Dissociation between the clinical course and chest imaging in severe COVID-19 pneumonia: A series of five cases

Damien Basille, MD, PhD[a,b,*], Marie-Anne Auquier, MD[c], Claire Andréjak, MD, PhD[a,b], Daniel Oscar Rodenstein, MD, PhD[d], Yazine Mahjoub, MD, PhD[e], Vincent Jounieaux, MD, PhD[a,b], on behalf of the A&P Group [1]

[a] *Pneumology Department, University Hospital Centre, Amiens, France*
[b] *AGIR Unit − UR4294, University Picardie Jules Verne, Amiens, France*
[c] *Radiology Department, University Hospital Centre, Amiens, France*
[d] *Pneumology Department, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium*
[e] *Anesthesia and Critical Care. Cardiac, Thoracic, Vascular and Respiratory Intensive Care Unit, University Hospital Centre, Amiens, France*

A R T I C L E   I N F O

A B S T R A C T

Background: Although an RT-PCR test is the "gold standard" tool for diagnosing an infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), chest imaging can be used to support a diagnosis of coronavirus disease 2019 (COVID-19) − albeit with fairly low specificity. However, if the chest imaging findings do not faithfully reflect the patient's clinical course, one can question the rationale for relying on these imaging data in the diagnosis of COVID-19.

Aims: To compare clinical courses with changes over time in chest imaging findings among patients admitted to an ICU for severe COVID-19 pneumonia.

Methods: We retrospectively reviewed the medical charts of all adult patients admitted to our intensive care unit (ICU) between March 1, 2020, and April 15, 2020, for a severe COVID-19 lung infection and who had a positive RT-PCR test. Changes in clinical, laboratory and radiological variables were compared, and patients with discordant changes over time (e.g. a clinical improvement with stable or worse radiological findings) were analyzed further.

Results: Of the 46 included patients, 5 showed an improvement in their clinical status but not in their chest imaging findings. On admission to the ICU, three of the five were mechanically ventilated and the two others received high-flow oxygen therapy or a non-rebreather mask. Even though the five patients' radiological findings worsened or remained stable, the mean $\pm$ standard deviation partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2:FiO_2) ratio increased significantly in all cases (from 113.2 ± 59.7 mmHg at admission to 259.8 ± 59.7 mmHg at a follow-up evaluation; p=0.043).

Interpretation: Our results suggest that in cases of clinical improvement with worsened or stable chest imaging variables, the PaO2:FiO2 ratio might be a good marker of the resolution of COVID-19-specific pulmonary vascular insult.

Introduction

Since the start of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak in the Hubei province of China, more than 151 million people had been infected and more than 3.1 million had died by the first week of May 2021 in the 213 countries, areas or territories covered by the United Nations.[1] The pandemic of coronavirus 2019 disease (COVID-19) hit France in late February 2020. Picardy was one of the country's most affected regions, with an incidence of confirmed infection of over 10 per 100,000 people on March 11th, 2020.[2] The number of patients admitted to the intensive care units (ICUs) in our tertiary hospital increased dramatically at this time, and forced us to reorganize our regional resources.[3,4] By April 21st, 2020, 81 COVID-19 patients had been admitted to our ICU.

Early diagnosis of COVID-19 is crucial for disease treatment and control, and the detection of viral nucleic acid in a reverse-

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                    ┌──────────────────┐
                    │   81 ICU patients │        ┌────────────────────────────────────────────────┐
                    │   with COVID-19   │        │ 35 patients excluded:                             │
                    └──────────────────┘         │ Lack of radiological data at follow-up: n = 22    │
                             │ ───────────────►   │ Non-severe COVID-19 pneumonia: n = 7              │
                             ▼                    │ COVID-19 without respiratory signs: n = 2         │
                    ┌──────────────────┐          │ Lost to follow-up: n = 4                          │
                    │ 46 ICU patients   │         └────────────────────────────────────────────────┘
                    │ with severe       │
                    │ COVID-19          │
                    │ pneumonia         │
                    └──────────────────┘
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Clinical and radiological improvement: n = 27	**Clinical improvement without radiological improvement: n = 5**	Clinical and radiological worsening: n = 14

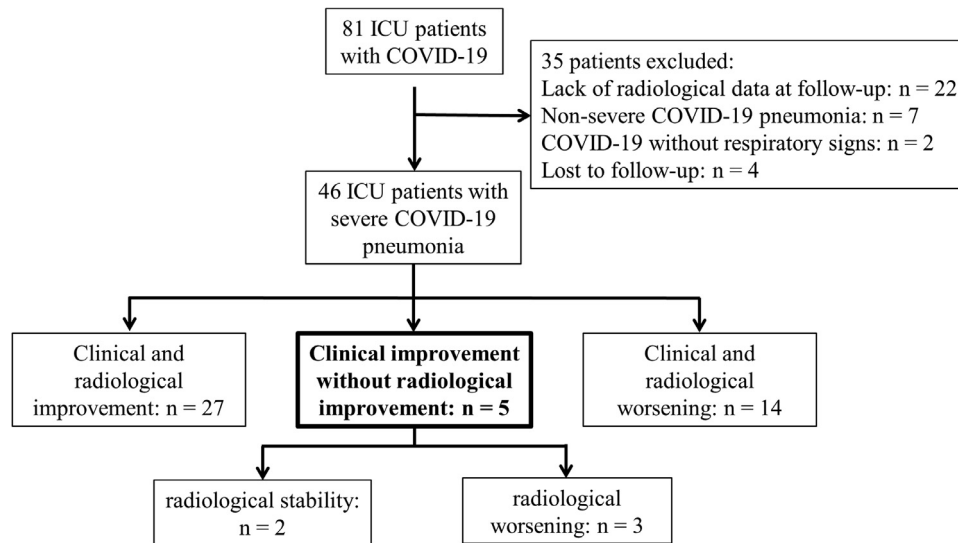| radiological stability: n = 2	radiological worsening: n = 3

Fig. 1. Study flow chart.

transcription polymerase chain reaction (RT-PCR) test remains the gold standard diagnostic tool. However, it has been suggested that the RT-PCR test's lack of sensitivity, insufficient stability and relatively long processing time weaken our ability to control the COVID-19 pandemic.[5] Moreover, RT-PCR assays for SARS-CoV-2 were not available in several countries during the epidemic period.[6] In this context, chest imaging can be used to support the diagnosis of COVID-19 pneumonia.[7,8] There is currently no consensus among the main radiology societies on the type of chest imaging to use in the diagnosis of COVID-19 pneumonia. The British Society of Thoracic Imaging and the Canadian Society of Radiologists suggested that a chest X-ray should be the first-line tool in stable patients.[9,10] Chest computed tomography (CT) is typically used to (i) assess patients with comorbidities and/or a high risk of disease progression and (ii) screen for complications. Chest CT can reveal early pneumonia with greater sensitivity than a chest X-ray. However, the sensitivity and the specificity of CT are lower in non-pandemic areas.[11−13] Therefore, the choice of the imaging modality depends on the judgment of clinical teams, the availability of local resources, and the expertise of local radiologists.

Relative to RT-PCR, chest CT offers good sensitivity, positive predictive values and negative predictive values, although the specificity is fairly low (97%, 65%, 83%, and 25%, respectively).[5] Nevertheless, the CT images used to diagnose COVID-19 pneumonia are not specific for SARS-CoV-2 virus infections, which cannot easily be distinguished from cases of viral pneumonitis due to influenza or other viruses. Despite this uncertainty, the imaging-based diagnosis of COVID-19 pneumonia may still be valuable in an appropriate epidemiologic context. However, if the clinical course differed from the change over time in the concomitant imaging findings for PCR-confirmed COVID-19 pneumonia, one could question the reliance on chest imaging when attributing pneumonia to the SARS-CoV-2 virus.

We therefore decided to compare clinical courses with changes over time in chest imaging findings among patients admitted to an ICU for severe COVID-19 pneumonia.

Methods

This study was conducted in Amiens-Picardie University Medical Center (Amiens, France). We retrospectively reviewed the medical charts of all adult patients with COVID-19 admitted to our ICU between March 1, 2020, and April 15, 2020. COVID-19 was diagnosed on the basis of nasopharyngeal swab specimens that were positive in a SARS-CoV-2 RT-PCR test. Severe COVID-19 pulmonary infection

was defined as respiratory failure requiring invasive mechanical ventilation or high-flow oxygen (through a high-flow nasal cannula or a non-rebreather oxygen mask) upon admission to the ICU. We compared the clinical course with the changes in chest imaging between admission and a follow-up evaluation. Patients were classified into three categories (Fig. 1): (i) those with clinical and radiological improvement, (ii) those with clinical and radiological worsening, and (iii) those with a clinical improvement but stable or worsening radiological findings. Clinical improvement was defined as weaning off mechanical ventilation or a significant decrease in the inspired oxygen fraction. Radiological improvement was defined as a decrease in the affected areas of the lung and the absence of new lesions. Only the patients with clinical improvement but no radiological improvement were selected for further analysis. The patients in this group were further subdivided into those with stable radiological findings and those with worse radiological findings. A radiologist with expertise in chest imaging analyzed the radiological data and validated the radiological outcome. For patients assessed with chest CT, the pneumonia extension was assessed according to the guidelines issued by the European Society of Radiology and the European Society of Thoracic Imaging.[14] For patients assessed with chest X-rays, we used the scoring system described by Borghesi and Maroldi.[15]

Variables assessed

The following data were obtained from the patients' medical charts: age, sex, comorbidities, self-reported smoking status, and body mass index (BMI). Following admission to the ICU, the results of arterial blood gas, ventilatory support mode and concomitant thoracic imaging data were recorded. The time interval between symptom onset and the initial evaluation was noted. The ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2:FiO_2) was computed for each patient. These data were also collected at the follow-up radiological evaluation (chest CT when it had been available for the initial evaluation, or a chest X-ray). In patients to whom oxygen was delivered through nasal prongs, the delivered FiO_2 was estimated using the equation published by Markovitz et al. (21% + 2.5% per L/min of additional oxygen).[16] Wilcoxon's paired test was used to compare the PaO_2:FiO_2 ratio at baseline and at follow-up.

Ethical considerations

In line with the French legislation on non-interventional studies, our institutional review board waived the need for written,

informed consent. The study database was registered with the French National Data Protection Commission (*Commission Nationale de l'Informatique et des Libertés*, Paris, France; reference: PI2020_843_0026, March 19th, 2020). The patients and their families were provided with verbal and written information on the study.

Results

Eighty-one patients with a positive SARS-CoV-2 RT-PCR test were admitted to our ICU and included in the study. In line with our exclusion criteria, thirty-five patients were excluded from the study (lack of radiological data at follow-up: *n*=22; non-severe COVID-19 pneumonia: *n*=7; COVID-19 without respiratory signs or symptoms: *n*=2; loss to follow-up: *n*=4). Of the 46 patients with severe COVID-19 pneumonia, the change in radiological status was assessed with a chest X-ray in 28 cases (60.9%) and with chest CT in 18 cases (39.1%). Twenty-seven patients showed a clinical and radiological improvement, 14 had clinical and radiological worsening, and 5 patients showed a discordant change (i.e. clinical improvement in the absence of radiological improvement) and were analyzed further (Fig. 1 and Table 1). The mean ± standard deviation age of the study population was 65.0 ± 7.8, and the mean BMI was 31.6 ± 6.1 kg/m^2. Three patients presented at least one comorbidity, and only one was a former smoker. The mean time from disease onset to ICU admission was 10.0 ± 6.1 days. At ICU admission, three patients were intubated and mechanically ventilated with a lung-protective strategy, whereas the other two patients were given high-flow oxygen therapy or a non-rebreather mask. The clinical course, blood gas levels, and chest imaging findings were then evaluated between 9 and 28 days after admission.

Cases presentation

Patient #1 was a 73-year-old man who required high-flow nasal oxygen therapy (flow rate: 50 L/min; FiO_2 = 100%), with a PaO_2:FiO_2 of 74. Mechanical ventilation was initiated on day 3, and the patient underwent two prone-positioning sessions (each lasting at least 16 h). Treatment with lopinavir/ritonavir (400/100 mg, twice daily) was initiated but was withdrawn after 7 days because of overdosing. The clinical course was complicated by ventilator-associated pneumonia (*Pseudomonas aeruginosa*) with concomitant pulmonary mucormycosis. The patient was weaned off mechanical ventilation on day 22 and switched to a Venturi oxygen mask (flow rate: 6 L/min; FiO_2 = 30%); the PaO_2:FiO_2 was 353. He was discharged to a pulmonary rehabilitation unit on day 43.

Patient #2 was a 53-year-old man who initially received oxygen through a non-rebreather mask (flow rate: 50 L/min; FiO_2 = 100%), with a PaO_2:FiO_2 of 75. On day 2, the blood gas profile worsened rapidly, and the patient was intubated, mechanically ventilated with inhaled nitric oxide (10 ppm), and underwent two prone-positioning sessions (each lasting at least 16 h). The patient was given remdesivir (100 mg/day for 10 days) and was weaned off mechanical ventilation on day 7. While breathing oxygen (4 L/min) through nasal prongs, the estimated PaO_2:FiO_2 was 256. The patient was discharged to home on day 16.

Patient #3 was a 70-year-old man who required lung-protective mechanical ventilation (Vt = 420ml; F = 25.min^{-1}), with a FiO_2 of 50%, a positive end-expiratory pressure (PEEP) of 15 cmH$_2$0, and no inhaled nitric oxide. The PaO_2:FiO_2 ratio was 216. The patient underwent eight prone-positioning sessions (each lasting at least 16 h) and received standard care (i.e. no specific antiviral agents were administered). Due to severe ICU-acquired weakness, he was tracheotomized on day 27 and was switched from volume-controlled ventilation to pressure support ventilation (pressure support = 8 cmH$_2$O, PEEP = 5 cmH$_2$O), with a FiO_2 of 30%. The PaO_2:FiO_2 ratio increased to

250. The tracheostomy was closed on day 40, and patient was discharged to a pulmonary rehabilitation unit on day 47.

Patient #4 was a 62-year-old man who required lung-protective mechanical ventilation (Vt = 430ml; F = 30.min^{-1}), with a FiO_2 of 80% FiO_2, a PEEP of 15 cmH$_2$O, and no inhaled nitric oxide. He underwent two prone-positioning sessions (each lasting at least 16 h) and was given lopinavir/ritonavir (400/100 mg twice daily) for 10 days. The PaO_2:FiO_2 ratio was initially 87 and increased to 186 on day 9. At this time, the patient was switched to pressure support ventilation (pressure support = 15 cmH$_2$O, PEEP = 12 cmH$_2$O), with a FiO_2 of 50%. He was weaned off mechanical ventilation on day 16 and discharged to a pulmonary rehabilitation unit on day 18.

Patient #5 was a 67-year-old man, who required venovenous extracorporeal membrane oxygenation and lung-protective mechanical ventilation (peak inspiratory pressure = 18 cmH$_2$O; F=20.min^{-1}), with a FiO_2 of 60%, a PEEP of 12 cmH$_2$O, and inhaled nitric oxide. The patient did not undergo any prone-positioning sessions. He was given lopinavir/ritonavir (400/100 mg twice daily) for 10 days. Venovenous extracorporeal membrane oxygenation was withdrawn on day 8. The PaO_2:FiO_2 was initially 114 and increased to 254 on day 21. At this time, the patient was on pressure support ventilation (pressure support = 18 cmH$_2$O, PEEP = 8 cmH$_2$O), with a FiO_2 of 50%. Due to severe ICU-acquired weakness, the patient was tracheotomized on day 25 and was transferred to a general hospital on day 27.

The radiological changes in the five patients between ICU admission and the follow-up evaluation are shown in Table 1 and Figs. 2 and 3. Despite the observed worsening or stability of the radiological findings, the PaO_2:FiO_2 increased significantly in all five patients (p=0.043). The mean PaO_2:FiO_2 ratio was 113.2 ± 59.7 mmHg at admission and 259.8 ± 59.7 mmHg at follow-up (Fig. 4).

Discussion

We observed statistically significant and clinically meaningful increases in PaO_2:FiO_2 in five ICU patients with severe COVID-19 pneumonia over a mean period of 18.0 ± 8.6 days, despite the lack of any improvement in the chest imaging. These observations suggest that the radiographic and clinical courses can diverge in some confirmed cases of COVID-19, and thus cast doubt on the reliability of chest imaging in the establishment of a firm diagnosis of SARS-CoV-2 infection.

In their retrospective study of 81 hospitalized COVID-19 patients, Shi et al. reported that the viral pneumonia manifested itself with typically abnormal chest CT findings - even in asymptomatic individuals. A rapid progression from focal, unilateral ground-glass opacities (GGOs) to diffuse, bilateral GGOs with consolidation can be observed within 1 to 3 weeks of infection.[17] Given that the imaging features of COVID-19 pneumonia can change rapidly, Pan et al. distinguished four typical disease stages.[18,19] According to this classification, the patients in our series were admitted to the ICU at different disease stages: early-stage disease for patient #1, progressive disease for patient #2; peak disease for patients #3 and #4, and absorption-stage disease for patient #5. Hence, Pan et al.'s classification was not appropriate for assessing the severity of COVID-19 pneumonia in our five patients.

Ai et al. reported that the specificity of chest CT for diagnosing COVID-19 infection was as low as 25%.[5] Indeed, the chest imaging features of COVID-19 pneumonia overlap markedly with those of other types of viral pneumonia. Although GGOs are frequently observed in *Adenoviridae, Herpesviridae* and *Picornaviridae* infections, consolidation is reported with *Adenoviridae, Herpesviridae* and other emergent *Coronaviridae*.[20] In view of this low specificity, the positive predictive value and the diagnostic accuracy are highly dependent on the pre-test probability, which in turn is determined by the epidemiological context. A recent meta-analysis by Kim et al. showed that in areas of low COVID-19 prevalence (range: 1−22.9%), chest CT

Table 1
Characteristics of the five patients selected for analysis.

	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5
Gender	Male	Male	Male	Male	Male
Age	73	53	70	62	67
BMI	27.2	30.9	42.1	27.4	30.2
Comorbidities	Hypertension, diabetes	None	Hypertension, diabetes, coronary artery disease	Obstructive sleep apnea syndrome, coronary artery disease, prostate cancer	None
Tobacco	No	No	No	Ex-smoker	No
Initial evaluation					
Time since symptom onset (days)	3	5	13	11	18
Initial chest imaging[a]	Chest CT: bilateral GGOs (extension: 30%)	Chest CT: bilateral GGOs (extension: 30%)	Chest X-ray: bilateral infiltrates (extension: 2/18)	Chest X-ray: bilateral infiltrates (extension: 6/18)	Chest X-ray: bilateral infiltrates, consolidation (extension: 8/18)
Initial ventilation or oxygen therapy	HF oxygen: Flow rate: 50 FiO_2 = 100%	Non-rebreather mask: Flow rate: 15 FiO_2 = 100%	VCV: F=25; Vt = 420; PEEP = 15; FiO_2 = 50%	VCV: F=30; Vt = 430; PEEP = 15; FiO_2 = 80%	ECMO + PCV: F=20; PIP = 18; PEEP = 12; FiO_2 = 60%;
PaO_2 (mmHg)	74.4	75.1	108	70.0	68.2
$PaCO_2$ (mmHg)	33.1	41.2	37.9	47.3	34.6
pH	7.48	7.41	7.32	7.35	7.47
PaO_2:FiO_2	74	75	216	87	114
Lactates (mmol:L)	3.1	1.8	2.1	1.6	2.4
Estimated GFR (ml/min)	102	143	17	84	113
CRP (mg:l)	397.1	175.2	163.1	357	329
Hemoglobin (g:dl)	11.4	12.0	11.8	11.8	10.9
Leukocyte count (10^3/mm^3)	7.2	10.3	7.1	7.0	7.1
Lymphocyte count (10^3/mm^3)	0.6	0.5	0.7	0.5	0.5
BNP (ng:L)	284	61	160	NA	NA
Therapy	Lopinavir -ritonavir	Remdesivir	No specific antiviral therapy	Lopinavir -ritonavir	Lopinavir -ritonavir
Second evaluation					
Time since first evaluation (days)	23	9	28	9	21
Follow-up chest imaging[a]	CT-scan: bilateral GGO, consolidation, (extension: 30%)	CT-scan: bilateral GGO, consolidation, (extension: 50%)	Chest x-ray: bilateral infiltrates, consolidation (extension: 8/18)	Chest x-ray: bilateral infiltrates, consolidation (extension:7/18)	Chest x-ray: bilateral infiltrates, consolidation (extension: 8/18)
Ventilation / oxygen therapy[b]	Venturi oxygen mask: Flow rate: 6 FiO_2 = 30%	Nasal prong: Flow rate: 4 FiO_2 = 31%	PSV: PS = 8; PEEP = 5; FiO_2 = 30%	PSV: PS = 15; PEEP = 12; FiO_2 = 50%	PSV: PS = 18; PEEP = 8; FiO_2 = 50%
PaO_2	106	79.7	74.5	92.9	127
$PaCO_2$	44	36.9	38.7	41.6	56.7
pH	7.38	7.44	7.43	7.42	7.35
PaO_2:FiO_2	353	256	250	186	254
Lactates (mmol:L)	1.4	1.3	2.1	2.9	1.5
Estimated GFR (ml/min)	41	49	118	90	137
CRP (mg:l)	94.3	NA	105.7	NA	105
Hb (g:dl)	7.2	10.4	8.4	10.9	9.5
Leukocyte count (10^3/mm^3)	5.4	8.0	7.1	14.9	16.6
Lymphocyte count (10^3/mm^3)	1.0	0.8	1.5	1.1	1.1

VCV: volume-controlled ventilation; ECMO: extracorporeal membrane oxygenation; PCV: pressure-controlled ventilation; PIP: peak inspiratory pressure; PSV: pressure support ventilation; GFR: glomerular filtration rate; CRP: C reactive protein; BNP: brain natriuretic peptide NA: not available

[a] For patients assessed with chest CT, our evaluation of the extension of pneumonia was based on the guidelines issued by the European Society of Radiology and the European Society of Thoracic Imaging.[14] For patients assessed with a chest X-ray, we used the scoring system published by Borghesi et Maroldi.[15]

[b] In patients treated with oxygen via nasal prongs, we considered that the effective FiO_2 increased by 2.5% per additional liter of oxygen flow.

screening of patients with suspected disease had a low positive predictive value (range: 1.5−30.7%).[13]

Shi et al. described four radiological outcome patterns on follow-up CT scan: initial progression to a peak level, followed by radiological improvement (46%); radiological improvement (14%); unchanged radiological appearance (9%) and radiological deterioration (32%).[17]

All our patients were revaluated at the absorption stage, and our results are quite similar to Shi et al.'s findings: we observed radiological improvement in 27 of the 46 evaluable patients (58.7%), an unchanged radiological appearance in two (4.3%), and radiological deterioration in 17 (37.0%). Five of our 46 patients presented with a discordant course (i.e. clinical improvement in the absence of
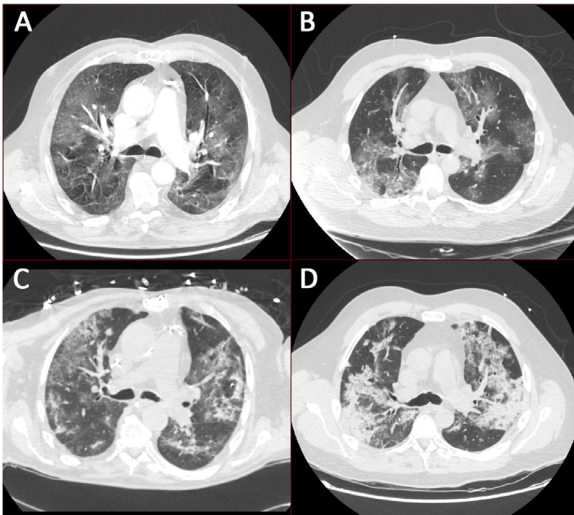
Fig. 2. Changes in the chest CT findings (lung parenchyma window) between ICU admission (A and B) and the follow-up evaluation (C and D) for patients #1 and #2.
• Patient #1: A and C; patient #2: B and D.

Fig. 4. Changes in the PaO$_2$:FiO$_2$ ratio between ICU admission and the follow-up evaluation.
PaO$_2$:FiO$_2$ ratio data are presented for each patient at baseline (ICU admission) and at the follow-up imaging evaluation.

radiological improvement). These results are similar to those reported by Bruns et al. who observed a possible discordance between the clinical course and radiological changes in patients with severe, community-acquired pneumonia.[21] The time to radiological resolution of the pneumonia appears to be correlated with older age and the number of lobes involved.[22] In these situations, however, the change in the PaO2:FiO2 ratio is correlated with the radiological change.

Gattinoni et al. have described two time-dependent chronological phenotypes among patients suffering from COVID-19 pneumonia.[23] The five cases reported here raise questions about the mechanism of the increase in the PaO2:FiO2 ratio during COVID-19 pneumonia. In fact, our observations suggest that the hypoxemia was due not only to lung parenchyma lesions but also to another pathophysiological mechanism. The discordant changes observed in our five patients (a dramatic increase in the PaO2:FiO2 ratio in the absence of a
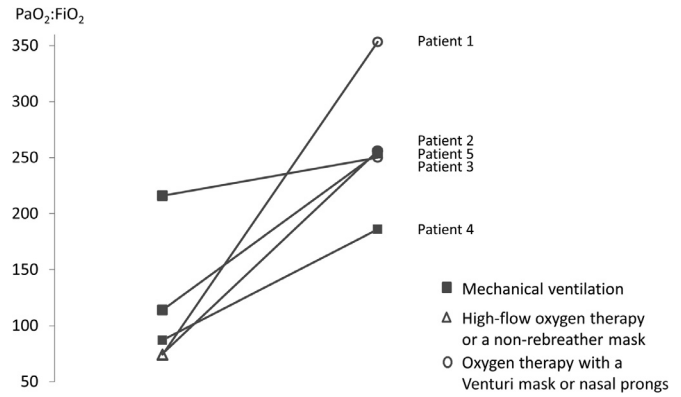
radiological improvement) support our "intrapulmonary shunt" hypothesis. Indeed, we recently hypothesized that all stages of COVID-19 are characterized by an elevated pulmonary blood flow and an intrapulmonary right-to-left shunt – prompting us to introduce the acronym AVDS for "acute vascular distress syndrome".[24,25]

Vascular abnormalities have been described by various researchers in histological or radiological studies of patients with COVID-19 pneumonia.[26−29] The vascular disorders induced by COVID-19 may result in an intrapulmonary shunt, which is generally masked by the diffuse damage to the lung parenchyma. In the study by Ai et al., 21 of the 601 patients (3%) with a positive RT-PCR test had negative chest CT findings - suggesting that the pulmonary vascular insult might be the only manifestation of the disease in some patients.[5] These patients should not be considered as being asymptomatic, since their pulmonary vascular insult might lead to an intrapulmonary shunt that can be only evidenced by contrast-enhanced echocardiography.[25] One can assume that hypoxemia will decrease upon recovery from the pulmonary vascular insult, regardless of the course of the lung's parenchymal lesions. The clear-cut PaO$_2$:FiO$_2$ ratio
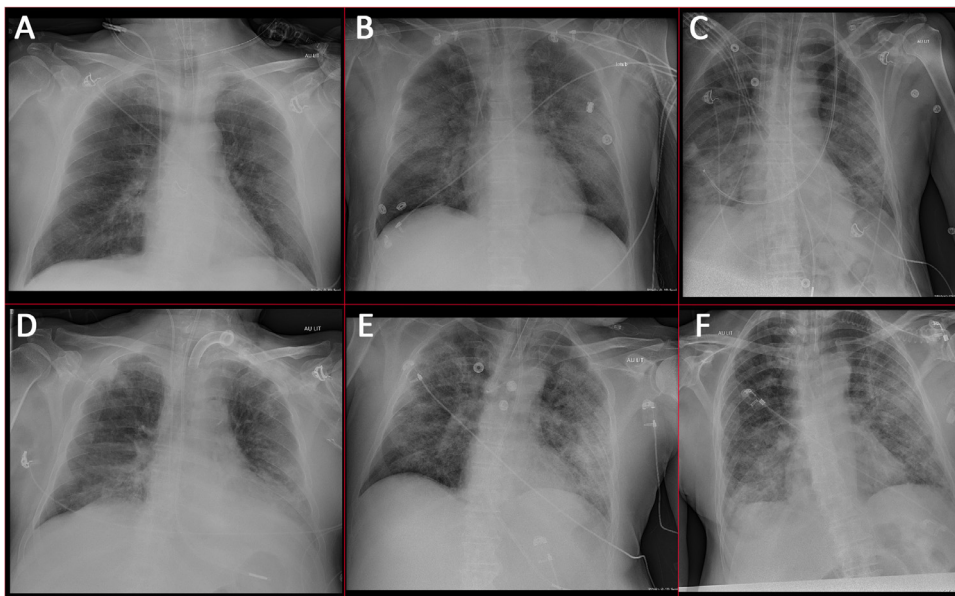

Fig. 3. Changes in the chest X-ray findings between ICU admission (A, B, and C) and the follow-up evaluation (D, E, and F) for patients #3, #4 and #5.
• Patient #3: A and D; patient #4: B and E; patient #5: C and F

improvement observed in our five patients (despite stable or worsening chest imaging results) argues in favor of this hypothesis.

Our study also had some limitations. Notably, the change in chest imaging findings was assessed with CT in only 18 of the 46 patients. For patients assessed with a chest X-ray, some radiological features (such as vascular enlargement and GGOs) may have been misclassified.

Conclusion

Our observation of five cases of significant clinical and blood gas improvements in patients with stable or worsening radiological findings suggests that chest imaging is not a reliable means of assessing the initial vascular damage and the likely outcome of some ICU patients with severe COVID-19 disease. The PaO2:FiO2 ratio could then be considered as a good marker of the resolution of the COVID-19-specific pulmonary vascular insult. Further clinical studies will be useful to confirm this result.

Members of the A&P group:

First name	Last name	Email adress
Anesthesia department:		
Norair	Airapetian	airapetian.norair@chu-amiens.fr
Nacim	Ammenouche	ammenouche.nacim@chu-amiens.fr
Louise	Badoux	badoux.louise@chu-amiens.fr
Guillaume	Bayart	baygui@orange.fr
Michael	Bernasinski	bernasinski.michael@chu-amiens.fr
Patricia	Besserve	besserve.christophe@chu-amiens.fr
Christophe	Beyls	beyls.christophe@chu-amiens.fr
Mathieu	Caboche	matthieu.caboche62@gmail.com
Fanny	Delanghe	delanghe.fanny@chu-amiens.fr
Amandine	Dubreucq	dubreucq.amandine@chu-amiens.fr
Hervé	Dupont	dupont.herve@chu-amiens.fr
Guillaume	Fevre	guillaume.fevre@hotmail.fr
Otillie	Fumery	fumery.otillie@chu-amiens.fr
Mathieu	Guilbart	guilbart.mathieu@chu-amiens.fr
Sebastien	Hinard	hinard.sebastien@chu-amiens.fr
Pierre	Huette	huette.pierre@chu-amiens.fr
Patrick	Jeanjean	jeanjean.patrick@chu-amiens.fr
Benoit	Lecat	lecat.benoit@chu-amiens.fr
Florent	Leviel	leviel.florent@chu-amiens.fr
Pierre-Yves	Macq	macq.pierre-yves@chu-amiens.fr
Stéphanie	Malaquin	malaquin.stephanie@chu-amiens.fr
Francois	Tinturier	tinturier.francois@chu-amiens.fr
Pierre Alexandre	Roger	roger.pierre-alexandre@chu-amiens.fr
Alexis	Salomon	salomon.alexis@chu-amiens.fr
Benjamin	Terassi	terasi.benjamin@chu-amiens.fr
Pulmonology department:		
Hortense	Carette	carette.hortense@chu-amiens.fr
Mélanie	Drucbert	drucbert.melanie@chu-amiens.fr
Ugo	Fouquet	fouquet.ugo@chu-amiens.fr
Géraldine	François	francois.geraldine@chu-amiens.fr
Alice	Henry	henry.alice@chu-amiens.fr
Isabelle	Mayeux	mayeux.isabelle@chu-amiens.fr
Julien	Monconduit	monconduit.julien@chu-amiens.fr
Elisabeth	Popin	popin.elisabeth@chu-amiens.fr
Claire	Poulet	poulet.claire@chu-amiens.fr
Lola	Soriot	soriot.lola@chu-amiens.fr
Bénédicte	Toublanc	toublanc.benedicte@chu-amiens.fr
Florence	Weppe	weppe.florence@chu-amiens.fr

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