SARS-CoV-2 Leakage From the Gas Outlet Port During Extracorporeal Membrane Oxygenation for COVID-19

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Patients with the coronavirus disease 2019 (COVID-19) sometimes develop refractory respiratory failure and may require venovenous extracorporeal membrane oxygenation (VV-ECMO). It is known that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is sometimes present in the blood of COVID-19 patients. VV-ECMO is often used for several weeks, and plasma leaks can occur, albeit rarely. Hence, in terms of infection control, a concern is that SARS-CoV-2 may leak from the gas outlet port of the oxygenator during ECMO support of critically ill COVID-19 patients. The aim of this study was to clarify whether SARS-CoV-2 leaks from the oxygenator during ECMO support. Five patients with critical COVID-19 pneumonia were placed on VV-ECMO. Silicone-coated polypropylene membrane oxygenators were used in the ECMO circuits for these patients. SARS-CoV-2 ribonucleic acid (RNA) was measured by quantitative reverse transcription polymerase chain reaction in serum and at the gas outlet port of the ECMO circuit at the time of circuit replacement or liberation from ECMO. SARS-CoV-2 RNA was detected in the gas outlet port of the ECMO circuit for three of the five patients. None of the medical staff involved in the care of these five patients has been infected with COVID-19. In conclusion, SARS-CoV-2 could leak to the gas outlet port of the ECMO circuit through silicone-coated polypropylene membranes during ECMO support of critically ill COVID-19 patients. *ASAIO Journal* 2021; 67;511–516

Key Words: COVID-19, severe acute respiratory syndrome coronavirus 2, extracorporeal membrane oxygenation, infection control

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Although many patients with the coronavirus disease 2019 (COVID-19) have a good prognosis, some patients with COVID-19 pneumonia develop refractory respiratory failure and may require mechanical ventilation. Furthermore, some patients with severe respiratory failure may require extracorporeal membrane oxygenation (ECMO) in addition to mechanical ventilation for respiratory support.[1]

However, in terms of infection control, a concern is that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may leak through the membrane from the blood during ECMO support of critically ill patients with COVID-19 pneumonia.[2] In fact, a previous study has reported the detection of SARS-CoV-2 in the nasal cavity, pharynx, feces, sputum, and blood of patients with COVID-19.[3] Another study also reported the detection of SARS-CoV-2 ribonucleic acid (RNA) in the blood of 15% of patients with COVID-19.[4] Although polymethylpentene (asymmetric) or silicone-coated polypropylene (composite) membrane oxygenators are designed to prevent plasma leakage during ECMO support, it can occur, albeit rarely, after several weeks of ECMO support.[5] Therefore, the virus might leak through the membrane from serum to the gas outlet port.

To our knowledge, no study has investigated whether SARS-CoV-2 can leak through a silicone-coated polypropylene membrane oxygenator. Therefore, we undertook this study to determine whether this can occur during venovenous (VV)-ECMO.

Materials and Methods

Study Design and Patient Selection

This single-center, prospective observational study was conducted between February and May 2020 at the Center Hospital of the National Center for Global Health and Medicine (NCGM), a tertiary-care teaching hospital located in Tokyo, Japan. Inclusion criteria were confirmed COVID-19 and the need for ECMO in addition to mechanical ventilation. This study was approved by the Institutional Review Board of the NCGM (G-003472-02). Written informed consent was obtained from all patients in this study.

Types of ECMO Circuits and How They Are Operated

Two centrifugal blood pump systems were used in each case: the HAS-CFP and HCS-CFP MERA Centrifugal Blood Pump System (Senko Medical Instrument Mfg. Co., Ltd., Tokyo, Japan). The circuit used was the MERA Exeline HP2/PCPS, which consists of a 3/8-inch-diameter heparin-coated polyvinyl chloride tube (Senko Medical Instrument Mfg. Co., Ltd.), an oxygenator (HPO-23WH-C; Senko Medical Instrument Mfg. Co., Ltd.), and

a centrifugal pump (HCF-MP23H; Senko Medical Instrument Mfg. Co., Ltd.). The oxygenator in this circuit consists of silicone-coated polypropylene membranes (membrane area = 2.3 m^2, oxygenator volume = 225 ml, oxygenator pressure tolerance = 500 mm Hg, and the manufacturer's recommended 6 hours of use). The drainage cannula was either the MERA NSH Heparinization Percutaneous Cardiopulmonary Support Cannula (PCKC-V-24/24Fr; Senko Medical Instrument Mfg. Co., Ltd.) or the QuickDraw (QD25/25Fr; Edwards Lifesciences Corporation, Tokyo, Japan). The return cannula was the MERA NSH Heparinization Percutaneous Cardiopulmonary Support cannula (PCKC-A-20/20Fr; Senko Medical Instrument Mfg. Co., Ltd.), which was inserted through the internal jugular or femoral vein. The gas-exchange capacity of the oxygenator may decrease because of condensation in the oxygenator. To prevent this, we have devised the following modification. First, warm air is blown into the oxygenator using a warming device (3M Bair Hugger Normothermia System; 3M Japan, Tokyo, Japan) to prevent condensation in oxygenator.[6,7] Second, the oxygenator is covered with a polyethylene sheet like a tent (Figure 1) to prevent cool outside air from causing condensation. For anticoagulation, intravenous heparin was administered to achieve a target activated clotting time of 180–200 s. We visually checked whether there was plasma leakage from the oxygenator at least three times a day. We replaced the circuit by the following criteria: 1) clots were detected within the circuit or oxygenator, 2) plasma leakage was detected, and/or 3) a decrease in the gas-exchange capacity of the oxygenator was detected and could not be easily solved.

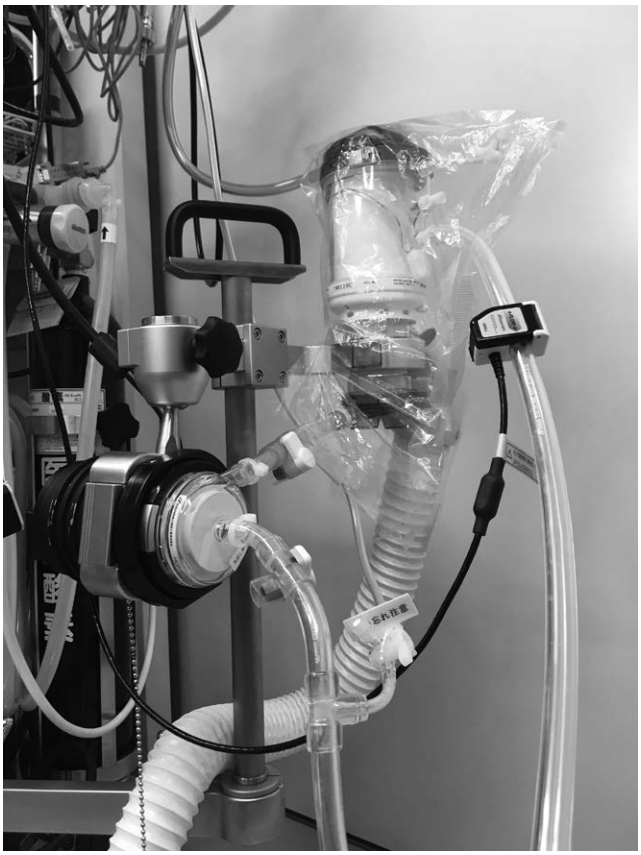

Figure 1. Oxygenator wrapped with a transparent polyethylene sheet.

The following data were collected: days from the onset of COVID-19 to the start of ECMO, duration of ECMO, duration of use for each oxygenator (from the start of oxygenator use to circuit replacement, liberation, or withdrawal), visible plasma leakage, sweep gas flow, centrifugal pump speed, prepump venous drainage pressure, preoxygenator pressure, postoxygenator pressure, blood flow in the ECMO circuit, and presence of viral RNA in the serum during ECMO support (if available).

Virus Measurement Conditions

For measurement of viral RNA in serum, blood was collected from the oxygenator blood gas sampling port in the ECMO circuit. For measurements of viral RNA in the gas outlet port of the oxygenator, swabs were taken of the lower membrane located 2–3 cm from the gas outlet port. Because medical staff were most likely to be exposed to the virus when handling the circuit, these samples were taken at the time of ECMO circuit replacement, liberation, or withdrawal.

Quantitative reverse-transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 was performed at the National Institute of Infectious Diseases, Japan, using the QuantiTect Probe One-step RT-PCR kit (Qiagen, Hilden, Germany) with the following probe and primer sets: WuhanCoV-N1f 5′-GGCCGCAAATTGCACAAT-3′, WuhanCoV-N1CG5AC-CCAA 3′, and WuhanCoV-N1pr-fam 5′-FAM-CCCCCAGCGCTTCAGCGTTCT-TAMRA-3′ targeting the nucleoprotein gene (29191-29251 in MN908947).[8]

Results

We performed ECMO for five patients with critical COVID-19 pneumonia between February and May 2020. All patients were judged to require ECMO because of refractory hypoxia and VV-ECMO circuits were used in all cases. After starting the centrifugal pump, we adjusted the round speed to achieve a blood flow rate of about 5 L/min referring to the prepump venous drainage pressure and we adjusted the sweep gas flow referring to arterial blood gas analysis results.

Table 1 shows the parameters for ECMO support. The mean running time of oxygenators was 7.4 days. During ECMO support, no visible plasma leakage occurred for all patients. The membrane pressure drop (preoxygenator pressure – postoxygenator pressure) was 79 mm Hg for patient 1 and 60 mm Hg for patient 5. Preoxygenator pressure for patients 2–4 was unable to be measured because of the equipment.

In all patients, SARS-CoV-2 RNA levels were measured in the serum of circuit blood and a swab taken of the gas outlet port in the VV-ECMO circuit at the time of circuit replacement or liberation from ECMO. Viral RNA levels in serum were measured in patients 1 and 2 for clinical purposes during ECMO support, and the results are shown in Table 2. Viral RNA was found in serum collected on days 5 and 7 from the start of ECMO in patient 1 and patient 2, respectively. At the time of circuit replacement or liberation from ECMO, however, viral RNA in serum was below the limit of detection in all patients (Table 2). In patients 1, 3, and 5, SARS-CoV-2 RNA was detected in the swabs of the gas outlet ports. Figure 2 shows

Table 1. Parameters for ECMO Operation

Parameters	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Time from onset of COVID-19 to start of ECMO (days)	10	15	6	18	18
Duration of ECMO (days)	12	20	5	12	23
Duration of use for each oxygenator (days) and days to exchanges					
Number used					
1st	7	10*	5*	12*	4
2nd	6*	11	Not used	Not used	15
3rd	Not used	Not used	Not used	Not used	5*
Visible plasma leakage	No	No	No	No	No
Mean value during ECMO operation (range)					
Sweep gas flow (L/min)	5.0 (3–6.5)	5.1 (3–6.5)	3.8 (3–5)	4.1 (3–5)	3.0 (0.5–4)
Blood flow (L/min)	4.8 (3.9–5.2)	4.2 (2–5.72)	5.0 (4.9–5.2)	5.0 (4.6–5.4)	5.1 (4.5–5.4)
Prepump venous drainage pressure (mm Hg)	–66 (–79 to –47)	–35 (–83 to 9)	–73 (–78 to –64)	–84 (–99 to –74)	–76 (–92 to –52)
Oxygenator pressure (mm Hg)					
Post	153 (106–173)	130 (78–180)	152 (138–164)	137 (125–152)	175 (147–190)
Centrifugal pump speed (rpm)†	3,460	3,040	3,440	3,420	3,550

*Used in this study.
†Mean value only.
COVID, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; rpm, round per minute.

Table 2. Measurements of SARS-CoV-2 RNA Levels (CT)*

Sample	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Serum	(Day from start of ECMO)				
	38.35 (day 5)	35.39 (day 7)	NA	NA	NA
	At circuit replacement or liberation from ECMO†				
	UDL	UDL	UDL	UDL	UDL
Gas outlet port of the oxygenator (day of ECMO use)					
	35.1 (day 6)	UDL (day 10)	38.28 (day 5)	UDL (day 12)	35.96 (day 5)

*Lower CT values indicate higher viral loads. The limit of detection of the PCR instrument is 10 copies per reaction.
†The number of days is the same as for the gas outlet port.
CT, cycle threshold; ECMO, extracorporeal membrane oxygenation; NA, not available; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; UDL, under detection limit.

the blood flow, sweep gas flow, and pressure after the oxygenator from the start of oxygenator use to circuit replacement or liberation from ECMO.

All patients were managed in a negative-pressure room, and all medical staff always used N95 masks, gowns, caps, and face shields to prevent infection with SARS-CoV-2 during ECMO support.[9] None of the medical staff involved in the care of these five patients, including doctors, nurses, clinical engineers, and rehabilitation staff, was found to be infected with COVID-19 by the end of July 2020.

Discussion

We performed this single-center, prospective observational study to investigate whether SARS-CoV-2 can leak through a silicone-coated polypropylene membrane oxygenator during VV-ECMO. Five patients were enrolled between February and May 2020. We first found SARS-CoV-2 RNA in the gas outlet port of the oxygenator at the time of circuit replacement or liberation from ECMO. This suggests that SARS-CoV-2 can leak through the silicone-coated polypropylene membrane oxygenator during VV-ECMO.

There are two possible explanations for the detection of viral RNA at the gas outlet port of the oxygenator. One is that the virus may have leaked inside the oxygenator through the membrane from serum, and the other is that it may have invaded from the external environment. However, the sweep gas that passes through the oxygenator flows in one direction and the oxygenator was covered with a polyethylene sheet, so we consider it unlikely that viral RNA entered from the external environment.

It is known that SARS-CoV-2 is sometimes detected in the serum of patients with COVID-19.[3,4] Therefore, if there is plasma leakage from the oxygenator, the virus may have been expelled from inside the oxygenator. Because of the limited number of measurements, we could not prove viremia in all patients, but it was detected in some patients (Table 2).

The silicone-coated polypropylene membrane oxygenator is designed to prevent plasma leakage by means of its silicone coating. A previous study suggested that the silicone coating does not completely cover the polypropylene membrane in this oxygenator.[10] In addition, a high membrane pressure drop (pre-oxygenator pressure – postoxygenator pressure) results in high resistance in the oxygenator. Thus, an increasing membrane

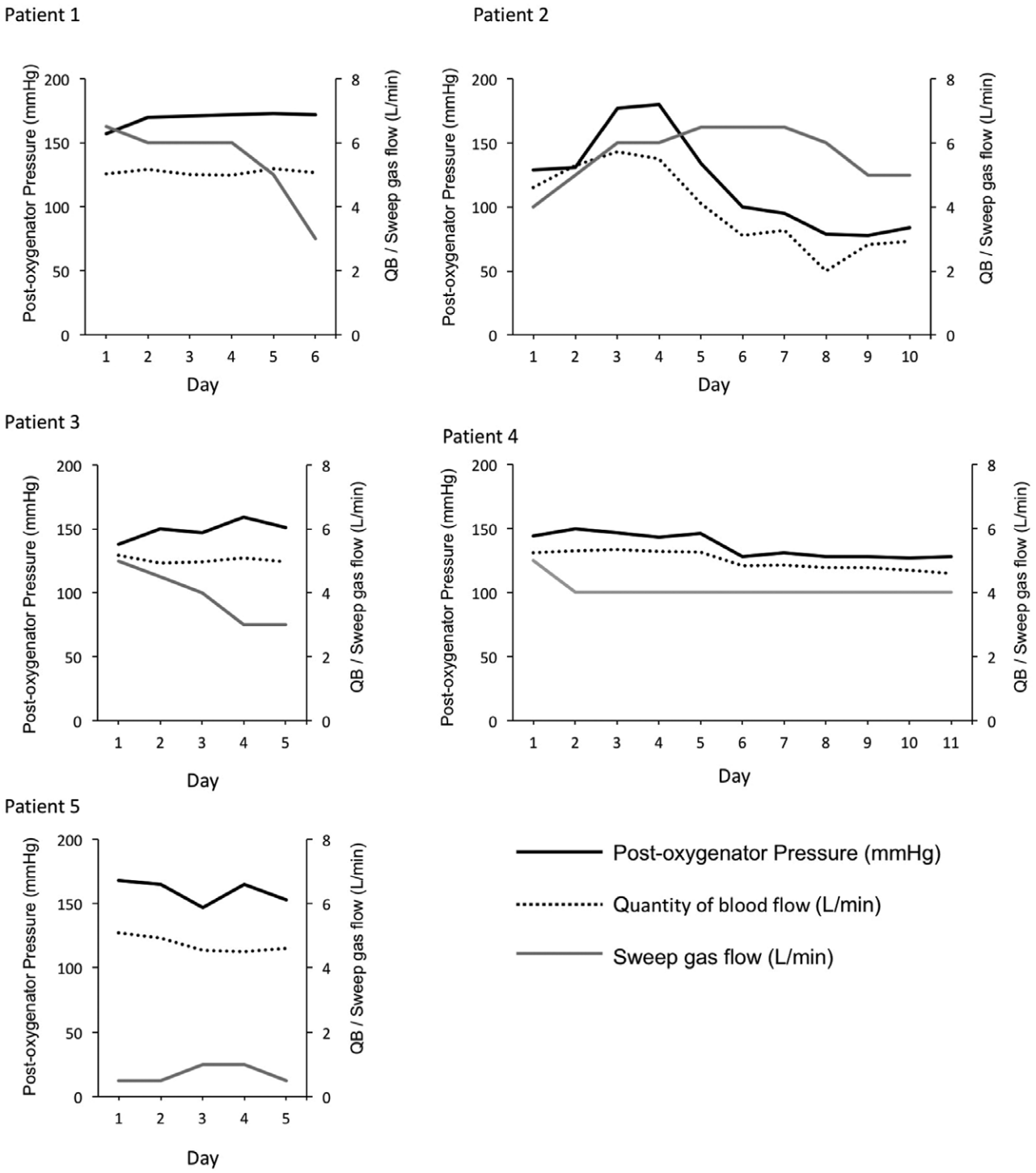

Figure 2. Time course of postoxygenator pressure, sweep gas flow, and quantity of blood flow in ECMO support. ECMO, extracorporeal membrane oxygenation; QB, quantity of blood flow.

pressure drop may be associated with membrane damage or deterioration.[5] We considered that high pressure could damage the silicone coating of the membrane, in turn leading to further plasma leakage. The oxygenator was not operated outside specified pressure range and no visible plasma leakage was observed in this study. However, there have been reports of invisible amounts of leakage within the pressure range tolerance specified by the manufacturer.[10] In addition, oxygenator was used beyond the manufacturer's recommendation than when used within the recommended duration of use. This could also be one of the reasons of leakage.

Then, viral RNA passing through the membrane from the serum could enter the gas phase. In addition, because the outlet of the oxygenator is dry, even if the plasma concentration of viral RNA in the serum is low, it could condense at the gas outlet port, increasing the viral RNA concentration. Although no

viral RNA was detected in serum measured at circuit replacement or liberation from ECMO (Table 2), our results suggest that viral RNA may have accumulated in the gas outlet port of the oxygenator, even though the viremia improved between the start of treatment and the time of measurement. It has also been reported that SARS-CoV-2 was detected on the plastic surface for as long as 7 days.[11]

We initially expected that high pressure in the oxygenator was associated with leakage of viral RNA. An additional factor could be deterioration of the coating because of long-term use, and long-term ECMO support is considered a risk factor for leakage. However, this study could not demonstrate that leakage of viral RNA leakage was associated with high pressure in the oxygenator or long-term use, and pressure measurement data were also limited. We think there are other factors that affect leakage, but they are difficult to elucidate with the limited number of cases and amount of clinical data in this study. We believe that further research is needed in the future.

In contrast to results of our study, Dres *et al.*[12] reported that SARS-CoV-2 does not spread through ECMO or dialysis membranes. However, differences between their study and ours were that they used a polymethylpentene membrane oxygenator and that the timing of sample collection was within 48 hours of starting treatment. In contrast, we detected SARS-CoV-2 RNA in the gas outlet port of the oxygenator at the time of circuit replacement or liberation from ECMO (Table 2). Thus, the differing results between these studies can be attributed to the properties of the membranes and the timing of sample collection.

The first difference is the material of oxygenators. The oxygenator used in the previous study had a polymethylpentene membrane with an asymmetric design.[12] On the other hand, we used an oxygenator with silicone-coated polypropylene composite membranes. Of course, the oxygenators used in this study had silicone-coated polypropylene membranes designed to prevent plasma leakage. In fact, we observed no visible plasma leakage in any of the five cases (Table 1).

The second difference is the timing of measuring SARS-CoV-2 RNA. Given that ECMO support can last for several weeks, we considered a long observation period to be necessary for determining whether the virus leaked through the membrane. Indeed, previous studies have reported that the average running time of ECMO was 218 hours[13] and that critically ill patients with COVID-19 required up to 47 days of ECMO support.[14] Given that viremia can persist for a long time in patients with severe COVID-19,[15] there is a possibility that the virus could leak after more than 48 hours following the initiation of ECMO. In addition, medical staff will handle the oxygenator at the time of circuit replacement or liberation from ECMO. Therefore, we decided to measure SARS-CoV-2 RNA at the gas outlet port of the oxygenator at the time of ECMO circuit replacement, liberation, or withdrawal. Although SARS-CoV-2 RNA was not detected in the serum of all patients at the time of circuit replacement or liberation from ECMO, SARS-CoV-2 RNA was detected at the gas outlet port of the oxygenator in 3 of the 5 patients. We also detected SARS-CoV-2 RNA in serum of patients 1 and 2 while they were on ECMO support (Table 2). In the study by Dres *et al.*,[12] samples at the gas outlet port of the oxygenator were obtained only within 48 hours after initiation of ECMO. This may account for their opposite results regarding leakage of SARS-CoV-2 RNA through the membrane. Unlike in their study, there was no condensate in the gas outlet port in the current study. We therefore took swabs of the gas outlet port. Swab methods are a general way to test for contamination with SARS-CoV-2,[16] so we do not think that the different collection methods account for these differing results.

Possible implications of the results of this study for clinical practice are as follows. First, the infectivity of the virus detected at the gas outlet port is not known, and it is also unclear whether protective measures are needed for gas outlet port. The sweep gas flow rate of ECMO is often temporarily increased to blow off dew condensation when the oxygenator is in the wet lung state. However, this maneuver might be dangerous for the medical staff because of potential dissemination of the virus. Therefore, covering the oxygenator with a polyethylene sheet may be useful for preventing viral spread in addition to preventing condensation in the oxygenator. Because of the appropriate use of personal protective equipment and covering the oxygenator, none of the medical staff involved in the care of these five patients, including doctors, nurses, clinical engineers, and rehabilitation staff, was found to be infected with COVID-19 by the end of July 2020.

Our study had several limitations. First, only five cases were investigated, so the findings cannot be readily generalized. Second, we could not check all the oxygenators we handled because of limitations on the RT-PCR measurements. In addition, the gas outlet port of the oxygenator could be measured only at the time of circuit replacement or liberation from ECMO, because swabs could damage the membrane of the oxygenator. In principle, it would be desirable to take measurements at multiple times to find out when viral RNA is detected at the gas outlet port of the oxygenator. Third, the amount of SARS-CoV-2 RNA in the swab of the ECMO gas outlet port was very small; although the presence of SARS-CoV-2 RNA was assessed, the infectivity is not known. Fourth, there is no direct evidence that SARS-CoV-2 leaked through the membrane. It may be necessary to confirm membrane damage by the electron microscopy. Finally, further study is warranted to examine whether SARS-CoV-2 RNA can be detected at gas outlet port of polymethylpentene membrane oxygenators at the time of circuit replacement or liberation from ECMO.

Conclusions

SARS-CoV-2 leakage might occur from blood to the gas outlet port of the oxygenator through silicone-coated polypropylene membranes during VV-ECMO support of critically ill COVID-19 patients. These results suggest that proper handling of the oxygenator in the ECMO system is a crucial consideration for infection control.

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