Cardiorenal Medicine

Research Article

Cardiorenal Med 2023;13:167–175
DOI: 10.1159/000530382

Received: December 29, 2022
Accepted: March 10, 2023
Published online: March 28, 2023

Artificial Diuresis: Animal Studies on Efficacy and Safety of a New Miniaturized Device for Extracorporeal Ultrafiltration

Anna Lorenzin[a, b] Luca Sgarabotto[a, b] Maria Laura Bacci[c] Alberto Elmi[c] Domenico Ventrella[c] Camilla Aniballi[c] Monica Zanella[a, b] Alessandra Brendolan[a, b] Luca Di Lullo[d] Claudio Ronco[b]

[a]Department of Nephrology Dialysis and Transplant St. Bortolo Hospital, Vicenza, Italy; [b]International Renal Research Institute of Vicenza (IRRIV), Vicenza, Italy; [c]Department of Veterinary Medical Science, Bologna University, Bologna, Italy; [d]Department of Nephrology, Rome, Italy

Keywords
Ultrafiltration · Animal study · Artificial Diuresis-1 · Extracorporeal therapy · Fluid overload · Miniaturized extracorporeal device

Abstract
Introduction: We have recently developed a new miniaturized device for extracorporeal ultrafiltration (UF) to be used in patients with fluid overload: Artificial Diuresis-1 (AD1) (Medica S.p.A., Medolla, Italy). The device has a reduced priming volume, operates at very low pressures and flow regimes, and is designed to perform extracorporeal UF at bedside. After accurate experiments were carried out in vitro, we report in this paper the results of in vivo UF sessions carried out in selected animals according to veterinary best practice. ***Materials and Methods:*** The AD1 kit is pre-filled with sterile isotonic solution and operates with a polysulfone mini-filter, MediSulfone (polysulfone at 50,000 Dalton). A collection bag with a volumetric scale is connected to the UF line, and the ultrafiltrate is obtained by gravity based on the height at which the ultrafiltrate collection bag is placed. Animals were prepared and anesthetized. The jugular vein was cannulated with a double-lumen catheter. Three 6-h sessions of UF were scheduled with a target fluid removal of 1,500 mL. Heparin was used as anticoagulant. ***Results:*** In all treatments, the target value of UF was obtained in the absence of major clinical or technical problems with a maximum deviation from the scheduled UF rate lower than 10%. The device resulted to be safe, reliable, accurate, and easily usable thanks to a user-friendly interface and its very small dimensions. ***Conclusions:*** This study opens the way for clinical trials in different settings including departments with low intensity of care and even in ambulatory centers or patient's home.

Introduction

Fluid overload (FO) is associated with unfavorable outcomes both in heart failure patients and in critically ill patients admitted to intensive care [1]. Several studies have documented the association of FO with increased risk of acute kidney injury and persistent reduction of renal function [2–4], prolonged mechanical ventilation [5], delayed wound healing [6], abdominal compartment

karger@karger.com
www.karger.com/crm

Correspondence to:
Anna Lorenzin, lorenzin.anna@gmail.com

Table 1. Characteristics of the studied animals

Animal ID	Age, year	Date of birth	Sex	Weight, kg
I31	1	March 12, 2021	M	50.00
I29	1	March 12, 2021	M	54.05
I50	1	March 16, 2021	M	48.00

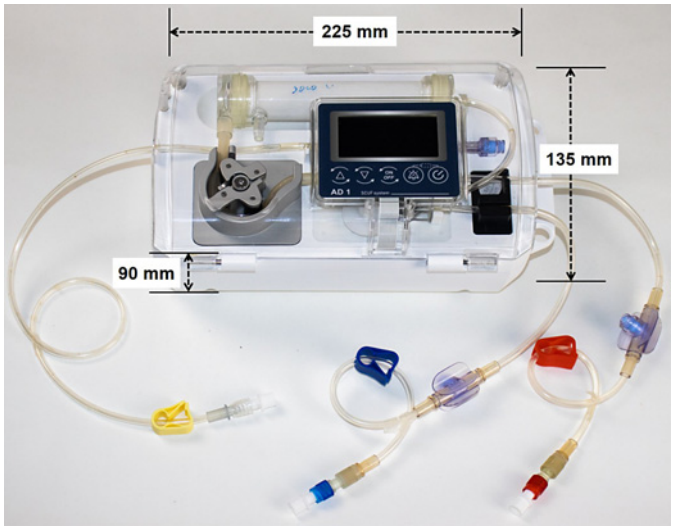

Fig. 1. AD1 system and its size.

syndrome [7], and increased mortality [8, 9]. FO leads to frequent hospitalization, longer hospital stay, and loss of autonomy of the patient, often causing difficult discharge [10]. The early identification of positive FO allows implementing strategies to prevent such complications and to resolve the disorder, moving the patient toward optimized fluid balance. Restrictive fluid administration strategy and high diuretic dose represent the cornerstone of FO management both in acute and chronic settings [11, 12]. When medical strategies directed at a "forced diuresis" fail, the use of extracorporeal therapy becomes mandatory.

According to the European Society of Cardiology and Heart Failure Association, extracorporeal isolated ultrafiltration (IUF) or slow continuous ultrafiltration should be considered for patients with refractory congestion without response to diuretic strategies [13]. Furthermore, UF can be applied in oliguric acute kidney injury patients or in conditions where fluid intake exceeds the capacity of the kidney to maintain neutral fluid balance. To date, IUF and slow continuous ultrafiltration are performed by conventional hemodialysis or continuous renal replacement therapy machines in hospitalized patients requiring trained staff.

In our institute, we have a long-lasting tradition of studying new technologies including wearable and portable devices for blood purification and ultrafiltration (UF) [14, 15]. Along these lines of research, in partnership with Medica S.p.A., we developed a new device called Artificial Diuresis-1 (AD1). The new equipment is a miniaturized portable device for UF described elsewhere in this issue [16, 17]. The basic concept is to make available to clinicians an easy-to-use UF equipment usable in different settings including general medical departments, ambulatory care centers, and even patient's home. Previous in vitro tests have demonstrated safety, reliability, and good usability of the equipment.

We designed the present study in collaboration with the Department of Veterinary Medical Science at Bologna University to evaluate the usability, efficacy, and safety of AD1 in a prolonged in vivo treatment in animals. For this purpose, we carried out several extracorporeal UF sessions in pigs, implementing a standardized protocol of evaluation.

Materials and Methods

Animals Studied

The animals included in the study were 1-year-old castrated male pigs of commercial hybrid breed, born at the experimental enclosure of the ASA Unit of the Department of Veterinary Medical Sciences, University of Bologna, Ozzano d'Emilia, Italy, and weighing between 48 and 54 kg (Table 1). Each animal underwent an UF session.

All the animals were housed in multiple cages, with a light/dark ratio of 12:12 (minimum 40 lux during the daytime), enriched with commercially available products such as Superchallengers, Porcichew, and wood. The pigs were fed with a formulation appropriate to their age and breed provided by CESAC Società Cooperativa Agricola, 48017 Conselice (Ra), a company specialized in the production of feed for farmed animals. The food was provided in the form of pellets, as it is ideal for maintaining the organoleptic and hygienic conditions. We allowed free access to water for all animals, while the food ration was provided twice a day, in the morning (about 07:30) and afternoon (15:30). All the procedures were approved by the Local Ethical Committee and by the Italian Ministry of Health as dictated by D.Lgs. 26/2014 (approval No. 304/2019-PR) in accordance with the European Directive 2010/63/EU on the protection of animals used for scientific purposes.

AD1 Equipment

It is a miniaturized device (225 × 135 × 90 mm and 1.3 kg of total weight), battery operated, and designed to perform IUF (shown in Fig. 1). The sole input parameter is the blood flow that can be set in a range between 5 and 60 mL/min. The central unit is equipped with a small display and a membrane keyboard to

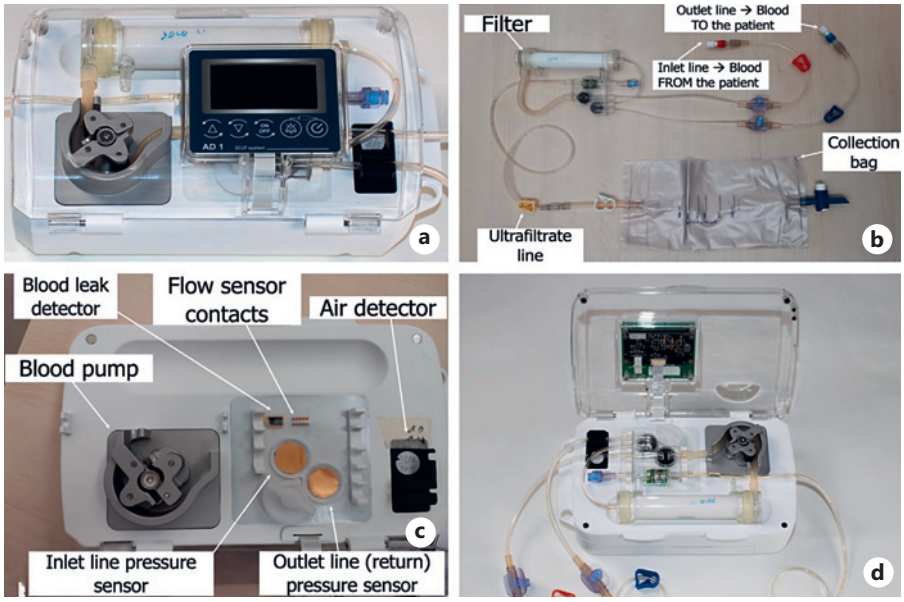

Fig. 2. a AD1 external case containing all hardware components. The membrane keyboard is placed on the polycarbonate cover for easy operations. The screen displays the blood flow, UF rate, cumulative weight of ultrafiltrate removed, access and return line pressures, battery charge, and treatment duration. AD1 system is handled through the membrane keyboard. **b** AD1 disposable circuit. The total priming volume (including the hemofilter) is 15 mL. **c** AD1 hardware with the cover open. The peristaltic pump (4.3×6.8 mm) allows a blood flow of 5–60 mL/min, with 5 mL/min increments. Inlet and outlet pressure sensors, air detector, blood leak detector, and flow sensor contact are clearly visible. **d** AD1 circuit cassette with filter, lines, and membrane pressure transducers are in place within the specific compartments inside the hardware.

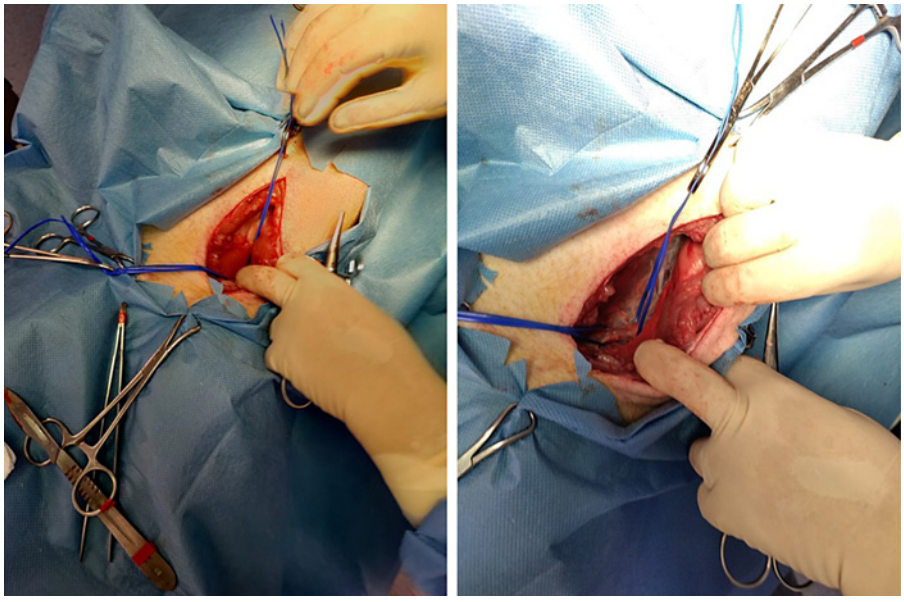

Fig. 3. Surgical insertion of the double-lumen catheter at the jugular site of the animals.

turn on/off the device, to reset/silence alarms, and to set blood flow (shown in Fig. 2a).

The disposable kit consists of a sensorized cassette strictly bound to the hemofilter, from which origins the tube system for the connection to the patient (shown in Fig. 2b). The cassette integrates an UF flow sensor that measures the instantaneous UF flow while the cumulative volume removed from the beginning of treatment is continuously updated. The hemofilter is a MediSulfone (polysulfone at 50,000 Dalton) 0.15 m^2, with a priming volume of 10 mL, a maximum TMP of 600 mm Hg, a K_{UF} 3 mL/h/mm Hg.

This kit is pre-filled with sterile isotonic solution which permits to avoid priming and air removal operations and makes the start of the treatment easier. A 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. The position of this bag is very important because, 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 position of the bag is, the greater the negative pressure, increasing the UF rate.

There are two independent microprocessors each with their own software: a control software and a protection software that independently monitor the various sensors and the same control software. The two systems interrupt the treatment and activate the alarm when necessary. A single treatment can last up to 24 h. All treatment data are recorded at 1-s intervals, and the software stores processing logs on its internal SD.

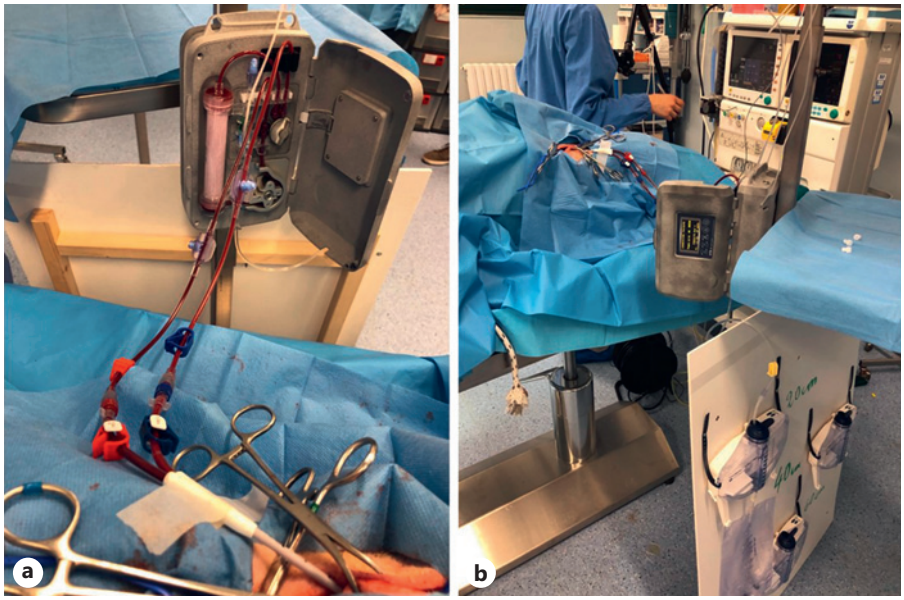

Fig. 4. Setting of clinical operations. The anesthetized animal is supine while undergoing extracorporeal UF. The extracorporeal circuit is visible with the device placed vertically at the bedside. The ultrafiltrate collecting bags are placed at different height from the level of the filter and this allows for fine regulation of the UF rate.

Anesthetic Protocol

All animals were fasted for 12 h prior to general anesthesia, while access to water was granted up to the moment of sedation. Pigs were deeply sedated upon intramuscular injection of a mixture of tiletamine/zolazepam (3 mg/kg; Zoletil, Virbac Italia, Milan, IT) and dexmedetomidine (0.02 mg/kg; Sedadex, Dechra Veterinary Products S.r.l., Turin, IT). Once lateral recumbency was achieved, peripheral vascular access was obtained by insertion of a 20-G catheter in the auricular vein, which was used to administer fluid therapy (10 mL/kg/h, NaCl 0.9%). General anesthesia was induced by sevoflurane (5%, SevoFlo, Zoetis, Parsippany-Troy Hills, NJ, US) in a 1:1 oxygen/air mixture via a breathing mask and maintained with the same halogenated agent (1.5–2.5%) once pigs were oro-tracheally intubated. Ventilation was mechanically maintained using an anesthesia delivery unit (Datex Ohmeda ADU S/5 S5, GE Co., Boston, MA, US) in volume-controlled ventilation mode, with tidal volume of 8–10 mg/kg, inhalation/expiration ratio of 1:2, and lung compliance of 1–2 mg/kg. The respiratory rate ranged between 6 and 13 breaths per minute to maintain normocapnia. Anesthetic monitoring included SpO_2, $ETCO_2$, ECG, IBP, and rectal T°C.

Vascular Access

UF sessions were carried out upon surgical insertion of a central catheter in the external jugular vein. The catheter (temporary set double-lumen catheter of 11.5 Fr, ref. HD9120105, Bioengineering Laboratories S.r.l.) was inserted by the veterinary surgeon according to the standard guidelines of veterinary medicine.

The surgical access was performed through the skin incision at the level of the left jugular groove, bounded by the sternocephalic and brachiocephalic muscles. The external jugular vein was isolated after dissection of the muscle bands and raised by vascular loops inserted cranially and caudally with respect to the catheter placement site. The wall of the vessel was partially cut, and the catheter was inserted (shown in Fig. 3).

Fluid Balance and Anticoagulation

Throughout the procedure, all animals received a fluid therapy quota of 10 mL/kg/h of normal saline (NaCl 0.9%) to maintain the hydration status constant. The body weight was monitored every 30 min, at least 13 measurements have been taken for each animal (0–6 h).

For the first two subjects, an initial bolus of heparin (2,000 UI) was administered after the insertion of the jugular catheter, and then a total infusion of 6,000 UI at the rate of 1,000 UI/h (20 UI/kg/h) was continuously infused. In the third animal, a higher dose of heparin was administered after the third hour of treatment for initial signs of circuit clotting. The dose was increased based on experience of the veterinary team, suggesting the possibility of using heparin doses up to 100–200 UI/kg in pigs without side effects. At the end of the procedure, the animals were sacrificed with an overdose of barbiturates.

UF Prescription

Prescribed UF targeted between 1,200 and 1,600 mL in 6 h, considering the catheter performance and the circuit features. Blood flow was set at 30 mL/min. The UF bag was positioned 20 cm below the device in order to get the prescribed UF volume (shown in Fig. 4).

According to previous in vitro experiments, this was expected to provide an UF rate between 3 and 5 mL/min. A backflush bolus of 10 mL of saline was delivered every 2 h in order to avoid protein deposition on the membrane and decrease in UF rate.

Sample Collection

Venous blood samples were collected for clinical chemistry (cloth activating tubes, Monovette®, SARSTEDT, Nümbrecht, DE) and gas analysis (heparin calcium tubes, Monovette®, SARSTEDT, Nümbrecht, DE) at different time points of the treatment: T0 = start of the UF, T1 = 2nd h, T2 = 4th h, T3 = 6th h (end of the treatment).

Table 2. Clinical parameters recorded at different time points during treatment

Animal ID	Time, min	HR, b/m	$EtCO_2$, %	SpO_2, %	Weight, kg	Systolic pressure, mm Hg	Diastolic pressure, mm Hg	MAP, mm Hg
I31	Baseline	80	38	99	56.00	85	60	74
	30	80	37	99	56.00	87	60	70
	60	70	36	100	56.05	80	57	63
	90	75	35	100	56.00	105	65	75
	120	67	35	100	55.90	110	70	85
	150	60	34	100	55.70	105	70	80
	180	58	31	100	55.70	110	70	85
	210	56	33	100	55.50	115	80	90
	240	50	31	100	55.50	120	75	90
	270	55	30	100	55.50	115	70	85
	300	50	36	100	55.50	110	70	82
	330	50	37	100	55.50	115	70	90
	360	50	36	100	55.50	115	65	80
I29	Baseline	100	50	99	62.30	105	65	80
	30	85	49	99	60.55	105	65	80
	60	80	49	99	60.75	110	78	90
	90	76	49	98	59.80	128	90	105
	120	70	50	97	59.95	130	90	110
	150	70	50	99	59.70	114	78	90
	180	69	50	99	59.35	110	75	88
	210	60	50	96	59.45	105	66	85
	240	68	50	99	60.50	118	75	93
	270	66	50	98	60.90	115	75	86
	300	62	50	99	61.45	110	70	85
	330	60	50	99	62.05	112	75	86
	360	55	50	98	62.60	108	66	80
I50	Baseline	80	44	99	51.85	84	52	62
	30	70	43	97	51.80	100	50	64
	60	65	43	97	51.80	105	58	75
	90	65	39	98	51.75	110	66	80
	120	62	38	97	51.80	115	66	80
	150	60	38	97	51.80	115	66	80
	180	60	38	97	51.70	115	60	80
	210	60	36	97	51.65	100	62	70
	240	50	34	97	51.65	100	56	70
	270	55	34	99	51.55	98	55	70
	300	55	34	98	51.55	98	55	70
	330	55	34	96	51.60	84	50	56
	360	50	34	98	51.55	80	40	56

HR, heart rate.

Results

In vivo tests were carried out uneventfully, and throughout the three treatments, we did not experience any significant clinical or technical problems. The animals remained clinically stable in terms of hemodynamics as demonstrated by the values of heart rate, blood pressure, oxygen saturation, CO_2%, and body weight (Table 2).

Biochemical parameters remained stable during treatments, as reported in Table 3. As expected, we did not register substantial variations from baseline of these parameters given the nature of the treatment applied (UF alone replacing mL/mL the UF volume).

We also monitored the behavior of the acid-base parameters that remained stable throughout all treatments (Table 4). The hematological status of the animals was stable for the whole duration of the treatments

Table 3. Biochemical parameters

Animal ID	Time point	Urea, mg/dL	Creatinine, mg/dL	Calcium, mg/dL	Albumin, g/dL	Na, mEq/L	K, mEq/L	Cl, mEq/L	Mg, mg/dL	Hct, %
I31	**T0**	23	1.69	10.3	3.17	139	3.5	97.3	1.86	26.8
	T1	22	1.61	10.0	2.91	142	4.0	102.6	2.23	26.8
	T2	21	1.52	9.8	2.87	140	3.7	101.5	2.21	25.5
	T3	21	1.47	9.8	2.81	142	3.9	104.3	2.19	25.3
I29	**T0**	28	1.30	9.8	2.63	143	3.7	100.7	2.34	31.3
	T1	25	1.24	10.0	2.60	143	4.1	102.0	2.70	28.5
	T2	25	1.13	10.0	2.59	139	4.0	102.2	2.76	30.3
	T3	25	1.09	10.3	2.56	145	4.1	104.8	2.64	25.4
I50	**T0**	36	1.21	9.8	2.36	144	3.8	102.4	2.22	25.9
	T1	34	1.19	9.9	2.25	146	4.2	105.4	2.67	25.5
	T2	32	1.12	9.9	2.22	143	3.9	103.6	2.28	26.6
	T3	32	1.10	10.3	2.18	143	3.9	105.1	2.27	25.2

Table 4. Acid-base status

Animal ID	Time points	PH	Ca++, mmol/L	HCO_3, mmol/L	BE, mmol/L	Osmolarity, mOsm/kg	Anion gap, mmol/L	Lactate, mmol/L
I29	**T0**	7.399	1.31	33.2	10.8	279.7	6.0	0.4
	T1	7.346	1.38	32.1	9.6	278.3	6.4	0.9
	T2	7.332	1.42	31.2	8.5	279.4	7.4	1.0
	T3	7.347	1.44	30.9	8.0	277.9	5.8	1.1
I31	**T0**	7.446	1.25	31.9	9.2	270.4	4.0	0.8
	T1	7.432	1.31	29.9	6.8	266.2	2.8	1.2
	T2	7.439	1.30	28.8	5.3	269.1	6.4	1.4
	T3	7.382	1.34	28.2	4.7	272.2	7.6	1.4
I50	**T0**	7.394	1.33	33.3	10.6	283.0	2.3	0.5
	T1	7.428	1.37	33.5	10.5	279.6	3.0	0.5
	T2	7.443	1.40	32.6	9.5	282.7	6.7	0.7
	T3	7.437	1.43	31.7	8.5	282.2	6.3	0.9

Table 5. Hematological status

Animal ID	Time points	HB, g/dL	Hct, %	RBCs/mm^3	PLTs/mm^3	WBCs/mm^3
I31	**T0**	10.8	31.2	6,220,000	345,000	12,840
	T1	9.5	27.7	5,560,000	340,000	11,360
	T2	9.2	26.4	5,340,000	350,000	9,930
	T3	8.8	25.2	5,100,000	330,000	9,750
I29	**T0**	9.1	26.4	4,690,000	551,000	14,370
	T1	8.8	25.6	4,620,000	560,000	15,940
	T2	8.6	24.8	4,500,000	556,000	13,500
	T3	8.6	24.5	4,460,000	504,000	11,100
I50	**T0**	8.6	25.4	4,840,000	506,000	19,050
	T1	8.4	24.7	4,770,000	481,000	16,060
	T2	8.5	24.1	4,740,000	443,000	14,130
	T3	8.3	24.1	4,700,000	444,000	13,390

Table 6. Coagulative parameters

Animal ID	Time	Time point	PT, s	Fibrinogen Clauss, g/dL	aPTT, s
I31	13:14	T0	11.7	1.58	43.6
	15:25	T1	11.5	1.77	36.9
	16:35	T2	11.8	1.81	40.1
	21:04	T3	12.0	2.12	45.6
I29	11:13	T0	12.1	2.87	32.2
	12:37	T1	11.4	2.79	23.5
	15:14	T2	11.2	2.93	18.3
	16:25	T3	11.4	2.86	36.3
I50	12:44	T0	10.3	1.95	73.5
	12:47	T1	10.5	1.98	24.0
	13:56	T2	11.3	2.00	79.1
	17:01	T3	13.8	2.03	120.0

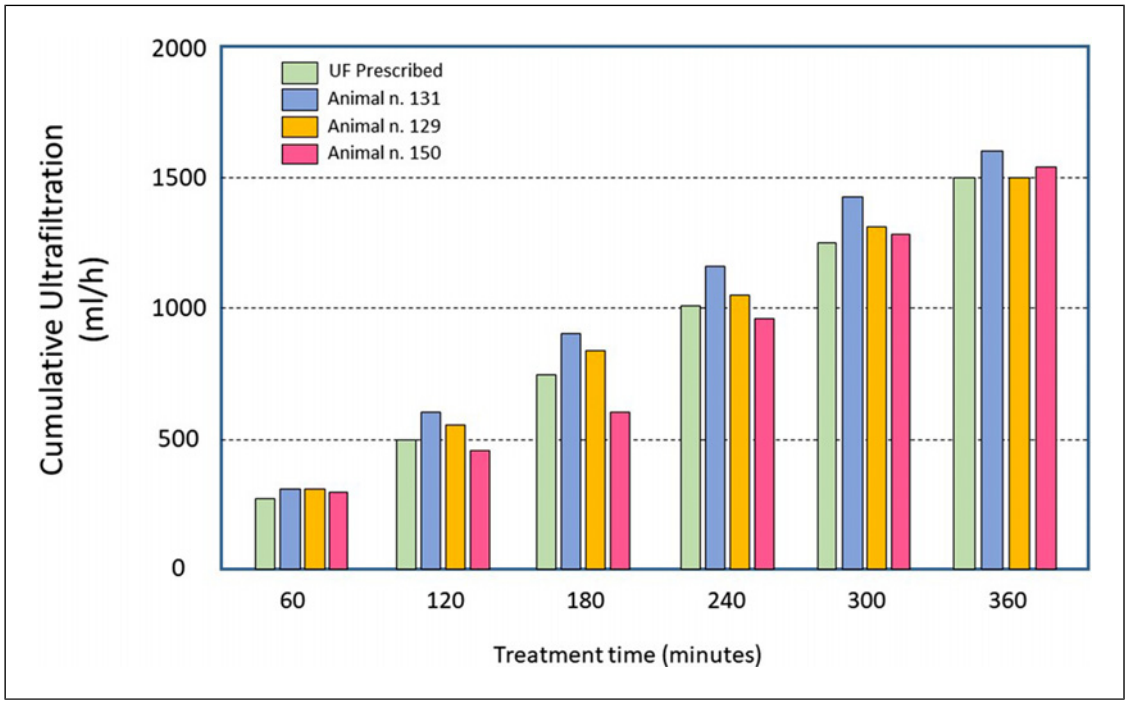

Fig. 5. Values of cumulative UF at each time point and final value of cumulative UF in the three animals compared to the prescribed/expected values.

(Table 5), and no blood losses were experienced during the extracorporeal circulation. Following heparin administration, the coagulative status was carefully monitored with no significant variations from baseline parameters (Table 6). In particular, no bleeding complications were observed.

The heparin administration protocol was maintained below the scheduled prescription for the first two animals as suggested by the veterinary team in light of careful monitoring of coagulation parameters. In the third animal, when initial signs of circuit clotting were observed (circuit pressure variation), the prescription was modified and increased until pressures were stabilized and filter performance was normalized. In spite of this, the protocol was always well below the upper limit suggested for extracorporeal circulation, and no bleeding complications were observed. This approach is the same as that utilized in humans during extracorporeal circulations.

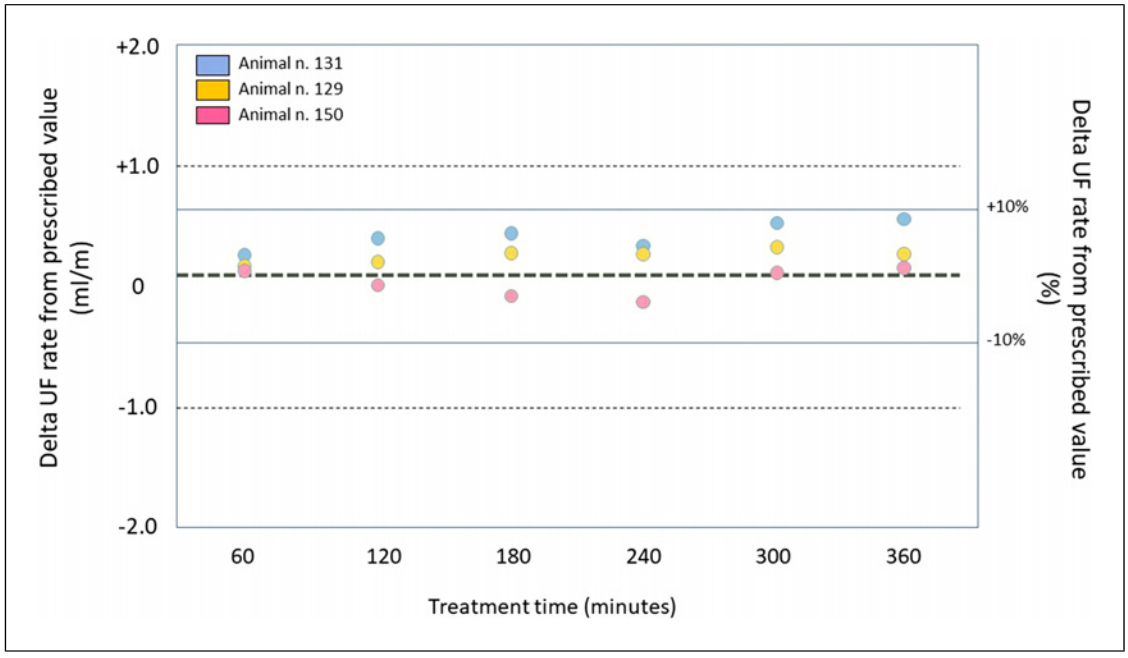

Fig. 6. Maximum deviation from the scheduled UF rate observed during treatment.

The performance of the device was excellent with no failures or significant technical problems. In particular, there was a remarkable correspondence between the prescribed amount of UF and the overall amount of UF obtained per hour and at the end of the treatments (shown in Fig. 5). The highest deviation from the scheduled value of UF rate is reported in Figure 6. It can be observed that maximum deviation from the prescribed value always remained below 10%. As a final consideration, we may describe this performance as similar to that of other predicated devices for extracorporeal UF.

Discussion

The reported tests in animals confirm the accuracy and reliability of the new AD1 device for extracorporeal UF. In particular, no significant complications or technical malfunctions were observed during the treatments. Animals underwent a typical session of extracorporeal UF, where classic prescription parameters were applied as we usually do in clinical routine. The device resulted to be usable thanks to the friendly user interface and displayed a remarkable accuracy in achieving the target values prescribed for each treatment. In all treatments, the device operations resulted to be safe without any technical or clinical problems.

The combination of reduced size, usability, accuracy, and safety render this new device particularly suitable for extracorporeal UF in different clinical settings, not exclusively for highly specialized hospital departments but also, possibly, for low intensity care departments, nursing homes, and even home patients with self-administration of the therapy. This opens the way to clinical trials for the application of AD1 in these settings.

Statement of Ethics

All the experimental procedures were performed upon dedicated protocol approval by the Italian Ministry of Health, as dictated by Legislative Decree 26/2014 (approval No. 304/2019-PR).

Conflict of Interest Statement

Professor Claudio Ronco: C.R., in the last 3 years, has 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 and Ashai. MD. Alessandra Brendolan: Medica. MD. Luca Sgarabotto, ENG. Anna Lorenzin, MD. Luca Di Lullo, DVM. Maria Laura Bacci, DVM. Alberto Elmi, DVM. Domenico Ventrella, and DVM. Camilla Aniballi have no conflicts of interest to declare.

Funding Sources

The study was conducted in collaboration with Medica S.r.l. on the basis of an agreement between Bologna University and Medica S.r.l.

Author Contributions

Study concept and design: Claudio Ronco, Luca Sgarabotto, Alessandra Brendolan, and Anna Lorenzin. Drafting of manuscript: Claudio Ronco, Anna Lorenzin, Luca Sgarabotto, and Monica Zanella. Critical revision of manuscript for important intellectual content: Monica Zanella, Maria Laura Bacci, Alberto Elmi, Domenico Ventrella, Camilla Aniballi, and Luca Di Lullo.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1 Gheorghiade M, Filippatos G, De Luca L, Burnett J. Congestion in acute heart failure syndromes: an essential target of evaluation and treatment. Am J Med. 2006;119(12 Suppl 1):S3–10. Epub 2006/11/23.
2 Claure-Del Granado R, Mehta RL. Fluid overload in the ICU: evaluation and management. BMC Nephrol. 2016;17(1):109. Epub 2016/08/04.
3 Schiffl H, Lang SM. Oliguria, fluid overload and recovery of renal function from acute renal failure requiring renal replacement therapy. Nephrol Dial Transplant. 2011; 26(12). 4150; author reply -1.
4 Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. Circulation. 2010;122(3): 265–72. Epub 2010/07/08.
5 Agostoni P, Marenzi G, Lauri G, Perego G, Schianni M, Sganzerla P, et al. Sustained improvement in functional capacity after removal of body fluid with isolated ultrafiltration in chronic cardiac insufficiency: failure of furosemide to provide the same result. Am J Med. 1994;96(3):191–9. Epub 1994/03/01.
6 Huang Q, Zhao R, Yue C, Wang W, Zhao Y, Ren J, et al. Fluid volume overload negatively influences delayed primary facial closure in open abdomen management. J Surg Res. 2014;187(1):122–7. Epub 2013/11/19.
7 Patel DM, Connor MJ Jr. Intra-abdominal hypertension and abdominal compartment syndrome: an underappreciated cause of acute kidney injury. Adv Chronic Kidney Dis. 2016;23(3):160–6. Epub 2016/04/27.
8 Katz SD. The plot thickens: hemoconcentration, renal function, and survival in heart failure. Circulation. 2010;122(3):233–5. Epub 2010/07/08.
9 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. Epub 2012/11/08.
10 Magee G, Zbrozek A. Fluid overload is associated with increases in length of stay and hospital costs: pooled analysis of data from more than 600 US hospitals. Clinicoecon Outcomes Res. 2013;5:289–96. Epub 2013/ 07/10.
11 Wang M, Zhu B, Jiang L, Wen Y, Du B, Li W, et al. Dose-response association between fluid overload and in-hospital mortality in critically ill patients: a multicentre, prospective, observational cohort study. BMJ open. 2020; 10(12):e039875. Epub 2020/12/30.
12 Marenzi G, Lauri G, Grazi M, Assanelli E, Campodonico J, Agostoni P. Circulatory response to fluid overload removal by extracorporeal ultrafiltration in refractory congestive heart failure. J Am Coll Cardiol. 2001;38(4): 963–8. Epub 2001/10/05.
13 Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016;18(8):891–975. Epub 2016/ 05/22.
14 Gura V, Ronco C, Nalesso F, Brendolan A, Beizai M, Ezon C, et al. A wearable hemofilter for continuous ambulatory ultrafiltration. Kidney Int. 2008;73(4):497–502. Epub 2007/12/07.
15 Ronco C, Fecondini L. The Vicenza wearable artificial kidney for peritoneal dialysis (ViWAK PD). Blood Purif. 2007;25(4):383–8. Epub 2007/09/06.
16 Boschetti G, Dalla Via A, De Rossi N, Garzotto F, Neri M, Pamato L, et al. Conceptual design of a mechatronic biomedical wearable device for blood ultrafiltration. In: Advances in Italian mechanism science. Berlin: Springer; 2017.
17 Lodi CA, Vasta A, Hegbrant MA, Bosch JP, Paolini F, Garzotto F, et al. Multidisciplinary evaluation for severity of hazards applied to hemodialysis devices: an original risk analysis method. Clin J Am Soc Nephrol. 2010;5(11): 2004–17. Epub 2010/09/04.