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Letters

High Prevalence of Deep Vein Thrombosis in Mechanically Ventilated COVID-19 Patients

Patients with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) pneumonia with SARS-CoV-2 present with coagulation disorders and marked susceptibility to thrombosis (1,2). However, the exact prevalence of deep vein thrombosis (DVT) has been poorly investigated, although the risk seems increased in intensive care unit (ICU) patients (3). Therefore, we decided to perform routine duplex ultrasound examination of the lower limb veins systematically in order to administer appropriate anticoagulation in all intubated and mechanically ventilated patients with SARS-CoV-2 pneumonia.

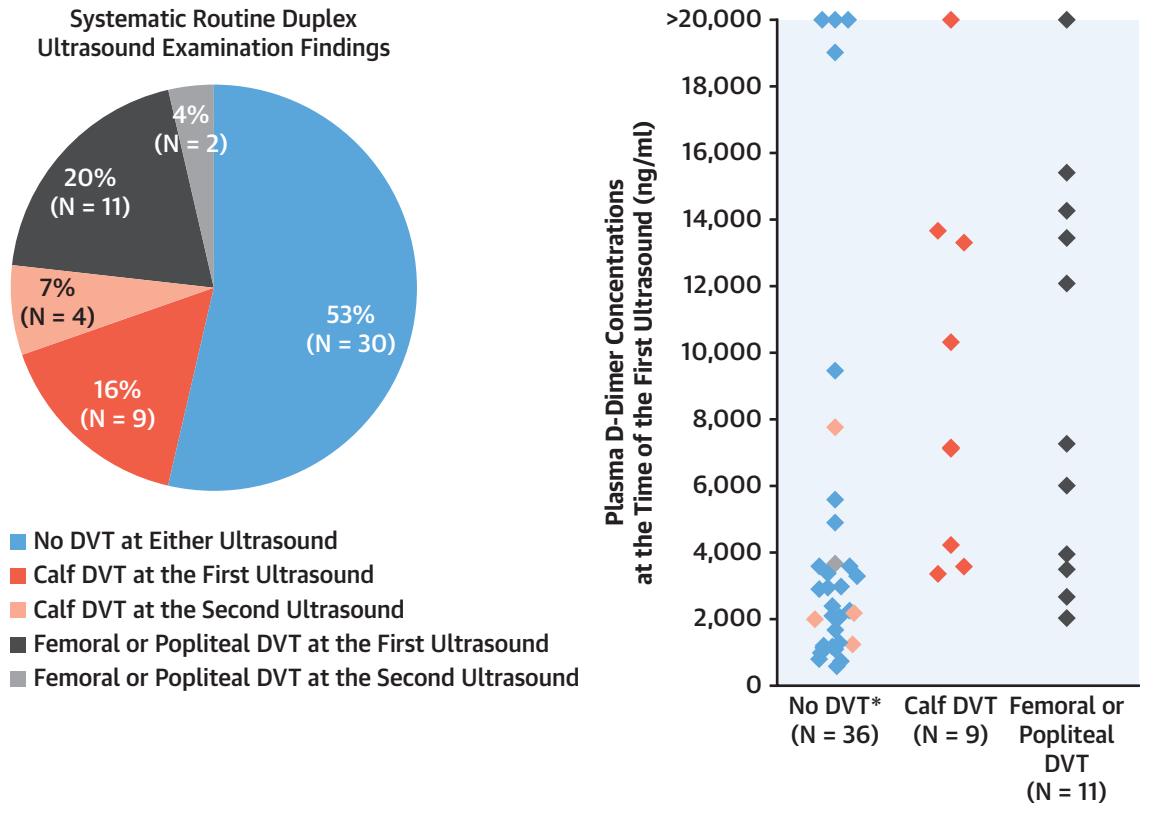
We conducted a prospective observational study in the medical and surgical critical care departments of Lariboisière University Hospital, Paris, France. Consecutive adults receiving invasive mechanical ventilation for SARS-CoV-2 pneumonia were included. Patients with previously diagnosed DVT or pulmonary embolism were excluded. During the hospital stay, prophylactic anticoagulation was administered as daily subcutaneous 4,000 IU enoxaparin and, if the glomerular filtration rate was <15 ml/min, as continuous intravenous infusion of daily 15,000 IU unfractionated heparin. Duplex ultrasonography and plasma D-dimer assessment (STA-Liatest-DDI-Plus, Stago, Asnières sur Seine, France) were performed in all patients during the first week of ICU admission. In patients without DVT on the initial ultrasound, a second ultrasound examination was performed ~7 days later. Quantitative variables are expressed as median (interquartile range) and categoric variables as percentages. The study was part of the French coronavirus disease 2019 cohort registry and was approved by our institutional ethics committee (IDRCB, 2020-A00256-33; CPP, 11-20 20.02.04.68737). When possible, signed informed consent was obtained from the patients or the next of kin.

From March 13 to April 3, 2020, 56 patients with SARS-CoV-2 pneumonia were included. Most of the patients were male (75%) with hypertension (46%), diabetes (45%), obesity (30%), and ischemic heart disease (20%). They required vasopressors in 32% of the cases. Prophylactic anticoagulation using enoxaparin or unfractionated heparin was administered in 41 patients (73%) and 8 patients (14%), respectively. Therapeutic anticoagulation was used in 7 patients (13%) to treat atrial fibrillation (n = 2) and manage extracorporeal membrane oxygenation (n = 5).

The initial ultrasound was performed 3 days (interquartile range: 2 to 4 days) post-intubation, corresponding to 10 days (interquartile range: 8 to 13 days) after the onset of the first symptoms. Twenty (36%) patients had DVT, among which 11 (20%) cases were proximal (popliteal or femoral) DVT. A second ultrasound examination was performed in 17 patients 8 days (interquartile range: 5 to 9 days) post-intubation, corresponding to 14 days (interquartile range: 11 to 15 days) after the first symptoms. Six patients (35%) acquired DVT; 2 (12%) cases were proximal despite prophylactic anticoagulation in 3 patients and therapeutic anticoagulation in the other 3. Overall, 26 of 56 patients (46%) were diagnosed with DVT, either proximal (n = 13, 23%) or calf (n = 13, 23%) (**Figure 1**). DVT patients had significantly higher plasma D-dimer compared with non-DVT patients (7,210 ng/ml [interquartile range: 3,770 to 13,550 ng/ml] vs. 2,225 ng/ml [interquartile range: 1,195 to 3,630 ng/ml], p = 0.0002) with no significant difference in plasma fibrinogen (7.4 g/l [interquartile range: 5.8 to 8.9 g/l] vs. 7.6 g/l [interquartile range: 5.5 to 8.5 g/l], p = 0.7).

Studies have reported a highly variable prevalence of DVT (between 2.0% [2] and 14.8% [3]) in ICU patients, most likely because of the absence of consistent screening. To the best of our knowledge, this is the first study performing systematic ultrasound examination for DVT diagnosis, thus providing data free of selection biases. Our data showed a remarkably high DVT prevalence (46%) and revealed the rapid time course of thrombus formation despite prophylactic anticoagulation. Importantly, 50% of the DVTs were popliteal or femoral, which are most often associated with thromboembolic events, consistent with the unexpectedly high number of pulmonary embolisms (21%) reported in SARS-CoV-2 pneumonia patients admitted to the ICU and

FIGURE 1 DVT and Plasma D-dimer in 56 Mechanically Ventilated SARS-CoV-2 Patients



(Left) Study groups as percentages of the total (numbers) according to the deep vein thrombosis (DVT) presence and site at the initial and second ultrasound. Color significance is detailed in the figure. **(Right) Diamonds** represent individual concentrations of D-dimer at the initial ultrasound according to the DVT presence and site, with the same color significance as in the left panel. In the "No DVT" group, the **salmon diamonds** and the **light blue diamonds** represent D-dimer in patients who developed femoral and calf DVT, respectively, at the second ultrasound. *Missing D-dimer in 1 patient with popliteal DVT at the second ultrasound. SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2.

occurring within a median time from ICU admission of 6 days (interquartile range: 1 to 18 days) (4).

Our data suggest that close monitoring of DVT occurrence is necessary in mechanically ventilated SARS-CoV-2 patients, and because ultrasound may not always be available, especially in epidemic settings, larger studies may investigate the diagnostic performance of D-dimers for DVT diagnosis in these patients. Moreover, the intensity of anticoagulation may need to be reconsidered based on future investigations to ensure more effective prevention (1).

In conclusion, we demonstrated a very high DVT prevalence including a high proportion of potentially life-threatening proximal DVT in mechanically ventilated SARS-CoV-2 patients despite standard prophylactic anticoagulant treatment, suggesting the need for close DVT monitoring and assessment of the risks/benefits of more intense anticoagulation regimens in this population.

*Sebastian Voicu, MD, PhD
Philippe Bonnin, MD, PhD
Alain Stépanian, MD, PhD
Benjamin G. Chousterman, MD, PhD
Arthur Le Gall, MD
Isabelle Malissin, MD
Nicolas Deye, MD, PhD
Virgine Siguret, MD, PhD
Alexandre Mebazaa, MD, PhD
Bruno Mégarbane, MD, PhD
*Lariboisière Hospital
APHP
Université de Paris
75010 Paris
France
E-mail: sebastoso@yahoo.com

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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Long-Term Mortality Following Transcatheter Atrial Septal Defects Closure in Comparison to the General Population

Transcatheter atrial septal defect closure (TAC) is a well-established therapy for most patients with secundum atrial septal defects (ASD) based on short-term data (1). In previous surgical studies, mortality was not significantly different from age-and-sex matched control subjects (2). TAC utilizes permanent occluders with the potential for arrhythmia, thromboembolism, and erosion and has an uncertain impact on long-term mortality. Studies that have assessed long-term outcomes following TAC were of limited quality, included mixed pediatric and adult populations and non-ASD interventions, and had variable follow-up durations (3). In addition, survival following TAC in comparison with the general population is unknown.

In this study, the long-term outcomes of adult patients who underwent TAC at the Peter Munk Cardiac Centre, Toronto, Ontario, Canada, were retrospectively determined using a local database linked to administrative databases until March 31, 2016. The maximum follow-up time was 18 years with a median of 9 years (interquartile range [IQR]: 5 to 11 years). TAC patients were age-and sex-matched 1:1 with population controls. The primary endpoint was all-cause mortality. Institutional ethics approval was obtained.

Among those screened, 69 (4%) patients had secundum ASDs that were not amenable for TAC and, therefore, underwent surgery. The TAC cohort was comprised of 1,518 patients of whom 1,278 were eligible for analysis. We excluded patients with missing baseline data (n = 69), Ebstein anomaly (n = 10), duplicate or non-updated records (n = 58), and non-Ontario residents (n = 103).

Among the TAC group (69% women, median age 48 years [IQR: 36 to 59 years]), 8% had atrial fibrillation (AF), 16% had pulmonary hypertension, and 15% had at least moderate tricuspid regurgitation. The Amplatzer Septal Occluder (ASO) (Abbott Structural Heart, Plymouth, Minnesota) was used predominantly (1,304 occluders, 97%) with a median occluder size of 24 mm (IQR: 19 to 28 mm). Multiple occluders were used in 66 patients (5%). Patients were prescribed aspirin for 6 months following TAC unless there were standard indications for oral anticoagulation.

The long-term mortality was 6.5% in TAC and 5.3% in control groups (**Figure 1**), and did not significantly differ (hazard ratio [HR]: 1.23; 95% CI: 0.92 to 1.65; $p = 0.16$). The rate of stroke was 1.6% in TAC and 0.9% in control, and did not differ significantly (HR: 1.68; 95% CI: 0.82 to 3.45; $p = 0.16$). The TAC group experienced more AF (16.2% vs. 3.6%; HR: 4.89; 95% CI: 3.61 to 6.63; $p < 0.001$) and higher rate of pacemaker implantation (2.3% vs. 0.6%; HR: 3.69; 95% CI: 1.68 to 8.08; $p = 0.001$) than control subjects. A total of 7 cases (0.5%) of device erosion were encountered following TAC.

This analysis demonstrates that mortality after TAC was not significantly different from age- and sex-matched control subjects over a median follow-up of 9 years. Similarly, the long-term risk of stroke following TAC did not significantly differ from the general population, which lessens concerns related to ASO thrombogenicity. The 5-year rate of AF following TAC in prior studies ranged between 2% and 15% (3). Despite the use of validated criteria for AF diagnosis in this analysis (4), the AF rate here (16.2%) is likely underestimated, as atrial arrhythmia can be clinically silent rendering the assessment of the true incidence challenging.

The short- and intermediate-term risk of device erosion after ASO implantation ranged between 0.04% and 0.3% in previous studies (5). Prior studies' estimates of device erosion were based on cases reported to the manufacturer or in the published data, which is subject to reporting bias