Mechanical Ventilation in COVID-19 Patients Supported With ECMO in Wenzhou, China: A Retrospective Study

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Research

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Abstract

Background

The function of Extracorporeal membrane oxygenation (ECMO) is to maintain cardiopulmonary function in critical patients diagnosed with Coronavirus (COVID-19). Under the protection of ECMO, we recorded and analyzed the results of ventilator treatment following the adjustment of ventilator settings.

Methods

This retrospective study enrolled six patients who received ECMO treatment. Clinical, laboratory and radiological characteristics, time of spontaneous respiration, and static lung compliance (CLst) were all recorded. Positive end-expiratory pressure (PEEP) and oxygen concentration (FIO₂) were adjusted to record changes in oxygen saturation (SpO₂), tidal volume (TV), peak airway pressure, and blood gas analysis.

Results

During analysis, one patient died of COVID-19 within 28 days, and two patients were successfully weaned off mechanical ventilation and ECMO. Patients with an improved condition have a longer time of spontaneous respiration and better CLst than those who worsen. With an instantaneous increase in FIO₂ alone or a combination of PEEP / FIO₂, SpO₂ and partial pressure of oxygen (PaO₂) both increased, but no significant change was observed in PaCO₂, PaO₂/FIO₂ and TV. With an instantaneous increase of PEEP alone, SpO₂, PaO₂, PaCO₂, PaO₂/FIO₂ and TV showed no significant change.

Conclusions

ECMO can save some patients' lives, but some patients will still suffer multiple organ failure and even death. The time of spontaneous respiration, CLst and TV may be a good choice for evaluating patients' lung situations. Increased PEEP may not significantly reduce lung exudation in COVID-19 patients supported by ECMO but further expand the over-expanded alveoli.

Introduction

In December 2019, an epidemic of a respiratory disease of indefinite etiology was found in Wuhan, Hube, China [1]. The newly discovered virus was named "New Coronavirus 2019" (2019-nCoV). Coronavirus belongs to the Coronaviridae family. Coronaviruses are a highly diverse, positive-sense, enveloped, single-stranded RNA virus [2]. This family contains viruses which cause the common cold to those that affect Middle East Respiratory Syndrome (MERS) and severe acute respiratory syndrome (SARS) [3,4]. Now the disease of COVID-19 pandemic is declared as global health emergency [5,6].

COVID-19 causes lung damage, and patients display symptoms which range from asymptomatic infection to severe breathing issues and acute respiratory distress syndrome (ARDS). The most common signs of COVID-19 include fatigue, dry cough, and fever [7-10]. The common computed tomography (CT) findings are appearance of bilateral pulmonary parenchymal ground-glass [11,12]. However, about 14 percent of cases are serious and 5 percent are critical with 2.3-5.3% case-fatality rate (CFR) in China and 3.1% globally [13-15]. ECMO is mostly used in ARDS patients for refractory hypoxemia as rescue therapy [16] due to the reduction of TV, FIO₂, PEEP and plateau pressure (pplat) [16-18]. ECMO may play a key role in medical treatment of some patients suffered with COVID-19 refractory hypoxic respiratory failure.

Wenzhou is situated in the southeastern part of Zhejiang Province, China and has a land area of 12,061 square kilometers and a population of more than 9 million. It is the most severe area of the COVID-19 epidemic in Zhejiang Province. As of September 22nd, 504 people have been infected with COVID-19 in Wenzhou (data from the official channels of China National Health and Health Commission, provincial and municipal health and health committees, and provincial and municipal governments). Our hospital is the unique designated treatment hospital for severe and critically ill patients in Wenzhou. A total 63 patients with COVID-19 have been treated, six of whom received ECMO treatment.

Current literature on mechanical ventilation in critically ill COVID-19 patients is limited, particularly in patients requiring ECMO therapy. This article observed six critically ill patients supported by ECMO in our hospital, adjusted ventilator parameters and observed the changes of the related indicators. This will provide a possible reference for ventilator settings and patient prognosis evaluation of critically ill COVID-19 patients with ECMO support.

Methods

Study design and participants

This retrospective cohort study was permitted by the Institutional Ethics Board of The First Affiliated Hospital of Wenzhou Medical University (No. KY2020-066). Six patients received ECMO treatment who were admitted to The First Affiliated Hospital of Wenzhou Medical University during 31st January to 11th February 2020 were enrolled. The patients with COVID-19 were diagnosed by using real-time reverse transcription polymerase chain reaction (RT-PCR) assay for pharyngeal and nasal swab specimens. About 6 patients with COVID-19 in this study were diagnosed by using WHO interim guidance [19]. As the patients were deeply sedated and analgesic, verbal consent was obtained from their family members.

Data collection

The patients' medical records were investigated by the investigators at the First Affiliated Hospital. Epidemiological, laboratory, clinical, and radiological characteristics were attained from electronic medical records and placed on data collection forms. The data was collected by a trained team of physicians. The manuscript was reviewed by all authors who guaranteed the completeness and accuracy of the data.

For each patient, following variables were estimated: (1) demographic statistics; (2) APACHE II scoring system (acute physiology and chronic health evaluation) upon admission; (3) time interval between onset of symptoms and admission; (4) time between admission and the start of invasive mechanical ventilation (IMV); (5) time between the start of IMV and ECMO; (6) blood gas analysis parameters before commencing ECMO; (7) ECMO settings; (8) inspiratory time and TV during spontaneous breathing (SPONT mode: pressure support ventilation, PSV, 15cmH₂O PEEP, 10cmH₂O FIO₂, 50%); (9) all patients were fully sedated, analgesic and muscle relaxant applied, FIO₂ and PEEP were adjusted in pressure controlled ventilation (PCV) mode and peak airway pressure (P_{peak}), TV, and blood gas analysis parameters were recorded; (10) static lung compliance (CL_{st}); (11) sepsis related organ failure assessment (SOFA score); and (12) whether they died within 28 days.

Statistical analysis

Continuous variables were articulated as medians and interquartile ranges or as simple ranges while counts and percentages were used to explain categorical variables. Shapiro-Wilk Normality Test was used for the normality test. The group t-test was used to compare the means of continuous variables when the data was distributed normally; Kruskal-Wallis Rank Sum Test was employed for non-parametric test. R package tableone was used to perform all statistical analyses. P<0.05 was used to define statistically significant relationship.

Results

Presenting characteristics

The study comprised six hospitalized patients with confirmed diagnose of COVID-19 supported by mechanical ventilation and ECMO. The median age was 73.50 years (SD, 15.97; range, 53-93 years), and four (66.7%) were men. The median duration from first displaying symptoms to hospital admission was eight days (SD, 3.58), APACHE II score at admission was 11.83 (SD, 3.97; range, 7-18), and the median estimated risk of death was 11.67% (SD, 5.85; range, 6-22) (Table 1). The median durations from admission to IMV and IMV to ECMO were 4.50 days (SD, 4.04) and 13.50 days (SD, 2.81) respectively. At the start of ECMO treatment, the patients' median oxygenation index (PaO₂/FIO₂) and partial pressure of carbon dioxide (PaCO₂) were 79.05 (IQR, 77.15- 81.85; range, 69-175.6) and 70.45mm Hg (SD, 17.48; range, 44.5-91.6), respectively. All patients were in ARDS. At the time

of analysis, one patient died of COVID-19 (16.7%) within 28 days, and two patients (33.3%) were successfully weaned off mechanical ventilation and ECMO (Table 1).

Imaging changes

Imaging examinations of all six patients with COVID-19 indicated that lung lesions deteriorated after admission. In the early stage, chest CT manifested as ground-glass opacity, involving both lungs and peripheral areas (Fig.1a). When ECMO was performed, chest CT showed severe consolidation of both lungs, even hepatoid changes, and normal lung tissue was rarely seen. Some peripheral lung tissues were over-inflated (Fig.1b). The chest CT of one patient following the removal of the ventilator and ECMO showed significant absorption of bilateral lung consolidation (Fig.1c).

Inspiratory time and TV during spontaneous breathing, CLST and SOFA score

Inspiratory time and TV were recorded during spontaneous breathing (SPONT mode, PSV 15cmH₂O, PEEP 10cmH₂O, FIO₂ 50%). CLst and SOFA score were recorded. The median inspiratory time, CLst and SOFA score were 0.48s (SD, 0.12; range, 0.21-0.61s), 8.55ml/cmH₂O (SD, 5.00; range, 1.1-13.6ml/cmH₂O), and 8.36 (SD, 3.75; range, 3-15). Patients with an improved condition demonstrated a longer inspiratory time [0.57 (0.04) vs. 0.42 (0.12); $p < 0.05$] and better CLst [12.70 (2.66) vs. 6.39 (4.60); $p < 0.05$] than those who had worsened (Table 2).

Ecmo parameters

One patient received venoarterial ECMO (VA ECMO), one received venovenous ECMO (VAV ECMO), and four received venoarterial-venous ECMO (VV ECMO). The median rotating speed, flow, sweep gas flow and oxygen concentration of ECMO were 3666.64rpm (SD, 600.86), 4.68 l/min (SD, 0.65), 6.71 l/min (SD, 2.36) and 100.00% (IQR, 100.00-100.00), respectively (Table 2).

FIO2 and PEEP of ventilator were adjusted in patients with COVID-19 supported by ECMO

All patients were fully sedated with analgesic and muscle relaxant, and adjusted oxygen concentration and PEEP in PCV mode, peripheral oxygen saturation (SpO₂), airway Ppeak, TV, and blood gas analysis parameters were all recorded.

With an increase of FIO₂, SpO₂ the partial pressure of oxygen (PaO₂) was increased ($P < 0.05$), but no significant change was observed in PaCO₂ ($P = 0.92$) and PaO₂/FIO₂ ($P = 0.95$) (Fig.2). Patients which died within 28 days demonstrated higher PaCO₂ and lower PaO₂/FIO₂ ($p < 0.05$). Patients with an improved condition had higher SpO₂, PaO₂, PaCO₂ and PaO₂/FIO₂ ($p < 0.05$) than those with a deteriorated condition (Table 3).

With an increase of PEEP, SpO₂ ($P = 0.92$), PaO₂ ($P = 1.00$), PaCO₂ ($P = 0.79$), PaO₂/FIO₂ ($P = 1.00$) and TV ($P = 0.46$) showed no significant change (Fig.3). Patient which died within 28 days showed lower PaO₂/FIO₂ ($P < 0.001$). Patients with an improved condition had higher PaCO₂ and TV ($P < 0.001$) than those with a deteriorated condition (Table 4).

With an increase of PEEP and FIO₂ alternately, SpO₂ and PaO₂ increased ($P < 0.05$), but no significant change was observed in PaCO₂ ($P = 0.94$), PaO₂/FIO₂ ($P = 0.16$) and TV ($P = 0.50$) (Fig.4). Patients which died within 28 days showed lower PaO₂, PaO₂/FIO₂ and TV ($p < 0.05$). Patients with an improved condition had higher SpO₂, PaO₂, PaCO₂, PaO₂/FIO₂ and TV ($p < 0.05$) than those with a deteriorated condition (Table 5).

Discussion

This study comprised six hospitalized patients with confirmed diagnose of COVID-19 supported by mechanical ventilation and ECMO. Consistent with other findings, men and elderly patients were more critically ill [7, 11, 13]. 66.7% of the patients in our study were men, with an average age of 73.50 years. After admission, the patients' conditions deteriorated sharply. The median durations from admission to IMV and IMV to ECMO were 4.50 days (SD, 4.04) and 13.50 days (SD, 2.81). At the start of ECMO, all patients had ARDS [PaO₂/FiO₂, 79.05 (IQR, 77.15- 81.85; range, 69-175.6)]. Some patients developed hypercapnia [PaCO₂, 70.45mm Hg (SD, 17.48; range, 44.5-91.6)]. All patients experienced multiple organ failure with an average SOFA score of 8.36

(SD, 3.75). At the time of analysis, one patient died of COVID-19 (16.7%) within 28 days, two patients (33.3%) were successfully weaned off mechanical ventilation and ECMO.

ECMO does not directly support the organs other than heart or lungs, except for oxygen delivery throughout the body and reducing lung damage caused by a ventilator. Patients will still have multiple organ failure, so therefore ECMO plays a limited role in new coronary pneumonia [20].

Imaging examinations of all six patients with COVID-19 indicated that the lung lesions deteriorated after admission. Upon admission, chest CT manifested as ground-glass opacity, involving both lungs and peripheral areas, which is typical with COVID-19 [11,12]. However, patients with lung injuries continue to worsen, and required invasive mechanical ventilation and ECMO support. Chest CT of a 53-year-old male patient during ECMO support revealed severe consolidation of both lungs, hepatoidosis.

Some current pathological studies [21-23] have discovered that the pathological changes of COVID-19 are mainly found in the lungs, plus injury of alveolar epithelial cells, the formation of hyaline membrane, and the proliferation of type II lung cells. However, merging of fibroblastic proliferation with fibrin forming clusters and extracellular matrix in airspaces is obvious. A large number of neutrophils were also found in the alveoli of patients, indicating a secondary pulmonary bacterial infection [22]. The six patients commonly had bacterial infections in their lungs, which aggravated lung damage and caused extensive consolidation of the lungs. It is surprising that the lung tissue lesions of two patients who were successfully withdrawn the ventilator and ECMO were obviously absorbed, and there appeared to be no severe pulmonary fibrosis. However, follow-up of these patients must be adhered to, assessing changes in their lung imaging and respiratory function, and evaluating their quality of life.

In this study, we found that the spontaneous breathing time and CLst of COVID-19 patients supported by ECMO were significantly reduced, which suggests that patients' lung compliance decreased.

With the inspiratory pressure unchanged, the instantaneous increase of PEEP alone or combination of PEEP/FIO₂ immediately showed a decrease in TV, and with the increase of PEEP alone or combination of PEEP/FIO₂, the TV showed a downward trend, although there was no statistically significance, but this still suggests that patients' lung compliance is reduced with an increase of PEEP. With an increase of PEEP alone or an increase of PEEP/FIO₂, the PaO₂/FIO₂ of patients did not increase significantly. We could not explain the above phenomenon until the later performance of a chest CT on a 53-year-old patient. The patient's chest CT showed that a large area of lung consolidation had almost no normal lung tissue, and some lung tissues were over-expanded. The chest X-rays of all six patients were similar, and all of them were "white lung". We speculate that increased PEEP may not significantly reduce lung exudation in COVID-19 patients supported by ECMO but may further expand the over-expanded alveoli.

For most patients, COVID-19-related ARDS patients may have similar respiratory system mechanisms to ARDS patients with other causes, and their treatment is in line with traditional ARDS treatment [24,25]. However, ARDS secondary to COVID-19 shows heterogeneous features [25-27]. In one study, two main phenotypes were proposed: type L (low elasticity, pulm ventilation / perfusion ratio, lung weight and recruitment) and type H (high elasticity, right to left shunt, lung weight and recruitment) [27]. The ventilator setting of ARDS emphasizes increasing PEEP and lung recruiting maneuvers (LRMs) for improvement of oxygenation and lung compliance [28,29]. However, the effectiveness of LRMs is still controversial due to lac of bedside methods which can measure alveolar recruitment and its influence on ventilator-associated lung injury (VILI) [29]. The higher PEEP values may make the lung expand excessively, which lead to the decrease of lung compliance [26]. It has been found that the major determinants of the heterogeneity of ARDS induced by covid-19 may be the degree of intravascular microthrombosis, hyperinfection and other complications [24,26]. More research is required to select more appropriate PEEP, particularly for COVID-19 patients with severe pulmonary lesions who require ECMO support.

In this study, we found that patients with an improved condition have longer inspiratory time, better CLst, higher SpO₂, PaO₂, PaCO₂, PaO₂/FIO₂ and TV than those with a worsening condition. Due to the role of ECMO, SpO₂, PaO₂, PaCO₂ and PaO₂/FIO₂ of patients cannot reflect the true situation of patients' lungs, so the time of spontaneous respiration, CLst and TV may be a good choice for evaluating patients' lung situation.

Conclusions

2019-nCoV can cause severe lung damage and ARDS in patients, which will ventilator or even ECMO support. ECMO can save the lives of some patients, but some patients will still suffer from multiple organ failure and even death. Time of spontaneous respiration, CLst and TV may be a good choice for evaluating patients' lung situation. Increased PEEP may not significantly reduce lung exudation in COVID-19 patients supported by ECMO but may further expand the over-expanded alveoli. Our research may provide some useful information for mechanical ventilation treatment of COVID-19 patients supported by ECMO. However, more research on mechanical ventilation is needed to guide the treatment of COVID-19 patients.

Abbreviations

2019-nCoV: New Coronavirus 2019; APACHE II scoring system: Acute physiology and chronic health evaluation; ARDS: Acute respiratory distress syndrome; CFR: Case-fatality rate; CLst: Static lung compliance; COVID-19: Coronavirus; CT: Computed tomography; ECMO: Extracorporeal membrane oxygenation; FIO2: Oxygen concentration; IMV: Invasive mechanical ventilation; LRMs: Lung recruiting maneuvers; MERS: Middle East Respiratory Syndrome; PaCO2: Partial pressure of carbon dioxide; PaO2: Partial pressure of oxygen; PaO2/FIO2: Oxygenation index; PCV: Pressure controlled ventilation; PEEP: Positive end-expiratory pressure; Ppeak: Peak airway pressure; Pplat: Plateau pressure; PSV: Pressure support ventilation; RT-PCR: Real-time reverse transcription polymerase chain reaction; SARS: Severe acute respiratory syndrome; SOFA score: Sepsis related organ failure assessment; SpO2: Oxygen saturation; TV: Tidal volume; VA ECMO: Venoarterial extracorporeal membrane oxygenation; VAV ECMO: Venovenous extracorporeal membrane oxygenation; VILI: Ventilator-associated lung injury; VV ECMO: Venoarterial-venous extracorporeal membrane oxygenation.

Declarations

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Author contributions: JY Pan, YR Lu and XR Wang conceived of the study and drafted the design; JJ Cai and SZ Qian carried out experimental procedures; JJ Cai and YC Ye performed data analysis; JY Pan and JJ Cai drafted the manuscript; all authors provided critical review of the manuscript and approved the final draft for publication.

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Availability of data and materials

The datasets generated analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This retrospective cohort study was permitted by the Institutional Ethics Board of The First Affiliated Hospital of Wenzhou Medical University (No. KY2020-066). As the patients were deeply sedated and analgesic, verbal consent was obtained from their family members.

Consent for publication

Written informed consent for publication was obtained from all authors.

Competing interests

All the authors state that there are no conflicts of interest related to this study.

References

1. Wuhan Municipal Health Commission. Report of clustering pneumonia of unknown etiology in Wuhan City. <http://wjw.wuhan.gov.cn/front/web/showDetail/20191231>. 2019. Accessed December 31 2019.
2. A Z, JF C, EI A, DS H, KY Y. Coronaviruses - drug discovery and therapeutic options. *Nature reviews. Drug discovery* 2016; 15(5): 327-347.
3. VC C, SK L, PC W, KY Y. Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. *CLIN MICROBIOL REV* 2007; 20(4): 660-694.
4. JF C, SK L, KK T, VC C, PC W, KY Y. Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease. *CLIN MICROBIOL REV* 2015; 28(2): 465-522.
5. Zhang L, Lin D, Sun X, Curth U, Drosten C, Sauerhering L, Becker S, Rox K, Hilgenfeld R. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α -ketoamide inhibitors. *SCIENCE* 2020: b3405.
6. Guo L, Ren L, Yang S, Xiao M, Chang, Yang F, Dela CC, Wang Y, Wu C, Xiao Y, Zhang L, Han L, Dang S, Xu Y, Yang Q, Xu S, Zhu H, Xu Y, Jin Q, Sharma L, Wang L, Wang J. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). *CLIN INFECT DIS* 2020.
7. D W, B H, C H, F Z, X L, J Z, B W, H X, Z C, Y X, Y Z, Y L, X W, Z P. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020.
8. Z W, B Y, Q L, L W, R Z. Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2020.
9. Q L, X G, P W, X W, L Z, Y T, R R, KSM L, EHY L, JY W, X X, N X, Y W, C L, Q C, D L, T L, J Z, M L, W T, C C, L J, R Y, Q W, S Z, R W, H L, Y L, Y L, G S, H L, Z T, Y Y, Z D, B L, Z M, Y Z, G S, TTY L, JT W, GF G, BJ C, B Y, GM L, Z F. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *The New England journal of medicine* 2020: 382(13): 1199-1207.
10. N C, M Z, X D, J Q, F G, Y H, Y Q, J W, Y L, Y W, J X, T Y, X Z, L Z. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet (London, England)* 2020: 395(10223): 507-513.
11. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, Liu L, Shan H, Lei C, Hui DSC, Du B, Li L, Zeng G, Yuen K, Chen R, Tang C, Wang T, Chen P, Xiang J, Li S, Wang J, Liang Z, Peng Y, Wei L, Liu Y, Hu Y, Peng P, Wang J, Liu J, Chen Z, Li G, Zheng Z, Qiu S, Luo J, Ye C, Zhu S, Zhong N, China MTEG. Clinical Characteristics of Coronavirus Disease 2019 in China. *The New England journal of medicine* 2020.
12. M C, A B, X M, N Z, M H, X Z, J C, W X, Y Y, ZA F, A J, K L, S L, H S. CT Imaging Features of 2019 Novel Coronavirus (2019-nCoV). *RADIOLOGY* 2020: 295(1): 202-207.
13. Z W, JM M. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020.
14. National Health Commission of the People's Republic of China. Coronavirus disease (COVID-2019) situation reports. <http://www.nhc.gov.cn/situation> reports/20200922. Accessed September 22 2020.
15. World Health Organization. Coronavirus disease (COVID-2019) situation reports. <https://www.who.int/docs/default-source/coronaviruse/situation> reports/Weekly Epidemiological Update 20200921. 2020. Accessed September 21 2020.
16. GJ P, M M, R T, A W, E A, MM T, CL H, A T, F C, N C, RK F, D E. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet (London, England)* 2009: 374(9698): 1351-1363.
17. M S, C S, M B, A N, J K, L M, D P, DJ C, C S, V P, P F, A C, C H. Mechanical ventilation management during extracorporeal membrane oxygenation for acute respiratory distress syndrome: a retrospective international multicenter study. *CRIT CARE MED* 2015: 43(3): 654-664.

18. JD M, L M, M D, T T, E F. Mechanical ventilation during extracorporeal life support (ECLS): a systematic review. *INTENS CARE MED* 2015; 41(6): 994-1003.
19. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance. [https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-nove-coronavirus-\(ncov\)-infection-is-suspected](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-nove-coronavirus-(ncov)-infection-is-suspected). 2020. Accessed January 31 2020.
20. G M, D F, D B. Preparing for the Most Critically Ill Patients With COVID-19: The Potential Role of Extracorporeal Membrane Oxygenation. *JAMA* 2020.
21. Z X, L S, Y W, J Z, L H, C Z, S L, P Z, H L, L Z, Y T, C B, T G, J S, P X, J D, J Z, FS W. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *The Lancet. Respiratory medicine* 2020; 8(4): 420-422.
22. S T, Y X, H L, L N, J G, M L, SY X. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc* 2020.
23. S T, W H, L N, H L, H X, SY X. Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2020.
24. 24.Schaller Tina, Hirschbühl Klaus, Burkhardt Katrin, Braun Georg, Trepel Martin, Märkl Bruno, Claus Rainer. Postmortem examination of patients with COVID-19. *JAMA* 2020; published online May 21. DOI:10.1001/jama.2020.8907
25. 25.Fan Eddy, Beitler Jeremy R, Brochard Laurent, Calfee Carolyn S, Ferguson Niall D, Slutsky Arthur S, Brodie Daniel. COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted? *Lancet Respir Med*, 2020, 8: 816-821.
26. 26.Sella Nicolò, Zarantonello Francesco, Andreatta Giulio, Gagliardi Veronica, Boscolo Annalisa, Navalesi Paolo. Positive end-expiratory pressure titration in COVID-19 acute respiratory failure: electrical impedance tomography vs. PEEP/FiO tables. *Crit Care*, 2020, 24: 540..
27. 27.Gattinoni Luciano, Chiumello Davide, Caironi Pietro, Busana Mattia, Romitti Federica, Brazzi Luca, Camporota Luigi. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med* 2020; published online April 14. DOI:10.1007/
28. s00134-020-06033-2.
29. 28. E F, D B, AS S. Acute Respiratory Distress Syndrome: Advances in Diagnosis and Treatment. *JAMA* 2018; 319(7): 698-710.
30. 29. T B, S G, O M, M Q, C G, M D, A B, S M. The standard of care of patients with ARDS: ventilatory settings and rescue therapies for refractory hypoxemia. *INTENS CARE MED* 2016; 42(5): 699-711.

Tables

Table 1. Presenting characteristics of patients with Coronavirus disease 2019 supported by ECMO.

	Normal Range	Total	Died within 28 days			Outcome		
			NO	Yes	P Value	Improvement	Deterioration	P Value
n		6	5	1		2	4	
Gender = male	NA	4 (66.7%)	4 (80.0%)	0 (0.0%)	0.333	2 (100.0)	2 (50.0)	0.467
Age, mean (SD)	NA	73.50 (15.97)	72.40 (17.60)	79.00 (NA)	NA	8.00 (1.41)	8.00 (4.55)	0.004
Onset of symptom to admission, d (mean (SD))	NA	8.00 (3.58)	9.20 (2.28)	2.00 (NA)	NA	8.00 (1.41)	13.75 (3.30)	1
APACHE II score, mean (SD)	NA	11.83 (3.97)	12.20 (4.32)	10.00 (NA)	NA	6.00 (0.00)	14.50 (5.00)	0.087
Estimated risk of death, % (mean (SD))	0-100	11.67 (5.85)	11.60 (6.54)	12.00 (NA)	NA	7.50 (4.95)	3.00 (3.16)	0.086
Time from admission to IMV, d (mean (SD))	NA	4.50 (4.04)	5.20 (4.09)	1.00 (NA)	NA	8.00 (1.41)	8.00 (4.55)	0.232
Time from IMV to ECMO, d (mean (SD))	NA	13.50 (2.81)	13.80 (3.03)	12.00 (NA)	NA	13.50 (3.54)	13.50 (3.00)	1
Before starting ECMO								
FiO2, mean (SD)	0-1	0.75 (0.14)	0.76 (0.16)	0.70 (NA)	NA	0.70 (0.28)	0.78 (0.06)	0.599
PaO2, mm Hg, mean (SD)	83-108	66.35 (13.38)	69.96 (11.23)	48.30 (NA)	NA	80.00 (11.03)	59.53 (8.46)	0.061
PaCO2, mm Hg, mean (SD)	35-45	70.45 (17.48)	68.58 (18.86)	79.80 (NA)	NA	85.50 (8.63)	62.92 (16.06)	0.148
PaO2/FiO2, median [IQR]	400-500	79.05 [77.15, 81.85]	80.20 [77.90, 82.40]	69.00 [69.00, 69.00]	0.143	127.90 [104.05, 151.75]	77.40 [74.93, 79.03]	0.165
Outcome, %								
Improvement	NA	2 (33.3%)	2 (40.0%)	0 (0.0%)		2 (100.0)	0 (0.0)	
Deterioration	NA	4 (66.7%)	3 (60.0%)	1 (100.0%)		0 (0.0)	4 (100.0)	

NA – not available; Improvement – the patient's condition improved and the ventilator and ECMO were removed; Deterioration – the patient's condition deteriorated or they died; $P < 0.05$ was used to define statistically significant relationship.

Table 2. Inspiratory time and TV during spontaneous breathing, CLst, SOFA score, and ECMO parameters in patients with Coronavirus disease 2019 supported by ECMO.

	Normal Range	Total	Outcome		
			Improvement	Deterioration	P Value
n		11	4	7	
Inspiratory time,s (mean (SD))	0.8 -1.2	0.48(0.12)	0.57 (0.04)	0.42 (0.12)	0.038
VT,ml (mean (SD))	6ml/kg	161.89 (106.65)	194.80 (47.53)	143.09 (129.20)	0.468
CLst, ml/cmH2O (mean (SD))	Male, 170±60 Female, 110±30	8.68 (5.00)	12.70 (2.66)	6.39 (4.60)	0.035
SOFA score	NA	8.36 (3.75)	6.00 (2.94)	9.71 (3.64)	0.117
ECMO_mode (%)					
VA	NA	1 (9.1%)	0 (0.0)	1 (14.3)	
VAV	NA	2 (18.2%)	0 (0.0)	2 (28.6)	
VV	NA	8 (72.7%)	4 (100.0)	4 (57.1)	
ECMO parameters					
Rotating speed (rpm) (mean (SD))	NA	3666.64 (600.86)	4109.50 (604.11)	3413.57 (462.37)	0.059
Flow, l/min (mean (SD))	NA	4.68 (0.65)	5.05 (0.72)	4.47 (0.55)	0.165
Sweep gas flow, l/min (mean (SD))	NA	6.71(2.36)	7.38 (1.97)	6.33 (2.61)	0.508
O2,% (median [IQR])	0-100	100.00 [100.00, 100.00]	100.00 [100.00, 100.00]	100.00 [100.00, 100.00]	0.45

NA – not available; Improvement – the patient's condition improved and the ventilator and ECMO were removed; Deterioration – the patient's condition deteriorated or they died; $P < 0.05$ was used to define statistically significant relationship.

Table 3. FIO2 of ventilator was adjusted in patients with Coronavirus disease 2019 supported by ECMO.

	Normal Range	Died within 28 days			Outcome		
		NO	Yes	<i>P</i> Value	Improvement	Deterioration	<i>P</i> Value
n		60	6		24	42	
SpO2,% (median [IQR])	94-100	100.00 [98.00, 100.00]	99.00 [98.25, 99.75]	0.471	100.00 [100.00, 100.00]	99.00 [98.00, 100.00]	0.009
PaO2,mm Hg (median [IQR])	83-108	97.65 [73.38, 203.00]	74.00 [72.05, 77.00]	0.067	228.65 [144.62, 309.95]	75.95 [71.50, 90.22]	<0.001
PaCO2,mm Hg (median [IQR])	35-45	44.65 [42.08, 46.80]	40.25 [40.12, 40.53]	0.003	48.40 [44.93, 51.55]	42.30 [40.30, 44.95]	<0.001
PaO2/FiO2 (median [IQR])	400-500	138.50 [113.19, 273.44]	99.05 [88.15, 115.71]	0.015	313.33 [251.71, 358.20]	118.47 [97.32, 133.19]	<0.001

Improvement – the patient's condition improved and the ventilator and ECMO were removed; Deterioration – the patient's condition deteriorated or they died; $P < 0.05$ was used to define statistically significant relationship.

Table 4. PEEP of ventilator was adjusted in patients with Coronavirus disease 2019 supported by ECMO.

	Normal Range	Died within 28 days			Outcome		
		NO	Yes	<i>P</i> Value	Improvement	Deterioration	<i>P</i> Value
n		100	10		40	70	
SpO2,% (median [IQR])	94-100	96.00 [93.00, 99.00]	97.00 [93.00, 97.00]	0.47	96.00 [93.00, 100.00]	97.00 [93.00, 98.00]	0.67
PaO2,mm Hg (median [IQR])	83-108	67.20 [60.48, 76.58]	62.45 [55.78, 66.83]	0.07	66.00 [63.68, 95.15]	67.15 [57.45, 74.05]	0.07
PaCO2,mm Hg (median [IQR])	35-45	43.65 [41.20, 45.60]	43.05 [42.20, 43.55]	0.273	45.40 [44.03, 47.00]	42.15 [40.23, 43.80]	<0.001
PaO2/FiO2 (median [IQR])	400-500	134.40 [120.95, 153.15]	124.90 [111.55, 133.65]	0.07	132.00 [127.35, 190.30]	134.30 [114.90, 148.10]	0.07
Ppeak,cmH2O (median [IQR])	NA	28.00 [22.00, 32.00]	27.00 [22.50, 31.50]	0.884	27.00 [22.00, 32.00]	28.00 [22.00, 32.00]	0.753
TV,ml (median [IQR])	6ml/kg	125.50 [64.05, 216.85]	23.10 [17.95, 30.15]	<0.001	187.20 [126.70, 237.00]	74.70 [21.40, 130.50]	<0.001

NA – not available; Improvement – the patient's condition improved and the ventilator and ECMO were removed; Deterioration – the patient's condition deteriorated or they died; $P < 0.05$ was used to define statistically significant relationship.

Table 5. PEEP and FiO2 of ventilator were adjusted alternately in patients with Coronavirus disease 2019 supported by ECMO.

	Normal Range	Died within 28 days			Outcome		
		NO	Yes	<i>P</i> Value	Improvement	Deterioration	<i>P</i> Value
n		80	8		32	56	
SpO2,% (median [IQR])	94-100	99.00 [96.00, 100.00]	98.00 [97.75, 98.00]	0.295	100.00 [98.00, 100.00]	98.00 [96.00, 99.00]	0.002
PaO2,mm Hg (median [IQR])	83-108	90.55 [71.05, 125.25]	70.55 [67.58, 73.72]	0.022	151.90 [83.65, 268.00]	76.70 [67.58, 93.95]	<0.001
PaCO2,mm Hg (median [IQR])	35-45	43.90 [41.08, 46.30]	42.25 [42.08, 42.42]	0.27	44.65 [43.20, 47.80]	42.05 [39.88, 45.83]	0.001
PaO2/FiO2 (median [IQR])	400-500	126.00 [106.89, 181.50]	98.21 [81.18, 122.50]	0.016	248.67 [123.56, 306.11]	117.03 [98.96, 134.24]	<0.001
Ppeak,cmH2O (median [IQR])	NA	29.50 [26.00, 33.25]	29.00 [26.00, 32.50]	0.907	29.00 [26.00, 32.50]	29.50 [26.00, 33.25]	0.78
TV,ml (median [IQR])	6ml/kg	110.00 [61.50, 180.70]	21.10 [17.55, 23.70]	<0.001	157.10 [108.25, 193.85]	65.90 [22.55, 129.60]	<0.001

NA – not available; Improvement – the patient's condition improved and the ventilator and ECMO were removed; Deterioration – the patient's condition deteriorated or they died; $P < 0.05$ was used to define statistically significant relationship.

Figures

Figure 1

Imaging examinations of patients infected with New Coronavirus 2019. a). Computed tomography images of a 55-year-old patient obtained on January 29th 2020 showed ground glass opacity in both lungs on day five after symptom onset. b). A 53-year-old male patient had a chest X-ray examination on March 12th 2020 and computed tomography examination on March 13th 2020. Chest computed tomography showed that the patient's lungs had diffuse consolidation with reduced gas content and showed liver-like changes. Some peripheral lung tissue was over-inflated. This patient was successfully weaned off the ventilator and extracorporeal membrane oxygenation. c). The chest computed tomography of one patient after the ventilator and extracorporeal membrane oxygenation were removed on April 14th 2020 showed significant absorption of bilateral lung consolidation. d). The chest computed tomography of a patient undergoing mechanical ventilation on April 15th 2020 indicated that there were thick fibrous cords and obvious fibrosis in both lungs after removal of the ventilator .

Figure 2

FIO2 of ventilator was adjusted in patients with COVID-19 supported by ECMO. After all patients were fully sedated with analgesic and muscle-relaxant, FIO2 was adjusted to 50%, 60%, 70%, 80%, 90%, 100% every 10 minutes in PCV mode (PI 15cmH2O/PEEP 10cmH2O). SpO2, PaO2, PaCO2 and PaO2/FIO2 were recorded. a). SpO2 changes. b). PaO2 changes. c). PaCO2 changes. d). PaO2/FIO2 changes.

Figure 3

PEEP of ventilator was adjusted in patients with COVID-19 supported by ECMO. In PCV mode (PI 15cmH₂O, FIO₂ 50%), PEEP was adjusted to 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 cmH₂O every 10 minutes in turn, SpO₂, PaO₂, PaCO₂, PaO₂/FIO₂, Ppeak and TV were recorded. a). PaO₂ changes. b). PaCO₂ changes. c). PaO₂/FIO₂ changes. d). TV changes.

Figure 4

PEEP and FIO₂ of ventilator were adjusted alternately in patients with COVID-19 supported by ECMO. In PCV mode (PI 15cmH₂O), it was adjusted to PEEP 5cmH₂O-FIO₂ 50%, PEEP10 cmH₂O-FIO₂ 50%, PEEP10 cmH₂O-FIO₂ 70%, PEEP12 cmH₂O-FIO₂ 70%, PEEP14cmH₂O-FIO₂ 90%, PEEP16 cmH₂O-FIO₂ 90 %, PEEP18 cmH₂O-FIO₂ 100%, PEEP20 cmH₂O-FIO₂ 100%, blood gas analysis was performed. SpO₂, PaO₂, PaCO₂, PaO₂/FIO₂, peak airway pressure and tidal volume were recorded. a). PaO₂ changes. b). PaCO₂ changes. c). PaO₂/FIO₂ changes. d). TV changes.