Deresuscitation during continuous renal replacement therapy: A before-after pilot study (The EARLY DRY COHORT)

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Abstract

Background: Active fluid removal has been suggested to improve prognosis following the resolution of acute circulatory failure. To standardize the deresuscitation strategy, we have implemented a routine care protocol to guide fluid removal during continuous renal replacement therapy (CRRT). We designed a before-after pilot study to evaluate the impact of this deresuscitation strategy on the cumulative fluid balance.

Methods: Consecutive ICU patients suffering from fluid overload and undergoing CRRT for acute kidney injury underwent a perfusion-based deresuscitation protocol combining a restrictive intake, continuous net ultrafiltration (UFnet) of 2 mL/kg/h, and both clinical and laboratory monitoring of perfusion (early dry group, N=42) and were compared to an historical group managed according to usual practices (control group, N=45). The primary outcome was the cumulative fluid balance at day 5 or at discharge. Secondary outcomes addressed the protocol safety. Adjustments were done with inverse probability of treatment weighting propensity score analysis.

Results: Adjusted cumulative fluid balance was significantly lower in the early dry group (median [IQR]: -7784 [-11833 to -2933] mL) compared to the control group (-3492 [-9935 to -1736] mL, p=0.04). The difference was mainly driven by a greater daily UFnet (31 [22-46] mL/kg/day *vs.* 24 [15-32] mL/kg/day, p=0.01). There was no significant difference between both groups regarding maximal arterial lactate level and maximal norepinephrine dose requirement.

Conclusion: Our perfusion-based deresuscitation protocol achieved a greater negative cumulative fluid balance compared to standard practices and was hemodynamically well tolerated. Those data suggest the feasibility of an interventional randomized clinical trial using a similar protocol.

Background

Fluid overload is commonly encountered in critically-ill patients and associated with poor clinical outcome, especially for patients with acute kidney injury and renal replacement therapy (1–5). The combination of important intakes initially required by the shock resuscitation and capillary leakage, then sustained by volumes of medication, transfusion, fluids of maintenance and/or nutrition, and inadequate outputs may generate deleterious tissue edema (6,7). In this context, some experts support an active deresuscitation strategy consisting in fluid removal to reduce the duration of fluid overload and accelerate recovery (R.O.S.E concept) (8). However, such a strategy may lead to harmful iatrogenic hypovolemia. In patients with continuous renal replacement therapy (CRRT), the equilibration of fluid balance is mainly driven by the net ultra-filtration (UFnet) setting, which ensures a nearly isotonic fluid removal (9). Many observational studies have found a U-shaped association between UFnet intensity during CRRT and outcome, thereby promoting a moderate UFnet rate to be applied (10–12).

Previous surveys reported a high heterogeneity in the clinical management of fluid removal (13–15). To guide the deresuscitation strategy and standardize practices, a routine care protocol has been

implemented in the study center for patients with fluid overload and treated with CRRT, combining restrictive intakes associated with the prescription of an UFnet and a surveillance of peripheral perfusion as suggested by expert guidelines (16). The peripheral perfusion has been clinically and biologically assessed at least four times a day in order to detect inadequate fluid removal-induced hypoperfusion.

Clinicians and experts have identified the need for controlled studies concerning fluid removal and its monitoring (13,16). Therefore, we conducted a pilot study to evaluate the impact of the perfusion-based deresuscitation strategy previously mentioned on the cumulative fluid balance and to answer some relevant questions about the design of a future randomized controlled trial.

Methods

Study design

We conducted a single-center before-after cohort study with a within-subject design at the *Hôpital Louis Pradel* (*Hospices Civils de Lyon*, France). Consecutive patients were eligible over two periods: from 1st January to 31th December 2020 (pre-intervention period) and 15th February to 15th August 2021 (intervention period). All data were prospectively and automatically recorded *via* the IntelliSpace Critical Care and Anaesthesia software (V H.02.01, Philips Healthcare, Andover, MA, USA) or the patients' computerized medical file (easily® V05.12.00.00, *Hospices Civils de Lyon*, France). Data were retrospectively collected during the pre-intervention period and prospectively collected during the intervention period. The two periods were separated by a run-in period of 6 weeks allowing to put the protocol in place. The study protocol was registered on clinicaltrials.gov (NCT05119361) and approved by the local ethics committee (IRB: 00013204). As the perfusion-based deresuscitation protocol was considered as a new standard of care, the institutional review board waived the need for written informed consent. According to French law, non-opposition to the use of patients' health data for research purposes was systematically proposed and the data collection was approved by the *Commission national de l'informatique et des libertés*. The manuscript followed the STROBE guidelines (17) and the completed checklist is available in Additional file 1.

Participants and study protocol

Eligible patients had to fulfil the following inclusion criteria: age > 18, need for CRRT for acute kidney injury, cumulative fluid balance above 5% (based on weight-related cumulative fluid balance or computerized cumulative fluid balance as defined below), and norepinephrine equivalent dose < 0.5 µg/kg/min (18). Exclusion criteria were: pregnancy, active bleeding, chronic intermittent hemodialysis, stroke with coma, advanced directives to withhold or withdraw life-sustaining treatment, and patient's opposition to the use of his/her personal health data. Patients meeting the inclusion criteria and admitted during the pre-intervention period were included in the control group, whereas those admitted during the intervention period were included in the early dry group. In the control group, the management of fluid balance during the deresuscitation phase (i.e. timing of initiation, intensity, monitoring, reason to

discontinue fluid removal, etc.) was left to the clinician discretion since there was no institutional protocol. By contrast, the complete deresuscitation perfusion-based protocol of the early dry group is illustrated in Figure 1.

Outcomes

The primary outcome was the computerized cumulative fluid balance at day 5, at death, or at discharge, automatically calculated by the software and defined as the difference between total intake (cumulative volume of medication, enteral and parenteral feeding, fluid loading, and transfusion products) and total output (cumulative volume of diuresis, surgical drainage, and UFnet).

Secondary outcomes were: 1) weight-related cumulative fluid balance defined by weight variations with electronic bed weighing = (weight at day 5 or discharge - weight on the day of inclusion) / weight on the day of inclusion, 2) inclusion rate of patients included in the early dry group to estimate the population of eligible patients in a large RCT, defined as the ratio between included patients to admitted patients, 3) hemodynamic tolerance of the protocol defined both by the incidence of hypoperfusion in the early dry group (number of events per day) and by the maximal arterial lactate level and maximal norepinephrine dose until day 5 or discharge in the two groups, 4) exploratory outcomes: weaning of mechanical ventilation at day 7 among live patients, weaning of renal replacement therapy at day 30 among live patients, mortality rate at day 30, number of ventilator-free days at day 30, number of renal replacement therapy-free days at day 30, number of norepinephrine-free days at day 30, number of organ failure-free days at day 30 (see Additional file 2 for definitions).

Statistical analysis

Considering recruitment difficulties in a previous study using a comparable strategy (19), we did not determine a sample size *a priori* but rather a study period to determine the feasibility of a RCT (the potential rate of inclusion). Missing data concerning Sepsis Organ Failure Assessment (SOFA) score were handled as previously described (20): missing score components at baseline were assigned the score of 0, otherwise the last value was used until new data were available. To handle missing values at baseline of other variables, required for inverse probability weighted adjustment, we used a random forest based process to impute missing data. The maximum iteration was set to 10. No imputation was carried out for other variables recorded after baseline. Variables with a rate of missing values greater than 25% were not analyzed.

Data were expressed as mean (standard deviation, SD), median [interquartile range, IQR], or count (percentage), as appropriate. Characteristics of the two groups were compared using the Student *t* test or the Mann-Whitney *U* test for continuous variables, and a χ^2 test or the Fisher exact test for categorical variables. As the cohort was observational, we adjusted the data to the inverse probability of belonging to the control group or to the early dry group by using a propensity score built on a logit model. Variables initially included in the model were all pertinent variables with a *P* value less than 0.2. UFnet and delay between the admission and the inclusion were not included in the model as the difference observed is a

direct consequence of the protocol application, nor was the acute respiratory distress syndrome due to the obvious collinearity with the COVID-19 status. Then we added age, arterial lactate, and vasoactive-inotropic score to balance groups regarding those three known prognostic factors (21–23). We considered no collinearity of variables if the square root of the variation to inflation ratio was less than 2. We then used the inverse probability to create a weighted pseudo population. To decrease the variability of the effect of the treatment, we truncated the weight to a maximum of the 99th percentile of all weights to decrease the impact of outliers. Each participant was weighted using the overlap weight approach, which down-weights individuals based on propensity score values. Covariate balance between the two groups was assessed after weighting, and we considered an absolute standardized difference of less than 0.1 as evidence of balance and 0.25 as acceptable balance considering the small sample size (24).

Statistical analyses were performed using R version 4.1.2 (R Core Team 2017, Vienna, Austria). IPW (25), missForest (26), and survey (27) packages were used. All tests were two-sided and a *P* value less than 0.05 was considered significant.

Results

All results of outcomes are reported as adjusted with inverse probability of treatment weighting propensity score analysis. Unadjusted results are available in Additional File 3. The number of missing values per variable is reported in Additional file 4.

Population

A total of 87 patients were included during the study period, 45 in the control group and 42 in the early dry group (Figure 2). At baseline, the median [IQR] age of patients was 62 [56-71] years, 51 (59%) were admitted for postoperative care and 45 (52%) presented a cardiogenic shock. The median [IQR] delay between admission and inclusion was 4 [2-9] days. Multiple organ failure was common, as 67 (77%) patients were mechanically ventilated, 18 (21%) had a circulatory support by extracorporeal membrane oxygenation, and the median [IQR] SOFA score was 13 [10-16]. They were hemodynamically stabilized as the median [IQR] arterial lactate level was 1.5 [1.1-2.1] mmol/L and the median [IQR] norepinephrine dose requirement was 0.3 [0.16-0.39] µg/kg/min. The median weight-related cumulative fluid balance at baseline was 12 [7-19] %. Baseline characteristics of the two groups before and after inverse probability weighting are reported in Table 1.

Impact on the fluid balance

The computerized cumulative fluid balance at day 5 or discharge was significantly lower in the early dry group (median [IQR]: -7784 [-11833 to -2933] mL) than in the control group (-3492 [-9935 to -1736] mL, p=0.04), as well as the weight-related cumulative fluid balance at day 5 or discharge (-7 [-15.4 to -3.9] % *vs.* -4.6 [-9 to -1.6] %, p=0.03). The daily UFnet was significantly greater in the early dry group (31 [22-46] mL/kg/day) than in the control group (24 [15-32] mL/kg/day, p=0.01), as was the total outputs at day 5 or discharge (14250 [11422-16994] mL *vs.* 11432 [9286-14639] mL, p=0.02). We observed no significant

difference regarding daily diuresis (4 [0-12] mL/kg/day *vs.* 10 [2-16] mL/kg/day, p=0.46) and total intakes at day 5 or discharge (7004 [3695-10091] mL *vs.* 7673 [5098-10057] mL, p=0.68). Considering intravascular volume indices, we observed a blood volume contraction in the early dry group as illustrated by an increase in the plasma protein concentration (15 [0-19] %) whereas there was no variation for the control group (0 [-7 - 9] %, p<0.01, Figure 3). Central venous pressure variations were not analyzed because of too many missing values.

Hemodynamic tolerance

There was no significant difference between the two groups in terms of maximal arterial lactate level, maximal norepinephrine dose requirement, and maximal vasoactive inotropic score during the study period. The daily number of hypoperfusion events was low in the early dry group (median [IQR]: 0.2 [0-0.8] event/day, Table 2), even if 25/42 (60%) patients experienced at least one episode.

Impact on the exploratory outcomes

At day 30, 33 (38%) patients from the early dry group and 37 (45%) from the control group had died (p=0.58), and the proportion of live patients weaned off renal replacement therapy was slightly lower in the early dry group (34, 64%) compared to the control group (37, 78%, p=0.33, Table 3).

Inclusion rate

The overall inclusion rate [95%CI] was 4.4 [3.5, 5.3] % considering all the patients admitted to the study ICU during the study period, and the inclusion rate was significantly lower in the control group (3.4 [2.4, 4.4] %) compared to the early dry group (6.4 [4.5, 8.3] %, p= 0.04). There was a trend towards a lower proportion of patients with fluid overload in the control group (59.3 [50.5, 68.2] %) compared to the early dry group (74.4 [64.7, 84] %, p=0.32).

Discussion

The main findings of the present study are: 1) perfusion-based deresuscitation achieved a greater negative cumulative fluid balance than usual practices, 2) perfusion-based deresuscitation was hemodynamically well tolerated, and 3) our inclusion rate confirms the feasibility of a randomized trial on this population.

Impact of the perfusion-based deresuscitation protocol on the fluid balance

Our study confirmed the efficacy of our protocol to early negate fluid balance for patients with fluid overload and defined as hemodynamically stabilized. The pre-intervention usual practices in our service were already to apply negative fluid balance cases during the deresuscitation phase, as illustrated by the values of the computerized and the weight-related cumulative fluid balances at day 5 or discharge. Those practices are coherent with recent guidelines from the International Fluid Academy and the usual practices observed in two recent surveys (8,13,15). However, the perfusion-based deresuscitation protocol

led to a significantly greater UFnet and a lower fluid balance, which reduces the exposure to fluid overload. Of note, the difference between the two groups observed in terms of cumulative fluid balance was mainly driven by the UFnet applied rather than by significant differences in intakes or diuresis, supporting that an active deresuscitation strategy by mechanical fluid removal is required. This is consistent with a previous study showing a probable incompressible amount of intakes in critically-ill patients related to enteral or parenteral feeding and medication (28). The range of daily UFnet applied in the early dry group was consistent with previous studies showing an association between UFnet values and a better prognosis (11,12,29). We can explain the gap between the targeted daily UFnet (48 mL/kg/day) and the observed daily UFnet by two mechanisms: iterative suspensions of UFnet due to hemodynamic instability (increased norepinephrine requirement over the threshold of 0.5 µg/kg/min or hypoperfusion events in accordance with our protocol) or technical considerations (such as hemofilter change, catheter malfunction, complementary exams) as previously observed for CRRT doses (30).

Hemodynamic tolerance of the perfusion-based deresuscitation protocol

Considering data about maximal norepinephrine dose, arterial lactate level, and vasoactive inotropic score, the perfusion-based deresuscitation protocol was well tolerated compared to the pre-intervention usual practices, which is consistent with previous deresuscitation protocols (19,31). However, even if the incidence of hypoperfusion episodes seemed low in the early dry group, more than half of the patients experienced at least one episode leading to UFnet suspension and hemodynamic optimization by the medical team. Hypoperfusion as defined in our study was not a known prognostic factor considering patients with CRRT, but it is physiologically plausible that it may impede organ failure recovery. Besides, capillary refill time has been described as a predictor of poor hemodynamic tolerance during RRT (32) and small variations in volemia can be detected by capillary refill time variations (33). In our opinion, it promotes strict hemodynamic monitoring during deresuscitation to avoid the side effects related to inadequate forced fluid removal. In this context, peripheral perfusion markers seem to constitute a promising tool (34,35).

Exploratory outcomes

The absence of statistically significant differences between the two groups in terms of outcomes supports the notion of safety of the perfusion-based deresuscitation protocol. We cannot rule out that potential iatrogenic hypoperfusion episodes could have been responsible for a lower weaning rate of CRRT among live patients, but the comparable maximal values of arterial lactate level and the trend towards a lower mortality in the early dry group do not support this hypothesis. The trends observed must be interpreted with caution, as our study was not designed and is underpowered to analyze such outcomes. Furthermore, results should not be interpreted as the impact of a deresuscitation strategy versus a liberal or a stabilization fluid strategy, as in the control group we observed that members of our team had already applied a deresuscitation strategy with UFnet before the perfusion-based deresuscitation protocol implementation.

Perspectives

The inclusion rate found herein was more important than in the study of Berthelsen *et al.*(19) and corresponded to more than 4 potential inclusions per month in our center, which is consistent with the inclusion rate observed in a previous study on CRRT (36). It is an important finding considering the feasibility of a future RCT, as the FFAKI-trial had to be stopped prematurely due to a low inclusion rate (19). We observed a relatively high proportion of fluid overload, defined by a weight gain greater than 5%, compared to other studies (37,38), maybe related to the continuous screening of fluid loading status during the whole intensive care unit journey and the high proportion of patients admitted for post-operative care and/or cardiogenic shock.

Strengths and limits of the study

Some limitations of the present study should be acknowledged. First, it is not an interventional randomized trial, even though the inverse probability weighting score approach allowed us to partially correct the initial group differences logically observed in the context of the COVID-19 pandemic characterized by a high variability in patient recruitment. Second, the small sample size did not allow us to strictly balance the two populations with standardized mean differences < 0.1 for all variables at baseline. Third, we cannot compare perfusion data between groups to fully describe the hemodynamic tolerance of the protocol, as peripheral perfusion and laboratory markers used in the perfusion-based deresuscitation protocol were not systematically evaluated before its implementation. Hence, we cannot strictly exclude that the perfusion-based deresuscitation protocol is responsible for hypoperfusion episodes with hidden side effects. Fourth, due to the lack of standardized definition in the literature, the deresuscitation phase and hypoperfusion criteria were specific to the present study. Fifth, the high rate of fluid overload observed in the study ICU participated in the relatively high inclusion rate and may have overestimated it. To finish, it was a single-center study, which limits the generalizability of the results.

Although pilot RCT about deresuscitation strategy in patients with CRRT have already been published, they have failed to be applicable in a large RCT (19) or to induce a negative fluid balance at day 5 (31). To our knowledge, we are the first to present a perfusion-based deresuscitation protocol of forced fluid removal by UFnet that is effective to decrease cumulative fluid balance. Our perfusion-based deresuscitation protocol seems safe, and the eligibility criteria are compatible with the conduction of a randomized clinical trial.

Conclusion

A composite perfusion-based deresuscitation protocol in patients with fluid overload and CRRT achieved a greater negative cumulative fluid balance at day 5 or discharge compared to usual practices without hemodynamic instability and complications. Those data suggest the feasibility of an interventional randomized clinical trial using a similar protocol aiming to assess its impact on morbidity and mortality.

Declarations

Ethics approval and consent to participate: The study protocol was approved by the local ethics committee (*Hospices Civils de Lyon*, IRB: 00013204). As the design was observational (in agreement with the French law n° 2012-300 of the 5th of March 2012 for research concerning data), the institutional review board waived the need for written informed consent. Non-opposition to the use of patients' health data for research purposes was systematically researched by email or post.

Consent to publication: Not applicable

Availability of data and material: All de-identified datasets may be available for secondary analysis upon reasonable request to the corresponding author.

Competing interests: Delphine Chesnel, Léa Didier, Martin Ruste, Matthias Jacquet-Lagrèze, Raouf Sghaier, Jean-Luc Fellahi have no conflict of interest related to this study.

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Authors' contributions

Study concept and design: *MR, MJL, JLF.*

Acquisition of data: *MR, MJL, RS.*

Interpretation of data: *MR, MJL, JLF, LD, DC.*

Drafting of manuscript: *MR, MJL*

Statistical analysis: *MR*

Study supervision: *MR, MJL*

Critical revision of the manuscript for important intellectual content: *MR, MJL, RS, LD, DC, JLF*

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Tables

Table 1: Baseline characteristics of the patients

	Baseline population			Propensity weighted population		
	Control group (n=45)	Early dry group (n=42)	*P* value	Control group	Early dry group	ASD
Age (years)	62 (±12)	62 (±12)	0.93	61 (±11)	61 (±14)	0.05
Male sex	28 (62)	31 (74)	0.35	51 (62)	57 (67)	**0.1**
Weight (kg)	79 (±16)	81 (±21)	0.75	79 (±16)	82 (±25)	**0.15**
Height (cm)	169 (±9)	172 (±9)	**0.06**	169 (±8)	171 (±11)	**0.19**
Usual GFR (mL/min/1.73m^2)	68 (±28)	66 (±27)	0.8	69 (±28)	68 (±26)	0.04
COVID-19 status (yes)	3 (7)	10 (24)	**0.05**	10 (12)	13 (15)	0.09
ARDS (yes)	8 (18)	14 (33)	**0.16**	26 (31)	21 (24)	**0.16**
Delay from admission to inclusion (days)	4 [1-8]	5 [3-10]	**0.18**	4 [1-9]	4 [2-8]	0.08
Admission category						
Medical	16 (36)	20 (48)	0.36	32 (39)	40 (46)	**0.14**
Surgical	29 (64)	22 (52)		50 (61)	46 (54)	
Shock category						
Distributive shock	33 (73)	33 (79)	0.75	59 (72)	61 (71)	0.005
Cardiogenic shock	25 (56)	20 (48)	0.6	41 (50)	51 (59)	**0.18**
Hemorrhagic shock	9 (20)	6 (14)	0.7	15 (18)	14 (16)	0.05
Organ support at inclusion						
Veno-arterial ECMO	12 (27)	6 (14)	0.25	23 (27)	20 (23)	0.09
Veno-venous ECMO	1 (2)	4 (9)	0.32	4 (5)	5 (6)	0.05
Mechanical ventilation	31 (69)	36 (86)	**0.11**	61 (74)	68 (79)	**0.12**
SOFA score at inclusion	12 [10-16]	15 [12-16]	**0.12**	13 [10-16]	14 [10-17]	**0.17**
Hemodynamic data at inclusion						
Norepinephrine dose (µg/kg/min)	0.35 [0.21-0.39]	0.26 [0.11-0.39]	0.39	0.3 [0.19-0.39]	0.32 [0.16-0.42]	0.05

Dobutamine dose (µg/kg/min)	0 [0-5]	0 [0-3]	0.33	0 [0-5]	0 [0-5]	**0.13**
Vasoactive inotropic score	36 [23-44]	27 [11-41]	0.35	34 [19-40]	36 [16-44]	0.07
Central venous pressure (mmHg)	9 [6-12]	7 [6-10]	**0.18**	8 [6-11]	8 [6-12]	0.07
Arterial lactate (mmol/L)	1.5 [1.0-2.2]	1.5 [1.3-1.9]	0.73	1.4 [1.0-2.2]	1.5 [1.3-2.3]	0.08
Fluid balance related data						
Diuresis at inclusion (mL/kg)	800 [160-1450]	382 [130-799]	**0.02**	592 [150-1177]	495 [173-1162]	**0.16**
WCFB at inclusion (%)	11 [6-20]	12 [8-18]	0.63	12 [6-20]	11 [7-17]	**0.2**
Total UFnet before inclusion (mL/kg)	14 [0-1666]	0 [0-516]	**0.14**	122 [0-3107]	0 [0-381]	**0.23**
CRRT related data						
Creatinine level at CRRT initiation (µmol/L)	257 [160-369]	295 [191-388]	0.43	267 [159-369]	239 [163-364]	**0.25**
Urea level at CRRT initiation (mmol/L)	18 [11-31]	25 [16-36]	**0.12**	19 [11-31]	22 [9-29]	0.03

Data are expressed as count (percentage), mean (±standard deviation), or median [interquartile range]. ARDS: acute distress respiratory syndrome, ASD: absolute standardized difference, CRRT: continuous renal replacement therapy, GFR: glomerular filtration rate, ECMO: extra corporeal membrane oxygenation, SOFA: sepsis organ failure assessment, UFnet: net ultrafiltration, WCFB: weighted-related cumulative fluid balance.

Table 2: Hemodynamic tolerance of deresuscitation between day 1 and day 5 or discharge adjusted with inverse probability of treatment weighting propensity score analysis

	Control group	Early dry group	*P* value
Maximal arterial lactate level (mmol/L)	2.0 [1.5-3.4]	1.8 [1.6-2.6]	0.46
Maximal norepinephrine dose (µg/kg/min)	0.4 [0.2-0.9]	0.3 [0.2-0.6]	0.51
Maximal vasoactive inotropic score	43 [17-100]	35 [20-63]	0.56
Number of hypoperfusions per day	-	0.2 [0.0-0.8]	-
Number of capillary refillings lasting more than 3 s per day	-	0.4 [0.2-1.2]	-
Number of time the arterial lactate level was greater than 2 mmol/L per day	-	0.0 [0.0-0.2]	-

Data are expressed as count (percentage) or median [interquartile range].

Table 3: Exploratory outcomes adjusted with inverse probability of treatment weighting propensity score analysis

	Control group	Early dry group	*P* value
SOFA score variation between inclusion and day 5 or discharge	-2 (±5)	-3 (±5)	0.49
Number of patients weaned off mechanical ventilation at day 7	40 (56)	47 (60)	0.77
Number of patients weaned off renal replacement therapy at day 30	37 (78)	34 (64)	0.33
Number of dead patients at day 30	37 (45)	33 (38)	0.58
Number of ventilator-free days at day 30	13 (±14)	14 (±14)	0.83
Number of norepinephrine-free days at day 30	12 (±13)	11 (±11)	0.65
Number of renal replacement therapy-free days at day 30	11 (±13)	10 (±12)	0.73
Number of organ failure-free days at day 30	9 (±11)	8 (±12)	0.74

Data are expressed as count (percentage) or mean (±standard deviation).

Figures

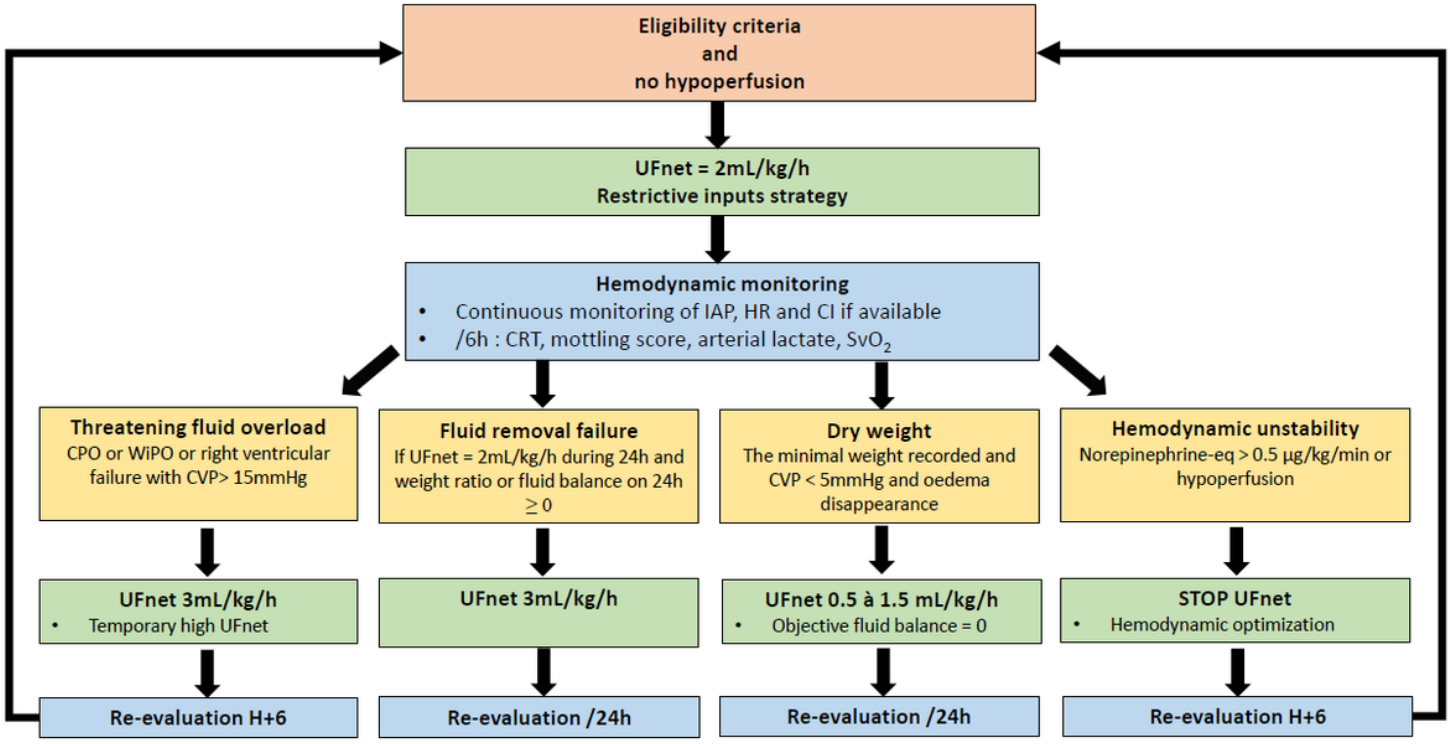

Figure 1

Study protocol for the early dry group *CI: cardiac index, CPO: cardiogenic pulmonary edema, CRT: capillary refilling time, CVP: central venous pressure, HR: heart rate, IAP: invasive arterial pressure, SvO_2: central venous oxygenation saturation, Norepinephrine-eq: Norepinephrine equivalent as described in* (20), *UFnet: net ultra-filtration, WiPO: weaning induced pulmonary edema.*

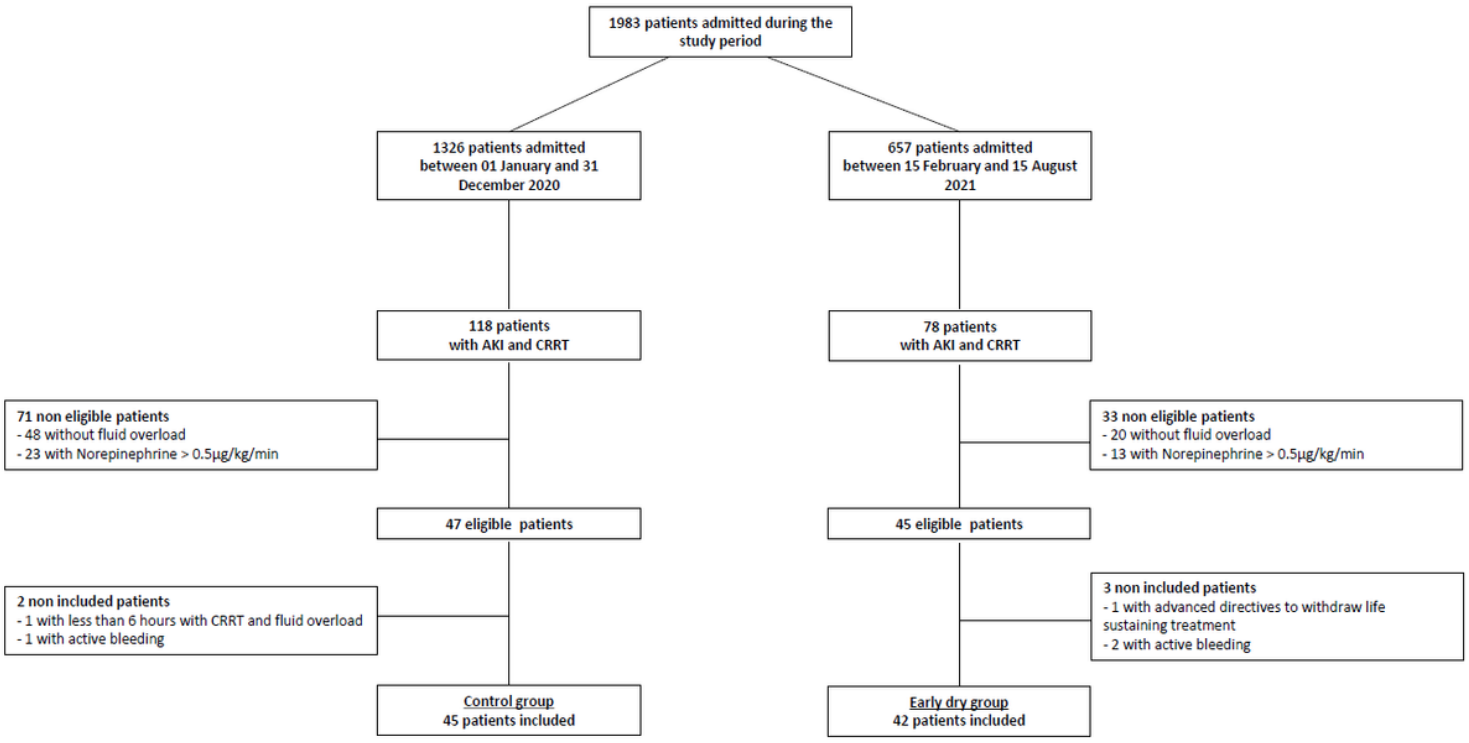

Figure 2

Study flow chart

AKI: acute kidney injury, CRRT: continuous renal replacement therapy

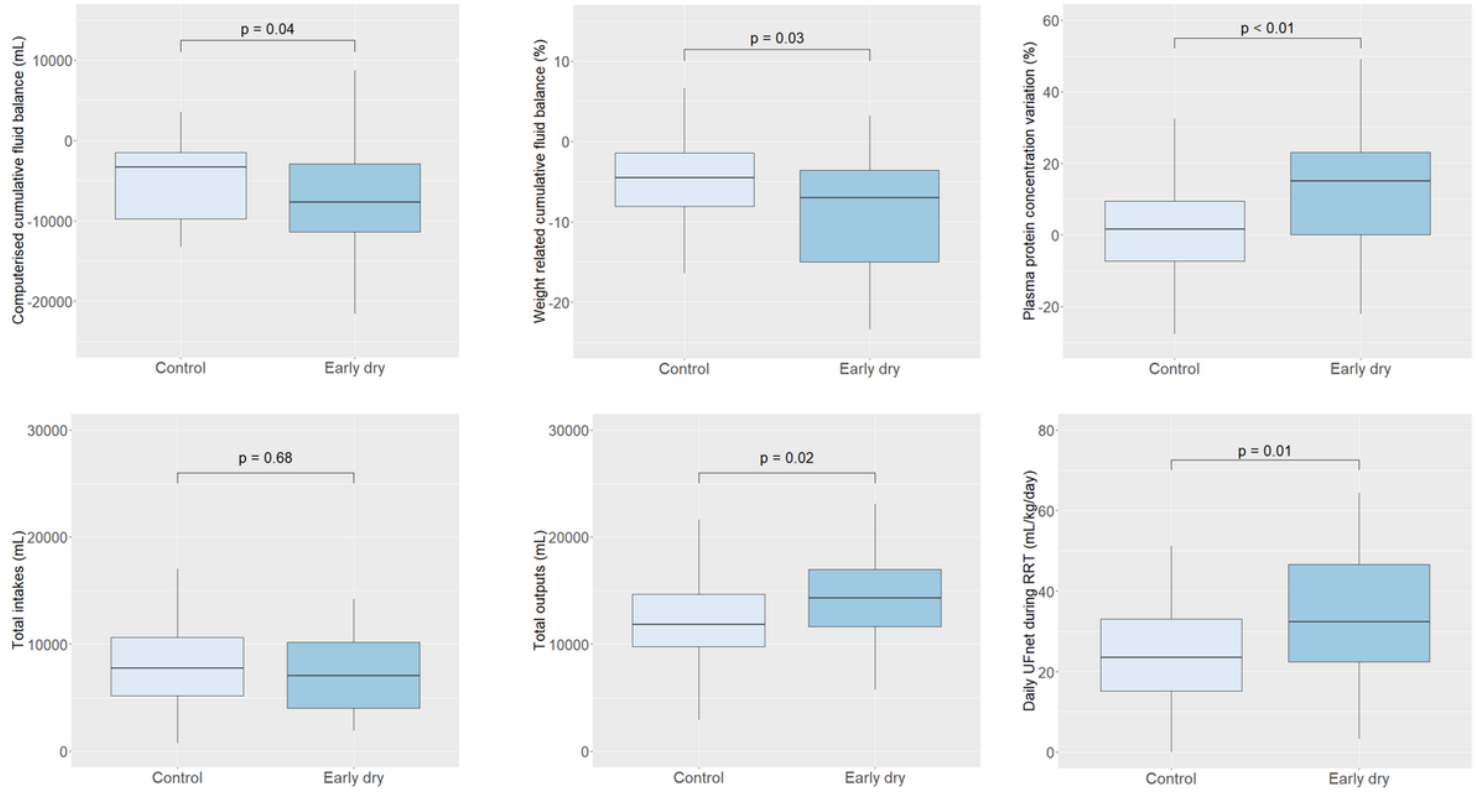

Figure 3

impact of the perfusion-based deresuscitation protocol on fluid balance, intakes, outputs, and plasma protein concentration at day 5 or discharge

RRT: renal replacement therapy, UFnet: net ultra-filtration.

Supplementary Files

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- Additionalfiles.docx