Surfactant replacement might help recovery of low-compliance lung in severe COVID-19 pneumonia

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The reviews of this paper are available via the supplemental material section.

To the Editor

There are still no validated therapies to treat severe pneumonia following SARS-CoV-2 infection. In the context of unproven treatments, there is a pressing need to understand the pathophysiology of the COVID-19 in critically ill patients requiring the intensive care unit (ICU) and mechanical ventilation, burdened by a high case fatality rate.[1]

Thanks to preclinical studies,[2–4] progress has been made on understanding viral aggression, showing that SARS-CoV-2 spike protein has a binding affinity to angiotensin-converting enzyme 2 receptor of alveolar type 2 (AT2) lung cells as the specific target. Accordingly, post mortem histopathological findings revealed desquamated AT2 cells present in alveolar spaces with viral cytopathic effect consisting of cytomegaly, as direct expression of viral damage.[5,6] Based on these recent reports, it seems reasonable to hypothesize a reduced AT2 cells number with low ability to synthesize and secrete endogenous surfactant in COVID-19 patients. To our knowledge, exogenous surfactant replacement has not been described so far in these patients to demonstrate this hypothesis. We here report five cases of critically ill COVID-19 patients undergoing exogenous surfactant instillation though the airways.

Methods
Patients with laboratory confirmed COVID-19 pneumonia were admitted and managed at our ICU from 20 March to 5 April 2020. They received poractant alfa (Curosurf©, Chiesi Farmaceutici, Parma, Italy) if they were under invasive mechanical ventilation (IMV) with both PaO_2/FiO_2 ratio <100 mmHg and low pulmonary static compliance (Cstat). Surfactant treatment was intended for compassionate use in very critical patients and, due to medication shortage, only five cases were treated.

Surfactant was instilled at the dosage of approximately 30 mg/kg of lean body weight (LBW)[7] diluted with normal saline (2 ml/kg LBW). Experimental therapy was administered through a three-way tap connected to the closed-loop suction catheter inserted into the endotracheal tube with the distal hole approximately 1 cm above the carina; half of the volume was administered while the patient was in the right lateral decubitus position, with the remaining dose given in the opposite lateral position 5 min apart. Deploying this route of instillation, we have preserved the safety of the operators according to the recommendations of the Italian Society of Anesthesiology and Intensive Care.[8]

Demographics and pre-existing diseases were taken from medical records, while clinical parameters and laboratory data were recorded throughout the ICU stay. Bronchial aspirates along with other microbiological analyses were performed every 3 days during ICU stay and whenever clinical or laboratory signs of a new ongoing infection occurred. Respiratory parameters were recorded before administration (T0) and 6 (T1), 12 (T2), 18 (T3), 24 (T4), 36 (T5) and 48 (T6) h apart. Physiological outcomes (change in PaO_2/FiO_2 and

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Cstat) were recorded over time. Rescue therapies (RTs) such as prone position or inhaled nitric oxide were recorded during the ICU stay; however, these therapies were not allowed between T0 and T4 in order to avoid further variables that could cause adverse events and, moreover, to verify the efficacy of the surfactant in the first 24h after the supplementation. Time to extubation or tracheotomy and 30-day survival were recorded as clinical outcomes. Finally, adverse events related to the administered surfactant or to the technique of instillation were also reported.

Results

Baseline characteristics, laboratory data, ventilatory parameters, timing and dosage of surfactant of the five treated patients are reported in Table 1. At T0, all patients showed high serum C-reactive protein values with lymphopenia, while patients 1 and 3 showed increased levels of procalcitonin (Table 1), but in all our cases we had no microbiological evidence of bacterial lung superinfection at time of surfactant administration. At T0, PaO_2/FiO_2 and Cstat ranged from 57 to 76mmHg and from 21.7 to 36.6ml/cmH$_2$O, respectively; in addition, the IMV elapsed time before the administration of exogenous surfactant was between 9 and 312h (Table 1).

The time course of PaO_2/FiO_2 and Cstat is illustrated in Figure 1. At T1, patients 2, 3, 4 and 5 increased PaO_2/FiO_2 by 67%, 76%, 22% and 41% respectively. All five patients nearly doubled their ratio at T4 [Figure 1(A)]. Referring to Cstat, all patients improved at T1 (between 14% and 48%) [Figure 1(B)].

RTs were applied as follows: patients 1 and 4 underwent prone position before T0, 2 and 1 cycle, respectively; in addition, patient 4 received inhaled nitric oxide at T5 and for the following 48h (15 parts per million); patient 3 had two prone position cycles after T6; patient 5 underwent five prone position cycles and inhaled nitric oxide for 36h (20 parts per million) before T0. Each prone position cycle lasted about 16h.

Three out of the studied patients were extubated, two were tracheotomized and four were alive at day 30 (Table 1). We did not record any severe adverse events; however, a transient mild desaturation, not exceeding the two percentage points of arterial oxygen saturation, was present in all patients due to the volume instilled into the trachea.

Discussion

In our experience five mechanically ventilated COVID-19 patients with very severe hypoxia and low pulmonary compliance were treated with intra-tracheal natural surfactant. All of them reported a physiological improvement and there was a positive outcome in four. Unfortunately, notwithstanding weaning success through tracheostomy, one patient (number 3) developed muscle weakness due to acute renal failure and then an invasive Aspergillosis, leading him to death. In addition, it should be noted that patients 1 and 5 were treated late as "last ditch" therapy, because they were extremely hypoxic and unresponsive to RTs. Although surfactant treatment was performed in a small-size cohort, and speculation on mortality may seem inadequate, we had an 80% of 30-day survival rate despite the severity of the patients treated. Two large case series, coming from China, recorded a 28-day survival rate ranging from 61.3% to 38.5%;[9,10] however, our small number of cases does not allow a comparison with these larger cohorts.

Our patients showed a very compromised pulmonary compliance consistent with one of the phenotypes reported among severe patients suffering from COVID-19 pneumonia.[11,12] Therefore, it is reasonable to consider that the lung recruitment strategy should be a target to prompt in these individuals,[11,12] Other than the appropriate ventilator setting, exogenous surfactant could appear as an alternative option .

Since the amount of synthesized endogenous surfactant could be reasonably decreased due to the AT2 cell damage in SARS-CoV-2 infection,[1–6,13] patients with this syndrome appear more similar to preterm infants than any other form of respiratory failure in adults. The increase in pulmonary compliance as obtained following poractant alfa instillation in our five cases would indicate its biological role as "recruiting therapy" in these specific patients.

Notwithstanding, the exogenous surfactant cannot be considered a suitable therapy for all patients with COVID-19 pneumonia. Rather, it may represent an option in those cases with a critical lung mechanics derangement. In daily clinical practice, this strategy could integrate with other RTs such as prone position, elevated Positive End-Expiratory Pressure setting or inhaled nitric oxide.

Table 1. Basal characteristics and outcomes of COVID-19 patients with severe pneumonia who underwent exogenous surfactant instillation.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	53	65	75	70	73
Sex	M	M	M	M	M
Weight/LBW* (kg)	85/61.5	77/55.8	77/58.5	90/60.0	120/69.2
Pre-existing diseases	None	Hypertension	Gout	Psoriatic arthritis Hypertension Hyperlipidemia	Hypertension Obesity Type 2 diabetes
SOFA score at T0	4	5	4	4	6
TLC at T0 (mm^3)	600	340	320	970	460
CRP at T0 (mg/dl)	38.8	33.2	14.9	12.5	14.3
PCT at T0 (ng/ml)	4.7	0.4	1.7	0.1	0.1
PaO_2/FiO_2 ratio at T0 (mmHg)	57	76	60	75	69
FiO_2 at T0	0.85	0.70	0.75	0.85	0.90
Cstat at T0 (ml/cmH$_2$O)	21.7	29.4	30.0	36.6	20.6
Driving pressure at T0 (cmH$_2$O)	28	22	20	18	35
TV at T0 (ml/kg)	7.1	8.4	7.8	7.3	6.0
Dosage of surfactant (mg/kg LBW)	25.7	34.4	32.8	35.3	34.7
IMV before surfactant (h)	59	9	13	19	312
Extubation or tracheotomy after surfactant (days)	Extubation at 8	Extubation at 3	Tracheotomy at 14	Extubation at 5	Tracheotomy at 15
Outcome at day 30	Alive	Alive	Dead at day 21	Alive	Alive

The PaO_2/FiO_2 ratio was defined as the ratio of the partial pressure of arterial oxygen to the percentage of inspired oxygen.
CRP, C-reactive protein; Cstat, pulmonary static compliance; FiO_2, fraction of inspired oxygen; IMV, invasive mechanical ventilation; LBW, lean body weight; M, male; PCT, procalcitonin; SOFA, Sequential Organ Failure Assessment; TLC, total lymphocyte count; T0, before administration; TV, tidal volume.
*Hume *et al.*[7]

Based on current reports,[1,14] typical acute respiratory distress syndrome (ARDS) as defined by the Berlin Criteria[15] and the respiratory failure due to COVID-19 pneumonia show other differences besides lung mechanics. Indeed, alveolar damage is different comparing COVID-19 and ARDS,[1–6] radiological presentations are different, onset of respiratory failure is much longer in COVID-19 after the beginning of symptoms, and symptoms are poorly correlated with lung imaging.[16] Therefore, severe COVID-19 pneumonia appears as unrelated to the grade of severity of a typical ARDS. Therefore, results (28-day survival) from randomized controlled trials in adults with ARDS[17] cannot be assumed as a reference to compare the outcome in COVID-19 patients treated with surfactant. Moreover, it would be important to phenotype COVID-19 patients based on their synthetic residual rate of the native surfactant to properly select candidates to replacement therapy. This can be achieved through mass spectrometric analysis using deuterated choline labeling, which would allow to plan the timing of administration and the number of instillations needed to restore a normal alveolar surface tension.[18]
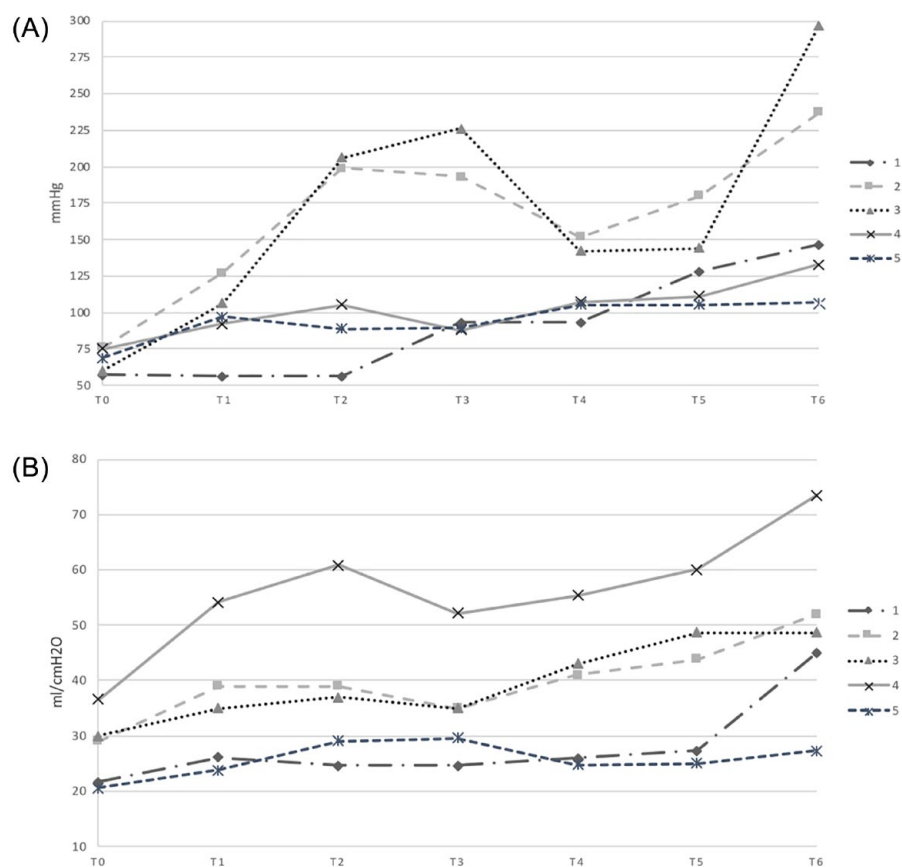
Figure 1. Time course of PaO_2/FiO_2 ratio of the five patients treated with surfactant expressed in absolute PaO_2/FiO_2 change from before administration (T0) to 48 h after administration (T6) (A). Time course of static compliance (Cstat) of the five patients treated with surfactant expressed in absolute Cstat change from T0 to T6 (B).
The legend on the right side of each graph differentiates treated patients 1 to 5.

Taking into consideration the pathogenesis of SARS-CoV-2 infection[1–6,13] and the differences between an adult with COVID-19 pneumonia or with typical ARDS, the administration of exogenous surfactant would be plausible in COVID patients with low-compliance lung. Ongoing randomized trials [ClinicalTrials.gov identifier: NCT04362059] [ClinicalTrials.gov identifier: NCT04375735] [ClinicalTrials.gov identifier: NCT04384731] [ClinicalTrials.gov identifier: NCT04389671] will clarify our hypothesis and possibly confirm these preliminary findings.

In conclusion, well aware of the limitations due to a restricted cohort of patients, our data show for the first time the potential of the instillation of exogenous surfactant in patients with severe COVID-19 pneumonia and low-compliance lung. Thus, our data can pave the way for the surfactant replacement strategy in this subgroup of patients; however, it is necessary to point out that validation through adequately powered studies is required before suggesting such treatment.

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Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest statement
The authors declare that there is no conflict of interest.

Ethics approval and consent to participate
In accordance with the rules of our Ethics Committee of Area Vasta Nord Emilia-Romagna, it was not necessary to obtain the approval due to the nature of the study, while consent to the treatment was collected by telephone from the closest relative for quarantine-related precautions.

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Supplemental material
The reviews of this paper are available via the supplemental material section.

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