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Characteristics of deep vein thrombosis in the critically ill COVID-19 patient – an observational cohort study with Doppler ultrasound measurements

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Abstract. – OBJECTIVE: COVID-19 is associated with an increased prevalence of deep venous thrombosis (DVT), mainly in the lower limbs. However, the characteristics and rheological conditions, which contribute to facilitating DVT occurrence have been poorly investigated. We aimed to report DVT characteristics, vein diameters and peak blood flow velocities (PBFV) in the common femoral veins (CFVs) of critically ill COVID-19 patients.

PATIENTS AND METHODS: We conducted a prospective single-center cohort study in March-October 2020 including all consecutive mechanically ventilated COVID-19 adults. Doppler ultrasound of the lower limbs was performed systematically during the first week of hospitalization. In DVT-free patients, a second Doppler ultrasound was performed seven days later. Data are expressed as medians (interquartile ranges) or percentages. Comparisons were performed using Mann-Whiney and Wilcoxon signed-rank tests or Fischer's exact tests, as appropriate.

RESULTS: Fifty-five patients [age, 63 years (56-74); female/male ratio, 0.62; body-mass index, 29 kg/m² (26-33); hypertension, 47%; diabetes, 38%; ischemic heart disease, 11%] were included. DVT was diagnosed in 19 patients (35%) including in 5 femoral (9%), 2 popliteal (4%) and 12 below-the-knee sites (22%). CFV diameter was increased to 12.0 mm (11.0-15.0) (normal range, 9.1-12) and PBFV reduced to 11.9 cm/s (8.8-15.8) (normal range, 21.3-49.2) [right-side values]. In four patients who had ultrasound before intubation, CFV diameter increased from 12.5 mm (11.8-13.3) before to 14 mm (13.6-15.3) after intubation (p = 0.008).

CONCLUSIONS: DVT in the CFV occurred in 9% of the critically ill COVID-19 patients with an overall 35%-DVT prevalence. Venous return difficulty evidenced by larger than normal CFV diameters and lower than normal PBFVs may have facilitated proximal DVT occurrence.

Key Words:
COVID-19, Peak blood flow velocity, Vein diameter, Deep venous thrombosis, Doppler ultrasound.

Abbreviations

COVID-19, Coronavirus disease 2019, DVT, Deep venous thrombosis, ICU, Intensive care unit.

Introduction

Severe coronavirus disease-2019 (COVID-19) may require intensive care unit (ICU) admission and mechanical ventilation to preserve sufficient oxygenation. COVID-19 is associated with severe viral pneumonia and lung inflammation leading to acute lung injury. In addition, there may be marked endotheliopathy[1] and coagulopathy facilitating thrombosis[2,3]. Blood hypercoagulability has been attributed to the imbalance between procoagulant factors and natural coagulation inhibitors, as supported by the extremely high fibrinogen, D-Dimer, factor VIII, and von Willebrandt factor in COVID-19 patients[2,4]. Blood hypercoagulability together with the endotheliop-

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athy and immobility resulting from sedation and invasive mechanical ventilation in the ICU, are creating optimal conditions for the occurrence of venous thrombosis[5,6].

Deep vein thrombosis (DVT) prevalence in critically ill COVID-19 patients has been determined in several studies[6-9] at a remarkably high level of 46-84%. Although its prevalence is well documented, detailed descriptive aspects of DVT and rheological conditions in the lower limb venous system that may have facilitated DVT have been poorly studied. However, these characteristics are useful for estimating the risk of thrombus migration and may thus influence patient management, especially with respect to physical therapy and passive or active mobilization. These characteristics may also improve our understanding of local pathophysiological processes contributing to DVT generation. We, therefore, designed this observational study to describe DVT characteristics and investigate rheological conditions of the lower limbs' veins in the critically ill COVID-19 patients.

Patients and Methods

Study Design

We conducted a prospective observational study in our ICU, which admits critically ill COVID-19 patients from the northern region of Paris, France. All consecutive adults (at least 18 years of age) mechanically ventilated to treat COVID-19-attributed pneumonia were included. The study started on March 13, 2020 (date of the first intubation of a COVID-19 patient in our department) and continued until October 30, 2020. Patients admitted during this period in our ICU without active COVID-19 pneumonia, who had previously diagnosed DVT or pulmonary embolism, and who did not require invasive mechanical ventilation were not included. The study was performed in agreement with the 2013 Declaration of Helsinki of the World Medical Association. This study was part of the COVID-ICU and French COVID-19 cohort registries. Our Institutional Ethics Committee approved the study (IDRCB, 2020-A00256-33; CPP, 11-20-20.02.04.68737).

COVID-19 was diagnosed using standard RT-PCR technique in swabs performed in the upper respiratory airways using Cobas™ SARS-CoV-2 kits (Roche, France). Supportive care included optimized protective mechanical ventilation, sedation and muscular paralysis according to guidelines[10] as well as vasopressors to maintain mean arterial pressure to at least 65 mmHg.

During ICU stay, prophylactic anticoagulation was administered with daily subcutaneous 40mg enoxaparin or 15,000 IU/day heparin[11]. Of note, increased prophylaxis with 40 mg enoxaparin twice daily had been started from April 2, 2020. Patients treated with extracorporeal membrane oxygenation or presenting atrial fibrillation received therapeutic anticoagulation.

Duplex Ultrasonography

In our ICU, we initially decided to perform duplex ultrasonography systematically in all COVID-19 patients treated with invasive mechanical ventilation, as we assumed that they were at higher risk of DVT and at higher risk of death than patients not requiring invasive mechanical ventilation. Due to the epidemic context characterized by limited resources and limited availability of ultrasound operators, we decided not to include non-intubated COVID-19 patients. Additionally, based on the clinical suspicion by the physician in charge, duplex ultrasonography was performed on a case-by-case basis in some patients not treated with invasive mechanical ventilation. If some of these patients required invasive mechanical ventilation, duplex ultrasonography was repeated at least once after intubation as part of the screening in intubated patients, and vein diameter and peak blood flow velocities (PBFV) were compared before and after intubation.

Duplex ultrasonography was performed using our routine ultrasonography device (Vivid-I™, General Electric, US) equipped with an adequate ultrasound probe to screen for DVT. Two certified Doppler ultrasound operators performed duplex ultrasonography examinations in all patients in the first week of hospitalization. In patients diagnosed with DVT on the initial ultrasound examination, therapeutic anticoagulation was started, and further ultrasound was not performed. In patients who were DVT-free on the initial ultrasound, an additional ultrasound examination was performed approximately 7 days later.

The presence of thrombus was evaluated by vein compression, color Doppler imaging and spectral Doppler waveforms, determined in the common femoral artery, allowing for the assessment of circulatory flow at this level, as recommended[12]. Compression was performed every 2 cm from the inguinal ligament to the ankle visu-

alizing the common femoral veins, the deep and superficial femoral veins, the popliteal veins, the posterior tibial and fibular veins and the gastrocnemius and soleus veins of the calf. Thrombus dimensions, the common femoral vein diameters and PBFVs were recorded.

In DVT patients, data were reported from the ultrasound showing the DVT. In non-DVT patients who had two duplex ultrasound examinations, we reported data from the first duplex ultrasound. If a patient had a duplex ultrasound before intubation, we reported data from the first duplex ultrasound after intubation.

Statistical Analysis

Quantitative variables are expressed as medians (25^{th}-75^{th} percentiles) and categorical variables as percentages. Parameters were compared between patients using Fisher's exact tests for categorical variables and Mann-Whitney U-tests for numerical variables. Paired samples were compared using Wilcoxon signed-rank tests. *p*-values < 0.05 were considered significant. Statistical analysis was performed using R version 3.6.3 (2020-02-29), "Holding the Windsock" Copyright (C) 2020, The R Foundation for Statistical Computing Platform.

Results

Fifty-five successive mechanically ventilated COVID-19 patients were included in the study. Four patients were not included due to pulmonary embolism diagnosis before ICU admission. Among the 55 patients, 34 (62%) were male, 26 (47%) had past history of hypertension, 21 (38%) diabetes, 22 (40%) obesity (defined as body mass index >30 kg/m^2) and six (11%) ischemic heart disease (Table I). Thirty-two patients (58%) required norepinephrine infusion. Therapeutic anticoagulation was used in 9 patients (16%), standard prophylaxis in 24 (44%) and increased prophylaxis in 22 (40%) (Table II). Eleven patients had refractory hypoxemia requiring extracorporeal membrane oxygenation.

Deep Vein Thrombosis

All patients had an initial ultrasound examination performed 2 days (1-4) after tracheal intubation, corresponding to 12 days (10-17) after the first symptoms. A second ultrasound examination was performed in 32 patients, 8 days (7-10) after intubation, corresponding to 18 days (15-24) from the first symptoms.

Table I. Characteristics of the 55 critically ill COVID-19 patients.

	All patients (N = 55)	Absence of DVT (N = 36)	Presence of DVT (N = 19)	*p*-value
Male gender, N (%)	34 (62)	21 (58)	13 (68)	0.5
Age (years)	63 (56-74)	63 (56-75)	65 (56-71)	0.8
Body-mass index (kg/m^2)	29 (26-33)	29 (25-35)	30 (27-31)	0.7
Hypertension, N (%)	26 (47)	18 (50)	8 (40)	0.09
Diabetes, N (%)	21 (38)	16 (44)	5 (26)	0.2
Ischemic heart disease, N (%)	6 (11)	5 (14)	1 (5)	0.8
Past heart failure, N (%)	8 (15)	6 (17)	2 (10)	0.8
Long-term anticoagulation, N (%)	2 (4)	2 (6)	0 (0)	0.3
Salicylate treatment, N (%)	7 (13)	6 (17)	1 (5)	0.2
First symptoms to tracheal intubation (days)	10 (7-15)	10 (7-16)	11 (6-14)	0.9
PaO_2/FiO_2 (mmHg)	138 (109-184)	140 (116-192)	137 (101-175)	0.9
Positive end-expiratory pressure (cm H_2O)	12 (10-13)	12 (10-13)	12 (12-14)	0.07
Inotropes/vasopressors, N (%)	32 (58)	23 (64)	9 (47)	0.3
Platelets (G/L)	236 (188-326)	215 (185-322)	254 (206-338)	0.4
Hemoglobin (g/dL)	10.5 (9.3-11.5)	10.5 (9.1-11.5)	10.4 (9.4-11.5)	0.8
Procalcitonin (ng/mL)	0.77 (0.20-2.80)	1.04 (0.28-4.38)	0.58 (0.18-1.39)	0.4
C-reactive protein (mg/L)	225 (129-281)	192 (86-263)	247 (218-285)	0.1
Fibrinogen (g/L)	7.2 (5.4-8.1)	6.6 (5.2-8.2)	7.4 (6.5-8.1)	0.4
Blood lactate (mmol/L)	1.5 (1.2-2.0)	1.6 (1.2-2.3)	1.4 (1.3-1.8)	0.4
Serum creatinine (µmol/L)	96 (64-145)	99 (64-155)	82 (64-130)	0.6
Interleukin-6 (IU/L)	147 (44-386)	171 (50-420)	94 (23-231)	0.2
Serum Alanine aminotransferase (IU/L)	35 (24-54)	31 (22-43)	35 (18-51)	0.5

PaO_2/FiO_2, ratio of arterial oxygen pressure to inspired fraction of oxygen.

Table II. Duplex ultrasound data in the 55 critically ill COVID-19 patients.

Parameters	Overall (n = 55)	Patients without DVT (n = 36)	Patients with DVT (n = 19)	*p*-value
Time from first symptoms to positive ultrasound (days)	14 (12-19)	NA	14 (12-19)	NA
Time from tracheal intubation to positive ultrasound (days)	6 (4-9)	NA	6 (4-9)	NA
Patients on standard prophylaxis	24 (44)	14 (39)	10 (53)	0.3
Patients on increased prophylaxis	22 (40)	16 (44)	6 (32)	0.4
Patients on therapeutic anticoagulation (enoxaparin 40 mg b.i.d.)	9 (16)	6 (17)	3 (16)	0.9
Peak blood flow velocity in the right common femoral vein (cm/s; normal range, 21.3-49.2)	11.9 (8.8-15.8)	11.7 (8.7-15.3)	13.0 (12.0-17.7)	0.2
Peak blood flow velocity in the left common femoral vein (cm/s; normal range, 21.1-52.8)	12.6 (9.0-14.6)	11.8 (9.0-14.8)	12.0 (10-14)	0.7
Common right femoral vein diameter (mm; normal range, 9.1-12.5)	12.0 (11.0-15.0)	12 (10.8-14.1)	15 (12.8-16)	0.049
Common left femoral vein diameter (mm; normal range, 9.4-11.4)	12.2 (11.2-14.5)	12.0 (11.0-13.7)	15.3 (12.1-16.9)	0.046

DVT, deep vein thrombosis; NA, not applicable.

Overall, 19 out of our 55 patients (35%) were diagnosed with DVT (Table II). The highest level of the thrombosis was situated in the femoral vein in five patients (9%), in the popliteal vein in two patients (4%) and below the knee in 12 patients (26%) (Table III, Figure 1). Among patients with increased prophylaxis or therapeutic anticoagulation, only one femoral, no popliteal but eight below-the-knee DVTs were observed. DVTs were bilateral in four patients (7%).

Spontaneous contrast, "sludge pattern", considered as pre-thrombotic state in the common femoral and/or popliteal veins was observed to various degrees in seven patients (19%) among those without DVT. An example of popliteal vein sludge is provided in Figure 1B.

Twenty-four and 31 patients were included before and from April 2, 2020, respectively. Ten among the 24 patients (42%) included before April 2 *vs.* 9 among the 31 patients (29%) included from April 2 had DVT (p = 0.33). Femoral or popliteal DVT was diagnosed in 6/24 patients (25%) included before April 2 and in 1/31 patients (3%) included from April 2 (p = 0.035). The patient presenting with DVT in this last group had a partial common femoral vein thrombus of 40 mm length and 13 mm largest diameter.

Table III. Characteristics of deep vein thromboses in the 19 critically ill COVID-19 patients with deep vein thrombosis..

Parameters	Patients with DVT (n = 19)
Most proximal DVT femoral vein, N (%)	5 (26)
Most proximal DVT popliteal, N (%)	2 (11)
DVT beneath popliteal vein, N (%)	12 (63)
Bilateral DVT, N (%)	4 (21)
Largest thrombus diameter (mm)	10 (5.9-12.0)
Estimated thrombus length (mm)	100 (43-290)
Floating thrombus, N (%)	6 (32)

DVT, deep vein thrombosis.

Femoral Vein Diameter and PBFV

The vein diameter was determined at 12.0 mm (11.0-15.0) in the right and at 12.2 mm (11.2-14.5) in the left common femoral veins. Of note, normal values found in a study which included non-intubated healthy subjects were 9.1-12.5 mm and 9.4-11.4 mm, respectively[13]. PBFV was 11.9 cm/s (8.8-15.8) in the right and 12.6 mm (9.0-14.6) in the left common femoral vein, normal values being 21.3-49.2 and 21.1-52.8 cm/s, respectively[13].

In four patients, ultrasound was performed on high flow oxygen before intubation and again after intubation. The diameters and blood flow velocities were compared before and after intubation (Figure 2). In all four patients, the common femoral vein diameter increased from 12.5 mm (11.8-13.3) before to 14 mm (13.6-15.3) after intubation (p = 0.008). PBFVs were 12.2 cm/s (10.5-17.8) before and 12.2 cm/s (8.9-17.1) after intubation (p = 0.3). They decreased in three patients after intubation but increased in one patient (Figure 2B).

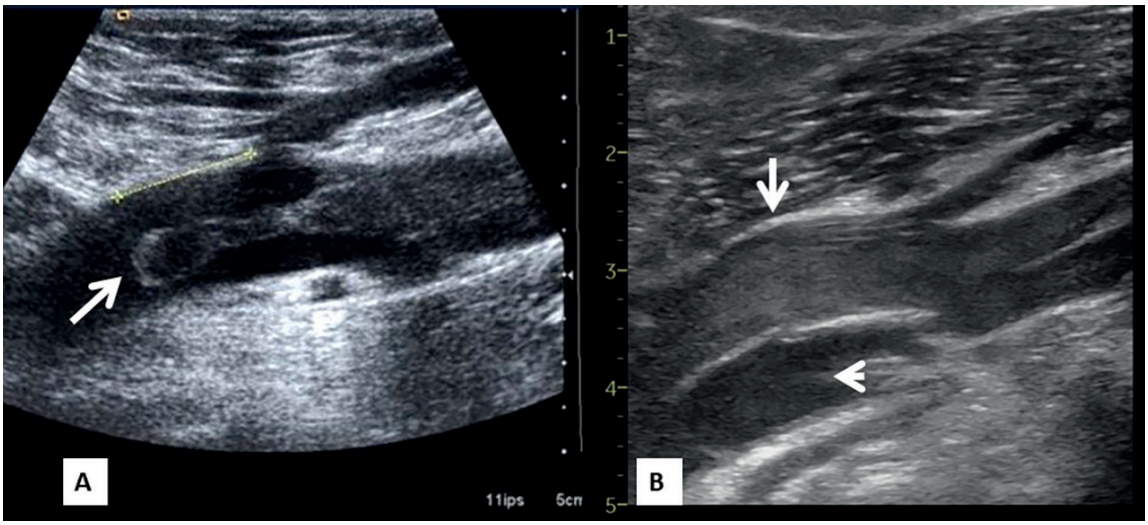

Figure 1. Deep vein thrombosis in two mechanically ventilated COVID-19 patients. **A,** Deep vein thrombosis of the common right femoral vein, with floating thrombus in the common femoral vein (*white arrow*). **B,** Popliteal vein with spontaneous contrast (*sludge, white arrow*) in a different patient. By comparison, the popliteal artery underneath is clear of spontaneous contrast (*arrowhead*).

Mortality

Twenty-eight patients (51%) died and 27 (19%) were discharged alive from the ICU. In two of the 20 deceased patients, pulmonary embolism with visible thrombi on thoracic imaging was identified as the cause of death. Both patients had proximal DVTs.

Discussion

To our knowledge, this is the first study to provide a detailed description of the characteristics of thrombosis and the rheological conditions in the common femoral veins in critically ill COVID-19 patients. The most important finding

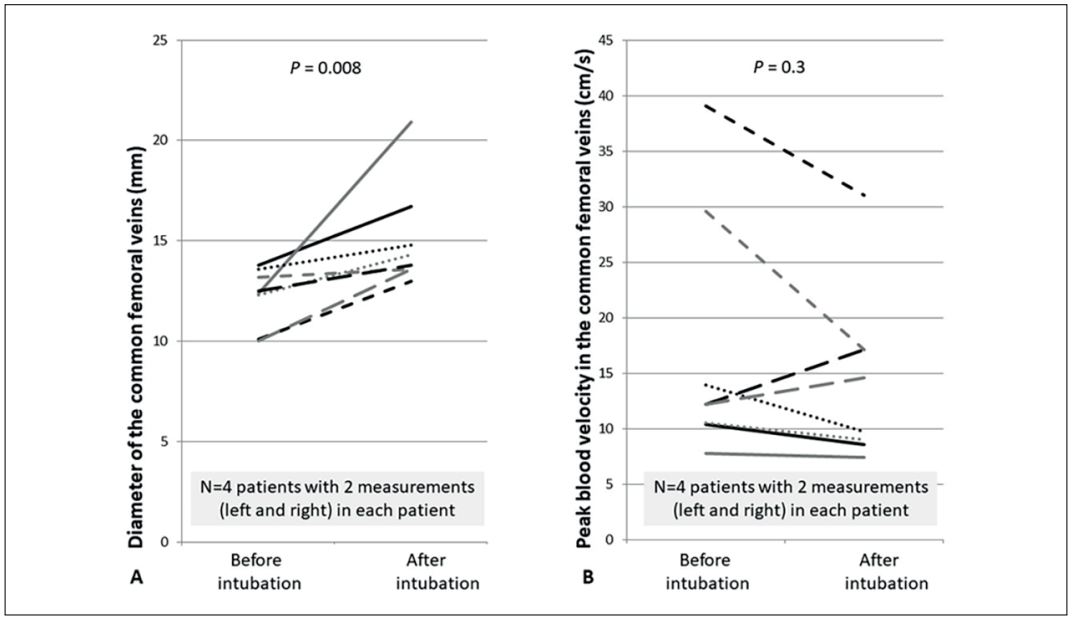

Figure 2. Diameters (**A**) and peak blood flow velocities (**B**) in the right and left common femoral veins before and after tracheal intubation in four critically ill COVID-19 patients. After intubation, the vein diameters significantly increased while the peak blood flow velocities decreased in three of the four patients but increased in one patient. A type of line represents each patient. Lines in black represent parameters in the right common femoral vein and lines in grey represent parameters in the left common femoral vein.

in our study is that 9% of the patients presented proximal thrombosis in the common femoral vein, which can be easily dislodged and generate pulmonary embolism. The second most important finding is that the common femoral veins have a larger diameter and lower PBFVs than values found in normal subjects[13]. Another finding of our study is that the diameter of the common femoral vein increased after intubation while the PBFV may increase in some patients and decrease in others.

Diagnosis of DVT and its localization are important issues for multiple reasons. Firstly, diagnosing DVT is important, as it results in anticoagulant treatment to ensure prevention of thrombosis extension and facilitate the spontaneous physiological thrombus lysis. Without effective anticoagulation, DVT may extend and give rise to life-threatening pulmonary embolism, given the local rheological conditions and hypercoagulability in critically ill COVID-19 patients[2,6,14-16]. Moreover, the pulmonary microcirculatory thrombosis that may occur as consequence of COVID-19, participates in the increased pulmonary arterial resistance and right ventricular pressures, and may consequently decrease velocities of venous return to the heart and contribute to peripheral venous stasis[17,18]. Based on postmortem studies, approximately 10% of COVID-19-attributed fatalities have been estimated to be caused by pulmonary embolism[18].

COVID-19-associated peripheral hemodynamic and rheological alterations have been observed during duplex ultrasound as pronounced sludge patterns, particularly in the lower limbs. These impairments may have resulted from the abnormal "brightness" of erythrocyte aggregates occurring in vessels with lowered blood flow velocities[19,20]. The sludge pattern may also be considered as a prothrombotic stage by itself[21].

Mechanically ventilated COVID-19 patients included in our study presented with severe acute respiratory distress syndrome and shock requiring vasopressors in more than half of the cases. Therefore, even small pulmonary emboli could have severely impaired oxygenation and circulatory function in our patients, given their drastically reduced cardiopulmonary reserve[22]. When DVT was diagnosed in proximal veins, patient mobilization and physiotherapy, used to decrease the risk of pressure injury and limit joint retraction and muscle atrophy[23], were performed cautiously to prevent thrombus migration, avoiding brisk mobilization and/or ample flexion of the leg and/or the thigh. However, no specific data are available on this.

Due to the observed high DVT prevalence, increased anticoagulant prophylaxis has been used in our ICU patients since April 2020, resulting in a significant decrease in proximal (femoral or popliteal) DVT prevalence as previously shown[11]. This strategy explains the lower DVT rate (35%) we observed in comparison to previous studies[6-9] including ICU patients showing prevalence up to 84%.

We observed larger common femoral vein diameters and decreased PBFVs, compared to the normal values reported in the literature[13]. These two major factors facilitate thrombosis due to venous stasis in comparison to normal subjects. Larger vein diameters decrease blood flow velocity if blood output remains unchanged. Moreover, according to the non-Newtonian fluid nature of the blood, a lower blood flow velocity increases viscosity and the risk of erythrocyte aggregate generation[24]. In addition, blood flow velocity in a vessel is highest in the center and decreases towards the vessel walls[25]. In mechanically ventilated patients with larger venous diameters, this property may even lead to lower velocities in the immediate vicinity of the endothelium compared to physiological conditions, resulting in increased venous stasis. This enhances the predisposition to thrombosis[25]. Although we only measured PBFVs in the common femoral veins, we strongly believe that our observations illustrate modifications in the overall lower limb venous network with likely decreased velocities compared to normal subjects[13,19].

Our study showed that invasive mechanical ventilation induces an increase in the common femoral vein diameter, which may be explained by the increased intrathoracic pressures that occur after intubation. This phenomenon is not specific to COVID-19 patients since it may occur in any mechanically ventilated patient. However, it is noteworthy since our COVID-19 patients were ventilated with relatively high levels of positive expiratory pressure, i.e., 12 cm H_2O (10-13), consistent with other reports[26]. This high intrathoracic pressure decreases venous return, increases venous pressure and thus favors vein distension, increasing their diameter. Here, we observed a significant increase in the common femoral vein diameters after intubation in four patients as compared with the pre-intubation diameters. However, we acknowledge that due to

the small number of examined patients, this requires cautious interpretation. When the diameter of the veins increases and the cardiac output does not change, blood velocities tend to decrease, as observed in three of the four patients (Figure 2B). In one patient, velocities increased despite vein diameter increasing after intubation. This may be due to increased overall cardiac output, as this patient developed sepsis, which increased his heart rate and cardiac output, probably explaining increased velocities of venous blood flow in the common femoral veins.

Our study has limitations. It has a single-center retrospective design with a relatively small number of patients. Therefore, results should be interpreted with caution. However, all patients in our center had ultrasound examinations during the hospital stay; therefore, a selection bias is unlikely. Patients in our study received several anticoagulant regimens as knowledge on hypercoagulation in COVID-19 and recommendations on patient management progressed. Increasing prophylaxis since April 2020 introduced additional variability in the studied population, as efforts were made to prevent thrombotic complications, but this was unavoidable. Our study examined changes induced by tracheal intubation in a limited number of patients, reflecting the fact that ultrasound was only systematically performed in intubated patients and on a case-by-case basis in non-intubated patients. DVT prevalence in non-intubated patients was lower, estimated at 16% and 10.5% in two studies performing systematic ultrasound screening[27,28]. Additionally, no comparison with COVID-free ventilated patients, who are supposed to have a lower incidence of DVT and possibly in relation to different underlying mechanisms was performed. We thus pursued a non-systematic approach in these patients, given the limited resources during the pandemic

Although experienced certified operators performed the whole-leg duplex ultrasound examinations, limitations related to the accuracy of the technique should be acknowledged. In femoral and popliteal veins, correlations between ultrasound and venography, the reference diagnostic technique, are good, with a reported sensitivity between 60%[29] and 100%[30]. However, in isolated calf veins thrombosis, sensitivity is much lower, i.e., 28.6%[29] to 36%[30] while specificity estimated at 98.6%[29]. Therefore, we cannot exclude that DVT prevalence, especially below the knee, was under- or overestimated.

Finally, since our study focused on DVT, we did not attempt to routinely assess pulmonary embolism prevalence and cardiac function. Due to the interrelated pathophysiology of venous rheology, cardiac function and pulmonary circulation are worthy of being evaluated in future studies.

Conclusions

Our study showed that common femoral DVT is not rare in critically ill COVID-19 patients. Potential predisposing local factors of thrombotic complications include increased vein diameter and lowered PBFVs. Future studies should evaluate the importance of ultrasound characteristics of thrombosis and rheological conditions in the overall management of COVID-19 patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethical Approval

The study was part of the COVID-ICU and French COVID-19 cohort registries and approved by our institutional ethics committee (N°, IDRCB, 2020-A00256-33; CPP, 11-20 20.02.04.68737).

Authors' Contribution

S.V., P.B. and B.M. have made substantial contributions to the conception and design of the study. All authors have contributed to the patient management and acquisition of data. S.V. and P.B. performed the analysis and interpretation of data. S.V., P.B. and B.M. drafted the manuscript. All authors read and approved the final version.

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