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Review

The role of rotational thromboelastometry (ROTEM) in understanding the coagulation problems in COVID-19 associated critical illness

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Abstract: In critically ill patients with COVID-19, concomitant abnormalities of coagulation have been seen with an unusually high incidence. Standard coagulation tests are limited in their ability accurately to reflect the severity of the pro-thrombotic phenotype observed in severe COVID-19 infections. In this narrative review we consider the role of rotational thromboelastometry (ROTEM) as a near bedside test allowing a more comprehensive assessment of haemostatic function in the context of COVID-19 infection. Comprehensive literature search was conducted on PubMed, revealing 13 publications on the subject. The coagulopathy of this disease process appears to be insufficiently represented with often normal conventional coagulation test parameters. Whilst not the perfect substitute for in vivo coagulation, studies utilising rotational thromboelastometry assays in COVID-19 patients have demonstrated increased maximum clot firmness (consistent with hyper-coagulability) and reduced maximum lysis (consistent with "fibrinolytic shutdown"). ROTEM appears to be a possible tool for risk stratification and to monitor the potential modulation of fibrinogen-dependent coagulation processes with enhanced anti-coagulation strategies. Precisely how these coagulation abnormalities can be modified by optimum, individualised medical interventions to improve clinical outcome, however, remains unclear.

Keywords: ROTEM, COVID-19, coagulation

1. Introduction

A global health emergency was declared by the World Health Organisation in January 2020 following the outbreak of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); the causative agent of coronavirus disease 2019 (COVID-19) infection. As of January 2021, there have been over 100 million reported cases and over two million COVID-19 associated deaths worldwide [1]. Whilst the clinical presentation of COVID-19 infection is hugely varied, in critically ill patients concomitant abnormalities of coagulation have been seen with an unusually high incidence of arterial and venous thromboembolic complications [2–4]. Evidence of hypercoagulability, rather than consumptive coagulopathy, contributing to morbidity and mortality has been demonstrated on both a macrovascular and microvascular level with high incidence of pulmonary embolism and other venous thromboembolism [5], in addition to post-mortem findings of micro-angiopathy and micro-thrombosis in pulmonary and other organs [6,7].

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As a consequence, the International Society on Thrombosis and Haemostasis (ISTH) developed guidelines whereby they recommended that all patients hospitalised with COVID-19 infection were considered for thromboprophylaxis with either unfractionated heparin (UFH) or low molecular weight heparin (LMWH) [8]. The ongoing propensity for thrombo-embolic complications, often despite prophylactic anti-coagulation [9] however, has led to the need to develop a greater understanding of the mechanisms driving hypercoagulability associated with COVID-19 infection in order to inform the optimum thromboprophylaxis strategy in these individuals.

Standard coagulation tests including prothrombin time (PT), international normalized ratio (INR), thrombin time (TT) and activated partial thromboplastin time (aPTT) are limited in their ability accurately to reflect the severity of the pro-thrombotic phenotype observed in severe COVID-19 infections [10]. Here, the role of rotational thromboelastometry (ROTEM) as a near bedside test allowing a more comprehensive assessment of haemostatic function in the context of COVID-19 infection will be considered. In this narrative review we aim to consider, firstly, does ROTEM analysis allow the prediction of thromboembolic complication and secondly, is it able to identify a specific sub-group of patients who would benefit from an individualised approach to anti-coagulation based upon these results?

2. Materials and Methods

We conducted an electronic search of the relevant literature using the PubMed• database with a search strategy relating to COVID-19 infection using keywords “COVID-19” OR “SARS-CoV-2” AND “ROTEM” OR “viscoelastic methods” to identify both current peer-reviewed and accepted online ahead of print publications. From the reference lists of these articles, further relevant studies were extracted and included for analysis. Studies were excluded if published in a language other than English or sole case reports.

ROTEM Tests

ROTEM allows real-time evaluation of the change in viscoelastic properties of whole blood during clot initiation, formation, stabilisation and lysis[11]. Unlike conventional coagulation tests using plasma alone, ROTEM offers the advantage of providing information about platelet function, degree of fibrinolysis and existence of hypercoagulability.

A ROTEM analysis includes assays evaluating intrinsic (INTEM) and extrinsic coagulation (EXTEM) pathways, respectively. The INTEM assay uses phospholipids and ellagic acid to activate and assess coagulation through the intrinsic pathway while the EXTEM assay utilises tissue factor to assess the extrinsic pathway. In addition to these variables, ROTEM also evaluates the isolated role of fibrin formation and polymerisation in clot formation (FIBTEM), which is achieved through the addition of a platelet inhibitor cytochalasin D [12].
The following parameters are described (Figure 1.):

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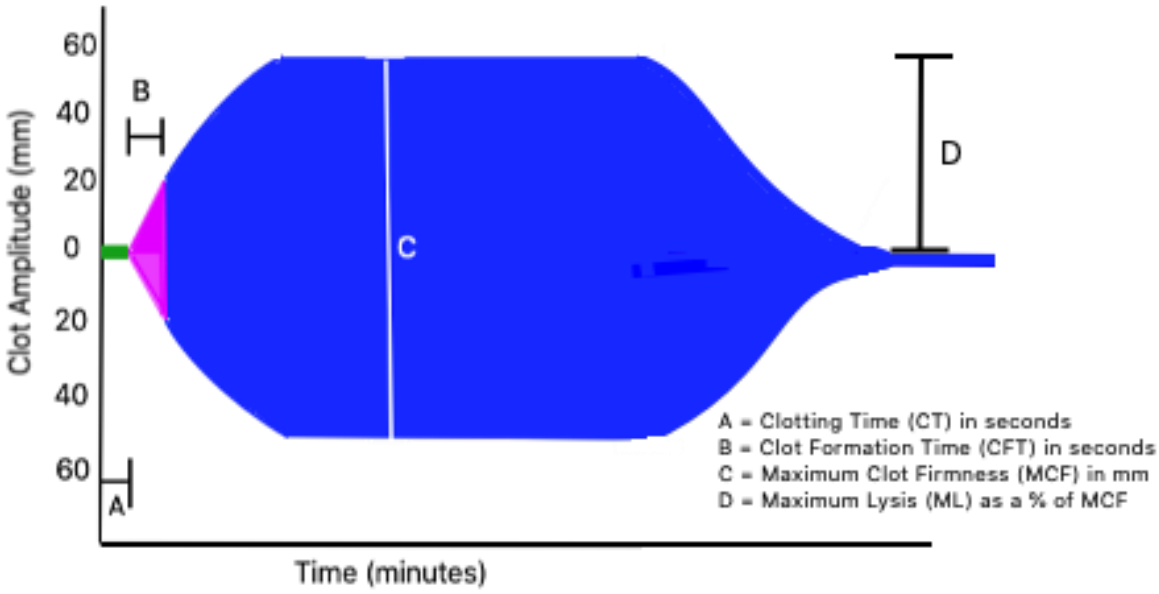

Figure 1: Graphic representation of ROTEM variables

- Clotting time (CT)– time elapsed in seconds from start of measurement until a clot 2mm in amplitude is formed. The amplitude recorded at 10, 20 and 30 min is referred to as A10, A20 and A30 respectively. The CT provides information about clot activation and initiation.
- Clot Formation Time (CFT) – a measure in seconds of the propagation phase of whole blood clot formation from a clot amplitude of 2mm to 20mm. Reduced CFT is indicative of hypercoagulability.
- Maximum Clot Firmness (MCF) – the maximum amplitude, in millimetres, reached during the test which provides information about the final strength of the clot.
- Maximum Lysis (ML) – defined as the difference between MCF and the lowest clot amplitude after MCF, reflecting fibrinolytic activity and clot stability.

3. Results

Presently, in addition to conventional coagulation tests, point-of-care ROTEM tests in the context of COVID-19 infection have been utilised predominantly in a research setting to characterise the coagulation profile of these patients. We found 13 studies, all from high-income countries, describing the use of ROTEM in COVID-19 (Table 1).

Table 1. Studies assessing coagulation parameters in COVID-19 patients using ROTEM

Study	Sample size (COVID-19)	Patient group	Age in years (median)	Comparison	ROTEM findings	Other
Creel-Bulos et al[22]	25	ICU patients	65	Reference values	EXTEM ML 1% in 44% patients	Higher incidence of VTE in group with fibrinolysis shutdown

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Pavoni et al[13]	40	ICU patients	61	Reference values	Reduced CFT. Higher MCF.	50% incidence VTE
Spiezia et al[16]	22	ICU patients	67	44 healthy matched controls	Reduced CFT. Higher MCF	23% incidence DVT
Ibañez et al[23]	19	ICU patients	60	Reference values	Higher MCF. Reduced ML.	26% incidence VTE
Almskog et al[19]	60	Hospital inpatients	61	86 healthy controls	Reduced CFT. Higher MCF	ROTEM differences more marked in HDU & ICU compared to patients receiving ward-level care
Blasi et al[20]	23	Hospital inpatients	64	Reference values	Higher MCF (FIBTEM).	Lysis more impaired in ICU patients compared to patients receiving ward-level care
Collett et al[24]	6	ICU patients	69	Reference values	Reduced CFT(INTEM). Higher MCF. Low ML	40% VTE incidence
van Veenendaal et al[17]	47	ICU patients	63	Reference values	Reduced CFT. Higher MCF	21% incidence VTE. Lower MCF in VTE sub-group
van der Linden et al[21]	26	ICU patients	57	Reference values	Higher MCF	With enhanced anticoagulation, FIBTEM MCF lower than standard anti-coagulation group.
Hoechter et al[14]	11	ICU patients	64	Non-COVID ARDS patients	Higher MCF (non-significant)	
Roh et al[18]	30	ICU patients	63	Non-COVID surgical patients	Higher MCF	33% incidence VTE in COVID-19 patients.

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						Lower MCF in VTE sub-group
Kruse et al[25]	40	ICU patients	67	Reference values	Higher MCF. Reduced ML	53% incidence of thromboembolic events. ML more impaired in this subgroup.
Corrêa et al[15]	30	ICU patients	61	Reference values	Higher MCF. Reduced ML	20% incidence of VTE

The summary of the findings display a homogeneity of coagulation abnormalities consistent with both hypercoagulability (reduced clot formation time and markedly increased clot firmness) and hypofibrinolysis (reduced maximum lysis), with a typical ROTEM result depicted in Figure 2.

Figure 2.

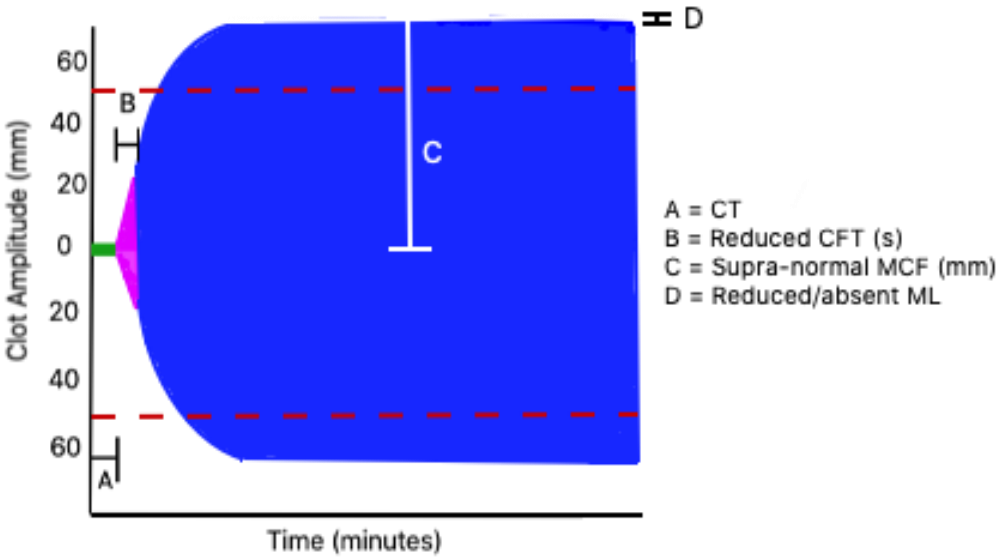

Figure 2: Graphic representation of ROTEM variables in COVID-19 patients

Pavoni et al.[13] retrospectively evaluated the ROTEM results of forty critically unwell patients with COVID-19 and demonstrated that these patients displayed a hypercoagulable state persisting over time despite treatment with appropriate thromboprophylaxis. A reduction in the CFT (INTEM and EXTEM) implied acceleration of the propagation phase of clot formation and increased MCF (INTEM, EXTEM and FIBTEM) and was consistent with a higher clot strength. The finding of increased MCF in ICU COVID-19 patients in comparison to non-COVID-19 ICU patients was corroborated by the work of Hoechter et al. [14]. Serial ROTEM results that were taken and analysed from thirty ICU COVID-19 patients on successive occasions between the day of admission to ICU and Day 14 in the work of Corrêa et al[15] provides further support for the persistence of the hypercoagulable state over time. Similarly, Spiezia and colleagues[16] compared ROTEM profiles in twenty two ICU COVID-19 patients with forty four healthy, matched controls and demonstrated a comparable reduction in CFT (INTEM and EXTEM) and increased MCF in all assays. These ROTEM findings of hypercoagulability have been further corroborated by the work of van Veenendaal et al.[17] who analysed ROTEM variables in 47 ICU COVID-19 patients who displayed a reduced CFT (INTEM and EXTEM) and increased MCF.

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Interestingly and contrary to expectation, COVID-19 patients with thromboembolic complications had an increased CFT (INTEM and EXTEM) and lower MCF (EXTEM) compared to patients without complications. The findings of a lower, albeit still supra-normal, MCF in COVID-19 ICU patients with venous thromboembolism was reiterated by the work of Roh et al. [18]. Almskog and colleagues [19] made an interesting observation in their study of ROTEM parameters in sixty hospital inpatients with COVID-19 infection. When comparing patients requiring a higher level of care to those with milder illness, they showed that the markers of hypercoagulability (reduced CFT and increased MCF) were more pronounced. The only slight contradictory findings come from a study by Blasi and colleagues [20] who demonstrated largely normal ROTEM parameters in twenty three COVID-19 patients (ICU and general ward level care) when compared to reference values. They did, however, demonstrate an elevated MCF in some patients and their in-depth data analysis data suggested that low-therapeutic anticoagulant regimens appear insufficient to downregulate the significant coagulation activation in COVID-19 patients. Van der Linden et al. [21] conducted a retrospective ROTEM analysis of two groups of ICU COVID-19 patients comparing the incidence of thromboembolic events in a standard thromboprophylaxis vs. an enhanced dosing regimen. In the first cohort with standard-dosing LMWH, the MCF (INTEM, EXTEM and FIBTEM) was elevated above upper normal reference limit in the majority of patients indicating hypercoagulation. In the second cohort of enhanced dose anti-coagulation, INTEM and EXTEM MCF were similarly elevated, whereas fibrinogen dependent (FIBTEM) MCF was significantly lower than the first cohort and associated with a non-significant reduction in thromboembolic events.
Among twenty one ICU COVID-19 patients, Creel-Bulos et al.[22] demonstrated that over 50% of patients met the criteria for fibrinolysis shutdown (EXTEM ML <3.5%) which was not apparent on conventional coagulation testing. Of the cohort of patients that went on to develop thromboembolic complications, 89% were from the sub-group of patients with "fibrinolysis shutdown". Likewise, the findings from Ibañez et al.[23] and Collett et al.[24] demonstrated supra-normal MCF and significantly reduced clot lysis in nineteen COVID-19 and six ICU COVID-19 patients respectively when compared to healthy control subjects. Lastly, Kruse et al.[25] used ROTEM analysis in a cohort of forty critically unwell COVID-19 patients. As with other studies, the MCF (INTEM, EXTEM and FIBTEM) was markedly elevated in the entire cohort while ML was reduced in INTEM and EXTEM. Under both conditions, ML was reduced and significantly lower in the group with thromboembolic complications. It was suggested by the authors that ROTEM analysis could serve as potential tool for patient stratification according to their prothrombotic risk.

Of the thirteen aforementioned studies, all support the existence of a marked hypercoagulability and reduction in clot lysis in the context of COVID-19 infection. Of particular interest is the possible association with disease severity and degree of hypercoagulability and hypofibrinolysis as a possible tool for risk stratification and the potential modulation of fibrinogen-dependent MCF with enhanced anti-coagulation strategies.

4. Discussion

Virus-associated hypercoagulation is not a novel phenomenon and has been well documented in both the severe acute respiratory syndrome Coronavirus 1 (SARS-CoV-1) and Middle East Respiratory Syndrome coronavirus (MERS-CoV) infections [26]. With regard to COVID-19 infections, however, the incidence of venous-thromboembolic complication occurs at twice the rate seen with influenza infections [2] implicating unique pathophysiological factors beyond that of 'sepsis-induced coagulopathy' alone. In general terms, the pathophysiology of hypercoagulability associated with COVID-19 includes the complex interaction between inflammatory and immune-mediated coagulation system activation resulting in elevated levels

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of fibrin-degradation products (D-dimer), fibrinogen and Factor VIII levels, increased thrombin-antithrombin complexes and a shortened activated partial thromboplastin time.

Whilst the studies referenced in Table 1 do allude to a consistency and degree of reproducibility of coagulation abnormalities, it is worth noting several pertinent limitations with regard to the use of thromboelastometric testing in this context and within the studies themselves. Firstly, ROTEM is validated in the context of determining the cause of bleeding rather than in its ability to predict thrombotic events. As such, it could be argued that the use of ROTEM to identify sub-groups of critically ill COVID-19 patients at most risk of thromboembolic events is beyond the realm for which it was originally designed. Secondly, the influence of the endothelium as an important co-factor of coagulation is unable to be considered in ROTEM analysis. Lastly, Hardy et al.[27] recently published an article highlighting key intrinsic limitations of ROTEM in studies investigating haemostasis in COVID-19. It was critiqued that ROTEM requires the use of unphysiologically elevated concentrations of EXTEM reagents to initiate clot formation and that fibrinolysis is initiated by endogenous, uninhibited plasminogen activators. These are often so low in concentration that fibrinolysis is negligible which may, in part, explain the impaired maximum lysis parameters.

Owing to the relatively small sample sizes analysed in the studies, comparison and extrapolation of findings must be done with caution. Presently, there is no universal definition of hypercoagulability from analysis of ROTEM results. Between studies, criteria determining hypercoagulability were made by comparison to a number of different parameters including: established reference ranges; healthy matched and unmatched subjects; and different patient groups (non-COVID ARDS and surgical patients, for example) [14,16,18,19]. Moreover, there was considerable inter-study variability with anti-coagulation in terms of the pharmacological agent (LMWH vs. UFH) used, the duration of anti-coagulation treatment prior to ROTEM testing and dosing (standard vs. enhanced regime) of anti-coagulation [13-25]. Investigation regarding thrombo-embolic complications was poorly standardised across studies with some relying on clinician discretion alone while others attempted to protocolise testing with serial lower-limb ultrasounds [13-25]. Finally, there was a wide variability in terms of the timing of viscoelastic measurements during hospital admission which will inevitability produce ROTEM results reflecting different stages of the disease course. With the changing haemostatic profile of patients critically ill with COVID-19 infection, the lack of standardisation makes assessment of the true degree of hypercoagulability and hypofibrinolysis challenging. To truly compare patient groups and assess therapeutic interventions, standardised ROTEM reference values are essential [27]. It seems likely that thromboelastometric testing may provide a more physiologically representative insight into the coagulopathy associated with COVID-19, however, larger, multi-centre studies are needed to allow risk stratification of those at highest risk of developing thromboembolic complications. It is possible, that ROTEM testing together with other more conventional assessment of hypercoagulation could reveal different clotting phenotypes, similarly as it has been described for hypo- and hyperinflammation in COVID-19 ARDS [28].

Clinical trials are currently underway investigating the utility of enhanced anti-coagulation and fibrinolytic treatment approaches for COVID-19 patients. Recently, enrolment of patients requiring critical care in the three ongoing multiplatform, international trials addressing enhanced anti-coagulation in COVID-19 patients (REMAP-CAP; NCT02735707, ACTIV-4; NCT04505774 and ATTACC; NCT04372589) were paused (as of December 21, 2020) due to an interim pooled analysis demonstrating futility of therapeutic-intensity anticoagulation in reducing the need for organ support over the first 21 days compared with standard-intensity prophylaxis in this patient subgroup [29]. With this in mind, it appears that enhanced anti-coagulation fails to target the relevant substrate(s) responsible for the high thromboembolic

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burden in critically unwell COVID-19 patients. A number of case reports investigating off-label administration of fibrinolytics (tissue plasminogen activator) in COVID-19 associated ARDS [30] prompted the randomised, controlled phase IIa clinical trial "STudy of Alteplase for Respiratory failure in SARS-Cov2/COVID-19"[31] which aims to test systemic administration of fibrinolytic therapy with tissue plasminogen activator (tPA; Alteplase) versus standard of care for patients infected with COVID-19 resulting in severe respiratory failure. The results are anticipated in the near future and the secondary outcome measure of in-hospital coagulation-related events may provide insight into tPA as a potential therapeutic option in instances of "fibrinolytic shutdown" in patients that may benefit from this targeted therapeutic approach.

5. Conclusions

Severity of COVID-19 illness is associated with the degree of coagulation system activation with a high incidence of thromboembolic complications contributing to morbidity and mortality. The coagulopathy of this disease process appears to be insufficiently represented with often normal conventional coagulation test parameters. Whilst not the perfect substitute for in vivo coagulation, studies utilising rotational thromboelastometry assays in COVID-19 patients have demonstrated increased maximum clot firmness (consistent with hyper-coagulability) and reduced maximum lysis (consistent with "fibrinolytic shutdown"). Precisely how these coagulation abnormalities can be modified by optimum, individualised medical interventions to improve clinical outcome, however, remains unclear. It is hoped that the upcoming publication of results from several ongoing clinical trials may shed some slight on this complex matter.

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