Research paper

Evaluation of coagulation status using viscoelastic testing in intensive care patients with coronavirus disease 2019 (COVID-19): An observational point prevalence cohort study

Luke Wallace Collett, MBBS, FCICM [a, b]
Samuel Gluck, BA, MA, MB, BChir, MRCoA (UK) [a, b, *]
Richard Michael Strickland, MBBS, FACEM, JFICM [a, b]
Benjamin John Reddi, MB ChB, FCICM [a, b]

[a] Intensive Care Unit, Royal Adelaide Hospital, Adelaide, SA, Australia
[b] School of Acute Medicine, University of Adelaide, Adelaide, SA, Australia

ARTICLE INFORMATION

ABSTRACT

Background: Coronavirus Disease-19 (COVID-19) is associated with a high rate of thrombosis, the pathophysiology of which is not well defined. Viscoelastic testing may identify and characterise hypercoagulable states which are not apparent using conventional coagulation assays.
Objectives: The objective of this study was to undertake viscoelastic evaluation of the coagulation state in critically ill adults with COVID-19—associated respiratory failure
Methods: This was a single-centre observational point prevalence cohort study of adults with COVID-19—associated respiratory failure requiring respiratory support in the intensive care unit. Coagulation status was evaluated using rotational thromboelastometry (ROTEM®) in conjunction with laboratory markers of coagulation.
Results: Six patients fulfilled inclusion criteria. Each patient had one ROTEM® performed. All patients had supranormal clot amplitude at 10 min (A10) and supranormal clot firmness (maximal clot firmness) measured in at least one ROTEM® pathway, and five were supranormal on all pathways. Minimal clot lysis was present on all analyses. Fibrinogen and D-dimer were elevated and routine markers of coagulation within normal ranges in all patients.
Conclusion: Patients with COVID-19—associated respiratory failure admitted to the intensive care unit exhibit a hypercoagulable state which is not appreciable on conventional tests of coagulation. Supranormal clot firmness, minimal fibrinolysis, and hyperfibrinogenaemia are key findings. Further research is required into the pathophysiology of this hypercoagulable state, as well as the harms and benefits of different anticoagulation strategies.

Crown Copyright © 2020 Published by Elsevier Ltd on behalf of Australian College of Critical Care Nurses Ltd. All rights reserved.

1. Introduction

Our understanding of the mechanisms by which the novel SARS-coronavirus-2, the virus causing coronavirus disease-2019 (COVID-19), causes organ failure and death continues to evolve. Several lines of investigation implicate a procoagulant tendency associated with COVID-19 which leads to microvascular and macrovascular thrombosis. Clinical reports of disproportionate rates of venous and arterial thromboembolism[1] are corroborated by histological evidence of thrombotic microangiopathy in postmortem studies of patients dying from COVID-19.[2] Intravascular thromboses can lead to local ischaemia, microhemorrhage, and inflammation which, in the lung, is consistent with the observations that a subset of patients exhibit profound hypoxia with relatively preserved lung

* Corresponding author at: Intensive Care Unit, Royal Adelaide Hospital, Adelaide, SA, Australia.
E-mail addresses: Luke.Collett@sa.gov.au (L.W. Collett), samuel.gluck@sa.gov.au (S. Gluck), Richard.Strickland@sa.gov.au (R.M. Strickland), Benjamin.Reddi@sa.gov.au (B.J. Reddi).

Table 1
Demographics (n = 6).

Demographics (n = 6)	Median [IQR]
Age	69 [64.2 to 73]
Male, n (%)	5 (83)
LOS ICU at the time of testing (days)	14 [10 to 15]
APACHE II at admission	43 [41 to 49.5]
APACHE II for 24 h before testing	75.5 [65.75 to 105.5]
SOFA ex GCS	7.5 [6.25 to 11.75]
Ventilated, n (%)	5 (83)
RRT, n (%)	2 (33)
ECMO, n (%)	0 (0)

APACHE II = Acute Physiology, Age and Chronic Health Evaluation II; ECMO = extracorporeal membrane oxygenation; GCS = Glasgow Coma Score, ICU = intensive care unit; LOS = length of stay; RRT = renal replacement therapy; SOFA = Sequential Organ Failure Assessment on the day of testing; IQR = interquartile range.

compliance.[3] Furthermore, thrombotic microangiopathy could underlie the acute kidney injury which affects up to 25.2% of patients with COVID-19 admitted to intensive care units (ICUs).[4]

Rotational thromboelastometry (ROTEM®) and thromboelastography (TEG) are viscoelastic point-of-care tests which provide functional analysis of clot development and fibrinolytic function. In addition to their role in bleeding,[5] they are able to identify a variety of patient populations at increased risk of thromboembolic events.[6] We undertook an observational cohort study to evaluate the coagulation state, as defined by viscoelastic testing, in patients admitted to the ICU requiring respiratory support for COVID-19–associated lung disease. Our objective was to identify whether these patients exhibited a procoagulant state.

2. Methods

We undertook a single-centre observational point prevalence cohort study in the 43 bed Intensive Care Unit of the Royal Adelaide Hospital, a metropolitan tertiary centre and South Australian designated hospital for COVID-19 in April 2020. Local ethics approval was granted, and waiver of consent obtained (Central Adelaide Local Health Network Human Research Ethics Committee

Reg 13102). All patients >18 y old with COVID-19–associated respiratory failure admitted to the ICU were identified using our electronic medical record (Sunrise, Allscripts, USA) from which demographic and clinical data were derived. Diagnosis of SARS-CoV-2 was performed with reverse transcription polymerase chain reaction (RT-PCR) from throat or nasal swab. The Sequential Organ Failure Assessment score was calculated as previously described[7], with neurological component excluded owing to limitations in performing this in the sedated patient. Peripheral (arterial) blood was analysed by ROTEM® (ROTEM® Sigma - Tem Innovations GmbH, Germany). EXTEM, INTEM, and FIBTEM pathways, representing contact pathway, tissue factor pathway, and fibrinogen component, respectively,[8] were analysed. Contemporaneous laboratory markers of coagulation and relevant blood pathology were recorded. Presence of lupus anticoagulant (LAC) was identified with dilute Russell's viper venom time and sensitive activated partial thromboplastin time tests. Patient records were reviewed 30 days after ICU discharge to determine the incidence of detected thromboembolic disease. Data are described using simple summary statistics using Stata, version 15.1 (StataCorp, College Station, TX, USA).

3. Results

Six patients met the study inclusion criteria during the study period. Demographic and clinical information are summarised in Table 1. Renal dialysis was provided through prolonged intermittent renal replacement therapy, with sessions complete for >6 h before blood sampling. Three patients were treated with prone positioning for respiratory failure, and no patients received pulmonary vasodilator therapy or extracorporeal membrane oxygenation. All patients were receiving thromboprophylaxis with 40 mg of enoxaparin administered subcutaneously daily. Each patient had one ROTEM® performed. ROTEM® and laboratory results are presented in Table 2. A representative ROTEM® from our cohort is presented in Fig. 1.

The most salient findings are the supranormal clot amplitude at 10 min and supranormal clot firmness in all analyses. In addition, the INTEM clot formation time was significantly reduced. Clot lysis

Table 2
Results.

Coagulation profile		Outside range, n (%)	Median [IQR]	Normal range
EXTEM	A10 (mm)	5/6 > NR (83)	70 [68.25 to 74.75]	43–63 mm
	CFT (s)	2/6 <NR (33)	48.5 [41 to 60.5]	46–149 s
	MCF (mm)	5/6 > NR (83)	74.5 [72.5 to 79.5]	55–72 mm
	ML (%)		1.5 [1 to 4.25]	0–15%
FIBTEM	A10 (mm)	6/6 > NR (100)	30.5 [28.25 to 40.25]	6–21 mm
	MCF (mm)	6/6 > NR (100)	38 [30.5 to 45.5]	6–21 mm
	ML (%)		0 [0 to 0]	0–15%
INTEM	A10 (mm)	5/6 > NR (83)	70.5 [66.25 to 71]	43–62 mm
	CFT (secs)	5/6 < NR (83)	39.5 [34.75 to 51]	62–130 s
	MCF (mm)	5/6 > NR (83)	75.5 [72.75 to 77.5]	51–69 mm
	ML (%)		0.5 [0 to 1.75]	0–15%
D-dimer (mg/L)			6.1 [2.585 to 9.66]	0–0.59 mg/L
PT (s)			14.7 [14.075 to 14.925]	12–16 s
INR			1.1 [1.025 to 1.1]	0.9–1.2
aPTT (s)			34 [30.25 to 43.75]	24–38 s
Fibrinogen (g/L)			7.5 [7.205 to 8.075]	1.5–4 g/L
Platelets x 10^9/L			290.5 [213 to 338]	150–450 × 10^9/L
ATIII (%)			83 [73.25 to 83.75]	80–125%
PrC (%)			113 [100.5 to 122.5]	65–130%
PrS (%)			122 [108 to 143.5]	65–155%
Lupus anticoagulant (dRVVT) n = 5 (secs)			6.1 [2.585 to 9.66]	31–51 s

A10 = maximum clot amplitude at 10 min; aPTT = activated partial thromboplastin time; ATIII = antithrombin III; CFT = clot formation time; dRVVT = Dilute Russell's viper venom time; INR = international normalised ratio; MCF = maximum clot firmness; ML = lysis index; PrC = protein C; PrS = protein S; PT = prothrombin time; IQR = interquartile range.
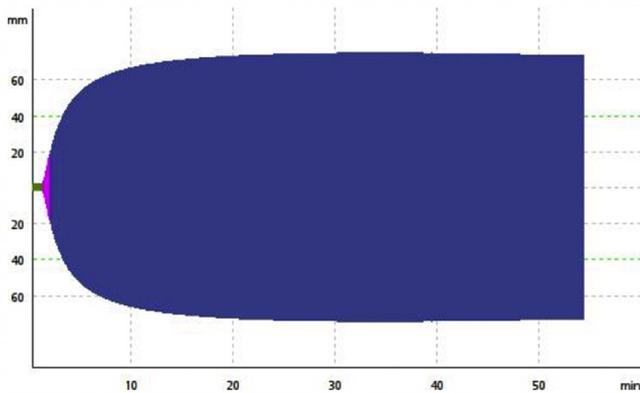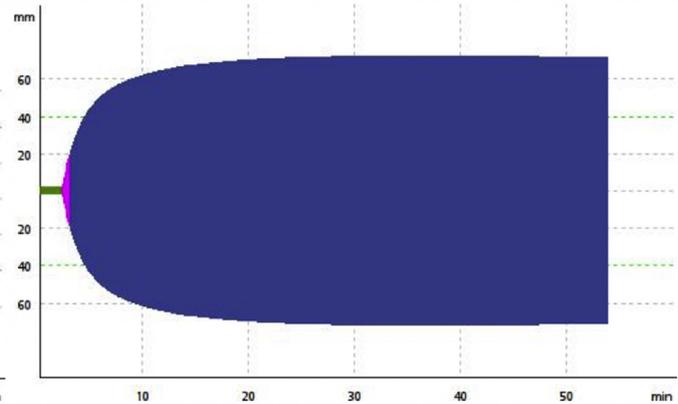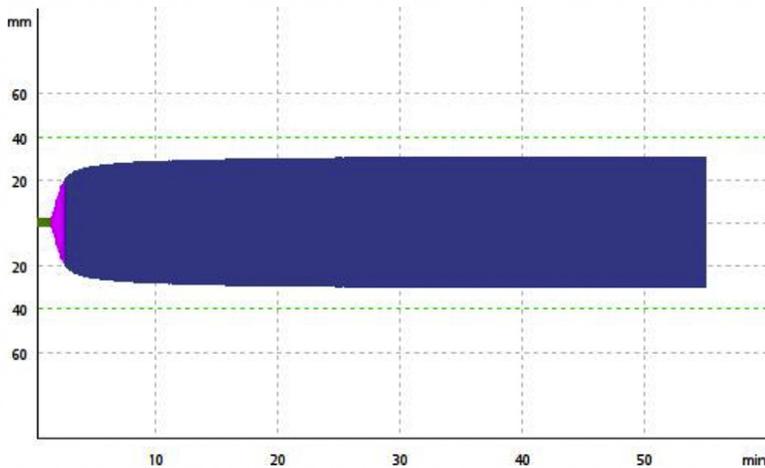
EXTEM

INTEM

FIBTEM

Fig. 1. ROTEM® from a representative patient. ROTEM® = rotational thromboelastometry.

was minimal (median <2%) in all analyses. In contrast, traditional coagulation parameters (prothrombin time, international normalised ratio, activated partial thromboplastin time, and platelet count) were within normal limits other than elevated fibrinogen and D-dimer. Endogenous anticoagulant proteins (antithrombin III, protein C, and protein S) were within normal range.

No patient had known arterial or venous thrombosis at the time of the study. Two patients later developed venous thromboembolism, one with pulmonary embolism, who underwent no deep vein thrombosis screening, and one with catheter-associated jugular vein thrombus. Both survived. A third patient died in the ICU, with venous thromboembolism not clinically suspected. The other three

patients were discharged from our hospital alive without identified thromboembolic disease, including one with a negative dedicated computed tomography pulmonary arteriography scan before hospital discharge.

4. Discussion

Our data indicate that patients with COVID-19 admitted to the ICUs exhibit a prothrombotic tendency as evaluated by viscoelastic testing of clot formation. These data are consistent with both the clinical observation that thromboembolic disease is overrepresented in patients with COVID-19 and histological evidence

of thrombotic microangiopathy in nonsurvivors of COVID-19. In patients with COVID-19, there is early limited evidence of a pro-coagulant pattern on ROTEM®[9,10] and TEG[11,12] that appears to be persistent beyond admission. This procoagulant pattern is not commonly found in other groups of critically ill patients.[13—15]

Our cohort had been admitted to the ICU for a median of 14 days at the time of testing. This is the first study to evaluate for a pro-thrombotic state this late in intensive care admission, and our findings suggest that thromboembolic complications should be considered as a cause of clinical deterioration throughout the ICU admission and potentially beyond.

Virus-associated procoagulant phenotypes have been noted previously in severe acute respiratory syndrome-1 and Middle Eastern respiratory syndrome coronavirus infections[16] although mechanisms remain unclear. Viral endotheliitis has been postu-lated, but the ROTEM® evaluation indicates that the procoagulant state is not dependent on an activated endothelial surface. COVID-19 has been associated with a hyperinflammatory state,[17] which may directly contribute to hypercoagulability.

Depression of fibrinolysis, identified by failure of clot lysis at 30 min on TEG, has been described in selected patients with severe COVID-19 infection in a single-centre study, with strong correlation to thromboembolic events and renal injury.[18] Our study identified similar results in unselected ICU patients, demonstrating that a persistent reduction in fibrinolysis and elevation in D-dimer was present throughout a small general COVID-19 ICU cohort, adding weight to this mechanism contributing to the increased thrombotic state of COVID-19.

Traditional clotting parameters were normal, consistent with findings from other studies.[10] We did not measure factor VIII levels, but it has been previously shown that these are elevated in COVID-19—infected ICU patients.[12] Importantly, endogenous antith-rombotic proteins such as antithrombin III and proteins C and S were not significantly altered. To our knowledge, this is the first study where these endogenous proteins have been measured in COVID-19 and suggests that deficiencies in these counter-regulatory proteins do not underlie the clotting tendency identi-fied in these patients.

Positive LAC has previously been described[19,20] in a large proportion of patients. In contrast, antiphospholipid antibodies were absent in the five patients assayed in our cohort. It is un-clear whether this is due to the small numbers in our study, differences in assays, or differences in timing of test performance. Of note, our tests were performed relatively late in the hospital presentation, and LAC can be transiently positive in acute viral infection.[21]

Our study has several limitations. Ours is a small, single-centre study, and findings can only be considered hypothesis generating, requiring validation in a larger multicentre cohort. The absence of a control group limits interpretation of our results; potential con-founders include prolonged critical illness, immobility, and co-morbidity. Our rate of thromboembolic disease was 33%, lower than reported in some other studies.[1,19] Routine imaging surveillance for deep vein thrombosis was not undertaken, in keeping with our standard practice before the COVID-19 pandemic and also in light of the potential risks of healthcare worker exposure to patients with COVID-19, potentially explaining why the detected incidence ap-pears low.

Future research priorities include (i) mapping changes in thrombotic tendencies over time, (ii) identifying efficacy and safety of anticoagulation strategies, and (iii) better understanding of the pathogenetic mechanisms of the prothrombotic state induced by SARS-CoV-2 and potentially other coronaviruses.

5. Conclusion

Patients with COVID-19—associated respiratory failure admitted to the ICU have a high prevalence of a hypercoaguable state which is not appreciable on conventional tests of coagulation. This is not explained by alterations in endogenous anticoagulant proteins or LAC. Supranormal clot firmness, minimal fibrinolysis, and hyper-fibrinogenaemia are key findings, and further research is required into the drivers of these markers, as well as the influence of anti-coagulant therapies on the prothrombotic state and patient outcomes.

Funding

Conflict of Interest

None of the authors have any interests to declare.

CRediT authorship contribution statement

Collett - conceptualisation, methodology, formal analysis, investigation, data curation, writing — original draft, writing — final draft.

Gluck - conceptualisation, methodology, investigation, data curation, writing — original draft.

Strickland - conceptualisation, methodology, investigation, data curation, writing — original draft.

Reddi - conceptualisation, methodology, formal analysis, investigation, data curation, writing — original draft, writing — final draft, Supervision.

References

[1] Klok FA, Kruip M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. Thromb Res 2020;191:148—50.

[2] Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in covid-19. N Engl J Med 2020;383:120—8.

[3] Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med 2020;46(6):1099—102.

[4] Centre ICNAaR. ICNARC report on COVID-19 in critical care. 2020.

[5] Wikkelsø A, Wetterslev J, Møller AM, Afshari A. Thromboelastography (TEG) or rotational thromboelastometry (ROTEM) to monitor haemostatic treatment in bleeding patients: a systematic review with meta-analysis and trial sequential analysis. Anaesthesia 2017;72:519—31.

[6] Harahsheh Y, Ho KM. Use of viscoelastic tests to predict clinical thrombo-embolic events: a systematic review and meta-analysis. Eur J Haematol 2018;100:113—23.

[7] Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. The SOFA (Sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related prob-lems of the European society of intensive care medicine. Intensive Care Med 1996;22:707—10.

[8] Akay OM. The double hazard of bleeding and thrombosis in hemostasis from a clinical point of view: a global assessment by rotational thromboelastometry (ROTEM). Clin Appl Thromb Hemost Offic J Int Acad Clin Appl Thromb Hemost 2018;24:850—8.

[9] Spiezia L, Boscolo A, Poletto F, Cerruti L, Tiberio I, Campello E, et al. COVID-19-Related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. Thromb Haemost 2020;120:998−1000.

[10] Pavoni V, Gianesello L, Pazzi M, Stera C, Meconi T, Frigieri FC. Evaluation of coagulation function by rotation thromboelastometry in critically ill patients with severe COVID-19 pneumonia. J Thromb Thrombolysis 2020;50:281−6.

[11] Ranucci M, Ballotta A, Di Dedda U, Bayshnikova E, Dei Poli M, Resta M, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J Thromb Haemostasis 2020;18(7):1747−51.

[12] Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangkul V, et al. Hypercoagulability of COVID-19 patients in intensive care unit. A report of thromboelastography findings and other parameters of hemostasis. J Thromb Haemostasis 2020;18(7):1738−42.

[13] Schött U, Larsson A. ROTEM: multiplate monitoring in the ICU and outcome scores. Crit Care 2014;18:P93.

[14] Crochemore T, Corrêa TD, Lance MD, Solomon C, Neto AS, Guerra JCC, et al. Thromboelastometry profile in critically ill patients: a single-center, retrospective, observational study. PloS One 2018;13:e0192965.

[15] Müller MC, Meijers JC, Vroom MB, Juffermans NP. Utility of thromboelastography and/or thromboelastometry in adults with sepsis: a systematic review. Crit Care 2014;18:R30.

[16] Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. J Clin Virol 2020;127:104362.

[17] Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;20(6):355−62.

[18] Wright FL, Vogler TO, Moore EE, Moore HB, Wohlauer MV, Urban S, et al. Fibrinolysis shutdown correlates to thromboembolic events in severe COVID-19 infection. J Am Coll Surg 2020;231(2):193−203.

[19] Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020;46(6):1089−98.

[20] Harzallah I, Debliquis A, Drenou B. Lupus anticoagulant is frequent in patients with Covid-19. J Thromb Haemost 2020. https://doi.org/10.1111/jth.14867. Online ahead of print.

[21] Abdel-Wahab N, Talathi S, Lopez-Olivo MA, Suarez-Almazor ME. Risk of developing antiphospholipid antibodies following viral infection: a systematic review and meta-analysis. Lupus 2018;27:572−83.