Renal Replacement Therapy for Patients Requiring Extracorporeal Membrane Oxygenation: A Multicenter International Survey

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Keywords
Renal replacement therapy · Extracorporeal membrane oxygenation · Vascular access · Difficulty · Practice

Abstract

Introduction: Patients receiving extracorporeal membrane oxygenation (ECMO) often require renal replacement therapy (RRT). The challenge of inserting a dialysis catheter (DC) could be solved by direct connection of RRT lines on an ECMO circuit (DCRE) without published guidelines. This study aimed to describe the practice of RRT in patients on ECMO, including the DCRE as well as the perception and concerns related to this technique. Methods: An international survey was worldwide sent via email to professionals involved in the management of ECMO. Respondents always or often performing RRT via the ECMO circuit were classified in the ECMO group, and those using a DC were classified in the DC group. Results: From March 2019 to October 2019, 298 participants answered the questionnaire from 46 different countries. Only 28% were working in pediatric departments. Among the 165 participants commonly performing RRT in patients on ECMO, 100 (61%) performed mainly RRT via the ECMO circuit, and 65 (39%) performed RRT via DC. Pediatric practice and a longer experience were the only noticeable characteristics of the ECMO group. The most reported concern regarding DCRE was the risk of air embolism (\(n = 84, 28\%\)), but the most encountered problem was unmanageable pressure alarms in RRT devices. Conclusion: The present study showed significant heterogeneity in RRT practices in patients on ECMO. The lower experience of the DC group, the high rates of concerns toward DCRE, and pressure alarm issues suggested that protocols and training may overcome reluctance and technical difficulties.

Introduction

Acute kidney injury is a frequent condition in patients requiring extracorporeal membrane oxygenation (ECMO). Up to 70\% [1–4] of adult patients and 60\% of children requiring ECMO need renal replacement therapy (RRT) [5]. An efficient RRT procedure is required to manage metabolic disorders and especially fluid overload [1, 4, 6–10]. Different options exist for performing RRT...
in these patients [1]. The classical option is to perform RRT via a dialysis catheter (DC). However, vascular access for DC insertion may not be easy because the ECMO circuit often occupies two vascular access sites. Insertion of a DC may be even more challenging in these patients receiving anticoagulation therapy and/or with coagulation disorders. Furthermore, DC may be associated with blood flow limitations and dysfunction, especially in left jugular and subclavian sites [11, 12], and adverse events [13–15]. Direct connection of RRT lines on an ECMO circuit (DCRE) may circumvent these problems and may allow higher blood flow [16]. Some studies have shown that DCRE is feasible and may increase RRT circuit life expectancy [17–19]. Nevertheless, this approach remains poorly described and has been associated with high pressures in the RRT circuit [19] that may be responsible for iterative interruptions of RRT sessions, loss of hemofilters, and inefficiency [20, 21]. Moreover, this technique requires manipulating ECMO circuits and exposes patients to a theoretical risk of air embolism, pumping stop, or blood loss.

In classical RRT, the main determinants of inadequate pressures and hemofilter clotting are related to the settings of RRT, including blood flow, volume replacement therapy, and the resulting filtration fraction as well as the type (e.g., citrate vs. heparin) and the level of anticoagulation [22]. In DCRE, the choice of connection locations can be challenging [23] because of high pressures in the different segments of the ECMO circuit. ECMO pressures mainly depend on ECMO cannula size, ECMO blood flow, and ECMO oxygenation membrane characteristics [24–26]. Specific protocols may help perform this technique more easily and safely [27]. However, to date, data are scarce to help physicians perform RRT in patients placed on ECMO [1], and a wide range of practices may exist. We hypothesized that DCRE is not overwhelmingly used and that its perceived level of difficulty may greatly vary.

The aim of our study was to assess existing practices of RRT in patients requiring ECMO and to identify factors associated with DCRE practice. Furthermore, we aimed to collect physician opinions and their concerns regarding DCRE.

### Materials and Methods

#### Study Design

This was an international cross-sectional study based on an online questionnaire targeting health care professionals involved in the management of ECMO. Centers managing ECMO were systematically identified on the internet using affiliations of articles related to this topic published within 5 years (n = 665). These centers and affiliated authors were searched using the PubMed database, and authors (P.A., M.T., and C.D.T.) collected data.

#### Questionnaire Building

The questionnaire was available on a general data protection regulation-compliant electronic survey using the SurveyMonkey® Web-based application. Survey questions were written in English and were distributed for comments using a modified Delphi technique to all members of the research group. After several revisions, the final questionnaire was approved and driven by all authors. The questionnaire was registered at the French Data Protection Authority (Commission Nationale de l’Informatique et des Libertés [CNIL]). The questionnaire is available in online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000522398).

#### Survey Description

The Web-based survey needed approximately between 15 and 20 min to be completed, and it was divided into the following four sections.
sections: main respondents’ characteristics, usual management of RRT, usual management of ECMO, and management of RRT in patients requiring ECMO. Questions assessing the frequencies of practices were assessed by 4-point Likert scale multiple-choice questions, labeled “never,” “rarely,” “often,” and “always.” To explore the perceived difficulty of performing DCRE, we used a visual analog slide scale ranging from 0 to 100 (0, no difficulty and 100, impossible to perform).

All questions covered key issues previously raised in the existing literature, including articles published by authors [18, 27]. Usual management of RRT refers to the way classical RRT is usually performed in each institution. The classification of the income level of countries was based on the World Bank database [28].

**Data Analysis**

We did not record information allowing to identify respondents. Respondents were classified as those working in adult departments and those working in pediatric departments. Likert data were analyzed by dichotomizing answers in two classes (negative answer: never/rarely vs. positive answer: often/always). The sum of the positive answers (often/always) could be superior or inferior to 100%. To assess characteristics associated with the use of DCRE, we compared the respondents who “always” or “often” performed DCRE (called the ECMO group) to those who “always” or “often” performed RRT via DCs (called the DC group). Therefore, participants who never/rarely performed RRT via DCs and never/rarely performed RRT via DCRE were excluded from this analysis. The difficulty rating of DCRE was categorized as “easy” and “difficult” with a cutoff of 50/100 corresponding to the third interquartile of global rating.

**Statistical Analysis**

The results are expressed as the median and interquartile range (25–75%) for continuous variables, and the results are expressed as numbers and percentages for categorical variables. Categorical data were analyzed using the y² or Fisher exact test when appropriate. Continuous data were compared using the Mann-Whitney U test. All reported statistical tests were 2-sided, and p values <0.05 were considered statistically significant. Statistical analysis was performed by R® 3.4.2 software.

| Table 2. Main fears and actual encountered problems with the DCRE procedure |
|--------------------------------------------------|
| **Fears** | **Problems already encountered** |
| At least one fear | 130 (44) | At least one problem | 98 (33) |
| Unstoppable arterial pressure alarm | 50 (17) | Unstoppable arterial pressure alarm | 58 (20) |
| Unstoppable venous pressure alarm | 36 (12) | Unstoppable venous pressure alarm | 44 (15) |
| Globally stressful | 35 (12) | Unstoppable TMP alarm | 23 (8) |
| Unstoppable TMP alarm | 32 (11) | Air embolism* | 26 (9) |
| Blood loss | 30 (10) | Insufficient RRT blood flow | 15 (5) |
| | | Significant blood loss | 6 (2) |
| | | High filtration fraction | 7 (2) |

* Categorical variables are expressed as n (%). DCRE, direct connection of RRT on ECMO; TMP, transmembrane pressure; RRT, renal replacement therapy. * Including micro air bubbles in the ECMO circuit without clinical consequences.

| Table 3. Main reasons for not performing DCRE reported by the DC Group |
|--------------------------------------------------|
| **Reasons** | **n = 65** |
| No institutional protocol | 31 (48) |
| No guidelines | 19 (29) |
| DCRE perceived as unsafe | 20 (31) |
| Difficult management of pressure alarms | 12 (19) |
| No Y connectors on the ECMO circuit | 12 (19) |
| Perceived as an inefficient technique | 1 (2) |

* Categorical variables are expressed as n (%). DCRE, direct connection of RRT on ECMO; DC, dialysis catheter; ECMO, extracorporeal membrane oxygenation; RRT, renal replacement therapy.

**Results**

**Overview of Respondents’ Characteristics**

From March 2019 to July 2019, 298 participants from 46 countries answered the questionnaire. The main characteristics of the respondents are shown in Table 1. Online supplementary Figure 1 shows the distribution of respondents’ countries. The two main respondents’ countries were France and the USA. Half of the respondents worked in departments managing less than 3 new patients on ECMO each month, and 37% managed ECMO for more than 10 years. The predominant usual RRT types were techniques using continuous modalities of RRT, and 62% of respondents declared often using femoral DCs. Slightly more than half of respondents reported citrate as the main anticoagulation in their usual practice of RRT.
### Table 4. Factors associated with DCRE practices

| General characteristics of ECMO DC groups | ECMO group ($n = 100$) | DC group ($n = 65$) | $p$ value |
|-------------------------------------------|-----------------------|--------------------|----------|
| Continent                                 |                       |                    |          |
| Europe                                    | 41 (41)               | 36 (55)            |          |
| North America                             | 35 (35)               | 13 (20)            | 0.066    |
| Asia                                      | 15 (15)               | 6 (9)              |          |
| Others                                    | 8 (8)                 | 10 (15)            |          |
| High income                               | 85 (85)               | 52 (80)            | 0.450    |
| Type of department                        |                       |                    |          |
| Cardiac surgery ICU                       | 38 (38)               | 28 (43)            | 0.626    |
| Polyaquent ICU                            | 22 (22)               | 27 (42)            | 0.012    |
| Medical ICU                               | 10 (10)               | 16 (25)            | 0.021    |
| Surgical ICU                              | 13 (13)               | 7 (11)             | 0.853    |
| Trauma center                             | 4 (4)                 | 7 (11)             | 0.111    |
| Pediatric ICU                             | 43 (43)               | 1 (2)              | <0.001   |
| Medical specialty                         |                       |                    |          |
| Medical intensivist                       | 36 (36)               | 26 (40)            | 0.723    |
| Anesthesiologist-intensivist              | 27 (27)               | 27 (42)            | 0.143    |
| Surgeon                                   | 6 (6)                 | 7 (11)             | 0.415    |
| Pediatrician                              | 17 (17)               | 1 (2)              |          |

| Usual management of ECMO for ECMO and DC groups | ECMO group ($n = 100$) | DC group ($n = 65$) | $p$ value |
|-------------------------------------------------|-----------------------|--------------------|----------|
| Centre ECMO experience >10 years                 | 49 (49)               | 25 (39)            | 0.003    |
| Personal ECMO experience >10 years               | 69 (69)               | 28 (43)            | 0.021    |
| ECMO case-volume >3 per month                    | 58 (58)               | 29 (45)            | 0.09     |
| Usual clotting prevention                        |                       |                    |          |
| Unfractionated heparin                          | 95 (95)               | 62 (95)            | 1        |
| Anticoagulation monitoring                      |                       |                    |          |
| aPTT                                            | 74 (74)               | 47 (72)            |          |
| Anti-factor Xa                                  | 60 (60)               | 35 (54)            | 0.937    |
| Thromboelastography                             | 28 (28)               | 16 (25)            |          |
| ECMO pressure monitoring                        | 78 (78)               | 45 (69)            | 0.280    |
| Systematic Y connectors on ECMO circuit         | 72 (72)               | 22 (34)            | <0.001   |

| Usual management of RRT for ECMO and DC groups  |                       |                    |          |
| Systematic Y connectors on ECMO circuit         | 72 (72)               | 22 (34)            | <0.001   |

| Type of RRT                                    |                       |                    |          |
| CVVHDF                                         | 55 (55)               | 38 (61)            |          |
| CVVH                                           | 25 (25)               | 13 (21)            | 0.121    |
| CVVHD                                          | 17 (17)               | 8 (13)             |          |
| IHD                                            | 3 (3)                 | 6 (9)              |          |
| Usual clotting prevention                      |                       |                    |          |
| Citrate                                        | 49 (49)               | 36 (57)            |          |
| Unfractionated heparin                         | 45 (45)               | 22 (35)            | 0.739    |
| Other                                          | 6 (6)                 | 7 (11)             |          |

Categorical variables are expressed as numbers and percentages. DCRE, direct connection of RRT lines on an ECMO circuit; RRT, renal replacement therapy; ECMO, extracorporeal membrane oxygenation; DC, dialysis catheter; CVVHDF, continuous veno-venous hemodiafiltration; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; IHD, intermittent hemodialysis.

Approach of RRT in Patients Placed on ECMO

In patients requiring RRT and ECMO, only 165 participants always or often practiced RRT either via the ECMO circuit or via DC. The ECMO group comprised 100 (61%) participants, and the DC group comprised 65 (39%) participants. Other participants reported never or rarely performing RRT via either DC or DCRE ($n = 81$). The remaining 52 participants did not answer this question.

Table 2 summarizes problems previously encountered during the DCRE procedure and concerns linked to it.
Forty-four percent of respondents reported concerns, while 33% had already encountered problems. The most reported problem and the most reported concerns were not similar (unmanageable pressure alarms and air embolism, respectively).

Reasons given by the participants of the DC group for not performing DCRE are listed in Table 3. The three main reasons were the absence of institutional protocol/guidelines, safety concerns, and unmanageable pressure alarms in the RRT device. Nine participants reported having stopped performing DCRE after having experienced problems.

Comparisons between the ECMO Group and the DC Group

The comparisons between the ECMO group and the DC group for general characteristics, usual RRT management, and usual ECMO management are shown in Table 4. Participants in the ECMO group reported a longer center and personal ECMO experience and more systematic Y connectors on ECMO circuits, and these participants were more often pediatric physicians. No significant differences regarding ECMO brand distribution, the size of ECMO cannulas, usual RRT settings, usual anticoagulation monitoring, or the rate of monitoring pressure of the ECMO circuit were found (analysis performed only among responses of adult departments for cannula sizes and RRT settings).

Technical Management of DCRE

Table 5 shows the management details of DCRE. Intermittent HD was seldom mentioned as an RRT choice for DCRE. Up to 61% reported modifying RRT or ECMO settings in case of high-pressure alarms. Figure 1 shows the preferred locations of connection reported by the 100 participants of the ECMO group. Between VA-ECMO and VV-ECMO, no difference was reported with most participants selecting a connection of both access (red-
colored arrow on Fig. 1) and return (blue-colored arrow on Fig. 1) RRT lines between the ECMO pump and the ECMO membrane. Table 6 shows the explanations for the choices of connection locations, mainly motivated by safety purposes.

**Difficulty Rating of DCRE and Training**

The boxplot representing the difficulty of performing DCRE on the analog visual scale from 0 to 100 for the pooled two groups is shown in online supplementary Figure 2. The median rating was 21 (5–50) interquartile range 25–75%, and 55% of respondents appreciated training sessions on DCRE versus 28% on RRT and 22% on ECMO. A comparison between the respondents who considered DCRE to be a difficult procedure and others (rating ≥50) is displayed in online supplementary Table 1. Personal and center experience in ECMO were the main factors associated with the perceived difficulty of DCRE. RRT settings and ECMO cannula sizes were not different.

**Discussion**

This first survey exploring the practice of RRT in patients on ECMO demonstrates heterogeneity in RRT practices in patients on ECMO. Among the 165 participants commonly performing RRT in patients on ECMO, 61% reported often practicing DCRE. However, up to 20% of participants found it difficult to perform RRT in patients on ECMO, and more than 50% were interested in receiving training on this issue.

DCRE was described early in the pediatric population, in which the challenge of vascular sparing is of utmost importance. As opposed to the adult population, the successful utilization of ECMO in children was defined in the 1970s [29], explaining the added expertise. Not surprisingly, our data confirmed that this technique is more common in pediatric practice.

We believe that factors impacting the life expectancy of the RRT filter and RRT pressures (ECMO cannula sizes, anticoagulation, and RRT settings) may influence the use of DCRE. However, the only relevant factors associated with DCRE practice were pediatric practice and personal/center experience in ECMO. Other expected factors, such as ECMO cannula size, were not associated with the use of DCRE. For example, the use of larger arterial cannulas may help reduce postpump pressure [24], which may decrease the frequency of postpump connection failures caused by high pressure in CVVH access lines. In contrast, the use of smaller arterial cannulas is safer when a percutaneous approach is chosen [30]. Small venous cannulas may generate marked negative pressures in the prepump ECMO line [25] inadequate for RRT connection. However, we did not find differences in ECMO cannula sizes between the ECMO group and the DC group (Table 4). In fact, CRRT devices are manufactured to be connected to central venous pressure ranging from 0 to 20 mm Hg. Pressures in the ECMO circuit are negative before the pump (segment 1) and positive between the pump and the oxygenator (segment 2) (Fig. 1) [18, 24, 25]. Extreme pressures may be particularly observed with small cannulas and with high ECMO blood flow [16, 24, 25].

There are different types of obstacles to using DCRE. There are technical issues with some specific ECMO brands not allowing Y connectors. Furthermore, several authors have suggested that some sites of connection are unsafe and not recommended [21, 31]. Our data showed that DCRE may cause changes in behavior in RRT practices and settings by some physicians, while others may consider this approach unwise, which may be a source of concerns. Protocols and training may be helpful for physicians with low experience in ECMO. Indeed, medical education, training, and simulation may overcome reluctance and problems, including those related to the management of RRT pressure and safety concerns. Further research to provide evidence and guidelines is necessary to legitimize and promote the use of DCRE.

The present study had several limitations. Answers were analyzed by participants and not by centers. It is possible that in few centers, two participants of the same team have answered the survey. We cannot determine how often it happened, but we assume that this was rare enough not to be problematic compared to the high number of respondents. We excluded a relatively large number of participants who never or rarely performed RRT in patients on ECMO from the ECMO and DC groups. This observation was in accordance with a previous study reporting a 20% rate of physicians never performing RRT in patients on ECMO [4]. There was a limitation based on the language of the questionnaire with potential bias in participants’ countries. The questionnaire was not tested for reliability or generalizability. The most interested participants may have willingly answered the questionnaire, while some participants did not answer all questions. It is possible that the participants most involved in these issues answered more carefully than others. In all surveys, answers may not provide reliable features of reality, especially regarding technical issues.
Conclusion

Our study demonstrated heterogeneity in the clinical practices of RRT in patients on ECMO with a substantial number of participants not using DCRE. There were discrepancies between participants’ concerns and actual encountered problems. Even though the methodology failed to demonstrate relevant technical issues limiting the practice of DCRE, the need for training and protocols to circumvent physicians’ concerns and reluctances is strongly supported by our results. Guidelines should be established to help promote good and safe practices.

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Statement of Ethics

Informed consent of the participant was not directly obtained but inferred by completion of the questionnaire/participation in the interview. This study was declared to the French Data Protection Authority (CNIL under the registered number 2223204). No animal or human participants were involved. Therefore, no funding was obtained, and there is no conflict of interest. Ethical Review Board: NA, an ethics statement is not applicable because this study is based exclusively on free and anonymous participation without sensitive information.

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Conflict of Interest Statement

Competing interests: No competing interests and no conflict of interest. The authors have no conflicts of interest to declare.

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Author Contributions

M.T., P.A., and C.T. designed the study and collected the data. All the authors analyzed and interpreted the data. M.T., P.A., and C.T. wrote the first version of the manuscript, with contributions from A.T.-D. and P.M.

All the authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All the authors read and approved the final manuscript. All participants consent for publication, and all the authors consent for publication and equally contributed to the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article or its supplementary material files. Further inquiries can be directed to the corresponding author. A preprint version of this article is available on ResearchGate DOI:10.21203/rs.3.rs-592881/v1.

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