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Renal Replacement Therapy in Extra-Corporeal Membrane Oxygenation

Patients: A Survey of Practices and New Insights for Future Studies

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FB, CEL, JLF and TR drafted the study design; FB and TR analysed the results and drafted the manuscript. All authors participated in the final manuscript preparation and agreed with the last version of the manuscript.

GLOSSARY

AKI: Acute kidney injury

CVVH: Continuous veno-venous haemofiltration

CVVHD: Continuous veno-venous haemodialysis

CVVHDF: Continuous veno-venous haemodiafiltration

CRRT: Continuous renal replacement therapy

ECMO: Extra-corporeal membrane oxygenation

ICU: Intensive care unit

KDIGO: Kidney Disease Improving Global Outcomes

RRT: Renal replacement therapy

UFH: Unfractionated heparin

VA-ECMO: Veno-arterial extra-corporeal membrane oxygenation

VV-ECMO: Veno-venous extra-corporeal membrane oxygenation

ABSTRACT

Background: Patients under extra-corporeal membrane oxygenation (ECMO) are at high risk of developing acute kidney injury and renal replacement therapy (RRT) is frequently needed. The aim of this study was to explore RRT use in ECMO patients, as no recommendations exist in this setting.

Methods: An online questionnaire about RRT management in ECMO patients was sent to the members of the ARCOTHOVA (Anesthésie-Réanimation Coeur-Thorax-Vaisseaux) association and to the GFRUP (Groupe Francophone de Réanimation et Urgences Pédiatriques).

Results: Ninety intensivists from adult ICU and twenty from paediatric ICU responded to the questionnaire. RRT use was common as 67% respondents reported that more than 25% of their ECMO patients needed RRT. RRT indications were similar between centres, with persistent anuria (83%), metabolic acidosis (80%), fluid overload (78%) and hyperkalaemia (80%) being the more prevalent. Continuous renal replacement therapy was the preferred technique (97%). Continuous veno-venous haemofiltration was predominant (64%) over continuous veno-venous haemodiafiltration (21%). Unfractionated heparin was employed as first line choice anticoagulation in 61% and regional citrate anticoagulation in 16%. Integration of RRT device directly into the ECMO circuit was the preferred configuration (40%) while parallel systems with separate catheter were used in 30%. When the integrated approach was chosen, RRT device was most frequently connected with inlet and outlet lines after the ECMO pump (58%) and pressure alarms were encountered for 60% of participants.

Conclusions: Our results highlight the high variability of practice between centres. They suggest the need to compare the integrated and parallel configurations of combining RRT and ECMO.

Keywords: Renal replacement therapy, Extra-corporeal membrane oxygenation, Acute kidney injury

1. BACKGROUND

Extracorporeal membrane oxygenation (ECMO) is increasingly used to manage patients with severe respiratory or cardiopulmonary failure. [1] Acute kidney injury (AKI) is one of the most frequent complication observed in intensive care unit (ICU) patients [2]. The risk is particularly high in ECMO patients due to their acute condition (sepsis, ischaemia, cardiopulmonary failure, vasopressor requirements) but also to the potential injurious effects of ECMO itself, such as systemic inflammation, prolonged hypoperfusion, ischemia-reperfusion injury, haemorheological variations, haemolysis or exposure to nephrotoxins [3]. Indeed, AKI may complicate the clinical course of more than 60 % of ECMO patients [4].

Considering this high incidence, renal replacement therapy (RRT) is frequently needed in this clinical setting [5]. Although the administration of RRT in ECMO patients has major implications, no specific recommendations exist to date [6]. The recent Kidney Disease: Improving Global Outcomes (KDIGO) Controversies conference identified the evaluation of RRT in this population as a research priority [7]. RRT in ECMO patients can be performed in three main ways: independent delivery using a separate vascular access, introduction of a haemofilter into the ECMO circuit or integration of the RRT device directly into the ECMO circuit [8]. The latter option includes different possibilities of connecting the RRT device to the ECMO circuit [9][10][11]. Briefly, the access lines of the RRT device can be connected before the ECMO pump where the intra-circuit pressure is negative, thus increasing the risk of air entrapment; alternatively, it can be connected post-ECMO pump where the intra-circuit pressure is highly positive (up to 600 mmHg), which may trigger high pressure alarms in the RRT circuit. The integrated approach requires interference with the ECMO circuit and draws attention to the safety aspects of this procedure.

To date, no robust clinical data support the use of either method, which has resulted in significant variability among centres. Furthermore, no study has assessed the current practices in this field in the adult population. The goal of this study was to explore RRT use in ECMO patients, especially the different connections employed, and to summarise the problems of pressure alarms encountered.

2. METHODS

2.1 Study design and recruitment

We performed a cross-sectional survey exploring the practices of RRT during ECMO therapy. An electronic questionnaire was sent to the members of the ARCOTHOVA (Anesthésie-Réanimation Coeur-Thorax-Vaisseaux) association and to the executive committee of the GFRUP (Groupe Francophone de Réanimation et Urgences Pédiatriques). Both, ARCOTHOVA and GFRUP are groups of experts, respectively involved in cardiothoracic critical care and paediatric critical care. The members of these associations are mainly from France and Switzerland. Responses from more than one clinician from the same department were allowed, assuming that clinical practice may vary due to the lack of evidence-based data on this subject. The questionnaire was sent to 794 physicians in January, February and June 2020, and was open until August 2020.

2.2 Survey description

The full survey is available in **Additional file 1**. It includes 22 questions of which most offered multiple choice questions and takes approximately ten minutes to complete. Survey questions were designed by two authors and distributed for comments and modifications within the study group. Questions 1-3 focussed on the characteristics of the centre and the

ICU, questions 4-8 explored the preferred modality and initiation strategies of RRT, questions 9-18 referred to the type of connection used for RRT and pressure alarms encountered, and questions 18-22 dealt with anticoagulation, RRT dose and haemofilter lifespan.

2.3 Statistical analysis

All variables were categorical and expressed as frequencies and percentages. Comparisons between groups were performed using the chi-square test. All reported *p* values were two sided, and a *p* value < 0.05 was considered statistically significant. Analysis was performed using SPSS version 23 (IBM SPSS, Chicago, IL)

3. RESULTS

3.1 PRACTICE IN ADULT PATIENTS

3.1.1 Respondents' characteristics (Table 1)

A total of ninety physicians from sixty different ICUs participated. Seventy-eight (87%) respondents worked in a university-affiliated hospital. Most participants (86%) managed both VA-ECMO and VV-ECMO techniques whereas only eight (9%) managed exclusively VA-ECMO and five (6%) exclusively VV-ECMO. Twenty-nine (32%) respondents stated that they performed ECMO routinely (*i.e.*, more than fifty ECMO patients per ICU per year).

Table 1: Characteristics of ICU centre

	n = 90 respondents
ECMO techniques performed	
VA-ECMO and VV-ECMO	77 (86)
VA-ECMO only	8 (9)
VV-ECMO only	5 (6)
Number of ECMO patients per year per ICU	
Less than 25	28 (31)
Between 25 and 50	32 (36)
Between 50 and 100	21 (23)
Between 100 and 200	5 (6)
More than 200	3 (3)
Estimated percentage of ECMO patients requiring RRT	
Less than 10%	5 (6)
Between 10% and 25%	25 (28)
Between 25% and 50%	41 (46)
Between 50% and 75%	12 (13)
Between 75% and 100%	7 (8)

Results are expressed as n (%)

3.1.2 RRT initiation is a common issue and indications are similar between centres (Table 2)

Provision of RRT to ECMO patients was considered a common problem as sixty (67%) respondents reported that more than twenty-five per cent of ECMO patients needed RRT. Concerning general indications for initiation of RRT, metabolic acidosis (80%), persistent anuria (83%), fluid overload (78%) and hyperkalaemia (80%) were more commonly reported than shock (28%), uremic encephalopathy (31%), serum creatinine rise (16%) or sepsis (3%). When asked for the most common primary indication for initiating RRT, most respondents indicated persistent anuria (44%), followed by severe metabolic acidosis (20%) and fluid overload (20%). Importantly, the vast majority (97%) of physicians gave the same criteria for initiation of RRT in ECMO patients as in the general ICU population.

3.1.3 Modalities and protocols of RRT are heterogeneous between centres (Table 2)

Only 58% of the respondents declared that they had a specific protocol for RRT in ECMO patients. Continuous renal replacement therapy (CRRT) was the preferred technique, and only 3% reported to use intermittent haemodialysis. Regarding the CRRT modality, convection was usually preferred over diffusion as continuous veno-venous haemofiltration (CVVH) was predominant (64%) compared to continuous veno-venous haemodiafiltration (CVVHDF) (21%) and continuous veno-venous haemodialysis (CVVHD) (11%). Not surprisingly, blood flow was related to the RRT modality; higher flows (*i.e.*, greater than 150 ml/min) were used in CVVH and CVVHDF compared to CVVHD ($p = 0.008$). The majority of respondents (56%) typically prescribed a RRT dose between 25 and 30 ml/kg/h; most of the remaining participants (27%) aimed for a higher dose between 30 and 35 ml/kg/h. Merely 13% prescribed doses greater than conventional practice (*i.e.*, more than 35 ml/kg/h).

Anticoagulation practices varied widely between centres. Unfractionated heparin (UFH) was by far the most commonly used anticoagulant employed as a first line choice (61%) while regional citrate anticoagulation represented 16% of the physicians' preferred choice. Interestingly, only 22% of participants stated that they used both of these anticoagulation strategies. Low molecular weight heparin was used only in the context of intermittent haemodialysis.

Table 2: RRT modalities

	n = 90 respondents
First-line RRT modality	
CVVH	58 (64)
CVVHD	10 (11)
CVVHDF	19 (21)
HDI	3 (3)
Indications retained for initiating RRT	
Metabolic acidosis	72 (80)
Persistent anuria	75 (83)
Fluid overload	70 (78)
Hyperkalaemia	72 (80)
Uremic encephalopathy	28 (31)
Elevated serum creatinine	14 (16)
Sepsis	3 (3)
Shock	25 (28)
Most prevalent indication for initiating RRT	
Metabolic acidosis	18 (20)
Persistent anuria	40 (44)
Fluid overload	18 (20)
Hyperkalaemia	9 (10)
Uremic encephalopathy	1 (1)
Elevated serum creatinine	1 (1)
Sepsis	0 (0)
Shock	3 (3)
Presence of a specific protocol for RRT in ECMO patients	
Yes	52 (58)
No	38 (42)
Use of different criteria from the one used in general ICU population for initiating RRT in ECMO patients	
Yes	3/88 (3)
No	85/88 (96)
RRT initiation dependent on haemodynamic stability	
Yes	5/75 (7)
No	70/75 (93)
Anticoagulation	
Unfractionated heparin only	55 (61)
Regional citrate anticoagulation only	14 (16)
Unfractionated heparin or Regional citrate anticoagulation	20 (22)
Low molecular weight heparin	1 (1)
RRT dose prescribed	
Less than 25 ml/kg/h	3 (3)

Between 25 and 30 ml/kg/h	50 (56)
Between 30 and 35 ml/kg/h	24 (27)
Between 35 and 40 ml/kg/h	9 (10)
More than 40 ml/kg/h	3 (3)
RRT blood flow prescribed	
Less than 100 ml/min	1 (1)
Between 100 and 150 ml/min	28 (31)
Between 150 and 200 ml/min	33 (37)
More than 200 ml/min	28 (31)
Estimated haemofilter lifespan	
Less than 12 hours	0 (0)
Between 12 and 24 hours	4 (4)
Between 24 and 48 hours	35 (39)
Between 48 and 72 hours	41 (46)
More than 72 hours	10 (11)
Results are expressed as n (%)	

3.1.4. Techniques of combining RRT and VA or VV-ECMO are numerous (Table 3)

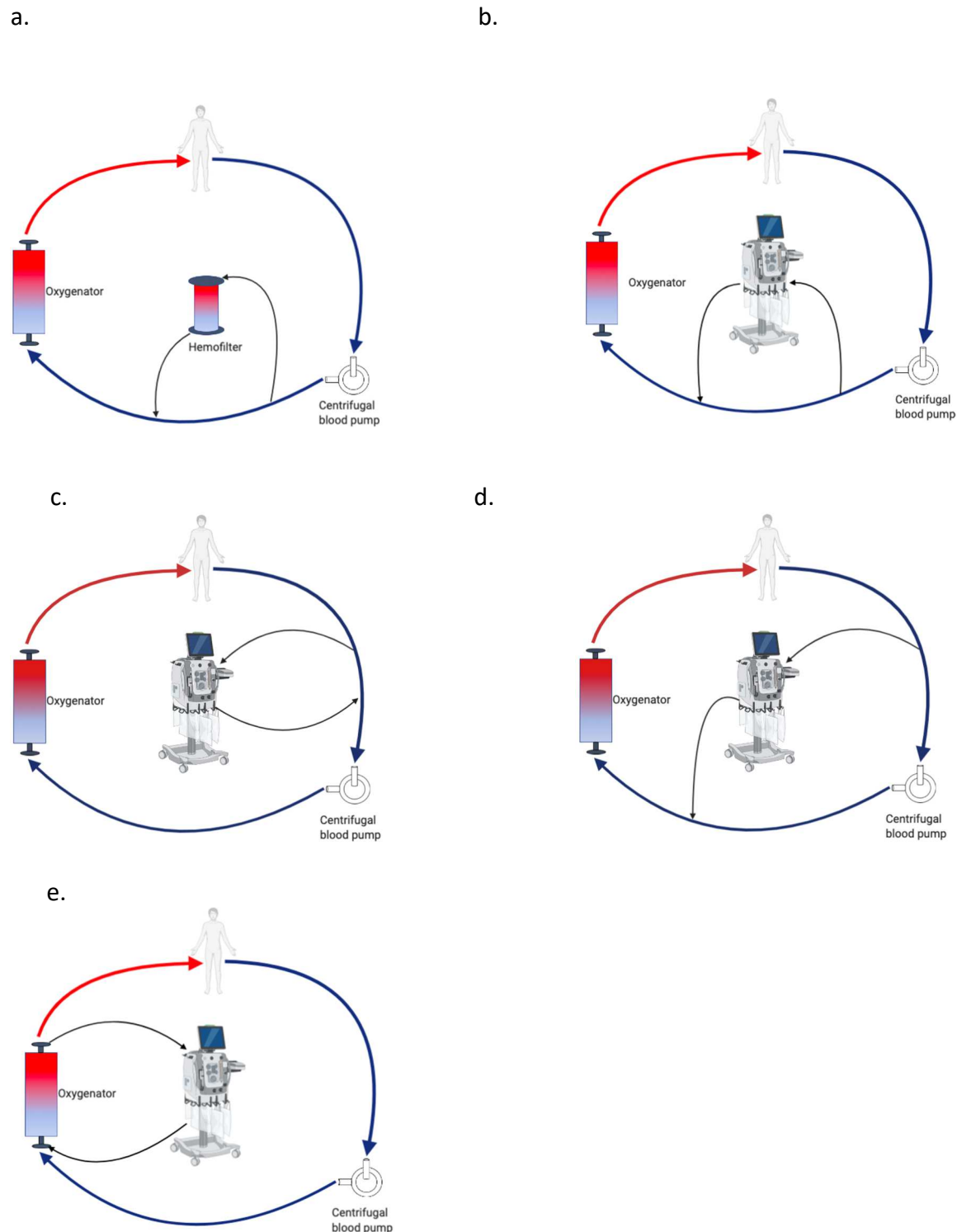
The preferred configuration of combining RRT and ECMO was the integrated approach for both VA-ECMO (40% of respondents) and VV-ECMO patients (44% of respondents). Alternatively, RRT was provided separately via parallel systems and a separate vascular access by 28% of the clinicians in the setting of VA-ECMO and by 32% in the setting of VV-ECMO. The remaining respondents indicated that they used either configuration of connection. When the integrated approach was chosen, the RRT device was most frequently connected with both inlet and outlet lines after the ECMO pump (**Figure 1B**) for both VA-ECMO (58%) and VV-ECMO (55%). Configurations, which include the connection of a line before the pump, were less popular. To note, physicians from two centres reported that they linked the outlet line of the RRT device to the reperfusion line in patients on VA-ECMO.

3.1.5 Recurrent pressure alarms are a widespread problem when the integrated approach is chosen (Table 3)

Pressure alarms were encountered repeatedly (*i.e.*, concerning more than 10% of RRT sessions) for approximately 60% of participants in both VA-ECMO and VV-ECMO patients.

The most commonly reported alarm related to high pressure in the inlet line (39% for VA-ECMO and 30% for VV-ECMO) and high pressure in the outlet line (18% for VA-ECMO and 26% for VV-ECMO). The two main interventions in these scenarios were switching to a parallel approach with a separate circuit or modifying RRT flows. Other participants reported to change the configuration of the integrated approach or to deactivate the alarms and pursue with the same parameters. A limited number (10% for VA-ECMO and 12% for VV-ECMO) of respondents reported that they adjusted the ECMO flow when faced with this situation.

Figure 1: Different integrated connections of RRT in ECMO patients



a. In-line method with a haemofilter directly connected on the ECMO circuit after the ECMO pump. b. Connection of inlet and outlet lines of RRT device after the ECMO pump. c. Connection of inlet and outlet lines of RRT device before the ECMO pump. d. Connection of the inlet line of RRT device before the ECMO pump and the outlet line of RRT device after the ECMO pump. e. Connection of inlet and outlet lines of RRT device on the oxygenator with a reverse flow in order to use the oxygenator as an air trap.

Table 3: Configurations of RRT device connection and pressure alarms encountered

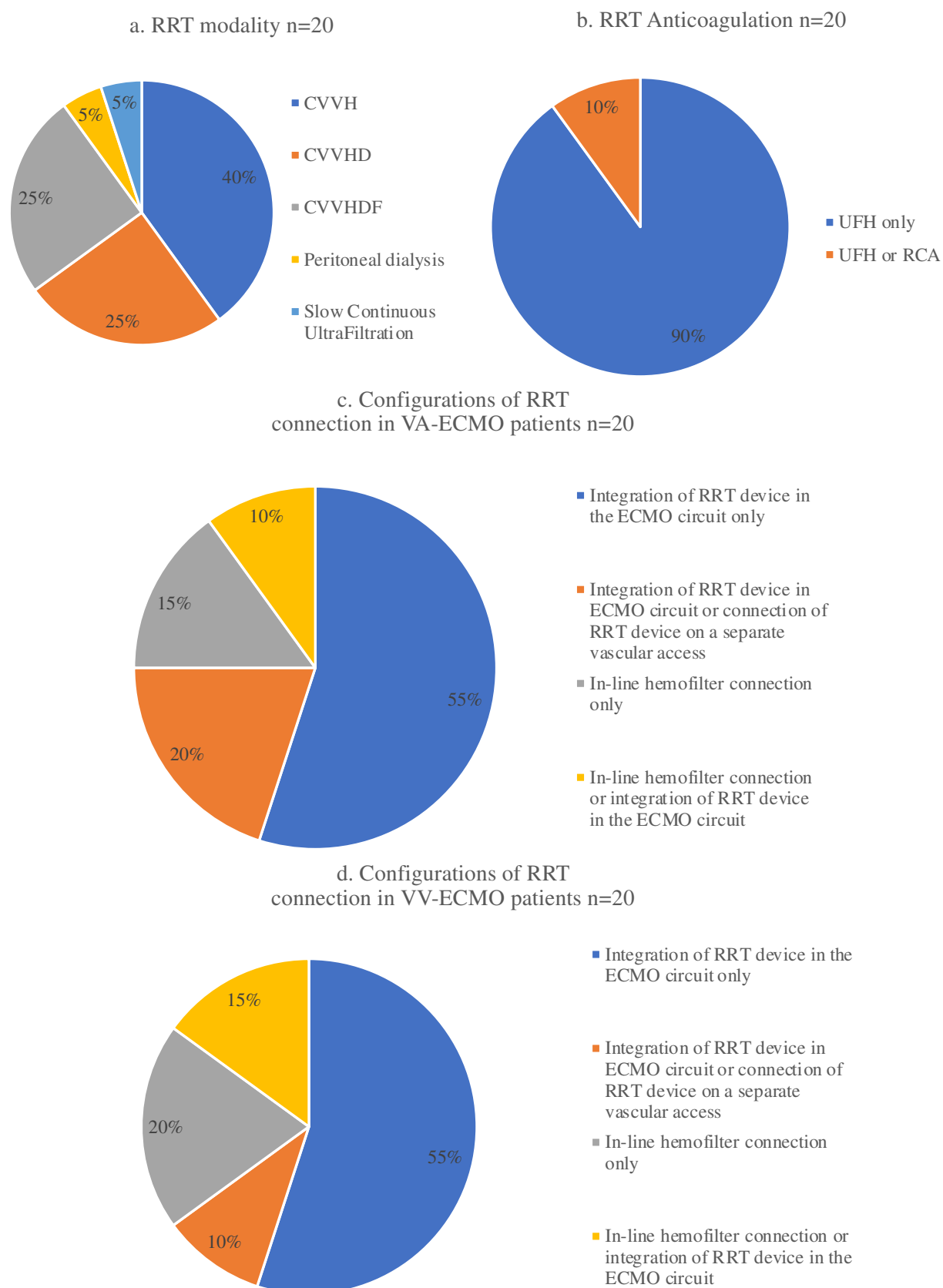
	VA-ECMO n = 85 respondents	VV-ECMO n = 82 respondents
Configuration of RRT device connection		
Integration of RRT device in the ECMO circuit	34 (40)	36 (43.9)
Connection of RRT device via separate vascular access	24 (28)	29 (32.2)
Integration of RRT device in ECMO circuit or connection of RRT device via a separate vascular access	27 (32)	17 (18.9)
When RRT is integrated in the ECMO the circuit		
	VA-ECMO n = 61 respondents	VV-ECMO n = 53 respondents
RRT connection modality		
Connection of inlet and outlet line after the ECMO pump (fig. 1b)	35 (57)	29 (55)
Connection of inlet and outlet line before the ECMO pump (fig. 1c)	11 (18)	10 (19)
Connection of inlet line after the pump and the outlet line before the ECMO pump (fig. 1d)	8 (13)	5 (9)
Connection on the ECMO oxygenator (fig. 1e)	8 (13)	8 (15)
Other	3 (5)	3 (6)
Pressure alarms on RRT device mostly encountered		
Elevated pressure on inlet line	24 (39)	16 (30)
Low pressure on inlet line	9 (15)	6 (11)
Elevated pressure on outlet line	11 (18)	14 (26)
Low pressure on outlet line	7 (12)	3 (6)
Absence of pressure alarms	23 (38)	20 (38)
Percentage of sessions during which pressure alarms are encountered		
Less than 10%	24 (39)	21 (40)
Between 10 and 25%	16 (26)	13 (25)
Between 25 and 50%	11 (18)	10 (19)
Between 50 and 75%	8 (13)	8 (1)
More than 75%	(3)	1 (2)
Action undertaken in case of persistent alarms on RRT device		
Deactivation of alarms	5/54 (9)	4/49 (8)
Switch the modality of connection of RRT on the ECMO circuit	6/54 (10)	9/49 (18)
Change of ECMO blood flow	6/54 (10)	6/49 (12)
Change of RRT parameters	20/54 (37)	15/49 (31)
Connection of the RRT device via separate vascular access	17/54 (32)	13/49 (27)
Results are expressed as n (%)		

3.2 PRACTICE IN PEDIATRICS

A total of twenty physicians from ten different ICUs responded. Most of them (90%) managed both VA and VV-ECMO. The main findings concerning practice in children are presented in **Figure 2**. The number of ECMO runs per year was lower than reported for adult ICUs, most of the centres treating less than twenty-five patients per year (**See additional file 2**). Sixty-five per cent of respondents reported that they had a specific protocol for the provision of RRT in ECMO patients. The preferred RRT modality was CVVH (40%), similar to adult practice. The decision to start RRT was mostly driven by the presence of anuria (60%) or fluid overload (40%). UFH use was ubiquitous and citrate anticoagulation was rarely chosen (10%). Integration of the RRT device into the ECMO circuit was the prevailing approach, mainly through connecting a RRT device to the circuit (55%) but also using an in-line haemofilter (15-20%).

Similar to adult practice, problems with alarm pressures were consistently encountered with the integrated technique (41% of participants reported them in more than 10% of RRT sessions). The most commonly reported approach in this situation was to deactivate the alarms (35%). Conversely, switching to a parallel system with a separate circuit and catheter was rare (5.9%).

Figure 2: Main results concerning practices in pediatric intensive care



4. DISCUSSION

Our survey provides an in-depth insight of RRT practices in ECMO patients. It clearly shows that the indications for initiating RRT are homogeneous, mainly driven by the presence of anuria, persistent metabolic acidosis or fluid overload. Clinicians seem to use the same criteria as for general ICU patients [12] and the same timing of initiation. The decisions appear to be in line with the conclusions of latest large studies on this subject that may have homogenised practice in the ICU [13], [14].

A striking finding of this study is the intensivists' considerable preference for CRRT in ECMO patient as only three centres reported the use of intermittent haemodialysis in these patients. This observation is most likely explained by the fact that ECMO patients are often haemodynamically unstable. Still, some studies have suggested that, with strict guidelines in place to improve tolerance and metabolic control, ICU patients with AKI as part of multiple-organ dysfunction syndrome can be treated with intermittent haemodialysis [15],[16]. However, no study has specifically assessed this question in ECMO patients, and to date, no modality has shown to be superior over another in the intensive care setting [17].

The reported prescribed RRT dose corresponds to the low range of KDIGO recommendations. Given the high percentage rate of sessions interrupted by alarms when the RRT and ECMO circuits are integrated, this finding may raise concern about the real RRT dose received by ECMO patients, which would inexorably be below the recommended doses in case of frequent interruptions. This could also explain why some centres prescribed a higher dose than recommended.

Regarding anticoagulation, the use of UFH is widespread, presumably because it is the preferred anticoagulation modality for the ECMO circuit [18] and because, in case there

is another indication of anticoagulation, the KDIGO guidelines recommend the use of an anticoagulation strategy adapted to this underlying condition [6]. Another explanation could be that citrate anticoagulation may increase the workload for staff in patients who already need a high level of care. Two studies [19], [20] have described the use of citrate anticoagulation in VV-ECMO patients. The authors observed that citrate was feasible, safe and effective and reduced the rate of CRRT circuit clotting. To our knowledge, no study has specifically explored this application in VA-ECMO patients in whom the risk of citrate accumulation is higher due to the presence of precipitating conditions, namely uncontrolled shock or liver failure.

When considering RRT in ECMO patients, the interaction between the two devices represents a challenge. In light of our results, the integrated approach is common practice, the most popular configuration being the one with both RRT lines placed after the pump for both VA and VV-ECMO. This configuration exposes patients to a lower risk of air embolism and may be easier to set up under safe conditions. Also, configuration with the RRT circuit integrated before the pump may trigger negative pressure alarms, especially when ECMO flow is unstable. Although the integrated approach is common practice, participants reported a high rate of problems with pressure alarms of the RRT device, demonstrating that this technique may not always be practical. Unfortunately, our study does not allow us to establish further details, but it highlights the drawbacks of this technique. We noted that 42.2% of participants did not have a specific protocol for RRT in ECMO patients, which can explain some of the difficulties encountered. Regarding the interventions applied in case of persistent alarms, around 40% of participants reported that they would modify the RRT flow or the ECMO flow. This underscores again the pitfalls of the integrated approach.

With regards to paediatrics practices, the integrated approach predominated, and in-line connection is sometimes used, whereas it is never employed by the respondents in the adult population. Moreover, participants avoid the use of a parallel system in children owing to the fact that obtaining a separate vascular access is more problematic. These results are in accordance with previously reported practices in this population [21]. Pressure alarms are also occurring routinely but controlled alternatively as many participants declared to set specific settings on the RRT device itself to deactivate the alarms. However, overriding the limits in case of very low negative pressure may expose patients to the risk of haemolysis and micro-embolisation and, in case of very high pressures, to altered haemofilter properties.

Our study has several limitations. First, the number of respondents is not high but reflects the fact that centres in which ECMO is a common technique are limited in France and Switzerland. However, respondents from most centres participated and therefore our results offer a substantial overview of practices in these countries. Secondly, a selection bias is presumably present, as physicians with a special interest in RRT are more likely to respond. Furthermore, due to the nature of this cross-sectional study, the data are declarative, so the exactitude of practices reported might not be completely accurate. They nevertheless provide a relevant picture of current practice. Finally, the survey results reflect practice in two countries, France and Switzerland, and are not reflective of practice in other countries.

5. CONCLUSION

The insights obtained from this survey offer an overview of RRT practice in adult and paediatric ECMO patients. This study highlights the high variability of practice between centres. Notably, it seems that the integrated approach of connecting the RRT device into the ECMO circuit is common despite its drawbacks and the lack of robust evidence-based data. Therefore, our results suggest the need to compare the integrated and the parallel configurations in future prospective studies, as both are commonly applied. Most of the previous clinical data related to this field focused on the RRT filter lifespan or did not compare the integrated and the parallel configurations [10][11][22]. We believe future explorations should assess which technique is the most suitable to obtain a constant blood flow in the RRT circuit without triggering pressure alarms in order to maximise filter lifespan and to deliver an appropriate RRT dose. Importantly, there is also an urgent need to focus on patient-centred outcomes such as long-term renal outcomes, catheter-related infection rate while assessing haemorrhagic or embolic complications or haemolysis. While comparing the different configurations on these outcomes, the role of the anticoagulation strategy should also be studied (*e.g.*, feasibility, efficacy and safety of regional citrate anticoagulation). Our results underscore the lack of data in this field as stated by the KDIGO controversies conference in 2020 [7] that defined as research priorities the need to develop a registry of ECMO patients receiving RRT and to compare the different anticoagulation strategies of the RRT circuit during ECMO.

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ADDITIONAL FILES

Additional file 1

File format .docx

Title: Questionnaire

Description of data: Questionnaire

Additional file 2

File format .docx

Title: Results concerning paediatric intensive care

Description of data: table 1 entitled "Characteristics of ICU centre", table 2 entitled "RRT modalities", table 3 entitled "Configurations of RRT device connection and pressure alarms encountered"