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Letter to the Editors-in-Chief

Right ventricular dilation: The additive effect of mechanical ventilation on pulmonary embolism in Covid-19 patients

We read with great interest the study of van Dam et al. presenting the radiographic characteristics of 23 patients with Covid-19 acute Pulmonary Embolism (PE) and right ventricular (RV) dilation. [1] In our opinion, a few, very interesting findings need further clarification, which may strengthen the value of the study.

Van Dam's paper confirms the increased incidence of thrombotic events in Covid-19 patients, as in the majority of the presented cohort, PE was an unexpected finding; the reasons for ordering a computed tomography pulmonary angiography (CTPA) were not indicative of PE presence [lack of clinical improvement after mechanical ventilation initiation and fever (61.3%)]. Even unexpected respiratory deterioration, especially in patients with pneumonia, is not a symptom usually suggesting PE. Only hemodynamic collapse (8.9% of the patients) strongly raises the clinical suspicion of PE. Therefore, van Dam's study supports the accumulating evidence of hypercoagulability and increased risk of thromboembolic events in Covid-19.

Recently, pulmonary vascular endothelialitis and thrombosis have been described in autopsy findings, indicating that increased pulmonary vascular resistances (PVRs) and RV dysfunction may be fundamental aspects of Covid-19 clinical spectrum [2]. Yet, patients with Covid-19 admitted to the intensive care unit (ICU) are at increased risk for pulmonary embolism occurrence despite prophylactic or even therapeutic administration of anticoagulation [3]. In our department we systematically evaluated the patients for thromboembolism with ultrasonography; a few presented Deep Vein Thrombosis (DVT) (surprisingly in the internal jugular vein, where a central venous line had been placed, a finding further supporting a hypercoagulable state), despite the use of a therapeutic dose of anticoagulation in all, starting from ICU admission (Fig. 1). Covid-19 coagulopathy may not be reversed with traditional therapies, but this needs further clarification.

Computed tomography obstruction index has been reported as an accurate measure to distinguish massive from sub-massive pulmonary embolism [4]. A Qanadli obstruction index greater than 40% or a Miller index greater than 50% is compatible with the presence of RV dilatation [4,5]. In the presented cohort, the Qanadli index was 23%, a thrombotic burden almost half of the one needed to induce RV dilation. As a score of this magnitude has not been correlated to the presence of right ventricular dysfunction, it is quite surprising that the patients presented a right ventricular to left ventricular ratio of 0.97, indicating almost severe RV dilation [4,5]. As the majority of the patients were mechanically ventilated in the present study (19/23 patients) we suppose that the CT was performed under mechanical ventilation in most of the patients. It is well known that mechanical ventilation in patients with acute respiratory distress syndrome may deteriorate RV function and even lead to acute cor pulmonale [6]; yet, heart-lung interactions may be pronounced in Covid-19 patients under mechanical ventilation. When lung compliance is relatively normal, as it has been reported in Covid-19 lung by Gattinoni and confirmed later by our group [7,8], substantial amount of the alveolar pressure is transmitted to the pleural pressure, restricting venous return and forcing the transition of lung Zone 3 regions to Zone 2 and even 1. A remarkable positive end-expiratory pressure (PEEP) de-escalation from the levels proposed by the ARDSnet, led to significant improvements in respiratory function (improving dead space ventilation and respiratory system compliance) and hemodynamics, decreasing by three-fold the need for vasopressors [8]. Moreover, PEEP effects may be rather exacerbated in the setting of non-recruitable lung regions, as in cases of focal but also in non-focal lung involvement, when extensive, multilobar ground glass opacifications are present (as in Fig. 1 in van Dam's study) [1,9]; increased PEEP levels, when not resulting in lung recruitment, may induce dead space ventilation and compression of the pulmonary vasculature, leading to increased pulmonary vascular resistance (PVR) and RV dilation and dysfunction. In fact, van Dam's study further strengthens the hypothesis of PEEP effects on RV dilation, as the embolic burden in Covid-19 PE is rather low, located in more peripheral arteries compared to PE patients without Covid-19 [1]. The presence of pulmonary thromboembolism combined with additional PEEP application may exceptionally increase PVRs. In our institution, Covid-19 mechanically ventilated patients presented a mean right ventricular end diastolic area/left ventricular end diastolic area [RVEDA/LVEDA] ratio of 0.97 ± 0.16 with a mean PEEP of 12 cmH_2O. PEEP de-escalation to 8 cmH_2O led to a significant reduction in RV size [RVEDA/LVEDA: 0.65 ± 0.13] (anecdotal reports). However, CTPA was not performed in any of our patients; in light of van Dam's study, an additive effect of PE on PEEP may have increased PVRs and resulted in the initial RV dilation; PEEP de-escalation decreased PVRs and RV dimensions. Therefore, it would be very informative if the authors could comment on the mechanical ventilator settings, and especially the PEEP levels, used in these patients at the time of CT performance.

Moreover, could the authors comment on the embolic load and location in the two subgroups of patients who presented a strong suspicion of PE (2 with hemodynamic collapse and 7 patients with sudden respiratory deterioration)? Even in the two patients with hemodynamic deterioration, could this partially be attributed to the mechanical ventilation effect? And if so, what was the PEEP level used? Moreover, the sudden respiratory deterioration in the subgroup of seven patients could have resulted from the worsening of Covid-19 pneumonia and not exclusively from pulmonary arterial disease (embolism). Fig. 1 in van Dam's study indicates that the respiratory deterioration could have resulted from the extensive parenchymal lung disease, rather than the arterial one.

Finally, was any patient re-evaluated with CTPA? Usually, emboli dissolve within a month in the majority of patients with segmental and subsegmental pulmonary embolism. As the natural history of Covid-19 hypercoagulability and thrombosis is totally unknown, it would be valuable information for the course of the disease.

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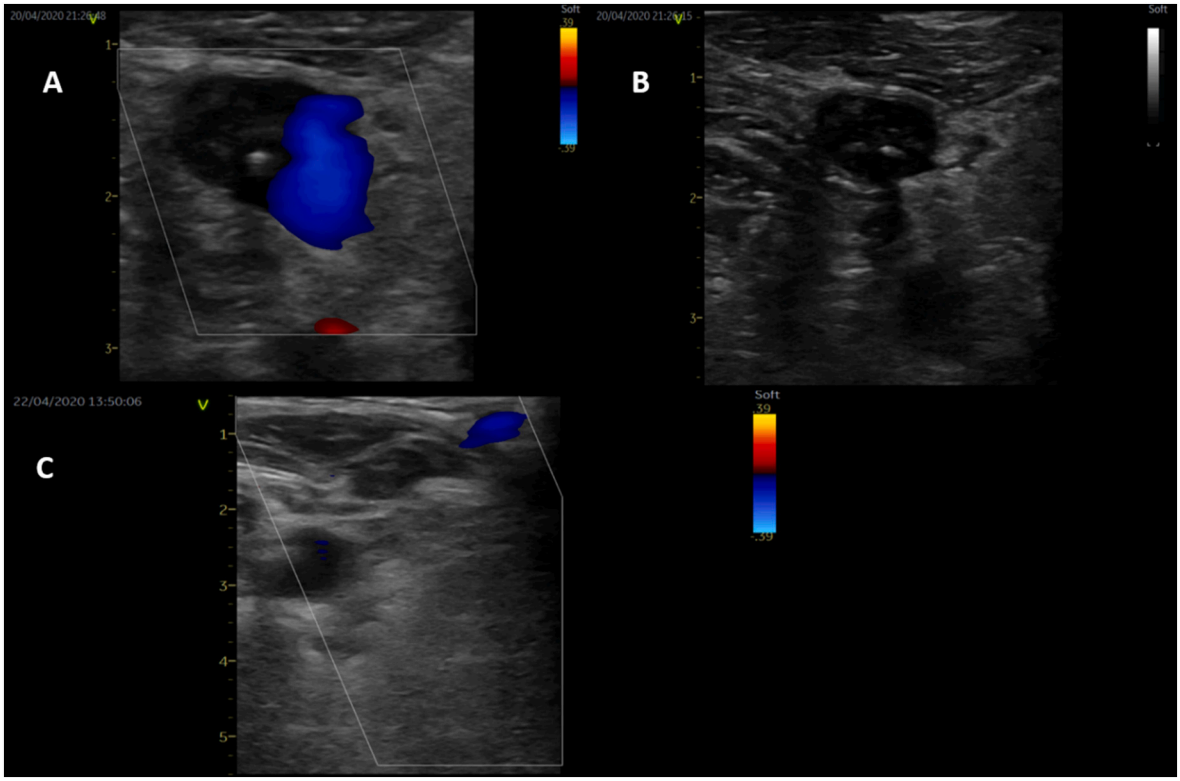

Fig. 1. Deep venous thrombosis in two patients receiving therapeutic anticoagulation.
A, B. Presence of a thrombus partially obstructing the left internal jugular vein in a 64-year old female patient with Covid-19.
C. Thrombus fully obstructing the left internal jugular vein in a 77-year old male patient with Covid-19.

In conclusion, Covid-19 patients present a state of hypercoagulability and are at increased risk to suffer from the formation of pulmonary vascular macrothrombi; van Dam's study confirms this notion. Additionally, PEEP application (externally squeezing alveolar vessel lumen) may further deteriorate the right ventricular size and, consequently, function in mechanically ventilated Covid-19 patients. Therefore, increased prophylactic dose of anticoagulation is recommended in Covid-19 patients. A systematic ultrasonographic evaluation for thrombosis occurrence should probably be adopted in severe Covid-19, especially when mechanically ventilated, so that therapeutic anticoagulation be promptly initiated. Finally, clinicians should be aware of all these factors -coagulopathy, PEEP effects, and lung infiltrate deterioration- that may account for the patients' clinical deterioration.

Declaration of competing interest

None.

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