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Thromboelastography demonstrates progressive hypercoagulability in COVID-19 patients admitted to ICU with respiratory failure

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Abstract

Thromboembolic complications are associated with COVID-19 owing to the hypercoagulable nature of the disease. Although patients with COVID-19 often have higher levels of fibrinogen and D-dimers, hypercoagulability has been attributed to various other factors too. In this prospective observational study conducted between April 2020 and June 2020, we compared coagulation parameters using thromboelastography in COVID-19 patients to non-COVID-19 patients admitted to ICU with respiratory failure. This study demonstrated a significant difference between the cohorts in functional fibrinogen (CFF) progressively from third day of ICU admission whilst there was no difference in the Clauss fibrinogen levels. COVID-19 patients also demonstarted supranormal R time indicating hypocoagulability. These mixed coagulation changes suggest targeting fibrinogen or platelets may prevent thromboembolic complications in COVID-19.

Keywords

COVID-19, Thromboelastography

Introduction

Hypercoagulability in COVID-19 is multifactorial involving increased thrombin generation, inhibition of thrombolysis, platelet hyperactivity and complement activation.[1,2] Thromboembolic complications are associated with increased mortality in COVID-19 and have been attributed to a virally induced hypercoagulable state.[3,4] Conventional coagulation tests (PT, INR, aPPT) are unable to detect hypercoagulability. We aimed to assess coagulation changes in patients admitted to the Intensive Care Unit (ICU) with COVID-19 compared to those with non-COVID-19 induced lower respiratory tract infections with similar clinical presentation using thromboelastography.

Methods

Ethical approval and the need for written consent were waived by the Trust Research and Development Department. Adult patients admitted to the Royal Free Hospital ICU between April 21st and June 8th, 2020 with a primary diagnosis of type I respiratory failure due to lower respiratory tract infection were included in this prospective observational study. Patients were considered COVID-19 positive if they had either a positive SARS-CoV-2 PCR or radiological features strongly suggestive of COVID-19 on chest computed tomography reported by consultant radiologist. Blood samples for thromboelastography and conventional clotting assays were taken on days 1, 3, 5 and 8 of the ICU stay. Thromboelastography (TEG) was performed using global haemostasis cartridges (TEG®6s, Haemonetics©) that incorporate citrated kaolin (CK), kaolin with heparinase (CKH), rapid TEG and functional fibrinogen (CFF). Data was collected prospectively and analysed using GraphPad Prism 8.4.3 (GraphPad Software, San Diego, USA).

Results

Data were collected on 24 adult patients. Fourteen patients were COVID-19 positive. Demographic characteristics, baseline admission laboratory tests, pre-admission anticoagulation and anticoagulation

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Table 1. Baseline demographic and admission laboratory data in COVID-19 positive and negative patients.

	COVID-19 positive	COVID-19 negative	
	N = 14	N = 10	P value
Age in years, mean (±SD)	55.64 (11.90)	53.40 (20.35)	0.737
BMI kg/square meter, median (IQR)	27.34 (4.75)	26.59 (4.52)	0.676
Male, n (%)	8 (57.14)	5 (50)	1.000
Caucasian, n (%)	5 (35.71)	6 (60)	0.408
Fully independent at admission, n (%)	12 (85.71)	7 (70)	0.615
Haemoglobin, g/L, mean (±SD)	110.10 (26.60)	101.80 (29.96)	0.488
White cell count, 10^9/L, median (IQR)	8.97 (12.14)	11.18 (6.78)	0.518
Neutrophils, 10^9/L, median (IQR)	7.31 (11.45)	9.62 (4.27)	0.341
Lymphocytes, 10^9/L, median (IQR)	0.89 (0.51)	0.77 (0.53)	0.428
C reactive protein, mg/L, median (IQR)	119 (121)	115 (246)	0.546
Procalcitonin, μg/L, median (IQR)	1.14 (3.99)	0.77 (36.93)	0.821
Creatinine, μmol/L, median (IQR)	89.50 (80.25)	154 (230.50)	0.118
eGFR, ml/min median (IQR)	82 (48.75)	57 (57.00)	0.177
Ferritin, μg/L, median (IQR)	564 (692.50)	254 (969.25)	0.159
Troponins, ng/L, median (IQR)	49.50 (90.25)	82.50 (196.50)	0.108
NT-proBNP, ng/L, median (IQR)	1259 (4513)	3153 (10093)	0.397
Hypertension, n (%)	7 (50)	2 (20)	0.210
Diabetes mellites, n (%)	6 (42.86)	2 (20)	0.388
Heart disease, n (%)	3 (21.43)	4 (40)	0.393
Chronic respiratory disease, n (%)	4 (28.57)	2 (20)	1.000
Chronic kidney disease, n (%)	1(7.14)	1 (10)	1.000
Chronic liver disease, n (%)	2 (14.29)	0 (0)	0.493
Long term anticoagulation, n (%)	1 (7.14)	1 (10)	1.000
Antiplatelet agents, n (%)	5 (35.71)	2 (20)	0.653
Prophylactic anticoagulation since admission, n (%)	7 (50)	8 (50)	0.210
Treatment dose anticoagulation, n (%)	6 (42.86)	1 (10)	0.172

Data shown as mean ± s.d., median [IQR] or n (%).

Table 2. Thromboelastography TEG®6s assays and conventional laboratory coagulation tests in COVID-19 positive and negative patients.

		COVID-19 positive	COVID-19 negative	
		N = 14	N = 10	P value
TEG CFF MA (normal range 15–32)	Day 1	39.4 (25.60–46.28)	31.0 (20.75–35.35)	0.125
	Day 3	41.2 (38.78–49.65)	31.2 (25.50–44.00)	0.046*
	Day 5	45.5 (43.40–50.30)	34.7 (19.65–38.35)	0.009**
	Day 8	47.7 (38.65–50.85)	32.3 (10.63–33.05)	0.054
TEG CKH R time (normal range 4.3–8.3)	Day 1	9.1 (7.47–15.55)	7.9 (6.27–9.50)	0.374
	Day 3	9.1 (7.72–10.42)	8.3 (7.17–12.08)	0.492
	Day 5	9.3 (7.00–10.30)	9.7 (7.55–11.55)	0.681
	Day 8	9.7 (6.22–11.98)	7.0 (6.62–9.32)	0.558
TEG CKH α angle (normal range 64.3–77.1)	Day 1	74.7 (70.13–78.03)	69.8 (46.35–76.00)	0.175
	Day 3	75.7 (71.65–77.25)	72.5 (63.90–76.80)	0.498
	Day 5	77.7 (74.40–79.80)	71.1 (61.80–76.45)	0.095
	Day 8	77.9 (67.50–79.03)	76.6 (60.50–78.83)	0.839
TEG CKH MA (normal range 52.3–68.9)	Day 1	67.2 (62.20–68.95)	65.2 (58.25–67.50)	0.328
	Day 3	68.9 (67.70–70.20)	62.5 (57.90–68.70)	0.026*
	Day 5	69.3 (68.00–70.70)	68.0 (50.40–69.05)	0.108
	Day 8	69.5 (66.95–72.30)	67.2 (46.48–69.38)	0.186
TEG CK R time (normal range 4.6–9.1)	Day 1	10.5 (9.15–17.30)	8.8 (6.75–10.70)	0.128
	Day 3	10.6 (8.22–13.00)	7.9 (7.00–13.50)	0.488
	Day 5	9.9 (7.20–12.00)	10.2 (7.25–14.25)	0.722
	Day 8	9.0 (5.70–20.73)	6.5 (5.87–8.52)	0.436
TEG CK α angle (normal range 63–78)	Day 1	72.6 (65.15–76.18)	67.2 (61.65–75.40)	0.723
	Day 3	74.2 (60.63–76.78)	71.7 (66.30–77.30)	0.975

(continued)

Table 2. Continued.

		COVID-19 positive	COVID-19 negative	
		N = 14	N = 10	P value
	Day 5	71.0 (50.50–78.20)	70.4 (65.25–75.80)	0.743
	Day 8	76.9 (57.90–78.65)	75.4 (64.93–78.23)	0.945
TEG CK MA (normal range 52–69)	Day 1	65.0 (61.20–68.73)	64.6 (58.70–68.45)	0.632
	Day 3	68.9 (66.83–70.93)	64.6 (57.90–69.30)	0.105
	Day 5	68.5 (66.30–70.30)	66.4 (50.3–67.90)	0.170
	Day 8	68.7 (64.33–70.55)	66.7 (46.85–68.40)	0.240
TEG CK Ly30 (normal range 0–2.6)	Day 1	0.2 (0.00–0.62)	0.2 (0.00–0.92)	0.971
	Day 3	0.1 (0.00–0.92)	0.0 (0.00–1.10)	0.924
	Day 5	0.0 (0.00–0.40)	0.2 (0.00–3.10)	0.614
	Day 8	0.0 (0.00–0.25)	0.3 (0.05–0.80)	0.231
Platelets (normal range 150–450 $\times$ 10^9/L)	Day 1	235.3 (81.10)	192.6 (94.09)	0.247
	Day 3	227.8 (94.72)	183.1 (106.60)	0.321
	Day 5	278.2 (128.50)	253.1 (142.80)	0.681
	Day 8	322.5 (143.20)	328.8 (202.00)	0.939
INR (normal range 1.0–1.3)	Day 1	1.1 (1.07–1.22)	1.2 (1.10–1.30)	0.209
	Day 3	1.0 (1.00–1.10)	1.1 (1.00–1.17)	0.767
	Day 5	1.1 (1.00–1.10)	1.0 (1.00–1.30)	0.792
	Day 8	1.1 (1.00–1.10)	1.1 (1.05–1.30)	0.792
aPTT (normal range 22–36)	Day 1	48.3 (42.05–52.15)	37.2 (32.53–46.05)	0.081
	Day 3	40.6 (37.80–44.70)	38.1 (32.63–48.10)	0.960
	Day 5	39.6 (36.3–43.10)	29.2 (28.30–42.10)	0.211
	Day 8	36.3 (33.80–47.50)	29.0 (28.30–39.30)	0.267
Clauss fibrinogen (normal range 1.5–4.5 g/L)	Day 1	5.8 (4.67–6.25)	4.4 (2.95–6.07)	0.149
	Day 3	6.2 (5.70–6.52)	6.2 (4.02–6.55)	0.881
	Day 5	6.0 (5.40–6.90)	5.2 (3.90–6.90)	0.264
	Day 8	5.3 (4.80–6.60)	5.6 (2.60–6.00)	0.422
D–dimer (normal range < 500 μg/L)	Day 1	1779 (711–3924)	6047 (1405–13809)	0.056
	Day 3	1980 (1032–4222)	3511 (1594–7646)	0.210
	Day 5	1678 (980–5797)	3534 (1412–12596)	0.289
	Day 8	2095 (994–6580)	1809 (1556–59831)	0.555

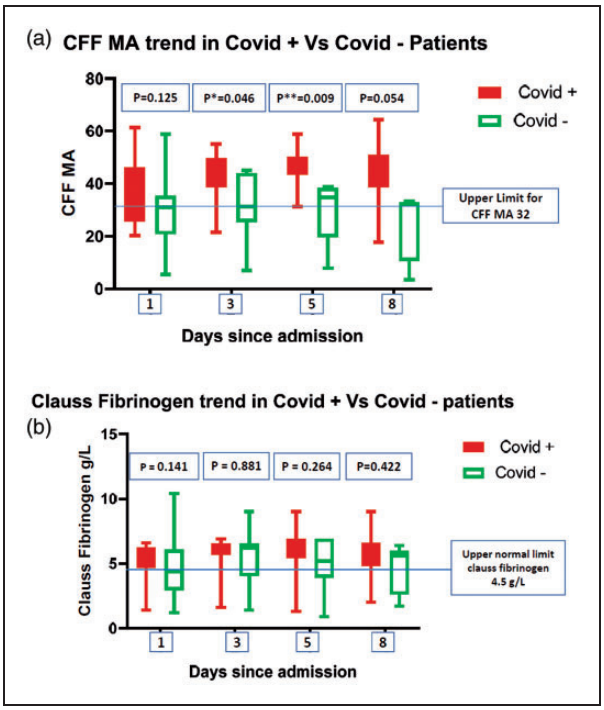

Figure 1. Comparision of trends in Functional Fibrinogen (CFF) and Clauss Fibrinogen in COVID-19 positive and COVID-19 negative patients.

during ICU admission were comparable between patients with and without COVID-19. (Table 1)

The CKH maximum amplitude (MA) was normal on admission in both cohorts and, while it remained normal in negative patients, in positive patients the MA subsequently became supranormal and was significantly higher than non-COVID-19 patients on day 3 (68.9 vs. 62.5, p = 0.026, Table 2). The CFF MA in COVID-19 patients was supranormal and increased throughout the ICU stay, while in COVID-19 negative patients the CFF MA remained stable at the upper limit of the normal range (Figure 1 and Table 2). There was no statistical difference in the median CFF MA on day 1 between the two cohorts (39.4 vs. 31.0, p = 0.125) however statistical significance was reached by day 3 (41.2 vs. 31.2, p = 0.046) and day 5 (45.5 vs. 34.7, p = 0.009). The CKH R time in COVID-19 patients was supranormal throughout the ICU stay, while it was normal in the non-COVID-19 group, although there was no significant difference.

Median Clauss fibrinogen was supranormal in both the groups during most of the ICU admission and there was no statistical difference between the groups (Figure 1 and Table 2). Median D-dimer

values were elevated in both the groups, although without significant difference. Mean platelet count, median INR and median aPTT in COVID-19 patients throughout the ICU stay were not significantly different to non-COVID-19 patients (Table 2).

Three out of 14 COVID-19 patients developed pulmonary emboli while none were observed in the COVID-19 negative group; there was no association with TEG or clotting results.

Discussion

This study revealed evidence of hypercoagulability in critically ill COVID-19 patients characterised by a supranormal clot strength and fibrinogen activity which increased with illness duration. Fibrinogen concentration did not differ between patient groups indicating a functional, rather than quantitative, hyperfibrinogenaemia in COVID-19 patients. Additionally, a clotting factor deficiency or dysfunction was demonstrated through the prolonged R time.

Similar findings have previously been described in COVID-19 with raised fibrinogen, D-dimer, prothrombin time and lower antithrombin levels.[5] However, there has been little description of a hypocoagulable component to COVID-19 which is key as heparin-based anticoagulation is a mainstay in most ICUs but may be inappropriate in view of the elevated aPTT and R time described here. Furthermore, many centres base their anticoagulation strategies on D-dimer values, which were shown here to be lower in COVID-19 patients.

Additionally, while thromboelastography in COVID-19 patients has shown prothrombotic patterns compared to healthy cohorts,[6–8] there is insufficient data comparing thromboelastography in COVID-19 with non-COVID respiratory compromise which appear to drive different coagulopathies.

Conclusion

Thromboelastography can assess the prothrombotic state in COVID-19, unlike conventional clotting tests. The mixed coagulopathy described here with increased MA, functional fibrinogen and prolonged R time suggests targeting platelet or fibrinogen activity may help prevent thromboembolism. Further investigation is required to establish whether TEG can identify patients at risk of thromboembolic complications or help guide individualised anticoagulation strategies.

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Declaration of conflicting interests

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