

Pulmonary Hemodynamics and Ventilation in Patients With COVID-19-related Respiratory Failure and ARDS

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Abstract

Background: It has been suggested that COVID-19-associated severe respiratory failure (CARDS) might differ from usual acute respiratory distress syndrome (ARDS) due to failing auto-regulation of pulmonary vessels and higher shunt. We sought to investigate pulmonary hemodynamics and ventilation properties in patients with CARDS compared to patients with ARDS of pulmonary origin.

Methods: Retrospective analysis of prospectively collected data of consecutive adults with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 patients treated on our ICU in 04/2020 and comparison of the data to matched controls with ARDS due to respiratory infections treated on our ICU from 01/2014 to 08/2019 and for whom pulmonary artery catheter data were available.

Results: CARDS patients (n = 10) had similar ventilation characteristics as compared to ARDS (n = 10) patients. Still, mechanical power applied by ventilation was significantly higher in CARDS patients (23.4 ± 8.9 J/min) than in ARDS (15.9 ± 4.3 J/min; $p < 0.05$). COVID-19 patients had similar pulmonary artery pressure but significantly lower pulmonary vascular resistance, as cardiac output was higher in CARDS vs. ARDS patients ($p < 0.05$). Shunt fraction and dead space were similar in CARDS compared to ARDS ($p > 0.05$) and was in both groups correlated with hypoxemia. The arterio-venous $p\text{CO}_2$ difference (DpCO_2) was elevated (CARDS 5.5 ± 2.8 mmHg vs. ARDS 4.7 ± 1.1 mmHg; $p > 0.05$) as was $P_{(v-a)}\text{CO}_2/C_{(a-v)}\text{O}_2$ ratio (CARDS mean 2.2 ± 1.5 vs. ARDS 1.7 ± 0.8 ; $p > 0.05$).

Conclusions: Respiratory failure in COVID-19 patients seems to differ only slightly from ARDS regarding ventilation characteristics and pulmonary hemodynamics. Differences are mainly due to increased CO_2 production in CARDS patients. Our data indicate microcirculatory dysfunction. More data needs to be collected to assure these findings and gain more pathophysiological insights in COVID-19 and respiratory failure.

Introduction

Severe acute respiratory syndrome-Coronavirus 2 (SARS-CoV-2) causes a disease termed COVID-19. Symptoms are ranging from mild upper airway symptoms to acute respiratory distress syndrome (ARDS). There are hints that some characteristics of respiratory failure in COVID-19 patients are different from acute respiratory distress syndrome as we know it from other causes e.g. viral or bacterial infection. We and others observed relatively normal respiratory mechanics¹ despite poor oxygenation. It has been suggested that in COVID-19-related ARDS (CARDS), this is in part due to defective pulmonary vasoregulation so that hypoxic pulmonary vasoconstriction does not occur, leading to ventilation/perfusion-mismatch and consequently may lead to profound hypoxemia². These findings and hypotheses led to the question if our present understanding of ARDS with regard to pulmonary hemodynamics and right heart failure can be transferred to CARDS.

Previous reports suggest that COVID-19 induces the massive release of cytokines, including interleukin 6 (IL-6) and hence it has been suggested to treat COVID-19 by IL-6 blockade. Increased pulmonary vascular resistance is a consequence of various factors including hypercarbia, acidosis, inflammation, vascular endothelial proliferation³ and hypoxic pulmonary vasoconstriction. There is ample evidence that perivascular inflammation triggered by various mediators, including IL-6, contributes to pulmonary vascular disease resulting in pulmonary hypertension. Pulmonary hypertension due to increased pulmonary vascular resistance is a common finding in ARDS^{4,5}. The exact prevalence of pulmonary hypertension in ARDS is not known^{4,6} and varies considerably across studies. These differences may result from general differences between cohorts, cardiovascular comorbidities, aetiology of ARDS and therapeutic interventions (e.g. permissive hypercapnia). ARDS normally is characterized by a low-pressure pulmonary oedema, shunt-related hypoxemia and reduced aerated lung volume causing severely impaired lung compliance. It is widely accepted, that ARDS patients with elevated pulmonary pressure are at risk of dying from right heart failure⁷.

In the present study, we compared CARDS patients to ARDS patients with regard to hemodynamic and derived physiologic parameters, to elucidate, if there are distinct features in CARDS that separate CARDS and ARDS with regard to ventilation and pulmonary hemodynamics.

Methods

This observational case-control study describes data of extended hemodynamic monitoring via pulmonary artery catheterization of 10 consecutive patients with laboratory confirmed COVID-19-related respiratory failure (CARDS) treated on our tertiary-care ICU in April 2020. Patients were mainly transferred for the possibility of ECMO support or for further management from hospitals under the surge of COVID-19 in near-by France. Further, we gathered the characteristics of mechanical ventilation, arterial blood gas and laboratory findings in these patients. Characteristics of ventilation and pulmonary hemodynamics were 1:1 compared to patients with ARDS due to pneumonia (n = 10). Groups were matched according to disease severity using the simplified acute physiology score II (SAPS II), PO_2/F_iO_2 ratio, age, sex and body mass index (BMI).

Ventilation was in pressure controlled mode in all patients. Generally, we targeted a protective ventilation approach, aiming at driving pressures below 15 cmH₂O and tidal volumes V_T of approx. 6 mL per kg of predicted bodyweight (PBW). Mean arterial pressure target is mainly 60–65 mmHg, if physiologic aims are reached. These include capillary refill time (i.e. warm periphery), urinary output (≥ 0.5 ml/kg/h) or lactate levels (≤ 2.0 mmol/l). Norepinephrine was the vasopressor of choice in patients with pH ≥ 7.25 . Inotrope use was initiated, if $S_{cv}O_2$ was below 65% despite adequate hemoglobin levels.

Measurements and data recording

Extended hemodynamic monitoring was established synchronized with collection of blood gas analysis. Briefly, after inserting a sheath catheter, a Swan-Ganz catheter (Edwards Lifesciences Corp., Irvine, CA,

USA) was advanced to the pulmonary artery till a curve characteristic for pulmonary capillary wedge pressure could be derived. Arterial and venous blood gases with parameters such as partial pressures of oxygen (pO_2) and carbon dioxide (pCO_2), hemoglobin, lactate, glucose, and pH were obtained via analysis on an ABL800 Blood Gas Analyzer (Radiometer, Copenhagen, Denmark).

Characteristics of ventilation correspond to the moment of data collection. Laboratory parameters were collected the same day of pulmonary artery catheterization. Protocols for hemodynamic measurement were identical for both cohorts.

Calculation of hemodynamic and physiologic parameters

Cardiac output (CO) was measured using pulmonary arterial catheters (PAC) with thermodilution technique. Cardiac index (CI) relates CO to body surface area, calculated according to Du Bois formula. The following variables were calculated: stroke volume ($SV = CO/HR$, mL); pulmonary pulse pressure ($PP = sPAP-dPAP$, mmHg); transpulmonary pressure gradient ($TPG = mPAP-PAWP$, mmHg); diastolic pressure gradient ($DPG = dPAP-PAWP$, mmHg); pulmonary vascular resistance ($PVR = TPG/CO$ Wood units: mmHg*min/L, or mmHg*s/mL); pulmonary arterial compliance ($C_{PA} = SV/PP$, mL/mmHg); time constant (RC time, $\tau = C_{PA} \times PVR$, s).

Further, we calculated the ratio of the venous–arterial CO_2 gap to arterial-venous oxygen content difference ($P_{(v-a)}CO_2/C_{(a-v)}O_2$) as $(P_vCO_2 - P_aCO_2)/(C_aO_2 - C_vO_2)$ with $C_aO_2 = (1.34 \text{ mL/g} \times S_aO_2 \times Hb) + (0.003 \text{ mL}/(\text{dL} \cdot \text{mmHg}) \times P_aO_2)$ and $C_vO_2 = (1.34 \text{ mL/g} \times S_vO_2 \times Hb) + (0.003 \text{ mL}/(\text{dL} \cdot \text{mmHg}) \times P_vO_2)$. DO_2 was calculated as $CO \times C_aO_2$ and VO_2 as $CO \times (C_aO_2 - C_vO_2)$. $P_{(v-a)}CO_2$ gap was calculated as $P_vCO_2 - P_aCO_2$. Calculation of estimated dead space fraction was done using a rearranged alveolar gas equation $V_D/V_T = 1 - [(0.86 \text{ mmHg} \times VCO_{2est}) / (VE \times P_aCO_2)]$ where VCO_{2est} is the estimated CO_2 production calculated gender specific from the Harris Benedict Eq. 8. Minute ventilation (VE) is obtained from the ventilator rate times expired tidal volume and P_aO_2 , P_aCO_2 from arterial gas analysis. Ventilatory ratio (VR), as a measure for ventilator efficiency was calculated as $(VE \times P_aCO_2)$ divided by $(100 \text{ mL}/\text{min} \times \text{predicted body weight (PBW; kg)} \times 40 \text{ mmHg (expected } P_aCO_2))$ ⁹. Predicted body weight was calculated according to the ARDSNet PBW calculator¹⁰. Pulmonary shunt fraction was calculated as $Q_S/Q_T = (C_cO_2 - C_aO_2)/(C_cO_2 - C_vO_2)$. Alveolar-arterial O_2 gradient ($A-aDO_2$) was calculated as $[F_iO_2 \times (\text{barometric pressure} - 47 \text{ mmHg}) - P_aCO_2/0.81] - [(P_aO_2 + \text{age in years}/4 \cdot \text{mmHg}) + 4]$. Barometric pressure was recorded on the day of pulmonary artery catheterization.

Mechanical power applied by ventilation was calculated by multiplying each component of the equation of motion by the minute ventilation using the following equation: mechanical power = $0.098 \times \text{tidal volumes} \times \text{respiratory rate} \times (P_{peak} - 0.5 \times \text{driving pressure})$ in J/min.

Statistical analysis

Data are reported as median (range) or median (range; mean \pm SD), if not otherwise indicated. Statistical analysis was performed with GraphPad Prism 5.02 (GraphPad Software, Inc., La Jolla, CA). Unpaired t-

test was used to test for differences between the groups as all groups showed Gaussian distribution in Kolmogorov-Smirnov test. P-values < 0.05 were considered significant.

Results

Baseline demographics and laboratory findings

All patients in the CARDS group received mechanical ventilation as result of SARS-CoV-2 infection with pneumonia and respiratory failure. These patients were matched to a historical cohort of ARDS patients treated on our ICU. SAPS II Score was 42 in the COVID-19 group (n = 10), and 41 in the ARDS group (n = 10). Patients in both groups had mild to severe ARDS, according to the Berlin classification of ARDS¹¹. P_aO_2/F_iO_2 did not differ between the two groups (118 vs. 120 in median; $p > 0.05$). Median age in CARDS patients was 62 years (range 59–71) compared to 71 in ARDS patients (range 45–85), $p > 0.05$. Nine out of ten CARDS and eight out of ten ARDS patients were male. Three of ten COVID-19 patients had obesity I°, three had normal BMI and 4 patients had light overweight, however there was no difference to ARDS patients. There was a statistically significant difference in body temperature during haemodynamic measurement. While ARDS patients had no fever (median 37.4 °C), every CARDS patient showed body temperature above 38.1 °C (median 38.5 °C).

Clinical characteristics and laboratory findings of the patients are shown in Table 1. In CARDS patients, CRP and Interleukin-6 was elevated. Procalcitonin was 0.69 ng/mL (0.09–276 ng/mL) in median. CRP in ARDS patients was slightly lower than in CARDS (104 vs. 234, $p > 0.05$). In CARDS D-Dimer levels were elevated with 3.2 mg/L (range 0.9–19.4 mg/L). Thrombocytes levels were in normal range. Renal function (creatinine 1.13 mg/dL) and liver function (bilirubin 1.15 mg/dL) were slightly decreased in both groups.

Table 1

Baseline characteristics and laboratory findings of CARDS patients (N = 10) compared to patients with ARDS due to pulmonary infections (N = 10) with invasive hemodynamic measurement (Interleukin 6 and PCT were not part of the laboratory routine for patients with usual ARDS at the time of evaluation).

Laboratory findings	CARDS; N = 10	ARDS; N = 10	P Value
	median (range; mean \pm SD)	median (range; mean \pm SD)	
Cause of ARDS	SARS-CoV2	7/10 CAP; 3/10 HAP	
SAPS	42 (29–54; 42 \pm 8)	41 (25–51; 38 \pm 8)	> 0.05
P _a O ₂ /FiO ₂	120 (57–171; 114 \pm 42)	118 (73–259; 142 \pm 65)	> 0.05
Age [years]	62 (59–71; 62.6 \pm 5.1)	71 (45–85; 69 \pm 12.2)	> 0.05
Male [N;%]	9/10; 90%	8/10; 80	
BMI [kg/m ²]	28.5 (24–33; 28 \pm 3)	27 (22–56; 32 \pm 11.4)	> 0.05
Norepinephrine	4/10; 40%	6/10; 60%	
Hemoglobin [g/dL]	9.4 (7.1–14; 10.0 \pm 2.2)	9.5 (7.1–12 – 2; 9.8 \pm 1.8)	> 0.05
Leukocytes [G/L]	9.45 (6.1–24.1; 11 \pm 5)	12.6 (1.7–31.4; 14 \pm 8)	> 0.05
Thrombocytes [G/L]	186 (71–320; 190 \pm 64)	137 (18–455; 165 \pm 129)	> 0.05
CRP [mg/L]	234 (94–399; 233 \pm 115)	104 (35–447; 152 \pm 117)	> 0.05
Creatinin [mg/dL]	1.1 (0.7–3.2; 1.3 \pm 0.7)	1.9 (0.5–4.6; 2.1 \pm 1.3)	> 0.05
Bilirubin [mg/dL]	1.2 (0.3–7; 1.6 \pm 2)	0.6 (0.2–1.5; 0.7 \pm 0.4)	> 0.05
Interleukin-6 [pg/mL]	471 (11–2397; 828 \pm 940)	n.a.	
PCT [ng/mL]	0.7 (0.09–276; 28 \pm 87)	n.a.	
BMI Body mass index; CARDS COVID-19 associated ARDS CAP community acquired pneumonia; HAP Hospital acquired pneumonia SAPS Simplified acute physiology score; CRP C-reactive protein; NT-proBNP N-terminal pro-B-type natriuretic peptide; PCT Procalcitonin;			

Characteristics of ventilation and blood gas analysis in COVID-19 and comparison to ARDS patients

All patients received ventilation in a pressure-controlled mode. Plateau pressure was 25 cmH₂O (range 20–32) in CARDS and 23 cmH₂O (range 20–28) in ARDS patients. PEEP and Δ P did not differ significantly between the two groups (CARDS PEEP: 10 cmH₂O; Δ P 14 cmH₂O vs. ARDS PEEP 12 cmH₂O; Δ P 18 cmH₂O; p > 0.05). Tidal volumes resulting from these pressure characteristics were 9 mL/kg in CARDS vs. 8 mL/kg in ARDS. None of the CARDS patients had tidal volumes less than 400 mL (median 613 mL; range 415–994 mL). Higher tidal volume in CARDS patients was a result of better compliance in these patients. Lung compliance was 42 mL/cmH₂O (range 27–77 mL/cmH₂O) in CARDS patients

compared to 37 mL/cmH₂O (range 23–67 mL/cmH₂O) in ARDS patients ($p > 0.05$). Only in four COVID-19 patients lung compliance was less than 40 mL/cmH₂O. 50% of the patients needed a PEEP equal to or higher than 10 cmH₂O to maintain an adequate oxygenation. Gas exchange was different between groups CARDS and ARDS with higher $P_a\text{CO}_2$ in the CARDS group (52 mmHg vs. 41 mmHg; $p > 0.05$), causing mild respiratory acidosis in CARDS (pH 7.33 vs. 7.46; $p < 0.05$) despite higher minute ventilation volume. The mechanical power applied by ventilation in CARDS patients was significantly higher than in ARDS patients ($p < 0.05$). **Table 2** shows characteristics of ventilation in CARDS patients compared to patients with usual ARDS.

Hemodynamic monitoring in CARDS vs. ARDS patients

We compared pulmonary hemodynamics as assessed by pulmonary artery catheter in CARDS compared to ARDS patients (**Table 3**). Time between diagnosis of respiratory failure and PAC insertion was in median 13 days in CARDS patients. ARDS patients received PAC insertion in median 7 days from diagnosis. Time between intubation and PAC was 11 days (1–21 days) in CARDS patients and 3 (0–9 days) in ARDS patients ($p < 0.05$). This delay was mainly due to the fact that most CARDS patients were diagnosed with respiratory failure, intubated and transferred to our ICU from other hospitals.

Pulmonary arterial hypertension was common in both, CARDS and ARDS patients. Nine out of ten CARDS and ARDS patients had elevated mPAP values above 25 mmHg. Systolic and diastolic pulmonary arterial pressure did not differ between groups ($p > 0.05$). Both groups had partly post-capillary pulmonary hypertension with pulmonary capillary wedge pressures higher than 15 mmHg. ARDS patients had combined pre- and post-capillary pulmonary hypertension ($\text{PVR} > 3 \text{ WU}$, $\text{DPG} \geq 7$), while CARDS patients showed more isolated post-capillary pulmonary hypertension (median $\text{PVR} \leq 3 \text{ WU}$, median $\text{DPG} = 7 \text{ mmHg}$). Only one patient in the CARDS group showed $\text{DPG} \geq 7 \text{ mmHg}$ and $\text{PVR} > 3 \text{ WU}$ meeting criteria of pre- and post-capillary pulmonary hypertension¹². PEEP was not correlated with PVR in either group ($p > 0.05$). The pulmonary vascular compliance C_{PA} as part of right ventricular afterload, showed no significant difference, being $4.1 \text{ mL} \times \text{mmHg}^{-1}$ in CARDS patients vs. $2.8 \text{ mL} \times \text{mmHg}^{-1}$ in ARDS patients. There was a negative correlation between PVR and C_{PA} . The product of $\text{PVR} \times C_{\text{PA}}$ was thus similar between groups ($p > 0.05$), however the higher C_{PA} in CARDS patients indicated sufficient RV-PA coupling. Indeed, no CARDS patient had right heart failure.

In both groups cardiac output was in a normal range. Patients with CARDS had significant higher cardiac output ($p < 0.05$) and slightly higher stroke volume ($p > 0.05$) than ARDS patients. Systemic vascular resistance (SVR) was significantly higher in patients with ARDS than in patients with CARDS ($p < 0.05$). No CARDS patient received inotropes. In the CARDS group 4 patients received norepinephrine during measurement and in the ARDS group 6 patients.

Physiological parameters derived from pulmonary artery catheter measurements and blood gas analysis in patients with CARDS and ARDS

As patients with CARDS presented with elevated $p_a\text{CO}_2$, we calculated the estimated CO_2 production for both groups ($\text{VCO}_{2\text{est}}$). Indeed, patients with CARDS had a statistically significantly higher estimated CO_2 production. Hence, the statistically significant higher minute ventilation noted in CARDS patients could not compensate the higher production. Ventilatory ratio (VR) was higher in patients with CARDS, but the difference did not reach statistical significance. The same was true for physiological dead-space (V_D/V_T). V_D/V_T was strongly correlated with VR in patients with CARDS ($p < 0.05$; Fig. 1A), but not patients with ARDS. In CARDS patients, there was a negative correlation between $P_a\text{O}_2/F_i\text{O}_2$ and ventilatory ratio ($p < 0.05$; Fig. 1B). Calculated shunt fraction was not different between groups.

The ratio of the venous–arterial CO_2 gap to arterial-venous oxygen content difference ($P_{(v-a)}\text{CO}_2/C_{(a-v)}\text{O}_2$ ratio) was not different between groups, however patients with CARDS had a higher ratio than patients with ARDS (2.0 vs. 1.6). Additionally, the difference between central-venous and arterial CO_2 ($\Delta p\text{CO}_2$) was different between groups, with a higher difference in CARDS patients (6.2 vs. 4.7 mmHg), but this difference did not reach statistical significance. Lactate levels, mixed venous oxygenation and alveolar-arterial Oxygen difference (AaDO_2) were similar in both groups. The parameters are summarized in Table 4.

Table 4

Physiological parameters derived from measurements in CARDS patients (N = 10) and ARDS of other causes (N = 10) acquired Swan-Ganz catheterization and blood gas analysis. Barometric pressure was recorded on the day of the actual Swan-Ganz catheterization.

Variable	CARDS; N = 10 median (range; mean \pm SD)	ARDS; N = 10 median (range; mean \pm SD)	p-value
$P_{(v-a)}\text{CO}_2/C_{(a-v)}\text{O}_2$	2.0 (0.5–5.6; 2.2 \pm 1.5)	1.6 (0.3–3.3; 1.7 \pm 0.8)	> 0.05
$\Delta p\text{CO}_2$ [mmHg]	6.2 (1.2–9.8; 5.5 \pm 2.8)	4.7 (2.5–5.3; 4.7 \pm 1.1)	> 0.05
$s_v\text{O}_2$ [%]	73 (69–79; 73 \pm 3)	68 (46–79; 68 \pm 9.6)	> 0.05
Lactate (art.)	1.4 (0.7–1.9; 1.4 \pm 0.3)	2.1 (0.6–3.4; 2 \pm 1)	> 0.05
AaDO_2 [mmHg]	278 (30–551; 298 \pm 146)	298 (79–546; 282 \pm 159)	> 0.05
$\text{VCO}_{2\text{est}}$ [mL/min]	347 (220–382; 336 \pm 47)	277 (217–374; 287 \pm 51)	< 0.05
VE [L/min]	13.0 (6.7–20.3; 13.4 \pm 4.2)	10.5 (7.5–13.2; 10.1 \pm 2)	< 0.05
Ventilatory ratio	1.9 (1.0–3.2; 2.0 \pm 0.8)	1.5 (0.8–2.6; 1.5 \pm 0.6)	> 0.05
Shunt Fraction [%]	23 (8–50; 26 \pm 13)	19 (7–55; 23 \pm 15)	> 0.05
V_D/V_T [%]	50 (11–69; 46 \pm 20)	41 (10–68; 43 \pm 18)	> 0.05
For calculation of parameters, please see methods section.			

Table 2: Mechanical ventilation characteristics of CARDS patients (n = 10) compared to mechanical ventilation characteristics of patients with ARDS (n =10).

Patient characteristics	CARDS; N = 10	ARDS; N = 10	P value
	median (range; mean \pm SD)	median (range; mean \pm SD)	
Body temperature [°C]	38.5 (38.1 – 39.3; 38.6 \pm 0.3)	37.4 (36.2 – 38.2; 37.3 \pm 0.7)	< 0.05
Compliance [mL/cmH ₂ O]	42 (27 – 77; 44 \pm 17)	37 (23 – 67; 39 \pm 13)	> 0.05
PEEP [cmH ₂ O]	10 (8 – 14; 10 \pm 2.3)	10 (5 – 14; 9 \pm 3)	> 0.05
Δ P [P _{plat} -PEEP]	14 (12 – 22; 16 \pm 3.7)	15 (8 – 18; 15 \pm 3.2)	> 0.05
Respiratory rate [/min]	18 (11 – 36; 21 \pm 8)	18 (16 – 22; 19 \pm 2)	> 0.05
Vt [mL/kg]	9 (5 – 14; 9 \pm 2.4)	8 (6 – 10; 8 \pm 1.1)	< 0.05
VE [L/min]	13.0 (6.7 – 20.3; 13.4 \pm 4.2)	10.5 (7.5 – 13.2; 10.1 \pm 2)	< 0.05
Mechanical power [J/min]	20.8 (12.2 – 38.3; 23.4 \pm 8.9)	14.1 (11.8 – 23.9; 15.9 \pm 4.3)	< 0.05
P _a O ₂ [mmHg]	77 (57 – 97; 75 \pm 14)	75 (67 - 115; 83 \pm 16.5)	> 0.05
P _a CO ₂ [mmHg]	52 (33 – 74; 51 \pm 12)	41 (26 - 73; 43 \pm 12)	> 0.05
pH	7.33 (7.29 – 7.43; 7.33 \pm 0.05)	7.42 (7.32 – 7.53; 7.43 \pm 0.1)	< 0.05

Abbreviations: **CARDS** Covid19-related acute respiratory distress syndrome; **PEEP** Positive end expiratory pressure; **Δ P** Difference between plateau pressure and PEEP; **Vt** Tidal volume; **MV** Minute volume; **Compliance** in mL/cmH₂O;

Table 3: Invasive Hemodynamics acquired by pulmonary artery of CARDS patients (N = 10) compared to ARDS of other causes (N = 10). Differences in time from intubation to PAC is due to the fact that most patients with CARDS were referred to our center.

Variable	CARDS; N = 10 median (range; mean ± SD)	ARDS; N = 10 median (range; mean ± SD)	p-value
Days from intubation to PAC	11 (1 – 21; 10 ± 6)	3 (10 – 9; 3 ± 2.9)	< 0.05
P _a O ₂ /F _i O ₂ ratio	120 (57 – 171; 114 ± 42)	134 (73 - 259; 149 ± 62.1)	> 0.05
PAPs [mmHg]	53 (23 – 62; 47 ± 13.3)	46 (27 – 61; 44 ± 9)	> 0.05
PAPd [mmHg]	24 (11 – 31; 23 ± 6.1)	25 (15 – 34; 25 ± 5.5)	> 0.05
PAPm [mmHg]	36 (16 – 44; 32 ± 8)	34 (20 – 46; 33 ± 6.8)	> 0.05
PCWP [mmHg]	18 (8 – 26; 17 ± 5.9)	16 (9 – 28; 17 ± 6.8)	> 0.05
PVR [dyn*s*cm-5]	133 (13 – 329; 139 ± 77)	248 (101 – 385; 242 ± 89.2)	< 0.05
WU*m ² [mmHg/L/min/m ²]	1.7 (0.2 – 4.1; 1.7 ± 1)	3.1 (1.3 – 4.8; 3 ± 1.1)	< 0.05
DPG [mmHg]	7 (1 – 10; 6 ± 5)	8 (3 – 19; 7 ± 4.6)	> 0.05
C _{PA} [mL/mmHg]	4.1 (2 – 11; 4.6 ± 2.4)	2.8 (2 – 6.1; 3.3 ± 1.3)	> 0.05
C _{PA} x PVR (τ) in seconds	7.3 (0.9 – 11.9; 6.9 ± 3.1)	9.0 (3.3 – 16.6; 9.1 ± 3.3)	> 0.05
SVR [mmHg*min*ml ⁻¹]	783 (515 – 1,171; 801 ± 168)	1,374 (539 – 1,985; 1,240 ± 481)	< 0.05
CO [L/min]	7.8 (6.4 – 11.8; 8.1 ± 1.7)	5 (1.9 – 8.5; 5.4 ± 1.5)	< 0.05
CI [L/min/m ²]	3.9 (2.7 – 6.4; 4.1 ± 1.1)	2.7 (1.7 – 3.8; 2.7 ± 0.7)	< 0.05
SV [mL]	95 (60 – 126; 95 ± 19)	50 (36 – 117; 61 ± 23.4)	< 0.05
NT-proBNP [pg/mL]	365 (70 – 77,275; 336 ± 23,082)	2671 (264 – 50,403; 8,996 ± 14,462)	> 0.05

Abbreviations: **CARDS** Covid19-related acute respiratory distress syndrome; **SAPS** Simplified acute physiological score; **PAPs** Systolic pulmonary arterial pressure; **PAPd** Diastolic pulmonary arterial pressure; **PAPm** Median pulmonary arterial pressure; **PCWP** Pulmonary capillary wedge pressure; **PVR** Pulmonary vascular resistance; **SVR** Systemic vascular resistance; **CO** Cardiac output; **CI** Cardiac index; **C_{PA}** Pulmonary artery compliance.

Discussion

The present study compared patients with CARDS to patients with ARDS. The main findings of our study are: i) the pulmonary hemodynamic is not profoundly altered in CARDS compared to usual ARDS and ii) auto-regulation of lung vessels seems to be largely intact in patients with SARS-CoV2-related lung failure, iii) mechanical ventilation intensity was statistically significant higher in CARDS compared to usual ARDS.

Usual ARDS is defined by decreased diffusion capacity and ventilation deficit as a consequence of inflammation and low compliance⁷, resulting in a “baby lung”. In addition, there is often pulmonary hypertension due to increased vascular resistance with the risk of consecutive right heart failure⁴. In COVID-19 patients admitted to our ICU we could not completely affirm these pathophysiological findings.

Further $p_a\text{CO}_2$ in COVID-19 patients was rather similar compared to patients with ARDS at 52 mmHg and 41 mmHg, respectively. Our data shows that all COVID-19 patients had tidal volumes and a compliance resulting in minute ventilation of 6 L/min to 20 L/min. These findings might not be typical for patients with ARDS. In these patients tidal volume is low for the compliance of the lung is decreased¹³. As CO_2 has a higher diffusion coefficient than O_2 , hypercapnia is normally a problem of ventilation rather than diffusion¹⁴. In usual ARDS, patients hypercapnia can be explained by low tidal volume and the following lack of alveolar ventilation. But in CARDS patients minute ventilation was not decreased. Our group of CARDS patients had significantly higher tidal volume and a higher compliance than ARDS patients. Matching these two groups by $P_a\text{O}_2$ and oxygenation index, these parameters were quite similar in both groups. The question that arises is the pathophysiology behind the hypercapnia despite high minute ventilation and preserved compliance. V/Q mismatch could be an explanation for the ineffective gas exchange in CARDS patients. Also, non-effective regulation of hypoxic vasoconstriction¹⁰ could be another reason why blood volume passes non-ventilated areas in the lungs and is not able to participate in gas exchange. However, we could not find differences between CARDS and ARDS with regard to calculated physiological dead-space and shunt fraction. Calculated dead-space in CARDS and ARDS patients was in the range expected according to $P_a\text{O}_2/F_i\text{O}_2$ ratio¹⁵. However, we found a significant difference in the estimated CO_2 production, which might explain at least some of the CARDS features. Indeed, the intensity of ventilation was significantly higher in CARDS patients than ARDS patients, but the intensity in CARDS patients was not surprisingly high and comparable to previously reported data in patients with ARDS¹⁶.

In ARDS patients there is often pulmonary hypertension as consequence of hypoxia or hypercapnia. Further, there is a higher rate of right heart failure and lower cardiac output in ARDS patients because of a higher right ventricular afterload^{17,18}. In CARDS patients we did not see signs of right heart failure or decreased cardiac output. The cardiac output in CARDS patients was 7.8 L/min in median compared to 6.1 L/min in ARDS patients (cardiac index 3.9 L/min/m² vs. 3.1 L/min/m²). Pulmonary vascular resistance was significantly lower in CARDS patients than in ARDS patients (133 dyn × sec × cm⁻⁵ in

COVID-19 vs. $248 \text{ dyn} \times \text{sec} \times \text{cm}^{-5}$ in ARDS patients). One reason for increased PVR is higher PEEP. It has been shown previously, that increasing the PEEP increases PVR in mechanically ventilated patients¹⁹. In our study, PEEP was similar in both groups and also pulmonary capillary wedge-pressure did not differ and there was no correlation between PEEP and PVR. The difference in PVR may thus simply result from increased cardiac output of CARDS patients. CARDS patients probably had an increased cardiac output in comparison to ARDS patients due to inflammation and low systemic vascular resistance.

Mean pulmonary arterial pressure was similar in COVID-19 patients and in patients with ARDS, nevertheless both groups showed pulmonary arterial hypertension to some degree. Both groups had post-capillary forms of pulmonary hypertension with PCWP > 15 mmHg, but the diastolic pressure gradient was 7 mmHg in median in CARDS patients vs. 8 mmHg in ARDS patients. With a DPG less than 7 mmHg there is no precapillary component in pulmonary hypertension according to the actual guidelines¹². In our study, the median DPG was 7 mmHg and PVR $1.7 \text{ WU} \times \text{m}^2$ (vs. DPG 8 mmHg, PVR $3.1 \text{ WU} \times \text{m}^2$ in ARDS) meaning the pulmonary arterial hypertension in CARDS may be more a result of a post-capillary component, than a precapillary. Hence, there was only a slight difference and a defect in pulmonary vascular regulation in the presence of hypoxemia and hypercapnia unable to avoid a pathologically high right-left shunt²⁰ can be ruled out. We did not calculate an unexpected high shunt in CARDS patients. Rather, an elevated CO_2 production might explain differences between CARDS and ARDS. Patients presented with prolonged fever and unexpected long periods of elevated inflammatory parameters, both might contribute to increased VCO_2 .

Early recommendations for COVID-19 patients with respiratory failure consisted in early invasive ventilation strategies to avoid contagious aerosols and the use of high PEEP analogue to usual ARDS²¹. These therapies may be most effective in patients with lower diffusion capacity and compliance but the benefit in ventilation/perfusion mismatch needs to be questioned. These recommendations may be effective in ARDS patients, however in CARDS patients an important cornerstone according to our data might be to limit excessive CO_2 production e.g. by rigorous temperature control.

Moreover veno-venous extracorporeal life support (vvECMO) should be considered to treat these patients. Six patients in the CARDS group received vvECMO therapy later on, because of increasing hypercapnia and $\text{pH} < 7.1$ at exhausted mechanical ventilation.

Limitations

Our study has several limitations that need to be considered. First, the sample size of this analysis is relatively small. However, PAC is only used in special situations in ARDS patients in clinical routine, rendering sample sizes small. Differences between groups in important values might be more pronounced, if sample size was bigger. A critical parameter like $P_{(v-a)}\text{CO}_2/C_{(a-v)}\text{O}_2$ might in fact reach statistical significance in larger samples. The fact that SARS-CoV-2 is still causing a global pandemic could be a favour in recruiting more patients.

Second, the comparator group for pulmonary hemodynamics could be more consistent and homogeneous. We compared hemodynamics of COVID-19 patients with ARDS that was not exclusively due to viral infection. However, hypoxic pulmonary vasoconstriction has been expected to work independently of a causative organism in the past.

Third, the time of PAC insertion in CARDS patients was distinctly later than in ARDS patients and measurement was only at one point in time. This was mainly due to the fact that as a tertiary care centre, we received patients with COVID-19 in the beginning of the pandemic from other hospitals where patients had already been treated for several days on ICUs. It seems that COVID-19 has different phenotypes according to the time of evaluation being less usual at the beginning and adopting a more usual phenotype after days of mechanical ventilation. Interestingly, despite the differences in time, we couldn't detect relevant differences between groups. Possibly, pathophysiology in COVID-19 is simply prolonged as compared to other respiratory diseases.

Conclusion

Our data do not support the assumption that CARDS (at a later stage) leads to changes in pulmonary vasculature distinct from ARDS due to pulmonary infections. Mechanical power applied to the lung of CARDS patients by ventilation was significantly higher than in ARDS patients. The data presented here could be useful to guide CARDS therapy, as we assume that the results apply also for other cohorts of patients with severe SARS-CoV2 infection. Further investigations are needed to elucidate the mechanisms behind SARS-CoV2 induced pulmonary pathology.

Declarations

Ethics approval and consent to participate

Informed consent for pulmonary artery catheterization as part of standard intensive care was obtained by the patient or legal representative. The institutional review board (Ärzttekammer des Saarlandes) registered the study, to use a PAC in patients with ARDS, irrespective of the infectious agent, in 2019 under the number 278/19. Informed consent for the analysis of data is waived by the institutional review board due to the anonymous and retrospective analysis of data.

Consent for Publication

Not applicable.

Availability of data and materials

Data can be provided on request addressed to the corresponding author. All data sharing statements are subject to conformity with German data protection legislation and rules (Datenschutzgrundverordnung - DSGVO).

Competing interests

R.B. received funding from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Grifols, Novartis, CSL Behring, German Federal Ministry of Education and Research (BMBF) Competence Network, Sander Stiftung, Dr. Rolf M. Schwiete Foundation, German Cancer help (Krebshilfe) and Mukoviszidose e.V. All other authors have no conflicts of interest to declare.

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Author's Contribution

A.B., F.S., G.D., S.M., A.O., C.J., M.K. Ho.W., T.M. and P.M.L. contributed to collection, review, and/or analysis of the data; A.B. and P.M.L. drafted the manuscript, R.M.M., C.L., He.W., and R.B. revised the manuscript for important intellectual content. All authors have seen and approved the final version of the manuscript. P.M.L. is the guarantor of the manuscript.

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Not applicable.

References

1. Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020.
2. Marini JJ, Gattinoni L. Management of COVID-19 Respiratory Distress. *JAMA* 2020.
3. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020;395:1417-8.
4. Zapol WM, Snider MT. Pulmonary hypertension in severe acute respiratory failure. *N Engl J Med* 1977;296:476-80.
5. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet* 1967;2:319-23.
6. Beiderlinden M, Kuehl H, Boes T, Peters J. Prevalence of pulmonary hypertension associated with severe acute respiratory distress syndrome: predictive value of computed tomography. *Intensive Care Med* 2006;32:852-7.
7. Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med* 2012;38:1573-82.

8. Roza AM, Shizgal HM. The Harris Benedict equation reevaluated: resting energy requirements and the body cell mass. *Am J Clin Nutr* 1984;40:168-82.
9. Sinha P, Fauvel NJ, Singh S, Soni N. Ventilatory ratio: a simple bedside measure of ventilation. *Br J Anaesth* 2009;102:692-7.
10. Acute Respiratory Distress Syndrome N, Brower RG, Matthay MA, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301-8.
11. Force ADT, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307:2526-33.
12. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J* 2015;46:903-75.
13. Hager DN, Krishnan JA, Hayden DL, Brower RG, Network ACT. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. *Am J Respir Crit Care Med* 2005;172:1241-5.
14. Petersson J, Glenny RW. Gas exchange and ventilation-perfusion relationships in the lung. *Eur Respir J* 2014;44:1023-41.
15. Radermacher P, Maggiore SM, Mercat A. Fifty Years of Research in ARDS. Gas Exchange in Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med* 2017;196:964-84.
16. Wang R, Sun B, Li X, et al. Mechanical Ventilation Strategy Guided by Transpulmonary Pressure in Severe Acute Respiratory Distress Syndrome Treated With Venovenous Extracorporeal Membrane Oxygenation. *Crit Care Med* 2020.
17. Mekontso Dessap A, Boissier F, Charron C, et al. Acute cor pulmonale during protective ventilation for acute respiratory distress syndrome: prevalence, predictors, and clinical impact. *Intensive Care Med* 2016;42:862-70.
18. Zochios V, Parhar K, Tunnicliffe W, Roscoe A, Gao F. The Right Ventricle in ARDS. *Chest* 2017;152:181-93.
19. Tyberg JV, Grant DA, Kingma I, et al. Effects of positive intrathoracic pressure on pulmonary and systemic hemodynamics. *Respir Physiol* 2000;119:171-9.
20. Dunham-Snary KJ, Wu D, Sykes EA, et al. Hypoxic Pulmonary Vasoconstriction: From Molecular Mechanisms to Medicine. *Chest* 2017;151:181-92.
21. Alhazzani W, Moller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med* 2020;46:854-87.

Figures

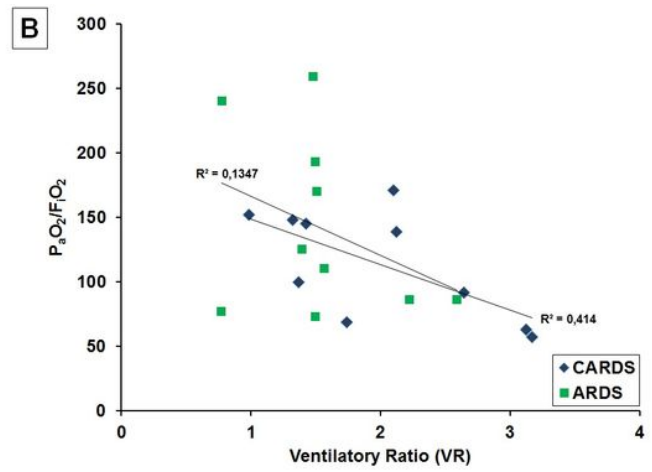
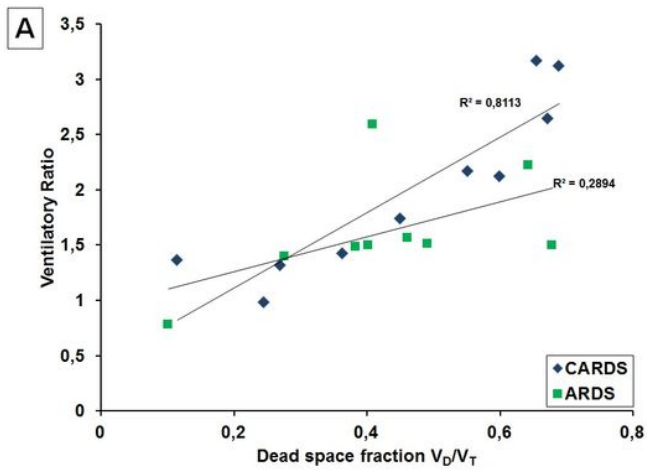


Figure 1

Correlation between ventilatory ratio (VR) and dead space fraction (V_D/V_T). There was a statistically significant association between VR and V_D/V_T in CARDS patients ($p < 0.05$). (B): Correlation between P_{aO_2}/F_{iO_2} ratio and VR.