



Questions about COVID-19 associated coagulopathy: possible answers from the viscoelastic tests

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Abstract

Abnormal coagulation parameters are often observed in patients with coronavirus disease 2019 (COVID-19) and the severity of derangement has been associated with a poor prognosis. The COVID-19 associated coagulopathy (CAC) displays unique features that include a high risk of developing thromboembolic complications. Viscoelastic tests (VETs), such as thromboelastometry (ROTEM), thromboelastography (TEG) and Quantra Hemostasis Analyzer (Quantra), provide “dynamic” data on clot formation and dissolution; they are used in different critical care settings, both in hemorrhagic and in thrombotic conditions. In patients with severe COVID-19 infection VETs can supply to clinicians more information about the CAC, identifying the presence of hypercoagulable and hypofibrinolysis states. In the last year, many studies have proposed to explain the underlying characteristics of CAC; however, there remain many unanswered questions. We tried to address some of the important queries about CAC through VETs analysis.

Keywords COVID-19 · Coagulopathy · Viscoelastic tests · Thromboembolic events

1 Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is characterized by a diffuse endothelial dysfunction and a hyperinflammation state that leads to a cytokine storm which enhances the risk of thrombotic complications. Multiple studies have reported a high incidence of venous thromboembolism (VTE) in coronavirus-2019 disease (COVID-19) patients, in particular pulmonary thrombosis (79%) [1–5]. Moreover, patients with severe COVID-19 manifested by acute respiratory distress syndrome (ARDS), have demonstrated extensive pulmonary

microvascular thromboses in available postmortem autopsies [6]; microvascular thrombosis may promote hypoxia through increased dead space leading to ventilation/perfusion (V/Q) mismatch or by promoting hypoxic vasoconstriction.

In the literature, a link between coagulation abnormalities and severe SARS-CoV-2 infection has been described [7] and several studies have found an association between increased plasma D-dimer levels and unfavorable prognosis in COVID-19 patients [8]. However, in severe COVID-19, the pulmonary inflammation can cause fibrin deposits within alveoli and pulmonary extravascular space, as confirmed in autopsies series [9] and the lysis of these deposits could contribute to the rise of D-dimer which would be thus not specific of intravascular fibrin formation [10, 11].

Patients with SARS-CoV-2 infection presented a peculiar form of coagulopathy, termed COVID-19 associated coagulopathy (CAC). CAC results from complex interactions between regulators of inflammation and coagulation; it is characterized by unique laboratory features different from either disseminated intravascular coagulation (DIC) and sepsis induced coagulopathy (SIC), such as the lack of consumption of platelets and coagulation factors. Increased fibrinogen, fibrin degradation products, prothrombin time (PT) and activated partial thromboplastin time (aPTT), have been described in patients with COVID-19 compared

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to healthy controls [12, 13]. Despite their dissemination and ease of interpretation, these measurements focus on quantity rather than functionality of clotting components and provide information on clot formation, but do not address clot stability and dissolution.

Viscoelastic tests (VETs), such as rotational thromboelastometry (ROTEM, Tem Innovations, Munich, Germany), thromboelastography (TEG System, Haemonetics) and Quantra (Quantra System, HemoSonics LLC, Charlottesville, VA), are global hemostasis assays able to assess coagulation function, platelets and fibrinogen contribution to clot formation and fibrinolytic components [14–17]. These devices have been utilized in trauma and surgical care as an adjunct to conventional coagulation tests for guiding resuscitation and transfusion strategies [18, 19]. In addition to the use in patients with a hypocoagulable state and bleeding tendency, VETs have been successfully used to detect hypercoagulable states in the setting of malignancy [20], trauma [21–23], intensive care unit (ICU) admission [24] and surgery [25, 26].

Recently, VETs appeared to play a role in assessing CAC. The purpose of this narrative review is to analyze the literature on the ability of VETs to evaluate the CAC, through possible answers to clinical questions.

2 The viscoelastic tests: parameters and interpretation

VETs (i.e. ROTEM, TEG and Quantra) are assays that measure changes in viscoelastic properties of whole blood. TEG and ROTEM are based on the same concept, described by Hartert [27], and measure the “shear modulus” of the clot, which represents its tendency to deform by the action of opposing forces. The shear modulus is defined as the ratio between shear stress and shear strain; it is not constant and changes along the process of clotting. In TEG a blood sample is injected in a cylindrical sample cup which rotates slowly through an area of 4.45° , every 5 s, along the longitudinal axis; a free pin is immersed in the blood and, as long as the coagulation process begins, it detects the variation of strength between the pin and the cup wall. In ROTEM the mechanism is the opposite, as it is the pin which moves through an area of 4.75° , while the cup is fixed. Moreover, in TEG, the movement is detected by a torsion wide and not optical as in the ROTEM device; this makes the TEG 5000 system more sensitive to movement artifacts. Actually, the new TEG 6s device is using an ultrasound technology.

TEG and ROTEM explore the coagulation pathway using added activators and additives. In TEG the most widely activator used is Kaolin (K-TEG) to explore the intrinsic coagulation pathway. Its ROTEM equivalent is the INTEM, which uses ellagic acid and phospholipids as activators.

To explore the extrinsic pathway, the systems use activators such as tissue factor (TF) alone (extrinsically-activated assay, EXTEM) or in combination with Kaolin (RAPID-TEG). The contribution of fibrin on the clot amplitude is explored using additive platelets inhibitors [i.e. Abciximab for TEG (Functional Fibrinogen, FF assay) and cytochalasin D (FIBTEM assay) for ROTEM].

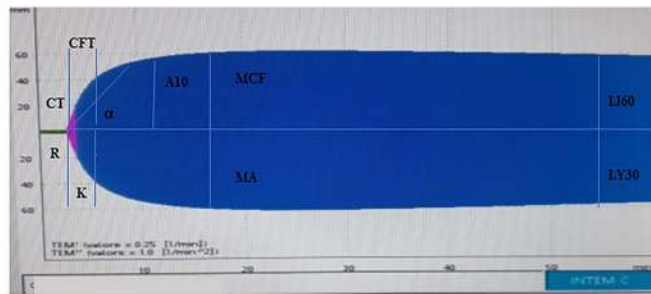
Based on time–resistance associations, TEG and ROTEM are characterized by tracings that represent a picture which starts from the beginning of clot formation throughout its lysis. In particular, TEG and ROTEM are able to detect both hypo- and hyperfunctional stages of the clotting process and are reliable rapid tests for the diagnosis of hyper or hypofibrinolysis [28–30]. In Fig. 1 the parameters obtained in TEG and in ROTEM and their meaning are shown.

Quantra System is based on technology called sonic estimation of elasticity via resonance, or sonorheometry [31, 32]. A multi-well plastic cartridge (Quantra QPlus) which includes four test channels allows to perform four parallel and independent measurements using different lyophilized reagent combinations in each channel. This technology is composed of three fundamental steps. First, an ultrasound pulse is transmitted in the blood sample to generate a shear wave, causing the sample to resonate. A series of ultrasound “tracking” pulses is then sent within the sample and the returning echoes are used to estimate the sample motion. The shear modulus of the sample is calculated by analyzing the sample motion pattern. This process is repeated every four seconds to form a signature curve that shows shear modulus vs. time. From this curve, the start of clot formation, or clot time, and the stiffness of the clot can be directly estimated. The combination of these two parameters provides information about the functional role of the coagulation factors, fibrinogen, and platelets in the sample. The Quantra system does not provide a TF activated clotting time (CT) and is limited to assess the intrinsic pathway (activation by kaolin). Furthermore, hyperfibrinolysis can only be detected in the Quantra system using a specific cartridge (QStat cartridge) [33]. No data are available whether the Quantra system can detect fibrinolysis shutdown which is an important issue in bacterial sepsis and COVID-19 [34–37].

The principal parameters evaluated in Quantra System are shown in the Fig. 2.

3 Hypercoagulability and hypofibrinolysis in COVID-19 patients: two sides of the same coagulopathy?

During infection, the coagulation cascade is activated as a physiological host defense to limit the spread of the pathogens [38]. In COVID-19 patients the severe inflammatory state can lead to severe derangement of hemostasis and



TEG	ROTEM	Parameters	What does it mean
R- Reaction time	CT- clotting time (clot initiation)	Time to reach to 2 mm amplitude	Period from the beginning of the clotting to start of fibrinogen polymerization
K-time	CFT- clot formation time (clot propagation)	Time to reach 20 mm amplitude	Estimation of velocity of the clot formation
α	α	Angle formed by tangent line from baseline to 20 mm	Same meaning as K and CFT
Not considered	A5-A10	Amplitude at 5 and 10 minutes	Estimation of clot strength at 5 and 10 minutes; it is correlated with MCF
MA- Maximum Amplitude	MCF- maximum clot firmness	Maximum amplitude of clot reached during the test	It reflects the mechanically strength of the clot and depends on platelets function, fibrin polymerization and factor XIII activity
LY30	LI30; LI45; LI60; ML- maximum lysis	LY30: percentage decrease in amplitude (MA) at 30 minutes after MA* LI60: percentage decrease in MCF at 60 minutes after CT ML: the lowest amplitude after MCF	Estimation of fibrinolysis.

Fig. 1 TEG and ROTEM parameters and their significance. *TEG and ROTEM fibrinolysis parameters refer to different starting points. Whereas, ROTEM LI30, LI45 and LI60 are measured 30, 45 and 60 min after CT, TEG LY30 is measured 30 min after MA. Since

TEG time to MA is about 30 min, LY30 is measured after about 60 min runtime as LI60 in ROTEM. In order to detect fibrinolysis shutdown, a runtime of 60 min (TEG LY30 or ROTEM LI60) is needed

Fig. 2 Quantra parameters and their significance

Quantra	What does it mean
CTH- clot time with heparinase	Heparinase neutralizes any potential heparin in the sample
CT- clot time	It provides an indication of the functional status of the coagulation factors that lead to fibrin formation
CTR- clot time ratio (calculated: CT/CTH)	It is used to determine the presence of residual heparin in the sample.
CS- clot stiffness	It combines information about platelets and fibrinogen function.
PCS- platelet clot stiffness (calculated: CS - FCS)	Platelet contribution to clot stiffness (calculated: CS - FCS)
FCS- fibrinogen clot stiffness	Fibrinogen contribution to clot stiffness

alteration of coagulation parameters [7, 13, 39], that has been demonstrated closely associated with worsening and death [7, 12].

In addition to the derangement of coagulation, endothelial activation/dysfunction contributes to the procoagulant

state [4, 40] leading to pulmonary vasculature endothelitis, microthrombosis and angiogenesis [6, 41, 42]. Here, TF expression by circulating monocytes and microparticles can be detected by ROTEM NATEM and interference

with endogenous heparin-like effect can be eliminated by NAHEPTEM CT [34, 43, 44].

In COVID-19, simultaneously with the increase in procoagulant activity through TF pathway and endothelial activation, the plasmin activity is suppressed by the reduction in urokinase-type plasminogen activator (uPA) and the increase in plasminogen activator inhibitor-1 (PAI-1) levels. Inflammation promotes local release of tissue plasminogen activator (tPA) and PAI-1 from endothelial cells [45] and activated platelets may also release large amounts of PAI-1. Thus, increased PAI-1 levels may be responsible for hypofibrinolysis and fibrin persistence. Elevated PAI-1 levels and the associated hypofibrinolytic state were reported in patients with SARS-CoV [46], while recent characterizations of COVID-19 patients have suggested an impaired global fibrinolysis [36, 37, 46–49]. A recent study performed in severe COVID-19 patients has reported a significant hypercoagulability associated with hypofibrinolysis combined with high levels of PAI-1 and increased thrombin activatable fibrinolysis inhibitor (TAFI) activation [50]. Endothelial injury, hypercoagulability, hypofibrinolysis and fibrinolysis shutdown support the increased risk of pulmonary microthrombosis [51], the pathophysiological substratum of severe acute respiratory syndrome associated to SARS-CoV-2, and macrothrombosis (i.e. deep vein thrombosis and pulmonary embolism) [52–54].

The usefulness of VETs to assess hypercoagulability in COVID-19 infection has been evaluated by some studies (Table 1). Panigada et al. [55] demonstrated a higher velocity of clot formation (i.e. R and K value of TEG shorter) in 50% (R value) and 90% (K value) of critically ill patients with COVID-19 than healthy population; moreover, maximum amplitude (MA) values were higher than reference population in 87% of COVID-19 patients. Similarly, Maatman et al. [56] showed a hypercoagulable feature (i.e. ≥ 2 hypercoagulable TEG parameters) in 58% of severe COVID-19 patients. Using ROTEM device, Spiezia et al. [57] confirmed, in COVID-19 patients with acute respiratory failure, a profile of severe hypercoagulability rather than consumption coagulopathy. In particular, ROTEM profiles were characterized by significantly shorter clot formation time (CFT) in INTEM ($p=0.0002$) and EXTEM ($p=0.01$) and by a higher maximum clot firmness (MCF) in INTEM, EXTEM and FIBTEM ($p<0.001$) in patients than in healthy controls. Similarly, Kruse et al. [37] found substantial abnormalities in the ROTEM analysis in 40 critically ill COVID-19 patients; MCF in INTEM, EXTEM, FIBTEM and HEPTTEM was markedly elevated in the entire cohort compared to reference values with median values of 74 mm, 75 mm, 34.5 mm and 73 mm, respectively. In the same line, Pavoni et al. [58] showed that in severe COVID-19 pneumonia hypercoagulability is detectable, characterized by an acceleration of the

propagation phase of blood clot formation and significantly increased clot strength; this hypercoagulable state persists during the first days after ICU admission, and it decreases over time. Recently, Hulshof et al. [59] observed in 36 critically COVID-19 patients a persistent increase in MCF that was more prominent in FIBTEM compared to EXTEM, highlighting an hypercoagulable state which was largely dependent on fibrinogen value. Moreover, the hypercoagulability associated to a severe hypofibrinolysis persisted at least six weeks despite anticoagulation.

Using Quantra as viscoelastic test, Ranucci et al. [60] confirmed that COVID-19 patients with ARDS had a procoagulant profile characterized by an increased clot strength (CS), with platelet and fibrinogen contribution to CS. Furthermore, after increasing the thromboprophylaxis these values decreased significantly. Similarly, Van der Linden et al. [61] found a reduction in fibrinogen-dependent hypercoagulation indicated by ROTEM analysis in ICU-treated COVID-19 patients after enhanced anticoagulation strategy.

Other studies confirmed that critically ill patients with COVID-19 have hypercoagulable viscoelastic profiles with an elevated MA or MCF, suggesting a significant fibrinogen and platelet effect on clot strength [62, 63].

Another important key contributor to COVID-19 thrombosis together with a hypercoagulable state, is the presence of hypofibrinolysis or fibrinolysis shutdown. Five [36, 37, 49, 64, 65] studies have highlighted the ability of VETs to diagnose the presence of severely impaired fibrinolysis rapidly at the bedside in critically ill COVID-19 patients. Using ROTEM parameters, a hypofibrinolytic state in COVID-19 patients, defined as lysis index at 60 min after coagulation time (LI60) in EXTEM of 99 (97–100%), was found by Ibanez et al. [64]. Kruse et al. [37] confirmed these results and found the maximum lysis (ML) in both EXTEM and INTEM to be markedly below normal value in 40 critically ill COVID-19 patients. Of note, the fibrinolysis shutdown in combination with increased D-dimer was the best predictor of thromboembolic events in critically ill COVID-19 patients. Similarly, Creel-Bulos et al. [36] investigated a population of 25 critically ill patients with COVID-19 and found the presence of fibrinolysis shutdown at ROTEM analysis in 11 patients (44%); the authors demonstrated again that fibrinolysis shutdown was a good predictor of thrombosis in severe COVID-19. Wright et al. [49] reported a fibrinolysis shutdown, evidenced by a complete shutdown of fibrinolysis at 30 min after maximum amplitude (LY30 on TEG) in 57% of a group of critically ill patients. Moreover, marked D-dimer elevation and TEG LY30 levels of 0% were seen in patient samples drawn more than two weeks of ICU stay, so suggesting a prolonged hypofibrinolytic state. In the same line, Pavoni et al. [65] comparing ROTEM analysis of critically ill patients with pneumonia not due to COVID-19 and due to COVID-19, observed a higher incidence of

Table 1 A Summary of published studies on use of TEG and ROTEM in COVID-19 patients; B summary of published studies on use of Quantra System in COVID-19 patients

A								
Study	Type VET	Population	n. patients	R (min)/CT (s) EXTEM	K (min)/CFT (s) EXTEM	Angle K (°)	MA (mm)/MCF (mm) EXTEM	LY30–LY60 (%)/LI30–LI60 (%)-ML (%) EXTEM
Wright [49]	TEG	ICU	44	5.8 (4.8–8.6)	N/A	71 (66–74)	73 (67–77)	0 (0–0.4) (LY30)
Panigada [55]	TEG 5000	ICU	24	6.3 (3.0–11.9)	1.5 (0.8–2.9)	69.4 (51.1–78.5)	79.1 (58–92)	7.8 (0–54.3) (LY30)
Maatman [56]	TEG 5000	ICU	12	4.8 ± 1.1	1.4 ± 1.1	69.6 ± 10.9	70.8 ± 8.5	0.8 ± 0.9 (LY30)
Spiezia [57]	ROTEM delta	ICU	22	75 ± 16	66 ± 20	N/A	69 ± 6	1 ± 3 (ML)
Kruse [37]	ROTEM sigma	ICU	40	86 (69.5–99.8)	46.5 (40–60.5)	N/A	75 (70.3–78)	3 (1.3–5.8) (ML)
Pavoni [58]	ROTEM sigma	ICU	40	78.3 ± 17.2	41.6 ± 11.4	N/A	76.6 ± 6.4	9.4 ± 6.6 (ML)
Yuriditsky [62]	TEG 5000	ICU	64	6.4 (4.8–9.17)	1 (0.8–1.3)	75.3 (69.9–78.4)	72.8 (67.9–77.6)	0.10 (0.00–1.20) (LY30)
Wallace Collett [63]	ROTEM sigma	ICU	6	N/A	48.5 (41–60.5)	N/A	74.5 (72.5–79.5)	1.5 (1–4.25) (ML)
Ibanez [64]	ROTEM sigma	ICU	19	78 (63–91)	41 (40–53)	N/A	74 (71–76)	100 (100–100) (LY30)
Pavoni [65]	ROTEM sigma	ICU	20	62.4 ± 9.6	47.4 ± 15.2	N/A	74.3 ± 3.2	9.5 ± 5.0 (ML)
Sadd [66]	TEG	ICU	10	4.45 (3.6–5.8)	1 (1–1.3)	78.25 (75.1–78.7)	71.95 (68.5–74.5)	0.75 (0–2.6) (LY30)
Bocci [67]	TEG 6s	ICU	40	7.1 (5.2–8.1)	1.1 (0.9–1.5)	74.9 (70.9–77.5)	69.8 (66.3–71.3)	0 (0–0) (LY30)
Tsantes [68]	ROTEM	ICU	11	73.5 ± 15.5	40.7 ± 13.0 [§]	N/A	75.7 ± 5.0 [§]	99.5 ± 1.0 (LI60)*
		Ward	21	73.5 ± 12.0	59.5 ± 24.9	N/A	72.4 ± 4.0	96.3 ± 2.9 (LI60)
Mortus [78]	TEG	ICU	21	10 ± 11	N/A	60 ± 23	67 ± 17	0.9 ± 1.8 (LY30)
Shah [79]	TEG 6s	ICU	187	7.37 ± 2.45	N/A	75.7 ± 3.4	69.3 ± 2.26	0.00 (0.00–0.05) (LY30)
Stattin [80]	TEG 6s	ICU	21	7.3 (6.7–8.2)	6.9 (6.7–8.2)	76 (75–78)	69 (68–71)	0.0 (0.0–0.2) (LY30)
van Veenendaal [81]	ROTEM sigma	ICU	47	85.5 ± 20.6	45.3 ± 10.0	N/A	77.3 ± 4.1	N/A
Salem [84]	TEG 6s	ICU	52	8.1 (6.7–10.6)	1.3 (1.2–1.9)	72.1 (67.2–74.4)	65.8 (59.6–68.7)	0.0 (0.0–0.1) (LY30)
Hoechter [96]	ROTEM delta	ICU	22	62 (56–68)	93 (55–97)	N/A	65 (63–70)	6.5 (4.5–9.0) (ML)
Spiezia [97]	ROTEM sigma	Ward	56	66 ± 9	48 ± 15	N/A	71 ± 6	1–2 (Range) (ML)
Roh [98]	ROTEM	ICU	30	108 ± 54	N/A	N/A	75 ± 5	N/A
Boscolo [106]	ROTEM	ICU	32	74 (64–88)*	60 (48–80)*	N/A	71 (65–75)	N/A
		Ward	32	65 (61–72)	43 (38–56)		72 (68–75)	
Almskog [107]	ROTEM sigma	Regular ward	40	70 (61–75)*	49 (43–63)	N/A	70 (66–73) [§]	100 (100–100) (LI30)
		Specialized ward (NIV)	20	90 (78–108)	46 (42–55)	N/A	76 (71–77)	100 (100–100) (LI30)
Blasi [108]	ROTEM sigma	ICU	12	70.5 (66.3–75)	N/A	N/A	71 (67–75.8)	100 (99.3–100) (LY60)*

Table 1 (continued)

Study	Type VET	Population	n. patients	CT	CTH	CTR	CS	PCS	FCS
Ranucci [60]	Quantra	ICU	16	139 (133–155)	N/A	N/A	55 (35–63)	43 (24–45)	12 (6–13.5)
Masi [99]	Quantra	ICU	17	152 (30–171)	130 (117–152)	1.1 (1.1–1.3)	49.9 (38.5–68)	38.5 (28.85–51.2)	12.8 (6.35–20.85)

ICU intensive care unit, NIV non-invasive ventilation, VET viscoelastic test, TEG thromboelastography, ROTEM rotational thromboelastometry, CT clotting time, R reaction time, K time, CFT clot formation time, MA maximum amplitude, MCF maximum clot formation, LY30 the decrease in clot firmness in percentage of maximum amplitude (MA) 30 min after MA, LI30–LI60 the residual clot firmness in percentage of maximum clot firmness 30 min (LI30) or 60 min (LI60) after CT, ML maximum lysis, CTH clot time with heparinase, CTR clot time ratio, CS clot stiffness, PCS platelet clot stiffness, FCS fibrinogen clot stiffness, N/A not available

* $p < 0.001$, § $p < 0.05$

fibrinolysis shutdown in 50% samples from patients with COVID-19 obtained 5 days after ICU admission.

Finally, three studies evaluated the impact of anticoagulation on VETs parameters. Sadd et al. [66] confirmed the hypercoagulability and a decreased or absent fibrinolysis by TEG in 10 ARDS critically ill patients with COVID-19 infection; in 4 of 10 patients who received thrombolytic therapy repeated TEG demonstrated improvement in coagulation index and lysis at 30 min reflecting reduced hypercoagulability and increased fibrinolysis. On the contrary, Bocci et al. [67] in 40 consecutive SARS-CoV-2 patients admitted to the ICU, found that TEG parameters did not significantly differ after a week of full dose systemic anticoagulation. In the same line, Tsantes et al. [68], with ROTEM device, demonstrated that critically ill COVID-19 patients had a hypercoagulability and fibrinolysis shutdown, despite the administration of therapeutic anticoagulant treatment.

In conclusion, from the current literature data, it emerges that, in COVID-19 patients, the use of VETs provides more comprehensive assessment of CAC than standard coagulation parameters and may identify the two sides of CAC such as hypercoagulability and hypofibrinolysis.

4 Can VETs predict thrombotic complications in COVID-19 patients?

VETs have proved be able to predict the risk of developing VTE in trauma and orthopedic settings [69, 70]. In particular, in trauma population, a hypercoagulable TEG profile, based on higher MA parameter, can predict VTE [71, 72]. The predictive value of ROTEM for thrombosis has also been demonstrated in cardiac and non-cardiac surgery as well as in cirrhosis and liver transplantation [73–77].

In COVID-19 population, ten studies evaluated the predictivity of VETs for VTE diagnosis, based on

hypercoagulable state and hypofibrinolysis. In Table 2 viscoelastic parameters derived from seven of ten studies analyzed are reported.

Wright et al. [49] showed that a fibrinolysis shutdown predicts VTE (area under the receiver operating characteristics curve (ROC) [AUC], 0.74 [95% CI, 0.58 to 0.9]; $p = 0.021$) in critically ill patients with COVID-19. In particular, a combination score with TEG LY30 of 0% and a D-dimer of > 2.600 FEU was associated with an increased risk of VTE ($p = 0.008$). In patients presenting neither elevated D-dimer nor fibrinolysis shutdown, the incidence of VTE was 0%; in contrast, in patients presenting elevated D-dimer and fibrinolysis shutdown, the incidence of VTE was 50%. Similar to this study, Kruse et al. [37] evidenced that hypofibrinolysis is an important contributor to the hypercoagulable state in COVID-19 patients. The authors demonstrated that ROC AUC to predict thrombosis for maximum D-dimer was 0.78 and for EXTEM ML was 0.8, but could be increased to 0.92 by the combination of maximum D-dimer and EXTEM ML. The optimum cut-off value for “max D-dimer (mg/l) – EXTEM ML (% of MCF at 60 min)” was 3.7. For standardized interpretation, the formula “max D-dimer (in mg/l) – 100 + EXTEM LI60 (in % of MCF)” might be preferable because this clearly defines the measurement time for fibrinolysis.

In a case series of critically ill COVID-19 patients [36], thrombotic events were found in 73% of cases with fibrinolytic shutdown and 89% of patients with thrombotic events met the criteria for fibrinolysis shutdown. Similarly, Mortus et al. [78] described in patients with high thrombotic events group (≥ 2 thrombotic events) a greater innate TEG MA than in the low events group (0–1 thrombotic events). In particular, elevated MA was observed in 10 patients (100%) in the high events group vs. 5 patients (45%) in the low events group. However, the sample size of this study was very small (21 patients). In the same way, Nougier et al. [50] using

Table 2 Summary of published studies on use of viscoelastic tests (i.e. TEG and ROTEM) in COVID-19 patients with thrombotic complications (TR) vs. non thrombotic (non-TR) complications or stratified by clotting index (CI)

Study	Type VET	Population (n)	TR incidence (%)	R (min)/CT (s) EXTEM	K (min)/CFT (s) EXTEM	Angle K (°)	MA (mm)/MCF (mm) EXTEM	LY30 (%) / LI30 – LI60 (%) – ML (%) EXTEM
Kruse [37]	ROTEM sigma	ICU TR	23	84 (69–96)	47 (40–61)	N/A	75 (69–78)	3 (0–5) (ML)*
		ICU non-TR	17	86 (70.5–107.5)	45 (40.5–56.5)	N/A	76 (72.5–78.5)	5 (3.5–8) (ML)
Yuriditsky [62]	TEG 5000	ICU CI > 3 (32)	11	5.25 (4.50–7.62) [§]	0.80 (0.80–1.00)*	77.3 (75.4–79.0)*	76.2 (72.1–81.0)*	0 (0–1.38) (LY30)
		ICU CI < 3 (32)	9	7.7 (5.52–9.35)	1.25 (1.02–1.67)	70.2 (63.7–75.1)	68.8 (62.0–74.3)	0.10 (0–1.15) (LY30)
Mortus [78]	TEG	ICU high TR (10)	62	7.1 ± 5°	N/A	68 ± 16°	75 ± 7°	0.6 ± 1 (LY30)°
		ICU low TR (11)		13 ± 14	N/A	52 ± 27	61 ± 21	3.5 ± 4.6 (LY30)
Shah [79]	TEG 6s	ICU TR (81)	43.3	7.7 ± 1.87	N/A	75.5 ± 3.5	69.3 ± 1.7	0.00 (0.00–0.00) (ML)
		ICU non-TR (106)		6.86 ± 3.22	N/A	75.7 ± 3.4	69.4 ± 3.06	0.00 (0.00–0.48) (ML)
Stattin [80]	TEG 6s	ICU TR (5)	16.1	6.2 (5.3–7.7)	6.5 (5.4–8.5)	76 (74–77)	70 (68–70)	0.0 (0.0–0.0) (LY30)
		ICU non-TR (26)		7.2 (6.4–8.2)	7.0 (6.2–7.7)	77 (76–79)	70 (69–73)	0.0 (0.0–0.2) (LY30)
van Veenendaal [81]	ROTEM sigma	ICU TR (10)	21.3	95.7 ± 17.4	54.1 ± 8.4 [§]	N/A	75 ± 5.9 [§]	N/A
		ICU non-TR (37)		82.8 ± 20.8	42.9 ± 9.2	N/A	77.9 ± 3.3	N/A
Salem [84]	TEG 6s	ICU TR (14)	26.9	7.7 (7.3–10.8)	1.3 (1.2–1.9)	73.2 (68–74.8)	66.7 (61.4–68.1)	0.0 (0.0–0.0) (LY30)
		ICU non-TR (38)		8.5 (6.2–10.8)	1.5 (1.2–1.9)	70.9 (67–74.3)	65.2 (59.4–68.9)	0.0 (0.0–0.2) (LY30)

ICU intensive care unit, VET viscoelastic test, TEG thromboelastography, ROTEM rotational thromboelastometry, CT clotting time, R reaction time, K time, CFT clot formation time, MA maximum amplitude, MCF maximum clot formation, LY30 the decrease in clot firmness in percentage of maximum amplitude (MA) 30 min after MA, LI30 – LI60 the residual clot firmness in percentage of maximum clot firmness 30 min (LI30) or 60 min (LI60) after CT, ML maximum lysis, CI clotting index, N/A not available

*p < 0.001, °p < 0.01, §p < 0.05

EXTEM reagent of ROTEM delta device with the addition of 0.625 µg/ml tPA (tPATEM), reported decreased clot lysis in COVID-19 patients admitted to ICU and internal medical department; this fibrinolysis resistance was more evident in patients who presented a thrombotic event compared with event-free patients.

On the other hand, Shah et al. [79] confirmed that TEG has hypercoagulable profile characterized by α angle and MA values at or above the upper limits of the normal reference range and extremely low LY30; however, the authors observed no differences in these parameters between patients who developed thrombotic complications and those who did not. In the same line, Stattin et al. [80], in 31 critically

ill patients, demonstrated no difference in MA between patients with or without thromboembolic events. Notably, van Veenendaal et al. [81] reported that ROTEM confirmed the hypercoagulable state in COVID-19, but hypercoagulability (increased clot firmness) did not predict thrombosis. However, the authors did not include fibrinolysis parameter in their analysis. Accordingly, their results were in-line with Kruse et al. [37] showing that clot firmness was increased in all critically COVID-19 patients, but only fibrinolysis shutdown and D-dimer were highly predictive for thrombosis, particularly if used in combination. Furthermore, in the van Veenendaal et al.'s study [81] clot firmness was lower and CFT longer in patients with VTE; the authors concluded

that heparin could have influenced ROTEM results. Actually, this results do not appear surprising: whereas hypercoagulability (increased clot firmness) has been shown to be predictive for thromboembolic events in several clinical settings [69–77], active thrombosis can result in decreased clot firmness in EXTEM and FIBTEM due to the consumption of platelets and fibrinogen. Accordingly, an increase in D-dimer/fibrinogen ratio has been reported as a marker of thrombosis and ischemic stroke [82, 83]. Alike, Salem et al. [84], using TEG device, did not find a significant association between a hypercoagulable state and thromboembolic events. Similarly, Yuriditsky et al. [62], demonstrated no significant differences in ROTEM parameters between critically ill COVID-19 patients with confirmed VTE and those without VTE. Finally, a small recent study [56] that evaluated twelve severe COVID-19 patients, documented the development of VTE in three patients with a hypercoagulable TEG; however, one patient with normal TEG parameters developed VTE.

In conclusion, VETs demonstrate a hypercoagulable state with increased clot firmness in hospitalized COVID-19 patients. However, hypercoagulability alone is not predictive for thrombotic events in critically ill COVID-19 patients. Here, fibrinolysis shutdown in ROTEM or TEG, particularly in combination with increased D-dimer, is highly predictive for thromboembolic events [37, 49]. Moreover, the interim analysis of the multiplatform randomized clinical trials (ACTIV-4a and REMAP-CAP and ATTACC [Antithrombotic Therapy to Ameliorate Complications of COVID-19]) [85] suggests that patients with moderate COVID-19 (hospitalized but not requiring organ support) may benefit from therapeutic anticoagulation (odds ratio for survival or reduced requirement for organ support, 1.57 (95% CI, 1.14 to 2.19), but critically ill patients with severe COVID-19 show an increased incidence of major bleeding (3.7% versus 1.8%) and mortality (OR for survival and decreased need for organ support, 0.76, 95% CI, 0.6 to 0.97). Therefore, the anticoagulation concept in COVID-19 might change from an escalating (intensified anticoagulation in critically ill COVID-19 patients) to a deescalating concept (decrease anticoagulation from therapeutic to prophylactic dose in critically ill COVID-19 patients presenting a decrease in clot firmness due to liver failure, bacterial superinfection, and/or DIC). Here, VTEs might help identifying COVID-19 patients with decreased need for anticoagulation (e.g., EXTEM MCF < 68 mm and FIBTEM MCF < 24 mm) or even increased risk of bleeding (e.g., EXTEM MCF < 50 mm and FIBTEM MCF < 14 mm) [86–90]. This could hypothesize a role of VETs not only in the identification of thromboembolic risk, but also in its treatment.

5 Is CAC different from hypercoagulability caused by bacterial agents?

Epidemiological studies indicated that severe sepsis, correlated to bacterial pneumonia, is associated with an increased risk to develop arterial and venous thrombosis, due to activation of the clotting system and inhibition of anticoagulant factors [91, 92]. The linear progression from SIC to DIC usually seen in septic patients [93], does not necessarily occur in COVID-19 patients, in whom it seems to be present a peculiar form of coagulopathy, termed as CAC. In contrast to CAC, bacterial sepsis is associated with early hypocoagulability and platelet dysfunction which also predicts mortality in bacterial sepsis [94, 95].

Using VETs, five studies with ROTEM [65, 68, 96–98] and one with Quantra [99], compared the grading of hypercoagulability of critically ill patients with acute respiratory failure due to infection from SARS-CoV-2 and other pathogens; one study instead compared non-critical patients [97]. Hoechter et al. [96] demonstrated, with ROTEM, that patients with COVID-19 pneumonia presented significantly shorter time from initial clot formation up to a clot amplitude of 20 mm (Time-to-Twenty, TT20) compared to non-COVID-19 pneumonia (143 vs. 155, $p=0.047$), whereas EXTEM CT and EXTEM CFT tended to be shorter in the COVID-19 patients (CT: 62 vs. 70, $p=0.09$, CFT: 93 vs. 84, $p=0.301$). Likewise, Pavoni et al. [65] reported a shorter clot propagation in COVID-19 compared to non-COVID-19 patients (CFT 47.4 ± 15.2 vs. 124 ± 31 , $p < 0.0001$); moreover, COVID-19 patients had a significantly higher clotting stabilization (i.e. MCF in EXTEM) than non-COVID-19 that persists over time. In Tsantes et al.'s study [68] a greater hypercoagulable state was detected in COVID-19 ICU patients than in non-COVID-19 ICU patients based on A10 and MCF parameters. Similarly, using the Quantra System, Masi et al. [99] observed that unlike non COVID-19 ARDS, COVID-19 ARDS was associated with a significant increase of clot stiffness and platelet and fibrinogen contribution to clot stiffness. Furthermore, similar results were reported in patients with acute COVID-19 pneumonia compared to other pneumonia, admitted to medical wards [97], even if alterations of ROTEM analysis were less marked. This indicates that the hypercoagulability of the SARS-CoV-2 infection is present even in a mild disease. Different results were reported by Roh et al. [98] that found slower coagulation kinetics on ROTEM testing in COVID-19 patients compared to matched non COVID-19 surgical patients in both the extrinsic [EXTEM CT 108 (54) vs. 57 (31), $p < 0.0001$] and intrinsic [INTEM CT 205 (65) vs. 169 (57), $p=0.01$] pathways; however, similarly to previous studies [65, 96, 97] a significantly higher clot strength

Table 3 A Summary of studies on use of TEG and ROTEM in COVID-19 patients compared to non-COVID-19 patients; B summary of studies on use of Quantra System in COVID-19 patients

A									
Study	Type VET	Population	n. patients	R (min)/CT (s)	K (min)/CFT (s)	MA (mm)/MCF (mm)	LY30 – LY60 (%) / LI30/ LI60 (%) – ML (%)		
								EXTEM	
Pavoni [65]	ROTEM sigma	ICU COVID-19	20	62.4 ± 9.6	47.4 ± 15.2°	74.3 ± 3.2°	9.5 ± 5.0 (ML)		
		ICU non-COVID-19	25	59 ± 6.1	124 ± 31	60.4 ± 5.6	7.2 ± 3.0 (ML)		
Tsantes [68]	ROTEM	ICU COVID-19	11	73.5 ± 15.5	40.7 ± 13.0	75.7 ± 5.0§	99.5 ± 1.0 (LI60)		
		ICU non COVID-19	9	70.5 ± 8.5	63.7 ± 34.7	69.4 ± 8.5	98.4 ± 2.1 (LI60)		
Hoechter [96]	ROTEM delta	ICU COVID-19	22	62 (56–68)	93 (55–97)	65 (63–70)	6.5 (4.5–9.0)		
		ICU non-COVID-19	14	70 (58–78)	84 (80–113)	66 (53–72)	5.0 (2.3–7.0)		
Spiezia [97]	ROTEM sigma	Ward COVID-19	56	66 ± 9	48 ± 15*	71 ± 6§	1–2 (Range) (ML)		
		Ward non-COVID-19	56	70 ± 11	62 ± 16	69 ± 6	2–3 (Range) (ML)		
Roh [98]	ROTEM	ICU COVID-19	30	108 ± 54*	N/A	75 ± 5°	N/A		
		ICU surgical patients	30	57 ± 31	N/A	65 ± 8	N/A		

B									
Study	Type VET	Population	n. patients	CT	CTH	CTR	CS	PCS	FCS
Masi [99]	Quantra	ICU COVID-19	17	152 (30–171)	130 (117–152)	1.1 (1.1–1.3)	49.9 (38.5–68)*	38.5 (28.85–51.2)§	12.8 (6.35–20.85)*
		ICU non-COVID-19	11	127 (137–193)	130 (114–150)	1.1 (1.0–1.2)	24.9 (20.2–42.0)	20.8 (17.9–33.6)	6.1 (4.0–8.2)

ICU intensive care unit, VET viscoelastic test, TEG thromboelastography, ROTEM rotational thromboelastometry, CT clotting time, R reaction time, K time, CFT clot formation time, MA maximum amplitude, MCF maximum clot formation, LY30 the decrease in clot firmness in percentage of maximum amplitude (MA) 30 min after MA, LI30–LI60 the residual clot firmness in percentage of maximum clot firmness 30 min (LI30) or 60 min (LI60) after CT, ML maximum lysis, CTH clot time with heparinase, CTR clot time ratio, CS clot stiffness, PCS platelet clot stiffness, FCS fibrinogen clot stiffness, N/A not available

*p < 0.001, °p < 0.0001, §p < 0.05

(MCF) in COVID-19 patients than in surgical patients was reported. Probably, the slower coagulation kinetics in COVID-19 patients depended on the inability to match COVID-19 patients to analogous non-COVID-19 controls with similar critical illness severity.

In conclusion, from the literature data available, based on the use of VETs, it is possible to assume that CAC is characterized by a more severe state of hypercoagulability than coagulopathy correlated to bacterial infection.

The summary of reported studies is shown in Table 3.

6 Care level in COVID-19 patients: what can we learn from the VETs?

COVID-19 is a viral disease that involves multiple organ systems while usually presenting as an acute febrile illness [100, 101]. Acute COVID-19 has three distinct phases: early infection, pulmonary involvement and severe hyperinflammation with systemic involvement [102]. Conventional coagulation tests (PT and aPTT levels) did not significantly differ between mild and severe COVID-19 cases [103]. Keeping in mind that inflammation-induced

coagulopathy is a very dynamic process, the detection of coagulation parameters with VETs could help identify at-risk patients in their course of illness. Recently, Mitrovic et al. [104], basing on ROTEM analysis of different severity of disease, observed that a hypercoagulable state characterized by clot formation acceleration, high clot strength and reduced fibrinolysis, was more frequent in advanced disease patients and patients with high interleukin-6. An Indian retrospective study, using TEG analysis, confirmed the presence of hypercoagulability that was more pronounced in severe forms of COVID-19 patients admitted to ICU [105].

Four studies [68, 106–108] have considered the difference in hypercoagulable profile and fibrinolysis between patients with COVID-19 admitted to ICU or specialized ward and general ward. Boscolo et al. [106] demonstrated, using ROTEM device, that COVID-19 patients with mild respiratory failure admitted to the internal medical ward had less severe hypercoagulability than critically ill patients. In particular, they presented lower FIBTEM MCF values related to fibrinogen levels than ICU patients. Tsantes et al. [68] confirmed that the degree of hypercoagulability in COVID-19 infection might be associated with disease severity. In

the same line Almskog et al. [107] found longer EXTEM CFT, lower EXTEM MCF and FIBTEM MCF in COVID-19 patients with mild respiratory failure admitted to general ward compared with COVID-19 patients admitted to specialized ward with severe respiratory failure. However, they found in severe COVID-19 patients longer EXTEM CT than in others, even if the authors could not exclude that part of the prolonged EXTEM CT observed in severe COVID-19 patients could be driven by heparin effect.

Regarding fibrinolysis, Blasi et al. [108] compared ROTEM parameters of 12 patients admitted to the ICU with those of 11 patients admitted to a general ward; they found greater hypofibrinolysis (LI60) in ICU patients than in others [100 (100–99.3), vs. 96 (94.4–97.8), $p < 0.001$].

In conclusion, hypercoagulable and hypofibrinolytic states are correlated with more severe COVID-19 infection and higher incidence of complications. This suggests the importance of need for different thromboprophylaxis approach for different severity of disease.

7 Limitations of viscoelastic methods

VETs are attractive because they address clot mechanical properties and fibrinolysis, but data on the use of VETs in COVID-19 patients has a number of limitations.

First, Kruse et al. [37] reported how the combination of EXTEM ML and maximum D-dimer can be used to stratify the risk of thrombotic events in critically ill COVID-19 patients. These results have to be confirmed in bigger observational trials and the effectiveness of a goal-directed anticoagulation management has to be assessed by interventional trials. Second, there is a lack of information to correlate VET data with the extent of thromboembolic damage due to the difficulty in performing instrumental examinations in COVID-19 patients with severe form of pneumonia. Third, most of published studies are single-center retrospective studies with a low sample size. Multicenter, observational trials with much bigger patient population are actually running (e.g. ROHOCO study in 10 countries and 14 hospital, recruiting more than 500 hospitalized COVID-19 patients (DRKS00023934) and TARGET study initiated by Kurizky et al. [109]).

In regard to methodology, VETs determination of fibrinogen contribution to clot firmness is based on the exclusion of platelets role to clot amplitude. The sensitivity of VETs to fibrinogen levels is quite variable depending on the test methodology [110]. Several studies demonstrated that the correlation between Clauss fibrinogen and ROTEM FIBTEM is superior to the correlation between Clauss fibrinogen and TEG FF assay since abciximab provides a less effective inhibition compared to cytochalasin D, and

therefore TEG FF assay is associated with more “platelet noise” [111–113].

In regard to fibrinolysis, it is initiated by the formation of fibrin and it is tightly controlled by a series of cofactors, inhibitors, and receptors [114]. Plasmin is the central enzyme in fibrinolysis and is activated from plasminogen by either of two primary serine proteases, tPA and uPA. However, in VETs, plasminogen activators are most often so low that fibrinolysis is negligible [115]; VETs results can be influence by hyperfibrinogenemia that is common in COVID-19. To overcome these limitations, some authors added exogenous tPA to induce fibrinolysis and validated a novel whole blood ROTEM (tPATEM) [50, 59, 116]. Notably, tPATEM assesses fibrinolysis resistance and not fibrinolysis shutdown; they have two different pathomechanisms [117]. However, such modified commercial reagents require manual pipetting that increases inter-observed variability. Added to this is the fact that the new VET device could lack sensitivity to the effect on the transient increase of tPA that could be present during initial stages of the COVID-19 [49].

Another important issue is the contribution of platelets to thrombotic process. VETs results are dependent on platelet activation by thrombin generated in the sample, making them insensitive to platelet inhibition by aspirin, non-steroidal anti-inflammatory medications or P2Y12 antagonists. They are also insensitive to disorders of primary hemostasis such as von Willebrand disease or defects in platelets adhesion. Therefore, VETs should be complemented by platelet function testing such as whole blood impedance aggregometry as published by Correa et al. in COVID-19 patients [118]. However, the effect of COVID-19 on platelet function seems to be lower compared to bacterial sepsis [95].

Finally, the lack of standardization of the VET devices can limit data comparison across different laboratories. ROTEM sigma, a close, cartridge based, fully-automatized viscoelastic testing system, reduces intra and inter-assay variability and therefore could allow more standardized and comparable data.

8 Conclusions

VETs assess dynamic aspects of hemostasis, regarding both clot formation and dissolution so allowing to evaluate a “dynamic” modification of hemostasis over time. They could provide to clinicians more information about the CAC, identifying at the patient bedside the presence of a hypercoagulable state and hypofibrinolysis, that are more evident than in coagulopathy during the sepsis.

In regard to VTE prediction, the results of VETs analysis demonstrate a hypercoagulable state that is not predictive for thrombotic events in critically ill COVID-19 patients.

The clinical application of VETs in patients with severe COVID-19 infection should be combined with biohumoral parameters (i.e. D-dimer) [37, 49].

Future studies on large patient populations should define the usefulness of VETs as prognostic markers of micro- and macrothrombosis in severe COVID-19 patients to improve morbidity and mortality. The dynamic coagulative approach based on the use of VETs, associated to laboratory tests, might help to guide a personalized anticoagulant strategy, well knowing that “one size does not fit all”.

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