Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

European Journal of Internal Medicine 104 (2022) 118–119

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Letter to the Editor

Supine vs prone position in mild to moderate COVID-19 pneumonia: The impact of proning on computed tomography findings

Dear Editor,

Blood gas exchange impairment and beneficial role of proning in mild to moderate pneumonia due to coronavirus disease 2019 (COVID-19) has been shown to be determined, at least in part, by a vascular pulmonary dysregulation [1,2]. In vivo histopathological findings are characterized in fact by dilated alveolar capillaries often placed in superimposed rows, dilated post-capillary venules, patchy type II pneumocytes hyperplasia, lymphocytic infiltrates more prominent around venules and accumulation of alveolar macrophages. Moreover, an overexpression of indoleamine dioxygenase, the enzyme involved in the control of vascular tone and lymphocytic traffic, has been demonstrated in the endothelial cells covering pulmonary capillaries and venules [2]. These observations [1–6] suggest that gravity might also play a role in the determination of pulmonary computed tomography (CT) scan features. The aim of our study was to compare CT scan modifications, in terms of density and extent, of pulmonary infiltrates in the switching from the supine to the prone position. This observational single-center prospective study was approved by the Ethical Committee of the Azienda USL Romagna and was part of the trial PAESI-COV-19, registered on ClinicalTrials.gov, NCT04741178 (retrospectively registered on February 4th 2021). Eligibility criteria included: confirmed diagnosis of COVID-19 pneumonia (RT-PCR and chest X rays infiltrates), awake patients spontaneously breathing with or without non-invasive oxygen supply (with mask, high flow nasal cannula or even helmet and C-PAP modality); capability of maintaining the prone position; age $\geq$ 18 years. One hundred twenty three consecutive patients were enrolled in a two months-period (2 November 2020 to 2 January 2021); fifty-two (24 females and 28 males) were included [mean age 81.2 $\pm$ 6.5 (66–93). Sixty-one patients were excluded being too fragile to collaborate(38 males and 21 females mean age 81.2+/−6.5) or because pregnant ($n = 2$). CT scan examinations were performed with a standardized protocol (120 KV with automatic dose modulation of in supine and prone position; slice thickness 1,25 mm; rotation time 0.6 ms; Lightspeed 16 slices; GE Milwaukee WI). The radiological semiquantitative score adopted was that one proposed by Zhou et al. [7], with a range from 0 to 48. Moreover, to quantify the variation of density in the gravity dependent vs non-gravity dependent lung zones, we introduced a weighted scoring system in which the extent of each radiological finding was multiplied by a number from 1 to 5, according to the increase of CT scan density of the finding. So that, the percentage of the extent for each finding was multiplied by 1 for ground glass; 2 for crazy paving; 3 for part-solid ground glass; 4 for consolidation with perilobular pattern; 5 for homogeneous, alveolar, consolidation. As result, each zone could potentially range from 0 to 500, (e.g. if the extent is 50%, half composed by ground glass and half by crazy paving, 25 was multiplied by 1 and 25 by 2 with a resulting weighted score of 25+50=75). The terminology adopted for each pattern was that present in the glossary of the Fleischner Society and in the recent COVID-19 literature. To quantify the entity of change in prone position, the gravity dependent zones in supine (posterior) were compared with the dependent zones in prone lying (anterior). Moreover, to identify the effects of proning on the overall lung parenchyma, a total score (resulting from the sum of each lung zone score) of the supine position was compared with the total score of the prone position. Finally, the presence and the entity of vessel enlargement was analyzed in both positions, measuring a target vein in the dorsal segment of the right upper lobe and in the postero-basal segment of the right lower lobe. Statistical analyses were performed using STATA16 (StataCorp., College Station, TX, USA). According to the acute respiratory distress syndrome (ARDS) score [8], the cohort was represented by 30 patients with a PaO2/FiO2-ratio $\geq$ 300; 17 patients with a 200 $\leq$ PaO2/FiO2-ratio $<$ 300, and 5 patients with 100 $\leq$ PaO2/FiO2-ratio $<$ 200. A coexistence of CT scan patterns was quite common. The most representative findings in the supine position were: crazy paving (23 cases); part-solid ground glass attenuation (33) and alveolar consolidation (33). After switching the position, most of these findings showed a substantial qualitative change; so in 33 cases with consolidation, 8 turned into part-solid ground-glass, 6 in crazy paving, 10 in perilobular pattern, and 6 in ground-glass attenuation. In 23 cases with crazy paving at baseline, 18 changed into a ground glass pattern, one case turned into part-solid attenuation, one case into perilobular attenuation; in 3 cases, the pattern remained substantially stable. Finally, in 33 patients with part-solid-ground glass aspects, 16 turned into pure ground-glass attenuation, 6 into a perilobular pattern ($n = 6$). In the remaining 11 subjects, the pattern remained unaltered. As final result, in prone position the parenchymal changes showed an overall less density attenuation, in which the most representative findings were: part-solid ground glass ($n = 20$); pure ground glass ($n = 14$); crazy paving ($n = 6$); and perilobular pattern ($n = 4$). The comparison of total supine score with the prone one showed in fact a drop of density with significant difference (median 635 [485]; $z = 5.08$, $p < 0.01$), and, above all, a significant decrease in density was documented in gravity dependent zones (supine vs prone: median 330 [245]; $z = 6.23$, $p < 0.0001$). Finally, the pulmonary veins showed a significant variation in diameter as well. The caliber of the selected vein in the supine position (median 6.60 [1.40]) were significantly higher compared to those in the prone position (median 4.5 [1.85]; $z = 6.26$, $p < 0.0001$). n 4 cases, we didn't observe any change of the diameter comparing the supine with the prone lying. In these 4 cases, a predominant perilobular pattern resembling an organizing pneumonia with a minimal vessel enlargement was present, as confirmed by cryobiopsy in one patient. In this study, we highlighted CT parenchymal modifications of proning in mild to moderate COVID-19 pneumonia patients, consisting in a significant

https://doi.org/10.1016/j.ejim.2022.06.012
Received 24 April 2022; Received in revised form 18 May 2022; Accepted 15 June 2022
Available online 17 June 2022

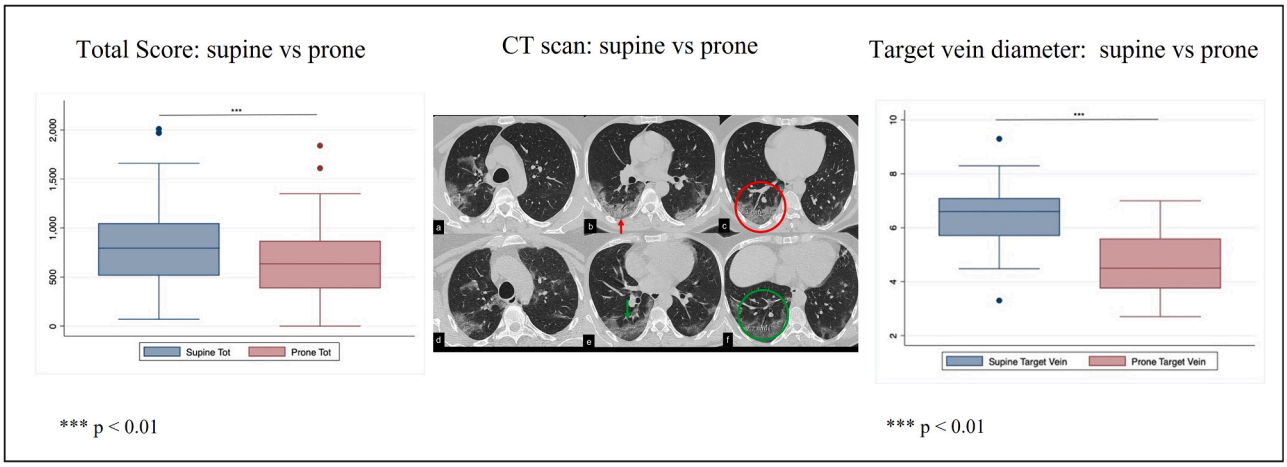

Fig. 1. Boxplots of the radiological scores in supine (blue) and prone (red) position: statistically significant levels ($p < 0.01$) were reported both in the total score and the target vein diameter, in the change from supine to prone position. In the center of the figure panel, CT scan in supine (a-c) and prone position (d-f). In supine: areas of peripheral ground glass and crazy paving attenuation are present in both lower lobes, associated with vessel enlargement (b; red arrow and c, red circle). Switching in the prone position (d-f), the areas of crazy paving are reduced in extension and density, becoming ground glass (e, green arrow) and the vessel enlargements disappear (e, green arrow; f, green circle).

drop of density and of extension, particularly in the gravity dependent zones, with a re-distribution of the infiltrates to the anterior ones (new-gravity dependent zones). The drop of density associated with a significant reduction of the calibre of the pulmonary veins while turning from supine to the prone position is to be explained by changes in vascularity distribution (Fig. 1). These effects related to the gravity might be due in fact to the reduction of alveolar vascular engorgement in the affected areas. Ackermann and coworkers [1], in autopsy, and our group in vivo [2], through lung cryobiopsies, documented this intra-parenchymal vascular overgrowth. A blood overflow was documented in the affected areas by dual energy CT scan by Lang et al. [9], and a reduction of right to left shunt and a more physiologic V/Q ratio when patients are proned were the key elements of the light-phenotype as suggested by Gattinoni et al. [10]. Our study confirms that in mild to moderate COVID-19 pneumonia CT findings are different from those observed in typical ARDS in which the histopathologic background is diffuse alveolar damage with hyaline membranes, interstitial and intra-alveolar edema, loss of surfactant and collapsed alveoli [1]. Ground glass attenuation, even alveolar consolidation change their density and position according to gravity and pulmonary veins diameter changes passing from supine to prone position.

The improvement, after pronation, in O_2 saturation has been clearly documented even in non intubated COVID-19 patients [11]. These effects are mainly explained by the improvement of the V/Q ratio (reduction of shunt) and our CT findings document that pulmonary vascular redistribution is evident in these subjects. In ARDS due to other causes, in which the histological background is diffuse alveolar damage, pronation under positive end-expiratory pressure is also beneficial. However in this scenario, the pathophysiology is different; these benefits seem to be mainly related to recruitment of collapsed alveoli, reduction of lung stress and strain [8,12].

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