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# Volatile Isoflurane in Critically Ill Coronavirus Disease 2019 Patients—A Case Series and Systematic Review

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**Objectives:** The ongoing coronavirus pandemic is challenging, especially in severely affected patients who require intubation and sedation. Although the potential benefits of sedation with volatile anesthetics in coronavirus disease 2019 patients are currently being discussed, the use of isoflurane in patients with coronavirus disease 2019–induced acute respiratory distress syndrome has not yet been reported.

**Design:** We performed a retrospective analysis of critically ill patients with hypoxemic respiratory failure requiring mechanical ventilation.

**Setting:** The study was conducted with patients admitted between April 4 and May 15, 2020 to our ICU.

**Patients:** We included five patients who were previously diagnosed with severe acute respiratory syndrome coronavirus 2 infection.

**Intervention:** Even with high doses of several IV sedatives, the targeted level of sedation could not be achieved. Therefore, the sedation regimen was switched to inhalational isoflurane. Clinical data were recorded using a patient data management system. We recorded demographical data, laboratory results, ventilation variables, sedative dosages, sedation level, prone positioning, duration of volatile sedation and outcomes.

**Measurements & Main Results:** Mean age (four men, one women) was 53.0 (± 12.7) years. The mean duration of isoflurane sedation was 103.2 (± 66.2) hours. Our data demonstrate a substantial improvement in the oxygenation ratio when using isoflurane sedation. Deep sedation as assessed by the Richmond Agitation and Sedation Scale was rapidly and closely controlled in all patients, and the subsequent discontinuation of IV sedation was possible within the first 30 minutes. No adverse events were detected.

**Conclusions:** Our findings demonstrate the feasibility of isoflurane sedation in five patients suffering from severe coronavirus disease 2019 infection. Volatile isoflurane was able to achieve the required deep sedation and reduced the need for IV sedation.

**Key Words:** acute respiratory distress syndrome; coronavirus disease 2019; critical care; deep sedation; severe acute respiratory syndrome coronavirus 2; volatile sedation

The ongoing coronavirus pandemic poses new and unprecedented challenges for the healthcare system. Severely affected patients may require elaborate critical care treatment including ventilation and extracorporeal membrane oxygenation (ECMO), demanding a sophisticated sedation regime.

To facilitate ventilator synchrony and prone positioning during critical care treatment of coronavirus disease 2019 (COVID-19) patients, deeper sedation levels are often indispensable. Based on recently published data and our own experiences regarding the need for unusually high doses of sedation in these patients, special considerations are warranted (1).

In this regard, the potential benefits of sedation using volatile anesthetics in COVID-19–induced acute respiratory distress syndrome (C-ARDS) have been increasingly discussed (2, 3).

Several studies have demonstrated the safe use of volatile anesthetics in critically ill patients, leading to a decreased duration of mechanical ventilation when treating classical acute respiratory distress syndrome (ARDS) (4–9). Known pharmacologic benefits of volatile anesthetics include a low accumulation and metabolism rate (isoflurane: 0.2%), bronchodilatory effects, and antiepileptic properties, which may be favorable for patients who fail to achieve adequate sedation or suffer from severe bronchospasm (8, 10). According to German national taskforce guideline (delirium, analgesia and sedation taskforce 2015), the use of volatile anesthetics for moderate-to-deep sedation is recommended in critically ill patients with (ARDS) (11).

As deep sedation is crucial and repeatedly required in critically ill COVID-19 patients, we assessed the use of isoflurane in patients with severe C-ARDS (12, 13).

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## METHODS

This is a retrospective, observational study conducted at University Hospital Frankfurt. The study was approved by the institutional ethic board of the University of Frankfurt (no 20-643). The need for informed consent from individual patients was waived due to the nature of a retrospective review.

### Patient Population

We included five patients admitted to the ICU who were previously diagnosed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or who tested positive for COVID-19 during treatment. No other than the five patients with COVID-19 included within this article were treated with volatile sedatives. SARS-CoV-2 infection was detected by real-time reverse transcriptase polymerase chain reaction (RT-PCR) testing of nasal and oropharyngeal swabs. The RT-PCR tests were based on the recommended standard of the World Health Organization and targeted the SARS-CoV-2 e-gene as a first-line screening, followed by confirmatory *RdRp* gene testing (14). All patients received mechanical ventilation using an ICU ventilator (Elisa 800; Löwenstein Medical, Bad Ems, Germany) and intensive care treatment according to current recommendations for managing C-ARDS (15–17). Sedation generally consisted of the administration of benzodiazepines and central $\alpha_2$ receptor agonists, supplemented by esketamine or propofol as indicated. No specific COVID-19 treatment protocols were defined, and treatment was solely at the discretion of the attending physicians, as was the decision to use volatile anesthetic for balanced sedation, performed as combination of isoflurane with sufentanil. In all patients undergoing ECMO therapy, an ultraprotective lung ventilation concept with a targeted volume of less than or equal to 4 mL $kg^{-1}$ was used (18). Volatile sedation under such therapy has already been successfully demonstrated in ARDS patients up to tidal volumes of 150 mL (19).

### Data Collection

Clinical data were continuously recorded using a patient data management system (MetaVision 5.4; iMDsoft, Tel Aviv, Israel). We recorded demographic data, laboratory results, ventilation variables, sedative dosages, clinical satisfaction of sedation level assessed by the Richmond-Agitation-Sedation Scale (RASS), prone positioning, duration of volatile sedation, and outcomes.

Sedation depth was determined by RASS, including the occurrence of asynchronous respiratory episodes and vegetative agitation (tachycardia, hypertension, sweating, tachypnea, and tears in the eyes not otherwise explained) (20). We defined a clinically satisfactory sedation with predominantly synchronous ventilation and the absence of vegetative agitation. The target sedation depth was a RASS less than –1; depending on the treatment, a RASS of –3 was defined as the target for patients in prone position or under ECMO therapy (17, 21).

Adequate ventilator synchrony was defined as clinical predominant absence of asynchronous phases observing the respiratory volume pressure curves by the attending staff.

"Triggering of stress response" was defined as follows: suboptimal sedation, resulting in high blood pressure and/or tachycardia and/or repeated coughing.

Patients were observed with special regard to the occurrence of the following possible complications:

- occurrence of an intolerance reaction or anaphylaxis;
- occurring of acute renal failure under isoflurane therapy;
- liver dysfunction measured by laboratory liver function tests;
- hemodynamic instability represented by clinical features of circulatory shock including hypotension, abnormal heart rates, arrhythmias, cold extremities, and/or advanced heart failure or necessity of resuscitation; and
- ventilator-associated events, that could not be clinically attributed to a deterioration of COVID-19 infection according to the Center of Disease Control Ventilator-Associated Event protocol (22, 23).

For inhalational isoflurane sedation, we used a minimum alveolar concentration (MAC)-driven application device (MirusTM; Pall Medical, Dreieich, Germany). The anesthetic conserving device enables automated end-expiratory control of volatile anesthetics and consists of an anesthetic reflector to conserve and readminister up to 90% of expiratory isoflurane.

The system monitors the end-tidal anesthetic concentration and performs an automatic dose correction to achieve a selected target MAC. Combining this system with a passive scavenging system (FlurAbsorbTM; Sedana Medical, Uppsala, Sweden) connected to the expiratory limb avoids ambient pollution of volatile anesthetics in the ICU (24).

## RESULTS

The patient demographic and clinical characteristics at admission, as well as the therapeutic interventions, are presented in **Table 1**. To provide an overview of hemodynamic and respiratory stability using isoflurane, please see **Figure 1*B*-*D***.

### Case 1

A 29-year-old woman had fever and chills for 3 days before she presented herself to a local healthcare provider. Intubation was necessary due to the respiratory failure.

Due to a persisting failure of adequate sedation, volatile sedation with isoflurane (MAC = 1.2) was initiated and enabled cessation of all IV sedatives, with a distinct improvement in ventilator synchrony. After 4 days of inhalational sedation, laboratory findings revealed a pulmonary bacterial superinfection accompanied by deterioration of the respiratory mechanics, leading to the implantation of a veno-venous ECMO system. Due to gradually decreasing tidal volumes (< 100 mL), sufficient sedation could no longer be achieved, and the sedation regimen had to be switched back to IV pharmaceuticals.

### Case 2

A 52-year-old man was admitted to the emergency department with an 8-day history of fever accompanied by shortening of the breath and fatigue. Subsequently, the patient developed refractory hypoxemia requiring mechanical ventilation and sedation.

During the further course of treatment and despite dose adjustments, sedation goals were very difficult to achieve. Additionally, episodic airway obstruction occurred, resulting in a switch to isoflurane (MAC 1.2) in combination with sufentanil. The use of the concept of balanced anesthesia enabled adequate sedation,

**TABLE 1. Clinical Characteristics of Patients Who Received Volatile Sedation With Isoflurane**

| Patients Characteristics | Patient No 1 | Patient No 2 | Patient No 3 | Patient No 4 | Patient No 5 |
|---|---|---|---|---|---|
| Sex | Female | Male | Male | Male | Male |
| Age, yr | 29 | 52 | 63 | 63 | 58 |
| Weight, kg | 128 | 110 | 113 | 85 | 97 |
| Body mass index, kg/m$^2$ | 43.2 | 40.4 | 36.9 | 26.2 | 31.0 |
| Simplified Acute Physiology Score II at time of admission, points | 42 | 57 | 22 | 84 | 22 |
| Coexisting chronic conditions | Hypertension, diabetes mellitus | Hypertension, asthma, tobacco abuse | Hypertension, liver cirrhosis, aortal stenosis, chronic renal failure, tobacco abuse | Asthma, tobacco abuse | Hypertension |
| Time to volatile sedation, d | | | | | |
| Since hospital admission | 8 | 15 | 12 | 15 | 7 |
| Since intubation | 3 | 10 | 11 | 6 | 6 |
| IV sedation prior to isoflurane, mean ± SD | | | | | |
| Dexmedetomidine, μg kg$^{-1}$ hr$^{-1}$ | 1 ± 0.3 | | | | |
| Clonidine, μg kg$^{-1}$ hr$^{-1}$ | | 3 ± 0.68 | 2 ± 1.06 | 3 ± 0.57 | 1 ± 0.85 |
| Midazolam, mg kg$^{-1}$ hr$^{-1}$ | 0.3 ± 0.08 | 0.2 ± 0.08 | | 0.3 ± 0.07 | 0.15 ± 0.08 |
| Lormetazepam, mg kg$^{-1}$ min$^{-1}$ | | | 0.01 ± 0.008 | | |
| Esketamine, mg kg$^{-1}$ hr$^{-1}$ | 0.4 ± 0.21 | 1 ± 0.22 | | 2 ± 0.68 | 1 ± 0.32 |
| Propofol, mg kg$^{-1}$ hr$^{-1}$ | | 1 ± 0.77 | | | |
| Analgesia | | | | | |
| Sufentanil, μg kg$^{-1}$ hr$^{-1}$, mean ± SD | 0.5 ± 0.09 | 0.2 ± 0.07 | 0.1 ± 0.05 | 0.3 ± 0.09 | 0.25 ± 0.09 |
| Prone positioning, hr | 40 | 48 | 0 | 28 | 108 |
| Duration of volatile sedation, hr | 119 | 121 | 8 | 62 | 206 |
| Maximum Richmond-Agitation-Sedation Scale deviation from required sedation depth[a] | | | | | |
| Prior to isoflurane (data collected in the last 30 min before initiation of volatile sedation) | + 4 points | + 5 points | + 3 points | + 4 points | + 4 points |
| Day 1 with isoflurane sedation (data were collected at 4 AM on the first day after isoflurane treatment began) | ± 0 points | ± 0 points | ± 0 points | ± 0 points | −1 points |
| After termination of isoflurane (data after termination of isoflurane were collected in the first 30 min after the change of volatile to IV sedation) | + 1 points | ± 0 points | +1 points | + 1 points | ± 0 points |
| Outcome | Survived | Survived | Survived | Still in ICU | Still in ICU |

[a]Δ Richmond-Agitation-Sedation Scale (RASS) represents the maximum difference between targeted and observed RASS for each patient. The targeted sedation depth was a RASS of −4 was during the observed period indicated.

and broncho-obstructive episodes were resolved as the pulmonary compliance increased within the first 12 hours accompanied by improved oxygenation (**Fig. 1*A***). Furthermore, a substantial improvement in ventilator synchrony in pressure-controlled ventilation mode was observed.

Following a marked improvement in the patient's condition, sedation was switched back to clonidine and midazolam for the successful performance of a percutaneous tracheostomy. Thereafter, the sedation was discontinued, and the patient was transferred to an acute rehabilitation center.

### Case 3

The third patient was a 63-year-old man with severe hypoxemia requiring mechanical ventilation. He was transferred to our tertiary university hospital owing to his numerous comorbidities (Table 1) and persistent respiratory failure.

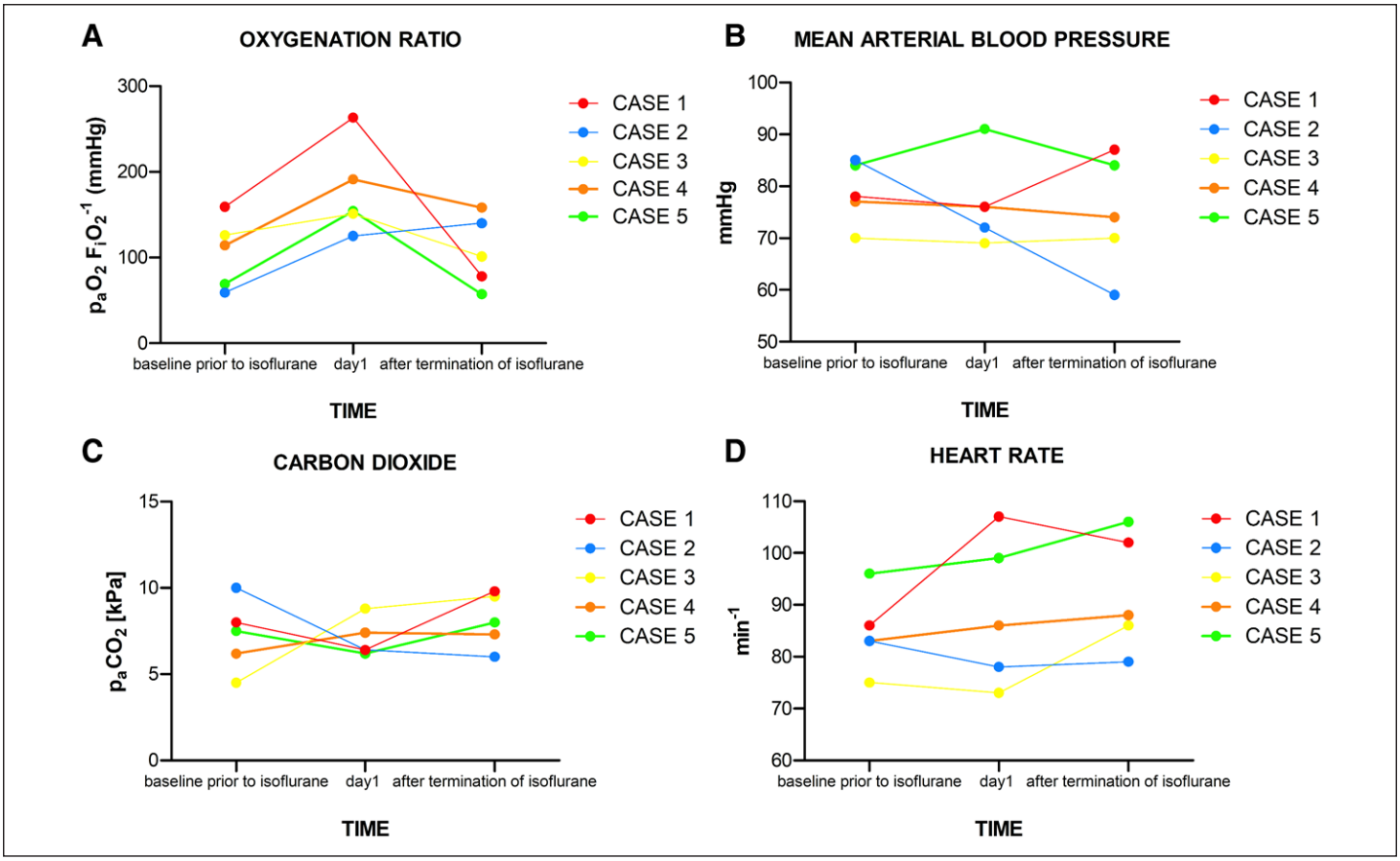


**Figure 1.** Oxygenation ratio, carbon dioxide, and hemodynamics during inhalation sedation with isoflurane over time. Oxygenation ratio, carbon dioxide and hemodynamics during inhalation sedation with isoflurane over time. The figure shows results of (**A**) oxygenation ratio, (**B**) $Paco_2$, (**C**) mean arterial blood pressure, and (**D**) heart rate over time. Data are presented as median. After termination of isoflurane = data after termination of isoflurane were collected in the first 30 min after the change of volatile to IV sedation, Baseline prior to isoflurane = data collected in the last 30 min before initiation of volatile sedation, day 1 = data were collected at 4 AM on the first day after initiation of isoflurane treatment, kPa = pressure in kilopascals, $min^{-1}$ = per minute, mm Hg= millimeters mercury, $Pao_2$ $Fio_2^{-1}$ = oxygenation level as quotient of $Pao_2$ and $Fio_2$.

In addition to moderate C-ARDS, the patient suffered from severe cardiac decompensation and sepsis. Aortic valve endocarditis caused by an infection of his implanted pacemaker was detected to be the underlying cause.

Following cardiac surgery, hemodynamic and respiratory condition improved substantially (Fig. 1). However, suboptimal sedation was observed with triggering of stress responses leading to repetitive desaturation, thus initiating isoflurane sedation (MAC 0.8). IV sedation was rapidly discontinued. Highly effective sedation (RASS –3/–4) was achieved under a balanced sedation regime, and the spontaneous respiratory rate decreased from 37 to 25 $min^{-1}$. Therefore, the targeted MAC was set to 0.5, and analgesia with sufentanil was discontinued. Additionally, a reduction of the respiratory minute volume from 15 to 9 L $min^{-1}$ was recorded, leading to hypercapnia, which resulted in respiratory acidosis with decreased catecholamine responsiveness. Because the respiratory mechanics improved rapidly, deep sedation was no longer required, and successful extubation was achieved on day after discontinuing the inhalational sedation. The patient presented an adequate neurologic status and could therefore be transferred to the normal ward a few days later.

## Case 4

A 63-year-old man with confirmed SARS-CoV-2 infection. Therefore, endotracheal intubation for invasive ventilation and prone positioning were required.

The patient was transferred to our tertiary university hospital for urgent initiation of venovenous ECMO. After the commencement of ECMO therapy and prone positioning, suboptimal sedation was observed despite unusually high doses of IV sedation. Concurrently, several bronchospastic episodes were observed. By switching the sedation to isoflurane (MAC 1.0) and sufentanil, stable hemodynamics and adequate sedation were achieved (Fig. 1, *B* and *D*). Despite the improved sedation levels and the associated increased respiratory synchrony, the tidal volumes gradually decreased, resulting in insufficient volatile sedation. The sedation regime was then switched from inhaled isoflurane back to an IV sedation method.

## Case 5

A 58-year-old patient presented to our emergency department due to increasing dyspnea, and COVID-19 was diagnosed. After 5 days of invasive ventilation, the implementation of venovenous ECMO was necessary. Due to concomitant acute renal failure, renal

replacement therapy was initiated. The deep sedation required for venovenous ECMO therapy and prone positioning was impossible with IV sedation. After initiating isoflurane sedation (MAC 0.5) in addition to sufentanil, a marked improvement in respiratory synchrony and adequate sedation levels were achieved. After 15 days of ECMO therapy, the tidal volume gradually decreased up to 87 mL despite ventilator adjustments, resulting in inadequate volatile sedation. The sedation was therefore switched back to IV sedation with clonidine and sufentanil.

During the observation period, the mean RASS was assessed as –3, –4, and –5 for 36.8%, 56.6%, and 6.6% of the time, respectively (data not shown). As reported, cases 2 and 4 showed a considerable clinical improvement of the bronchial-obstructive episodes.

## DISCUSSION

This case series of five patients demonstrates the feasibility of using isoflurane for the inhalational sedation of critically ill COVID-19 patients.

To the best of our knowledge, no studies have investigated the effect of isoflurane sedation in patients suffering from C-ARDS so far, and it remains understudied whether the observed pathophysiologic pulmonary abnormalities, such as exudative and proliferative phases of a diffuse alveolar injury, might have an impact on the feasibility of volatile sedation (25–27). As increasingly discussed, inhalation of volatile anesthetics might be of some benefit in COVID-19–infected patients (2, 3).

At present, sedation regimens for COVID-19 patients are based on the standard guidelines for critical care and on previous experiences in treating patients with "classic" ARDS. Although the Surviving Sepsis Campaign recommends considering the use of neuromuscular blocking agents (NMBAs) for deep sedation in cases of persistent ventilator dyssynchrony and prone positioning, more detailed recommendations for pharmacologic sedation are not yet available (28).

NMBAs were applied in our therapy concept in the first 48 hours after intubation (29–31). The application of NMBAs has not been necessary in any of the patients included in this study after the initiation of inhalational sedation. This enabled patients to breathe spontaneously during most of the treatment period. The role of spontaneous breathing during mechanical ventilation in ARDS has not yet been conclusively clarified and is still discussed (32, 33). Since the net impact depends on the severity of the lung damage, the optimal ventilation strategy regarding the ventilation mode has to be considered individually.

Several authors have recommended deep sedation for these patients, especially to minimize the potential aerosol generation from coughing and thus protect medical personnel and to provide optimal patient care (15, 34, 35). In contrast to patients with "classic" ARDS, the experiences of our department and others highlight that a large proportion of COVID-19 patients may require unusually high sedation levels (1, 3). The underlying reasons for these high sedation requirements are not yet understood but may be related to younger age and good health of some patients prior contracting COVID-19. However, in regard to our data, this assumption does not correspond to the patients we observed and requires further research.

Inhalational sedation may therefore be a suitable and promising alternative for patients with C-ARDS, also in light of the reported shortage of sedative pharmaceuticals (8, 36). Additionally, there may be further beneficial effects regarding the frequently observed need for long-term ventilation in C-ARDS patients and the associated facilitation of ventilator synchrony, prone positioning, and ECMO therapy that requires deeper sedation levels (1).

However, it has to be mentioned that regardless of the volatile conserving device used, the required components are not very common in intensive care medicine and therefore represent the primary limitation for widespread use. A conceivable elimination of this limitation can be overcome by the pandemic-related use of anesthesia circuit components from the operating room (37).

Our experience with the use of volatile sedation in five patients with C-ARDS was in line with previous studies on the use of isoflurane in critically ill patients (7, 9). We did not observe any renal or hepatic toxicity, as it has been described for volatile sedation (38, 39). In fact, we were able to rapidly and closely control the depth of sedation; this has also been reported in previous patient cohorts (40).

As presented, our experiences reinforce that the use of volatile sedation depends on achieving an adequate tidal volume. To maintain an adequate respiratory uptake of isoflurane, a sufficient respiratory minute volume is essential and may be limited by a lung-protective ventilation strategy, especially during ECMO treatment.

Rand et al (19) and Meiser et al (41) showed that volatile sedation is feasible in patients undergoing ECMO therapy These studies demonstrated that despite ultraprotective ventilation with low tidal volumes and poor lung function, adequate sedation with volatile anesthesia could be achieved. However, all patients presented in this study who underwent ECMO therapy suffered from extensive COVID-19–associated lung damage, which resulted in low tidal volumes applying ultraprotective lung ventilation. Tidal volume less than 100 mL precluded sufficient sedation with volatile anesthetics, resulting in a switch back to IV sedation.

The feasibility of administering volatile anesthetics during a cardiopulmonary bypass has already been demonstrated; however, this has not yet been described for the ECMO circuit in ICUs but should be considered as a future therapeutic approach, especially in regard to our observations (42).

In addition to the predominantly favorable effects of isoflurane in the treated patients, respiratory depression related to the pharmacodynamics of inhalational anesthetics was observed in one patient (case 3) as a result of volatile sedation at the end of a prolonged weaning process (43). In line with current recommendations, we therefore suggest adhering to bedside sedation algorithms and verifying the safety criteria to avoid inappropriate deep or prolonged sedation when applying volatile sedation in COVID-19 patients (44). We observed a reduced need for opioid sedation during treatment and an improved lung function with regard to the $Pao_2/Fio_2$ ratio. Most notably, in cases 2 and 4, volatile isoflurane successfully resolved the multiple broncho-obstructive episodes. In regard to the proven impact of underlying respiratory diseases and their attribution to a worse progression and outcome of COVID-19, volatile sedation could be beneficial in improving the COVID-19–associated lung injury (45).

Some limitations must be taken into account when interpreting our results.

Although relevant sequestration through the polymethylpentene membrane of modern oxygenators has not yet been demonstrated, the transient absorption of gaseous isoflurane from the polyvinylchloride tubes of the ECMO circuit may impact the patient (46, 47). Furthermore, the small number of five patients displaying different comorbidities and age does not allow a detailed analysis of the dynamics of sedation or pharmacokinetic mechanisms in critically ill COVID-19 patients. Additionally, we did not consider the interindividual dynamics of ventilation, sedation, and lung mechanics when interpreting the data. Due to the short and limited observation time, we carefully avoid to overclaim our findings. The authors feel confident that the observations obtained within this study are applicable to patients suffering from COVID-19 requiring critical care. Further research and long-term observational studies of COVID-19 patients who receive isoflurane sedation are necessary to clarify the pharmacodynamic mechanisms and clinical effects in order to establish a dose-response relationship.

## CONCLUSIONS

In this first report of applying volatile sedation in patients with C-ARDS, we demonstrated the feasibility of isoflurane sedation in five cases. The use of volatile isoflurane achieved the required deep sedation and even a reduction of IV sedation accompanied by improved pulmonary function.

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