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Letter to the Editor

Pulmonary embolism among critically ill patients with ARDS due to COVID-19

To the editor,

Recent reports have suggested that patients with coronavirus disease 2019 (COVID-19) acute respiratory distress syndrome (ARDS) have high incidence of acute pulmonary embolism (APE) [1,2]. However, specific information characterizing these patients are scarce. We therefore aimed to investigate clinical, radiological and ventilation characteristics associated with APE among critically ill patients with COVID-19 ARDS.

All consecutive patients admitted between March 17 and April 5, 2020 in the ICUs at the Besançon University Hospital meeting the criteria of ARDS (Berlin definition) [3], with laboratory-confirmed SARS-CoV-2 infection and available computed tomography pulmonary angiography (CTPA) (performed during ICU stay according to the course of the clinical respiratory status) were enrolled. Relevant clinical, laboratory data, ventilator settings and respiratory-system mechanics were obtained from medical records. In the context of the COVID-19, the French National Information Technology and Liberty Committee (Commission nationale informatique et liberté, CNIL) considers that, for monocentric observational research associated with COVID-19, information and consent of patients and families is not required. This research was registered at the Clinical Research and Innovation Center (DRCI) of the Besançon University Hospital with the number 2020/501. All reported P values were two-sided, with a significance level set at $P < 0.05$. Statistical analysis was performed with R version 3.5.0 and RStudio version 1.1.453 (R Foundation for Statistical Computing, Vienna, Austria).

Forty-four patients with COVID-19 ARDS were included. The mean age was 63.8 ± 12.0 years, 82% were male and only one patient was current smoker. Hypertension (50%), diabetes (27%), obesity (49%) and cardiovascular disease (20%) were the most frequent comorbidities. Mean sequential organ failure assessment (SOFA) was 4.4 ± 1.7 and all patients had moderate to severe ARDS.

Seventeen patients (39%) had confirmed APE. Demographic characteristics, comorbidities and SOFA were similar between patients with and without APE (Table 1A). Regarding COVID-19 CT pattern, all patients had bilateral lesions and more than half had more than 50% of affected lung parenchyma. There was no relationship between CT pattern or disease severity and the presence of APE (Table 1A). Most patients with APE had only segmental emboli (59%) and none had proximal emboli. In addition, none of the patients exhibited acute right heart failure.

At the time of APE diagnosis, no differences were found between both groups for the use of anticoagulant therapy, invasive mechanical ventilation, neuromuscular blockers, inhaled pulmonary vasodilators, renal replacement and vasopressor (Table 1B). In addition, ventilator settings, respiratory-system mechanics including lung compliance and PaO_2/FiO_2 ratio did not differ in patients with and without APE. However, patients with APE had significantly more prone positioning sessions (Table 1B). Furthermore, APE was associated with higher levels of D-dimer but not with higher levels of troponin and BNP. Finally, mortality and outcome at 28 days did not differ between patients with and without APE (Table 1A).

Recent studies have reported that COVID-19 in critically ill patients was associated with a high incidence of APE [1,2,4]. This suggest that CTPA should probably be performed systematically in patients with COVID-19 ARDS at ICU admission and in case of respiratory worsening during ICU stay. Several mechanisms might explain this high frequency. Prone positioning increases intra-abdominal pressure and therefore can lead to inferior vena cava compression and lower limb venous congestion [5]. It may therefore be possible that the higher rate of prone positioning sessions in ARDS due to COVID-19 could be associated with the occurrence of APE consecutive to inferior vena cava compression. Another possible mechanism is that the alternance of supine and prone position at regular intervals, could promote multiple successive embolization from peripheral clots. Moreover, the average number of sessions in our study was higher than in non-COVID-19 ARDS [6]. In addition, mechanical ventilation with high PEEP level increases pulmonary vascular resistance and contributes to right ventricular dysfunction and venous return impairment [7,8]. Finally, several studies indicate that COVID-19 patients have a hyperinflammatory profile possibly related to uncontrolled immune response to SARS-CoV-2 infection [9]. Overall, the combination of a sustained inflammatory status and of mechanical conditions (i.e. prone positioning and mechanical ventilation) may participate in increasing the risk of thromboembolism in patients with COVID-19 ARDS. However, this theorical negative effect should be balanced with the unquestionable benefits of prone positioning in ARDS [6] and reinforces the importance of dedicated anticoagulation strategies in these patients.

Indeed, recent studies have shown that high regimen thromboprophylaxis (i.e. subcutaneous enoxaparin 4000 international units bid or therapeutic unfractionated heparin) may decrease the occurrence of APE [4]. In line with this, the French society of hemostasis and thrombosis currently proposes to consider routine therapeutic or intermediate-dose anticoagulation in patients with severe COVID-19 [10].

Another important feature of our study is that patients with and without APE had similar PaO_2/FiO_2 ratio concurrently with similar lung static compliance. This might indicate that APE seems not to account significantly for additional gas exchange impairment among patients with COVID-19 ARDS.

Finally, the fact that all patients with APE had segmental emboli and that none had proximal embolism could suggest localized thrombus formation in the pulmonary arteries (i.e. in situ thrombosis). This reinforces the hypothesis that COVID-19 is associated with micro-vascular rather than macro vascular impairment [11].

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Table 1A
Main characteristics and outcome of patients.

	Patients with APE ($n=17$)	Patients without APE ($n=27$)	*P* value
Age (years)	65.4 ± 11.7	62.9 ± 12.3	0.51
Male	16 (94)	20 (74)	0.2
Body-mass index (kg/m^2)	28.7 ± 4.1	30.4 ± 4.7	0.22
Comorbidities			
Hypertension	6 (35)	16 (59)	0.12
Diabetes	4 (24)	8 (30)	0.65
CVDs	4 (24)	5 (19)	0.69
Smoking	1 (6)	0	0.81
Recent surgery	0	0	–
DVT	0	1 (4)	1
Cancer	1 (6)	4 (15)	0.67
Time between symptoms and ICU admission (days)	8.1 ± 4.2	6.9 ± 4.7	0.43
SOFA	4.4 ± 1.5	4.4 ± 1.8	0.86
CT pattern of COVID-19[a]			
Early	4 (24)	9 (33)	0.87
Progressive	7 (41)	10 (37)	
Peak	6 (35)	7 (26)	
Absorption	0	1 (4)	
Extent of COVID-19 lesions			
Bilateral	17 (100)	27 (100)	1
1–25%	3 (18)	4 (14)	0.82
26–50%	3 (18)	8 (30)	
51–75%	5 (29)	8 (30)	
> 76%	6 (35)	7 (26)	
Outcome at 28 days			
Extubated	11 (65)	17 (63)	0.91
Died in hospital	3 (18)	4 (15)	0.80
Discharged from hospital	3 (18)	5 (19)	0.94

Values are mean ± standard deviation or number of patients (percentage of total). APE: acute pulmonary embolism; ARDS: acute respiratory distress syndrome; CVD: cardiovascular disease; DVT: deep venous thrombosis; SOFA: sequential organ failure assessment.

[a] Legend of CT pattern [12]: stage 1 (early): mainly ground glass opacities (GGO) with partial crazy-paving pattern; stage 2 (progressive): GGO extended to more pulmonary lobes with more crazy-paving pattern and consolidation; stage 3 (peak): mainly consolidation with decreased ratio of GGO and crazy-paving pattern; stage 4 (absorption): consolidation is partially absorbed without any crazy-paving pattern.

Table 1B
Characteristics of the patients at the time of APE diagnosis.

	Patients with APE ($n=17$)	Patients without APE ($n=27$)	*P* value
ICU Therapy			
Vasopressors	2 (12)	4 (15)	1
Renal-replacement therapy	0	0	–
Antibiotic	17 (100)	27 (100)	1
Antiviral	14 (82)	14 (52)	0.04
Anticoagulant	17 (100)	21 (78)	0.10
LMWH/UFH	15/2	21/0	0.37
Dose (preventive/semi-curative/curative)[a]	4/10/1	10/6/5	0.09
Oxygen therapy	17 (100)	27 (100)	1
Invasive mechanical ventilation	16 (94)	25 (93)	1
Neuromuscular blockers	14 (82)	24 (89)	0.66
Prone positioning	12 (75)	11 (42)	0.05
Number of sessions per patient	5.3 ± 2.4	3.2 ± 2.3	0.04
Duration of sessions, hours	18.1 ± 1.7	17.9 ± 1.4	0.76
Duration of prone positioning strategy, days	7.5 ± 2.7	4.8 ± 3.1	0.03
Inhaled pulmonary vasodilators	2 (12)	1 (4)	0.55
Extracorporeal membrane oxygenation	0	0	1
Ventilator settings and respiratory-system mechanics			
Tidal volume (ml per kg of PBW)	6.0 ± 0.3	6.1 ± 0.4	0.83
PEEP (cm of water)	11.6 ± 1.9	11.1 ± 2.4	0.54
Respiratory frequency (breaths per min)	25 ± 3	23 ± 3	0.10
CstRS (ml per cm of water)	38.1 ± 8.2	42.2 ± 10.7	0.30
Arterial blood gazes			
PaO_2 (mm Hg)	84.5 ± 28.6	75.5 ± 16.4	0.24
PaO_2/FiO_2 (mm Hg)	202.0 ± 73	195 ± 71	0.74
$PaCO_2$ (mm Hg)	49.1 ± 14.5	45 ± 14	0.49
Laboratory findings			
D-dimer, µg/mL	5.3 ± 6.3	1.9 ± 1.2	0.03
Troponin, pg/mL	0.38 ± 1.6	0.03 ± 0.05	0.12
BNP, pg/mL	99 ± 153	32 ± 27	0.19

Values are mean ± standard deviation or number of patients (percentage of total). Significant results are in bold. BNP: brain natriuretic protein; CstRS: static compliance of the respiratory system; FIO_2: fraction of inspired oxygen; LMWH: low molecular weight heparin; $PaCO_2$: partial pressure of arterial carbon dioxide; PaO_2:partial pressure of arterial oxygen; PBW: predicted body weight; PEEP: positive end-expiratory pressure; UFH: unfractionated heparin.

[a] Semi curative: subcutaneous enoxaparin 4000 international units bid or unfractionated heparin with a target of anti Xa at 0.2–0.3.

Limitations of the current study include the relatively small number of patients, the single-center setting and its observational nature and the absence of multivariate analysis regarding risk factors for APE.

To conclude, we found that higher rate of prone positioning sessions could be associated with pulmonary embolism among patients with COVID-19 ARDS. Further studies are needed to confirm these results.

Disclosure of interests

The authors declare that they have no competing interest.

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T. Soumagne [a,*]
H. Winiszewski [a]
G. Besch [b]
N. Mahr [a]
T. Senot [b]
P. Costa [c]
F. Grillet [d]
J. Behr [d]
B. Mouhat [e]
G. Mourey [f]
A. Fournel [f]
N. Meneveau [e]
E. Samain [b]
G. Capellier [a]
G. Piton [a,1]
S. Pili-Floury [b,1]

[a] *Medical Intensive Care Unit, Besançon University Hospital, Besançon, France*
[b] *Anaesthesiology and Surgical Intensive Care Unit, Besançon University Hospital, Besançon, France*
[c] *Surgical and Medical Vascular Unit, Besançon University Hospital, Besançon, France*
[d] *Department of Radiology, Besançon University Hospital, Besançon, France*
[e] *Cardiology Unit, Besançon University Hospital, Besançon, France*
[f] *Hematology Unit, Besançon University Hospital, Besançon, France*

[*] Corresponding author.
E-mail address: thibaud_soumagne@live.fr
(T. Soumagne)

[1] Gaël Piton and Sébastien Pili-Floury equally participated to the work.

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