patients: females 6451 mm 100 (5511–8148), males 5984 mm 100 (5119–6899) vs 5778 mm 100 (4998–6655), $p < 0.001$ / 5662 mm 100 (4704–6385), $p = 0.0105$. **Conclusion:** Unlike other assays measuring variations in a single component during coagulation, the thromboelastographic method records a profile of real-time continuous WB clot formation, and may provide extensive informations on haemostasis in neoplastic patients before surgery.

Key Words: cancer, thromboelastography, hypercoagulable state, thromboelastometry, surgery.

Venous thromboembolism (VTE) is seven fold increased in patients with malignancy when compared to patients not affected by solid tumors [1]. Malignancy induces an acquired thrombophilic state [2]; therefore, in almost all cancer patients a sub clinical activation of blood coagulation takes place, even without symptoms of thrombosis. The hypercoagulable state in cancer arises mostly from the capacity of tumour cells to express and release specific procoagulant activities like cancer procoagulant (CPA) and tissue factor (TF) and to interact with the host's endothelium, platelets and monocytes-macrophages inducing a prothrombotic phenotype within these cells [3]. The association between malignancy and VTE such as the relationship between tumor growth and coagulation activation has been known since Trousseau's time [4]. Nowadays it is evident that the coagulation system plays an important role in the biology of malignant tumors: the activation of haemostasis induces a continuous formation and

removal of fibrin which mediates the adhesion of tumor cells to endothelium facilitating their migration through the tissues and contributing to tumor progression [5]. Recent studies have revealed a nonhaemostatic role of TF in generation of coagulation proteases and subsequent activation of proteases activated receptors (PARs) on vascular cells. This TF dependent signaling contributes to a variety of biological processes including inflammation, angiogenesis and metastasis [6]. The prothrombotic state of cancer patients is enhanced by therapeutic interventions, such as surgery, chemotherapy, hormone therapy, radiotherapy and it is related to disease stage and to the site of origin of the primary tumor: patients with haematological cancer have the highest risk of VTE, followed by those with lung and gastrointestinal cancers [1, 6]. Therefore quantification of the magnitude of the thrombotic risk associated with malignancy and anti-cancer therapy is essential to use anticoagulant drugs which selectively interfere with haemostatic mechanisms probably protecting patients both from VTE and from tumor progression [7]. Studies on haemostatic system in cancer patients show an increase in clotting factors levels, markers of thrombin and fibrin generation, fibrinolytic proteins and thrombocytosis [8]. However, none of the coagulation activation markers has any predictive value

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Abbreviations used: AUC – area under curve; CFT – clotting formation time; CPA – cancer procoagulant; CT – clotting time; MCF – maximum clot firmness; PARs – proteases activated receptors; TF – tissue factor; VTE – venous thromboembolism.

for the occurrence of the thrombotic events in one individual patient [9]. Since reliable methods, that could have a higher predictive value for thrombosis risk, are needed, our aim is to get better informations evaluating the profile of extended time coagulation analysis. Thus, the investigation of coagulation dynamics in whole blood could, in our opinion, disclose an abnormal pattern in cancer patients, especially in those at increased thrombotic risk. Current laboratory clotting techniques cannot fully identify subjects with an increased thromboembolic risk: their performance in plasma and the addition of buffered solutions limit their relevance to overall dynamic clot formation in whole blood [10]. In contrast ROTEM® thrombelastometry specifically assess overall coagulation kinetics and strength in whole blood, providing a global assessment of haemostatic function [11].

Therefore the aim of this study was to investigate whether an hypercoagulable state, revealed by ROTEM®, can be an important variable to evaluate the coagulation derangements in patients affected by cancer of the digestive tract.

MATERIALS AND METHODS

Patients. 50 patients with histologically confirmed solid cancer of the digestive tract were studied. 23 were male, 27 were female and all aging 61.5 (45–79 years). The criteria for inclusion in the study have been: patients with a carcinoma of the digestive tract without history of VTE who were candidate for surgery. 147 healthy subjects (71 M, 76 F) selected on the basis of sex and age were enrolled in our study as control group. The study was approved by Ethics Committee of the Institute. Informed consent was collected from all participants.

Sample collection. Blood samples were drawn between 8 am and 9 am, after 12 h of fasting. The blood (nine volumes) was placed in tubes with 0.109 M of trisodium citrate (one volume) until analysis.

Test procedure. A recent thromboelastometric method (ROTEM®; Pentapharm Ltd, Munich, Germany; distributed in Italy by Dasit, Milano), based on the thrombelastography after Hartert, was employed [12]. Measurements were performed on a ROTEM Coagulation Analyzer. Citrated blood samples were recalcified with CaCl₂ (star-TEM®, reagent) and activated with tissue thromboplastin from rabbit brain (ex-TEM, reagent) for monitoring the extrinsic system. The ROTEM® analysis determines the onset of the coagulation process: clotting time (CT); the kinetics of clotting formation and stability: clotting formation time (CFT) and maximum clot firmness (MCF) (Fig. 1, a). The ROTEM® software also calculates the novel parameters according to Sorensen [14] such as MaxVel, t-MaxVel, AUC by data derived from the ROTEM curve. MaxVel describes the maximum velocity of the clot formation. It is the maximum rate of clot formation, the maximum of the one derivative curve.

t-MaxVel describes the time from start of the measurement till MaxVel (maximum of the one derivative) is reached. It is a parameter similar to CT.

AUC describes the area under the velocity (one derivative) curve and is equivalent to MCF in a curve where the test had been run till MCF had been reached [14] (Fig. 1, b).

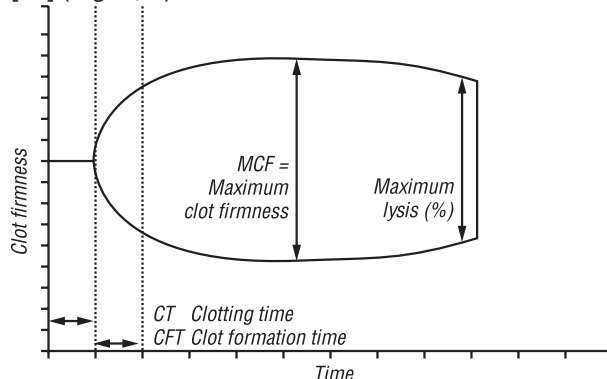


Fig. 1, a. Standard thrombelastographic tracking (CT, CFT, MCF)

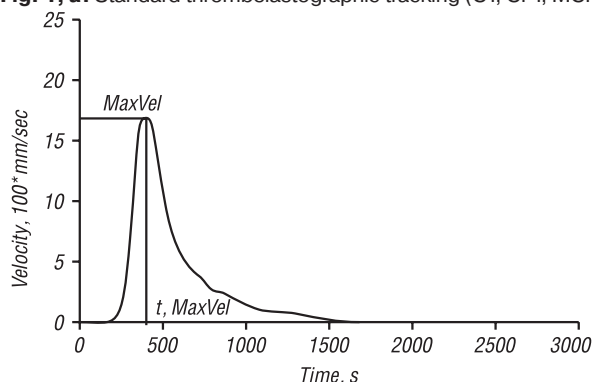


Fig. 1, b. ROTEM curve displayed by ROTEM Gamma software Velocity profile, the first derivative of the ROTEM tracking; maximum velocity (MaxVel), time to maximum velocity (t-MaxVel), area under curve (AUC) from Sorensen [13]

Statistical analysis. Statistical significance of the differences of values between patients and the healthy controls was calculated by the Mann — Whitney U test. The differences were considered statistically significant only for p-values less 0.05 (Tables 1, 2).

Table 1. ROTEM standard parameters in neoplastic patients and in healthy reference subjects

Healthy Males	Median	5P	95P	p value	Patients Males	Median	5P	95P
CT	53	42	74,8	0.1975	CT	50	42	71,2
CFT	80	59	122,4	0.9384	CFT	80	50,2	128,7
MCF	69	53,6	90	0.0135	MCF	63	56	73,7
Healthy Females	Median	5P	95P	p value	Patients Females	Median	5P	95P
CT	51	42	59	0.1210	CT	50	38,3	58,7
CFT	78	62	100	0.0128	CFT	72	32	92,4
MCF	69	59	95,8	0.9911	MCF	70	59,9	82,5

Medians and reference range (5–95% percentile) for controls and patients.

Table 2. ROTEM velocity parameters in neoplastic patients and in healthy reference subjects

Healthy Males	Median	5P	95P	p value	Patient Males	Median	P5	P95
MaxV	13	10	21,8	0.001	MaxV	18	11	27
MaxV-t	115	59,8	180,8	0.0002	MaxV-t	81	50,1	135,9
AUC	5662	4703,6	6385	0.0105	AUC	5984	5118,7	6899,2
Healthy Females	Median	5P	95P	p value	Patients Females	Median	P5	P95
MaxV	15	11,8	22	0.001	MaxV	19	14,3	49,5
MaxV-t	115	56,8	166	0.001	MaxV-t	65	48,6	112,8
AUC	5778	4998	6655	0.001	AUC	6451	5514,8	8148,4

Medians and reference range (5–95% percentile) for controls and for patients.

RESULTS

Standard parameters of ROTEM (CT, CFT, MCF) were not different in cancer patients as compared to controls. CT (in cancer patients): females 50 s (38.3–58.7), males 50 s (42–71.2) vs 51 s (42–59), $p = 0.1210/53$ s (42–74.8), $p = 0.1975$ (in controls). CFT (in cancer patients): females 72 s (32–92.4), males 80 s (50.2–128.7) vs 78 s (62–100), $p = 0.0128 / 80$ s (59–124.4), $p = 0.9384$ (in controls). MCF (in cancer patients): females 70 mm (59.9–82.5), males 63 mm (56–73.7) vs 69 mm (59–95.8), $p = 0.9911/69$ mm (53.6–90), $p = 0.0135$ (in controls). The analysis showed: an increase in MCF in male controls as compared to patients and a shorter CFT in female patients than in controls (Table 1). The continuous coagulation data from a 50 min-time course were transformed into dynamic velocity profiles of WB clot formation [14] (Fig. 2).

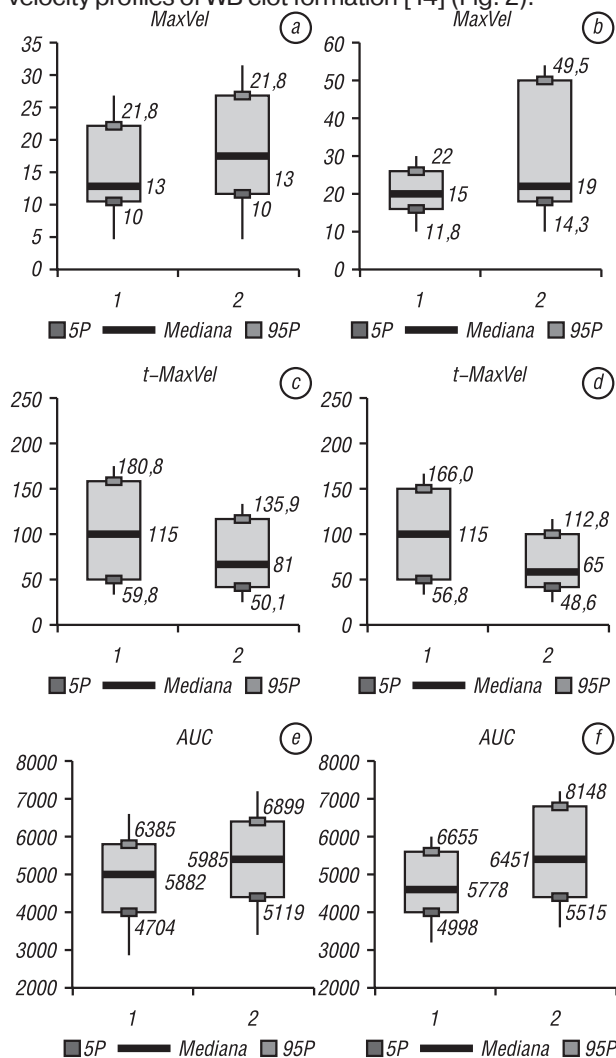


Fig. 2, a, b, c, d, e, f. (box plot): medians and reference range (5–95% percentile) of MaxVel, t-Max Vel, AUC for controls and patients

There were higher MaxVel in female controls as compared to male controls. The results were in accordance with earlier studies [11]. The ROTEM® velocity parameters resulted significantly different in patients when compared to the parameters of healthy subjects. The MaxVel was increased (cancer patients): females 19 mm 100/ s (14.3–49.5), males 18 mm 100/ s (11–27) vs 15 mm 100/s (11.8–22), $p < 0.001/13$

mm 100/s (10–21.8), $p < 0.001$ (controls). The t-MaxVel was shortened (cancer patients): females 65 s (48.6– 112.8), males 81 s (50.1–135.9) vs 115 s (56.8–166), $p < 0.001/115$ s (59.8–180.8), $p = 0.0002$ (controls). The AUC was increased (cancer patients): females 6451 mm 100 (5515–8148), males 5984 mm 100 (5119–6899) vs 5778 mm 100 (4998–6655), $p < 0.001/5662$ mm 100 (4704–6385), $p = 0.0105$ (controls) (Table 2).

DISCUSSION

Reliable markers and methods to predict thrombotic risk are essential to clinical management, especially for high- risk patients, i. e., cancer patients undergoing therapeutic interventions. Most laboratory tests actually used for studying haemostasis are performed on platelet-poor plasma with clotting [15] or chromogenic [16] end points. Nowadays, thanks to a better understanding of the role of platelets, leukocytes and erythrocytes in the clotting process, to evaluate thrombin generation during blood coagulation has become the best approach in order to assess the global complex process [17]. However, whereas thrombin generation tests are difficult to perform in real time clinical practice [18], thrombelastographic recording of the whole blood coagulation process is anticipated to indirectly reflect the course of thrombin generation . The classical thrombelastography produces a profile of the overall rheological changes occurring during coagulation and in the past it has been prevalently used to assist clinicians in the control of after-surgery bleeding. A newer modification of classical thrombelastography is thromboelastometry (ROTEM®), which avoids some technical limitations of the traditional method, such as sensitivity to vibrations or mechanical shocks. ROTEM uses a ball bearing system for power transduction which makes it easily transportable and less susceptible to mechanical stress, movement and vibration. Furthermore, the activation of the samples accelerates the measurement process and enhances reproducibility compared with conventional thromboelastography [11]. The data obtained with this new technique are continuous, digital and retrievable for further calculations; by processing of data the thrombelastographic time course can be transformed into a dynamic velocity profile of the changes in blood elasticity occurring during WB clot formation. The instruments software is used to calculate three new parameters in the assessment of coagulation dynamic properties. The pattern of the new values: MaxVel, t-MaxVel, AUC, display a remarkable degree of similarity between endogenous thrombin potential (thrombogram) and thrombelastographic model. Therefore the profile of whole blood coagulation by thrombelastography, as an indirect measure of thrombin generation, may provide extensive informations on haemostasis, not only for the clinical management of bleeding but also for thrombophilic states [19]. *In vivo* markers of coagulation activation (prothrombin fragment 1 + 2 / F1 + 2) and fibrinolysis (tissue plasminogen activator /t-PA) correlate very well

with ROTEM® clotting time (CT) and maximal lysis (ML) in a validation of rotation thrombelastography model of systemic activation of coagulation and fibrinolysis [22]. TEG has been successfully used in clinical setting to detect hypercoagulable states. A postoperative hypercoagulable state, as revealed by TEG, was associated with thrombotic complications in a wide group of surgical patients followed during postoperative period until discharge [23].

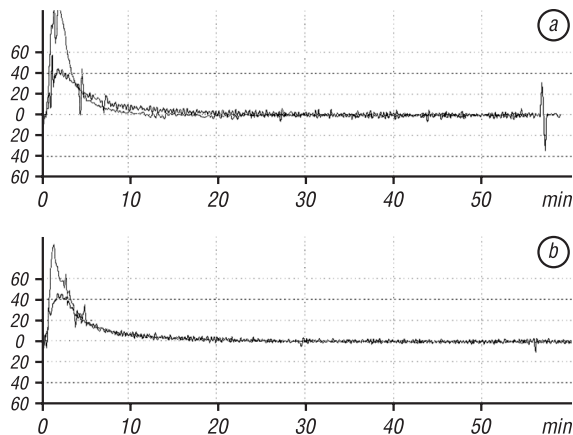


Fig. 3. Velocity profiles of WB clot formation before surgery in neoplastic patients and in healthy subjects. (a) Healthy male subject (red) and male patient (green) velocity profile (b). Healthy female subject (red) and female patient (green) velocity profile

The correlation between thrombotic complications and hypercoagulability confirms that surgical patients are at high risk for hypercoagulability and that this plays an important role in the pathogenesis of thrombosis. In patients affected by malignant disease, thrombosis is the most frequent complication and the second cause of death [24]. Surgical interventions in these patients increase the risk of postoperative VTE (approximately two-three fold) in comparison to the risk in non-cancer patients undergoing the same procedures. The American College of Chest Physicians (ACCP) has stratified patients with malignancy in the highest risk category of surgical patients and urged routine thromboprophylaxis [25]. Therefore, especially for high-risk patients, it is strongly desirable to use a one's disposal test characterized by a higher predictive value of the thrombotic event.

Thrombelastography represents a valuable method which monitors haemostasis under low shear environment as a whole dynamic process instead of revealing information on isolated parts of the different linked pathways. Indeed thrombelastometry provides information about the whole process of clot formation which results from interdependent steps: coagulation activation, thrombin production, fibrin formation and polymerization, platelet activation, platelet-fibrin interaction.

In conclusion, the use of thrombelastometric method has reduced the need of substitutive therapies for the clinical management of bleeding problems during major surgical interventions (liver transplantations, cardiovascular procedures, neurosurgery) [26]. Finally, the authors feel that the diagnosis of hypercoagulable state by using thrombelastometry, in patients

at higher thrombotic risk (especially cancer patients during surgery), could provide a rationale for more targeted prophylactic antithrombotic treatments.

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ТРОМБОЭЛАСТОГРАФИЯ КАК МЕТОД ОЦЕНКИ РИСКА ТРОМБОЗА ПРИ ОПУХОЛЯХ ПИЩЕВАРИТЕЛЬНОГО ТРАКТА

Предпосылки исследования: количественная оценка риска тромбоза, связанного со злокачественными заболеваниями и противоопухолевой терапией, обязательно включает в себя применение средств-антикоагулянтов, защищающих больного от развития венозной тромбоэмболии (VTE) и возможно прогрессии заболевания. Тем не менее ни один из маркеров активности коагуляции не имеет прогностической ценности с точки зрения возможности возникновения тромбоза у каждого отдельно взятого пациента. Современные методы оценки свертывания крови не отражают образование тромба в динамике; наоборот, метод тромбозэластографии дает возможность специфически оценить кинетику свертывания крови в целом.

Цель: определить, в какой мере активность коагуляции, определяемой методом тромбозэластометрии, отражает состояние гиперсвертываемости крови у больных онкологического профиля после хирургического вмешательства. *Пациенты и методы:* обследованы 50 больных раком пищеварительного тракта в дооперационный период (27 женщин, 23 мужчины, средний возраст 61,5 года (45–79 лет) и 147 здоровых доноров (71 мужчина, 76 женщин). Применяли метод тромбозэластометрии, основанный на тромбозэластографии Гартерта, с использованием анализатора коагуляции фирмы ROTEM. Текущие данные о свертывании за 50 мин измерений представили в виде динамичных профилей вязкости при образовании сгустка крови.

Результаты: стандартные параметры (период коагуляции (CT), период образования сгустка (CFT), максимальная плотность сгустка (MCF) больных онкологического профиля близки к контрольным. CT у больных онкологического профиля составлял: у женщин — 50 с (38,3–58,7), у мужчин — 50 с (42–71,2) vs 51 с (42–59), $p = 0,1210/53$ с (42–74,8), $p = 0,1975$ в контрольной группе. CFT у таких пациентов составлял: у женщин — 72 с (32–92,4) у мужчин — 80 с (50,2–128,7) vs 78 с (62–100), $p = 0,0128 / 80$ с (59–124,4), $p = 0,9384$ в контрольной группе. MCF у больных онкологического профиля составлял: у женщин — 70 мм (59,9–82,5), у мужчин — 63 мм (56–73,7) vs 69 мм (59–95,8), $p = 0,9911 / 69$ мм (53,6–90), $p = 0,0135$ в контрольной группе. У женщин показатели вязкости крови MaxVel были выше, чем у мужчин. Показатели MaxVel повышены у таких пациентов: у женщин — 19 мм/100 с (14,3–49,5) у мужчин — 18 мм/100 с (11–27) vs 15 мм / 100 с (11,8–22), $p < 0,001 / 13$ мм / 100 с (10–21,8), $p < 0,001$ в контрольной группе. Показатель t-MaxVel понижен у больных онкологического профиля: у женщин — 65 с (48,6–112,8), у мужчин — 81 с (50,1–135,9) vs 115 с (56,8–166), $p < 0,001 / 115$ с (59,8–180,8), $p = 0,0002$ в контрольной группе. Показатель AUC у повышен у женщин — 6451 мм 100 (5511–8148), у мужчин — 5984 мм 100 (5119–6899) vs 5778 мм 100 (4998–6655), $p < 0,001 / 5662$ мм 100 (4704–6385), $p = 0,0105$. *Выводы:* в отличие от других методов, измеряющих вариации отдельных компонентов системы свертывания крови, метод тромбозэластографии отражает текущий профиль образования сгустка в режиме реального времени и является информативным способом оценки состояния гемостаза у онкологических больных.

Ключевые слова: рак, тромбозэластография, состояние гиперкоагуляции, тромбозэластометрия, хирургия.