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Influence of utilizing hemodialysis membranes outside-in on solute clearance and filtration efficiency – One step towards a novel combined lung and kidney support device

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ABSTRACT

Many membrane oxygenator patients suffer from renal disfunction. For these patients, a novel device integrating artificial lung and kidney support is being developed. Although outside-in blood flow is standard for membrane oxygenators, this is not typical for hemodialysis systems. The effect of outside-in blood flow on the efficiency of hemodialysis fibers for continuous hemodialysis and hemofiltration is yet unclear.

This study evaluates the efficiency of commercial hemodialyzer membranes utilized outside-in compared to traditional inside-out mode regarding clearance of urea and creatinine, and ultrafiltration coefficient during in-vitro tests with porcine blood. Our results showed that dialyzers (1.2 m^2, asymmetric hollow fibers) utilized outside-in had similar clearances of urea and creatinine compared to dialyzers used in the traditional mode ($p > 0.7$). However, outside-in dialyzers had an ultrafiltration coefficient four times lower than dialyzers applied in a conventional way, but adequate fluid removal could be achieved by controlling pressures in the system. This in-vitro study indicates that outside-in fibers could be sufficiently effective to maintain typical continuous renal replacement therapy doses. We regard this as one step towards a novel device with a mixed membrane fiber bundle utilizing blood flow outside both hemodialysis fibers and gas exchange fibers to provide simultaneous lung and kidney support.

1. Introduction

1.1. Novel membrane oxygenator with integrated kidney support – the need for a new membrane specification

Up to 70% of extracorporeal membrane oxygenation patients (ECMO) suffer with consecutive acute kidney injury [1,2], requiring additional continuous renal replacement therapy (CRRT). CRRT relies on veno-venous hemodialysis (CVVHD), hemofiltration (CVVH) and/or hemodiafiltration (CVVHDF) to regulate the patient's volume balance and eliminate blood toxins [1]. Currently, hospitals worldwide combine ECMO and CRRT in two separate circuits, with separate membrane oxygenator and hemodialyzer [1,3], resulting in increased risks of blood coagulation [3,4], infection, bleeding, blood cell damage [4,5], and several drawbacks in controlling intra-circuit pressure differences [6]. Considering these risks [3,5–7], novel approaches to combine extracorporeal lung and kidney support in a single device are being explored both in hollow fiber based and microfluidic artificial lungs [7,8].

Our research group has been developing a novel hollow fiber artificial lung that integrates kidney support to reduce current treatment drawbacks, such as lowering the risk of blood activation by the use of less artificial surfaces [7]. This novel device (RenOx) would combine the

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functions of membrane oxygenator and hemodialyzer, integrating gas exchange and hemodialysis fibers, in a way that blood flowing through the device would simultaneously receive oxygen, while carbon dioxide, blood toxins, and excess fluid are being removed [7,9]. In oxygenators, gas is transported in the lumen of gas exchange fibers while blood flows outside of the fibers, see Fig. 1. Efficient oxygen exchange is achieved by the contact of red blood cells with the hollow fibers transporting gas, and by the mixing of the blood flow in the oxygenator, required to overcome saturation boundary layer limitations [10,11]. On the other hand, hemodialyzers applied in CRRT use semi-permeable hollow fibers able to remove blood toxins such as urea and creatinine, and eliminate excess fluid from the blood. In conventional treatment, blood flows inside the lumen of hemodialysis fibers (i.e. inside-out mode), see Fig. 1, while dialysis fluid and/or effluent flow outside of the fibers [12].

To support the lung and kidney simultaneously, the RenOx would have to provide sufficient gas exchange capacity, blood toxins clearance and excess fluid removal. Regarding lung support, our previous study [9] evaluated in which number and configuration gas exchange fibers could be replaced by dialysis fibers while maintaining a high gas exchange performance in our oxygenator. Our results showed that a prototype with 25% of oxygenator fibers closed, simulating dialysis fiber layers, maintained 90–95 % of the oxygen transfer capacity of an unmodified oxygenator. This prototype delivered up to 55 $mL_{oxygen}/L_{Blood\ flow}$ at a blood flow rate of 140 mL/min, above the level of 50 $mL_{oxygen}/L_{Blood\ flow}$ estimated to keep stable respiratory physiology in an average adult patient [11,13]. This indicates that several fiber layers in our oxygenator contributed to gas exchange by mixing the blood flow [9]. Therefore, previous in-vitro [9] and in-vivo [14] studies indicate that a mixed membrane bundle combining fibers that transport gases (oxygenation fibers) and fibers that contribute to blood mixing (oxygenation and dialysis fibers) could provide sufficient lung support.

Sufficient gas exchange rates can only be achieved in the RenOx if blood flows and mixes outside of both gas exchange and hemodialysis hollow fibers, see Fig. 1. Thus, in the RenOx bundle, hemodialysis fibers need to be utilized in an reversed way than their traditional use with blood flowing outside the fibers (i.e. outside-in). Dedicated hemodialysis fibers for outside-in use are not yet commercially available [15], therefore, commercial hemodialysis fibers would need to be utilized outside-in for a proof of concept of our novel device.

In practice, dialysis fibers utilized outside-in as part of the RenOx should provide levels of clearance and fluid removal sufficient to support the kidney during CRRT. CRRT treatment is required to provide an effluent volume dose of 20–25 $mL/kg_{patient}/h$ for the treatment of AKI [16–18]. This CRRT dose can be defined as the total effluent flow rate (i.e. dialysate flow rate (mL/h), fluid removal flow rate (mL/h), and replacement fluid rate (mL/h)) leaving the dialyzer normalized by the patient's weight [16,18]. Assuming a 1:1 relationship between effluent volume and urea clearance, this would translate to approximately 20–25 $mL/kg_{patient}/h$ urea clearance to support the patient's kidneys [19,20]. In addition, typical fluid removal rates around 2 $mL/kg_{patient}/h$ are recommended to maintain fluid balance [16,20,21].

Nevertheless, it is yet unclear if dialysis fibers operating outside-in could achieve similar CRRT doses as fibers utilized in traditional inside-out mode. Classic dialyzer mass transfer theory would predict no difference in the clearance of small solutes when dialysis fibers are utilized inside-out or outside-in [22–24]. Regarding the direction of mass flux, solutes such as bicarbonate are often delivered from outside the fibers to inside the fibers during conventional dialysis, or in systems for on-line clearance measurements [25,26]. However, multiple correlated and complex factors can influence solute and fluid removal by dialysis fibers utilized outside-in, especially in the treatment of full blood.

1.2. *Hemodialysis fibers utilized outside-in*

1.2.1. *Diffusive solute transport in the outside-in hemodialyzer*

The diffusion of a specific solute across the dialyzer can be described by Fick's law [27], which defines that the diffusive flux (J_D) of a specific solute is proportional to its diffusion coefficient (D), the solute concentration gradient between blood and dialysate (ΔC_B), and the effective membrane area available for admitting the solute (a_{eff}).

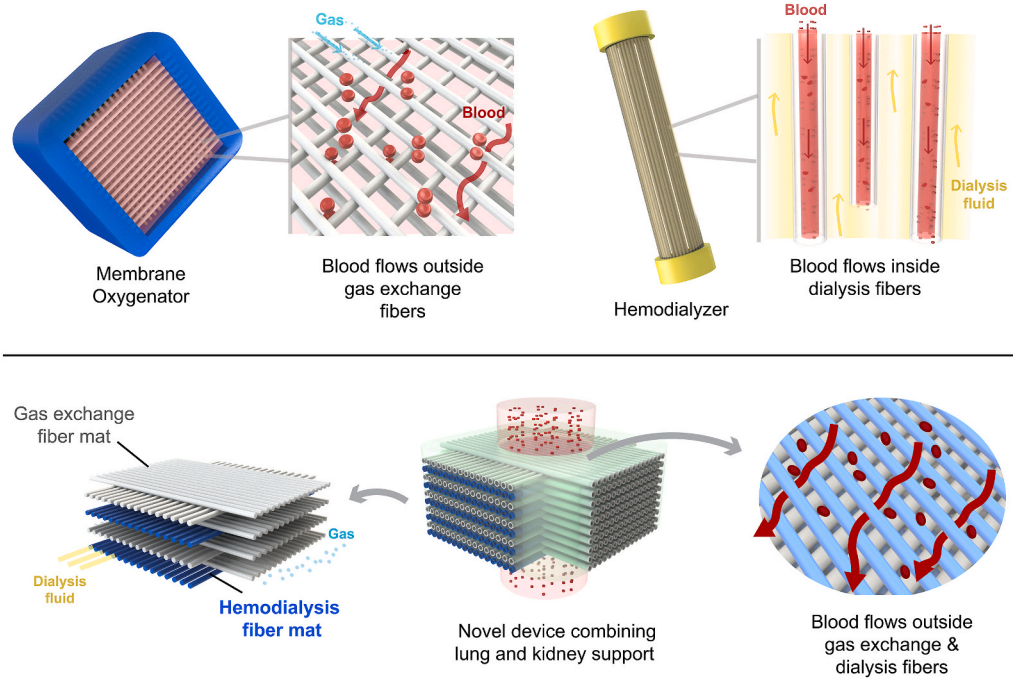

Fig. 1. Scheme representing blood flow in different membrane based organ support devices. Blood flows outside of gas exchange hollow fibers in membrane oxygenation (top left), while blood flows inside of hemodialysis hollow fibers in a dialyzer (top right). In the development of a novel device combining lung and kidney support blood would be required to flow and mix outside of both gas exchange and hemodialysis fibers (bottom).

$$J_D = \frac{D}{\Delta x} \bullet (\Delta C_B) \bullet a_{eff}$$

In contrast, solute flux is inversely proportional to the pathway distance the solute has to diffusive (Δx) related to membrane thickness and the boundary layer thickness on the blood and dialysate compartments [27,28]. Therefore, differences in 1) boundary layer thickness on the blood side and dialysate sides, and 2) solute diffusivity can influence solute mass transfer in the dialyzer.

Boundary layer thickness is influenced by multiple parameters including flow path geometry and flow velocity. Dialyzers utilized outside-in present a different flow path geometry in both blood and dialysate compartments when compared to traditional dialyzers. In the outside-in configuration, blood flows through channels between the fibers, being mixed and following a less uniform flow path. In addition, if the equivalent diameter of the channels between the fibers is larger than the fiber inner diameter, blood flow velocity outside the fibers would be smaller than blood flow velocity inside the fibers, as shown in Fig. 2 and supplementary material. A lower blood flow velocity outside the fiber would be related to the formation of thicker boundary layer on the blood compartment ($>\Delta x_{blood}$), increasing mass transfer resistance, ultimately limiting solute transfer. Dialysate flow path would also be modified in the outside-in configuration. Dialysate would flow inside the fibers, where a higher dialysate velocity could lead to reduced mass transfer resistance on the dialysate side ($<\Delta x_{dialysate}$), improving mass transport efficiency and clearance.

A combined influence of modifying flow patterns on both blood and dialysate compartments can play a role on the overall solute removal efficiency by the outside-in dialyzer. This effect adds to the complex influence of whole blood behavior on diffusive clearance. Whole blood presents a different viscosity depending on blood composition, flow conditions and flow pathway [31]. The viscosity of the diffusion medium (i.e. whole blood) determines solute diffusivity [32] and therefore, solute diffusive clearance. The effect of feed viscosity on solute transport has been evaluated for dialyzers utilized inside-out [33,34]. However, feed viscosity appears to influence solute transport in different ways when utilizing viscous solution or whole blood, as a suspension of blood cells [33,34].

1.2.2. *Convective solute and fluid transport in the outside-in hemodialyzer*

Convection refers to fluid flow through the membrane, also known as ultrafiltration, driven by a pressure difference across the membrane between the blood and dialysate compartments [27]. Fluid crossing the membrane carries solutes, contributing to solute removal by a mechanism known as solvent drag. The ultrafiltration flux (J_F – volume transferred per membrane surface area) is a function of the membrane hydraulic permeability (L_p), and the driving pressure gradient across the membrane (Δp).

$$J_F = L_P(\Delta p)$$

Membrane characteristics such as mean pore size and pore size distribution can significantly affect membrane filtration capacity and membrane ultrafiltration coefficient (K_{UF}). Both membrane permeability and selectivity depend on pore size and pore geometry [35]. Most commercial hemodialysis hollow fibers are prepared with an asymmetric pore structure comprising a thin selective layer (<50 nm) with smaller pores and an outer supportive layer with larger pores, see Fig. 3. In traditional inside-out configuration, the inner selective layer optimizes the removal of small (<500 Da) and middle molecules (500–60, 000 Da) [27,36], while preventing blood cells, proteins, and macromolecules such as serum albumin from permeating the membrane. During traditional inside-out mode, this selective layer is designed to be in direct contact with the blood, see Fig. 3. However, in outside-in mode, blood would come into direct contact with the larger pores. Thus, proteins and macromolecules flowing outside of the fibers could more easily permeate such pores, leading to pore obstruction and narrowing, see Fig. 3. Especially when ultrafiltration is present, this effect could be potentially increased, since a pressure difference is applied, forcing fluid to permeate the membrane, also potentially dragging macromolecules and blood cells to the pores.

Therefore, differences in pore size and pore geometry in the outer membrane layer could influence plasma filtration rate and solute clearance during outside-in use. This effect was verified by Yamashita et al. [37] that showed an almost 4 times higher permeation of albumin when asymmetric membranes operate outside-in, due to the wedge like pore structures in these membranes.

The application of dialysis fibers outside-in has been previously described in the literature, and has gained relevancy after a study described the use of outside-in fibers to prolong filter life without clotting [38]. However, previous studies utilized dialysis membranes outside-in in different operational conditions than CRRT, in test medium that differed from whole blood, or for other final applications such as in a cytopheretic device for cytokine removal [39], as summarized in Table 1. A practical study evaluating key factors such as clearance and filtration efficiency of outside-in dialysis fibers for the delivery CRRT is lacking, especially in the treatment of whole blood. Therefore, this study aims to evaluate the efficiency of commercial hemodialyzer membranes utilized outside-in with blood flowing outside of the hollow fibers in terms of 1) diffusive and convective clearance of urea and creatinine, and 2) ultrafiltration coefficient of the membrane system. The efficiency of outside-in continuous hemodialysis and continuous hemofiltration was compared with traditional inside-out membrane application. This study aims to provide practical insights for future application of dialysis fibers outside-in, including the development of a novel membrane

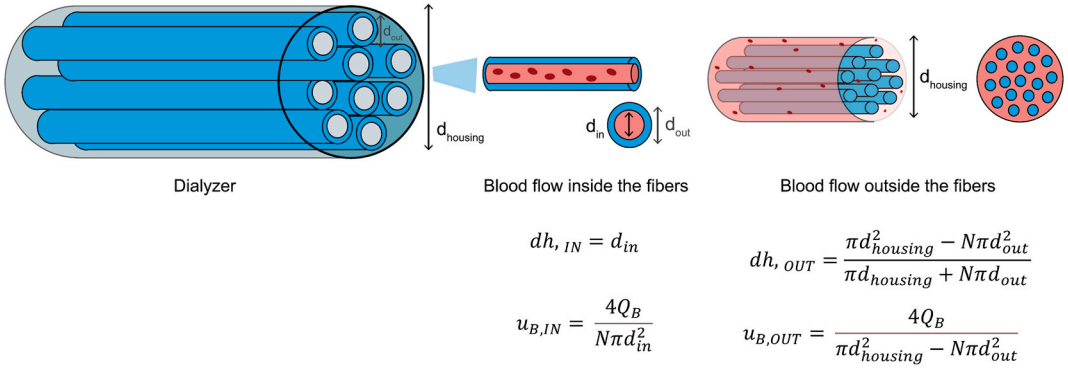

Fig. 2. A dialyzer with cylindrical housing diameter ($d_{housing}$) integrates multiple hollow fibers. Blood flow velocity and effective flow diameters vary if blood flows inside or outside the fibers. Blood flowing inside fibers follows an effective diameter $d_{h,IN}$ equal to the fiber inner diameter (d_{in}). Velocity inside the fibers ($u_{B,\ IN}$) depends on blood flow rate (Q_B), the number of fibers in the dialyzer (N), and d_{in}. Blood flowing outside the fibers has a velocity $u_{B,\ OUT}$, following an effective diameter ($d_{h,OUT}$) that can be estimated based on $d_{housing}$, and the fibers outer diameter (d_{out}). Scheme and equations modified from Refs. [27,29,30].

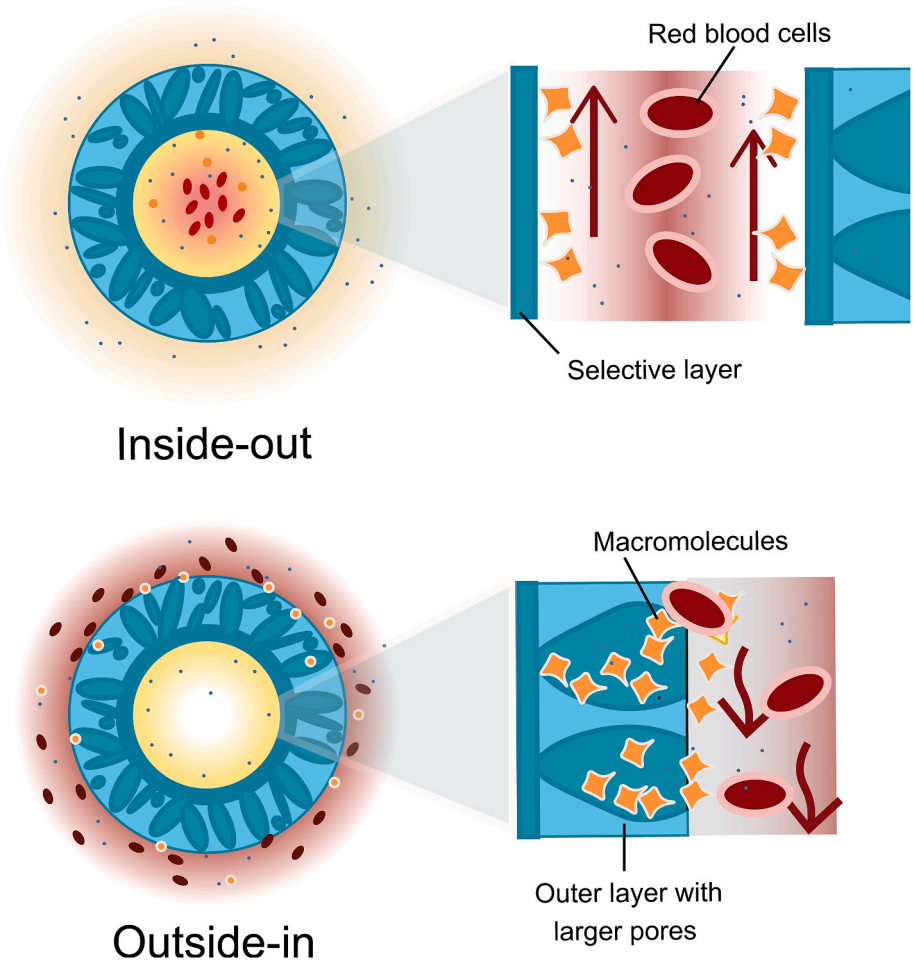

Fig. 3. Top: In traditional inside-out application, blood flows in the lumen of asymmetric hemodialysis hollow fibers. The membrane's selective layer with smaller pores is found in the inner side (top right). Small blood solutes are represented by the smallest blue dots. Bottom: During outside-in use, blood flows in the inter-fiber spaces, mixing around the fibers, where a layer of larger pores is typically found on the membrane surface (bottom right). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

device combining lung and kidney extracorporeal support.

2. Methodology

2.1. Selection of continuous renal replacement therapy parameters

Typical continuous renal replacement therapy parameters for continuous venous-venous hemodialysis (CVVHD) and continuous venous-venous hemofiltration (CVVH) were identified [16,41], see Table 2. These studies present typical CRRT operational conditions for the treatment of adult patients. Although, filter area is not explicitly specified, in contemporary CRRT, filters with membrane areas higher than 1 m^2 are routinely utilized for adult treatment [42]. The area of the filter selected for our experiments (1.2 m^2) is comparable to the area of dialyzers typically utilized in the treatment of adult patients. Therefore, the described operational conditions in Table 2 could be valid to simulate typical adult CRRT treatment in our tests.

Considering typical prescribed CRRT conditions, our continuous hemodialysis experiments applied a blood flow rate of 150 mL/min, and dialysate flow rates of 30 mL/min and 50 mL/min. For continuous hemofiltration experiments we applied a blood flow rate of 150 mL/min, and an ultrafiltration rate of 20 mL/min. The same flow rates were used to test both inside-out and outside-in dialyzers, see Table 2.

2.2. Blood preparation

Blood preparation followed the guidelines described in ISO 8637:2016 [43] for testing hemodialyzers, hemodiafilters, and hemofilters. Fresh porcine blood was collected from a local slaughterhouse (Haaksbergen, Netherlands) and filtered into a transport canister by using a polyamide mesh filter. Pooled blood from different animals was collected due to the blood volume necessary for the experiments (10 L). The ISO 8637:2016 suggests the use of bovine blood for tests, however, porcine blood has better availability in the European Union, and was chosen for these tests. Moreover, since this evaluation's goal is to assess effects of blood flow and membrane-blood interaction on device efficiency, porcine blood could provide valid results for our purposes, considering porcine blood analogy to human blood [44,45]. Moreover, considering that this study is part of the development of a novel artificial lung device with combined kidney support, the ISO 7199:2016 [46] for testing membrane oxygenators allows the use of porcine blood for testing.

The 10 L canister was prepared with 6 mL/L_{Blood} of sodium chloride solution 0.9% and 1.8 mL/L_{Blood} of glucose solution 50% and with 15,000 I.U./L heparin-sodium for full anticoagulation (activated clotting time (ACT) $>$ 1000 s). Systemic heparin anticoagulation is the predominant agent used clinically during membrane oxygenation, and therefore was selected for these trials. In the laboratory, blood was diluted with sodium chloride solution 0.9% to reach a hematocrit level

Table 1
Overview of previous literature describing the utilization of dialysis hollow fibers outside-in (i.e. blood flowing outside the fibers).

Modality	Test fluid	Test solute	Operational conditions	Dialyzer data	Main findings	Possible limitations	Reference
Outside-in dialysis	Aqueous solution	Creatinine, bromophenol blue, vitamin B12, chymotrypsin	Flow rate outside the fibers = 200 mL/min, flow rate inside the fibers = 500 mL/min	Commercial dialyzers (1–2.2 m^2) with asymmetric or homogenous membrane	Membrane permeability and chymotrypsin clearance was larger in asymmetric membranes utilized outside-in.	Experiments performed with water solutions, possibly not reflecting performance in treatment with whole blood.	[23]
Outside-in filtration	Aqueous solution	Vitamin B12, α-chymotrypsin, albumin, dextran solutions	Flow rate outside the fibers = 200 mL/min, ultrafiltration rate = 10 mL/min	Commercial dialyzers (2.1 m^2) with asymmetric or homogenous membrane	Sieving coefficient of albumin was higher for asymmetric membranes operating outside-in. Small solute sieving was similar between modes.	Similar effects have not yet been analyzed with whole blood.	[37]
Outside-in dialysis	Human plasma	Hippuric acid bound to albumin, and indoxyl sulfate bound to albumin	Flow rate outside the fibers = 10 mL/min, flow inside the fibers = 5 mL/min	Miniaturized dialyzer (0.0016 mm^2) with dual layer hollow fiber mixed matrix membrane	Mixed matrix membranes utilized outside-in provided a superior removal of protein-bound uremic toxins compared to mixed matrix membranes used inside-out.	Experiments performed with a miniaturized dialysis system with membranes not yet marketed for application in outside-in filtration mode.	[15]
Outside-in filtration	Whole blood	Urea, creatinine, potassium	Flow rate outside the fibers = 1.2 L/min, ultrafiltration rate = 70 ml/h	Mixed membrane bundle combining gas exchange and dialysis membranes (total area of 1.3 m^2).	Hemofiltration rates of 70 ml/h could be maintained during 270 min of in-vivo tests.	System's solute clearance and ultrafiltration coefficient was not completely evaluated.	[14]
Outside-in filtration	Whole blood	–	Blood flow = 75–300 mL/min, ultrafiltrate rate = 1.5–2.0 mL/min	Commercial dialyzer (1.5 m^2)	Successful hemofiltration for 100 h using outside-in operation.	Study focused on evaluating outside-in operation for longer hemofiltration with reduced clotting.	[38]
Outside-in plasma separation	Whole blood	–	Flow rate outside the fiber = 500 mL/min, ultrafiltration rate 100 mL/min	Commercial plasma separation filters.	Plasma filters operating in outside-in mode enabled a higher blood flow rate and filtration rates to be achieved.	Operating conditions and goals differ than the ones applied in CRRT.	[40]
Outside-in citokyne removal	Whole blood	Proinflammatory citokynes	Clinical tests applying CRRT conditions	Selective Cytopheretic Device (2.0 m^2).	Cytopheretic device utilizing outside-in membranes can remove proinflammatory messengers such as cytokines.	System has an complementary function to CRRT.	[39]

of 32 ± 3 %, and a plasma protein content of 60 ± 5 g/L. Blood samples of 1.5 mL were centrifuged (Mikro 220 centrifuge, Hettich, Westphalia, Germany) at 2000 rpm for 10 min to achieve blood plasma separation. Plasma protein content was measured at 280 nm with a spectrophotometer (NanoDrop™ 2000/2000c, Thermo Fisher, Waltham, United States).

2.3. Clearance measurements in blood

ISO 8637:2016 standard was formulated for traditional inside-out use of hemodialysis fibers, and clearance measurements are recommended to use water as test fluid. Nevertheless, since we intended to assess if blood mixing and blood interaction with outside-in fibers would affect solute clearance, our protocol adapted the guidelines of ISO 8637:2016 for performing clearance tests with blood as test fluid instead of water.

Urea (98%, Thermo Fisher Scientific, Waltham, United States) and creatinine (98%, Thermo Fisher Scientific, Waltham, United States) were added to the blood to achieve a final solute concentration of 15–35 mmol/L, and 500–1000 μmol/L respectively. A waiting time of 30 min was taken before the start of the clearance tests to ensure urea and creatinine concentrations equilibrated between plasma and red blood cell content [47]. Blood canisters were swirled gently before filling the test circuit to prevent sedimentation of blood cells. Sodium chloride solution 0.9% was used as dialysis fluid during hemodialysis clearance experiments.

The in-vitro test set-up consisted of a warming circuit and a test circuit. The complete circuit was primed and degassed using sodium chloride solution 0.9%. In the warming circuit, blood leaving the reservoir (8F INSPIRE reservoir, Sorin Group, Mirandola, Italy), passed through a membrane oxygenator with integrated heat exchanger (Sorin 8F INSPIRE, Sorin Group, Mirandola, Italy) to warm the blood to 37 ± 1 °C. The membrane oxygenator was solely used as a heat exchanger, and no gas permeated the membrane oxygenator. Warm blood was then returned to the reservoir which kept blood within this set temperature.

The test circuit was used to assess clearance of solutes and the ultrafiltration coefficient of dialyzers used in inside-out and outside-in mode. The test loop integrated two commercial dialyzers (SmartFlux HP 120 – high flux dialyzers, Medica, Medolla, Italy) connected in parallel, see Fig. 4. Dialyzers contained asymmetric polyethersulfone (PES) hollow fibers (PUREMA, 3M-Membrana, Wuppertal, Germany) with 1.2 m^2 of surface area, Table 3 presents dialyzer specifications. The inside-out test loop contained a dialyzer used in a conventional mode with blood flowing inside of the fibers, while dialysis fluid flowed outside the fibers through the conventional dialysate compartment, see Fig. 4. The dialyzers were oriented in a vertical position, blood entered through the bottom blood port of the dialyzer, and dialysis fluid entered through the top dialysate port of the dialyzer, in counter-current with the blood flow. Effluent left through the bottom dialysate port of the dialyzer. In contrast, in the outside-in test loop, dialyzers were used in an outside-in configuration with blood flowing outside of the fibers, and dialysis fluid flowing inside of the fibers. In this case, blood entered through the bottom "dialysate port" of the dialyzer, while dialysis fluid entered the top "blood port" of the dialyzer, and effluent left through the bottom blood port of the dialyzer, as shown in Fig. 4. Only one test loop, either the inside-out test loop or the outside-in test loop, was tested at a time. Dialyzers were used only once, and dialyzers from the same lot were used for all tests.

2.3.1. Diffusive clearance by dialysis

Warmed blood was sent to the test circuit with the aid of a roller pump (HL 20, Getinge, Gothenburg, Sweden), and flowed through the dialyzer connected either in an inside-out or outside-in configuration. Continuous hemodialysis conditions were applied with blood flow rate set to 150 mL/min, and dialysis fluid set to 50 mL/min initially, and then to 30 mL/min. These flow rates were selected to simulate CRRT

Table 2
Typical conditions applied in continuous renal replacement therapy and selected parameters that simulate continuous hemodialysis (CVVHD) and hemofiltration (CVVH) in our experiments with dialyzers used inside-out and outside-in.

	CRRT mode	Blood flow rate (mL/min)	Dialysis fluid rate (mL/min)	Ultrafiltration rate (mL/min)	Reference
Typical reported conditions	CVVHD	100–250	15–60	0	[16,41]
	CVVH	100–250	0	15–60	[16,41]
Experimental conditions	CVVHD inside-out	150	30 & 50	0	Based on references [16,41]
	CVVHD Outside-in	150	30 & 50	0	
	CVVH Inside-out	150	0	20	
	CVVH Outside-in	150	0	20	

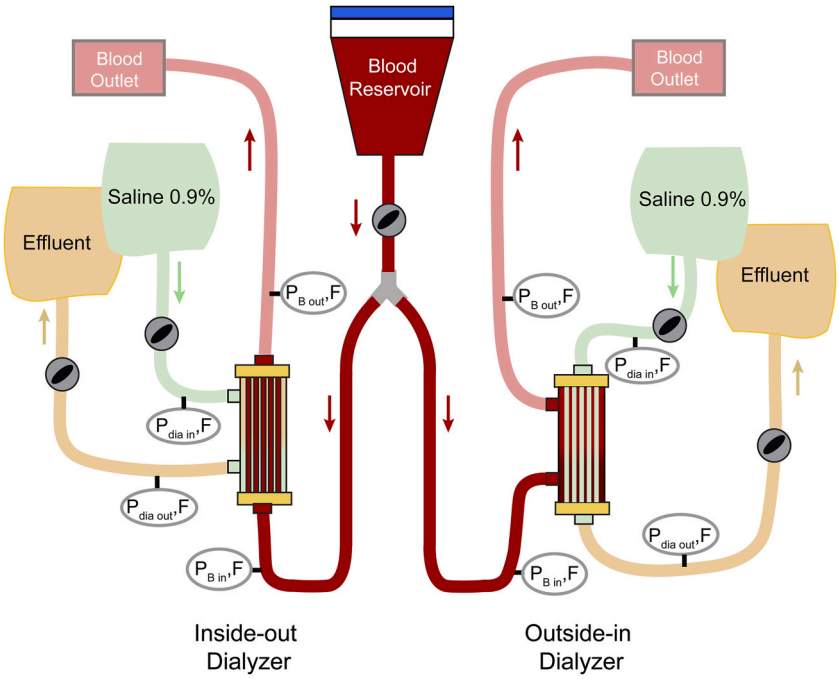

Fig. 4. Schematic view of the circuit used in our experiments to test the efficiency of commercial dialyzers applied in an inside-out mode – blood flow inside the fibers (left), and outside-in mode – blood flow outside the fibers (right). Arrows represent fluid flow direction. Pressure sensors (P), and flow sensors (F) were used to monitor conditions in the circuit. A single test loop, either the inside-out test loop (left) or the outside-in test loop (right), was tested at a time.

Table 3
Characteristics of the commercial dialyzer and membrane utilized in our experiments. The urea mass transport coefficient (K_0A) was calculated with clearance and flow data provided by the manufacturer (feed flow rate = 200 mL/min, dialysate flow rate = 500 mL/min) as described in the supplementary material.

Surface area	1.2 m^2
Fiber inner diameter	200 μm
Fiber outer diameter	260 μm
Priming volume	69 mL
Ultrafiltration coefficient (K_{uf})	55 mL/h/mmHg
Mass transport coefficient (K_0A) calculated for urea with manufacturer data	839 mL/min
Number of fibers	7200 fibers
Effective fiber length	248 mm

treatment conditions as discussed in section 2.1. One roller pump was used to control dialysis fluid flow, and another to control effluent flow rate. In diffusivity clearance experiments, a transmembrane pressure (TMP) near zero was targeted, meaning that average pressure in the blood inlet ($P_{blood\ in}$) and outlet ($P_{blood\ out}$) compartments, and pressure in the dialysate inlet ($P_{dia\ in}$) and outlet ($P_{dia\ out}$) compartments would be similar, see Equation (1), leading to approximate zero net filtration.

$$TMP = \frac{P_{blood\ in} + P_{blood\ out}}{2} - \frac{P_{dia\ in} + P_{dia\ out}}{2} \quad \text{Eq. 1}$$

After stable conditions of temperature, flow, and pressures were established, blood samples were taken pre-dialyzer and post-dialyzer at 10 min and 20 min of treatment. Samples were analyzed within approximately 10–30 min after collection for urea and creatinine concentrations using an i-STAT point of care blood analyzer in combination with CHEM8+ cartridges (both, Abbott, Chicago, United States). Blood passed only once through the dialyzer and was not recirculated through the test circuit, thus instant clearance at the sampling time was measured.

Solute clearance is defined as the ratio between solute mass removal rate and blood solute concentration [32], and was calculated by Equation (2).

$$K = \left(\frac{c_{blood\ inlet} - c_{blood\ outlet}}{c_{blood\ inlet}}\right) * Q_B + \frac{c_{blood\ outlet}}{c_{blood\ inlet}} * Q_F \quad \text{Eq. 2}$$

Where K represents solute clearance (mL/min), $c_{blood\ inlet}$ the concentration of solute in the blood entering the dialyzer (mmol/L), $c_{blood\ outlet}$ the concentration of solute in the blood leaving the dialyzer (mmol/L), Q_B the blood flow rate (mL/min), Q_F the filtrate flow rate (mL/min). In the case of diffusive clearance, filtrate flow rate was considered equal to zero. The i-STAT point of care device analyzes solute concentration in samples of whole blood accounting for plasma and blood cells, thus,

whole blood flow was used for clearance calculations.

2.3.2. Convective clearance by ultrafiltration

In convective clearance experiments, blood flow rate was set to 150 mL/min and no dialysis fluid permeated the hemodialyzer. An effluent rate of 20 mL/min was set and controlled with the aid of a roller pump. In convective clearance tests a positive net filtration was targeted. Clearance was calculated according to Equation (2).

2.4. Ultrafiltration coefficient

Ultrafiltration tests were performed right after clearance tests. A blood flow rate of 150 mL/min was set, and no dialysis fluid permeated the dialysate compartment. After stable temperature, flow rate, and pressure conditions were achieved, transmembrane pressure was measured at different ultrafiltration rates varying between 0 and 45 mL/min. The transmembrane pressure of the system was defined as the difference between the arithmetic mean of blood inlet ($P_{blood\ in}$) and blood outlet ($P_{blood\ out}$) compartments, and the pressure in the effluent compartment ($P_{effluent}$), as described by Equation (4). Paired ultrafiltration rate and TMP measurements were made for the dialyzers. Multiple TMP measurements were taken for the same ultrafiltration rate to account for pressure variations. Thus in a test, a corresponding average transmembrane pressure was calculated for a specific ultrafiltration rate. The ultrafiltration coefficient was calculated as the slope of the regression line between the averaged transmembrane pressure for the different experiments when a certain ultrafiltration rate was applied, Equation (3).

$$K_{UF} = \frac{Q_{UF}}{TMP} \quad \text{Eq. 3}$$

$$TMP = \frac{P_{blood\ in} + P_{blood\ out}}{2} - P_{effluent} \quad \text{Eq. 4}$$

This calculation of K_{uf} does not account for colloid osmotic pressure [48], but it is a measure of the global K_{uf} of the system [49]. Q_{uf} is considered as the total ultrafiltration flow representing the net flow leaving the dialyzer, including filtration and back-filtration. TMP was considered the resultant pressure of the system accounting for differences in pressures at the blood inlet, blood outlet, dialysate inlet and dialysate outlet.

2.5. Statistical analysis

Statistical analysis was performed in SPSS Statistics 28 (IBM, Armonk, United States) and RStudio (Foundation for Statistical Computing, Vienna, Austria). Clearance results were analyzed for a normality distribution utilizing a Shapiro-Wilk test. The homogeneity of variances was evaluated by Levene's test. An independent student T-test (two-sided) was performed to evaluate if the efficiency of dialyzers used inside-out and outside-in differed from each other in terms of urea and creatinine clearance, p-values <0.05 were considered statistically significant.

3. Results and discussion

3.1. Clearance measurements in blood

3.1.1. Diffusive clearance by dialysis

Urea and creatinine clearance obtained for inside-out and outside-in hemodialysis at a blood flow rate of 150 mL/min and different dialysate flow rates are reported in Fig. 5. For the lower dialysate flow rate of 30 mL/min, dialyzers in a conventional inside-out mode cleared 31 ± 6.6 mL/min of creatinine, and 35 ± 7.4 mL/min of urea. On the other hand, dialyzers in an outside-in configuration achieved a clearance of 30 ± 4.3 mL/min for creatinine, and 36 ± 6.2 mL/min for urea. Clearance of urea and creatinine at a dialysate flow rate of 30 mL/min was not statistically significantly different between dialyzers used inside-out and outside-in ($p = 0.7$ and $p = 0.9$ respectively).

At a higher dialysate flow rate of 50 mL/min, dialyzers utilized inside-out achieved an urea clearance of 59 ± 5.3 mL/min, and a creatinine clearance of 58 ± 6.8 mL/min. On the other hand, dialyzers utilized outside-in cleared 69 ± 6.1 mL/min of urea, and 57 ± 10 mL/min of creatinine. At this dialysate flow rate, clearance of creatinine was not statistically significantly different between outside-in and inside-out dialyzers ($p = 0.8$). However, urea clearance was statistically significantly higher by approximately 10 mL/min for outside-in dialyzers ($p = 0.003$).

Clearance of urea, a smaller solute with higher diffusivities than creatinine, was in average ~17% higher than creatinine clearance during outside-in dialysis, however, statistically significant differences were only observed for tests with a dialysate flow of 50 mL/min.

For small solutes such as urea and creatinine (<500 Da), the blood side resistance, the membrane resistance, and the dialysate side resistance to mass transfer are relevant for the resulting clearance [27]. However, when dialysate flow rate is smaller than blood flow rate and smaller than the dialyzer mass transport coefficient (K_0A), clearance of small solutes is reported to be mainly limited by dialysate flow rate [50]. The reported dialyzer K_0A for urea clearance is calculated to be ~840 mL/min in tests with aqueous solutions performed by the manufacturer,

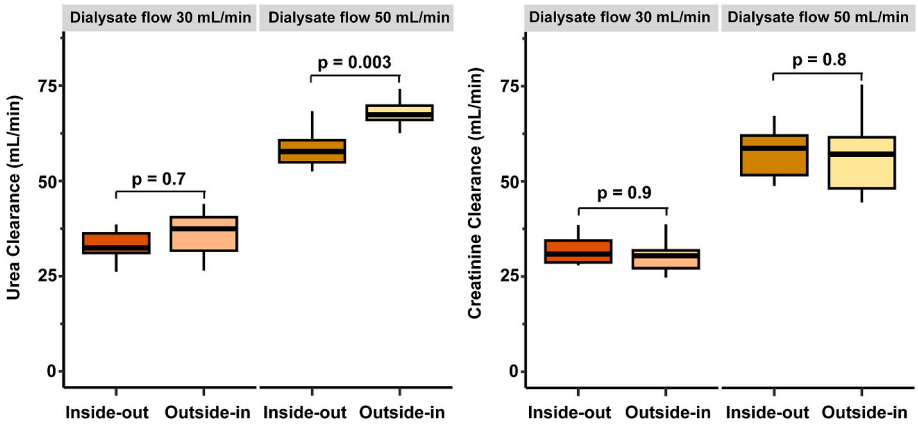

Fig. 5. Urea and creatinine clearances (mL/min) obtained for hemodialyzers used inside-out and outside-in in diffusive mode with dialysis flow rates of 30 mL/min and 50 mL/min. Boxplots show median (N = 8), hinges show 1st and 3rd quartile, and whiskers minimum and maximum sample values no further than 1.5x IQR (inter quartile range) from the hinge. Clearance by outside-in dialyzers was not statistically significantly different than for inside-out dialyzers ($p > 0.7$), except for urea clearance at 50 mL/min ($p = 0.003$).

see Table 3 and supplementary material. In our experiments with whole blood, K_0A for urea is estimated to be reduced to approximately 600 mL/min, and 300 mL/min when the dialyzer is operating at a dialysate flow of 50 mL/min and 30 mL/min respectively, see supplementary material. Therefore, in our experiments simulating CRRT conditions, dialysate flow rates were at least 3 times lower than the blood flow rate, and smaller than the estimated mass transfer area coefficient of the dialyzer [51]. Indeed, our results show that urea and creatinine clearance in both inside-out and outside-in modes was directly dependent and nearly equal to the dialysate flow rate. A higher dialysate flow rate of 50 mL/min resulted in higher clearances and higher estimated dialyzer mass transport coefficient. This could be explained by the higher fluid velocity on the dialysate side when dialysate flow rate increases, which contributes to a reduced resistance to solute transfer by limiting the growth of boundary layers on the dialysate side. Similar results were observed by Leypoldt et al. [51] for the inside-out configuration when low dialysate flow rates were applied.

Nevertheless, differences in dialysate flow geometry and blood flow geometry appear to have little influence on solute clearance during our experiments. In outside-in operation, dialysate flowing inside our dialyzer's fibers would have a theoretical dialysate velocity that is approximately 46% higher compared to dialysate fluid velocity outside the fibers, see supplementary material. Higher dialysate velocity inside the fibers could reduce mass transfer resistance on the dialysate compartment improving solute clearance. In addition, outside-in blood flow could affect solute clearance due to variations in blood viscosity, solute diffusivity, and boundary layer disruption. However, in general, inside-out and outside-in modes had similar small solute clearance, despite a different flow geometry on the dialysate and blood compartments. This indicates that dialysate flow rate was the main limitation to the transfer of urea and creatine, and that differences in flow pathway were less important for the clearance of these small solutes. However, outside-in blood flow could influence the clearance of larger solutes than urea and creatine, for which the effect of blood mixing and concentration polarization can be of higher influence, or in tests with different operational conditions than the ones applied here, especially if blood flow rate is further reduced [50].

Similar results were reported by Yamashita et al. [23,37,52] while studying the performance of commercial dialyzers utilized outside-in. Clearances of creatinine ($K_{outside\text{-}in}/K_{inside\text{-}out} = 0.96$) and vitamin B12 ($K_{outside\text{-}in}/K_{inside\text{-}out} = 1$) were similar for dialyzers used inside-out and outside-in during dialysis. Differences in clearance between inside-out and outside-in modes only became important for the larger solute chymotrypsin (25,000 Da). Therefore, Yamashita's study with water and ours with full blood indicate that the diffusive clearance of small solutes such as urea and creatinine are similar when dialyzers are utilized inside-out or outside-in. For these small solutes, clearance by the inside-out and outside-in mode appear to be in line with classic mass transport theory, which predicts no difference in small solute clearance if feed if provided inside or outside the fibers [22].

In a practical way, these results indicate that hemodialysis fibers outside-in could achieve similar performance as traditional inside-out fibers regarding the dialysis of small solutes. Considering the treatment of a hypothetical female patient of 80 kg, in the tested CRRT conditions, hemodialysis fibers used outside-in could achieve delivery doses of approximately 22.5 $mL/kg^{-1}_{patient}h$ at a dialysate flow rate of 30 mL/min, and a dose of 42.8 $mL/kg^{-1}_{patient}h$ at a dialysate flow rate of 50 mL/min. These doses were similar to the ones obtained with dialysis fibers used inside-out and higher than the minimum required dose of 20–25 $mL/kg^{-1}_{patient}h$ required for kidney support during CRRT [18,19]. As an example, in a hypothetical 24-h treatment, the hemodialyzer used outside-in could clear urea and creatinine in a total of 43 L of body fluid, which correspond to clearing the total body water volume (or urea distribution volume) of the supposed 80 kg female patient.

In our experiments, small deviations in clearance could be related to experimental limitations. Our experiments were performed with the use of roller pumps which can generate pulsatile flows. Since clearance was measured instantaneously at the sampling time, pressure and flow rate variations could lead to deviations in clearance results.

3.1.2. Convective clearance by ultrafiltration

Clearance of urea and creatinine in conditions of continuous hemofiltration are reported for dialyzers used inside-out and outside-in, Fig. 6.

At an ultrafiltration flow rate of 20 mL/min, dialyzers in inside-out mode were capable of clearing 22 ± 3.3 mL/min of creatinine, and 23 ± 4.1 mL/min of urea, while dialyzers in outside-in mode cleared 25 ± 4.0 mL/min of creatinine, and 21 ± 3.0 mL/min of urea. Clearance of urea and creatinine were not statistically significantly different between dialyzers utilized inside-out or outside-in ($p > 0.2$). In addition, for the same dialyzer mode, urea clearance was not significantly different from creatinine clearance ($p > 0.1$).

Dialyzers used inside-out and outside-in achieved similar convective clearances of urea and creatinine. In both filtration modes, clearance was directly dependent on the set ultrafiltration rate. During ultrafiltration, an applied transmembrane pressure forces plasma to permeate the membrane. Urea and creatinine, present in blood and plasma, are smaller than the average membrane pore size [36], and therefore can easily pass through the membrane structure while being dragged by the ultrafiltrate flow [27]. Considering the mass balance of fluid across the dialyzer, urea and creatinine would leave the dialyzer at a similar rate as the effluent. We indeed observed that solute clearance was nearly equal to the applied effluent rate. Some of the clearance values were slightly higher than the set ultrafiltration rate, this variation could have occurred due to experimental limitations, such as the use of a roller pump with pulsatile flow. However, resulting clearance was still around 20 mL/min, within the observed error ranges.

Differences in flow and pore distribution between the outside-in and inside-out dialyzers have not cause a measurable difference in convective clearance of urea and creatinine. In this sense, the absence of an outer selective layer, which could cause the permeation of solutes and macromolecules through the larger pores, have not significantly influenced clearance of urea and creatinine in the outside-in mode. This could be explained by the size of the tested solutes. Urea and creatinine

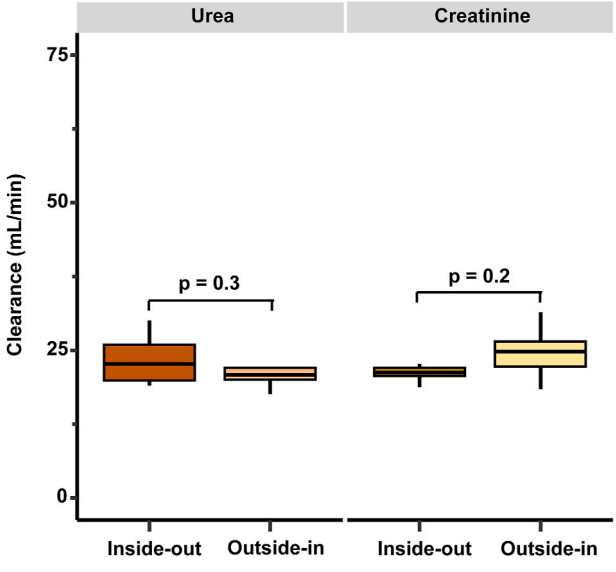

Fig. 6. Clearance of urea and creatinine (mL/min) obtained for dialyzers used inside-out and outside-in applied in convective mode. Boxplots show median (N = 8), hinges show 1st and 3rd quartile, and whiskers minimum and maximum sample values no further than 1.5x IQR (inter quartile range) from the hinge. Clearance by outside-in hemofiltration was not statistically significantly different compared to inside-out hemofiltration ($p > 0.2$).

are small molecules with high diffusion coefficients. Thus, concentration polarization effects and differences caused by blood flow mixing could be less significant in the CRRT conditions tested. Nevertheless, filtration of larger solutes or in different operational conditions can influence convective solute clearance by the outside-in configuration.

Our results are in line with previous studies that evaluated outside-in hemofiltration. Yamashita et al. [37] found no difference in the sieving of smaller solutes including creatinine, vitamin B12, and α-chymotrypsin (25,000 Da) during inside-out and outside-in ultrafiltration.

In a practical manner, our results show that convective removal of urea and creatinine can be achieved with similar efficiencies between outside-in and inside-out dialyzers. Considering the treatment of a hypothetical female patient of 80 kg, outside-in dialyzers could achieve a convective treatment dose of approximately 16 $mL/kg_{patient}/h$. Although this is lower than the typical required dose of 20–25 $mL/kg_{patient}/h$, in continuous hemofiltration treatment, a pre- and/or post-replacement fluid dose is routinely applied to maintain fluid balance in the patient [41]. Thus, the replacement fluid dose would add up to the total dose to achieve required CRRT delivery values [18].

3.2. Ultrafiltration coefficient

The ultrafiltration coefficient of inside-out and outside-in dialyzers was calculated as the slope of the regression line between the net measured ultrafiltration flow rate at different transmembrane pressures, see Fig. 7. The ultrafiltration coefficient for the system used inside-out was 0.77 mL/min/mmHg (or 46.1 mL/h/mmHg), while the ultrafiltration coefficient of the outside-in system was 0.19 mL/min/mmHg (or 11.7 mL/h/mmHg). A range of ultrafiltration rates and TMPs between and above values typically applied in CRRT was measured to provide a broader analysis spectrum, considering that different operational parameters could be relevant for the RenOx application.

The resulting regression lines had a coefficient of determination (R^2) higher than 0.8, which indicate a good linear fitting of the data in the region of TMP tested. Pressure variations were present, especially at higher ultrafiltration rates for outside-in dialyzers, which could lead to

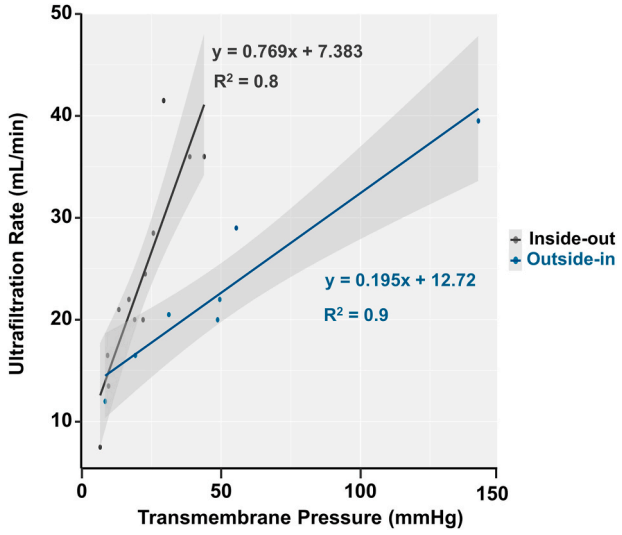

Fig. 7. Relation between ultrafiltration rate (mL/min) and transmembrane pressure (mmHg) measured for hemodialyzers used inside-out and outside-in. A total of 64 paired (ultrafiltration rate and TMP) measures were made for inside-out dialyzers, and 52 paired measures were made for outside-in dialyzers. Average transmembrane pressures for each ultrafiltration rate are represented (points) together with a 95% confidence interval for the measured data (grayed area). The ultrafiltration coefficient was calculated as the slope of the regression line between the ultrafiltration flow rate at different averaged transmembrane pressures.

changes in the measured ultrafiltration coefficient as indicated by the 95% confidence interval for the curves in Fig. 7. Nevertheless, the obtained ultrafiltration coefficient for inside-out dialyzers of 46 mL/h/mmHg was comparable to the one available in the dialyzer's manufacturer data sheet, reported to be 55 mL/h/mmHg [51].

Inside-out dialyzers had an ultrafiltration coefficient almost 4 times higher than dialyzers used outside-in. Proteins and macromolecules present in blood can stagnate and deposit near the membrane wall [53,54]. In the case of inside-out use, an inner membrane layer of tiny pores assists in preventing large proteins and blood cells from permeating the membrane. In addition, blood flow can help in reducing macromolecule concentration polarization near the membrane surface [28]. This differs in outside-in use, where blood comes in direct contact with a layer of large pores and where blood flows between irregular channels between the fiber spaces. In hollow fibers used outside-in, blood proteins, macromolecules, and blood cells can more easily partially or fully enter the larger pores causing pore blocking or narrowing, which could reduce membrane permeability. This effect would be more important at higher ultrafiltration rates, in which a higher concentration of macromolecules could be forced near the membrane wall. Moreover, blood flow outside the fiber is less uniform and in theory with a lower blood flow velocity. This can lead to the formation of more concentrated boundary layers near the membrane. All these could contribute to reducing the ultrafiltration coefficient of dialyzers used outside-in.

K_{uf} for the outside-in system could not be directly compared to previous studies, however, Wiegmann et al. [55] reported that dialysis fibers utilized outside-in dialysis maintained hemofiltration rates up to 1.2 mL/min for 270 min during in-vivo experiments, although authors reported no details on the corresponding transmembrane pressures.

Typical CRRT treatment requires a net fluid removal rate of approximately 2 $mL/kg_{patient}/h$ [16]. Assuming the care of a hypothetical female patient of 80 kg, around 160 mL_{fluid}/h would need to be removed during treatment. Considering our results, a traditional inside-out dialyzer could achieve this rate of fluid removal with the application of transmembrane pressures as low as 4 mmHg. A device using traditional hemodialysis fibers in outside-in mode would require higher transmembrane pressures of around 14 mmHg to achieve the same fluid removal rate. A higher TMP could be achieved by controlling the pressures in the dialysate and blood compartments, for instance by modifying flow rates, device position, and/or device design to manage pressure drop. This indicates that pressure monitoring in outside-in systems would be important to achieve desired fluid removal rates.

In addition, a novel device combining lung and kidney support would incorporate hollow fiber mats in a configuration different from conventional dialyzers. Furthermore, this device would operate with a higher blood flow rate, required for membrane oxygenation, which could generate different pressures than the ones found in CRRT. Therefore, the reduced ultrafiltration coefficient of commercial dialysis fibers used outside-in could pose a limitation to net fluid removal in this mode. Especially in an application with high blood flow rates, generating higher pressures in the blood compartment, which could possibly lead to further pore obstruction and TMP variations. Dedicated dialysis hollow fibers manufactured for outside-in hemofiltration, which present an outer selective layer [15], could prevent protein and macromolecules from clogging the pores and allow higher ultrafiltration coefficients to be achieved by future systems applying the outside-in mode.

In this sense, this study is limited in providing a practical and standardized proof of concept to compare the performance of dialysis fibers utilized outside-in compared to inside-out mode. Future studies evaluating the feasibility of outside-in dialysis fibers, especially in a bundle combining gas exchange fibers and hemodialysis fibers, should utilize a mixed membrane bundle in the final configuration to evaluate system cross-talk and the control of pressures on the blood side, dialysate side, and gas side. Moreover, it is relevant that for future evaluation of our combined device utilizing the outside-in mode we analyze the mass transport coefficient of the system at different operating conditions, and

solute mass balance error to verify data reliability. Also, the effect of outside-in configuration for the clearance of middle and large molecules is essential for future feasibility analysis. Finally, a lung and kidney support device combining gas exchange and outside-in dialysis fibers in one bundle with a surface area comparable to the one of a single oxygenator [9], will allow for treatment with a lower number of cannulas, pumps, and tubing [7] compared to the current ECMO plus CRRT approach. This will possibly lead to lower blood activation, thrombus formation, and blood cell damage. However, future studies must determine the actual blood cell damage caused by the use of such combined device, where both dialysis fibers and gas exchange fibers operate at high blood flow rates necessary for blood oxygenation. This should be conducted in a standardized approach following the ISO 7199:2016 to allow comparison of blood cell damage between the novel and state-of-the-art treatments.

4. Conclusions

We evaluated the performance of commercial dialyzers utilized outside-in compared to dialyzers in traditional inside-out mode in terms of urea and creatinine clearance, and ultrafiltration coefficient. For this purpose, the ISO8637:2016 standard was adapted for testing diffusive and convective clearance during in-vitro tests with porcine blood under continuous renal replacement therapy conditions. Clearance of urea and creatinine during hemodialysis and hemofiltration were not significantly different between dialyzers utilized outside-in and inside-out, except for tests with a dialysate flow rate of 50 mL/min, where outside-in fibers achieved a higher urea clearance. Nevertheless, the ultrafiltration coefficient of dialyzers used outside-in (11.7 mL/h/mmHg) was about 4 times smaller than the one obtained for inside-out dialyzers, which could be explained by the absence of a membrane outer selective layer in the outside-in modality. Overall, our results show that outside-in hemodialyzers achieved similar small solute clearance dose as traditional dialyzers, which was sufficient to provide a required CRRT dose of 20–25 mL/$kg_{patient}$/h assuming the treatment of a hypothetical 80 kg patient. Therefore, this study indicates that dialysis fibers utilized outside-in could provide sufficient levels of clearance of urea and creatinine, as well as fluid removal, if pressures in the system are adequate. This insights are relevant for the development of a novel membrane device combining gas exchange fibers and outside-in hemodialysis fibers to support both the lungs and the kidneys simultaneously.

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CRediT authorship contribution statement

Ana Martins Costa: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation. **Frank R. Halfwerk:** Writing – review & editing, Supervision, Resources, Formal analysis. **Jan-Niklas Thiel:** Writing – review & editing, Data curation. **Bettina Wiegmann:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Michael Neidlin:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Jutta Arens:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

We have shared our research data as supplementary material.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.memsci.2024.122575.

References

[1] H. Chen, R.G. Yu, N.N. Yin, J.X. Zhou, Combination of extracorporeal membrane oxygenation and continuous renal replacement therapy in critically ill patients: a systematic review, Crit. Care 18 (6) (2014), https://doi.org/10.1186/s13054-014-0675-x.
[2] C. Sorino, N. Scichilone, C. Pedone, S. Negri, D. Visca, A. Spanevello, When kidneys and lungs suffer together, J. Nephrol. 32 (5) (2019) 699–707, https://doi.org/10.1007/s40620-018-00563-1.
[3] B. Seczynska, W. Krolikowski, I. Nowak, M. Jankowski, K. Szuldrzynski, W. Szczeklik, Continuous renal replacement therapy during extracorporeal membrane oxygenation in patients treated in medical intensive care unit: technical considerations, Ther. Apher. Dial. 18 (6) (2014) 523–534, https://doi.org/10.1111/1744-9987.12188.
[4] M. Ostermann, M. Connor Jr., K. Kashani, Continuous renal replacement therapy during extracorporeal membrane oxygenation: why, when and how? Curr. Opin. Crit. Care 24 (6) (2018) 493–503, https://doi.org/10.1097/MCC.0000000000000559.
[5] S. Costantini, M. Belliato, F. Ferrari, G. Gazzaniga, M. Ravasi, M. Manera, M.E. De Piero, A. Curcelli, A. Cardinale, R. Lorusso, A retrospective analysis of the hemolysis occurrence during extracorporeal membrane oxygenation in a single center, Perfusion (2022) 2676591211073768, https://doi.org/10.1177/02676591211073768.
[6] C. de Tymowski, P. Augustin, H. Houissa, N. Allou, P. Montravers, A. Delzongle, Q. Pellenc, M. Desmard, CRRT connected to ECMO: managing high pressures, ASAIO J. 63 (1) (2017) 48–52, https://doi.org/10.1097/MAT.0000000000000441.
[7] A. Martins Costa, F. Halfwerk, B. Wiegmann, M. Neidlin, J. Arens, Trends, advantages and disadvantages in combined extracorporeal lung and kidney support from a technical point of view, Front. Med. Technol. 4 (2022) 909990, https://doi.org/10.3389/fmedt.2022.909990.
[8] A.A. Setty, T.Y. Chiang, J.A. Santos, B.C. Isenberg, E.M. Vedula, R.A. Keating, D. W. Sutherland, J.T. Borenstein, Toward microfluidic integration of respiratory and renal organ support in a single cartridge, Artif. Organs 47 (9) (2023) 1442–1451, https://doi.org/10.1111/aor.14603.
[9] A. Martins Costa, F.R. Halfwerk, J.-N. Thiel, B. Wiegmann, M. Neidlin, J. Arens, Effect of hollow fiber configuration and replacement on the gas exchange performance of artificial membrane lungs, J. Membr. Sci. 680 (2023) 121742, https://doi.org/10.1016/j.memsci.2023.121742.
[10] G. Catapano, A. Wodetzki, U. Baurmeister, Blood flow outside regularly spaced hollow fibers: the future concept of membrane devices? Int. J. Artif. Organs 15 (6) (2018) 327–330, https://doi.org/10.1016/S0376-7388(00)00615-3.
[11] T.V. Brogan, L. Lequier, R. Lorusso, G. MacLaren, G. Peek, Extracorporeal Life Support: the ELSO Red Book, fifth ed., Extracorporeal Life Support Organization, Ann Arbor, Michigan, 2017.
[12] Y. Raharjo, M.N. Zainol Abidin, A.F. Ismail, M.Z. Fahmi, Saiful, M. Elma, D. Santoso, H. Haula, A.R. Habibi, Dialysis membranes for acute kidney injury, Membr. Biochem. 12 (3) (2022) 325, https://doi.org/10.3390/membranes12030325.
[13] R.H. Bartlett, Physiology of extracorporeal gas exchange, Compr. Physiol. 10 (3) (2020) 879–891, https://doi.org/10.1002/cphy.c190006.
[14] B. Wiegmann, A. Maurer, R. Zhang, P. Zardo, A. Haverich, S. Fischer, Combined pulmonary and renal support in a single extracorporeal device, ASAIO J. 59 (4) (2013) 433–438, https://doi.org/10.1097/MAT.0b013e318292e887.
[15] O.E.M. ter Beek, M.K. van Gelder, C. Lokhorst, D.H.M. Hazenbrink, B.H. Lentferink, K.G.F. Gerritsen, D. Stamatialis, In vitro study of dual layer mixed matrix hollow fiber membranes for outside-in filtration of human blood plasma, Acta Biomater. 123 (2021) 244–253, https://doi.org/10.1016/j.actbio.2020.12.063.
[16] E.J. See, R. Bellomo, How I prescribe continuous renal replacement therapy, Crit. Care 25 (1) (2021) 1, https://doi.org/10.1186/s13054-020-03448-7.
[17] C. Ronco, R. Bellomo, P. Homel, A. Brendolan, M. Dan, P. Piccinni, G. La Greca, Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial, Lancet 356 (9223) (2000) 26–30, https://doi.org/10.1016/S0140-6736(00)02430-2.

[18] E. Vasquez Jimenez, S.J. Anumudu, J.A. Neyra, Dose of continuous renal replacement therapy in critically ill patients: a bona fide quality indicator, Nephron 145 (2) (2021) 91–98, https://doi.org/10.1159/000512846.
[19] W.R. Clark, M. Leblanc, Z. Ricci, C. Ronco, Quantification and dosing of renal replacement therapy in acute kidney injury: a reappraisal, Blood Purif. 44 (2) (2017) 140–155, https://doi.org/10.1159/000475457.
[20] J.A. Neyra, A. Tolwani, CRRT prescription and delivery of dose, Semin. Dial. (2021), https://doi.org/10.1111/sdi.12974.
[21] J.A. Neyra, L. Yessayan, M.L. Thompson Bastin, K.M. Wille, A.J. Tolwani, How to prescribe and troubleshoot continuous renal replacement therapy: a case-based review, Kidney360 2 (2) (2021) 371–384, https://doi.org/10.34067/KID.0004912020.
[22] A.S. Michaels, Operating parameters and performance criteria for hemodialyzers and other membrane-separation devices, Trans. Am. Soc. Artif. Intern. Organs 12 (1966) 387–392.
[23] A.C. Yamashita, T. Ono, N. Tomisawa, Verification of physicochemical structures of dialysis membrane using reversal dialysis technique, Hemodial. Int. 21 (Suppl 2) (2017), https://doi.org/10.1111/hdi.12595. S3-S9.
[24] R.L. Fournier, Basic Transport Phenomena in Biomedical Engineering, fourth ed., CRC Press, 2017 https://doi.org/10.1201/9781315120478.
[25] H.D. Polaschegg, Automatic, noninvasive intradialytic clearance measurement, Int. J. Artif. Organs 16 (4) (1993) 185–191.
[26] N.G.T. Petitclerc, A.L. Reyniew, B. Bene, A model for non-invasive estimation of in vivo dialyzer performances and patient's conductivity during hemodialysis, Int. J. Artif. Organs 16 (1993) 585–591, https://doi.org/10.1177/039139889301600804.
[27] F. Mohajerani, W.R. Clark, C. Ronco, V. Narsimhan, Mass transport in high-flux hemodialysis: application of engineering principles to clinical prescription, Clin. J. Am. Soc. Nephrol. 17 (5) (2022) 749–756, https://doi.org/10.2215/CJN.09410721.
[28] L. Pstras, C. Ronco, J. Tattersall, Basic physics of hemodiafiltration, Semin. Dial. 35 (5) (2022) 390–404, https://doi.org/10.1111/sdi.13111.
[29] M. Raff, M. Welsch, H. Göhl, H. Hildwein, M. Storr, B. Wittner, Advanced modeling of highflux hemodialysis, J. Membr. Sci. 216 (1) (2003) 1–11, https://doi.org/10.1016/S0376-7388(02)00552-5.
[30] R. Lipkis, Heat transfer to laminar flow in a round tube or flat conduit—the graetz problem extended, Trans. Am. Soc. Mech. Eng. 78 (2) (1956) 447–448.
[31] E.E. Nanne, C.P. Aucoin, E.F. Leonard, Shear rate and hematocrit effects on the apparent diffusivity of urea in suspensions of bovine erythrocytes, ASAIO J. 56 (3) (2010) 151–156, https://doi.org/10.1097/MAT.0b013e3181d4ed0f.
[32] A. Einstein, Über die von der molekularkinetischen Theorie der Wärme geforderte Bewegung von in ruhenden Flüssigkeiten suspendierten Teilchen, Ann. Phys. 322 (8) (1905) 549–560, https://doi.org/10.1002/andp.19053220806.
[33] J. Waniewski, J. Poleszczuk, M. Pietribiasi, M. Debowska, A. Wojcik-Zaluska, W. Zaluska, Impact of solute exchange between erythrocytes and plasma on hemodialyzer clearance, Biocybern. Biomed. Eng. 40 (1) (2020) 265–276, https://doi.org/10.1016/j.bbe.2019.04.003.
[34] D. Schneditz, N. Sauseng, Diffusive solute transport in hollow fiber dialyzers is not affected by variable feed viscosity, Biocybern. Biomed. Eng. 42 (4) (2022) 1112–1122, https://doi.org/10.1016/j.bbe.2022.09.003.
[35] D.M. Kanani, W.H. Fissell, S. Roy, A. Dubnisheva, A. Fleischman, A.L. Zydney, Permeability–selectivity analysis for ultrafiltration: effect of pore geometry, J. Membr. Sci. 349 (1) (2010) 405–410, https://doi.org/10.1016/j.memsci.2009.12.003.
[36] A. Boschetti-de-Fierro, M. Voigt, M. Storr, B. Krause, MCO membranes: enhanced selectivity in high-flux class, Sci. Rep. 5 (2015) 18448, https://doi.org/10.1038/srep18448.
[37] A.C. Yamashita, T. Kakee, T. Ono, J. Motegi, S. Yamaguchi, T. Sunohara, Semi-quantitative evaluation of asymmetricity of dialysis membrane using forward and backward ultrafiltration, Membr. Biochem. 12 (6) (2022), https://doi.org/10.3390/membranes12060624.
[38] S.S. Dukhin, Y. Tabani, R. Lai, O.A. Labib, A.L. Zydney, M.E. Labib, Outside-in hemofiltration for prolonged operation without clogging, J. Membr. Sci. 464 (2014) 173–178, https://doi.org/10.1016/j.memsci.2014.01.069.
[39] J.A. Tumlin, L. Chawla, A.J. Tolwani, R. Mehta, J. Dillon, K.W. Finkel, J.R. DaSilva, B.C. Astor, A.S. Yevzlin, H.D. Humes, The effect of the selective cytopheretic device on acute kidney injury outcomes in the intensive care unit: a multicenter pilot study, Semin. Dial. 26 (5) (2013) 616–623, https://doi.org/10.1111/sdi.12032.
[40] J.K. Unger, V.R. Janssen, A. Kashefi, C. Haltern, B. Klosterhalfen, Y. Fischer, A. M. Gressner, R. Rossaint, Enhancing filtration rates by the use of blood flow around the capillaries of plasmafilters: an in vitro study, Int. J. Artif. Organs 24 (11) (2001) 821–831, https://doi.org/10.1177/039139880102401111.
[41] Z. Ricci, S. Romagnoli, C. Ronco, Renal replacement therapy [version 1; peer review: 4 approved], F1000Res 5, https://doi.org/10.12688/f1000research.6935.1, 2016.
[42] A. Lorenzin, M. Neri, F. Garzotto, C. Ronco, Chapter 165 - solute and water kinetics in continuous therapies, in: C. Ronco, R. Bellomo, J.A. Kellum, Z. Ricci (Eds.), Critical Care Nephrology, third ed., Elsevier, Philadelphia, 2019, pp. 1000–1005.e1, https://doi.org/10.1016/B978-0-323-44942-7.00165-5.
[43] DIN EN ISO 8637-1 – Extracorporeal systems for blood purification – Part 1: Haemodialysers, haemodiafilters, haemofilters and haemoconcentrators (ISO/DIS 8637-1:2016), DIN Deutsches Institut für Normung e. V., Beuth Verlag GmbH, Berlin, 2016.
[44] T. Jikuya, T. Tsutsui, O. Shigeta, Y. Sankai, T. Mitsui, Species differences in erythrocyte mechanical fragility: comparison of human, bovine, and ovine cells, ASAIO J. 44 (5) (1998) M452–M455.
[45] S. Klaus, S. Körfer, K. Mottaghy, H. Reul, B. Glasmacher, In vitro blood damage by high shear flow: human versus porcine blood, Int. J. Artif. Organs 25 (4) (2002) 306–312, https://doi.org/10.1177/039139880202500409.
[46] ISO 7199:2016 – Cardiovascular Implants and Artificial Organs — Blood-Gas Exchangers (Oxygenators), International Standardization Organization, Switzerland, 2016.
[47] D. Schneditz, Y. Yang, G. Christopoulos, J. Kellner, Rate of creatinine equilibration in whole blood, Hemodial. Int. 13 (2) (2009) 215–221, https://doi.org/10.1111/j.1542-4758.2009.00351.x.
[48] D. Schneditz, TMP revisited: the importance of plasma colloid osmotic pressure in high-flux dialyzers, Nephrol. Dial. Transplant. 26 (2) (2011) 411–413, https://doi.org/10.1093/ndt/gfq784.
[49] A. Ficheux, C. Ronco, P. Brunet, A. Argiles, The ultrafiltration coefficient: this old 'grand inconnu' in dialysis, Nephrol. Dial. Transplant. 30 (2) (2015) 204–208, https://doi.org/10.1093/ndt/gft493.
[50] J.K. Leypoldt, C.D. Kamerath, J.F. Gilson, G. Friederichs, Dialyzer clearances and mass transfer-area coefficients for small solutes at low dialysate flow rates, ASAIO J. 52 (4) (2006) 404–409, https://doi.org/10.1097/01.mat.0000227687.88929.08.
[51] Medica SPA - seamless innovation for life quality. https://www.medica-spa.com/, 2023. (Accessed 1 September 2023).
[52] A.C. Yamashita, H. Masaki, E. Kobayashi, T. Sukegawa, Evaluation of solute penetration across the polysulfone membrane with vitamin E coating, Hemodial. Int. 19 (Suppl 3) (2015) S20–S25, https://doi.org/10.1111/hdi.12348.
[53] M. Fukuda, H. Saomoto, T. Mori, H. Yoshimoto, R. Kusumi, K. Sakai, Impact of three-dimensional tortuous pore structure on polyethersulfone membrane morphology and mass transfer properties from a manufacturing perspective, J. Artif. Organs 23 (2) (2020) 171–179, https://doi.org/10.1007/s10047-019-01144-0.
[54] M. Fukuda, H. Yoshimoto, H. Saomoto, K. Sakai, Validity of three-dimensional tortuous pore structure and fouling of hemoconcentration capillary membrane using the tortuous pore diffusion model and scanning probe microscopy, Membranes 10 (11) (2020), https://doi.org/10.3390/membranes10110315.
[55] B. Wiegmann, A. Maurer, R. Zhang, P. Zardo, A. Haverich, S. Fischer, Combined pulmonary and renal support in a single extracorporeal device, ASAIO J. 59 (4) (2013) 433–438, https://doi.org/10.1097/MAT.0b013e318292e887.