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Aquapheresis (AQ) in Tandem with Extracorporeal Membrane Oxygenation (ECMO) in Pediatric Patients

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Abstract: Children with cardiopulmonary failure requiring extracorporeal membrane oxygenation (ECMO) are at risk for fluid overload (FO) despite the normal estimated glomerular filtration rate (eGFR). It has been shown that survival in the intensive care unit (ICU) is inversely proportional to FO. Therefore, fluid removal, or prevention of FO, in these critical cases has the potential to improve survival. Aquapheresis (AQ), a procedure used for fluid removal, with success in patients with heart failure has also been used in children with acute oliguric kidney injury (AKI), to prevent and treat FO. The purpose of this article was to describe the use of Aquadex FlexFlow® for AQ in pediatric patients on ECMO, as a means to provide a simplified and safe form of fluid removal with minimal impact on ECMO therapy. The principal variables collected include patients' demographics, urine output, serum creatinine, withdrawal and infusion pressures, ultrafiltration (UF) rates, and ECMO flow ranges, along with length of stay in pediatric ICU and survival. Patient survival was 100% with preserved eGFR. The ECMO flows were not affected by AQ. Urine output decreased somewhat during therapy, with little AQ machine pressure variations. Range of UF tolerated without hemodynamic abnormalities was 1.24–6.2 mL/kg/h, allowing the patients to maintain their pre-AQ body weight, while receiving intravenous (IV) nutrition and medications. This article describes the use of AQ in tandem with ECMO in a user-friendly and safe way to provide UF in children requiring cardiopulmonary support, with minimal flow and hemodynamic disturbance. **Keywords:** ECMO, fluid overload, acute kidney injury, pediatric. *J Extra Corpor Technol. 2019;51:163–8*

Fluid overload (FO) in the intensive care setting adversely affects survival, both in adults and in children (1,2). Many of these patients have acute kidney injury (AKI), where continuous renal replacement therapy (CRRT) has been shown to be beneficial in correcting metabolic abnormalities, allowing for adequate nutrition and maintenance of desired fluid balance. However, some patients only require ultrafiltration (UF) therapy. UF is a process by which plasma water is removed from whole blood by applying a transmembrane pressure across a semipermeable membrane (3), with aquapheresis (AQ) being a form of providing controlled UF.

In an international survey of pediatric centers using extracorporeal membrane oxygenation (ECMO), renal support therapy (RST) was indicated for FO in 30–50% and for its prevention in 5–30%. Most often an in-line hemodiafilter and IV pumps were used to monitor and manage UF rates, although IV pumps were inaccurate in 40% of cases, especially with slow continuous UF (SCUF) in patients weighing <10 kg (4). Askenazi DJ et al. (5) performed CRRT in infants and children adapting the Aquadex FlexFlow® (CHF Solutions, Inc., Eden Prairie, MN) equipment used for controlled UF.

The purpose of this article was to describe the use of AQ in pediatric and infant patients on ECMO, as a means to provide a simplified and safe form of fluid removal with minimal impact on ECMO therapy. To date, there are no

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published reports regarding the use of Aquadex FlexFlow® in tandem with ECMO in children or adults, although modified UF setups have been described, using hemoconcentrators (6).

DESCRIPTION

Equipment and Setup

AQ is a technique of controlled UF performed with the help of a hemofilter—made up of polysulfone hollow fibers, loaded onto a console (Aquadex FlexFlow®; CHF Solutions, Inc.) with a software integrating and controlling the rates of blood flow and desired UF, with the help of pressure sensors. There is no dialysis fluid port, and the priming volume of the circuit is 35 mL. There is no evidence of cytokine removal or diffusion across the semipermeable membrane. By contrast, CRRT circuit requires a larger hemofilter (the lowest priming volume of the presently approved circuit being 93 mL for the M60 set) with an additional port for dialysate and uses a larger console with a software integrating the rates of blood flow, desired UF, dialysate, and replacement fluid, in addition to precision scales on which solutions are suspended. The CRRT filters used for infants and small children are made up of polyacrylonitrile (AN69), carrying the risk of bradykinin release, not seen with Aquadex FlexFlow® system. Askenazi DJ et al. (5) described in detail the specifications of Aquadex FlexFlow® system.

To establish the optimal AQ-ECMO connection, we performed various circuit configurations in a "water laboratory" setting. We envisioned the optimal circuit connections based on how the inflow to and outflow from Aquadex FlexFlow® affect the withdrawal (Pw; recommended range −300 to −20 mmHg) and the infusion pressures (Pi; recommended range 20–300 mmHg) to achieve the desired UF. The ultrafiltrate, the result of negative transmembrane pressure applied on the semipermeable hemofilter membrane, is collected in a bag suspended from a weight scale. The UF pressure (Pu) should be maintained within the recommended range (−250 to 200 mmHg) and should not adversely impact the ECMO flow rates. According to the technical specifications, the low pressure limits of the Aquadex FlexFlow® are in the range of 0–20 mmHg for infusion and 0 to −20 mmHg for withdrawal and are strictly driven by safety requirements to identify blood leaks from tubing and immediately stop the pumps if leaks occur. The high pressure limits are in the range of −325 to −350 mmHg for withdrawal and 325–350 mmHg for infusion. The maximum pressure was chosen in the original design to make sure that the maximum blood flow (40 mL/min) can be delivered for an industry standard range of catheters and for the length and size of the blood circuit tubing. After the design choice of maximum pressure, all testing for circuit reliability and calibration for flow accuracy was based on the range of pressures from minimum to maximum. The design choice for Aquadex FlexFlow® is similar to the choices made for dialysis machines (7).

We decided to connect AQ to ECMO circuit pre-centrifugal pump and pre-oxygenator, as the air bubble detector can provide an additional safety measure. Higher Pi was noted when the withdrawal line was connected distally from the infusion line connection to the ECMO circuit.

As such, we found the best places to insert the AQ circuit to be pre-pump and pre-oxygenator. To adjust both the inflow and outflow, we have interposed connectors (see Figure 1). Prior ECMO circuit setups used in our institution did not have these connectors with tubing, and the "water laboratory" trials prompted their addition to the initial setup. Patients receive heparin based on protocols established for ECMO anticoagulation, and no additional anticoagulation is required.

Training of nursing staff responsible for operation of the Aquadex FlexFlow® system was initially completed by the manufacturer for a subgroup of nurses (as super-users). Bedside nursing staff was trained by the super-users with lectures, a "water laboratory" trial, and both written and machine setup post-knowledge assessment based on User Guide. If one follows the respective console instructions, the setup of an AQ circuit takes about a third of the time needed to set up the CRRT circuit (~7 vs. 21 minutes, respectively).

Patients and Clinical Parameters

Patients were treated and followed up at our center between July 2018 and January 2019. All data were retrieved via the electronic medical records (Epic, Verona, WI) and de-identified, and consent for inclusion in this report was obtained from parents.

Variables collected include the following: age, gender, ethnicity, principal diagnosis and comorbidities, serum creatinine at the start of AQ, height (cm), weight (kg), %FO calculated from the formula (%FO = ["Fluid In" {*L*} – "Fluid Out" {*L*}/ICU admission weight {kg} × 100]) (2), urine output (mL/kg/h), connection characteristics, blood flow rate (Qb, expressed in mL/min), and UF rate (mL/kg/h). In addition, ranges of Pw and Pi were recorded during therapy, along with hemodynamic changes, complications, and circuit changes during the AQ therapy, if observed. Plasma-free hemoglobin (PFH) was monitored during the therapy as per the ECMO protocol.

ECMO flow rates pre-AQ, during AQ, and after AQ were recorded. Duration of therapy, length of stay (LOS) in Pediatric Intensive Care Unit (PICU), and patient survival were documented. The serum creatinine (mg/dL) along with estimated glomerular filtration rate (eGFR) was

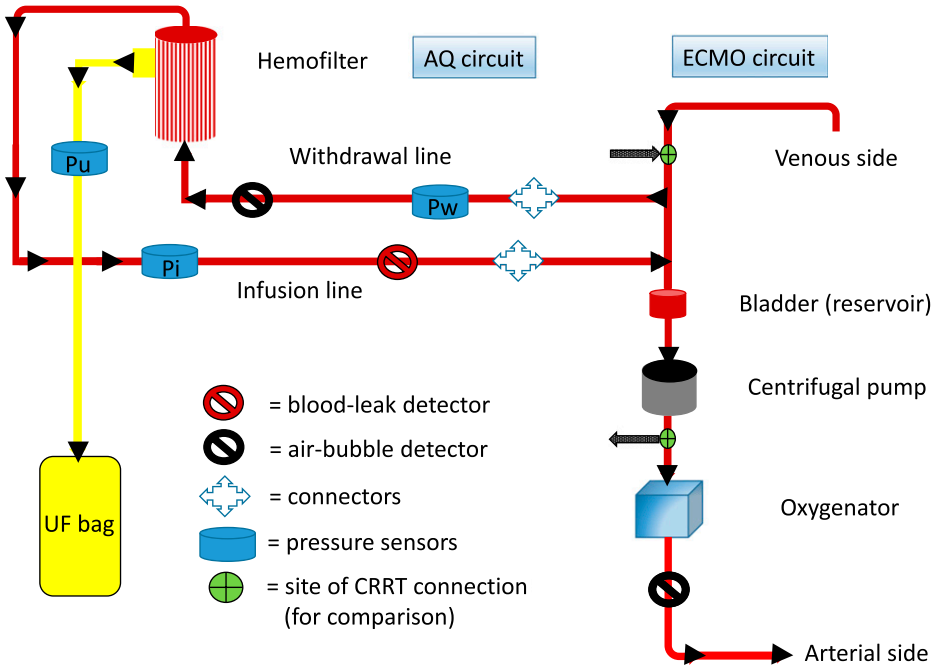

Figure 1. Optimal connection between AQ and ECMO circuits.

noted at the start and end of AQ, as well as at the last follow-up testing. eGFR was estimated based on modified Schwartz' formula, expressed in mL/min/1.73 m^2, when appropriate.

Patient 1: A 4-year-old girl was admitted for vasopressor-refractory septic shock due to *Streptococcus pyogenes*. She developed cardiopulmonary arrest and was cannulated for venoarterial (VA) ECMO support. On ECMO day 3, she was placed on AQ because of AKI stage 3 and FO. She achieved successful UF. She was liberated from AQ and ECMO on ECMO day 4. Her cardiopulmonary and renal function recovered, and she was transferred to inpatient rehabilitation on hospital day 13. She was discharged home 5 days later and continued follow-up with neurology and rehabilitation services.

Patient 2: A 3-year-old girl was admitted to the hospital with a recurrent pericardial effusion, myocardial dysfunction, abdominal pain, nonketotic hypoglycemia, and a history of abnormal autoimmune laboratory testing raising suspicion for an underlying autoimmune disorder. She was supported with vasoactive infusions. While in the ICU, she developed cardiac arrest associated with concern for cardiac tamponade. She underwent emergent pericardiocentesis and cardiopulmonary resuscitation. She was cannulated for VA ECMO because of severely impaired myocardial function on hospital day 3. She subsequently tested positive for parainfluenza virus. On ECMO day 2, she developed FO and AKI stage 3 for which AQ was initiated via the ECMO circuit. On ECMO day 3, AQ was stopped and the patient was liberated from ECMO. She recovered and was discharged home on hospital day 21.

Patient 3: A 9-month-old girl was transferred from an outside facility because of severe left ventricular dysfunction with a dilated left ventricle. She subsequently developed cardiac arrest and required cannulation for VA ECMO support. On ECMO day 2, she developed decreased responsiveness to diuretic therapy in the face of FO, pulmonary edema, and AKI stage 2. AQ was initiated and continued in tandem with ECMO circuit for 4 days. AQ resulted in successful fluid removal and no adverse sequelae to the patient. Of note, she had a visible clot in the ECMO circuit and developed an elevated PFH. She was liberated from extracorporeal support on ECMO on day 6, and AQ was terminated at that time (AQ day 4). She tested positive for parvovirus and her course was perceived to be consistent with myocarditis. She continued to improve clinically and was discharged home on hospital day 20.

This series of patients (Table 1) were all Hispanic females, from 10 to 54 months of age, with significant cardiovascular pathology, who required ECMO for cardiopulmonary support and developed FO that varied between 4.47 and 18.78%. Following AQ, the serum creatinine decreased by ~.1 mg/dL, with small change in the eGFR. Urine output pre-AQ was 4–4.9 mL/kg/h and post-AQ was 1.5–4.3 mL/kg/h. The range of UF tolerated without hemodynamic abnormalities was 1.24–6.2 mL/kg/h. The first two patients received therapy for 17 and 21 hours,

respectively, whereas the third patient was on AQ for 92 hours, with one circuit change, as per recommendations. ECMO flow ranges can be seen in Table 2. Although PFH increased briefly in the first two patients described, patient 3 was found to have a clot in the venous cannula, felt to be the cause of elevated PFH, which ultimately decreased by the end of AQ therapy. The eGFR was not affected by the higher PFH, all survived after PICU stays of 13–21 days (Table 3), and eGFR normalized in all three patients as of the last testing.

Table 1. Initial patient characteristics and pre-AQ variables.

Initial Variables/Patient	Patient 1	Patient 2	Patient 3
Age (years, months)	4, 6	3, 10	0, 10
Gender (M/F)	F	F	F
Ethnicity	Hispanic	Hispanic	Hispanic
ECMO access	VA	VA	VA
AKI stage	3	3	2
Peak serum creatinine (mg/dL)	1.4	1.65	.56
Indication for AQ	FO	FO	FO
Height (cm)	104	104.2	72
Weight (kg) at the start of AQ (bedscale)	17.4	17.2	8.06
FO since admission (%)	13.95	18.78	4.47
Serum creatinine (mg/dL) at the start of AQ	.7	1.5	.28
eGFR (modified Schwartz', when appropriate) (mL/min/1.73 m^2, desired >90)	61	29	–
Urine output (mL/kg/h)	4	4.9	4.7

Table 2. Variables related to ECMO therapy and impact of AQ.

ECMO + eGFR Variables\Patient	Patient 1	Patient 2	Patient 3
ECMO parameters—flow ranges (L/min)	2.3–2.42	2.42–2.56	1.15–1.2
PFH, pre-AQ	30	60	30
PFH, during AQ—range (desired <50)	30–160	30–60	70–450
PFH, post-AQ	ND	ND	120
Creatinine, serum (mg/dL), average during AQ—mean ± SD; median	.68 ± .02; .68	1.47 ± .04; 1.5	.36 ± .1; .32
eGFR (modified Schwartz', when appropriate) average during AQ—mean ± SD; median (mL/min/1.73 m^2, desired >90)	63.5 ± 2; 63	29.67 ± .89; 29	–
Serum creatinine (mg/dL) at the end of AQ	.67	1.4	.19
eGFR (modified Schwartz', when appropriate) at the end of AQ (mL/min/1.73 m^2, desired >90)	64	31	–

ND, not done.

Table 3. Technical parameters of AQ therapy and follow-up data.

AQ Variables/Patient	Patient 1	Patient 2	Patient 3
Qb (mL/min)	20	25	35
Pw (mmHg)—range; median	−20 to −36; −34	–	−20 to −49; −37
Pu (mmHg)—average	62	–	78
Pi (mmHg)—range; median	47 to 70; 59	–	15 to 70; 28
Output (L) during AQ	5.58	8.92	7.41
UF rate (mL/kg/h)—range; mean ± SD	2.47–6.2; 4.33 ± .8	1.39–4.65; 2.32 ± .6	1.24–5.21; 2.96 ± .7
Number of circuit changes	–	–	1
Complications during AQ	none	none	none
urine output at the end of AQ (mL/kg/h)	1.5	2.9	4.3
Weight (kg) at the end of AQ (bedscale)	17.4	17.2	8.2
Duration of AQ (hours)	17	21	92
LOS in PICU	13	17	21
Survival Y/N	Y	Y	Y
Age at the last visit (years, months)	4, 10	4, 3	1, 4
Last serum creatinine (mg/dL)	.35	.32	.23
Last eGFR (modified Schwartz') (mL/min/1.73 m^2, desired >90)	123	137	144

COMMENT

We report our initial experience of using AQ to augment fluid removal in infants and children supported with ECMO. We have prevented further FO in our patients, without adversely affecting the ECMO flows or renal function, as evidenced by the ability to liberate the patients from ECMO and demonstrate normal renal function at the last follow-up.

Severe FO occurs in pediatric patients on ECMO, and as it worsens, both duration of therapy and mortality increase (4). Center-specific guidelines often exist to manage fluid balance in this critically ill population, although timing and type of therapy have not been elucidated.

CRRT in combination with ECMO has been proven to be effective, decreasing the duration of ECMO and LOS (8). However, the use of CRRT or SCUF is less precise in children weighing less than 10 kg because of rapid volume shifts in this ECMO population (4). Although terminated early, a randomized trial of diuretic use vs. AQ (using Aquadex FlexFlow® system) (3) has demonstrated that within 30 days after discharge, patients in the adjustable UF group (AQ) experienced fewer cardiovascular events than those in the adjustable diuretic group.

Symons JM et al. (9) reported that using an automated monitor for UF is superior to a free-flow system during extracorporeal life support (ECLS), reducing variability and increasing accuracy, shortening the duration of both ECLS and CRRT. Hence, the use of the AQ system in selected cases appears warranted, especially because separate control of UF confers a significant survival benefit (6).

Addressing FO early in a patient's disease course may positively impact outcomes in pediatric patients on ECMO. Clinical options include early institution of fluid removal if urine output does not achieve a neutral or negative fluid balance to prevent FO (i.e., fluid restriction and diuretics) or initiate fluid removal after FO develops (RST). Several challenges and opportunities exist: 1) using a system designed precisely for fluid removal that is accurate down to low volumes of UF as opposed to using a system that has been modified outside of the manufacturer's specified use to do so; 2) the system for SCUF that we historically used requires an intravenous pump to control the fluid removal. Medical literature has demonstrated that using an intravenous pump in this manner can be a source of error in fluid removal and highlights the need for better accuracy in SCUF on ECMO (10); 3) AQ has the potential to eliminate the source of error because the AQ console is used instead of an IV pump not designed for the purpose of SCUF, whereas the AQ equipment has been validated through testing (6); 4) the AQ can be set up and initiated by trained ICU nurses as the access for AQ is readily available when the ECMO circuit is set up. On the other hand, when SCUF is implemented, a perfusionist is required to establish the access in the ECMO circuit. In our PICU, ECMO specialists run the ECMO circuit and many of the ECMO specialists are not perfusionists. The ability to set up the AQ circuit by trained ICU nurses is an advantage from a personnel standpoint such that it can be performed at any time of day or night and without having to use perfusion team resources; 5) built in safety features of the AQ circuit that do not exist with SCUF using IV pump, such as the air bubble detector on the AQ circuit serving as a secondary safety check on the system.

In summary, the integration of AQ with an ECMO circuit has several benefits over other modalities for the end user caring for the patient on ECMO support, including ease of setup; minimal interruption or decrease in ECMO flows and, thus, less hemodynamic instability when placed in the circuit; user-friendly software; and a backup battery that allows for transport of the patient without interruption in therapy. In addition, the disposable circuit with the hemofilter provides safety monitoring for blood leak detection, air detection, and an optional hematocrit monitor that can be used on the circuit. From a bedside nursing perspective, AQ requires little troubleshooting for the duration of therapy when integrated with the ECMO circuit. A limitation encountered in very small infants was the minimum effluent rate increase of 10 mL per hour, limited by the software, which occasionally leads to hemodynamic changes.

In conclusion, the use of Aquadex FlexFlow® system in tandem with the ECMO circuit in infants requiring VA ECMO support is possible. In addition, this application of AQ is able to prevent and treat FO with minimal impact on patients' hemodynamics and bedside resources. Larger scale studies are needed to find the safe range of PFH during AQ, and further work will be needed to demonstrate safety and efficacy of AQ during ECMO.

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