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Minimized Hemodiafiltration for Extracorporeal Membrane Oxygenation in Infants

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Abstract

Background Fluid overload is a serious complication in the treatment of infants with extracorporeal membrane oxygenation (ECMO). Volume overload leads to prolonged ECMO therapy if left untreated. The renal replacement therapy of choice in pediatric patients is peritoneal dialysis or conventional dialysis using a "large" hemofiltration machine via a Shaldon catheter or directly connected to the ECMO system. This study describes the implementation of a novel minimized hemodiafiltration (HDF) system in pediatric patients on ECMO.

Methods This retrospective analysis included 13 infants up to 5 kg who underwent 15 veno-arterial (V-A) ECMO runs with HDF. A minimized HDF system is integrated into an existing ECMO system (18 mL priming volume), connected post-oxygenation to the venous line, before the ECMO pump. Two infusion pumps are attached to the inlet and outlet of the hemofilter to control the HDF system.

In addition to retention values (creatine and urea) at six defined time points, flow rates, dialysis parameters, and volume withdrawal were examined, as well as the number of HDF system changes.

Results With a mean ECMO runtime of 156 hours, the HDF system was utilized for 131 hours. The mean blood flow through the hemofilter was 192 mL/min. The mean dialysate flow was 170 mL/h, with a mean volume deprivation of 39 mL/h. The HDF system was changed once in seven cases and twice in three cases.

Conclusion There were no complications with the minimized HDF system in all 15 applications. It allows safe patient volume management when treating infants with ECMO, with effective elimination of urinary substances.

Keywords
- hemodiafiltration
- infants
- creatinine clearance
- ECMO
- hemofiltration
- urea
- phosphate

Introduction

Extracorporeal membrane oxygenation (ECMO) is a treatment option for pediatric patients with congenital heart defects requiring mechanical circulatory support, especially in case of low-cardiac-output syndrome. The Society of Thoracic Surgeons reports that the frequency of the use of perioperative ECMO in cardiac surgery is 2.8%.[1] In

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conjunction with the underlying cardiac problem, decreased micturition up to acute renal failure may occur before or during treatment. Classic therapies are hemodialysis using a Shaldon catheter or peritoneal dialysis. Both procedures can lead to application-related complications or side effects, such as increased peritoneal pressure on the visceral organs and/or the heart. Standard continuous renal replacement therapy (CRRT) devices are limited by access problems, system failures due to clotting with extremely large uncoated surfaces or blood–air contact. Utilization of CRRT devices on ECMO can result in undesired overfiltration or other complications.

The CRRT devices used for hemodiafiltration (HDF) in adult patients offer simplified possibilities to integrate a CRRT device with an ECMO system, due to higher conceptualization of internal pressures.[2] In the pediatric field, this is not feasible, as the volume ratio between the CRRT device and the patient's blood volume is worse. Confronted with these problems, the implementation of a novel minimized pediatric HDF system for volume deprivation on the running ECMO system was conceptualized and implemented after internal clinical consultation in the treatment team.

Patients and Methods

In a retrospective analysis from July 2019 to April 2022, 13 infants up to 5.1 kg who underwent 15 venoarterial (V-A) ECMO runs with HDF were included in case of a low-flow syndrome. The study was approved by the local research ethics board of the university hospital (ID-No. 22–120-Br) and was conducted in accordance with the Declaration of Helsinki.

The use of the minimized HDF system can be integrated into the current ECMO circuit (MiniLung petite kit with 1/4" DP3 pump head and the Hilite LT800 oxygenator, Fresenius, Bad Homburg, Germany) as a renal replacement therapy. To install an HDF in the existing ECMO system, a connector (¼"– ¼" with Luer Lock) is inserted in the venous line. The novel HDF system consists of two Infusomat Space P and a customized HDF set including a hemofilter HPH-Junior (HDS Set Art. No. M10414 Terumo, Tokyo, Japan) with a membrane surface of 0.09 m^2 and 8 mL priming. The HDF system has a total priming of 18 mL, including the hemofilter (►**Fig. 1**). The HDF system is installed on the blood side as a pressure-dependent passive bypass in the ECMO (post-oxygenator; pre-DP3 ECMO pump connected to the newly integrated ¼"– ¼" connector; ►**Fig. 2**). After de-airing of the HDF system, the hemofilter is inverted

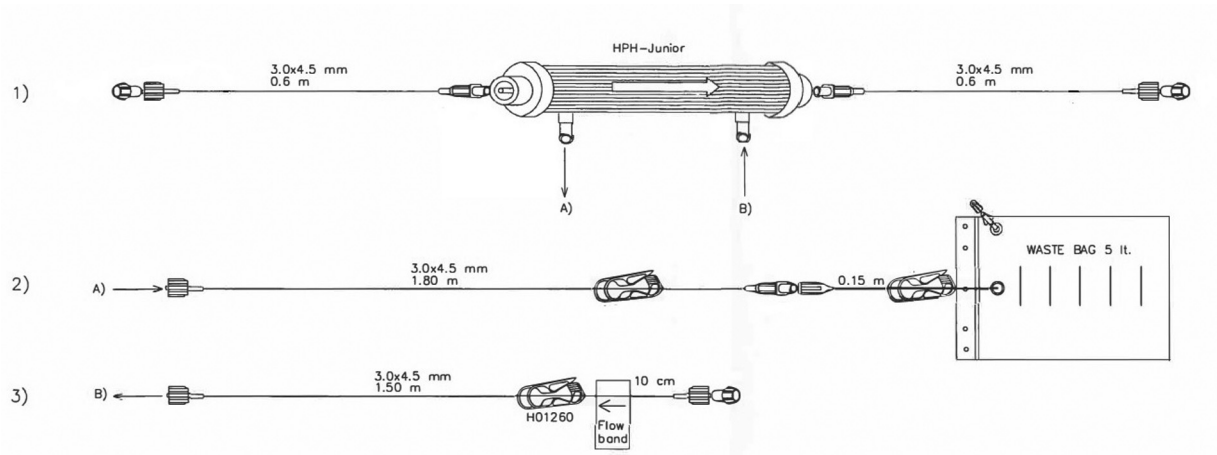

Fig. 1 Set drawing hemodiafiltration system for pediatric patients (HDS set art. no. M10414 Terumo, Tokyo, Japan).

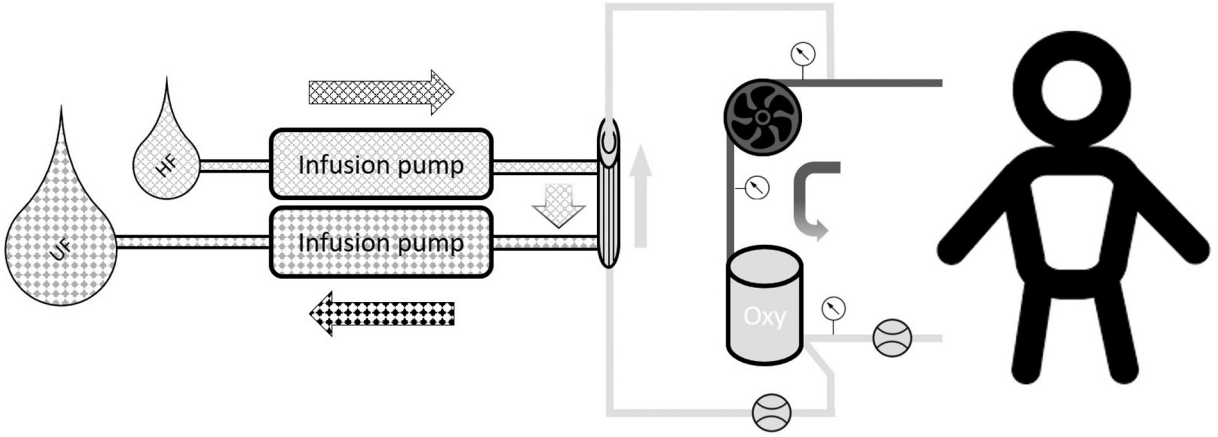

Fig. 2 Pediatric hemodiafiltration system devices connected to the extracorporeal membrane oxygenation (ECMO) circuit. Hemofiltration (HF); ultrafiltration (UF).

Table 1 Demographic data and system deployment times

	Median (min–max)
Age (d) at ECLS implantation	8 (2–162)
Body weight (kg)	3.8 (2.7–5.1)
Duration of ECLS (h)	156 (82–214)
Duration of HF (h)	131 (42–211)
Blood flow of HF (mL/min)	192 (100–250)
Dialysate flow (mL/h)	170 (50–230)
Deprived volume (mL/kg/h)	11 (4–21)

Abbreviations: extracorporeal life support (ECLS); hemofiltration (HF).

before use so that the blood inlet is at the highest point of the hemofilter. Positioned this way, small air bubbles, if any, are trapped at the top inlet of the hemofilter and will not get back into the ECMO system.[3]

HDF blood flow was monitored using an ultrasonic flow probe sensor with a single-use Perfusion Sensor R (Fumedica, Switzerland), which is inserted between the oxygenator and the line connected to the filter. This can be used to regulate the maximum permissible flow rate through the HPH-Junior hemofilter of 300 mL/min, if necessary. Two infusion lines are connected on the dialysate side of the hemofilter. A hemofiltration solution (e.g., Duosol 4 mmol/L K, B. Braun, Melsungen, Germany) is connected as dialysate to the supply line ("inlet" marked) to the hemofilter and the second line (marked "drain") leads from the hemofilter to the 5 L waste bag, in which the effluent Ultrafiltrate is collected. The flow of both infusion lines is regulated or controlled by two Space P infusion pumps (B. Braun). For better effectiveness of the clearance and transfer rate, the dialysis fluid is passed over the membrane of the hemofilter in a countercurrent to the direction of the blood flow.

The creatinine, urea, and phosphate courses were analyzed at six time points. Preoperatively (M0), the highest value between surgery and start of HDF therapy (M1), the highest (M2) and the lowest (M3) values, as well as after 12 hours (M4), 24 hours (M5), and 36 hours (M6) after the end of HDF therapy. Outcome data were defined as ECMO waiting and hospital discharge.

The existing coagulation management for ECMO treatment was maintained unchanged (due to local standard operation procedure) despite installation of the HDS. The target ranges are as follows: activated partial thromboplastin time (aPPT) of 60 to 80 seconds; Prothrombin time (Quick) $>50\%$; Antithrombin (AT) $>90\%$; platelets $>90{,}000/\mu L$; fibrinogen >100 mg/dL; and Hb of 10 to 12 g/dL.

A statistical analysis was performed with SPSS (version 28.0.0.0). The values are given as median with minimum and maximum values. The only exception are the flow data of the hemofilter; these are given as mean values $\pm$ single standard deviation.

Results

Within the observation period, 13 patients aged 8 days (minimum: 2; maximum: 162) and weighing 3.8 kg (minimum: 2.7; maximum: 5.1) received 15 pediatric HDF runs of this type, in conjunction with an ECMO system and could be analyzed retrospectively (►**Table 1**).

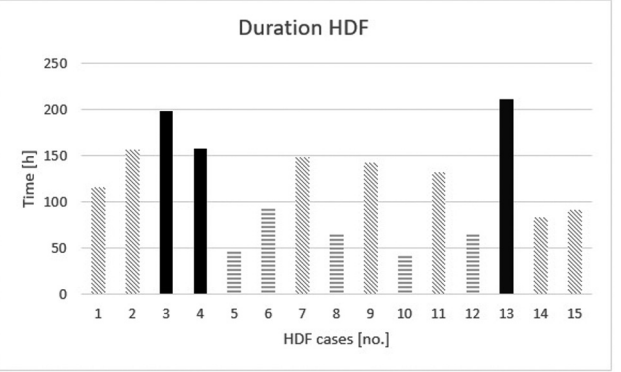

Fig. 3 Runtime of the hemodiafiltration (HDF) system in the 15 applications (*horizontal lines*: no change; *diagonal lines*: one-time system change; *black*: two-time change).

The mean passive and unthrottled blood flow through the hemofilter was 192 ± 50 mL/min. The mean dialysate flow was 170 ± 55 mL/h, with a mean volume deprivation of 11 ± 5 mL/kg/h. HDF was on average performed over a period of 131 hours (minimum: 42 hours; maximum: 211 hours), with the hemofilter being changed once in seven cases and twice in three cases (►**Fig. 3**).

In some cases, material hardening of the infusion lines in the Infusomat Space P occurred after 48 hours, which could be remedied in all cases by reinserting the line into the infusion pump with an offset of a few centimeters. Technical problems related to ECMO and HDF use were not recorded in any of the cases.

The laboratory parameters of creatinine, urea, and phosphate are listed in ►**Fig. 4**. Both urinary substances increase from M0 to M1 (creatinine: 0.52 vs. 0.88 mmol/L; urea: 15 vs. M1 41 mg/dL). Phosphate decreased from M0 to M1 (1.8 vs 1.7 mmol/L).

Of the 13 patients, 2 underwent two ECMO runs each. One patient was reoperated after weaning and then required a second V-A ECMO. The other patient was supported with V-A ECMO pre- and postoperatively with two ECMO systems, thus being counted twice. Weaning was possible in 12 of the 15 ECMO runs (80%; 10/13 patients) and 8 patients were discharged home (61% survival).

Discussion

Acute kidney injury and fluid overload could be successfully treated in the patients treated in the present case series by using the minimized pediatric HDF system on the running ECMO system, with effective volume removal and adequate clearance.

Gorga et al identified overhydration of pediatric patients on ECMO as an independent factor for hospital survival, both at the beginning of CRRT and at its end.[4] In a survey of 60 pediatric facilities offering ECMO therapy, the use of some form of hemofilter in the ECMO circuit was found to be increasingly common. Forty-five percent of the clinics used a

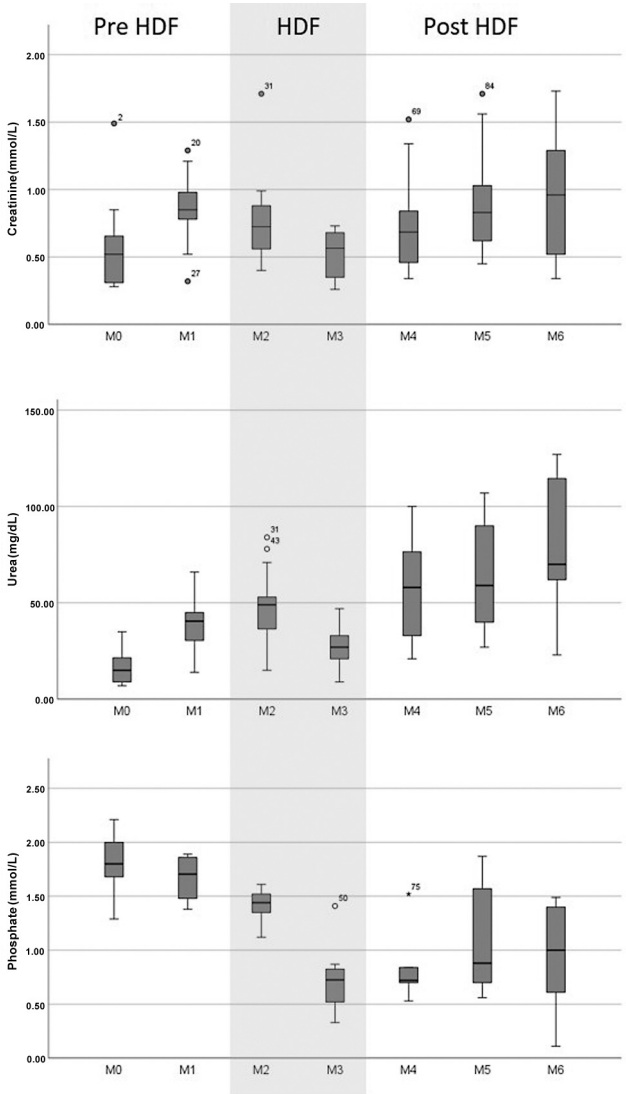

Fig. 4 Laboratory parameters of creatinine, urea, and phosphate at the different time points (preoperative [M0], indication [M1], the highest [M2], and the lowest [M3] values at HDF [*light gray highlighted area*], as well as the 12-hour [M4], 24-hour [M5], and 36-hour [M6] values after the end of HDF therapy). Simple *boxplot* with median; °, mild outlier (1.5–3.0*interquartile range (IQR)); *, extreme outlier (>3.0*IQR).

conventional dialysis machine, while 8% used only an inline hemofilter and the remaining respondents reported using both procedures.[5]

The smallest dialysis system currently available on the market is the "Carpediem" (Medtronic) for patients with a body weight in the range of 2.5 to 9.0 kg with a minimum priming volume of 27 mL.[6] The priming volume could be reduced by 33% with the system presented here. In addition, there is no blood–air contact, which could occur due to possible bubble traps. Another advantage is that this HDF system does not require an extra pump. The hemofilter is passively perfused utilizing the pressure gradient between the arterial and venous lines.

To not exceed the maximum blood flow of 300 mL/min via the hemofilter, an inline flow sensor (Fumedica, Muri, Swiss) was installed in the "AV shunt." Through the flow control, clot or impairments on the blood side with failure of the HDF system would also be detected at an early stage. The ECMO flow to the arterial cannula was measured directly after the oxygenator with a flow measurement integrated in the ECMO console and the targeted treatment was ensured.

In a technical excursion, the DP3 diagonal pump flow, as in any other nonocclusive pump, is dependent on pre- and afterload. This means that when the AV shunt is opened for HDF therapy, the patient's blood flow remains relatively constant given the same speed of the ECMO pump. However, there is an increased flow through the oxygenator, comprised of the patient blood flow plus the HDF flow. Therefore, the maximum permissible flow via the oxygenator and the pump head must be observed during use.

The use of an AV shunt offers additional advantages. For example, during weaning, when the patient blood flow is reduced to, for example, 150 mL/min, the additional flow via the AV shunt results in a total flow between 350 and 400 mL/min through the oxygenator, preventing clot formation due to low flow.

In all applications, the dialysis performance of the hemofilter was consistent. The volume depletion could be adjusted in a wide range from 0 to 200 mL/h. For intensive care physicians, this was a controlled way to specifically drain the patient and reduce edema. A very fine control of the water–electrolyte balance was made possible by this system. In very small patients ($\leq$3 kg; $n = 5$), there sometimes was the problem that the application of intravenous medication alone would have led to a distinctly positive balance. This could be prevented at an early stage without the administration of diuretics and the accompanying nephrotoxicity.

With the application of the new HDF system in our ECMO circuit, there were no complications on the blood side.

Due to the small size and ability to mount the infusion pumps on the ECMO mast, mobility of the ECMO is preserved. There is no need to suspend CRRT during transfer to and from the operating theater, catheter interventions, or imaging studies.

According to the internal clinical Standard Operating Procedure, the HDF system is changed after 72 hours, "tip to tip," or in the event of a ECMO system change. There were no complications with exchanges during the observation period. The 18-mL blood volume could be completely infused back into the infant in every case, which avoided unnecessary blood loss. In rare cases, the inlet Infusomat showed an air bubble alarm. Due to an empty dialysate bag, cavitation occurred on the dialysis side of the hemofilter in two cases. By replacing the solution, the system could continue to operate quickly. To safely avoid this problem, the preset hemofiltration volume on the Infusomat was set to 4,800 mL, with a 5,000-mL hemofiltration solution bag. The Infusomat would set off an alarm early to avoid complete emptying of the dialysate system.

At the same time as the HDF system was established, the standard "dialysis" laboratory report, which also contains phosphate, was used in consultation with neonatal nephrology. We were able to detect the occurrence of hypophosphatemia worthy of treatment in several cases. The phosphate standard value was set between 0.9 and 2.9

mmol/L and sometimes went below the lower limit, due to high and efficient dialysis. This could be adequately treated by detecting the phosphate level and substitute by adding supplements to the "mixing bag." Phosphate is an important energy supplier in the body as an essential part of the energy-carrying molecule adenosine triphosphate (ATP). A severe phosphate deficiency can lead to confusion, epileptic seizures, coma, impaired respiratory drive, reduced intestinal activity, and perioperative weakening of the heart muscle.

This provided proof that, in addition to technical feasibility, adequate volume withdrawal in hyperhydrated infants with anuria can be performed while the ECMO is running. When using the HDF system, the diagonal pump required little to no adjustment to maintain stable flows to the patient. With a blood volume of 18 mL, the pediatric HDF system is not only technically superior to a conventional CRRT device but also with regard to the inflammatory response or necessary transfusion of blood. Thus, the connection of the minimized pediatric HDF system represents an uncomplicated and gentle alternative treatment option to conventional CRRT procedures. In the context of the case series, the technical application was safe, and the system worked perfectly with the mentioned products.

Conclusion

In the present analysis, it was possible to show that modern treatments are possible in complex pediatric patients through an interdisciplinary approach. In addition to effective volume withdrawal to prevent or reduce edema and acute postoperative renal failure, the described pediatric HDF on ECMO can be a technically safe application to perform successful medical treatment. Additional vascular access such as "Shaldon catheters" for dialysis can be dispensed with here. Thus, the connection to minimized pediatric HDF via ECMO is an uncomplicated and gentle alternative to conventional CRRT procedures.

Conflict of Interest
None declared.

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