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Letter to the Editors-in-Chief

Effect of therapeutic anticoagulation on gas exchange in mechanically ventilated COVID-19 patients: A secondary analysis of the COVID-HEP trial

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Introduction

SARS-CoV2 infections can progress to acute hypoxemic respiratory failure (AHRF) and adult respiratory distress syndromes (ARDS). Thrombotic microangiopathy of the pulmonary vasculature has been reported in autopsy series and might contribute to the occurrence of AHRF in SARS-CoV2 pneumonia. Based on this rationale therapeutic anticoagulation could improve gas exchange among COVID-19 patients with AHRF. This concept was tested in the pilot trial (HESACOVID) [1], which randomized 20 COVID-19 patients requiring mechanical ventilation to either therapeutic or prophylactic enoxaparin. The authors observed an improvement of oxygenation in the therapeutic group at 7 and 14 days compared to the prophylactic group. Although multiple studies have failed to demonstrate the benefit of therapeutic anticoagulation versus prophylactic anticoagulation in reducing mortality [2], the impact on gas exchange has been much less studied. We recently published the results of a multicenter, randomized controlled trial, including acutely ill medical COVID-19 patients with D-dimer >1000 ng/mL or critically ill COVID-19 patients with a 30-day follow-up [3]. As a secondary analysis of the COVID-HEP trial, our aim was to explore the impact of therapeutic anticoagulation on the evolution of gas exchange (PaO2/FiO2 or P/F ratios) among mechanically ventilated patients, similarly to the HESACOVID trial.

Methods

The COVID-HEP multicenter, open-label, randomized controlled trial of therapeutic-dose vs. low- or intermediate-dose anticoagulation for hospitalized patients has been described elsewhere [3]. It included patients with a biologically proven COVID-19 infection and a severe disease, defined by an admission D-dimer level >1000 ng/mL for acute medical wards, or a hospitalization in intermediate care/intensive care units (IMCU/ICU). Inclusion had to occur within 48 h of hospital admission or admission to the ICU. Exclusion criteria included ongoing therapeutic anticoagulation for any indication other than COVID-19, contraindication to therapeutic anticoagulation, a high risk of bleeding, ongoing pregnancy, extreme body weight (<40 kg and >150 kg), and participation to another clinical trial.

For this pre-specified secondary analysis, we analyzed only mechanically ventilated patients at baseline. Patients were randomized to therapeutic "high-dose" anticoagulation (enoxaparin 1 mg/kg twice daily or unfractionated heparin (UFH) according to anti-Xa dosing), or to an "intermediate-dose" anticoagulation (enoxaparin 40 mg b.i.d. or UFH 15000 IU daily if body weight < 100 kg, or enoxaparin 60 mg b.i.d. or UFH 20000 IU daily if ≥100 kg). We followed participants for 30 days and screened for proximal deep vein thrombosis between day 5–10 with compression ultrasound. Ethics approval from all centers and informed consent from all patients or their relatives were obtained.

PaO2/FiO2 ratios were those recorded at the time of inclusion, then daily until day 7 (independently of the duration of invasive mechanical ventilation (IMV)). One participant had only 2 measured P/F ratios (baseline and day 7). Seven participants had a total of 11 missing P/F ratios (6 % of all measures) from baseline to day 7. Missing P/F ratios were replaced by an estimate of P/F based on FiO2 and SaO2 values [4]. We used a mixed linear model comparing the improvement slopes of the P/F ratios over time between the 2 groups. We conducted a sensitivity analysis by excluding the 11 estimated P/F ratios. All statistical analyses were conducted on R software, version 4.0.2, and all statistical tests were two-sided with a significance level of 5 %.

Results and discussion

A total of 23 patients were included, 14 in the high-dose group and 9 in the intermediate-dose group (Table 1). The median SOFA scores at baseline were similar (6), as was the FiO2 (40 % in high-dose group vs 38 % in intermediate-dose group). All patients except one, in the intermediate-dose group, received dexamethasone. Over study time, none received extracorporeal membrane oxygenation and 57.1 % vs. 66.7 % used prone position sessions in the high-dose vs. intermediate-dose group. Three participants were censored in the high-dose group because of study withdrawal, all after the first seven days.

At baseline and at 7 days, mean P/F ratios were 24.6 kPa (SD 7.6)

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Table 1
Patient characteristics at baseline.

	High dose (n = 14)	Low dose (n = 9)
Mean Age (years)	61.6 (12.2)	63.1 (12.6)
Mean Body mass index	31.9 (4.3)	28.9 (5.7)
Women	5 (35.7 %)	3 (33.3 %)
Caucasian	11 (78.6 %)	5 (55.6 %)
Diabetes	1 (7.1 %)	3 (33.3 %)
Hypertension	6 (42.9 %)	5 (55.6 %)
Previous cardiovascular disease	1 (7.1 %)	0 (0.0 %)
Chronic pulmonary disease	1 (7.1 %)	1 (11.1 %)
Active cancer	0 (0.0 %)	1 (11.1 %)
History of venous thromboembolism	0 (0.0 %)	0 (0.0 %)
PE excluded prior inclusion	10 (71.4 %)	7 (77.8 %)
D-dimer baseline		
Median (IQR)	1130 (768–1400)	1338 (542–1841)
FiO_2% baseline		
Median (IQR)	40 (32–49)	38 (35–40)
SOFA at baseline		
Median (IQR)	6 (5–7)	6 (4–7)
First study treatment		
Enoxaparin	8 (57.1 %)	7 (77.8 %)
Unfractionated heparin	6 (42.9 %)	2 (22.2 %)
Use of vasopressor	10 (71.4 %)	7 (77.8 %)
Use of dexamethasone	14 (100.0 %)	8 (88.9 %)
Use of tocilizumab	2 (14.3 %)	1 (11.1 %)

and 27.8 kPa (SD 6.9) in the high-dose group and 22.2 kPa (SD 5.2) and 25.6 kPa (SD 8.1) in the intermediate-dose group, respectively. This increase of P/F ratios did not statistically or meaningfully differ between both groups (p = 0.54) (Fig. 1). The results of the sensitivity analysis excluding extrapolated P/F ratios were similar (data not shown, p = 0.73). Median durations of mechanical ventilation and ICU stay were 9 and 10 days, and 8 and 9 days, respectively. Also, in the high-dose group vs. the intermediate-dose group, the 30-day mortality (9.1 % vs. 22.2 %, P = 0.38), risk of arterial thrombosis (7.1 % vs. 22.2 %, P = 0.36), risk of VTE (0 % vs. 11.1 %, P = 0.21) and risk of major bleeding (7.1 % vs. 22.2 %, P = 0.28) did not differ at 30 days.

We found no effect of high-dose anticoagulation on early respiratory status in ventilated COVID-19 patients, which contrasts with the results the HESACOVID study [1]. However, some differences should be noted. First, the observation period was longer (14 days) in the HESACOVID study. Second, the control group differed across studies: The HSACOVID used a prophylactic anticoagulation while the COVID-HEP study used an intermediate-dose anticoagulation in the control group. Finally, patients were more profoundly hypoxemic at baseline in the HESACOVID study (FiO2 70 % vs 40 % in our study) and more severe (SOFA score 10 vs 6). Moreover, pulmonary embolism was ruled out in almost 3/4 of the patients included in the COVID-HEP study. These elements may contribute to the reduced benefit of high-dose anticoagulation in the latter study.

Nevertheless, there is homogeneous data showing the lack of clinical improvement by therapeutic anticoagulation in several international platform studies (REMAP-CAP, ACTIV-4a and the ATTACC) [5]. If concrete data on gas exchange are missing, it is unlikely that a difference would be meaningful since no difference was shown in terms of number of days free of cardiovascular or respiratory organ support.

The effects of anticoagulants in ARDS have been tested in small preclinical and clinical trials, even before the COVID-19 pandemic with mitigated results [6] and their use is currently not recommended. As therapeutic heparinization alone could be insufficient to re-establish vascular patency, systemic thrombolysis has also been proposed by some authors. In a pilot randomized clinical trial including 15 patients [7] with severe COVID-19 ARDS and D-dimer levels >3000 ng/mL, patients were randomized to one of the following 3 regimens: low dose tissue plasminogen activator followed by therapeutic anticoagulation with UFH, therapeutic anticoagulation with UFH or prophylactic anticoagulation with UFH. The magnitude of improvement of P/F ratio at 48 h was modest (−15.8 %) and all 5 patients randomized to thrombolytic therapy died. Douin et al. retrospectively used data from a multicenter cohort study of critically ill adults with COVID-19 (STOP-COVID registry) to examine the safety and efficacy of tPA in this setting

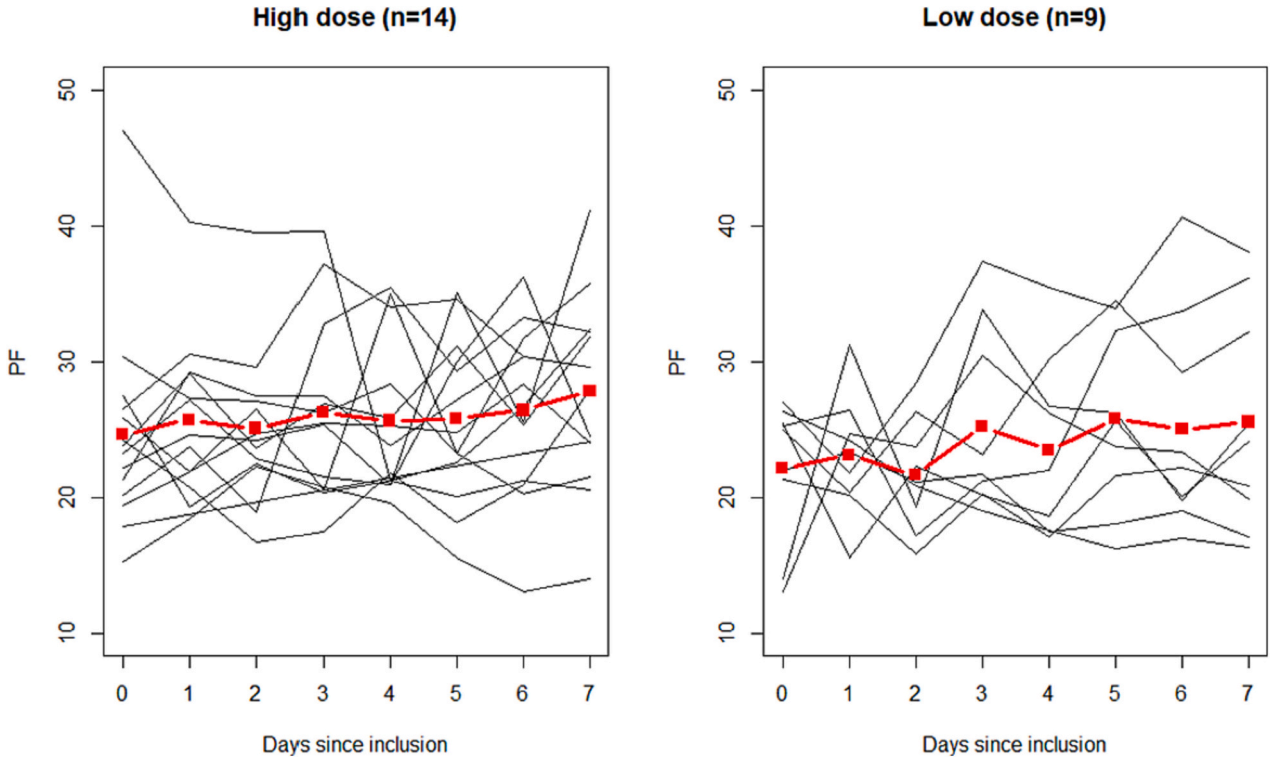

Fig. 1. Mixed linear model comparing the improvement slopes of the ratios over time between the high dose and low dose groups (p = 0.54).
PF = PaO2/FiO2 ratio, in Kpa.
Slope within each study arm: Low dose arm: 0.52 (95%CI 0.04 to 1.01), p = 0.03. High dose arm: 0.33 (95%CI −0.07 to 0.72), p = 0.104.

[8]. All patients who received tPA for confirmed pulmonary embolism (PE) or suspected PE within 14 days after ICU admission were included and followed for 14 days until discharge or death. Among 5154 patients, 93 received tPA. P/F ratios were not improved and six patients experienced a major bleed. Finally, a recent open-label trial randomized 50 adults with COVID-19-induced respiratory failure requiring mechanical ventilation and showed that the combination of tPA bolus plus heparin was safe [9]. The authors noted a significant improvement in P/F ratios when tPA was administered as a bolus, which was not longer the case when given continuously.

None of these studies was powered to formally prove or exclude the utility of fibrinolytic therapy or anticoagulation to improve the oxygenation. From a pure physiological point of view, the possibility that increased lung perfusion could improve oxygenation is not unequivocal. Although microvascular thrombosis may increase dead space ventilation, it is worth remembering that the dead space effect (low perfusion in relation to ventilation, $V/Q > 1$) per se does not lead to hypoxemia, or only indirectly by the development of low V/Q in other areas of the lungs by redistribution of perfusion from obstructed lung vessels, which can be aggravated by the loss of hypoxic vasoconstriction. ARDS is above all characterized by diffuse alveolar damage that leads to an inflammatory cell-rich proteinaceous edema, local alveolar hypoventilation and atelectasis. Perfusion of these areas ($V/Q < 1$ or 0) leading to admission of non-oxygenated blood to the arterial systemic circulation (shunt effect) remains the main cause of hypoxaemia [10] and in this setting, reperfusion by any means should only provide marginal benefit.

We acknowledge important limitations. In this pre-planned subgroup secondary analysis, the number of observations was low. Patients were only observed over the first 7 days and improvement beyond that cannot be ruled out. Patients in the control group received intensified prophylaxis which may have lessened the effects of anticoagulation.

Nevertheless, we did not observe that therapeutic anticoagulation of COVID-19 ARDS patients treated with mechanical ventilation modified P/F ratios on the first 7 days, compared with intermediate-dose anticoagulation.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] A.C.B. Lemos, D.A. do Espirito Santo, M.C. Salvetti, Therapeutic versus prophylactic anticoagulation for severe COVID-19: a randomized phase II clinical trial (HESACOVID), Thromb. Res. 196 (2020) 359–366.
[2] L.K. Moores, T. Tritschler, S. Brosnahan, et al., Thromboprophylaxis in patients with COVID-19: a brief update to the CHEST guideline and expert panel report, Chest 162 (1) (2022) 213–225.
[3] M. Blondon, S. Cereghetti, J. Pugin, et al., Therapeutic anticoagulation to prevent thrombosis, coagulopathy, and mortality in severe COVID-19: the swiss COVID-HEP randomized clinical trial, Res. Pract. Thromb. Haemost. 6 (4) (2022), e12712.
[4] T.W. Rice, A.P. Wheeler, G.R. Bernard, et al., Comparison of the SpO2/FIO2 ratio and the PaO2/FIO2 ratio in patients with acute lung injury or ARDS, Chest 132 (2) (2007) 410–417.
[5] Investigators R-C, Investigators AC-a, Investigators A, Therapeutic anticoagulation with heparin in critically ill patients with Covid-19, N. Engl. J. Med. 385 (9) (2021) 777–789.
[6] M. Camprubi-Rimblas, N. Tantinya, J. Bringue, R. Guillamat-Prats, A. Artigas, Anticoagulant therapy in acute respiratory distress syndrome, Ann. Transl. Med. 6 (2) (2018) 36.
[7] F. Rashidi, S. Barco, P. Rezaeifar, et al., Tissue plasminogen activator for the treatment of adults with critical COVID-19: a pilot randomized clinical trial, Thromb. Res. 216 (2022) 125–128.
[8] D.J. Douin, S. Shaefi, S.K. Brenner, et al., Tissue plasminogen activator in critically ill adults with COVID-19, Ann. Am. Thorac. Soc. 18 (11) (2021) 1917–1921.
[9] C.D. Barrett, H.B. Moore, E.E. Moore, Study of alteplase for respiratory failure in SARS-CoV-2 COVID-19: a vanguard multicenter, rapidly adaptive, pragmatic, randomized controlled trial, Chest 161 (3) (2022) 710–727.
[10] L. Gattinoni, S. Coppola, M. Cressoni, M. Busana, S. Rossi, D. Chiumello, COVID-19 does not Lead to a "Typical" acute respiratory distress syndrome, Am. J. Respir. Crit. Care Med. 201 (10) (2020) 1299–1300.

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