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RESEARCH LETTER

Systemic Inflammatory Response Syndrome Is a Major Contributor to COVID-19–Associated Coagulopathy

Insights From a Prospective, Single-Center Cohort Study

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Coronavirus disease 2019 (COVID-19) is associated with a systemic coagulopathy[1] favoring thromboembolic complications, which occur in 15% to 30% of critically ill patients with COVID-19.[2,3] This coagulopathy remains poorly documented and data on thrombin generation and fibrinolysis are lacking.

We characterized the coagulation and fibrinolysis profiles of patients with COVID-19 with acute respiratory distress syndrome (ARDS).

From October 2019 to April 2020, 28 consecutive patients with severe ARDS were referred to our tertiary intensive care unit and included in this prospective single-center cohort study. The protocol was approved by a research ethics committee (CPP Ouest III, 2019-A01160-57), and the study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from patients or their relatives. Blood samples were collected on admission for a comprehensive coagulation/fibrinolytic pathways analysis. To better assess the in vivo dynamics of clot formation, stabilization, and lysis, we used a global coagulation assay assessing changes in viscoelastic properties of whole blood.

We compared 11 patients with ARDS included before the COVID-19 pandemic (influenza pneumonia, n=4; bacterial pneumonia, n=2; other causes of ARDS, n=5) with 17 patients with COVID-19. Baseline characteristics of the patients with and without COVID-19 did not differ and are presented in the Table. Briefly, the median age was 45 years; most patients were men (68%), overweight (32.1%), or obese (57.1%); and a few of them had additional comorbidities. On admission, all patients were receiving thromboprophylaxis according to current guidelines. Pulmonary embolism was incidentally diagnosed in 3 out of 17 patients with COVID-19. Coagulation and fibrinolysis profiles are presented in the Table.

In addition, von Willebrand factor antigen and activity did not differ between groups and were 3- to 4-fold higher than the upper limit of normal range (median, 4.44 and 2.86 IU/mL, respectively, in the overall population). Compared with patients without COVID-19, patients with COVID-19 exhibited significantly higher levels of procoagulant factors, mainly fibrinogen (median, 810 mg/dL versus 710; P=0.03), factor V (median, 1.53 IU/mL versus 0.73; P<0.0001), factor VIII (median, 2.97 IU/mL versus 1.61; P=0.03), and acute phase reactants including C-reactive protein (P=0.05) and α1-acid glycoprotein (P=0.02). All of these measures were strongly correlated with each other (P<0.05 for all correlations). In contrast, antithrombin, protein C, and protein S levels were within the normal range and did not differ between groups. Prothrombin fragment 1 and 2 levels did not differ between patients with and without COVID-19 and were 2- to 3-fold higher than the upper limit of normal range. Thrombin–antithrombin complex levels were increased in both groups but significantly lower in patients with COVID-19 (median, 7.69 μg/L versus 22.63; P=0.03). Fibrinolysis profiles showed factor XIII, plasminogen, and α2-antiplasmin activities within the normal range in both groups, whereas tissue

Key Words: COVID-19 ■ respiratory distress syndrome, adult ■ systemic inflammatory response syndrome

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Table. Main Clinical and Biological Characteristics of Patients With and Without COVID-19 With Severe Acute Respiratory Distress Syndrome on Admission

Variables	Normal Range	Overall Population (n=28)	Non–COVID-19 Acute Respiratory Distress Syndrome (n=11)	COVID-19 Acute Respiratory Distress Syndrome(n=17)	*P* Value
Clinical characteristics					
Age, y	—	45 (33–56)	34 (28–55)	48 (42–58)	NS
Male	—	19 (68)	7 (64)	12 (71)	NS
Body mass index, kg/m^2	—	30.5 (28–35.75)	29.3 (26–35)	31.0 (28.8–40.5)	NS
Obesity	—	16 (57.1)	5 (45.5)	11 (64.7)	NS
Current smoker	—	2 (7)	2 (18)	0 (0)	NS
CCI	—	1 (0–1.75)	1 (0–2)	1 (0.5–1.5)	NS
SOFA score	—	11 (8–17)	9 (7–17)	12 (9–17)	NS
SAPS-II score	—	52 (42 –69)	57 (37–81)	52 (43–63)	NS
ISTH DIC score	—	4 (14)	4 (36)	0 (0)	0.0161
Pao_2/FiO_2, mm Hg	—	59 (47–70)	64 (50–77)	57 (47–66)	NS
$PaCO_2$, mm Hg	—	56 (47–61)	56 (48–60)	56 (47–62)	NS
pH	—	7.32 (7.22–7.38)	7.32 (7.20–7.35)	7.33 (7.23–7.38)	NS
Biomarkers of inflammatory response and tissue damage					
C-reactive protein, mg/L	<5	272.3 (128.6–364.2)	136.2 (92.42–314.7)	320.2 (158.7–367.3)	0.05
α1-acid glycoprotein, g/L	0.5–1.2	2.272 (1.933–2.731)	2.123 (1.914–2.255)	2.508 (1.909–3.196)	0.0228
Ferritin, ng/mL	10–250	—	—	2001 (1274–2987)	—
Lactate dehydrogenase, IU/L	140–245	531.5 (431.3–828.8)	451.0(339.0–574.0)	606.0 (444.0–901.0)	NS
Complete blood count					
Hemoglobin concentration, g/L	120–160	96 (83–121)	110 (78–125)	92 (84–116)	NS
Leucocyte count (×10^9/L)	4–10	14.9 (10.8–19.3)	17.2 (9.1–24.3)	13.2 (10.6–16.4)	NS
Neutrophil count (×10^9/L)	2–2.75	11.3 (8.8–15.3)	15.2 (3.4–22.2)	10.8 (8.8–13.8)	NS
Lymphocyte count (×10^9/L)	1.5–4	0.85 (0.65–1.22)	1.05 (0.62–1.28)	0.78 (0.66–1.21)	NS
Platelet count (×10^9/L)	150–400	247 (199–277)	231 (160–245)	262 (224–334)	0.05
Standard coagulation parameters					
aPTT, s	30–39	43.5 (38.7–66.3)	52.7 (34.5–150.7)	42.4 (38.8–47.6)	NS
PT, s	11–13.5	15 (14.03–16.28)	16.30 (15.0–17.70)	14.90 (13.7–15.3)	NS
Fibrinogen, mg/dL	<400	770 (600–905)	710 (490–790)	810 (640–945)	0.0322
von Willebrand factor levels, IU/mL					
von Willebrand factor antigen	0.55–1.20	4.44 (3.38–5.20)	3.94 (3.28–4.90)	4.48 (3.62–5.29)	NS
von Willebrand factor activity	0.55–1.20	2.86 (1.73–3.51)	2.65 (1.67–3.71)	3.13 (1.90–3.47)	NS
Extrinsic pathway parameter, IU/mL					
Factor VII	0.70–1.20	0.89 (0.76–1.09)	0.60 (0.21–0.74)	0.84 (0.75–0.91)	0.0363
Intrinsic pathway parameters, IU/mL					
Factor VIII	0.60–1.20	2.49 (1.61–3.55)	1.61 (1.48–2.53)	2.97 (2.14–3.64)	0.0318
Factor IX	0.60–1.20	1.71 (1.21–2.14)	1.39 (0.96–2.19)	1.74 (1.31–2.13)	NS
Factor XI	0.60–1.20	1.17 (0.94–1.32)	1.08 (0.48–1.24)	1.21 (1.00–1.39)	NS
Factor XII	0.60–1.20	0.73 (0.38–0.93)	0.76 (0.25.0–98)	0.64 (0.39–0.92)	NS
Common pathway parameters, IU/mL					
Factor II	0.70–1.20	0.89 (0.76–1.04)	0.78 (0.71–0.89)	0.99 (0.87–1.12)	0.0084
Factor V	0.70–1.20	1.15 (0.76–1.60)	0.73 (0.42–0.91)	1.53 (1.22–1.72)	<0.0001
Factor X	0.70–1.20	1.02 (0.85–1.18)	0.83 (0.78–0.99)	1.15 (1.01–1.19)	0.0013
Coagulation inhibitors, IU/mL					
Antithrombin activity	0.80–1.20	0.71 (0.64–0.92)	0.70 (0.53–0.73)	0.83 (0.66–0.94)	NS

(*Continued*)

Table. Continued

	Normal Range	Overall Population (n=28)	Non–COVID-19 Acute Respiratory Distress Syndrome (n=11)	COVID-19 Acute Respiratory Distress Syndrome(n=17)	*P* Value
Protein C activity	0.70–1.40	0.88 (0.73–1.02)	0.90 (0.45–1.06)	0.86 (0.73–1.02)	NS
Protein S activity	0.55–1.20	0.52 (0.36–0.70)	0.52 (0.36–0.65)	0.57 (0.35–0.75)	NS
Markers of thrombin generation					
Prothrombin F1+2, pmol/L	69–229	715.3 (278.3–1019)	809.6 (162.8–1235)	500.3 (306.1–796.6)	NS
Thrombin–antithrombin complexes, µg/L	0–4.2	10.21 (4.81–38.55)	22.63 (10.44–104.9)	7.69 (3.80–23.92)	0.0385
Fibrinolysis parameters					
Factor XIII activity, IU/mL	0.70–1.40	0.72 (0.47–0.89)	0.74 (0.60–0.84)	0.72 (0.36–0.91)	NS
Plasminogen activity, IU/mL	0.80–1.40	1.22 (1.03–1.70)	1.10 (0.92–1.22)	1.36 (1.18–1.85)	0.0318
α2-Antiplasmin activity, IU/mL	0.80–1.40	1.35 (1.20–1.44)	1.31 (0.77–1.55)	1.36 (1.26–1.43)	NS
tPA antigen, ng/mL	1–12	36.2 (22.5–53.3)	26.3 (9.1–52.6)	37.8 (30.8–60.0)	0.0482
PAI-1 antigen, ng/mL	7–43	94.3 (60.1–119.1)	69.00 (38.8–126.8)	95.20 (74.5–118.7)	NS
Fibrin degradation products					
D-dimer, mg/L	<0.5	6.51 (3.65–14.38)	8.39 (5.33–11.18)	4.64 (3.20–20.0)	NS
Fibrin monomer, µg/mL	<5	6.12 (5.0–40.64)	14.93 (5.0–71.58)	5.0 (5.0–26.61)	NS
Coagulation profile assessed by viscoelastic tests*					
Clot time, s	113–164	147.0 (134.0–172.8)	137 (137–193)	152 (130–171)	NS
Heparinase clot time, s	109–150	130.0 (114.8–150.8)	130 (114–150)	130 (117–152)	NS
Clot time ratio	<1.2	1.1 (1.025–1.3)	1.1 (1.0–1.2)	1.1 (1.1–1.3)	NS
Clot stiffness, hPA	13.0–33.2	41.85 (24.83–65.0)	24.9 (20.2–42.0)	49.9 (38.5–68)	0.0077
Platelet contribution to clot stiffness, hPA	11.9–29.8	33.2 (20.13–48.80)	20.8 (17.9–33.6)	38.50 (28.85–51.2)	0.014
Fibrinogen contribution to clot stiffness, hPA	1.0–3.7	8.3 (5.6–16.7)	6.1 (4.0–8.2)	12.8 (6.35–20.85)	0.00051
Other procoagulants					
Lupus anticoagulant (dRVVT, number positive)	—	14 (50)	5 (45)	9 (53)	NS
Antiphospholipid antibodies IgM (number positive)†	—	15 (54)	8 (73)	9 (53)	NS
Antiphospholipid antibodies IgG (number positive)†	—	13 (46)	7(64)	6 (35.2)	NS
Antiplatelet factor 4/heparin antibodies (number positive)	—	0 (0)	0 (0)	0 (0)	NS

Categorical variables are reported as number (frequency) and continuous variables as median (interquartile range). Categorical variables were compared with the Fisher exact test and continuous variables with the nonparametric Mann-Whitney test. Spearman test was used to measure the strength of association between two variables. All statistical tests were 2-tailed, and a *P* value <0.05 was considered statistically significant. Statistical analysis was performed using GraphPad Prism version 8.4.2 for Windows (GraphPad Software, La Jolla, CA). aPTT indicates activated partial thromboplastin time; CCI, Charlson Comorbidity Index; COVID-19, coronavirus disease 2019; DIC, disseminated intravascular coagulation; dRVVT, dilute Russel's viper venom time; IgG, immunoglobulin G; IgM, immunoglobulin M; ISTH, International Society of Hemostasis and Thrombosis; NS, nonsignificant; PAI-1, plasminogen activator inhibitor-1; PT, prothrombin time; SAPS-II, Simplified Acute Physiology Score; SOFA, Sepsis-Related Organ Failure Assessment; and tPA, tissue plasminogen activator.

*Assessed using the Quantra Hemostasis analyzer (Quantra System, HemoSonics LLC, Charlottesville, VA) with the QPlus Cartridge.

†PHOSPO–LISA IgG/IgM (Theradiag; Marne-la-Vallée, France); includes antiphosphatidyl serin, antiphosphatidyl ethanolamine, anticardiolipin S, and antib2GP1 antibodies.

plasminogen activator and PAI-1 (plasminogen activator inhibitor-1) antigen levels were increased in both groups, with significantly higher tissue plasminogen activator values in patients with COVID-19 (median, 37.8 ng/mL versus 26.3; *P*=0.048). Tissue plasminogen activator and PAI-1 levels were closely correlated (*r*=0.65, *P*<0.001), and both measures correlated with lactate dehydrogenase levels (*P*=0.006 and *P*=0.03, respectively). Fibrin degradation products, including D-dimer and fibrin monomers, were similarly increased in both groups. None of the patients with COVID-19 presented disseminated intravascular coagulation. Compared with patients without COVID-19, patients with COVID-19 exhibited twice higher values of clot strength (median, 49.9 versus 24.9 hPa; *P*=0.0077), platelet contribution to clot strength (median, 38.5 versus

20.8 hPa; *P*=0.014), and fibrinogen contribution to clot strength (median, 12.8 versus 6.1 hPa; *P*<0.001). Clot strength was strongly correlated with fibrinogen (*r*=0.425, *P*=0.02), factor V (*r*=0.385, *P*=0.043), and factor VIII (*r*=0.497, *P*<0.001), but not with PAI-1 levels (*r*=–0.102; *P*=0.606). Antiphospholipid antibodies and lupus anticoagulant were found positive in almost half of patients, without difference between groups.

We observed that unlike non–COVID-19 ARDS, COVID-19 ARDS was associated with a significant increase in procoagulants, which closely correlates with the elevation of acute phase reactants. This led to a pronounced imbalance between procoagulants and anticoagulants and uncontrolled thrombin generation. Endothelial dysfunction, reflected by von Willebrand factor release, and hypoxia-mediated hypercoagulability also participate in the procoagulant state[1,4] but are nonspecific because they were observed in all patients with ARDS. In patients with COVID-19, tissue plasminogen activator and PAI-1 correlated with lactate dehydrogenase, suggesting a potential role of pulmonary endothelial cell dysfunction in the local regulation of coagulation/fibrinolysis balance and in situ pulmonary thrombosis. We did not observe any fibrinolysis shutdown. A role for antiphospholipid antibodies in COVID-19–associated coagulopathy has been suggested, but we observed a high frequency of antiphospholipid antibodies in all patients with ARDS.

We acknowledge that this study has several limitations, including its small sample size, its single-center design, the use of a single time point for biomarkers evaluation, and comparison between two groups of patients with ARDS who may have different clinical courses. Therefore, our results cannot be generalized to all patients with COVID-19.

In conclusion, our findings suggest that the systemic inflammatory response is a major contributor to COVID-19–associated coagulopathy, supporting the concept of thromboinflammation.[5]

ARTICLE INFORMATION

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Disclosures

None.

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