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Trend and Pattern of 100 Acute Respiratory Distress Syndrome Patients Referred for Venovenous Extracorporeal Membrane Oxygenation Treatment in a National Referral Center in North Italy During the Last Decade

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Objective: Current evidence supports centralization of patients with refractory acute respiratory distress syndrome (ARDS) to institutions with a high level of expertise and with extracorporeal membrane oxygenation (ECMO) capabilities. The aim of this study was to analyze and report the data of transferred refractory ARDS patients managed with venovenous (VV) ECMO at a national referral center over the last 11 years.

Design: Observational study.

Setting: Referral center in Italy.

Participants: The study comprised 100 patients treated from May 2009 to November 2020.

Interventions: None.

Measurements and Main Results: The mean age was 54 ± 14 years, and 65% of patients were male. Patients were treated throughout the year, with seasonal peaks in the winter months. The majority of patients were referred from hospitals within the Lombardia region (81%), mainly from the city of Milan and surrounding area (36% of the total). The most common etiology of refractory ARDS was H1N1 influenza A (42 patients [42%]), followed by bacterial pneumonia (35 patients [35%]), and severe acute respiratory syndrome due to Sars-CoV-2 infection (five patients [5%]). All patients were severely hypoxic at the time of VV ECMO treatment. No transport-related complication was recorded. The most common configuration used in the authors’ clinical practice was a bicaval dual-lumen configuration (61 patients [61%]), followed by a femoro-jugular configuration (38 patients [38%]). The intensive care unit survival rate was 55%.

Conclusions: Referral to a specialized center for VV ECMO treatment should be considered expeditiously in case of refractory ARDS, which often is lethal. Transport of patients with an unstable condition, although challenging, is feasible, and centralization of patient care is associated with good outcomes.

Key Words: acute respiratory distress syndrome; intensive care unit; referral; venovenous extracorporeal membrane oxygenation; VV ECMO; mortality

THE ROLE of venovenous extracorporeal membrane oxygenation (VV ECMO) in the treatment of patients with refractory acute respiratory distress syndrome (ARDS) continues to evolve.1,9 Technical advances and the clinical challenges of the H1N11,10,11 and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)5 pandemics have driven further attention toward VV ECMO. In particular, existing reports have strengthened the recommendation for referral to a...
specialized center for consideration of extracorporeal support treatment early after failure of improvements with mechanical ventilation. In fact, most patients treated with VV ECMO originally are identified as needing a treatment upgrade in remote hospitals and then are transferred to tertiary care centers.

In Italy, a network of selected intensive care unit (ICU) centers, named “ECMOnet,” was created in 2009 to provide advanced extracorporeal support for severe refractory hypoxemia after ARDS as a result of the H1N1 influenza A virus. Throughout the last decade, ECMOnet has continued its work, including through the ongoing SARS-CoV-2 pandemic, allowing for the centralization and treatment of hundreds of patients per year who originated from referral centers. Herein the authors report the experience of one of the referral centers contributing to the ECMOnet since the development the network.

The aim of the present study was to analyze and report data on refractory ARDS patients transferred from remote hospitals and managed with VV ECMO at the authors’ referral center.

Methods

The present study was in compliance with Helsinki declaration. With the approval of the institutional local ethical committee, data were retrieved from record charts, were stored electronically, and were anonymized before database insertion. All adult patients referred from remote hospitals and treated with VV ECMO for refractory ARDS at the authors’ institution from May 2009—November 2020 were included in the study.

When physicians in a remote hospital encountered failure of optimal treatment and refractory hypoxia in ARDS patients undergoing mechanical ventilation, they were able to discuss their case with a specialist in the ECMO center via a national phone number in order to decide how to continue treatment and whether to centralize the patient in the referral center. If needed, the ECMO team could travel to the referring site to take care of the extracorporeal support implantation and patient transport. Transport was carried out with an ambulance or with an air transport, depending on distance, weather conditions, and ECMOnet center resources. The ECMOnet referral centers of the Lombardia region are shown in Supplementary Fig 1. Center specialists performed percutaneous cannulation via the Seldinger technique with the femoro-jugular or femoro-femoral approach or a bicaval dual-lumen configuration (since 2012). Management of ECMO patients and ECMO team organization were in line with the authors’ previous reports. The Sequential Organ Failure Assessment (SOFA) score, Simplified Acute Physiology Score (SAPS) II score, and the VV ECMO specific-ECMOnet score were calculated.

Analysis was performed with Microsoft Excel 2019 (Microsoft, Redmond, WA). All data are reported as percentages for categorical variables and as means and standard deviations or medians with interquartile range for continuous variables.

Results

Between May 2009 and November 2020, 143 patients affected by severe ARDS were treated with VV ECMO at the authors’ center, 100 of whom were transferred and represent the study population. Baseline characteristics are shown in Table 1. The mean age was 53 ± 14 years, and 65 patients were male (65%). The SOFA score at admission was 12 ± 5, the ECMOnet-specific score was 6 ± 3, and the SAPS II score was 64 ± 25. The most common etiology of refractory ARDS was H1N1 influenza A, with 42 patients (42%), followed by bacterial pneumonia in 35 patients (35%), and SARS-CoV-2 ARDS in five patients (5%).

Distribution of the patients by month and year of the start of ECMO treatment is reported in Supplementary Figs 2 and 3, respectively. The most represented year was 2015 with 20 patients (20%), and the months with more cases were winter months as follows: 29 in February (29%), 18 in January (18%), and 13 in March (13%) when seasonal influenza contributed to the increased need for VV ECMO.

The most common mode of transport was ambulance, with 80 patients (80%), followed by air transport with 20 cases (20%) (Table 2). Moreover, 35 patients (35%) were transported on ECMO that had been implanted in a remote hospital by the ECMO team.

The majority of patients were transferred from hospitals within the Lombardia region (81%), mainly from the city of Milan and the surrounding area (36% of the total) (Supplementary Fig 4). The most common configuration used in the authors’ clinical practice was the bicaval dual-lumen configuration, with 61 patients (61%), followed by the femoro-jugular configuration in 38 (38%). The median pre-ECMO partial pressure of arterial/fraction of inspired oxygen oxygen ratio was 64 (52-77), the median pre-ECMO positive end-expiratory pressure was 12 (10-15) cmH2O, and the duration of pre-ECMO mechanical ventilation was two (one-five) days (Table 2). Thirty-five patients (35%) were treated with noninvasive ventilation before ECMO, and pronation was performed in 22 patients (22%). Pronation during VV ECMO was performed in seven patients (7%). The ICU survival rate was 55%.

Table 1

| Parameter                  | Value     |
|----------------------------|-----------|
| Age, y mean ± SD           | 53 ± 14   |
| Sex male, n (%)            | 65 (65%)  |
| Psychiatric comorbidity, n (%) | 13 (13%) |
| Neurologic comorbidity, n (%) | 8 (8%)    |
| Immunologic comorbidity, n (%) | 12 (12%) |
| Cardiovascular comorbidity, n (%) | 51 (51%) |
| Respiratory comorbidity, n (%) | 21 (21%) |
| Obesity, n (%)             | 23 (23%)  |
| Diabetes, n (%)            | 15 (15%)  |
| Disability, n (%)          | 5 (5%)    |
| Renal failure, n (%)       | 4 (4%)    |
| Shock at presentation, n (%) | 57 (57%) |
| SOFA score                 | 12 ± 5    |
| ECMOnet score              | 6 ± 3     |
| SAPS II score              | 64 ± 25   |

Abbreviations: ECMO, extracorporeal membrane oxygenation; SAPS, Simplified Acute Physiology Score; SD, standard deviation; SOFA, Sequential Organ Failure Assessment.
The median number of days of VV ECMO treatment was nine (five-17).

Discussion

Herein, data on 11 years of experience treating refractory ARDS with VV ECMO and centralization from remote hospitals in a national referral center are described. The authors’ experience is encouraging and in line with existing reports and literature. The present study demonstrated that the creation of a network for the management of severe ARDS patients allows for the centralization and upgrading of treatment for refractory cases. In this context, a 55% ICU survival rate was observed.

Most patients were transferred from remote hospitals within the same region as the ECMO treatment center, and only 19% were out-of-region patients.

The extreme degree of pre-ECMO hypoxia of the study population should be underlined. Indeed, the pre-ECMO partial pressure of arterial oxygenation/fraction of inspired oxygen ratio was 75.9 ± 29.5 in the CESAR trial, 73 ± 30 in the EOLIA trial, and 64 (52-75) in the present study’s population (Fig 1). In addition to hypoxia, the patients in the present study were extremely sick before treatment; shock at presentation was observed in 57 patients (57%) and patients had a high mortality risk at baseline as predicted by the SOFA, SAPS II, and ECMOnet-specific scores. Therefore, the team of ECMO specialists adopted the same indications for treatment compared to the other studies, but the patients were more compromised. Despite extreme critical illness, the patients experienced an ICU survival of 55%.

The considerable number of patients referred to the specialty center for ECMO treatment (100 of a total of 143 patients treated in the same period) was possible because the center is a high-volume referral center for extracorporeal support. The number of patients treated was greater than what has been reported recently by other national ECMO treatment centers. Transferred patients came from several remote facilities that did not have an ECMO program; this aspect is very important because referring and treating patients in a more experienced center considerably improves survival. The most commonly used mode of transport was ambulance, in 80% of cases, whereas air transport was less common (20%). This distribution confirmed that large referral centers principally treat patients coming from a nearby hospital. Air transport, which is used for long distance travel, is less common for the ECMOnet center because the distribution of referring centers was designed to reduce the need of more expensive and risky air medical services. Furthermore, it is worth noting that, although most patients came from nearby hospitals, the organization of patient transport nevertheless was demanding in terms of resources and time. Indeed, even though time from activation of the ECMO team for transport until patient admission in the

| Table 2 Patient Transport Data and Pre-ECMO Parameters |
|---------------------------------|----------------|
| Parameter                       | Value          |
| Transport by ambulance, n (%)    | 80 (80%)       |
| Air transport, n (%)             | 20 (20%)       |
| Transport on VV ECMO, n (%)      | 35 (35%)       |
| PaO2/FiO2 pre-ECMO, median (IQR)| 64 (52-75)     |
| PEEP pre-ECMO cmH2O, median (IQR)| 12 (10-15)    |
| Days of MV pre-ECMO, median (IQR)| 2 (1-5)       |
| NIV pre-ECMO, n (%)              | 35 (35%)       |
| Pronation pre-ECMO, n (%)        | 22 (22%)       |
| Bicaval dual-lumen configuration, n (%) | 61 (61%) |
| Femoro-jugular configuration, n (%) | 38 (38%) |
| Femoro-femoral configuration, n (%) | 1 (1%)        |

Abbreviations: FIO2, fraction of inspired oxygen; PaO2, partial pressure of arterial oxygen; IQR, interquartile range; NIV, noninvasive ventilation; PEEP, positive end-expiratory pressure; MV, mechanical ventilation; VV ECMO, venovenous extracorporeal membrane oxygenation.

Fig 1. Comparison of the patients’ population from the present study, the CESAR trial, and the EOLIA trial. ECMO, extracorporeal membrane oxygenation; FIO2, fraction of inspired oxygenation; MV, mechanical ventilation; NIV, noninvasive ventilation; PaO2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; VV, venovenous.
A dedicated VV ECMO multidisciplinary team should be identified and trained
Patient management and treatment should be consistent across team members
The team should be trained to work together
Each team member should be skilled in every treatment step (including transport of patient, VV ECMO implantation, critical care)
Reproducible preparation of the procedure and procedure itself
Essential but clear communication
Always learning from experience (post-case debriefing and discussion)

Abbreviation: VV ECMO, venovenous extracorporeal membrane oxygenation.

referral center ICU was not collected in detail, in the authors’ experiences, this process took at least 12 hours in all cases. In such a context, the success of the network’s VV ECMO program is based on a few key elements that were followed systematically and improved over time; these factors are summarized in Table 3. Briefly, the identification of a committed multidisciplinary VV ECMO team and the continuous training of the team members were the starting point. Team members should be skilled in every treatment step (including transport of patient, VV ECMO implantation, critical care) and trained to work together. Principles of treatment and patient management were consistent across team members. Furthermore, in order to provide VV ECMO availability at any time of the day, the preparation for procedures and the procedures themselves (eg, patient transport, patient cannulation) were as standardized as possible. Post-case debriefings also were crucial because much learning also came from experience. As a result of this process, patient transport was safe and successful for all patients, and no cannulation-related or transport-related complications were recorded.

As previously discussed, the most common configuration used in the authors’ clinical practice was the bicaval dual-lumen configuration, with 61 patients (61%). The dual-lumen cannula has become widely used since its introduction because it allows for easy management, nursing, mobilization, and rehabilitation of patients while on VV ECMO support.

The median duration of VV ECMO support in the present study was nine (five-17) days, which was very similar to that of the CESAR 15 and EOLIA trials, 12 which reported VV study was nine (five-17) days, which was very similar to that rehabilitation of patients while on VV ECMO support. It allows for easy management, nursing, mobilization, and the cannula has become widely used since its introduction because lumen configuration, with 61 patients (61%). The dual-lumen port-related complications were recorded. As a result of this process, patient transport was safe and successful for all patients, and no cannulation-related or transport-related complications were recorded.

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The median duration of VV ECMO support in the present study was nine (five-17) days, which was very similar to that of the CESAR 15 and EOLIA trials, 12 which reported VV ECMO durations of nine (six-16) days and 15 ± 13 days, respectively (see Fig 1). Concerning periodic trends of VV ECMO use, the present study’s data highlighted that there are some seasonal peaks, especially in the winter months, whereas during pandemics, many patients were treated in almost every month of each year. For these reasons, intensivists always should be ready to face severe ARDS, since outbreaks of novel respiratory diseases may occur and represent a healthcare concern. Notably, over a few months, the SARS-CoV-2 pandemic was responsible for cases of VV ECMO treatment in non-winter months.

Although no definitive mortality benefit has been shown in randomized trials, 12,14 it is clear to clinicians that patients with severe refractory ARDS without ECMO may experience death in a short timeframe in case of failure of conventional therapies. Providing ECMO allows for time to treat the underlying conditions, keeps the patient alive, and allows for patient recovery. The authors are aware that ECMO represents only a supportive treatment for the patient, whereas specific therapy for the underlying cause always is required to achieve successful treatment. The lungs have great regenerative capacities with minimal residual disability, but without any diagnosis and ad hoc therapy, ECMO and mechanical ventilation become futile. Providing VV ECMO treatment, therefore, is crucial in selected situations, but best results are obtained in referral centers. The present study’s data in a large population of transferred patients confirmed this finding and showed that a good survival rate can be achieved in such a critically ill population who require hospital transfer.

The authors acknowledge that this study had some limitations. The main limitation is that it was a single-center experience; therefore, the results may have limited external validity. However, it should be highlighted that this was the largest study on VV ECMO and referral ever reported in Italy and that the data were in line with randomized evidence from recent reports (see Table 1). Furthermore, all the possible aspects of VV ECMO patient management were not addressed. However, this was beyond the scope of this study, and the authors underline that very recent and contemporary data are provided. Again, it also would be interesting to have information on all the patients who were referred for VV ECMO treatment consideration at the authors’ institution but who, after evaluation with the ECMO team, were not transferred and received optimization of treatment in remote hospitals. Analysis of such data and patient outcome would add relevant information to the present report, but these data were not systematically registered or recorded for the present study; however, these data are now being collected to perform a more complete analysis of referral of severe ARDS patients to the authors’ institution.

Conclusion

Refractory ARDS is a severe disease and, if not treated with VV ECMO, often is lethal. Providing VV ECMO treatment requires a high level of expertise because its management is complex and laborious for all healthcare providers involved. Referral of the most severe cases is crucial for outcome, although demanding. Tertiary care centers always should be ready to promptly transfer and centralize the most unstable patients.

Conflict of Interest

The authors have no conflicts of interest to declare. The study was supported by departmental funds.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2021.04.037.
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