Diagnostic performance of a rapid ultrafiltration test to assess preload dependence in critically ill patients treated with continuous renal replacement therapy.

UF CHALLENGE Study

This is a translation from the original French document.
In case of discrepancy, the original French version shall prevail.

The publication of results related to this protocol can be find at: https://ccforum.biomedcentral.com/articles/10.1186/s13054-025-05674-3 (Biscarrat et al. 2025 Critical Care)

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Protocol Version
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SUMMARY

Background / Rationale

A positive fluid balance is a risk factor associated with increased mortality in intensive care (Vaara et al. 2012, *Critical Care*). Continuous renal replacement therapy (CRRT) is an effective means of regulating fluid overload in patients with acute kidney injury in critical care settings. However, this organ support technique may induce episodes of hemodynamic instability. Such episodes often lead to discontinuation of fluid removal during CRRT, although these events are not necessarily associated with cardiac preload dependence (Bitker et al. 2016, *Crit Care*; Chazot et al. 2021, *Crit Care*). Therefore, the causal link with ultrafiltration is not always certain, and fluid removal could potentially be continued.

Currently, the best means of identifying a preload-dependent hemodynamic profile is a postural maneuver (passive leg raise or Trendelenburg), which is a validated test for assessing the impact of insufficient venous return on cardiac output (Monnet et al. 2016 *Intensive Care*; Yonis et al. 2017 *Crit Care Med*). However, these maneuvers only identify patients who are *already* preload-dependent. To date, no clinical test is available to identify patients at risk of becoming preload-dependent and thus suffering the deleterious consequences of inappropriate fluid removal.
We aim to evaluate a novel predictive test based on a rapid ultrafiltration challenge, which could reveal a patient's transition into preload dependence. Validation of this test would allow adjustment of net ultrafiltration (fluid removal) according to the hemodynamic response in terms of cardiac preload.

Primary Objective

To assess the diagnostic performance of a rapid ultrafiltration test (without distinguishing between 15- and 30-minute trials) in detecting preload dependence in critically ill patients treated with continuous renal replacement therapy, by quantifying the change in cardiac index induced by the test and comparing it to that induced by a postural maneuver (reference standard) performed after the ultrafiltration test.

Secondary Objectives

- To assess the diagnostic performance of the 15-minute and 30-minute rapid ultrafiltration tests, respectively, using the same methodology.
- To determine the optimal threshold of cardiac index variation that defines preload dependence for each test (pooled and separately), with calculation of sensitivity, specificity, positive and negative predictive values.
- To compare the diagnostic performance of ultrafiltration tests (pooled and separate) with that of the pre-test postural maneuver.
- To compare the diagnostic performance between the 15-minute and 30-minute tests.
- To evaluate the impact of ultrafiltration tests on additional hemodynamic variables (absolute values and relative changes from baseline): central venous pressure, heart rate, mean and pulse arterial pressure, extravascular lung

water, pulmonary vascular permeability index, and global end-diastolic volume index.
- To assess the ability of ultrafiltration tests (pooled and separate) to predict hemodynamic instability with preload dependence occurring within 8 hours following the test.

Methodology / Study Design
- Pilot study
- Physiological, prospective, single-center, open-label
- Sequential crossover design with sealed-envelope randomization of intervention order
- Diagnostic test evaluation (rapid ultrafiltration challenge)

Primary Endpoint
Diagnostic performance of a rapid ultrafiltration test (regardless of duration), assessed by the area under the ROC curve (receiver operating characteristics) of cardiac index variation compared to the reference measurement (postural maneuver performed after the test).

Secondary Endpoints
- Diagnostic performance of the 15-minute and 30-minute rapid ultrafiltration tests, assessed by ROC analysis of cardiac index variation and comparison with the reference maneuver.
- Optimal thresholds (and 95% CI) of cardiac index variation for each test, determined using the Youden index, with associated sensitivity, specificity, PPV, and NPV.
- Comparative diagnostic performance of ultrafiltration tests (pooled and separate) versus pre-test postural maneuver, and between tests (15 vs. 30 minutes).
- ROC AUC values compared using DeLong's method.
- Hemodynamic variables measured by cardiac output monitoring (CVP, HR, MAP, pulse pressure, EVLW, PVPI, GEDVi), analyzed as absolute values and changes from baseline, correlated with cardiac index variation.
- Incidence of hemodynamic instability (tachycardia, hypotension, decreased cardiac index, mottling) within 8 hours after the ultrafiltration test.

Target Population
Adult ICU patients (under mechanical ventilation and sedation) with acute kidney injury (KDIGO stage 3) requiring continuous renal replacement therapy initiated within the past 14 days.

Sample Size
N = 20 evaluable patients, each undergoing 2 tests → total of 40 rapid ultrafiltration challenges.

Study Duration

- Inclusion period: 18 months
- Maximum participation per patient: 72 hours
- Total study duration: 18 months + 3 days

Expected Outcomes

The current reference dynamic test (passive leg raise or Trendelenburg) remains imperfect in assessing tolerance to fluid removal during CRRT, with sensitivity <80%. The UF challenge may prove more sensitive, particularly in patients at the borderline between the ascending and plateau phases of the Frank-Starling curve. This simple, dynamic, low-cost test could help clinicians individualize ultrafiltration prescriptions, avoid deleterious hypotension, and rapidly integrate into clinical practice. Currently, no specific dynamic test exists to evaluate the safety and efficacy of fluid removal in this population.

GENERAL INFORMATION

Title: Diagnostic performance of a rapid ultrafiltration test to assess preload dependence in critically ill patients treated with continuous renal replacement therapy.

Project Identifiers and Update History

- Sponsor Code: 69HCL21_1250
- ClinicalTrials.gov registration number: NCT05214729
- CPP Sud-Est VI favorable opinion date: XX/XX/XXXX

Version History

Version	Date	Reason for Update
1	02/11/2021	Initial draft
2	16/03/2022	Comments from CPP

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SCIENTIFIC JUSTIFICATION

Current State of Knowledge – Rationale

A positive fluid balance has been shown to be an independent risk factor for mortality in intensive care, particularly in patients with septic shock, ARDS, and acute kidney injury. Fluid overload can impair the function of several organs, including the kidneys. Ultrafiltration contributes to controlling fluid balance. Compared to liberal fluid strategies, conservative strategies including ultrafiltration during dialysis may accelerate extubation in ARDS patients.

The main risk of excessive fluid removal is hemodynamic instability. Intra-dialytic hypotension is deleterious and may impair renal recovery. Hypotension during dialysis often leads to interruption of ultrafiltration, negatively impacting fluid balance control. A high ultrafiltration rate is associated with increased mortality, although no universal threshold exists.

Excessive depletion may reduce cardiac output when patients are preload-dependent (on the ascending portion of the Frank-Starling curve). However, not all hypotensive episodes are preload-dependent; some relate to vasoplegia or myocardial dysfunction.

Currently, the most reliable tool for diagnosing preload dependence is a dynamic test: passive leg raise (supine) or Trendelenburg (prone) with continuous cardiac output monitoring. A ≥10% increase in cardiac output indicates preload dependence. Studies, including work by our team, confirm sensitivity and specificity >85%. This test performs well to identify patient who are preload-dependent, and who are consequently at higher risk of preload-dependent hypotension. Yet, in preload-independent patients (i.e. those with a negative passive leg raising test, no validated predictive test exists for ultrafiltration-related hypotension in relation with their switch to a preload-dependent status.

Research Hypothesis

A 250 mL rapid ultrafiltration challenge (15 or 30 minutes) may help identify preload-independent patients at risk of becoming preload dependent during CRRT

Justification of Methodological Choices

- Sequential crossover design: each patient serves as their own control, limiting variability.
- Randomization of challenge order prevents bias.
- 250 mL volume chosen as it mimics passive leg raise (~300 mL).
- Two rates (15 vs. 30 minutes) tested to assess the effect of ultrafiltration kinetics and plasma refilling.

The PiCCO® Monitoring Device

The device combines transpulmonary thermodilution and pulse contour analysis for continuous cardiac output and displays advanced hemodynamic parameters (extravascular lung water, pulmonary vascular permeability index, global end-diastolic volume index).

Benefit/Risk Assessment

- Benefit: collective, through validation of a new predictive test.
- Risk: minimal, transient hemodynamic instability possible
- No additional invasive procedures required.

Expected Outcomes

A UF challenge may have higher diagnostic performance than the passive leg raising test to identify patients at the transition between preload independence and dependence. It is simple, dynamic, inexpensive, and potentially useful in guiding ultrafiltration in CRRT patients.

RESEARCH OBJECTIVES

Primary Objective

To evaluate the diagnostic performance of a rapid ultrafiltration challenge (250 mL over 15 or 30 minutes) in detecting preload dependence in preload independent critically ill patients treated with continuous renal replacement therapy.

Diagnostic accuracy will be assessed by the change in calibrated cardiac index induced by the ultrafiltration challenge compared with the reference postural maneuver (passive leg raise or Trendelenburg) performed *after* the challenge.

Secondary Objectives

1. To evaluate separately the diagnostic performance of the 15-minute and 30-minute UF challenges.
2. To determine the optimal threshold of calibrated cardiac index variation defining preload dependence for each test (pooled and separate), with sensitivity, specificity, PPV, and NPV.
3. To compare diagnostic performance of UF challenges (pooled and separate) with that of the pre-test postural maneuver.
4. To compare diagnostic performance between the 15-minute and the 30-minute challenges.
5. To assess the effect of ultrafiltration challenges on other hemodynamic parameters (absolute values and relative changes from baseline): central venous pressure (CVP), heart rate (HR), mean arterial pressure (MAP), pulse pressure, extravascular lung water (EVLW), pulmonary vascular permeability index (PVPI) and global end-diastolic volume index (GEDVi)
6. To evaluate the ability of ultrafiltration challenges to predict hemodynamic instability with preload dependence within 8 hours after the test.

STUDY DESIGN / METHODOLOGY

Type of Research

- Pilot study
- Physiological, prospective, single-center, open-label
- Sequential crossover design with randomization of challenges' order
- Diagnostic test evaluation

Study Population

Inclusion Criteria

- Adults ≥18 years hospitalized in the ICU
- Mechanical ventilation and sedation
- Acute kidney injury KDIGO stage 3
- CRRT initiated <14 days before inclusion
- With a calibrated continuous cardiac index monitoring device in place (PiCCO®, Pulsion Medical, Feldkirch, Germany)

- Informed consent (patient or representative)

Exclusion Criteria

- Arterial lactate > 4 mmol/L
- Calibrated cardiac index < 2 or > 4 L/min/m^2
- Preload dependence identified within the preceding 2 hours
- ECMO
- Acute hemorrhage
- End stage chronic kidney disease or renal graft recipient
- Acute stroke with coma
- Fulminant hepatitis
- Inability to perform PLR: amputation, inferior vena cava obstruction, abdominal compartment syndrome
- Pregnancy or breastfeeding
- Imminent death
- Decision of withholding of care
- Patients under legal protection (guardianship, trusteeship, detention)
- Already included in the study

Number of Patients

- 20 patients included
- Each patient undergoes 2 ultrafiltration challenges (15- and 30-minute, in randomized order)
- Total: 40 evaluable challenges

Randomization

- Randomized order determined by sealed envelope method
- Each patient serves as their own control

Blinding

- Not feasible given the study design

Co-interventions

Recommendation for not changing any of the following parameters, prescription or settings during the trial's interventions:

- Sedation
- Mechanical ventilation
- Vasopressor and inotrope support
- Fluid bolus therapy or transfusion

Study Procedures

1. Baseline data collection (demographics, clinical scores, renal data, hemodynamics)

2. Calibration of the monitoring device and pre-test postural maneuver (PLR or Trendelenburg) during 1 minute with collection of the relative change in continuous cardiac index
3. Ultrafiltration challenge: 250 mL over 15 or 30 minutes (randomized), by setting a UF flow of 1000 ml/h or 500 ml/h, respectively
4. Re-calibration of the monitoring device and post-test postural maneuver (reference standard, PLR or Trendelenburg) during 1 minute with collection of the relative change in continuous cardiac index
5. Repeat sequence for second challenge after a wash-out period of 24h (cross-over design)
6. Follow-up: monitoring for 8 hours post-test for instability

Data Collected

- Demographics: age, sex, weight, height
- Clinical: history, reason for ICU admission, severity scores (SAPS II, SOFA)
- Renal: CRRT indication and parameters
- Hemodynamics: CI, CVP, HR, MAP, PP, EVLW, PVPI, GEDVi (before/after each step), vasopressor dosage
- Ventilatory settings: VT, PEEP, FiO2, arterial blood gas results
- Results of the pre and post-test postural maneuvers
- Any severe and non-severe adverse events

ENDPOINTS / EVALUATION CRITERIA

Primary Endpoint

The diagnostic performance of the rapid ultrafiltration challenge (pooled 15- and 30-minute tests).

- Performance assessed by the area under the ROC curve (AUC) of cardiac index variation.
- Reference: continuous cardiac index relative variation induced by the post-test postural maneuver performed after the challenge.

Secondary Endpoints

1. Respective diagnostic performance of the 15-minute and 30-minute challenges (ROC AUC).
2. Determination of the optimal threshold of cardiac index variation (Youden index) with sensitivity, specificity, PPV, and NPV.
3. Comparative performance of challenges (pooled and separate) versus the pre-test postural maneuver.
4. Comparison of diagnostic performance between the 15-minute and 30-minute challenges ROC AUCs compared using DeLong’s test.
5. Analysis of additional hemodynamic parameters: CVP, HR, MAP, Pulse pressure, EVLW, PVPI and GEDVi (absolute values and relative changes, correlated with cardiac index variation).

6. Incidence of hemodynamic instability within 8 hours post-test (tachycardia, hypotension, decreased CI, mottling).

Study duration

- Inclusion period: 18 months
- Maximum participation per patient: 72 hours
- Total study duration: 18 months + 3 days

Sample size

- 20 patients planned.
- Each undergoes 2 ultrafiltration challenges (15- and 30-minute, randomized).
- Total: 40 evaluable ultrafiltration challenges.

The sample size was chosen pragmatically, consistent with the pilot/exploratory nature of the study.

STUDY PROCEDURES AND CONDUCT

Overall Study Flow

1. Screening and Inclusion
    - Verify inclusion and exclusion criteria.
    - Provide information to patient or legally authorized representative; obtain consent in compliance with French law.
2. Baseline Assessment
    - Collect demographics and clinical data (age, sex, weight, height, SAPS II, SOFA, reason for ICU admission, history).
    - Record renal data (CRRT indication and parameters, time since CRRT initiation).
    - Baseline hemodynamic measurements: CI, CVP, HR, MAP, PP, EVLW, PVPI, GEDVi, vasopressor dosage
    - Mechanical ventilation settings
3. Randomization
    - Determine challenge sequence (15 vs 30 minutes) using sealed envelopes.
4. Pre-test postural maneuver
    - Passive leg raise (supine) or Trendelenburg (prone).
    - Record hemodynamic parameters before and during maneuver.
5. Ultrafiltration Challenge
    - Remove 250 mL with UF over 15 or 30 minutes.
    - Monitor CI and hemodynamic parameters continuously.
    - Record parameters at the end of challenge.
6. Post-test Postural Maneuver (Reference)
    - Repeat maneuver (PLR or Trendelenburg).
    - Record hemodynamic parameters before and during maneuver.
7. Follow-up
    - Any hemodynamic instability episodes occurring over the following 8h

8. Second Ultrafiltration Challenge
    - After a 24h wash-out period, repeat procedure with the alternate duration (30 or 15 minutes).
    - Same sequence: pre-test maneuver → challenge → post-test maneuver.
9. Follow-up
    - Monitor for 8 hours post-challenges.
    - Record any hemodynamic instability.

Data Management

- Data recorded in a secure **electronic case report form (eCRF)**.
- Source documents: ICU medical files, CRRT charts, PiCCO® data, nursing observation sheets.
- Data entry performed by investigators, validated and monitored by sponsor.

Safety Monitoring

- Continuous monitoring of cardiac output and hemodynamics during challenges.
- **Adverse events (AEs) and serious adverse events (SAEs)** recorded and reported.
- Risks: transient hypotension or tachycardia, reversible and clinically manageable.

Premature Discontinuation

Patients may be withdrawn if:

- Consent withdrawn.
- Serious adverse event occurs.
- Investigator deems it in patient's best interest.
- Limitation of therapeutic effort decided.
- Technical impossibility (e.g., PiCCO® failure, CRRT interruption).

SAFETY EVALUATION AND RISK MANAGEMENT

Potential Risks for Participants

- The ultrafiltration challenge consists of removing 250 mL of ultrafiltrate over 15 or 30 minutes.
- Main anticipated risk: transient hemodynamic instability, such as hypotension, tachycardia, decreased cardiac index, or mottling.
- These events are expected to be limited, reversible, and continuously monitored with PiCCO® cardiac output monitoring.
- No additional invasive procedure is required beyond standard ICU monitoring.

Adverse Events (AEs) and Serious Adverse Events (SAEs)

- Adverse Event (AE): any unfavorable or unintended medical occurrence during research, whether or not related to the investigational procedure.

- Serious Adverse Event (SAE): an event that results in death, is life-threatening, requires or prolongs hospitalization, results in significant disability, or is deemed medically significant by the investigator.

Collection and Reporting

- All AEs and SAEs occurring from the start of ultrafiltration challenges until 8 hours post-procedure will be documented in the eCRF.
- The investigator will assess causality (related or not to the ultrafiltration challenge).
- SAEs must be reported to the sponsor within 24 hours of investigator awareness.
- The sponsor will notify relevant authorities (CPP, ANSM if applicable) in compliance with French regulations.

Measures for Participant Safety

- Continuous monitoring ensures early detection of instability.
- If instability occurs (e.g., MAP <60 mmHg, sustained tachycardia, cardiac index decrease >20%), the ultrafiltration challenge will be immediately stopped, and corrective treatment administered (fluids, vasopressors, etc.).
- The investigator may withdraw the patient from the study in case of unacceptable risk.

STATISTICAL ANALYSIS

General Principles

- Analyses performed using R software (latest version available).
- Two-sided significance level set at 0.05.
- 95% confidence intervals reported.
- Analyses conducted on the intention-to-treat and per-protocol population (patients with at least one evaluable ultrafiltration challenge).

Primary Analysis

- The primary endpoint is the diagnostic performance of the ultrafiltration challenge (15- and 30-minute tests pooled).
- Performance assessed by calculating the area under the ROC curve (AUC) of cardiac index variation compared with the post-test postural maneuver.
- AUC values will be reported with 95% confidence intervals.

Secondary Analyses

1. Diagnostic performance of the 15-minute and 30-minute ultrafiltration challenge alone (ROC AUC).
2. Determination of the optimal threshold of cardiac index variation (Youden index) defining preload dependence, with sensitivity, specificity, PPV, and NPV.
3. Comparative diagnostic performance of ultrafiltration challenges (pooled and separate) versus the pre-test postural maneuver, compared using the

respective ROC AUCs of 15-minute and 30-minute challenges using DeLong's test.

4. Analysis of additional hemodynamic parameters (CVP, HR, MAP, PP, EVLW, PVPI, GEDVi) in absolute values and relative changes from baseline, correlated with cardiac index variation using Pearson or Spearman correlation.
5. Description of the incidence of hemodynamic instability within 8 hours post-test, expressed as proportions with 95% confidence intervals.

Handling of Missing Data

- Missing data will not be imputed.
- Analyses will be based on available data.
- The extent and reasons for missing data will be described.

Interim Analysis

No interim analysis is planned.

QUALITY ASSURANCE, ETHICS, AND DATA MANAGEMENT

Regulatory and Ethical Aspects

- The study will be conducted in compliance with the Declaration of Helsinki (2013 version) and the principles of Good Clinical Practice (ICH E6 R2).
- The protocol, patient information, and consent form have been submitted to and approved by the CPP Sud-Est VI (Comité de Protection des Personnes).
- The study has been declared to the CNIL (Commission Nationale de l'Informatique et des Libertés) in accordance with French law and the General Data Protection Regulation (GDPR, EU 2016/679).
- Any substantial protocol amendments will be submitted for approval to the CPP and, if necessary, to the French National Agency for Medicines and Health Products Safety (ANSM).

Informed Consent

- Informed consent must be obtained from each participant or their legally authorized representative before any research-specific procedure.
- If the patient regains decision-making capacity, consent will be sought again for continuation.
- Consent procedures comply with the French Jardé Law for research involving human subjects.

Confidentiality and Data Protection

- Participant data will be coded with a unique study identifier.
- Only authorized members of the research team and sponsor will access identifiable data.
- Data will be securely stored in a password-protected electronic case report form (eCRF).

- In compliance with GDPR and French law, participants may access, rectify, or delete their data by contacting the sponsor.

Monitoring and Quality Assurance

- The sponsor's Clinical Research Unit (Hospices Civils de Lyon) will conduct monitoring visits to ensure compliance with the protocol and regulatory requirements.
- Source data verification will be performed to ensure consistency between medical records and eCRF entries.
- Monitoring activities will be documented in formal monitoring reports.

Archiving

- Essential study documents (protocol, CRFs, monitoring reports, patient files, consent forms) will be archived for 15 years after study completion.
- Electronic data will also be securely stored by the sponsor for the same duration.

Insurance

- The sponsor has subscribed to an insurance policy covering the civil liability of investigators and institutions involved, in accordance with Article L.1121-10 of the French Public Health Code.

Publication and Communication of Results

- Results will be submitted for publication in a peer-reviewed international scientific journal.
- Authorship will follow the criteria defined by the International Committee of Medical Journal Editors (ICMJE).
- Negative or inconclusive results will also be published.
- Results may be presented at national and international scientific meetings.

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