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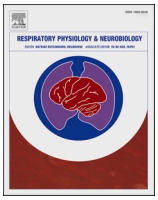

Short communication

Pathophysiology of hypoxemia in mechanically-ventilated patients with COVID-19: A computed tomography study

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ABSTRACT

The pathogenesis of hypoxemia during acute respiratory distress syndrome caused by SARS-CoV-2 infection (C-ARDS) is debated. Some observations led to hypothesize ventilation to perfusion mismatch, rather than anatomical shunt, as the main determinant of hypoxemia. In this observational study 24 C-ARDS patients were studied 1 (0–1) days after intubation. Patients underwent a CT scan analysis to estimate anatomical shunt and a clinical test to measure venous admixture at two fractions of inspired oxygen (FiO_2), to eliminate oxygen-responsive mechanisms of hypoxemia (ventilation to perfusion mismatch and diffusion limitation). In 10 out of 24 patients venous admixture was higher than anatomical shunt both at clinical (≈50 %) and 100 % FiO_2. These patients were ventilated with a higher PEEP and had lower amount of anatomical shunt compared with patients with venous admixture equal/lower than anatomical shunt. In a subset of C-ARDS patients early after endotracheal intubation, hypoxemia might be explained by an abnormally high perfusion of a relatively low anatomical shunt.

1. Introduction

Hypoxemia is commonly attributed to an abnormal venous admixture due to either a limited diffusion of oxygen through the alveolar-capillary membrane (diffusion limitation), a reduction of ventilation compared to perfusion (V/Q mismatch), or the perfusion of non-aerated alveoli (anatomical shunt). While hypoxemia due to the first two mechanisms can be corrected with supplemental oxygen, hypoxemia due to the anatomical shunt cannot. Hypoxemia during acute respiratory distress syndrome (ARDS) is generally attributed to an enlarged anatomical shunt (Pesenti et al., 1983; Gattinoni et al., 2006).

The pathophysiology of hypoxemia in COVID-19 ARDS (C-ARDS) is unclear. Some patients are severely hypoxemic despite a small anatomical shunt (Bos et al., 2020; Gattinoni et al., 2020a).

In this study we aimed to clarify the relative contribution of anatomical shunt (oxygen-unresponsive), diffusion limitation and V/Q mismatch (oxygen-responsive) to venous admixture in C-ARDS patients. We hypothesized that venous admixture exceeded anatomical shunt due to the presence of oxygen-responsive mechanisms.

2. Material and methods

This observational study was approved by our institutional review board (Comitato Etico Indipendente IRCCS Istituto Clinico Humanitas, protocol number 465/20, approved on March 17, 2020). Informed consent was obtained according to local regulations. All procedures were performed in accordance with the good clinical practice principles of the European Medicines Agency and the Declaration of Helsinki. The study was conducted in our intensive care unit during COVID-19 pandemic (March 2020-April 2021). Patients were eligible if they met the following criteria: i. laboratory confirmed COVID-19; ii. ARDS (ARDS Definition Task Force, 2012), needing mechanical ventilation with sedation and paralysis; iii. less than three days elapsed from intubation; iv. clinical need for lung computed tomography (CT) scan. Patients too unstable to be transferred to the radiology unit or with pulmonary air leak were excluded. Mechanical ventilation was set by the attending physician and kept constant throughout the study. Following a recruitment maneuver at an end-inspiratory airway pressure of 45 cmH_2O, anatomical shunt was estimated with a lung CT scan taken at

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end expiration with the endotracheal tube clamped, at the clinically-set PEEP. Each slice of the lung CT scan was manually segmented for subsequent analyses: using a dedicated software (SoftEFilm, Elekton; Nova Milanese, IT) and MATLAB (The MathWorksInc; Natick, MA), we measured the total (tissue and gas) volume, the tissue weight, and the gas volume of the whole lung and its four compartments: non-aerated (density above –100 Hounsfield Units), poorly-aerated (density between –100 and –500 H.U.), normally-aerated (density between –500 and –900 H.U.), and over-aerated (density below –900 H.U.). Assuming uniform distribution of pulmonary blood flow, we defined the anatomical shunt as the non-aerated lung weight compartment, expressed as percent of total lung weight (Cressoni et al., 2008).

After returning to the ICU a second recruitment maneuver was performed and mechanical ventilation was resumed as set by the attending physician. After 20 min of equilibration time, venous admixture was measured from arterial and central venous blood oxygen contents (Riley and Cournand, 1949) with FiO_2 initially set according to the clinical need (clinical FiO_2) and then increased to 100 %. Respiratory system mechanics were measured with end-inspiratory and end-expiratory pauses. Compliance and driving pressure were calculated using standard formulas.

The outcome of this study was the difference between anatomical shunt and venous admixture measured with clinical and 100 % FiO_2. To account for some measurement inaccuracy, venous admixture was considered higher than anatomical shunt if the difference between the two was greater than 10 % (i.e. venous admixture > anatomical shunt x 1.1). We quantified the relative contribution of anatomical shunt to venous admixture as anatomical shunt/venous admixture at clinical FiO_2 x 100. The sample size was based on feasibility considerations. Comparisons were performed using Mann-Whitney rank-sum test or Wilcoxon signed-rank test, applying Bonferroni correction for multiple comparisons.

3. Results

The study was conducted in our intensive care unit during COVID-19 pandemic (March 2020-April 2021). We studied 8 non-consecutive patients from 17/03/2020 to 31/05/2020. During this period 20 patients did not meet eligibility criteria: for 10 patients none of the study's authors was available, in 10 cases a CT scan had already been performed and was not considered clinically indicated to repeat a second CT scan. Furthermore, 15 patients had exclusion criteria: 13 were too unstable to be transferred to the radiology unit and 2 had evidence of pulmonary air leak. We then enrolled 16 consecutive patients from 01/01/2021 to 30/04/2021. During this period of time 6 patients did not meet all eligibility criteria: 4 patients weren't deeply sedated/paralyzed, 2 patients transferred from other hospitals came to our Center after more than three days of mechanical ventilation.

Patients were studied 1 (0–1) days after intubation. Baseline demographic and mechanical ventilation data are shown in Table 1. On average, the anatomical shunt was 30 (18–36)%, similar to venous admixture measured with either clinical (28 (16–37)%, p = 0.977) or 100 % FiO_2 (23 (17–35)%, p = 0.587). The venous admixture did not change when the FiO_2 was increased (28 (16–37)% vs 23 (17–35)%, p = 0.391). In 10 (42 %) patients, venous admixture at clinical FiO_2 was *higher* than anatomical shunt, which represented 61 (42–81)% of total venous admixture. Even in these patients, increasing the FiO_2 to 100 % did not decrease venous admixture (Fig. 1). These 10 patients differed from the other 14 for their higher PEEP but not for their circulating D-dimer (698 (407–1138) vs 558 (284–1059) ng/ml, p = 0.380) and C-reactive protein (8 (3–18) vs 8 (2–16), p = 0.770) (Table 1).

4. Discussion

In patients within three days of endotracheal intubation and mechanical ventilation for C-ARDS anatomical shunt represents a relevant proportion of total lung weight. While on average we found no differences between venous admixture and anatomical shunt, the individual behavior was variable and more than one third of patients had a venous admixture at clinical FiO_2 *higher* than the anatomical shunt.

Venous admixture is the *ideal* shunt that explains the observed hypoxemia. It should not be affected by (oxygen-responsive) diffusion limitation and V/Q mismatch when measured with 100 % FiO_2 (Farhi and Rahn, 1955). Ten patients had a venous admixture larger than the anatomical shunt even when ventilated with pure oxygen. There, one can hypothesize hyper-perfusion of collapsed lung regions due to local vasodilation or vascular obstruction of aerated lung areas (Gattinoni et al., 2020b; Santamarina et al., 2020). Of note, these patients were ventilated with higher PEEP than the others, possibly resulting in some vascular closure with blood flow diversion towards the anatomical shunt (thus worsening hypoxemia). While blood flow might be diverted from normally- to non-aerated lung units also due to local vascular thrombosis, we could not find any difference in D-dimer levels in blood or inflammatory markers between these two groups of patients.

Some limitations of this study are worth mentioning. First, venous admixture was measured using central, rather than mixed, venous blood. Second, we did not measure blood flow distribution within the lungs, thus we may have overestimated true anatomical shunt. Third, we did not properly assess the effect of PEEP.

Table 1
Characteristics of the overall population and of patients divided by venous admixture at clinical FiO_2 lower/equal or higher than the anatomical shunt.

Variable	All patients (n = 24)	Qs/Qt ≤ shunt (n = 14)	Qs/Qt > shunt (n = 10)	P-value*
Age, years	65 (61–70)	65 (61–73)	65 (61–67)	0.953
Male, n (%)	16 (70)	11 (79 %)	5 (50 %)	0.204
Body mass index, kg/m^2	28 (24–29)	25 (24–29)	28 (23–29)	0.837
Ventilatory Parameters				
Tidal volume, ml/kg IBW	6.1 (6.0–6.7)	6.1 (5.9–6.4)	6.3 (6.1–6.9)	0.394
Respiratory rate, breaths/min	18 (16–20)	18 (16–22)	16 (15–20)	0.154
Fraction of inspired oxygen, %	50 (50–55)	50 (50–60)	50 (50–50)	0.367
PEEP, cmH_2O	10 (10–12)	10 (10–10)	15 (10–15)	0.001
$P_{aw,plat}$, cmH_2O	20 (18–23)	20 (17–20)	22 (19–26)	0.077
Driving pressure, cmH_2O	9 (8–10)	9 (8–10)	8 (7–11)	0.745
$Compliance_{rs}$, ml/cmH_2O	46 (36–53)	46 (36–52)	46 (36–58)	0.860
Gas exchange				
$PaCO_2$, mmHg	49 (43–54)	50 (42–57)	48 (45–51)	0.597
PaO_2, mmHg	85 (70–102)	85 (70–100)	92 (70–112)	0.500
PaO_2/FiO_2, mmHg	169 (140–210)	169 (142–188)	183 (138–242)	0.349
Ventilatory ratio, l/minute	1.4 (1.2–1.8)	1.5 (1.3–1.9)	1.4 (1.2–1.5)	0.279
Hemodynamic Parameters				
Mean arterial pressure, mmHg	78 (72–84)	78 (73–80)	77 (71–90)	0.999
Heart rate, beats/minute	66 (58–75)	70 (58–77)	66 (61–68)	0.614
$ScvO_2$, %	75 (73–79)	75 (60–78)	76 (75–81)	0.187
Arterial lactate, mmol/l	1.1 (0.9–1.4)	1.1 (0.9–1.4)	0.9 (0.8–1.2)	0.287

List of abbreviations: FiO_2, fraction of inspired oxygen; Qs/Qt, venous admixture; IBW, ideal body weight; PEEP, positive end-expiratory pressure; $P_{aw,plat}$, plateau airway pressure; $Compliance_{rs}$, compliance of the respiratory system; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; PaO_2/FiO_2, arterial partial pressure of oxygen divided by fraction of inspired oxygen; $ScvO_2$, central venous oxygen saturation of hemoglobin

* p-value for comparison between patients with venous admixture at clinical FiO_2 lower/equal than anatomical shunt vs patients with venous admixture at clinical FiO_2 higher than anatomical shunt

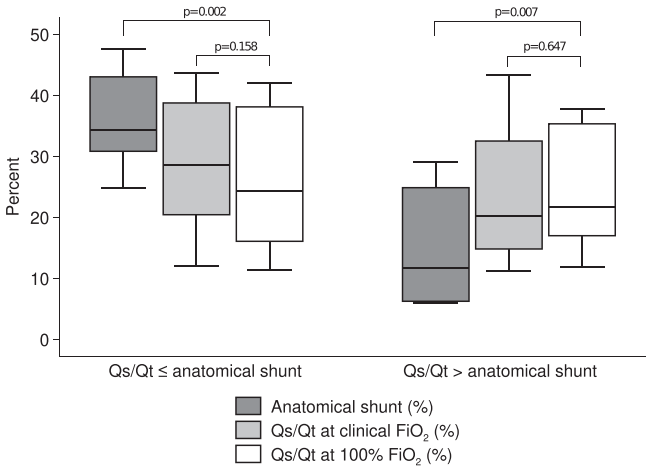

Fig. 1. Venous admixture and anatomical shunt in the two group of patients. Anatomical shunt (dark grey bars), venous admixture at clinical FiO_2 (light grey bars) and venous admixture at 100 % FiO_2 (white bars) in patients divided based on their venous admixture at clinical FiO_2 equal/lower (left) or higher (right) than the anatomical shunt. A p-value<0.0125 was considered statistically significant to account for multiple comparisons between groups. As groups were defined based on the difference between Qs/Qt at clinical FiO_2 and anatomical shunt, the comparison between these two groups was not performed. Qs/Qt, venous admixture.

5. Conclusions

In a small group of C-ARDS patients, the venous admixture frequently exceeded the anatomical shunt, as if other mechanisms contributed to hypoxemia. The response to pure oxygen ventilation suggests hyper-perfusion of the non-aerated lung as a possible mechanism of hypoxemia in these patients.

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CRediT authorship contribution statement

AS takes responsibility for the content of the manuscript, including the data and all the analyses. AS contributed to the conception and design of the study, data analysis and interpretation, and wrote the manuscript. AP contributed to the conception and design of the study, collection, analysis, and interpretation of the data, and critically revised the manuscript. MF and FP contributed to the collection, analysis, and interpretation of the data and revised the manuscript. LP and CM contributed to the collection of the data and revised the manuscript. AA, and MC contributed to the conception and design of the study, interpretation of the data, and revised the manuscript. All authors read and approved the final version of the manuscript.

Declaration of Competing Interest

None.

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