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Development of a new miniaturized system for ultrafiltration

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Abstract

Acute decompensated heart failure and fluid overload are the most common causes of hospitalization in heart failure patients, and often, they contribute to disease progression. Initial treatment encompasses intravenous diuretics although there might be a percentual of patients refractory to this pharmacological approach. New technologies have been developed to perform extracorporeal ultrafiltration in fluid overloaded patients. Current equipment allows to perform ultrafiltration in most hospital and acute care settings. Extracorporeal ultrafiltration is then prescribed and conducted by specialized teams, and fluid removal is planned to restore a status of hydration close to normal. Recent clinical trials and European and North American practice guidelines suggest that ultrafiltration is indicated for patients with refractory congestion not responding to medical therapy. Close interaction between nephrologists and cardiologists may be the key to a collaborative therapeutic effort in heart failure patients. Further studies are today suggesting that wearable technologies might become available soon to treat patients in ambulatory and de-hospitalized settings. These new technologies may help to cope with the increasing demand for the care of chronic heart failure patients. Herein, we provide a state-of-the-art review on extracorporeal ultrafiltration and describe the steps in the development of a new miniaturized system for ultrafiltration, called AD1 (Artificial Diuresis).

Keywords Extracorporeal ultrafiltration · Artificial Diuresis · Wearable · Portable · Miniaturization · Heart failure · Fluid overload

Introduction

History of extracorporeal ultrafiltration

Fluid retention and accumulation with consequent expansion of the extra-cellular volume has always been a major challenge in medicine. Ancient reports provide information on the "dropsy of the chest" and other edema conditions identifying salt as a primum movens for water retention together with cardiac and renal dysfunction. The treatment of such conditions has been originally based on diaphoretics, purgatives, or mechanical removal of body fluids through bleeding, leeching, or lancing (subcutaneous needles) [1]. These heroic remedies were rapidly abandoned, first with the discovery of sulfanilamide-induced sodium bicarbonate diuresis, mercurial diuretics, and then safer diuretics such as thiazides and others. Nevertheless, hospitalization for heart failure and other edematous conditions continued to represent a challenge for physicians and a burden for health care system even in recent years [2]. Rales, dyspnea, and other symptoms due to fluid overload generally

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dominate the clinical picture at patient admission [3]. Emergency congestion treatment generally resolves the symptoms, but patients are often discharged with residual fluid overload that may lead to frequent readmission [4–8]. Acute decompensated heart failure and other fluid overload conditions are generally treated with intravenous diuretics which may however display limited efficacy in specific pathological conditions such as acute or chronic kidney disease and hypoalbuminemia [9]. In these circumstances, extracorporeal techniques of fluid removal have progressively become an important resource.

Extracorporeal ultrafiltration was first described by Silverstein and Henderson in the mid-1970s [10, 11]. They utilized a highly permeable hollow fiber filter equipped with a polysulfone membrane to remove fluid by filtration in series with hemodialysis or as an isolated ultrafiltration circuit (Fig. 1). After these experimental treatments, the advent of arterio-venous hemofiltration allowed a simplified procedure of extracorporeal fluid removal in critically ill patients and emergency conditions [12]. Soon, the advent of double-lumen central venous catheters led to the use of veno-venous pumped circulation. Special pumps and fluid balance systems were developed with easier application of ultrafiltration treatments [13, 14]. In the following years, specific machines were designed to perform different continuous renal replacement therapy techniques, including ultrafiltration [15]. However, the complexity of these machines limited the application in cardiology wards, and extracorporeal ultrafiltration remained underutilized. For this reason, new simplified machines specifically dedicated to ultrafiltration in cardiac patients were developed, and the therapy began its application in clinical routine [16, 17]. Dedicated equipment (e.g., Aquadex System 100 (CHF Solutions Brooklyn Park, MN, US) and Dedyca (Bellco, Mirandola, Emilia-Romagna, Italy)) have been specifically designed for extracorporeal ultrafiltration especially in patients with heart failure and fluid overload (Fig. 1). Such machines provide data on the circuit pressures allowing early detection of filter dysfunction and access-related issues. Furthermore, ultrafiltration rate is controlled volumetrically allowing a precise regulation of filtration fraction and net fluid loss from the patient. New technologies made possible to expand the spectrum of applications of extracorporeal ultrafiltration with a clearer definition of indications, criteria for initiation, and adequate prescription [18, 19]. Interesting experiments and clinical studies were carried out in the last decade when pediatric machines and wearable devices for ultrafiltration were successfully utilized in pediatric and adult patients with fluid overload resistant to diuretics [20, 21]. The advantage offered by reduced priming volume and low circuit flows/pressures, suggested that development of a simple, portable/wearable, battery-operated ultrafiltration equipment could represent the ideal solution to make extracorporeal ultrafiltration widely available and easily applicable in different clinical settings. These considerations led us to implement the new concept of "Artificial Diuresis" and the creation of the related device AD1 (Artificial Diuresis 1), the matter of description in this paper.

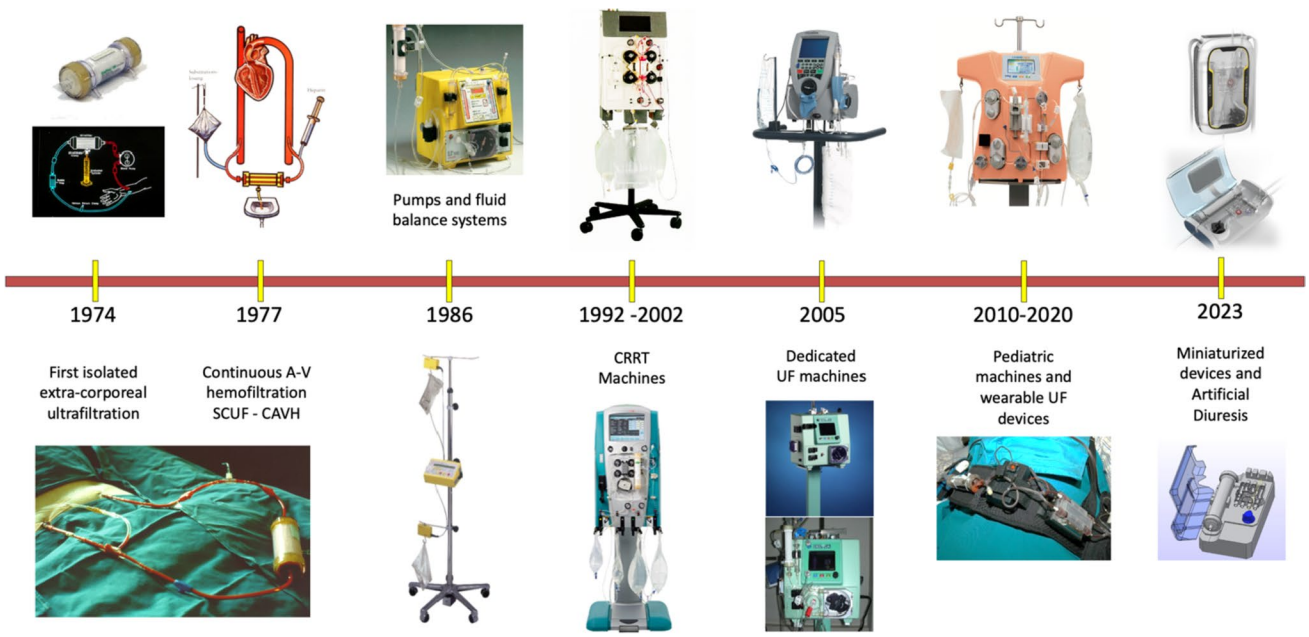

Fig. 1 Evolution of extracorporeal blood purification hardware. A-V indicates arterio-venous; CAVH, continuous arterio-venous hemofiltration; CRRT, continuous renal replacement therapy; SCUF, slow continuous ultrafiltration; and UF, ultrafiltration

First steps toward the future

First portable wearable devices

The first experimental animal studies with a portable device designed to perform continuous hemodialysis, the so-called wearable artificial kidney, were carried out in pigs at the beginning of the current century [22]. Twelve animals underwent an 8-h session, half of them with a blood flow of 44 mL/min and the other half with 75 mL/min. The filter had an area of 0.2 m^2, and the total device weight was 2.27 kg. Fluid removal rate could be scaled up to 700 mL/h, and the average rate was 100 mL/h [22].

A further step in wearable ultrafiltration equipment specifically designed for heart failure patients was achieved in 2006. Again, an experimental animal model with pigs backed up the device's suitability for human use [25]. The applicability of this proposed belt-worn hardware solely for ultrafiltration and not for hemodialysis enables a less intricate design and reduces the weight of the device to 1.135 kg. Nine pigs, weighing on average 57 kg completed an 8-h session of isolated ultrafiltration. The maximal fluid removal rate was 700 mL/h. The average fluid removal rate was 106 mL/h, and the average blood flow was 65 mL/min. Fluid removal was regulated by a volumetric pump or manually adjusted by partial or total occlusion of the tube downstream the ultrafiltration filter [25]. The principle of ultrafiltration relies on a pressure gradient between the blood and ultrafiltrate compartments. By increasing the resistance to the blood flow by compressing the downstream line of the filter, the hydrostatic pressure within the blood compartment increases along with the pressure gradient (i.e., blood minus ultrafiltrate compartment pressures) and thus the ultrafiltration rate.

The first human trial with this device intended for isolated ultrafiltration was carried out in our center (Fig. 2) [21]. However, previous studies with portable devices for maintenance hemodialysis were carried out, and they showed us that technical problems might become more evident for longer therapies (e.g., clotting circuit, battery life, and air sensor) [23, 24]. In our group, six patients on maintenance hemodialysis were recruited to execute a single session. These patients already had double-lumen catheters as long-term vascular access. In five patients, the session length was 6 h, and in one patient, it was 4 h. The ultrafiltration filter had a polysulfone membrane, displaying 2500 hollow fibers and a nominal area of 0.25 m^2. The device had one peristaltic pump to propel the blood and another two micropumps [26] to control heparin infusion and ultrafiltration rate. The fluid removal rate ranged from 120 to 288 mL/h (average 192 mL/h), and mean total fluid removed at session completion was 1084 mL. Mean blood flow was 116 mL/min, and the amount of sodium removed was 151 mmol. There were no changes in sodium or potassium plasma concentrations pre- versus posttreatment because ultrafiltration removes plasma water and electrolytes in the same proportion. As regards hardware performance, no issues were recorded. Additionally, no clinical complications were observed [21].

Fig. 2 Wearable hemofilter for continuous ambulatory ultrafiltration. Patient ambulates while carrying out the treatment. Adapted with permission from Kidney Int reference 21

Projects of wearable devices to execute peritoneal dialysis and peritoneal ultrafiltration have been envisioned to be utilized in patients already on maintenance peritoneal dialysis regimens. Of course, intrinsic complexities such as the need for a peritoneal dialysis catheter insertion are not comparable to the simplicity of peripheral vascular access in the case of extracorporeal ultrafiltration. Therefore, envisioned wearable devices for peritoneal dialysis are not a suitable tool to manage patients with acute decompensated heart failure or other acute congestive conditions and are out of the scope of this review [27–29]. In Table 1, a summary of studies with wearable devices for ultrafiltration is displayed.

Pathophysiology of congestion

The current literature uses the terms fluid accumulation and fluid overload interchangeably [30–32]. This condition results from the inability to manage the body's surplus of

Table 1 Summary of wearable ultrafiltration devices major studies

First author, year of publication, journal	Device/weight	Resemblance	Purpose	Design	• Mean blood flow (Q_B) • Mean ultrafiltration rate (Q_{UF}) • Treatment duration
Gura, 2005, Contrib Nephrol	Wearable artificial kidney (WAK)/ 2.3 kg	Belt	Hemodialysis and ultrafiltration	Experimental (in vivo), 12 pigs	• Q_B 44 or 75 mL/min • Q_{UF} 100 mL/h • 8 h
Gura, 2006, ASAIO J	Wearable continuous ultrafiltration system/1.1 kg	Belt	Isolated ultrafiltration	Experimental (in vivo), 9 pigs	• Q_B 65 mL/min • Q_{UF} 106 mL/h • 8 h
Davenport, 2007, Lancet	Weatable artificial kidney (WAK)/5 kg	Belt	Hemodialysis and ultrafiltration	Clinical trial, one group design, $n=8$	• Q_B 59 mL/min • Q_{UF} 200 mL/h • 4 h
Ronco, 2007, Blood Purif	Vicenza Wearable Artificial Kidney for Peritoneal Dialysis (ViWAK PD)/0.2 kg	Belt	Peritoneal dialysis and ultrafiltration	In vitro	Not applicable
Gura, 2008, Kidney Int	Wearable hemofilter for continuous ambulatory ultrafiltration	Belt	Isolated ultrafiltration	Clinical trial, one group design, $n=6$	• Q_B 116 mL/min • Q_{UF} 192 mL/h • 6 h
Ronco, 2015, Blood Purif	Wearable/portable ultrafiltration system (WAKMAN)	Jacket	Hemodialysis and ultrafiltration	In silico	Not applicable
Gura, 2016, JCI Insight	Wearable artificial kidney (WAK)/5 kg	Belt	Hemodialysis and ultrafiltration	Clinical trial, one group design, $n=7$	• Q_B 42 mL/min • Q_{UF} 42 mL/h • 24 h
Ronco, 2023	Artificial Diuresis 1 (AD-1)/1.135 kg	Tablet case	Isolated ultrafiltration	In vitro, saline 0.9%, bovine blood, and human whole blood	• Q_B 20, 35, 50 mL/min • Q_{UF} 480 mL/h (Q_B 50 mL/min and water column 20 cm • Q_{UF} 660 mL/h (Q_B 50 mL/min and water column 40 cm) • Q_{UF} 750 mL/h (Q_B 50 mL/min and water column 60 cm)
Ronco, 2023	Artificial Diuresis 1 (AD-1)/1.135 kg	Tablet case	Isolated ultrafiltration	Experimental (in vivo), 3 pigs	• Q_B 30 mL/min • Q_{UF} 230 mL/h • 6 h
Ronco, 2023, ongoing	Artificial Diuresis 1 (AD-1)/1.135 kg	Tablet case	Isolated ultrafiltration	Clinical trial, open-label, randomized, crossover, $n=12$, AD-1 versus standard CRRT machine	• Q_B 50 mL/min • Q_{UF} variable • 12 h

CRRT continuous renal replacement therapy

water and sodium. Therefore, congestion is a broad clinical phenotype in which the retention of fluids is the cornerstone for its diagnosis. The assessment of congestion is based on physical examination [33], currently enhanced by ultrasonography [34, 35], biomarkers (e.g., natriuretic peptides) [36], imaging techniques, and invasive monitoring [37]. In addition, as nearly as 80% of the patients admitted to the hospital during an episode of acute heart failure present signs and symptoms of congestion [38]. Acute heart failure is mainly precipitated by acute coronary syndromes, atrial fibrillation, infections, hypertensive crisis, and poor patient adherence to dietary and pharmacological prescriptions [39]. A current approach is to subphenotype patients with congestion into those predominantly with intravascular congestion (i.e., hypertension, distended jugular veins, and turgid inferior vena cava) or predominantly with tissue congestion (i.e., pitting edema, ascites, and pleural effusion) [33]. Irrespective of the subphenotype, fluid removal is indicated, albeit the fluid removal rate should be lower in patients with the tissue congestion phenotype to reduce the risk of hypotension secondary to intravascular fluid depletion. Finally, congestion may lead to impairment and dysfunction in many

organs. Organ perfusion depends on the difference between mean arterial pressure minus central venous pressure. In patients with congestion, the latter is increased, reducing perfusion pressure to the tissues [40].

The basics of ultrafiltration

Ultrafiltration is a mechanism of plasma water and crystalloid transfer (devoid of colloids or cells) across a semipermeable membrane. This process depends on a transmembrane pressure gradient, which is the result of hydrostatic pressure of blood subtracted by the blood oncotic pressure and by the hydrostatic pressure in the ultrafiltrate compartment [41–43]. The transmembrane pressure gradient can be augmented by either increasing the positive hydrostatic pressure in the blood compartment or by generating a negative pressure in the ultrafiltrate compartment.

Pathophysiology of ultrafiltration and treatment monitoring

The mechanisms involved in the process of extracorporeal fluid removal are complex [14]. It is important to understand them as well as to provide accurate monitoring of the patient during treatment. Patient hydration status should be carefully determined, and prescriptions should be made accordingly. Indications and objectives of the therapy should be clearly defined such as the overall amount of fluid to be removed within a time window [44]. Furthermore, treatment modality and parameters to achieve desired results should be decided: single or multiple sessions, frequency, duration of each session, blood flow, anticoagulation, and ultrafiltration rate within each session. During treatment, circuit pressures, fluid removal (total volume and removal rate), filter patency, and access function should be monitored [45]. At the same time, clinical parameters such as patient's blood pressure, heart rate, and coagulation status should be carefully recorded and evaluated [46].

Fluid overload status can be monitored with repeated measurement of bioelectrical impedance and body weight [47], while biomarkers such as natriuretic peptides may represent an important additional information. Brain natriuretic peptide (BNP), a hormone, and its precursor N-terminal proBNP (prohormone) [36] levels at admission and after ultrafiltration represent useful tools to define dry and wet values. A significant decrease after treatment (BNP < 250 pg/mL) correlates with outcomes such as event-free survival [18, 48]. However, in cases of kidney dysfunction, the exact relationship between BNP and the severity of heart failure remain to be clarified [48].

Acute kidney injury (AKI) may occur due to excessive or too fast ultrafiltration. In this situation, AKI is secondary to kidney hypoperfusion [49]. While this can be detected by a rise in serum creatinine, new AKI urinary biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) and the product of tissue inhibitor of metalloproteinases-2 with insulin-like growth factor-binding protein 7, [TIMP-2]•[IFGBP7], can help to make and early diagnosis of kidney stress or damage [50–53]. Total ultrafiltration and ultrafiltration rate can be modulated based on biomarkers trend [54]. Increment in serum creatinine, even if above 0.3 mg/dL, may only represent a condition of hemoconcentration rather than a kidney injury if the concentration of urinary biomarkers remains unchanged. It has been demonstrated that during decongestive treatments with diuretics, the rise in serum creatinine is not associated with worse renal outcomes, reassuring that this trend is a consequence of hemoconcentration [9].

The removal of ultrafiltrate from blood leads to a temporary hemoconcentration with an increase in hematocrit and protein concentration. This condition normally leads to a progressive water transfer from the extravascular space, and even from the intracellular compartment, into the vascular compartment due to oncotic forces. This process, defined as intravascular refilling, may be insufficient in case of cardiac dysfunction or it may be too slow in case of rapid fluid removal. In both situations, intravascular blood volume decreases with a progressive increase in heart rate, volume-dependent hypotension, and general hemodynamic instability [55, 56]. To avoid significant intravascular volume depletion, blood volume sensors were developed based on relative hematocrit variations during treatment. The alarm of hemoconcentration (or blood volume variation) can be set to a given percentual threshold, generally between 7 and 10%, to allow activation of specific feedback interventions (e.g., reduction or stopping of ultrafiltration rate, increment in vasopressor dose) and to make ultrafiltration therapy safer and well tolerated [57]. This allows individualization of the ultrafiltration rate based on the patient's capacity for intravascular refilling. Hemodynamic instability (i.e., intraprocedural hypotension) may also occur when an excessive amount of fluid is removed from the patient, and in this case, clinical signs and symptoms are generally associated with a substantial variation of the bioelectrical impedance parameters. It is therefore quintessential to establish a target patient's dry weight. In very slow ultrafiltration rates, blood volume sensors are generally less useful and unnecessary. The physician will decide the frequency of sessions, the number of sessions, and the duration of each session based on patient's characteristics which may change over time. Ultrafiltration rates varying from 150 to 300 mL/h are generally planned in long daily treatment (6 to 8-h sessions) in fluid overload patients which avoids inducing intravascular volume depletion. A rapid fluid removal in a short session (e.g., 1000 mL/h) may be indicated in a patient with acute pulmonary edema to resolve pulmonary congestion

and symptoms. However, the subsequent sessions are better planned with slow fluid removal to achieve the predefined dry body weight. Continuous 24-h sessions are generally prescribed in the intensive care unit for oliguric (i.e., urine output < 0.5 mL/kg/h) [58] patients usually receiving large amounts of fluids for different purposes like administration of sedatives, vasopressors, neuromuscular blocking agents, parenteral nutrition, and antibiotics [59]. The goal of extracorporeal ultrafiltration in these patients is to achieve an even or slightly negative daily fluid balance. The removal of plasma water by ultrafiltration implies a parallel removal of sodium. In the case of free water intake or low sodium infusions, the sodium pool in the patient may be reduced, thus reducing the trend toward fluid retention. This phenomenon can be planned by prescribing complex treatments such as hemodialysis or hemofiltration where sodium and water removal can be dissociated [60].

Clinical experience of ultrafiltration in acute heart failure

Retrospective [61] and single-arm pilot studies had favorable results for patients that underwent ultrafiltration [62]. These exploratory studies were the starting point for confirmatory trials. In the early 2000s, the use of ultrafiltration devices gained traction and prompted the conceptualization and execution of four major randomized controlled trials [63–66]. In brief, the trials had debatable designs, conflicting results, and one was prematurely terminated due to lack of funds [66]. Of utmost relevance, these four randomized controlled trials had different primary outcomes, namely, weight loss and dyspnea (Fig. 3A) [63], 96-h change in serum creatinine and weight loss (Fig. 3B) [64], rehospitalizations during 1-year follow-up (Fig. 3C) [65], and time to first heart failure event during 90 days following hospital discharge (Fig. 3D) [66]. This diversity in the primary endpoints complicates the comparison between these studies.

Nonetheless, praiseworthy approaches deserve to be mentioned. Specifically, a tailored ultrafiltration regimen was applied in the CUORE trial under the guidance of continuous hematocrit assessment because hemoconcentration correlates with inadequate fluid efflux from the interstitial compartment toward the blood compartment [65]. As already mentioned, in these situations, patients with depleted intravascular volume are prone to present hypotension. Therefore, hemoconcentration prompted the investigators to reduce the ultrafiltration rate, reducing the chance of hypotension. In contrast, when the hematocrit remained steady, this reinforced that the pace of ultrafiltration was adequate or even should be increased [65].

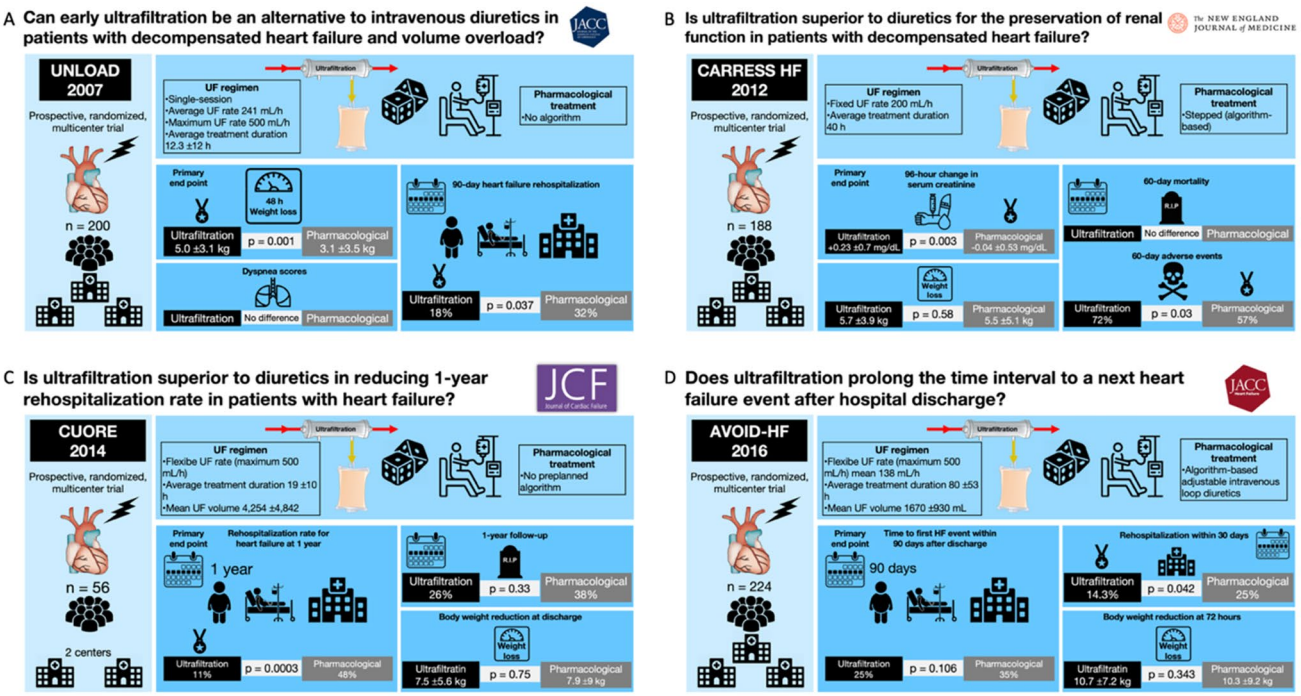

Fig. 3 Visual description of the four major randomized controlled trials to investigate efficacy and safety of extracorporeal blood purification. On the top of the figures, the research question is displayed and the journal in which the study was published. Methods, design, and results are showed in the other boxes. **A** UNLOAD trial. **B** CARRESS HF trial. **C** CUORE trial. **D** AVOID-DF trial. Reproduced with permission from Karger

On the contrary, in the CARRES-HF trial, the researchers confronted isolated ultrafiltration against diuretic therapy as competing rather than adjunctive therapies. Additionally, the fluid removal rate was fixed at 200 mL/h in the ultrafiltration arm [64]. In routine clinical practice, as already mentioned, a dynamic prescription is required. Such comparison including a fixed ultrafiltration rate precludes the generalizability of the study findings into real-world scenarios. Moreover, the ultrafiltration rate should ideally be adjusted to the patient's body weight because intravascular refilling rate and total body water volume depend on body weight. In-depth reviews of these trials have been published elsewhere [46, 67–69]. In summary, these trials were not able to answer clinical conundrums.

The latest guidelines of the European Society of Cardiology, published in 2021, considered ultrafiltration as a rescue therapy [70]. The treatment should be considered in patients with acute or chronic heart failure manifesting refractory volume overload unresponsive to diuretics. For this statement, the class of recommendation was IIb, and the level of evidence was C.

Moving toward the future with Artificial Diuresis

Rationale for Artificial Diuresis and new technology

The management of fluid overload relies on restrictive dietary intake, forced pharmacological diuresis, and extracorporeal ultrafiltration. The last requires complex machinery and trained nurses. Previous disappointing results in ultrafiltration trials discussed above might be correlated, at least in part, to the complexity of the techniques [68]. Therefore, there is an emerging demand for new extracorporeal ultrafiltration technology to provide safe and effective fluid removal with a simpler and easier modality. We have analyzed the problem and came up with the rationale for creation of a miniaturized device able to provide soft extracorporeal ultrafiltration that will meet the needs of simplicity, safety, and sustainability. Moreover, this device will likely enable the self-administration of the therapy. Such hardware could represent a quantum leap in managing fluid overload, and we branded this combination of technology and modality as "Artificial Diuresis."

Several aspects support the project and deserve to be listed:

(a) Clinical demand: fluid overload increases the risk of major adverse cardiovascular events (MACE) and mortality [71, 72]. When diuretics fail, extracorporeal ultrafiltration is recommended [62, 70, 73]. However, various techniques of ultrafiltration may present complications due to excessive or too rapid fluid removal [18, 74]. This provides the rationale for a system capable to generate slow and gentle ultrafiltration at a rate similar to physiological diuresis (Artificial Diuresis). This approach may be used not only for rescue treatments but also for long-term repeated elective treatments. For this, a change in physician mentality is also required.

(b) Technical demand: current technology for ultrafiltration is represented by rather complex machines derived from the experience of hemodialysis. They are bulky, and their design is old-fashioned requiring well-trained personnel, specialized environment, and large bore catheters. Thus, the rationale for a smaller, simpler, easy-to-use device in clinical routine emerges clearly. Advances in technology may help to incorporate new miniaturized elements in the circuit, which should have an ergonomic design and smaller dimensions. Ideally, the equipment should be able to handle reduced (i.e., less than 60 mL/min) blood flows to allow the therapy execution via peripheral vessel cannulation.

(c) Logistic and organization: there is shortage of personnel and space in the hospital and the Artificial Diuresis project could respond to several unmet needs. Small hardware dimensions and battery-operated pumps could allow for use in different settings. Pre-assembled, low volume disposable circuits might offer safety and simplicity of operations. User-friendly software interface could allow for self-administration of the therapy by the patient and easy troubleshooting. Its application could be extended to outpatient environments including patient's home.

(d) Demand for sustainable therapeutic programs: the economic burden of chronic illness such as heart and kidney failure represent a challenge for health care providers. The cost of hospitalization for decompensated heart failure is progressively increasing [2]. The use of a small and simple system for periodic fluid removal could reduce hospitalizations, complications, and ultimately, related costs. The possibility of home-based, self-administered treatments may significantly reduce the financial commitment of society. Furthermore, the development of miniaturized and portable technology might allow for clinical application of Artificial Diuresis in low-income countries.

(e) Ethical rationale: the commitment of the scientific community to improve patient's quality of life should be as strong and effective as that of improving morbidity and mortality [75, 76]. Patients may in fact reconcile their disease with their capacity for human relations and possibility to live as normal as possible social lives.

Potential applications and indications for Artificial Diuresis

The multi-faceted rationale of this project suggests its possible utility in different clinical settings outlined here: (a) acute heart failure to achieve optimal management of fluid overload; (b)

Table 2 Technical specifications of AD1 device

Feature	Description
External dimensions	Length 225 mm; width 135 mm; height 90 mm
Weight	1.135 kg
Filter priming volume	~15 mL
Blood flow (Q_B) range	5–60 mL/min (roller blood pump)
Ultrafiltration flow (Q_{UF}) range	2–5 mL/min
Arterial access pressure range	−100 to +100 mmHg
Venous access pressure range	−50 to +200 mmHg
Ultrafiltration flow meter accuracy	Delivered dose/prescribed dose ± 10%
Air sensor	Detects bubbles ≥ 0.05 mL
Maximal treatment duration	Disposable set → 24 h
Battery	Rechargeable, autonomy of 6 to 10 h depending on the speed pump; replaceable during ongoing therapy lithium-ion
User interface	Graphic; monochromatic display 128 × 64 pixels; membrane keyboard with 5 keys → (a) power on/off—confirm; (b) start/stop pump—confirm speed pump; (c) speed increase; (d) speed decrease; (e) reset alarm/battery replacement
Motion detector	3-axis accelerometer to detect movements thus preventing false alarms
Internal memory	2 GB microSD card; not accessible from the outside; used to store treatment log
Bluetooth® connectivity	Bluetooth® low energy (BLE) 5.0 with integrated antenna
Needle detachment sensor	Optical sensor plugged into a disposable tape stuck to the needle

AD1 Artificial Diuresis 1, *SD* secure digital

critical illness where management of the fluid balance is fundamental but often difficult; (c) kidney transplant recipients with oliguria due to delayed allograft function; (d) patients on extracorporeal membrane oxygenation (ECMO) to maintain fluid balance during or after the treatment; (e) edematous conditions including nephrotic syndrome, liver cirrhosis with ascites, and chronic heart failure; in addition, periodic scheduled ultrafiltration sessions in such conditions may reduce symptoms and rehospitalizations; (f) fluid overload in pediatric patients because the miniaturized nature of the device represents an outstanding opportunity for small-sized patients; (g) management of fluid overload in hemodialysis and peritoneal dialysis patients where adequate balance cannot be achieved during standard sessions; and (h) home-based treatment of fluid overload. The simplicity of the device could represent a doorway for the expansion of extracorporeal ultrafiltration therapy in general.

Artificial Diuresis project development

In silico

Requisite components and structure

The principle behind any development in the biomedical field must be patient safety and proven real benefit for the patient. In extracorporeal ultrafiltration, low flows/pressures and balance accuracy are quintessential to minimize side effects and symptoms. We decided in conjunction with Medica S.p.A. (Medolla, Emilia-Romagna, Italy) to undertake a project called "Artificial Diuresis 1 (AD1)": development of a new portable/wearable miniaturized device designed to perform extracorporeal ultrafiltration in multiple clinical settings. Other requisites were simple handling, compact structure, safe operations and adequate alarms, portable/wearable, and battery-powered miniaturized hardware (Table 2); moreover, the possibility to use peripheral vascular access, easy exchange of disposable circuits, easy operator interface, easy troubleshooting with immediate recognition of alarm cause, easy cleaning, and disinfection of the hardware. An initial drawing reported in Fig. 4 clearly describes the intended portability and wearability of the device. We established the number of safety controls and sensors to make the system comparable in terms of operations to standard equipment for ultrafiltration.

From there, we moved to prototype development. The motor of the rotary blood pump dictated the dimensions of the final device. We dimensionally adjusted all other components to achieve a minimum size and weight.

Device description and operations

The AD1 prototype system whose details are reported in Fig. 5 and Supplementary Fig. 1 features a hardware component with a polycarbonate case containing the electromechanical elements (pump with rotor and stator, pressure

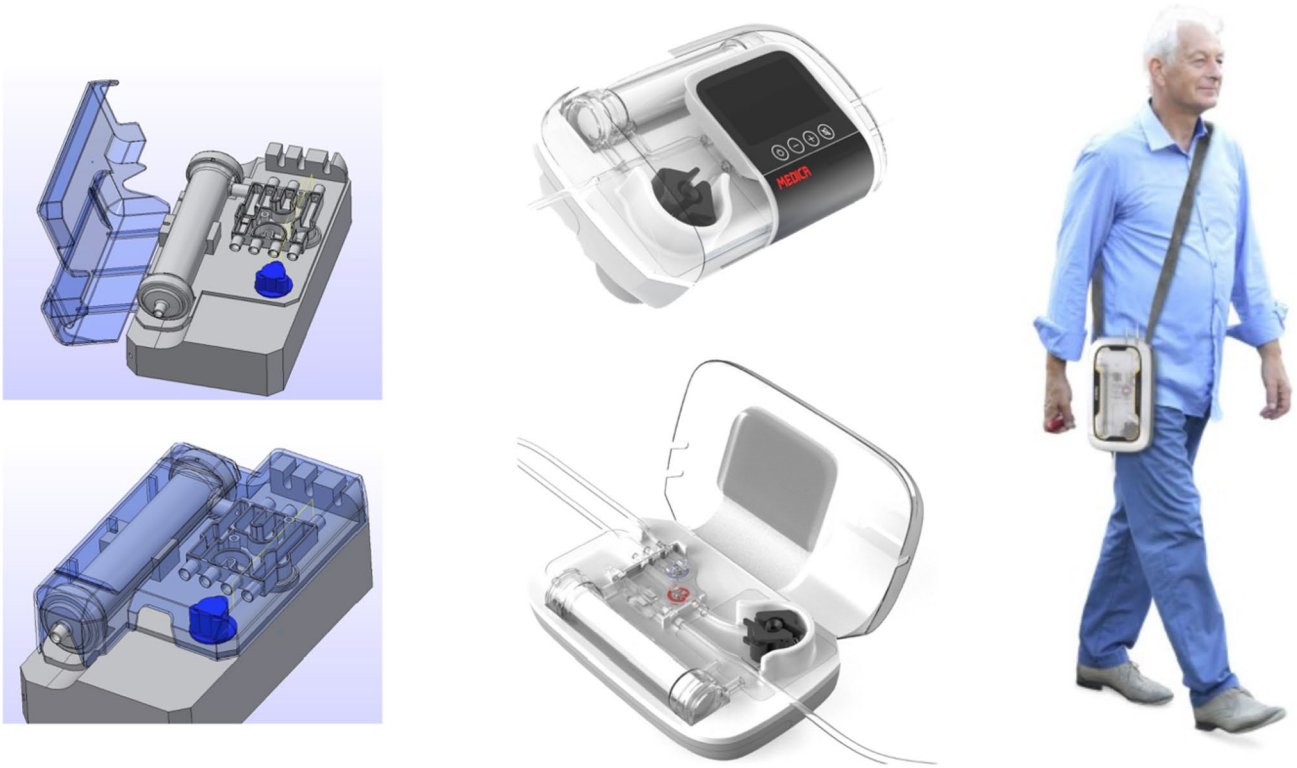

Fig. 4 Graphic representation of the concept design for a miniaturized portable/wearable ultrafiltration equipment as we proposed to the development team. From the original drawing, we moved to a professional 3D model and a visual representation of the possible utilization in a wearable modality

transducers, optical sensors, display, electronic circuits, and software). The device weighs 1.135 kg with the battery and measures 225 × 135 × 90 mm. The disposable is a closed, sterilized, saline-primed circuit with a hollow fiber polysulfone filter, tubing, pressure sensors, flow sensors, and air and blood leak detector fully incorporated. Heparin is used as an anticoagulant with intermittent bolus administration unless the patient is already on anticoagulation therapy. A backflush port in the inlet line is available for periodic lavages to avoid stagnation or membrane fouling in the blood compartment.

Ultrafiltration occurs spontaneously, and the ultrafiltrate column between the filter port and the collection bag generates transmembrane pressure. In the previous portable ultrafiltration devices, ultrafiltration was produced thanks to an increase of hydrostatic pressure in the blood compartment. In AD1 device, the pressure gradient is governed by the position of the collection bag (negative pressure is generated by the height of the ultrafiltrate column, eliminating the need of an additional pump). AD1 performs continuous ultrafiltration operating at low blood flows of 60 mL/min or less. This can be achieved with a thin double-lumen catheter [e.g., 2.2 mm (6.5 Fr)] and low-pressure regimens (gravity). This simplifies the treatment, and the operator just needs to set the blood flow on the membrane keyboard and the position of the ultrafiltrate collecting bag. The keyboard allows the operator to turn the device on and off, reset or silence alarms, and change the speed of the blood pump. The central unit integrates a microSD card to collect all the data of the processing logs. The device transfers data wirelessly via Bluetooth®. In case of a pressure or air detection alarm, the blood pump stops immediately. Ultrafiltration rates are between 1 and 5 mL/min, (i.e., 60 to 300 mL/h) with extremely low risk of technical and clinical complications. In Fig. 5, we report a visual description of the hardware and the disposable, while in Supplementary Fig. 1, the details of the circuit and the relevant sensors are reported.

The disposable cassette consists of a monitored circuit tightly attached to the hemofilter that includes the lines from and to the patient. The cassette integrates an ultrafiltration flow sensor that monitors the ultrafiltration rate and the cumulative ultrafiltration volume removed since the beginning of each treatment. A graduated ultrafiltrate collection bag is connected to the ultrafiltration line so that the operator can read the removed volume without accessing the display.

The transmembrane pressure that produces ultrafiltration depends on the position of the ultrafiltrate collection bag. The lower the bag, the higher the negative pressure on the ultrafiltrate compartment. Thus, the hydrostatic pressure gradient

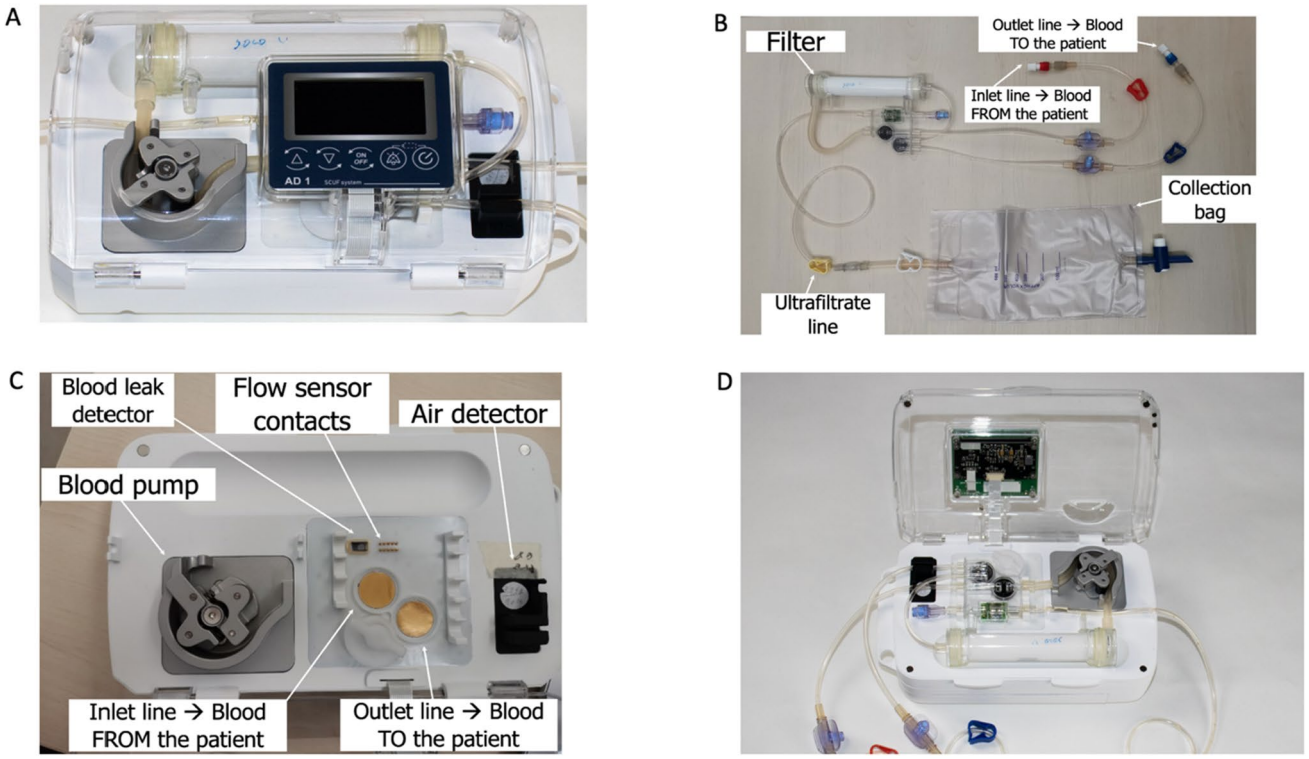

Fig. 5 The actual AD1 system. **A** External case containing all hardware components. The membrane keyboard is placed on the polycarbonate cover for easy operations. The screen displays the speed of the blood pump, the ultrafiltration rate, the cumulative weight of the ultrafiltrate removed, the access and return line pressure, the battery charge, and the duration of the treatment. In case of an alarm (audible signal according to medical regulations), the type of problem is displayed on the screen. Depending on the alarm type (high or low priority), the treatment may be interrupted automatically (e.g., pressure or air detection alarm). The information can be transferred via Bluetooth® to other smart devices. At the same time, prescription changes can easily be made via the membrane keyboard. **B** Disposable circuit. **C** Hardware with the open cover is ready to receive the circuit cassette. The peristaltic pump (4.3 × 6.8 mm) permits a blood flow from 5 to 60 mL/min, with 5 mL/min increments. The sensors are clearly visible. The air sensor detects bubbles larger than 0.05 mL while the optical blood sensor can detect free hemoglobin concentrations up to 1% in the ultrafiltrate line. The blood flow sensor integrates the pressure sensors that couple with the membrane on the cassette. The access and return pressures are visible on the display. This coupling system between the membrane allows detection of the suction and return pressures without exposure of blood to air. **D** Circuit cassette with filter, lines, and membrane pressure transducers are in place within the specific compartments inside the hardware. The total priming volume of the whole circuit (including the hemofilter) is 15 mL. Reproduced with permission from Karger

between the ultrafiltrate compartment and blood compartment (i.e., transmembrane pressure) will increase and, consequently, the ultrafiltration rate. The polysulfone filter has a surface area of 0.15 m^2, a priming volume of 10 mL, and an ultrafiltration coefficient of 3 mL/h/mm Hg. It is connected to the cassette, which is pre-filled with sterile isotonic saline solution making the priming procedure easy and safe. When the pump starts, the system collects approximately 20 mL of blood from the patient simultaneously pushing the isotonic solution into a waste system. After completion of this phase, the actual treatment begins. Every step, including battery status, is monitored at 1-s intervals.

In vitro experiment

The experiment was carried out in the facilities of the "Fondazione International Renal Research Institute of Vicenza–IRRIV," to evaluate the performance of the AD1 in different situations [77]. The variables tested were as follows:

a) Different access devices, namely, no specific access (directly placing venous and arterial lines in the blood), a 7-Fr pediatric central venous catheter (16 cm length); 10 Fr (70 cm length), or-12 Fr (24 cm length) double lumen hemodialysis catheters
b) Three defined blood flows of 20, 35, and 50 mL/min
c) Placement of the collection bag vertically downward in respect to the device's position, namely, at 20, 40, or 60 cm below the device

AD1 was integrated into a closed loop circuit primed with citrate-anticoagulated human blood, hematocrit 31%, and total volume of 320 mL. Blood was placed in a reservoir in

which the tip of a double-lumen catheter was inserted or the arterial (inlet) and venous (outlet) blood lines of the circuit were directly inserted. The ultrafiltrate line was connected to the collection bags (Fig. 6). In addition, unfractionated heparin was added (25,000 IU) in the circuit.

The connection of the circuit with an external meter via "T" fittings allowed the measurement of ultrafiltrate flow, arterial (inlet) and venous (outlet) pressures. During all the experiment steps, the ultrafiltrate generated was returned to the circuit, and 20 mL of isotonic saline was used to backflush AD1 circuit.

For each set, all the measurements were carried out with combinations of blood access (catheter diameter), height of the hydrostatic column (20 cm, 40 cm, and 60 cm), and blood flow (20, 35, and 50 mL/min). An exception occurred for the 7-Fr catheter, in which the measurements were taken exclusively with a blood flow of 20 mL/min. The resulting ultrafiltration flow is represented in Fig. 7.

Ultrafiltration flows were directly proportional to catheter diameter, blood flow, and hydrostatic column extension (Supplementary Fig. 2A). The results of the arterial (inlet) and venous (outlet) lines pressures are depicted in

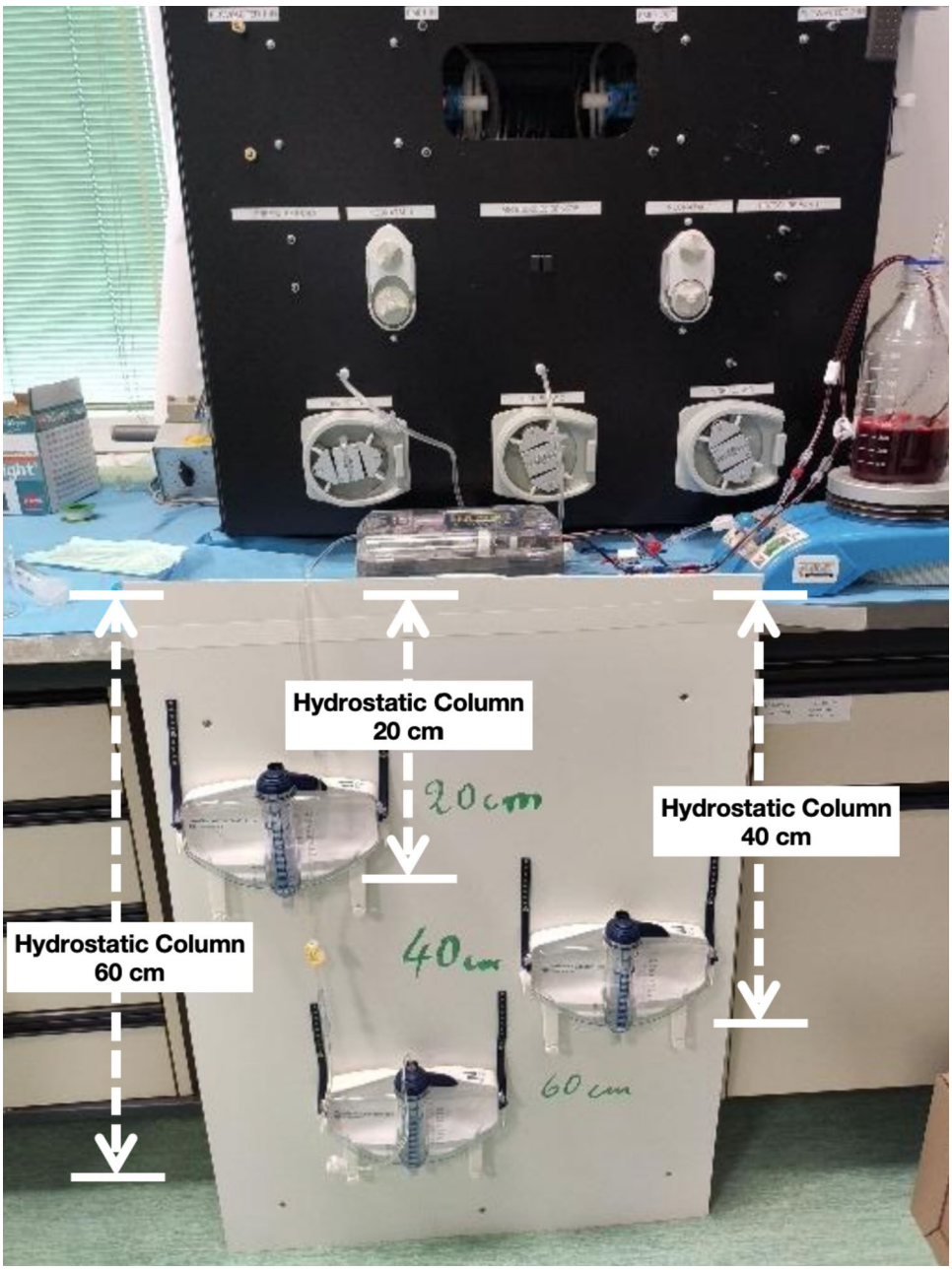

Fig. 6 In vitro experimental study settings. AD1 device arterial and venous lines are connected to a double lumen catheter. The tip of the catheter is placed in the blood contained in the reservoir (left). AD1 is shown in the center of the picture. Three graduated collection bags, originally purposed for urine output measurements, displayed marks corresponding to 10-mL increments. The ultrafiltrate line was connected to the collection bag placed 60 cm below AD1. The other two collection bags were placed vertically below 20 and 40 cm from AD1. The reservoir was sitting on a magnetic stirrer 10 cm above AD1, blood temperature was kept at 37 °C. Reproduced with permission from Karger. AD1 indicates Artificial Diuresis 1

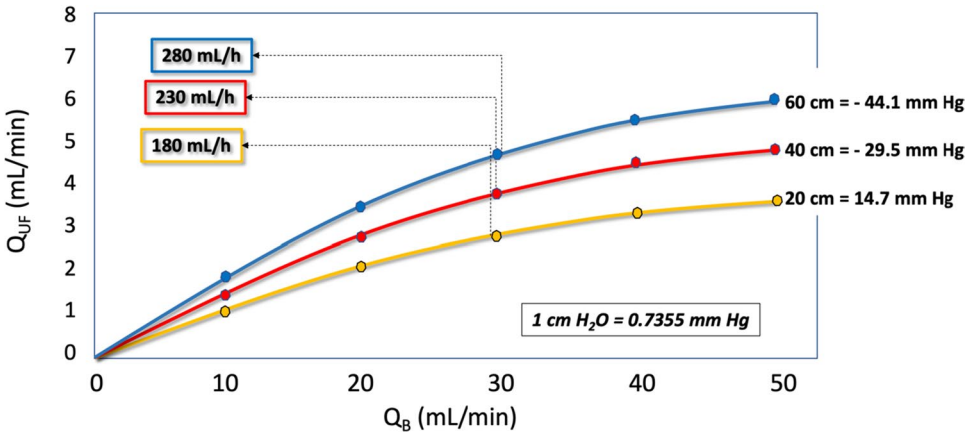

Fig. 7 Estimation of ultrafiltration flow. In this graphic, the two independent variables, which are blood flow and height of the hydrostatic column, will define the ultrafiltration flow (dependent variable). Q_B is displayed in the *x*-axis, and each of the colored curves represents a different blood flow. Q_{UF} is displayed in the *y*-axis. Reproduced with permission from Karger. Q_B indicates blood flow; Q_{UF}, ultrafiltration flow

Supplementary Fig. 2B. No technical problems and leakages were observed during the procedures.

In vivo animal studies

After encouraging and consistent results obtained in the in vitro experiment, we proceeded to animal experiments [78]. The animals were 1-year-old male pigs with a weight ranging from 48 to 54 kg and each animal underwent a single ultrafiltration session.

After general anesthesia, left jugular vein was isolated, and an incision was performed as the entry site for inserting an 11.5-Fr double-lumen catheter. After catheter placement, a bolus of intravenous unfractionated heparin (2000 IU) was administered followed by a continuous intravenous infusion of unfractionated heparin (6000 IU) delivered at 20 IU/kg/h.

Blood flow was 30 mL/min, the collection bag was positioned vertically 20 cm below the device, and the estimated removal rate was expected to range from 3 to 5 mL/min (i.e., 180 to 300 mL/h). Blood samples were collected for biochemical analysis in the following sequence at four-time points: before the experiment, after 2, 4, and 6 h of treatment.

Pigs underwent a single 6-h ultrafiltration session (Supplementary Fig. 3). No intraprocedural hypotension episodes were recorded. Other clinical parameters such as heart rate, peripheral oxygen saturation, end-tidal CO_2, and body weight were not altered in a clinically meaningful manner. Biochemical analysis including electrolyte concentrations remained unchanged, and there were no bleeding events. During one of the procedures, an additional intravenous bolus (100 IU/kg) was empirically administered because of initial signs of filter clotting. Mean total fluid removed after the 6-h session varied between 1200 and 1600 mL (Fig. 8A). The maximum variation between the ultrafiltration dose prescribed confronted to the delivered dose was less than 10% in all procedures (Fig. 8B).

Human study protocol

After successful in silico simulations and in vitro and in vivo animal experiments, exploratory human studies can be planned [79]. This is the traditional pipeline for the

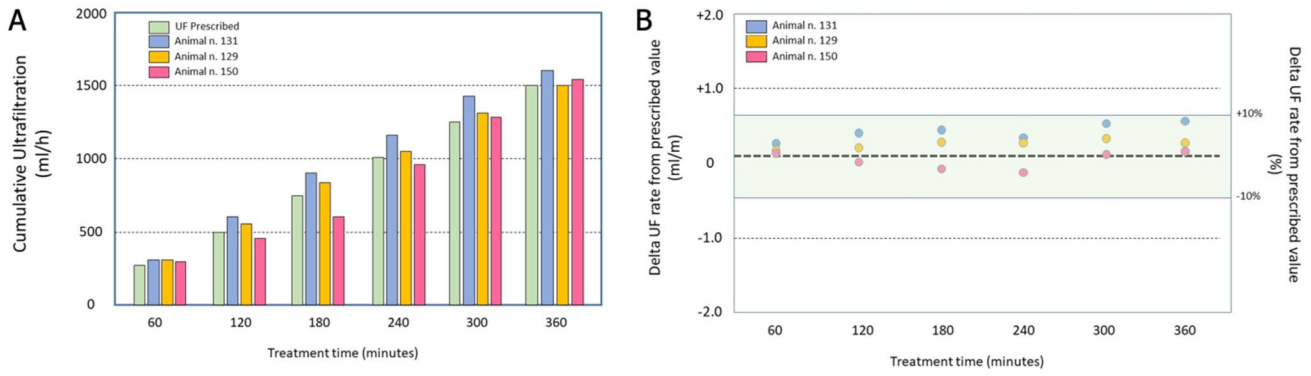

Fig. 8 **A** Cumulative ultrafiltration volume. **B** Percentual variation between prescribed versus delivered ultrafiltration rate. Reproduced with permission from Karger. UF indicates ultrafiltration

development of clinical devices. Our center has proposed and submitted to regulatory approval a single-center, crossover, randomized, open-label, pilot study to assess the safety and efficacy of AD1 (Medica S.p.A., Medolla, Emilia-Romagna, Italy) in comparison with a standard continuous renal replacement therapy machine (PrisMaX, Baxter Healthcare Corporation, Deerfield, Illinois, USA). The latter can perform continuous isolated ultrafiltration. The main goal is to analyze safety events during the treatment of isolated ultrafiltration in patients with fluid overload. This trial will not have pre-defined run-in or washout phases. Each patient will perform only one treatment with either machine. Patients will be recruited from the Department of Nephrology, Dialysis, and Kidney Transplant and the Department of Critical Care at San Bortolo Hospital, Vicenza, Veneto, Italy.

Eligibility criteria:

1. Both genders
2. Established chronic kidney disease G5D patients on maintenance hemodialysis for at least 12 weeks, carrying out in-center sessions, presenting with at least 2.5 kg body weight in excess of predefined adequate body weight (dry weight)
3. Established chronic kidney disease G5D patients on maintenance hemodialysis for at least 12 weeks, hospitalized in the intensive care unit, and carrying out sessions in this unit, presenting with at least 2.5 kg body weight in excess of predefined adequate body weight (dry weight)
4. Intensive care unit patients presenting acute kidney injury stage 3D (requiring hemodialysis), in whom fluid overload is detected, and extracorporeal ultrafiltration is indicated according to the attending physician evaluation
5. Aged over 18 years

Exclusion criteria:

1. Planned renal transplant within the study intervention period
2. Planned conversion to peritoneal dialysis or transfer to another center
3. Pregnancy or breastfeeding
4. Indication for hemodialysis, hemodiafiltration, or hemoadsorption according to the attending physician
5. Patients with current infection by human immunodeficiency virus, hepatitis B, hepatitis C, or SARS-CoV-2
6. Impossibility of the patient or the next of kin to provide informed consent

For patients carrying out in-center regimens, isolated ultrafiltration sessions will have a duration from 4 to 6 h, and the total fluid removal will range from 500 to 1500 mL, tailored by the treatment goals. For intensive care unit patients, the duration of sessions will vary from 6 to 12 h and total ultrafiltration volume will range from 1000 to 1200, according to the clinical need. Systemic anticoagulation might be provided in the absence of contraindications. For patients already receiving anticoagulants, no anticoagulation for the therapy will be used. After randomization, patients will be assigned to initiate a therapy with one of the machines, and the second therapy will be carried out with the other machine.

We defined primary safety outcomes to include the incidence of clinical events such as intraprocedural hypotension, air embolism, bleeding events, hemolysis, hypothermia, electrolyte imbalance, anaphylactoid reactions, and circuit clotting. Furthermore, primary efficacy outcome will be the percentual variation between prescribed versus delivered total ultrafiltration volume.

We planned to analyze other safety outcomes including of clinical events such as cramps, nausea, vomiting, headache, fever, chills, chest pain, and pruritus. Secondary efficacy outcome will be the measurement of user-friendliness and technical complications. We will assess these efficacy endpoints by completing a satisfaction questionnaire by patients and nurses who use the device and measuring technical issues requiring nurse intervention (troubleshooting). We plan to recruit 15 patients [80–82].

If safety and efficacy outcomes are achieved, next, we must evaluate the profile of patients with heart failure refractory to diuretics. Subsequently, researchers in the field of cardiorenal medicine and intensive care will certainly be encouraged to carry out randomized controlled trials. We believe this is a groundbreaking and innovative investigation, justifying the application of human and financial resources to this project. The long-term goal will be to assess the beneficial adjuvant effects of a miniaturized portable device associated with diuretics to improve the management of fluid-overloaded patients in acute and chronic settings.

Conclusion

There is an increased challenge to manage patients with fluid overload and frequent hospitalizations due to congestion. These conditions with highly negative clinical outcomes represent a burden for health care systems. Extracorporeal ultrafiltration represents an exceptional tool to manage congested patients when fluid intake restriction and/or diuretics fail. At the same time, ultrafiltration can be an additional treatment in patients undergoing chronic renal replacement therapy when adequate fluid balance cannot be achieved. Finally, ultrafiltration could be managed outside intensive care departments if adequate training of the personnel and simplified technology are provided. Along these lines, the development of the miniaturized, simple, and easy-to-use equipment AD1 seems to respond to several unmet technical and clinical needs. The rationale for the project and the results achieved in vitro

and in animals are presented in this review. The protocol for human use is in place and authorized. We are confident that this new machine will represent a quantum leap in the modern approach to fluid management in congested patients. Its application may find several options in various environments including ambulatory and home care with simplified or even self-administration of the procedure. The era of portable/wearable ultrafiltration has come. We now need to increase the awareness about simplicity, feasibility, and clinical benefits of this novel approach.

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Author contribution CR: conceptualization (lead); data curation (equal); formal analysis (equal), funding acquisition (lead); investigation (equal); methodology (lead); project administration (lead); resources (lead); writing—original draft (equal); writing—review and editing (equal); and supervision. AL: data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); writing—original draft (supporting); and writing—review and editing (equal). LS: data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); writing—original draft (supporting); and writing—review and editing (equal). TR: writing—original draft (lead) and writing—review and editing (equal). GR-G: writing—original draft (lead) and writing—review and editing (equal). All authors were responsible for critical revision of the manuscript and approved the final version before submission.

Availability of data and materials Not applicable.

Declarations

Ethics approval and consent to participate Not applicable.

Competing interests CR has received funding for lectures and been consultant or advisory board member for Asahi, Astute, B. Braun, Baxter, bioM´erieux, Bioporto, CytoSorbents, Estor, Fresenius Medical Care, General Electric (GE), Jafron, Medtronic, and Toray. TR has received funding for lectures and been consultant or advisory board member for AstraZeneca, B. Braun, Baxter, bioMérieux, Boehringer Ingelheim, Contatti Medical (CytoSorbents), Eurofarma, Fresenius Medical Care, Jafron, Lifepharma, and Nova Biomedical. 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 article.

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