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# BMJ Open Comparison of a preventive or curative strategy of fluid removal on the weaning of mechanical ventilation: a study protocol for a multicentre randomised open-label parallel-group trial

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## ABSTRACT

**Introduction** Fluid overload is associated with a poor prognosis in the critically ill patients, especially at the time of weaning from mechanical ventilation as it may promote weaning failure from cardiac origin. Some data suggest that early administration of diuretics would shorten the duration of mechanical ventilation. However, this strategy may expose patients to a higher risk of haemodynamic and metabolic complications. Currently, there is no recommendation for the use of diuretics during weaning and there is an equipoise on the timing of their initiation in this context.

**Methods and analysis** This study is a multicentre randomised controlled trial comparing two strategies of fluid removal during weaning in 13 French intensive care units (ICU). The preventive strategy is initiated systematically when the fluid balance or weight change is positive and the patients have criteria for clinical stability; the curative strategy is initiated only in case of weaning failure documented as of cardiac origin. Four hundred and ten patients will be randomised with a 1:1 ratio. The primary outcome is the duration of weaning from mechanical ventilation, defined as the number of days between randomisation and successful extubation (alive without reintubation nor tracheostomy within the 7 days after extubation) at day 28. Secondary outcomes include daily and cumulated fluid balance, metabolic and haemodynamic complications, ventilator-associated pneumonia, weaning complications, number of ventilator-free days, total duration of mechanical ventilation, the length of stay in ICU and mortality in ICU, in hospital and, at day 28. A subgroup analysis for the primary outcome is planned in patients with kidney injury (Kidney Disease: Improving Global Outcomes class 2 or more) at the time of randomisation.

**Ethics and dissemination** The study has been approved by the ethics committee (Comité de Protection des Personnes Paris 1) and patients will be included after informed consent. The results will be submitted for publication in peer-reviewed journals.

## Strengths and limitations of this study

- This large randomised controlled trial may help establish strong recommendations with a high level of evidence on routine clinical practice during weaning from mechanical ventilation.
- The sample size of this trial has been designed to have the power to show an absolute reduction of the weaning duration.
- The individual study assignments of the patients will not be masked (given the characteristics of the two strategies under evaluation, a double-blind trial, was deemed not possible).

**Trial registration number** NCT04050007.  
**Protocol version** V.1; 12 March 2019.

## INTRODUCTION

### Background and rationale

Mechanical ventilation is a cornerstone treatment for the critically ill, which is however associated with complications. A major objective is, therefore, to separate patients from the ventilator as quickly as possible, but without exposing them to the risk of extubation failure.<sup>1</sup> Pulmonary oedema is a frequent cause of difficult weaning and extubation failure, up to 60% in recent series.<sup>2,3</sup> A positive fluid balance has also been identified as an important risk factor for difficult weaning and extubation failure.<sup>4-6</sup> More generally, a positive fluid balance is associated with a poor prognosis in different populations of critically ill patients such as those with acute respiratory distress syndrome,<sup>7</sup> acute kidney injury<sup>8</sup> or septic shock.<sup>9</sup> A ‘de-escalation’ or

'deresuscitation' strategy consisting of early fluid removal to obtain a negative fluid balance as soon as the haemodynamic state is stabilised has been suggested.<sup>6</sup> Nevertheless, the implementation of such strategy faces many difficulties in terms of monitoring methods and therapeutic targets. In patients with acute respiratory distress syndrome<sup>7</sup> or sepsis,<sup>10</sup> a conservative fluid management strategy is associated with an improvement in haemodynamic parameters despite an increase in urine output. The conservative approach also results in a significant improvement in oxygenation and a trend towards a shorter duration of artificial ventilation and ICU stay.<sup>7</sup> During the specific phase of weaning from mechanical ventilation, a randomised trial (BMW trial) demonstrated that a strategy of fluid removal guided by measurement of the plasmatic B-type natriuretic peptide significantly reduced the duration of weaning.<sup>11</sup> Fluid overload is clearly associated with an increased risk of extubation failure and the increase in cardiac preload is one of the main mechanisms leading to weaning-induced cardiac failure, especially in patients with chronic cardiac disease. Thus, in case of obvious fluid overload, obtaining a negative fluid balance before the next spontaneous breathing trial (SBT) is a reasonable option that has not, however, been yet evidenced.<sup>12</sup>

### Hypothesis

The hypothesis of the present study is that a preventive and systematic strategy of fluid removal (initiated before the weaning phase, as soon as the patients are stabilised) would shorten the duration of weaning from mechanical ventilation as compared with a strategy of curative fluid removal (initiated only in case of weaning failure from cardiovascular origin).

### Objectives

#### Primary objective

The main objective is to evaluate the impact of a strategy of preventive fluid removal (as compared with a curative fluid removal) on the duration of weaning from mechanical ventilation.

#### Secondary objectives

To compare the following endpoints between the two groups:

1. metabolic complications (hypernatremia, hypokalaemia, acute kidney injury) at day 28.
2. Haemodynamic complications at day 28.
3. Daily and cumulated fluid balance at day 28.
4. Weaning complications at day 28, including failure of the first spontaneous breathing trial, reintubation within the 7 days after extubation,<sup>13</sup> use of unplanned non-invasive ventilation or high flow oxygen therapy within the 7 days after extubation, tracheostomy.
5. Number of ventilator-free days within the 14 and 28 days following randomisation.

6. Total duration of mechanical ventilation from intubation to successful extubation (patient alive without invasive ventilation within 7 days after extubation).
7. Ventilator-associated pneumonia.
8. Length of stay in ICU.
9. Mortality in ICU, in hospital and at day 28.
10. Duration of weaning according to acute kidney injury at the time of randomisation.

## METHODS AND ANALYSIS

### Trial design

This study is a multicentre, randomised (1:1) open-label trial with two arms, to test the superiority of a preventive fluid removal strategy, as compared with a curative fluid removal strategy.

The trial accords with the Standard Protocol Items: Recommendations for Interventional Trial guidelines.

### Study setting

This study will take place in at least 13 ICUs in France. Patients flowchart is detailed in [figure 1](#).

### Eligibility criteria

#### Inclusion criteria

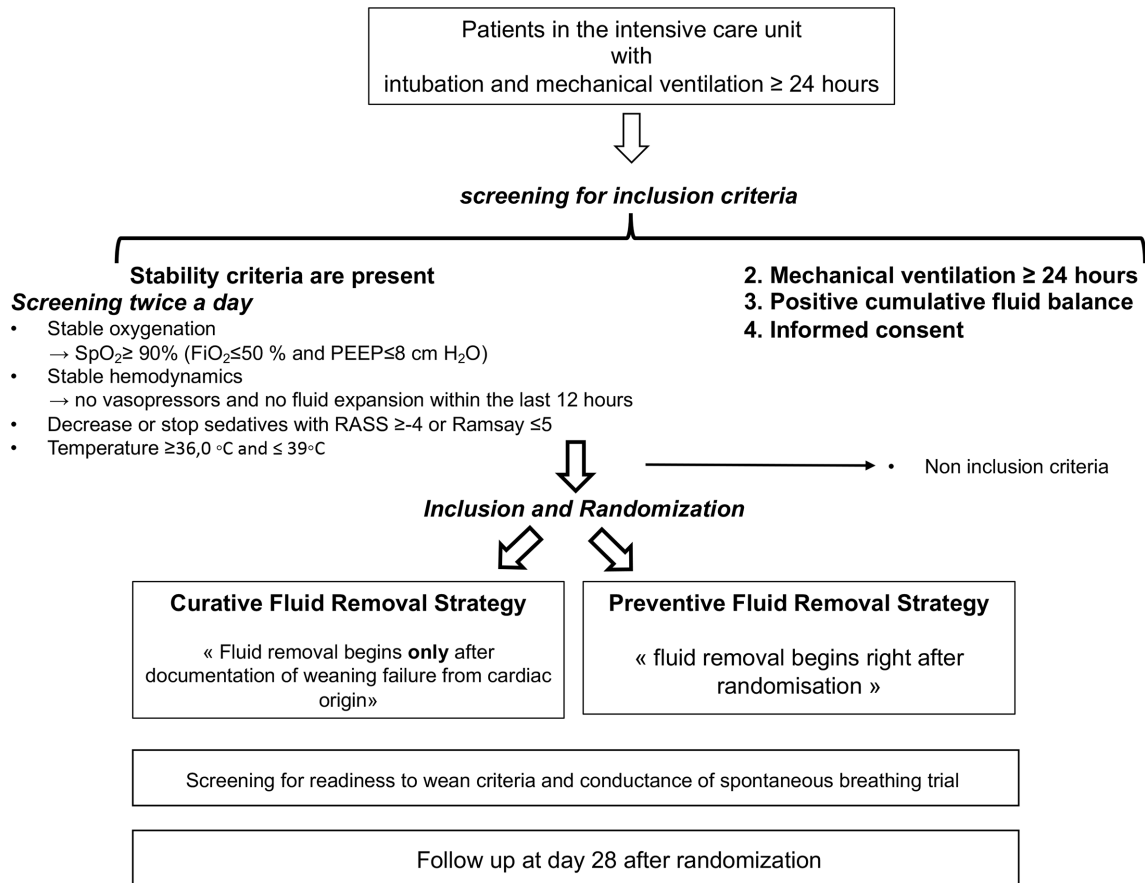
Adult patients admitted in ICU will be eligible as soon as they meet all of the following criteria:

1. Age >18 years.
2. Intubation and mechanical ventilation  $\geq 24$  hour.
3. Positive cumulative fluid balance or increase in body weight since admission.
4. Clinical stability as defined by: (1) stable oxygenation ( $SpO_2 \geq 90\%$  with  $FiO_2 \leq 50\%$  and Positive end expiratory pressure (PEEP)  $\leq 8$  cm  $H_2O$ ), (2) stable haemodynamics (no vasopressors and no fluid expansion within the last 12 hours), (3) sedation was stopped or decreased within the last 48 hours with stable neurologic state (with Richmond Agitation Sedation Scale (RASS)  $\geq -4$  or Ramsay  $\leq 5$ ), (4) temperature is  $>36^\circ C$  and  $<39^\circ C$ .
5. Informed consent is signed by the patient or next of kin or emergency procedure.

#### Non-inclusion criteria

Patients fulfilling one of the following criteria will not be included:

1. Extracorporeal membrane oxygenation.
2. Pregnancy or breast feeding.
3. Allergy to furosemide, sulfamides or spironolactone.
4. Tracheotomy.
5. Hydrocephaly.
6. Acute right ventricle failure.
7. Cardiac arrest with estimated poor prognosis.
8. Already enrolled in an interventional study on weaning from mechanical ventilation.
9. Guillain-Barre syndrome, myasthenia gravis.
10. Planned extubation on the day of inclusion.
11. Criteria of clinical stability (as described above in inclusion criteria) present since more than 24 hours.



**Figure 1** Flowchart of the patient and study design.

12. Natriemia >150 mEq/L, kaliemia <3.5 mEq/L, metabolic alkalosis with pH >7.5.
13. Administration of iodinated contrast within the last 6 hours.
14. Ongoing or planned use of artificial kidney within the next 48 hours.
15. No affiliation to the health insurance system.
16. Patient under curatorship.
17. Imprisoned patient.

## Intervention

### Preventive fluid removal strategy

Preventive fluid removal will be initiated right after the randomisation in all patients with a positive fluid balance or with an increase in weight since the ICU admission.

### Curative fluid removal strategy

The initiation of fluid removal will be considered by the attending physician only in case of difficult weaning deemed of cardiac origin (failure of the spontaneous breathing trial or failure of the decrease in the ventilator support, if this failure is associated with one of the following three categories of signs of weaning-induced pulmonary oedema). First, clinically, weaning-induced pulmonary oedema will be suspected in patients presenting three among five of the following conditions: (1) previous cardiovascular disease, (2) previous respiratory disease, (3) sudden onset of severe hypertension

during the spontaneous breathing trial, (4) increase in heart rate and (5) bilateral crackling auscultation. Second, by using echocardiography (performed by the attending physician), weaning-induced pulmonary oedema will be suspected in case of increase in left ventricle filling pressure at the end of the spontaneous breathing trial. Third, biologically, weaning-induced pulmonary oedema will be suspected by using biomarkers (B-type natriuretic peptide or plasma protein concentration) (figure 2).<sup>12 14–18</sup>

### Fluid removal protocol

Both groups will follow the same protocol of fluid removal, involving fluid intake restriction, diuretic administration and electrolyte compensation (only the timing will be different). The daily total volume of fluids will be limited (<1500 mL/24 hours) and sodium intakes will be restricted to the minimum (nutrition and drugs). Furosemide will be administered (as intravenous bolus doses of 0–30 mg every 3 hours, to achieve a target urine output of 4.5–9 mL/Kg/3 hours) (see table 1). Fluid intake restriction and diuretic administration will be continued for at least 48 hours after extubation. Sodium, potassium, urea, creatinine and arterial blood gases will be monitored daily.

Recommendations will be given to prevent and/or treat possible adverse events related to diuretic treatment, as detailed hereafter

**Clinical criteria****(at least three)**

- Chronic respiratory disease
- Chronic cardiovascular disease
- Increase in systolic blood pressure > 180 mmHg
- Increase in heart rate > 130 min<sup>-1</sup>
- Bilateral crackling auscultation or frothy bronchial secretions

**Cardiac Echo criteria****(both are necessary)****Increased in left ventricle filling pressure at the end of the spontaneous breathing trial**

- E/A > 0.95 and  E/E' > 8.5

**Biological criteria****Plasma concentration at the end of the spontaneous breathing trial**

- $\nearrow$  plasma protein concentration > 5% or   $\nearrow$  hemoglobin > 5%

**Biomarkers at the end of the spontaneous breathing trial**

- $\nearrow$  BNP  $\geq$  48 ng/L or   $\nearrow$  NT- proBNP  $\geq$  185 pg/mL

**Figure 2** Criteria suggesting weaning failure from cardiac origin. BNP, brain natriuretic peptide; E/A, early (E) over late (A) diastolic wave velocities at the mitral valve; E/e', E wave over tissue doppler early (e') wave velocity at the lateral mitral valve annulus.

- ▶ If urine output exceeds 36 mL/kg/12 hours or blood potassium is <4.0 mEq/L while receiving diuretics, blood electrolytes will be checked within the next 12 hours.
- ▶ In the event of metabolic alkalosis with furosemide, acetazolamide will be added (250 mg every 8 hours if pH >7.45 or 500 mg every 8 hours if pH >7.50) in the absence of contraindications (history of hypersensitivity to acetazolamide or sulphonamides; severe hepatic, renal or adrenal insufficiency or history of renal lithiasis).
- ▶ If blood potassium is <4.5 mEq/L during diuretic therapy, supplemental potassium will be given ( $\geq$ 4 g/day if blood potassium is <4.0 mEq/L or  $\geq$ 3 g/day if blood potassium is between 4.0 mEq/L and 4.4

mEq/L). Magnesium supplements ( $\geq$ 1.5 g/day) will be given routinely during diuretic treatment.

- ▶ In case of acute kidney injury under diuretic treatment, the management will depend on the KDIGO stage:
  - Stage 1: echocardiography will be considered to search for left ventricle dysfunction (enabling dobutamine therapy), hypovolaemia or congestion.
  - Stage 2: echocardiography will be considered (see above) and the fluid removal protocol will be temporarily suspended.
  - Stage 3: the fluid removal protocol will be stopped.
- ▶ If blood sodium exceeds 150 mEq/L, hypotonic solutions may be given to increase the daily fluid intake above 500 mL (no salt intake).
- ▶ If iodinated contrast agent injection is expected to be needed, diuretic administration will be suspended 6 hours before and 6 hours after the infusion.

The other conditions requiring furosemide discontinuation will be as follows: metabolic alkalosis with arterial pH >7.55, blood potassium <3.0 mEq/L, blood sodium >155 mEq/L, acute kidney injury (stage 2 KDIGO), urine output >9 mL/kg/3 hours and hypotension requiring fluid bolus or vasopressor therapy. When diuretic treatment will be stopped because of one of these abnormal findings, it can be reinstated after correction

**Table 1** Algorithm of diuretics administration

Initial dose of furosemide (mg)	Urine output (mL/kg/3 hours)	Subsequent doses of furosemide (mg)
20	<4.5	30
	4.5–6	20
	6–7.5	15
	7.5–9	10
	>9	0



of the abnormal value, in accordance with the inclusion and non-inclusion criteria. The first furosemide dose after reinstatement will be half the last dose administered.

### Strategy of weaning, extubation and prevention of extubation failure

In both groups, the weaning process and postextubation management will be protocolised based on national guidelines.<sup>19</sup> Use of sedatives and analgesia will be left at the discretion of the physician as per the local protocol, but daily cumulative doses will be collected. The presence of the following readiness to wean criteria will be screened every morning and will trigger a weaning trial (either T-tube or pressure support trial with pressure support set at 7 cmH<sub>2</sub>O and zero-end expiratory pressure for a duration between 30 min and 60 min):

1. Patients under pressure support with positive-end expiratory pressure  $\leq 5$  cmH<sub>2</sub>O, FiO<sub>2</sub>  $\leq 40\%$ , SpO<sub>2</sub>  $\geq 90\%$  and respiratory rate  $< 30$ /min without signs of respiratory muscles labouring.
2. No vasopressors, heart rate  $< 130$ /min and systolic blood pressure between 95 mm Hg and 160 mm Hg.
3. Temperature between 36.5°C and 38.5°C.
4. Sedatives stopped with RASS score between -1 and +1.
5. Audible cough during tracheal suctioning or spontaneously.
6. Need for less than three suctioning during the last 4 hours.

In case of success of the weaning trial, investigators will be encouraged to proceed with extubation on the day of the trial. In case of failure of the weaning trial, a new trial will be performed daily as long as weaning criteria are met, until success and extubation. Failure of the weaning trial will be defined according to the usual criteria from the International Conference Consensus on Weaning,<sup>20</sup> as development during the trial of any of the following events: (1) respiratory rate  $> 35$  breaths/min, (2) increased accessory muscle activity, (3) SpO<sub>2</sub> persistently below 90% (or below 88% in case of underlying chronic lung disease) on FiO<sub>2</sub>  $\geq 0.4$  or at least 6L/min of oxygen, (4) haemodynamic instability defined as heart rate persistently above 140 beats/min or systolic blood pressure  $< 90$  mm Hg or  $> 180$  mm Hg, with signs of hypoperfusion (appearance of cyanosis or mottling), (5) depressed mental status or agitation.

After extubation, prophylactic use of non-invasive ventilation alternating with high-flow nasal oxygen between non-invasive ventilation sessions will be recommended in patients with risk factors for extubation failure.<sup>13 19 21</sup>

### Criteria for reintubation

To ensure the consistency of indications across sites and reduce the risk of delayed intubation, investigators will be suggested to reintubate patients if one of the following criteria is fulfilled: (1) cardiac arrest, (2) decreased level of consciousness associated with respiratory pauses, (3) inability to cope with abundant bronchial secretions, (4)

aspiration, (5) shock state with the need for vasopressor, (6) respiratory failure, (7) unplanned surgery.

### Outcomes

#### Primary outcome

The primary outcome is the duration of weaning as defined by the time elapsed between the day of randomisation and the day of successful extubation (patient alive, with no tracheostomy and no reintubation within the 7 days following extubation) until day 28. If the patient dies without being extubated within 28 days after randomisation, the patient will count as weaning failure, and the duration of weaning will be of 28 days.

#### Secondary outcomes

Secondary outcome will include the following:

1. Percentage of patients with metabolic complications among: hyponatremia  $> 150$  mEq/L, hypokalaemia  $< 2.5$  mEq/L, acute renal failure with KDIGO stages 2 and 3, before day 28.
2. The occurrence before day 28 of any haemodynamic complications among hypotension with systolic blood pressure  $< 90$  mm Hg, introduction or increase in vasopressors dose, use of fluid expansion, atrial fibrillation, ventricular fibrillation.
3. Daily and cumulated fluid balance as assessed by the difference between all fluid intakes (nutrition, hydration, drugs, perfusions) and fluid outputs (urine output, digestive suctioning, pleural drainage).
4. The rate of patients who failed the first spontaneous breathing trial, as defined by the International Conference Consensus on Weaning<sup>20</sup> (see above).
5. The rate of reintubation within the 7 days after extubation.
6. The rate of use of unplanned non-invasive ventilation and high flow oxygen.
7. The rate of tracheostomy.
8. The number of days alive and free from mechanical ventilation (including intubation and non-invasive ventilation) between randomisation and day 14 and day 28.
9. The total number of days of mechanical ventilation (from intubation to successful extubation), until day 28.
10. The percentage of patients with ventilator-associated pneumonia.<sup>22</sup>
11. The duration of ICU and hospital stays, until day 28.
12. Percentage of deaths in the ICU, in the hospital and at day 28 among patients.

### Sample size and its statistical justification

A statistician calculated the sample size by estimating by simulation (2000 data sets) under a Weibull distribution using the following hypotheses derived from the BMW trial<sup>11</sup>: a cumulative incidence of successful extubation of 60% by day 7 and 80% by day 28 taking into account a competitive risk of death of 13% by day 7 and 16% by day 28. We determined that the enrolment of 410 patients



(205 patients per group) would provide a power of 90% to show an absolute reduction of weaning duration of 1.6 days (4.9 days for the curative strategy versus 3.3 days for the preventive strategy) with a two-sided alpha level of 0.05 using a likelihood ratio test in a Fine & Gray model with a time interaction term.

### Recruitment

The expected initial duration of patient enrolment is 2 years, starting in February 2020. The chronogram of the study is as follows:

1. End of 2018: national grant award.
2. 2019: approval by an independent ethics committee.
3. 2020–2021: inclusion of patients.
4. 2021–2022: end of inclusions, monitoring of participating centres and queries to investigators; cleaning and closure of the database; blind review to determine protocol violation, to define intention-to-treat and per-protocol analysis populations.
5. 2022–2023: data analysis, writing of the manuscript and submission for publication.

As of 21 December 2020, 84 patients have been randomised in the study.

### Assignment of intervention and data collection

After obtaining consent from the patient or her/his relative, all inclusion/exclusion criteria will be checked by the investigator before randomisation. Randomisation will be stratified on centre and left ventricle ejection fraction ( $>$  or  $\leq 45\%$ ) at the time of randomisation and carried out by connecting to the centralised electronic-case report form (e-CRF website ‘Cleanweb’ provided by Telemedicine technologies. Data will be collected on the e-CRF by a trained investigator or research assistant at each centre.

Patient follow-up and data collected are detailed in the study flowchart (table 2).

### Statistical methods

All the analyses will be performed by the study statistician according to a predefined statistical analysis plan, using R software (R Foundation for Statistical Computing, Vienna, Austria) or Statistical Analysis System (SAS) latest versions. A two-tailed p value of less than 0.05 will be considered as indicating statistical significance.

In accordance to the **CONsolidated Standards Of Reporting Trials (CONSORT)** statement, a flow diagram will describe the progress of patients of the two groups through the phases of the trial (enrolment, intervention allocation, intervention received, follow-up and data analysis). The analysis will be performed on an intention-to-treat basis. In case of premature stop or withdrawal from the study, patients would not be substituted. Missing value will be described and, according to nature and frequency, multiple imputation methods will be used. A per-protocol analysis will be held as sensitivity analysis, excluding patients wrongly randomised or who did not receive allocated intervention.

Comparative analysis will systematically be done with (main analysis) and without adjustment on randomisation stratification factors. No interim analysis is planned.

### Descriptive analysis

The continuous variables will be summarised with the classic parameters of descriptive analysis (median, IQRs and extreme values or mean and SD), while indicating the number of missing data. Categorical variables will be presented in the form of absolute frequency and percentage in each modality. Censored variables will

**Table 2** Flowchart of timing in collection of different variables

Procedures and assessments	Screening	Inclusion visit and randomisation (day 0)	Daily visits	Study end (day 28)
Inclusion and non-inclusion criteria	X			
Enrolment				
Information		X		
Consent		X		
Intervention				
Preventive strategy		o		o
Curative strategy				o
Assessments				
Characteristics of the patient*		X	X	X
Characteristics of ventilation and fluid management†		X	X	X
Adverse events			X	X
ICU stay and hospital stay				X
Vital status				X

\*Characteristics of the patient include age, gender, height, weight, severity score indicated by the Simplified Acute Physiological Score II and the Sepsis-related Organ Failure Assessment score, underlying chronic cardiac or respiratory disease, date and reason for admission/intubation, duration of intubation prior randomisation, weaning characteristics.

†Characteristics of ventilation and fluid management include ventilator settings, blood samplings, urine output, fluid intakes, cardiac echo, chest X-ray. ICU, intensive care unit.

be described by Kaplan-Meier plots. Variables will be described for the whole group and separately for each arm.

### Analysis of the primary outcome

The duration of weaning from mechanical ventilation, as defined by the number of days between randomisation and successful extubation at day 7 (patients alive, no reintubation, no tracheostomy), will be compared between the two groups using a Fine & Gray model, with a likelihood ratio test, in order to take into account the competitive risk of death. A time-interaction term will be used to take into account the proportional hazard assumption violation. Subdistribution HR associated with the preventive strategy will be estimated with its 95% CI.

### Analysis of secondary outcomes

Rate of metabolic and haemodynamic complications, rate of ventilator-associated pneumonia, extubation success, reintubation, tracheostomy and mortality at the various predefined times will be compared between the two groups using logistic models. Mean daily and cumulative fluid balance calculated until the ICU discharge and ventilatory free days at day 14 and day 28 will be compared between groups using a linear regression. Weaning duration and lengths of stay will be compared between the two treatment groups using similar models as for primary outcome. The effect of the preventive strategy on mortality (in ICU, at day 28 and at in hospital) will be evaluated using Cox models.

### Predetermined subgroup analysis

The effect of acute kidney injury prior to randomisation on the efficacy of the preventive strategy of fluid removal will be investigated by introducing an interaction term in the Fine & Gray model. If significant, a subdistribution HR associated with the preventive strategy will be estimated.

### Data monitoring

The trial will be overseen by a steering committee (principal investigator, senior investigator and methodologist) regarding the progression and monitoring of the study. Research assistants will regularly monitor all the centres on site to check adherence to the protocol and the accuracy of the data recorded. An investigator at each centre will be responsible for daily patient screening, enrolling patients in the study, ensuring adherence to the protocol and completing the electronic case report form. Since both strategies are currently used in routine practice, no data safety monitoring board was required by the ethical committee.

## ETHICS AND DISSEMINATION

### Consent to participate

The patient will be included after having provided a written informed consent to the investigator. If the patient is not able to understand the information given, he/

she can be included if the same procedure is completed with a next of kin. Eligible patients who will be unable to receive information and for whom a substitute decision-maker would not be present may be included through a process of deferred consent. After the patient's recovery, she/he will be asked if she/he agrees to continue the trial. The protocol has been approved by an independent Ethical Committee (Comité de Protection des Personnes Paris 1).

### Confidentiality

Data will be handled according to French law on data protection and European General Data Protection Regulation. All original records will be archived at trial sites for 15 years.

### Declaration of interest

This study was funded by a grant from the French Ministry of Health obtained in 2018 (Programme Hospitalier de Recherche Clinique). The sponsor is Assistance Publique—Hôpitaux de Paris, AP-HP (Délégation à la Recherche Clinique et à l'Innovation, DRCI).

### Access to data

Investigators will make available the documents and individual data strictly required for monitoring, quality control and audit of the study to dedicated persons, in accordance with law.

### Dissemination policy

Findings will be published in peer-reviewed journals and presented at national and international meetings. Communications, reports and publication of the results of the study will be placed under the responsibility of the principal investigator-coordinator of the study and the steering committee. Reporting will follow CONSORT statement and rules of publication will follow the international recommendations according to *The Uniform Requirements for Manuscripts* (ICMJE, April 2010).

### Individual participant data sharing statement

Data are available on reasonable request. The procedures carried out with the French data privacy authority (Commission Nationale de l'Informatique et des Libertés) do not provide for the transmission of the database, nor do the information and consent documents signed by the patients. Consultation by the editorial board or interested researchers of individual participant data that underlie the results reported in the article after deidentification may nevertheless be considered, subject to prior determination of the terms and conditions of such consultation and in respect for compliance with the applicable regulations.

### Patient and public involvement

Patients and public were not involved in the study design. Participants will have access to the findings of the study on request.





## DISCUSSION

Up to now, there are no randomised controlled trials available on the timing of initiation of fluid removal during weaning. Liberation from mechanical ventilation is a crucial process that can be associated with complications that can delay extubation.<sup>1</sup> Increasing the duration of mechanical ventilation at the time of weaning is associated with an increased risk of mortality.<sup>23</sup> The objective of the present study is to reduce the duration of weaning, a major outcome for the critically ill patients highlighting the relevant dividends of this trial for the future. Among the numerous factors associated with weaning failure, the role of fluid overload has been highlighted in several reports.<sup>4 5 7 16 24</sup> In several studies, successful weaning was achieved after diuretic treatment in patients who had evidence of weaning-induced pulmonary oedema.<sup>2 16 24</sup> However, the timing of fluid removal is still a matter of discussion and there are currently no guidelines that recommend the use of diuretics at the initiation of weaning. Of note, a recent retrospective study found that a negative fluid balance on day 3 of ICU stay was associated with lower 30-day mortality whether occurring spontaneously or achieved with deresuscitative measures.<sup>6</sup> A study examining the relationship between loop diuretic use and hospital mortality in critically ill patients with vasopressor support found a reduced mortality in patients who received diuretics.<sup>25</sup> Nevertheless, another study did not confirm this association on 13 000 patients from a national database.<sup>26</sup>

There are several advantages for using a preventive fluid removal strategy as tested in the current trial. First, it may allow to achieve a negative fluid balance before starting the spontaneous breathing trial, a condition that may reduce the risk of weaning failure from cardiac origin.<sup>2 11 24</sup> Second, as a positive fluid balance has been associated with worse outcomes,<sup>7 27 28</sup> it is tempting to limit it early in the ICU course and if possible to achieve a negative fluid balance as soon as the patient is stabilised. However, such a preventive strategy may be associated with some complications, like dehydration with renal failure,<sup>8</sup> electrolyte imbalances,<sup>7 26</sup> hypotension and atrial fibrillation.<sup>29</sup> Given this equipoise, the current trial aims at comparing the preventive fluid removal strategy with a more conservative strategy initiated only in case of weaning failure from cardiac origin.<sup>12</sup> Before starting diuretics in patients of the curative group, investigators of the present trial will have to document the presence of weaning-induced pulmonary oedema via clinical signs, echocardiography markers<sup>18</sup> or biomarkers<sup>15 16</sup> that have been proposed in the literature.<sup>12</sup>

The use of diuretics will be standardised with a robust and validated algorithm.<sup>11</sup> In addition, preventive measures will be associated for a careful management of fluid removal and electrolytes. To reduce biases and ensure a satisfactory comparison between preventive and curative groups, the weaning process will be protocolised based on the current national guidelines.<sup>19</sup> Of note, spontaneous breathing trial will be performed based on a daily

screening for readiness to wean criteria and preventive strategies for extubation failure will be applied based on the most recent evidences.<sup>13 21 30</sup>

In summary, this trial is an open-label randomised controlled trial testing two strategies for fluid removal (preventive vs curative) to reduce the duration of weaning from mechanical ventilation. This kind of comparison has never been performed before. Therefore, this trial may help establish international recommendations with a high level of evidence for weaning from mechanical ventilation to eventually improve the outcomes of patients exposed to mechanical ventilation.

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