

# The Science of Extracorporeal Ultrafiltration: Introducing a Novel Miniaturized Device

Luca Sgarabotto<sup>a,b,c</sup> Amir Kazory<sup>d</sup> Alessandra Brendolan<sup>a,b</sup> Luca Di Lullo<sup>e</sup>  
Monica Zanella<sup>a,b</sup> Claudio Ronco<sup>a,c</sup>

<sup>a</sup>International Renal Research Institute of Vicenza (IRRIV), Vicenza, Italy; <sup>b</sup>Department of Nephrology, San Bortolo Hospital, Vicenza, Italy; <sup>c</sup>Department of Medicine, University of Padova, Padova, Italy; <sup>d</sup>Division of Nephrology, Hypertension, and Renal Transplantation, University of Florida, Gainesville, FL, USA; <sup>e</sup>Department of Nephrology and Dialysis, L. Parodi – Delfino Hospital, Colferro, Italy

## Keywords

Heart failure · Cardiorenal syndrome · Fluid overload · Congestion · Ultrafiltration · Miniaturization

## Abstract

**Introduction:** Fluid overload has been associated with untoward outcomes in a variety of clinical settings. Isolated extracorporeal ultrafiltration (UF) allows for mechanical extraction of excess fluid and optimization of volume status without the established risks associated with use of high-dose diuretics. Conventional machines for renal replacement therapy can be used to perform isolated UF. However, they typically need high blood flow rates with high circuit volumes and the therapy has to be performed by trained nurses. Herein, we describe a novel device, the Artificial Diuresis-1, or AD 1 (Medica S.p.A., Medolla, Italy), which is a portable technology designed to perform extracorporeal UF at bedside. **Materials and Methods:** The AD 1 uses a polysulfone mini-filter to generate ultrafiltrate with the help of two forces: blood flow (Qb) and gravity (based on the height at which the ultrafiltrate collection bag is placed). In vitro experiments were performed using human blood to evaluate vascular access pressures and ultrafiltrate

volumes using various central venous catheters (CVCs; 12 Fr bilumene, 10 Fr with 2 separate lumens, pediatric catheter 7 Fr). A variety of combinations were tested with Qb of 20, 35, 50 mL/min and collection bag height at 20, 40, 60 cm, measuring the UF rate per minute while monitoring the pressures in the venous and arterial lines and filtration fraction. **Results:** The device's performance was as expected. Regarding the pediatric CVC, it was possible to perform measurements only with a Qb of 20 mL/min due to increased venous pressure. UF rates when lines were directly connected to the blood container as well as for CVC Tesio ranged from 3.7 to 11 mL/min, for the CVC Niagara™ from 4.5 to 12.5 mL/min, and for the CVC 7 Fr from 8.5 to 10 mL/min. The pressures of the vascular accesses were kept within a range of –5/–40 mm Hg for the artery and +10/+70 mm Hg for the vein. The highest venous pressure values were found with the CVC 7 Fr (+80/+100 mm Hg). **Conclusions:** This novel device allows to treat patients with fluid overload in a variety of settings, from low-intensity department such as long-term care facilities to the intensive care unit. The device is small and portable, has a simple design, and is user friendly. Future studies will be needed to evaluate whether gentle UF and treatment of volume overload will translate into improvement in clinical

outcomes such as a reduction in congestion-related hospital admissions.

© 2023 The Author(s).  
Published by S. Karger AG, Basel

## Introduction

Volume overload can be defined as an increase in body weight greater than 5% or a progressive pathological accumulation of fluids defined as positive fluid balance [1]. Volume overload is associated with adverse outcomes. Several studies have found a strong association between congestion and increased risk of acute kidney injury, delayed recovery of renal function [2], prolonged mechanical ventilation [3], wound healing [4], abdominal compartment syndrome [5], and increased mortality [6–8]. It also leads to longer hospitalizations and loss of patients' autonomy [6].

Identification of the patients that are at risk of developing volume overload is of utmost importance; early detection of the positive fluid balance allows for implementation of strategies to prevent it. On the other hand, it has been shown that complete resolution of fluid overload is associated with better outcomes such as mortality and rehospitalization [9].

Fluid restriction and diuretics are currently the mainstay of treatment of acute or chronic fluid overload [10, 11]. High-dose intravenous administration of the loop diuretics, whether as bolus or continuous infusion, is commonly used in the acute setting [11]. In case of diuretic resistance, one strategy to maintain the natriuretic effect is sequential blockade of the nephron with inhibition of the Na/Cl co-transporter of the distal tubule [12]. Acetazolamide may also be useful for combination therapy by increasing urinary sodium excretion [13].

When medical strategies to “force” diuresis fail, the use of extracorporeal therapy becomes mandatory. Among renal replacement therapies, there are continuous renal replacement therapies (CRRTs) that according to the KDIGO 2012 guidelines are preferred in patients with hemodynamic instability and dialysis needs [14]. Isolated ultrafiltration (UF) or slow continuous ultrafiltration is a method that by definition does not require high blood flow rates ( $Q_b$  50–150 mL/min, UF rate 50–500 mL/h) and allows for an adequate serum refilling by the fluids accumulated in the interstitium, resulting in an improved hemodynamic tolerance to the treatment [15].

According to the European Society of Cardiology (ESC) and American Heart Association, UF can be considered for patients with persistent congestion that is

not responding to diuretic strategies [16]. Various studies have been performed to evaluate the efficacy of isolated UF in the management of volume overload in patients with acute heart failure and congestion. These studies explored whether use of UF is advantageous compared to diuretics for the management of acute heart failure [17–19, 1]. In general, they showed that UF can provide more efficient fluid extraction and reduce the rate of heart failure-related hospitalization [20].

While the timing of initiation of UF for congestion has not been studied carefully, in general, recent evidence suggests that there is no clear benefit for early initiation of renal replacement therapy (RRT) [21]. As such, it would be beneficial to develop a technology that allows management of patients with fluid overload and diuretic resistance who are not yet candidates to start CRRT. This type of technology could be used together with diuretics and represent an intermediate measure before the start of the traditional RRT in this subset of patients.

Current extracorporeal UF sessions are performed with standard hemodialysis or CRRT machines that, however, need power supply, are bulky, and require immobilizing the patient at the bedside. Furthermore, these machines are not designed to be used at home or to be self-operated by the patient. The unmet clinical need of a simplified UF procedure creates the rationale for the design and development of a new machine with specific characteristics such as portability, no need of power supply (battery charged), user-friendly operations. The low blood flows, required by this miniaturized system, allow to utilize any type of access, including a peripheral cannula or a vein-to-vein circulation. Due to the low UF rates, monitoring could be less intensive. The system would not require any water supply as in the case of complex dialysis equipments.

## Materials and Methods

This device weighs 1.3 kg with the battery and measures 225 × 135 × 90 mm. It is designed to perform slow continuous ultrafiltration using low  $Q_b$  (5–60 mL/min). The management of the treatment is very simple as the parameters that need to be set are limited to  $Q_b$ , the treatment time, and the desired UF rate that ideally will not exceed 5 mL/min (average 1–2 mL/min), reducing the risk of serious complications such as hypotension during treatment.

The central unit is equipped with a small display and a membrane keyboard that allow the control of the device by the operator; there is access limitation to prevent the patient from inadvertently changing the settings. The device without the disposable is shown in Figure 1.



**Fig. 1.** Central unit.

The main information available on the display panel is the speed of the blood pump, the UF rate, the cumulative weight of ultrafiltrate removed, the access and return line pressure, the battery charge, and the duration of the treatment, in addition to any active alarm. The keyboard allows the operator to turn the device on and off, to reset or silence alarms, and to 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 allows Bluetooth connection.

Extracorporeal circulation is achieved through a peristaltic pump with a  $Q_b$  varying from 5 to 60 mL/min, with 5 mL/min increments. The pump size is  $4.3 \times 6.8$  mm. The alarm system consists of an audible alarm that complies with medical regulations. Depending on the alarm type (high or low priority), the treatment may be interrupted automatically (e.g., pressure or air detection alarm).

It incorporates an air sensor that detects bubbles larger than 50  $\mu$ L, a blood loss sensor which is optical and works by reflection through the walls of the disposable cassette. The blood leak detector can detect free hemoglobin concentrations of up to 1% and is placed at the level of the UF channel.

In case of an air alarm, the system will stop the blood pump, and the operator has to connect a syringe to the appropriate port until the air bubble is sucked out. The flow sensor integrates the pressure sensors that couple with the membranes on the cassette. The access and return pressures are visible on the display. This coupling system between the membranes allows to detect the suction and return pressures without exposure of blood to air. The device is portable and incorporates an accelerometer that turns off pressure alarms when the device is moving.

The access detachment system is an additional security system that is applied directly with a patch at the level of the vascular access and through an optical sensor detects any bleeding at the level of venous return. The disposable kit consists of a sensorized cassette tightly attached to the hemofilter that includes the tubatism necessary for the connection of the patient. The cassette

integrates an UF flow sensor that monitors the UF rate and the cumulative UF volume removed since the beginning of each treatment. A port integrated into the circuit allows the connection of a syringe to flush the hemofilter with saline solution. An ultrafiltrate collection bag with a volumetric scale is connected to the UF line so that the operator can read the removed volume without accessing the display.

Depending on the height at which the effluent collection bag is placed, a negative pressure will be created in the UF chamber; the lower the bag, the more negative pressure develops. Through the UF sensor, the software detects changes in UF levels. The hemofilter is tightly connected to the cassette which is called Artificial Diuresis-1 filter (Medica S.P.A., Medolla, Italy). It is a polysulfone filter with a molecular weight cutoff of 50,000 dalton and a surface area of 0.15  $m^2$ , a priming volume of 10 mL, a maximum transmembrane pressure (TMP) of 600 mm Hg, and a UF coefficient (KUF) of 3 mL/h/mm Hg. This kit is supplied prefilled with sterile isotonic saline solution (which will then be eliminated) so that priming and air removal operations are not necessary, making it more user friendly. The kit is taken out of its envelope and is connected in a single step to the device, after which the patient can be connected to the device. The total priming volume of the whole circuit (including the hemofilter) is 20 mL to minimize the risk in case of circuit loss. The device contains two microprocessors, each with its own software. One is the control software, while there is a protection software on a separate microprocessor that independently monitors the sensors. The same control software which, if necessary, activates the alarm and interrupts the treatment.

When first switched on, the system performs an efficiency check (memory, battery charge, and the alarm system) and awaits confirmation to start a new treatment. The next step is the kit installation phase during which the device asks the operator to connect the box to the device, close the lid, and start the treatment. Only when the cassette is fully connected, the device allows the operator to start the treatment. Once confirmed, the system moves the pump inside, after which the patient connection phase can begin, as can be seen in Figures 2a and b. Once the pump starts, the system collects approximately 20 mL of blood from the patient while simultaneously pushing the isotonic solution into a waste system. After completion of this phase, the actual treatment begins.

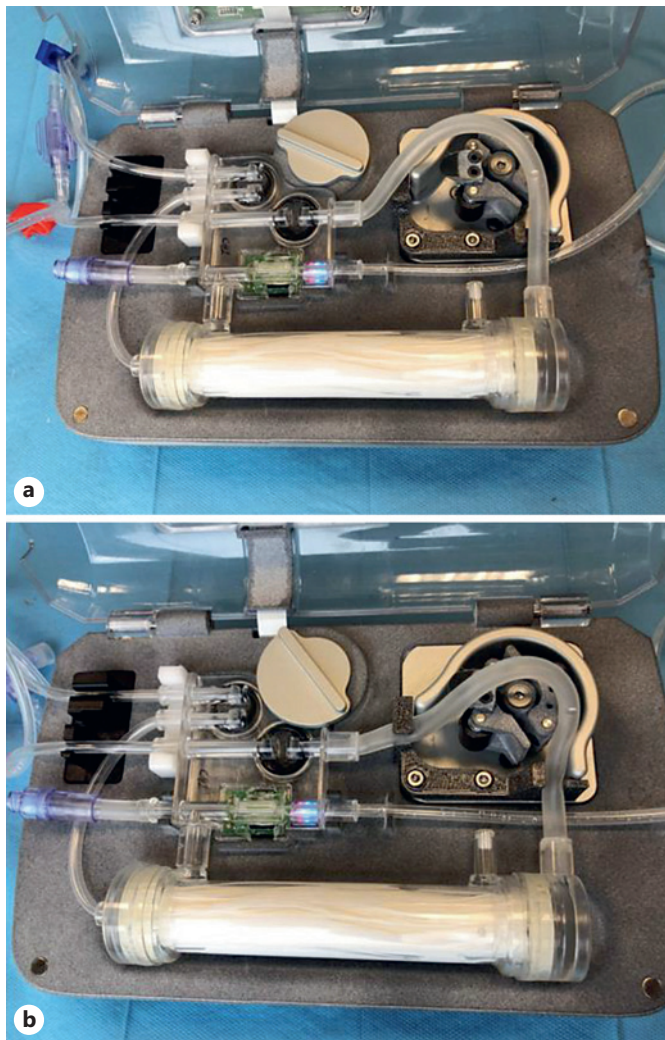
Treatment comes to an end or can be stopped by pressing a button for 3 s. Then it enters the blood restitution state. The device asks the operator to disconnect the arterial line. Once confirmed, approximately 15 mL of blood will be pumped into the patient. Once done, the patient will be disconnected and treatment will end.

The software stores processing logs on its internal SD card. All treatment data are captured and recorded with 1-s intervals and can be downloaded by the app via Bluetooth. They can be used to analyze trends or alarms related to the whole session in detail. In addition to information on the treatment, these data also contain the alarms and the state of charge of the battery.

#### *Experiment Design*

In the bioengineering laboratory of the International Renal Research Institute of Vicenza (IRRV), we evaluated the efficiency of the device and its calibration. We used human blood that was anticoagulated with citrate, a hematocrit of 31%, the volume of 320 mL, with different flow rates ( $Q_b$  20, 35, and 50 mL/min) and





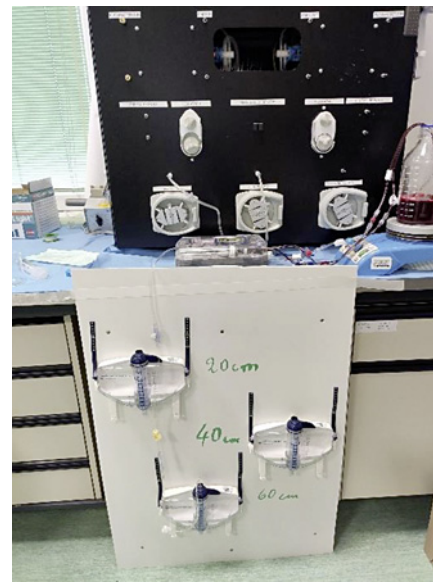
**Fig. 2.** **a** Disposable insertion into the central unit. **b** The pump rolling in the tubatism automatically once the treatment is started.

placing the ultrafiltrate collection bag at various heights (20, 40, and 60 cm).

The measurements were planned at 5-min intervals and were preceded by a 30-s flow stabilization time interval. Venous and arterial pressures as well as UF rate were measured and recorded. A panel was built with three collection devices that were obtained from urinometers used in intensive care unit to precisely measure ultrafiltrate volume in increments of 10 mL. The three collection systems were fixed at 20, 40, and 60 cm below the device, as can be seen in Figure 3. The fluid container used in the experiments was placed 10 cm above the device using a heating plate that kept the blood/isotonic saline at a temperature of 37°C through a magnet.

The pressures of the arterial and venous lines were obtained through a detection device to which the device was connected through T-tubes. Four types of vascular access were used.

- Lines directly in contact with the container placed at 10 cm height.



**Fig. 3.** Experimental setting.

- Double-lumen central venous catheter (CVC), coaxial lumen of 7 Fr (Arrow International Inc Subsidiary of Teleflex Incorporated 24000 Bernville USA), 16 cm (arterial lumen 14 Ga, venous lumen 18 Ga, with priming vol of 0.32 mL in the venous lumen and 0.47 mL in the arterial lumen, capable of holding flows of up to 25 and 83 mL/min for the venous and the arterial lumens, respectively).
- 24cm Niagara™-type high-flow CVC 12 Fr.
- CVC-type Tesio (medCOMP Germany) double-lumen separate femoral 10 Fr, 70 cm long.

The blood was placed within a glass container and anti-coagulated with 25,000 U of unfractionated heparin. The accuracy of the blood flow rates at 3 different speeds (20, 35, and 50 mL/min) was verified by clamping the UF line and collecting the fluid from the venous line in a Falcon™ 50 mL-type container for 1 min.

Measurements of the UF and pressures of the venous and arterial lines were performed by connecting the device to an external meter with T-fittings. The accuracy of the blood pump speed was verified by clamping the UF line and measuring the amount of blood exiting from the venous line both at the beginning and at the end of the measurements.

At the end of each measurement, the volume of ultrafiltrate obtained was reintroduced into the glass to avoid changes in the hematocrit. In addition, at the end of each third measurement, 20 mL of isotonic saline was used to backflush the circuit.

Measurements were then carried out for the duration of 5 min, each preceded by 30 s of observation for the stabilization of the flow for each of the 3 heights (20, 40, and 60 cm) at 3 different speeds (20, 35, and 50 mL/min) for a total of 9 measurements. The tests with the high-flow CVC-type Niagara™ and Tesio were then repeated. We measured and recorded venous and arterial pressures 1 min after the start of UF. For each speed (20, 35, and 50 mL/min), the line pressures of the clamped UF line were determined. All these tests were performed at a speed of only 20 mL/min for the pediatric CVC.

**Table 1.** UF obtained at the different Qb and different heights (H) of the collection bag for the different vascular access

|                         | Without central lines | CVC 12 Fr (Niagara) | CVC 10 Fr (Tesio) | CVC 7 Fr (pediatric) |
|-------------------------|-----------------------|---------------------|-------------------|----------------------|
| Qb 20 mL/min<br>H 20 cm | 3.7 mL/min            | 4.5 mL/min          | 3.5 mL/min        | 8.5 mL/min           |
| Qb 20 mL/min<br>H 40 cm | 5.7 mL/min            | 6.5 mL/min          | 5.5 mL/min        | 9.5 mL/min           |
| Qb 20 mL/min<br>H 60 cm | 7 mL/min              | 7.2 mL/min          | 7 mL/min          | 11 mL/min            |
| Qb 35 mL/min<br>H 20 cm | 5.7 mL/min            | 6.4 mL/min          | 5.5 mL/min        | –                    |
| Qb 35 mL/min<br>H 40 cm | 7.7 mL/min            | 8.7 mL/min          | 7.7 mL/min        | –                    |
| Qb 35 mL/min<br>H 60 cm | 9.3 mL/min            | 10 mL/min           | 9.3 mL/min        | –                    |
| Qb 50 mL/min<br>H 20 cm | 6.7 mL/min            | 8.5 mL/min          | 6.7 mL/min        | –                    |
| Qb 50 mL/min<br>H 40 cm | 9.3 mL/min            | 10.8 mL/min         | 9.3 mL/min        | –                    |
| Qb 50 mL/min<br>H 60 cm | 11.7 mL/min           | 12.5 mL/min         | 11 mL/min         | –                    |

## Results

During these tests, the pump, its display, and the battery were functioning appropriately. No problems were detected for the alignment of the disposables, nor was there any leakage. The performance of the whole device was exactly as planned and expected.

Two cycles of tests with blood recirculation were performed. On both occasions, the ultrafiltrate volume was returned into the blood container at the end of each measurement so that the hematocrit would not change, leading to alterations in subsequent measurements.

The ultrafiltration/minute (UF/minute) values were verified at 20 mL/min, 35 mL/min, and 50 mL/min for the three heights (20, 40, and 60 cm) with the four types of the abovementioned vascular accesses. For the pediatric CVC, it was not possible to detect the values for blood flows above 20 mL/min due to high venous pressures, risk of coagulation of the circuit, and damage to the integrity of the filter due to excessive transmembrane pressure values. They were backflushed by clamping the UF line and connecting a 50-mL syringe to the huer and slowly injecting 20 mL of isotonic saline into the circuit.

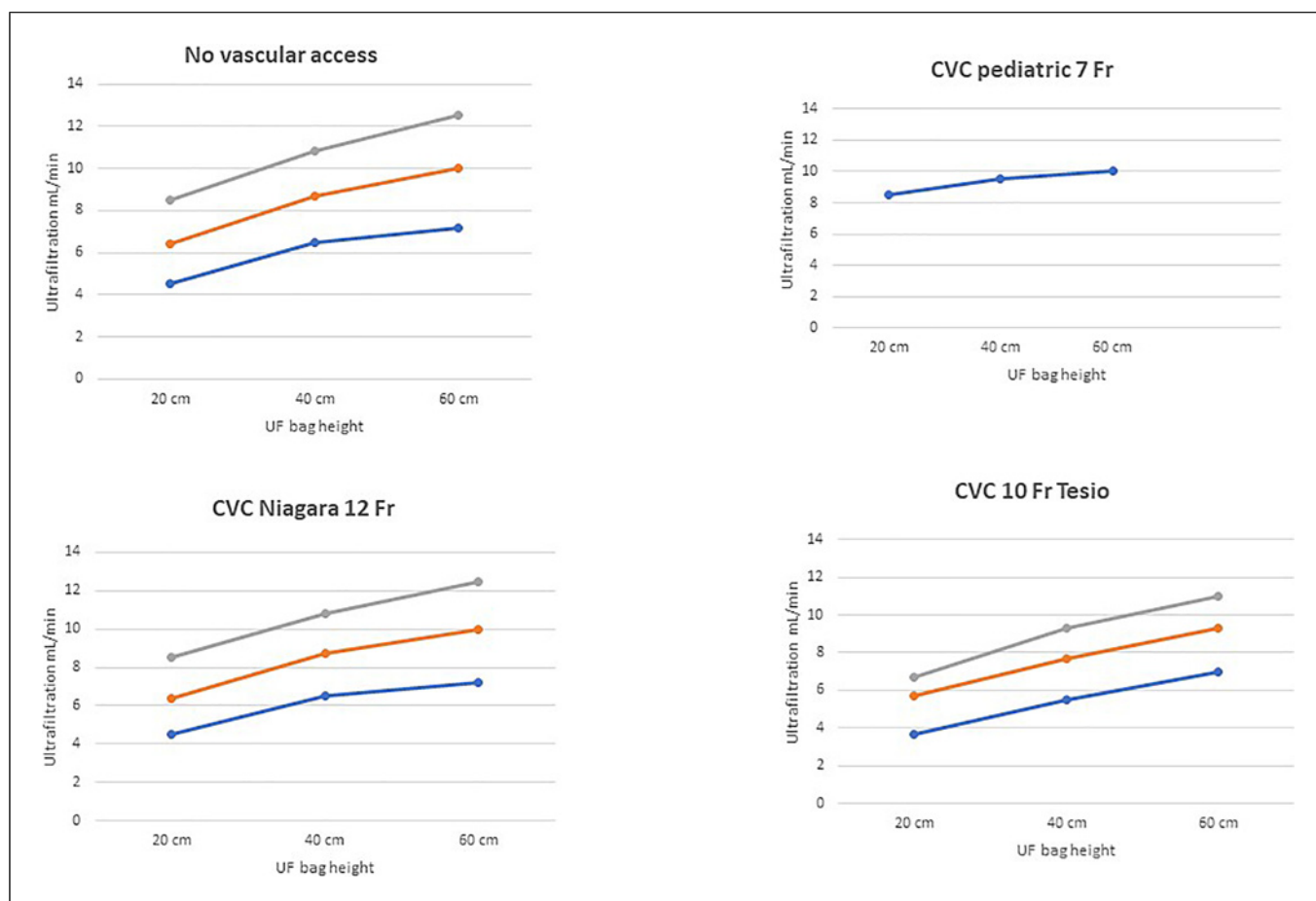
The UF values were incremental and directly proportional to the increase in the speed of the blood pump and the height of the UF collection bag. UF rates were found to be 3.7–11.5 mL/min for lines directly in contact with blood and 4.8–12 mL/min for CVC 12 Fr. For Tesio

CVC, they were 4.5–10.5 mL/min, and for pediatric CVC, the rates were 9–11 mL/min for the speed of 20 mL/min (see Table 1; Fig. 4).

The bloodline pressure values observed for tests with lines directly in contact with blood varied from –2 and –10 mm Hg, CVC Tesio from –10 to –40 mm Hg, CVC Niagara™ –4 to –15 mm Hg, and pediatric CVC remained at –20 mm Hg. The venous pressures for the tests performed with lines directly in contact with blood were maintained between +3 and +18 mm Hg, for the high-flow CVC type Niagara™ between +20 and +30 mm Hg, for CVC Tesio between +30 and +70 mm Hg and for the pediatric CVC at the only speed of 20 mL/min for the 3 heights the venous pressures were variable from +80 to +100 mm Hg, as can be seen in Figures 5–8.

### *Recommendations for the Safe and Effective Use of the Device*

- Adequate training and skill assessment must be ensured prior to the use of the device.
- The device implies an extracorporeal circulation; thus, it should be adequately monitored and operated.
- Because UF rate is dependent on the position of the UF collecting bag, special attention should be placed to this aspect during treatment.
- An adequate prescription should be made according to patient's fluid assessment and according to vascular access capabilities.



**Fig. 4.** UF values with blood Htc 31%.

- e) Adequate anticoagulation should be provided, and patient coagulation as well as circuit patency should be carefully monitored.
- f) Alarm silencing should be immediately followed by the investigation of the cause.

## Discussion

Fluid overload is frequently observed in a number of settings such as heart failure and patients with end-stage kidney disease that are treated with hemodialysis or peritoneal dialysis [1]. Several studies have observed that a positive fluid balance during hospital admission is associated with adverse outcomes [6, 22–24] including increased hospitalization rate, infections, cardiovascular remodeling, and mortality [5–25].

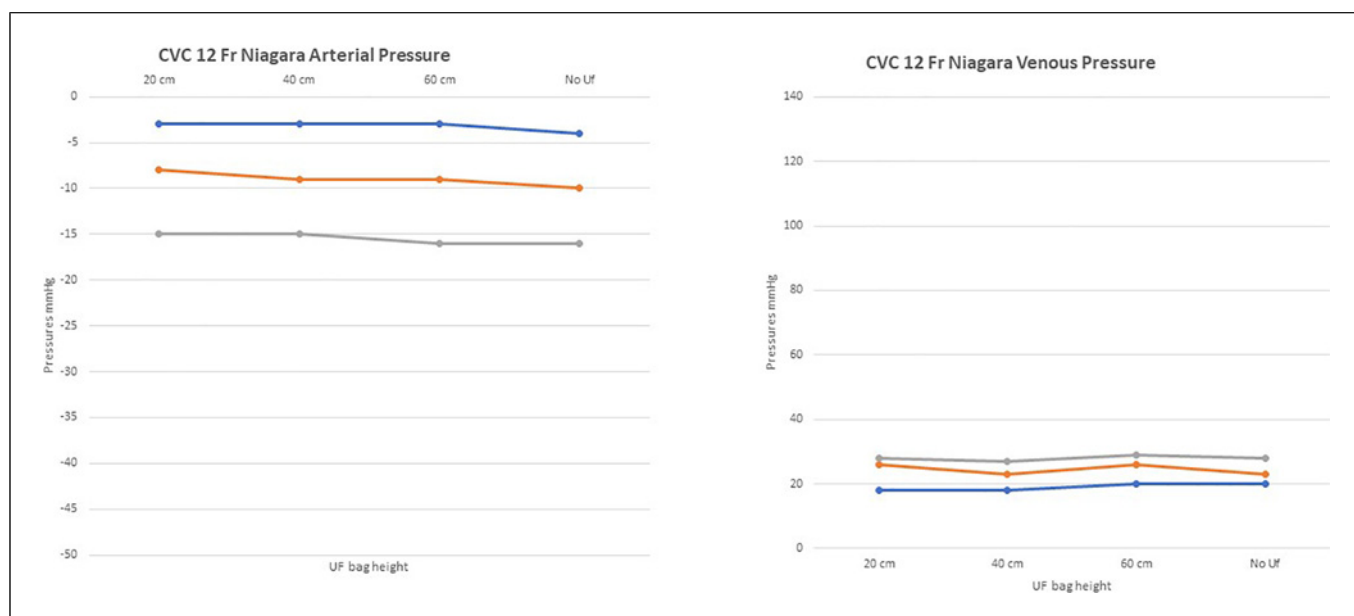
While conservative fluid management strategies can be helpful in preventing fluid overload in a subset of patients,

those with hemodynamic instability typically receive significant amount of fluid that could result in progressive congestion [26]. In cases where renal function is affected, there might be a need for mechanical extraction of fluid to avoid the untoward effects of lingering congestion [21–27].

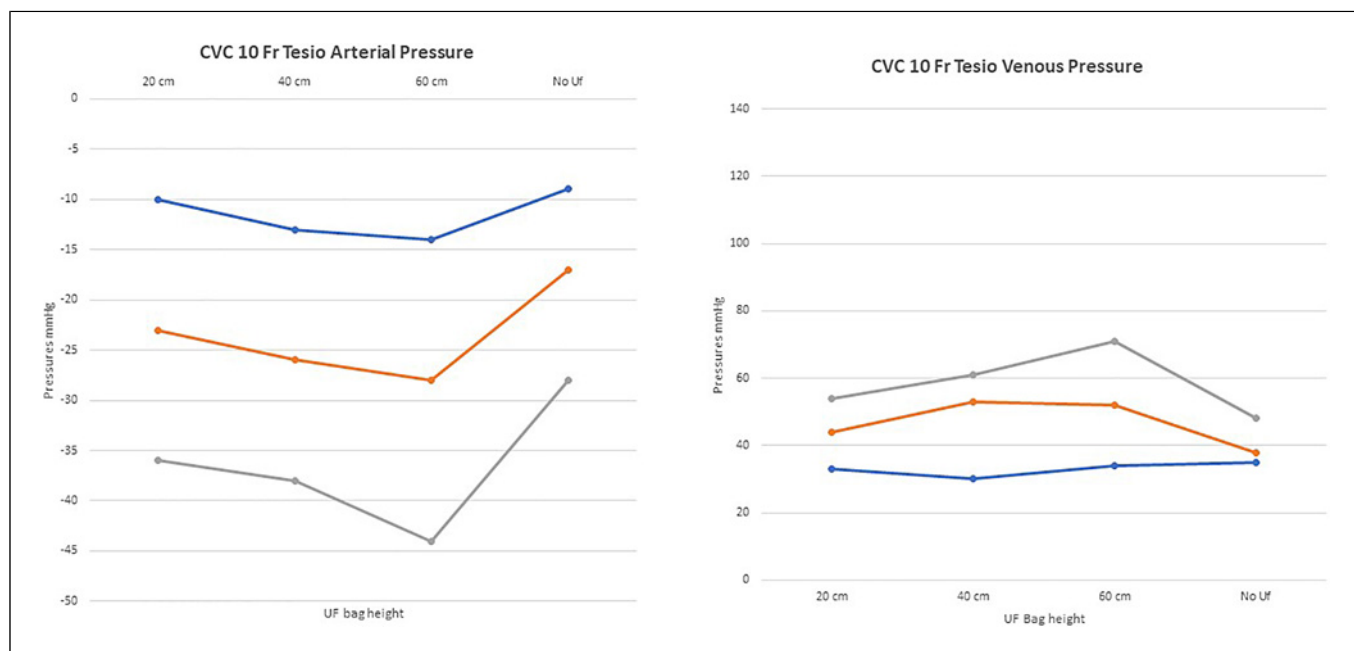
Slow UF with fluid removal rate of 1–1.75 mL/kg/h has been proposed to be an optimal target [7–28]. This allows for progressive removal of the fluid from the serum that is matched to plasma refill rate, hence leading to gradual unloading of fluid from the interstitium that can be tolerated by a patient with tenuous hemodynamic status.

The devices that are typically used for this purpose are derived from the technology used for conventional RRT. They require the use of trained personnel and vascular accesses that are able to provide high blood flows.

Our goal has been to develop a simple, small, portable, battery-operated device that uses gravity to treat patients



**Fig. 5.** Arterial and venous pressures with blood and CVC high-flow Niagara™.

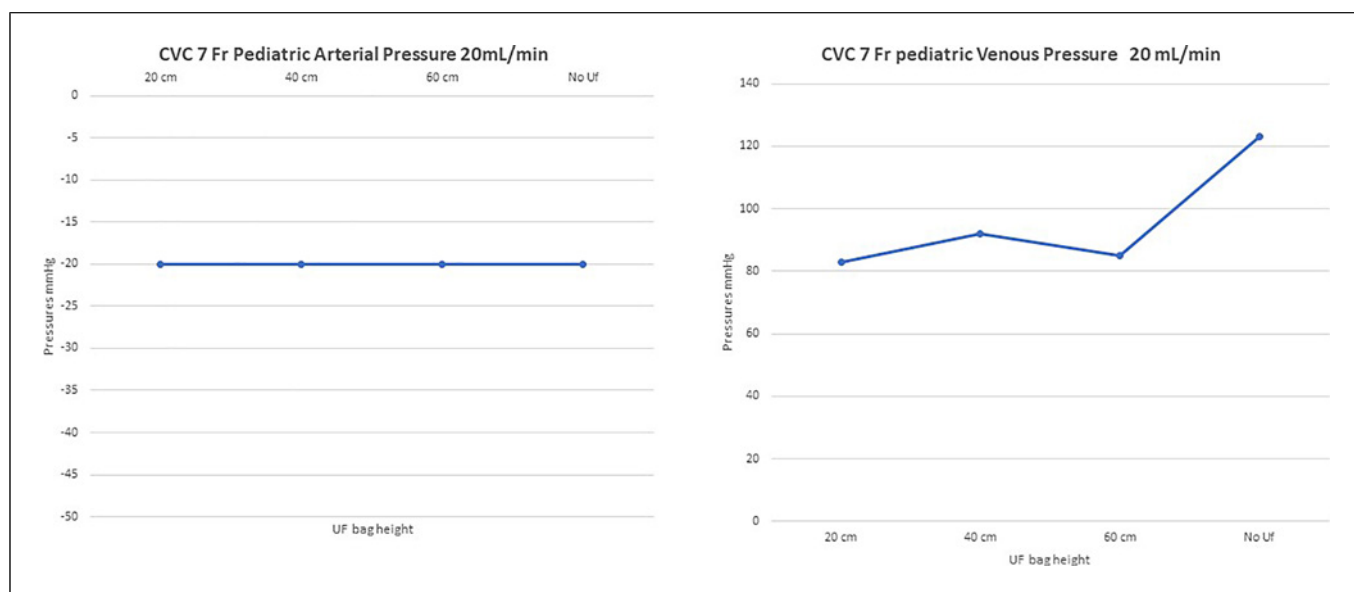


**Fig. 6.** Arterial and venous pressures with blood CVC Tesio.

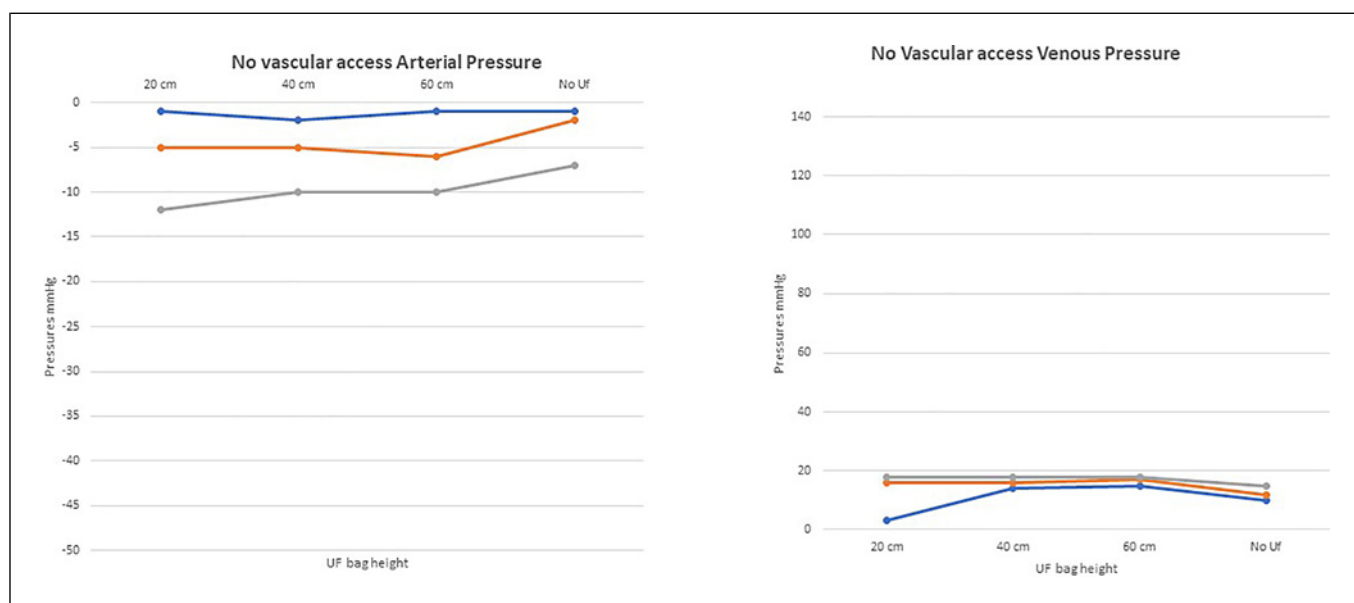
with fluid overload even in nonintensive care settings or dialysis units without requiring the presence of specialized nursing staff and possibly even self-management by the patient. While the AD 1 device is still in an

experimental phase, it does have the potential for applications in a variety of settings.

The possibility of performing isolated slow UF without the complications observed with hemodialysis such as



**Fig. 7.** Arterial and venous pressures pediatric CVC 7 Fr Qb 20 mL/min.



**Fig. 8.** Arterial and venous pressures with blood and no vascular access.

hypotension and electrolyte abnormalities makes it feasible to use this device to manage fluid overload at home. In the context of the development of portable artificial kidneys, this conceptual approach is a continuation of the project that was started in Vicenza with the wearable artificial kidney, the first portable artificial kidney [29].

This user-friendly device is meant to be used by nonspecialized personnel. It does not require priming as the disposable circuit is already filled with a sterile isotonic saline solution, which is transferred into a dedicated bag at the beginning of the therapy. The display is easy to use with an easy-to-use interface.



Since the volume of blood processed is very low at only 20 mL (e.g., about a tenth of a conventional RRT machine), clotting of the circuit would not result in significant blood loss. The autonomy of the battery allows using the device for 24 h consecutively with the possibility of changing the battery during treatment.

In the IRRIV laboratory, we have demonstrated the functionality of the device, the prolonged autonomy of the battery system, and the possibility of achieving high UF volumes with modest blood flows ranging from 20 to 50 mL/min that can be obtained with a peripheral vascular access or a low-flow CVC. Securing an appropriate vascular access is critical for any form of extracorporeal therapy; the possibility of using small catheters perhaps inserted peripherally could be considered highly advantageous.

The treatment is intended to be applied with a central double-lumen catheter of small dimensions. In case of unavailability of a central line, lower blood flows down to 25–30 mL/min can be obtained with vein-to-vein circulation as largely demonstrated by previous experience. In case of self-operations by the patient, a central catheter is required as in the case of typical home hemodialysis procedures.

The absence of an UF pump in the device makes its calibration critical. This is because UF is determined by only two parameters: the  $Q_b$  and the height at which the ultrafiltrate collection bag is placed.

We observed the capability of the device to generate high UF rates ranging from 220 to 600 mL/h. Due to lack of a mechanical pump for UF, the decongestive process is less easily adjustable. As the treatment progresses, the removal of plasma water may lead to hemoconcentration, an increase in filtration fraction, and an increased risk of clotting of the circuit. As such, this therapy would require anticoagulation by either unfractionated or low-molecular-weight heparin. In order to address this potential complication, the ultrafiltrate collection bag can be moved upwards (to decrease UF rate), the diameter of UF line can be reduced, or a filter with smaller surface area can be used in order to reduce the flow of the ultrafiltrate.

## Conclusion

Fluid overload, whether chronic or acute, is commonly encountered in clinical medicine in a variety of settings. In certain circumstances such as pulmonary edema and respiratory failure in the context of renal dysfunction or diuretic resistance, extracorporeal therapy for mechanical fluid removal may be necessary. Slow fluid extraction is

commonly the preferred strategy for patients with concomitant hemodynamic instability.

The development of a simple, miniaturized, user-friendly system to perform extracorporeal UF could prove useful in these patients. While it can be used as a complementary modality in the hospital, whether in the intensive care setting or medical ward, AD-1 can also be used at home by those patients with worsening chronic congestion such as those with heart failure or those with end-stage kidney disease who have difficulty with excessive interdialytic weight gain. Further studies are needed for more precise calibration of this device which will subsequently be tested in vivo for evaluation of its efficacy and safety.

## Statement of Ethics

The ethical committee approval was waved by the Internal Review Board since only in vitro experiments were conducted, according to the good practice of the utilization of blood bank.

## Conflict of Interest Statement

Professor Claudio Ronco: CR in the last 3 years consulted, was part of the advisory board or received fee for speaker board from Asahi, Baxter, BioMerieux, Aferetica, CytoSorbents FMC, GE, Jafron, Medica, B. Braun, AstraZeneca, and Medtronic. MD Monica Zanella: Glaxo, Asahi. MD Alessandra Brendolan: Medica. MD Luca Di Lullo, MD Amir Kazory, and MD Luca Sgarabotto: none.

## Funding Sources

The study was supported in part by a research grant from Medica.

## Author Contributions

- Study concept and design: Professor Claudio Ronco, Luca Sgarabotto, and Alessandra Brendolan.
- Drafting of manuscript: Professor Claudio Ronco, Luca Sgarabotto, and Amir Kazory.
- Critical revision of manuscript for important intellectual content: Amir Kazory, Luca di Lullo, and Monica Zanella.

## Data Availability Statement

The results of this in vitro study are available and they have been utilized for the submission to the Ethical Committee (n° protocol 5422) of the in vivo study that is going to be soon performed in our hospital.

## References

- Messmer AS, Zingg C, Muller M, Gerber JL, Scheffold JC, Pfortmueller CA. Fluid overload and mortality in adult critical care patients-A systematic review and meta-analysis of observational studies. *Crit Care Med*. 2020 Dec; 48(12):1862–70.
- Vaara ST, Korhonen AM, Kaukonen KM, Nisula S, Inkinen O, Hoppu S, et al. Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study. *Crit Care*. 2012 Oct 17;16(5):R197.
- Koc V, Delmas Benito L, de With E, Boerma EC. The effect of fluid overload on attributable morbidity after cardiac surgery: a retrospective study. *Crit Care Res Pract*. 2020 Dec 4;2020:20204836862.
- Prowle JR, Echeverri JE, Ligabo EV, Ronco C, Bellomo R. Fluid balance and acute kidney injury. *Nat Rev Nephrol*. 2010 Feb;6(2): 107–15.
- Malbrain MLNG, Marik PE, Witters I, Cordemans C, Kirkpatrick AW, Roberts DJ, et al. Fluid Overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice. *Anaesthesiol Intensive Ther*. 2014;46(5):361–80.
- Murugan R, Balakumar V, Kerti SJ, Priyanka P, Chang CCH, Clermont G, et al. Net ultrafiltration intensity and mortality in critically ill patients with fluid overload. *Crit Care*. 2018 Sep 24;22(1):223.
- Tehrani S, Shawwa K, Kashani KB. Net ultrafiltration rate and its impact on mortality in patients with acute kidney injury receiving continuous renal replacement therapy. *Clin Kidney J*. 2021;14(2):564–9.
- Balakumar V, Murugan R, Sileanu FE, Palevsky P, Clermont G, Kellum JA. Both positive and negative fluid balance may be associated with reduced long-term survival in the critically ill. *Crit Care Med*. 2017 Aug; 45(8):e749–57.
- Claire-Del Granado R, Mehta RL. Fluid overload in the ICU: evaluation and management. *BMC Nephrol*. 2016 Aug;17(1):109.
- Patel Y, Joseph J. Sodium intake and heart failure. *Int J Mol Sci*. 2020 Dec;21(24):9474.
- Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, et al. The use of diuretics in heart failure with congestion: a position statement from the heart failure association of the European Society of Cardiology. *Eur J Heart Fail*. 2019 Feb;21(2): 137–55.
- Brisco-Bacik MA, Ter Maaten JM, Houser SR, Vedage NA, Rao V, Ahmad T, et al. Outcomes associated with a strategy of adjuvant metolazone or high-dose loop diuretics in acute decompensated heart failure: a propensity analysis. *J Am Heart Assoc*. 2018;7(18):e009149.
- Lin J, Zhuang HZ, Zhi DY, Qi Z, Bai J, Dong L, et al. Impact of cumulative fluid balance during continuous renal replacement therapy on mortality in patients with septic acute kidney injury: a retrospective cohort study. *Front Med*. 2021 Nov;8(8):762112.
- Palevsky PM, Liu KD, Brophy PD, Chawla LS, Parikh CR, Thakur CV, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. *Am J Kidney Dis*. 2013 May;61(5):649–72.
- Lorenzin A, Ronco C. Solute and water kinetics in continuous therapies. *From: critical care nephrology*.
- Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;2021 Sep 21;42(36):3599–726.
- Bart BA, Goldsmith SR, Lee KL, Redfield MM, Felker GM, O'Connor CM, et al. Cardiorenal rescue study in acute decompensated heart failure: rationale and design of CARRESS-HF, for the Heart Failure Clinical Research Network. *J Card Fail*. 2012 Mar; 18(3):176–82.
- Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med*. 2012; 367(24):2296–304.
- Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol*. 2007 Feb;49(6):675–83.
- Costanzo MR, Negoianu D, Jaski BE, Bart BA, Heywood JT, Anand IS, et al. Aquapheresis versus intravenous diuretics and hospitalizations for heart failure. *JACC Heart Fail*. 2016 Feb;4(2):95–105.
- The STARRT-AKI Investigators; Wald R, Adhikari NKJ, Bellomo R, da Costa BR, Dreyfuss D. Timing of initiation of renal replacement therapy in acute kidney injury. *N Engl J Med*. 2020 Jul 16;383(3):240–51.
- Wilson S, Mone P, Jankauskas SS, Gambardella J, Santulli G. Chronic kidney disease: definition, updated epidemiology, staging, and mechanisms of increased cardiovascular risk. *J Clin Hypertens*. 2021 Apr;23(4):831–4.
- Hung SC, Kuo KL, Peng CH, Wu CH, Lien YC, Wang YC, et al. Volume overload correlates with cardiovascular risk factors in patients with chronic kidney disease. *Kidney Int*. 2014;85(3):703–9.
- Duffy M, Jain S, Harrell N, Kothari N, Reddi AS. Albumin and furosemide combination for management of edema in nephrotic syndrome: a review of clinical studies. *Cells*. 2015 Oct;4(4):622–30.
- Lopez T, Banerjee D. Management of fluid overload in hemodialysis patients. *Kidney Int*. 2021 Dec;100(6):1170–3.
- Gupta R, Testani J, Collins S. Diuretic resistance in heart failure. *Curr Heart Fail Rep*. 2019 Apr;16(2):57–66.
- Balakumar V, Murugan R. Kidney replacement therapy for fluid management. *Crit Care Clin*. 2021 Apr;37(2):433–52.
- Serpa Neto A, Naorungroj T, Murugan R, Kellum JA, Gallagher M, Bellomo R. Heterogeneity of effect of net ultrafiltration rate among critically ill adults receiving continuous renal replacement therapy. *Blood Purif*. 2020 Oct 7;50(3):336–46.
- Castro AC, Neri M, Nayak Karopadi A, Lorenzin A, Marchionna N, Ronco C. Wearable artificial kidney and wearable ultrafiltration device vascular access-future directions. *Clin Kidney J*. 2019;12(2):300–7.