Faculté de Médecine et de Maïeutique
Lyon Sud - Charles Mérieux

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# Effet du gradient de température sur le risque d'instabilité hémodynamique pendant l'épuration extra rénale continue en réanimation : une analyse de médiation causale

***Effect of temperature gradient on hemodynamic instability risk during continuous renal replacement therapy: a causal mediation analysis***

## THESE D'EXERCICE EN MEDECINE

Présentée à l'Université Claude Bernard Lyon 1

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**Lorna Fraire**

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Sous la direction du **Dr Laurent Bitker**

Université Claude Bernard Lyon 1

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**Title**: Effect of temperature gradient on hemodynamic instability risk during continuous renal replacement therapy: a causal mediation analysis

**Running head**: CRRT temperature gradient and HIRRT risk

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## ABRIEVATION LIST

| | |
|---|---|
| **HIRRT** | Hemodynamic Instability related to Renal Replacement Therapy |
| **ICU** | Intensive Care Unit |
| **AKI** | Acute Kidney Injury |
| **CRRT** | Continuous Renal Replacement Therapy |
| **$T°_{CRRT}$** | Extracorporeal circuit temperature |
| **$T°_{core}$** | Core temperature |
| **CO** | Cardiac Output |
| **$\Delta T°$** | Temperature gradient |
| **MAP** | Mean Arterial Pressure |
| **RRT** | Renal Replacement Therapy |
| **CVP** | Central Venous Pressure |
| **HR** | Heart Rate |
| **SVI** | Stroke Volume Index |
| **CI** | Cardiac Index |
| **TPTD** | Transpulmonary Thermodilution |
| **PLR** | Passive Leg Raising |
| **CVVH-hep** | Continuous Veno-Venous Hemofiltration with heparin |
| **CVVHD Cica** | Continuous Veno-Venous Hemodiafiltration using citrate anticoagulation |
| **CCO** | Continuous Cardiac Output |
| **IPTW** | Inverse Probability of Treatment Weighting |
| **CBPS** | Covariate Balancing Propensity Score |
| **SOFA** | Sepsis-related Organ Failure Assessment |
| **ADE** | Average Direct Effect |
| **ACME** | Average Causal Mediated Effect |
| **CCI** | Continuous Cardiac Index |
| **SLED** | Sustained Low-Efficiency Dialysis |

# TABLE DES MATIÈRES

## ABSTRACT

**Introduction**: Lowering extracorporeal circuit temperature ($T°_{CRRT}$) below core temperature ($T°_{core}$) during continuous renal replacement therapy (CRRT) may decrease hemodynamic instability (HIRRT) by affecting cardiac output (CO) and vasomotor tone. This study aimed to evaluate the causal relationship between core-to-CRRT temperature gradient and HIRRT longitudinal risk.

**Methods**: This ancillary analysis of a prospective, single-center study (NCT03139123) included patients with stage 3 acute kidney injury, who received CRRT for <24h and had continuous cardiac index monitoring. $T°_{CRRT}$, $T°_{core}$ and hemodynamics parameters were collected 4-hourly between inclusion and day 7. Temperature gradient ($\Delta T°$) corresponded to $T°_{core} - T°_{CRRT}$. HIRRT (defined as a mean arterial pressure < 65 mmHg requiring therapeutic intervention) were reported hourly. A mediation analysis evaluated the effect of $\Delta T°$ on HIRRT longitudinal risk during follow-up, mediated through cardiac output and mean arterial pressure.

**Results**: 42 patients were enrolled in this ancillary analysis (age 68 [58–76], SOFA 12 [8–15] and 33 (79%) with sepsis), and were followed over 119 [57–143] hours (N=1012 observations). Increasing $\Delta T°$ was significantly associated with higher heart rate, CO and mean arterial pressure (MAP), and lower norepinephrine dose, and reduced HIRRT risk in univariate analysis (0.97 [0.95–0.99] per 0.1°C increase, *P*<0.01). Causal mediation showed that $\Delta T° \geq 0°C$ significantly decreased HIRRT risk through improved MAP and CO (mediated: 55% and 38% of the total effect, respectively).

**Conclusions**: During CRRT, increasing $\Delta T°$ led to a lower risk of HIRRT, through an improvement in both MAP and CO.

## INTRODUCTION

Hemodynamic instability related to renal replacement therapy (HIRRT) is a complication observed with all renal replacement therapy (RRT) techniques commonly used in the intensive care unit (ICU). It is associated with higher mortality, uncontrolled fluid balance and poorer renal recovery. HIRRT is multifactorial and its onset may be consequential to the underlying clinical condition's evolution or inadequate RRT settings, which may alter cardiac output (CO) or decrease systemic vasomotor tone, uncompensated by physiological feedback (1).

Most often, fluid removal by net ultrafiltration is identified as being the sole factor (and RRT setting) responsible for an episode of HIRRT, but other mechanisms may also play a role (2). Continuous RRT (CRRT) is a strong contributor to body heat loss through heat dissipation in the extracorporeal circuit and has led to the use of extracorporeal heating devices to compensate thermal loss. On the other hand, excessive heat transfer to the patient may alter vasomotor tone (arterial but also venous, with an unknown effect on venous return and cardiac preload) and cardiac output (through an increase in heart rate), which may potentially generate macrocirculatory compromise, hemodynamic instability and an increased risk of HIRRT.

Cooling the extracorporeal circuit during RRT may hence theoretically improve hemodynamic stability in critically ill patients, but its effects during CRRT remain insufficiently studied. During intermittent hemodialysis, *Edrees et al.* (3) observed a significant reduction in hypotensive episodes when the dialysate temperature was set at 35°C compared to 37°C. In patients undergoing CRRT, *Robert et al.* (4) showed that setting the replacement fluid's temperature at 36°C over 6h increased mean arterial pressure (MAP) while allowing for a decrease in catecholamine infusion dosage but did not account for the temperature gradient existing between body core temperature and the extracorporeal circuit.

We hypothesized that setting the extracorporeal circuit temperature ($T°_{CRRT}$) below core temperature ($T°_{CORE}$) during CRRT may decrease HIRRT risk, through the effects of relative heat loss on cardiac output and vasomotor tone. The primary objective of the study was to evaluate the causal relationship existing between core-

to-CRRT temperature gradient and HIRRT longitudinal risk, mediated by MAP and cardiac output, in patients treated with CRRT.

## METHODS

### *Design*

We performed an ancillary analysis of the PRELOAD CRRT study (5) (NCT03139123), a prospective, observational, single-center study conducted between May 2017 and September 2020 in the medical ICU of the Croix Rousse university hospital in Lyon, France. The study was approved by an ethics committee (CPP Ile de France IV, ID-RCB 2017-A00483-50). The PRELOAD CRRT study aimed to describe the prevalence of preload-dependent HIRRT during CRRT.

### *Study population*

Eligible patients were adults with Kidney Disease – Improving Global Outcome (KDIGO) stage 3 acute kidney injury undergoing CRRT for less than 24 hours and monitored by means of a calibrated continuous cardiac output monitoring device. Exclusion criteria were impossibility or contraindication to perform postural maneuvers (lower limb amputation, inferior vena cava obstruction, pregnancy, intracranial hypertension), decision to withhold treatment, lack of affiliation to social security, legal protective measures, and previous participation in the study. Patients were followed for a maximum of 7 days from the time of inclusion, or until death, or until the study procedures could no longer be performed (due to discontinuation of CRRT or CO monitoring).

### *Temperature monitoring and management*

Temperatures were collected 4-hourly during the observation period. $T°_{CORE}$ was continuously monitored at the tip of the PiCCO® arterial catheter (Pulsion Medical, Feldkirch, Germany) positioned in the femoral artery, and automatically reported in electronic ICU charts. 4-hourly $T°_{CORE}$ was further categorized into three classes: hypothermia (< 36°C), normothermia (36 to 37.5°C), and hyperthermia (> 37.5°C).

$T°_{CRRT}$ corresponded to the temperature set on the CRRT monitor by the treatment team and was collected every 4 hours. $T°_{CRRT}$ was adjustable by steps of

1°C between 35°C to 39°C on the monitors (Multifiltrate Pro, Fresenius Medical Care, Germany). Effective extracorporeal circuit fluid temperatures were not measured.

Consequently, 4-hourly core-to-CRRT temperature gradient (∆T°), defined as the difference between $T°_{CORE}$ and $T°_{CRRT}$, was positive if $T°_{CORE}$ was superior to $T°_{CRRT}$ and negative if it was inferior to $T°_{CRRT}$. 4-houlry observations were further classified based on ∆T° into three categories: ≥0°C resulting in heat loss, between –2 to 0°C considered neutral heat transfer, and < –2°C indicating heat gain.

For descriptive reasons, we classified patients into 3 groups based on the predominant, non-neutral, temperature gradient observed during the observation period: ∆T° < –2°C group if more than 30% of the patient's 4-hourly observations had a ∆T° < –2°C, ∆T° ≥0°C group if more than 30% of 4-hourly observations had a ∆T° ≥0°C, and ∆T° –2°C to 0°C group if none of the 2 preceding conditions were met.

Temperature management and $T°_{CRRT}$ setting were not protocolized, with the limit that the treating team targeted normothermia in all patients, using any available means, including $T°_{CRRT}$ modifications. Furthermore, in case of hypothermia, external warming blankets could be used. Room temperatures were maintained within a controlled range of 19°C to 24°C.

***Participants follow up***

The following data were collected prospectively in electronic case report forms every 4 hours during follow-up: MAP, central venous pressure (CVP), heart rate (HR), stroke volume index (SVI), cardiac index (CI), preload dependence status, global end-diastolic volume index, extravascular lung water index, pulmonary vascular permeability index and systemic vascular resistance index. Indexed values were normalized to body surface (Dubois's formula), and norepinephrine dosage (as tartrate) to ICU admission body weight.

***Hemodynamics measurements***

We monitored patients with acute circulatory failure with a calibrated continuous cardiac output device using pulse-contour analysis (PiCCO® system, Pulsion Medical, Feldkirch, Germany), with transpulmonary thermodilution (TPTD) calibration

performed every 4 hours using three injections of normal saline performed on the venous central line.

The assessment of preload dependence involved passive leg raising (PLR), deemed positive if the continuous cardiac output (CCO) increased by more than 10%, or Trendelenburg maneuvers, positive if CCO > 8%. High-quality hemodynamic monitoring criteria included correct positioning at the phlebostatic level of all pressure probes (CVP and MAP) and fast flush test verifications to maintain accurate pressure readings.

Episodes of HIRRT, defined by MAP < 65 mmHg requiring therapeutic intervention (fluid resuscitation, increase or introduction in norepinephrine, $UF_{NET}$ decrease or cessation), were also tracked and reported hourly throughout patient follow-up.

***CRRT settings***

The clinician in charge determined the indication, CRRT modality, and settings in accordance with international guidelines and unit protocols. CRRT was indicated for patients with acute circulatory failure meeting the initiation criteria of the delayed strategy of the AKIKI trial. CRRT modalities included continuous veno-venous hemofiltration with heparin (CVVH-hep) or continuous veno-venous hemodialysis with regional citrate anticoagulation (CVVHD CiCa) using Fresenius Medical systems.

CVVH-hep was the preferred technique for patients with indication for systemic anticoagulation, acute liver failure, or any contraindications to citrate regional anticoagulation (arterial lactate > 4 mmol/L, metformin intoxication), or based on clinician preference.

CRRT monitors (with integrated heating systems) were the Fresenius Multifiltrate Pro with an AV-1000S membrane (Fresenius Medical Care, Bad Homburg, Germany). Replacement fluids were Hemosol B0 (Baxter, Deerfield, IL, USA), or MultiBic K0 (Fresenius Medical Care, Bad Homburg Germany) for CVVH, and Ci-Ca Dialysate K2 (Fresenius Medical Care, Bad Homburg Germany) for CVVHD. CRRT effluent flow rate was set at 20-25 $ml.kg^{-1}.h^{-1}$, using ICU admission body weight. Blood flow rate was set to 200-300 $ml.min^{-1}$ with CVVH, and to one twentieth (in $ml.min^{-1}$) of the dialysate flow

rate (in $ml.h^{-1}$) for CVVHD with citrate regional anticoagulation, as per manufacturer recommendations.

***Statistics***

No sample size calculation was performed for the ancillary study; sample size calculation of the PRELOAD CRRT study is reported in the princeps publication. Statistical analyses were preformed using the R software (version 4.1.3). A *P* value under 0.05 was used to define statistical significance. Continuous data are reported using median [interquartile range] and categorical data using count (percentage).

The analysis was performed on all included patients, including those whose observation period did not reach day 7. Missing variables during follow-up were imputed on 10 datasets by predictive mean matching for continuous variables and logistic regression for categorical variables. Comparison between study groups of continuous variables measured at inclusion was performed using the Kruskal-Wallis test, and the Fisher test for categorical variables.

In all following models and regression analysis described below, mixed effects were used with the visit number (continuous) as the random slope nested in a random intercept corresponding to the patient identification number. Variables were scaled and centered prior to regression; transformation was considered in case of significant skewness. Also, because temperature gradient was correlated with $T°_{CORE}$ (coefficient of correlation *r* 0.73, coefficient of determination $R^2$ 0.53) and potentially affected by other covariates (age, sepsis, invasive mechanical ventilation, CRRT set blood flow and sedation), an inverse probability of treatment weighting (IPTW) vector was determined using the covariate balancing propensity score (CBPS, **Supplemental figure S1**) to weight models' coefficients.

Association of temperature gradient with longitudinal hemodynamics was first performed using categorized $\Delta T°$ within each $T°_{CORE}$ categories in bivariate analysis (including the evaluation of the interaction between the 2 explanatory variables). Then the association of $\Delta T°$ with longitudinal hemodynamics was evaluated using $\Delta T°$ as a continuous explanatory variable, with or without CBPS weighting. A sensitivity analysis

was performed in the subset of observations with a normal $T°_{CORE}$ (between 36°C and 37.5°C).

Univariate association of demographics, severity of disease variables, longitudinal hemodynamics and weighted temperature gradient with HIRRT longitudinal risk (i.e. the risk of presenting an HIRRT in the following 4 hours of the index observation) during follow-up were evaluated using generalized linear regression models (using the binomial law), expressed using their odds ratio and corresponding 95% confidence interval. A sensitivity analysis of HIRRT risk prediction by temperature gradient in observations with a normal $T°_{CORE}$ was also performed (without weighting). This was followed by a multivariate regression analysis, using variables deemed physiologically relevant to predict HIRRT risk. Multicollinearity and interactions were systematically checked for. Quadratic factors applied to continuous predictors were also tested. The models' calibration and goodness-of-fit were evaluated using the C-statistic and the Hosmer-Lemeshow test, respectively.

***Multiple causal mediator analysis***

**Supplemental figure S2** shows the hypothesized causal relation existing between $\Delta T°$ and HIRRT risk, mediated through mean arterial pressure and cardiac output (including the effect of cardiac preload) by means of directed acyclic graph. The figure also shows the pre-treatment confounders that were accounted for by the IPTW-based CBPS, and the post-treatment confounders associated with HIRRT risk (non-cardiovascular Sepsis-related Organ Failure Assessment [SOFA], arterial lactate concentration and norepinephrine dose).

Then, a multiple causal mediator analysis was performed, using the methodology developed by Imai and Yamamoto (6), which allows the conjunct assessment of multiple mediators (i.e. cardiac output and MAP). Weighted temperature gradient dichotomized as being ≥ 0°C or < 0°C was used in the mediation models to predict HIRRT risk in the following 4 hours. From these models, the average direct (ADE) and average causal mediated (ACME) effects were quantified, with corresponding 95% confidence intervals. Sensitivity analyses were performed using a $\Delta T°$ cutoff of –1°C, in the subset of observations with normothermia, and based on the preload dependence status. Robustness of mediation models to unidentified confounders (i.e.

sequential ignorability) were evaluated by varying a correlation ρ parameter existing between the residuals of the mediator and outcome regressions (7).

## RESULTS

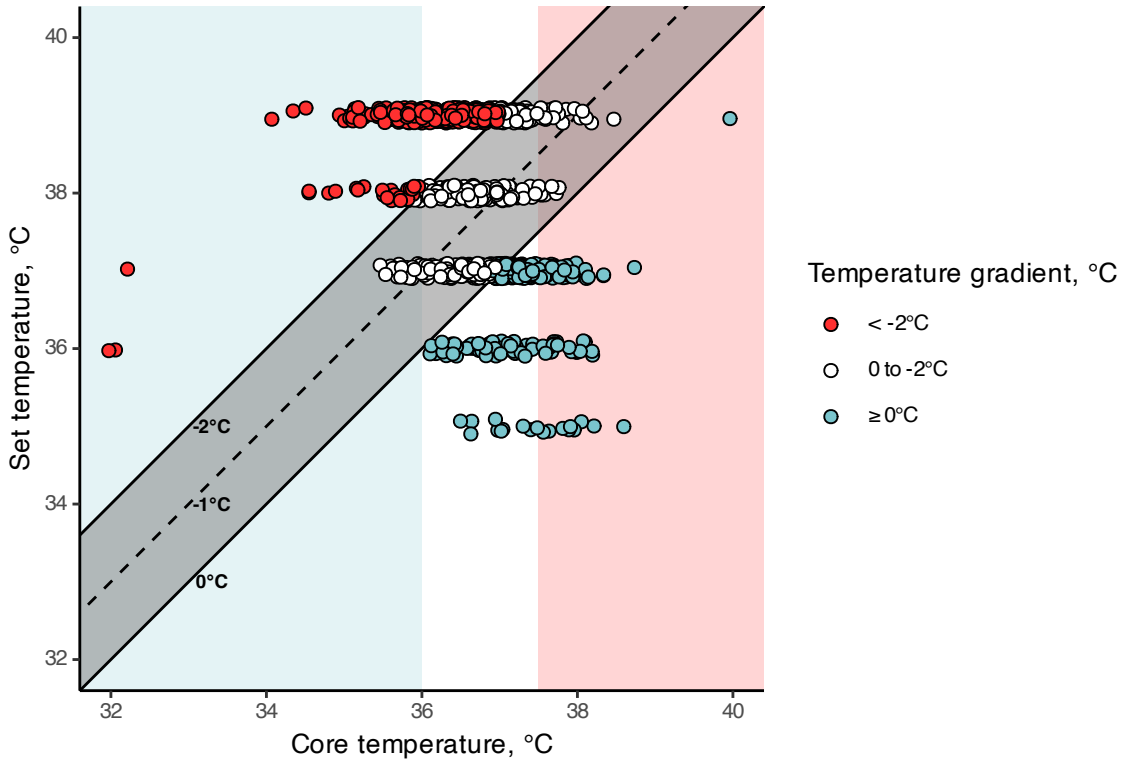
### *Cohort description*

Forty-two patients were enrolled and were followed over 119 [57–143] hours, for a total of 1012 observations. Median age was 68 [58–76], 62% patients were males, the SOFA score was 12 [8– 15], and 52% were in septic shock at time of inclusion. Patients' characteristics at inclusion are reported in **Supplemental table S1**. The delay between ICU admission and CRRT initiation was 1 [0–3] days. The CRRT settings at inclusion were similar between the 3 groups and the principal CRRT modality was CVVH-hep (**Supplemental table S2**). Baseline hemodynamics are shown in **Supplemental table S3**.

### *Temperature course over time*

Median $\Delta T°$ during follow-up was -1.3 [-2.4– +0.1] °C. At time of inclusion, $T°_{CORE}$ were significantly different between the 3 groups of temperature gradient ($P<0.01$) and most patients were in the [36 to 37,5°C] $T°_{CORE}$ group (**Supplemental table S4**). **Figure 1** shows the relationship between $T°_{CORE}$, $T°_{CRRT}$, and temperature gradient. **Supplemental figure S3** shows $T°_{CORE}$, $T°_{CRRT}$, and temperature gradient over the observation period (**Supplemental figure S4)** for temperatures' longitudinal course over time in individuals

**Figure 1. Core temperature, CRRT set temperature and temperature gradient**




The figure shows the relationship between core temperature (measured on the PiCCO® device in arterial femoral bloodstream) and the set temperature on the CRRT monitor. A negative temperature gradient indicates that the core temperature was below the set temperature on the CRRT monitor. The grey shade corresponds to temperature gradient between -2°C and 0°C. Data points are categorized based on the temperature gradient value (< -2°C in red, between -2 and 0°C in white, and ≥ 0°C in blue). The blue and red shades represent hypothermia (core temperature < 36°C) and hyperthermia (>37.5°C of core temperature).

### *Association of temperature gradient with hemodynamics*

A $\Delta T° \geq 0°C$ in normothermic and hyperthermic $T°_{CORE}$ observations was associated with higher MAP, cardiac output, heart rate and lower norepinephrine dose (**Figure 2, Supplemental figure S5** for observed values). When considered continuously, a 1°C increase in $\Delta T°$ was associated with a significant increase in MAP, heart rate and cardiac output but not with SVI or the relative change in CCI (continuous cardiac index) during a postural maneuver (**Table 1**).

**Table 1. Association of temperature gradient with hemodynamic parameters during follow-up.**

| | Temperature gradient, per 1°C increase | | | | | |
|---|---|---|---|---|---|---|
| **Variables (4-hourly observations)** | **Unweighted All observations** | ***P* value** | **Weighted All observations** | ***P* value** | **Unweighted Normothermic observations*** | ***P* value** |
| Mean arterial pressure, mmHg | 1.05±0.33 | <0.01 | 1.05±0.39 | 0.01 | 1.06±0.44 | 0.02 |
| Cardiac index, $L.min^{-1}.m^{-2}$ | 0.10±0.02 | <0.01 | 0.07±0.02 | 0.00 | 0.09±0.03 | <0.01 |
| Heart rate, $min^{-1}$ | 2.90±0.43 | <0.01 | 2.2±0.45 | 0.00 | 2.53±0.58 | <0.01 |
| Stroke volume index, $ml.m^{-2}$ | -0.12±0.24 | 0.61 | -0.13±0.28 | 0.55 | -0.08±0.33 | 0.76 |
| Relative change in CCI during postural maneuver, % | 0.49±0.34 | 0.15 | 0.24±0.37 | 0.57 | 0.72±0.46 | 0.33 |
| Norepinephrine dose (tartrate), $\mu g.kg^{-1}.min^{-1}$ | -0.04±0.02 | 0.13 | -0.08±0.02 | 0.01 | -0.04±0.02 | <0.01 |

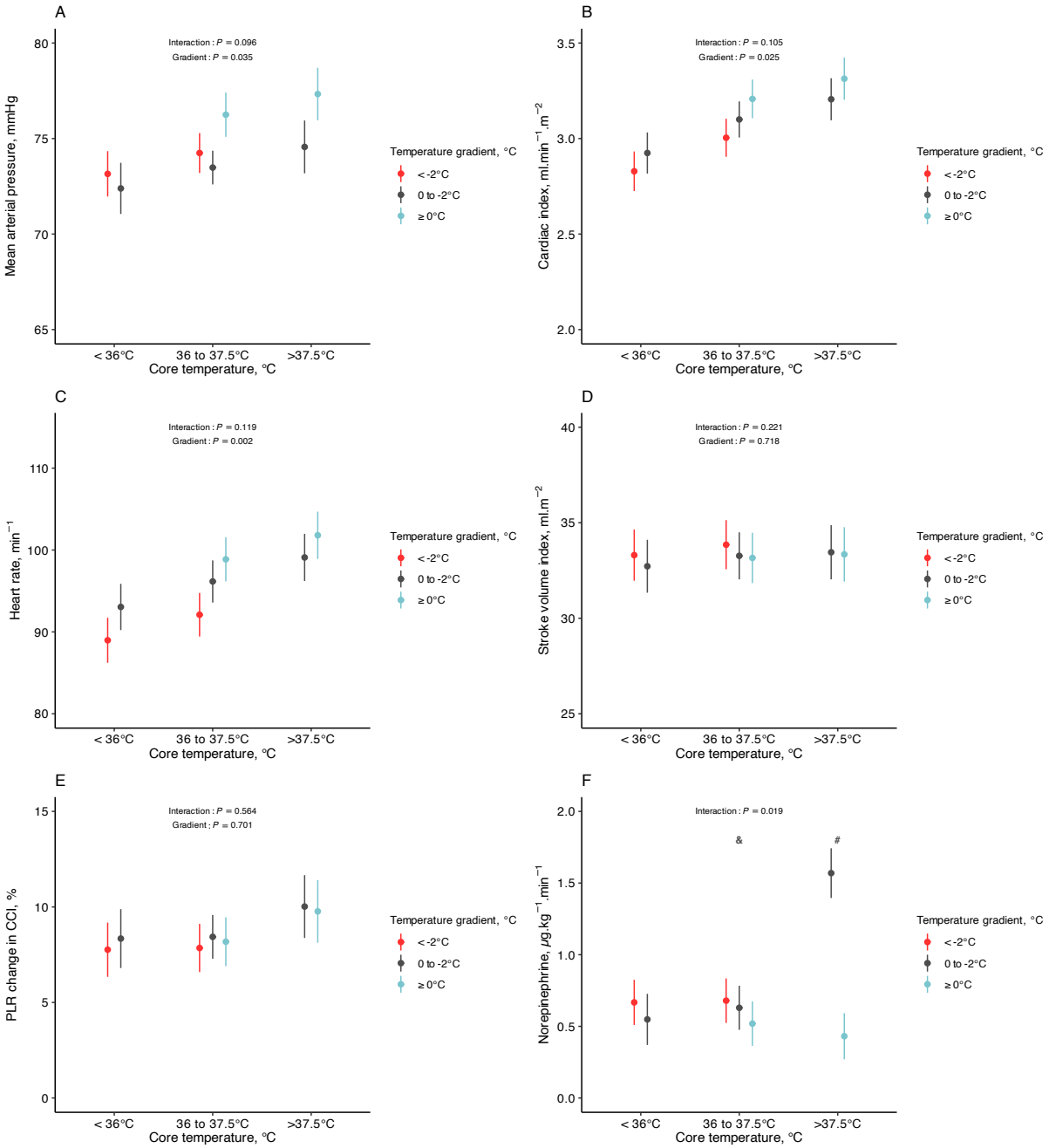
Data is estimate ± standard error

*: observations with a core temperature between 36 and 37.5°C

Mixed effects linear regression models were run on 10 imputed datasets (N=1012 observations in each dataset), with temperature gradient as the fixed effect, the hemodynamic variable as the dependent variable, visit number as the random slope nested in a random intercept corresponding to the patient identification number. Variables were scaled and centered prior to regression (norepinephrine required additional transformation using the Box-Cox method due to leftward skewness). Fixed effects were then pooled using Rubin's rule and descaled to the original hemodynamic parameter scale. Models included an offset corresponding to the baseline hemodynamic value at time of inclusion. Weighting was performed using the CBPS method to adjust for the effect of pre-treatment confounders on temperature gradient. P values were bootstrapped over 500 replicate datasets.

CCI: continuous cardiac index by pulse contour analysis

**Figure 2. Association of hemodynamic parameters with temperature gradient and core temperature.**



The figure shows the mean value of mean arterial pressure (A), cardiac index (B), heart rate (C), stroke volume index (D), relative change in CCI during a postural maneuver (E) and norepinephrine dose (F) based on the core temperature category (x axis) and the temperature gradient (< -2°C in red, between -2 and 0°C in grey, and ≥ 0°C in blue) during longitudinal follow-up (4-hourly observations). The represented values are the marginal means (and associated standard error) determined from a mixed effect model with the hemodynamic parameter as the dependent variable, temperature gradient category and core temperature category as the explanatory variables (with an interaction term if significant). Models' random effects were a random slope of visit number nested in a random intercept corresponding to the patient identification number. An offset was inserted in the model, corresponding to the hemodynamic parameter value at baseline. Marginal means were determined in 10 imputed datasets (N=1012 observations in each dataset), and pooled using Rubin's method. Variables were scaled prior to regression (with additional Box-Cox transformation for norepinephrine due to leftward skewness) and descaled after. For all variables, interaction between the 2 explanatory variables was checked. If significant, a post-hoc pairwise comparison was performed using Sidak's method. P values were bootstrapped over 500 replicate datasets. Collinearity between the 2 categorical variables was eliminated using a variance inflation factor < 3.

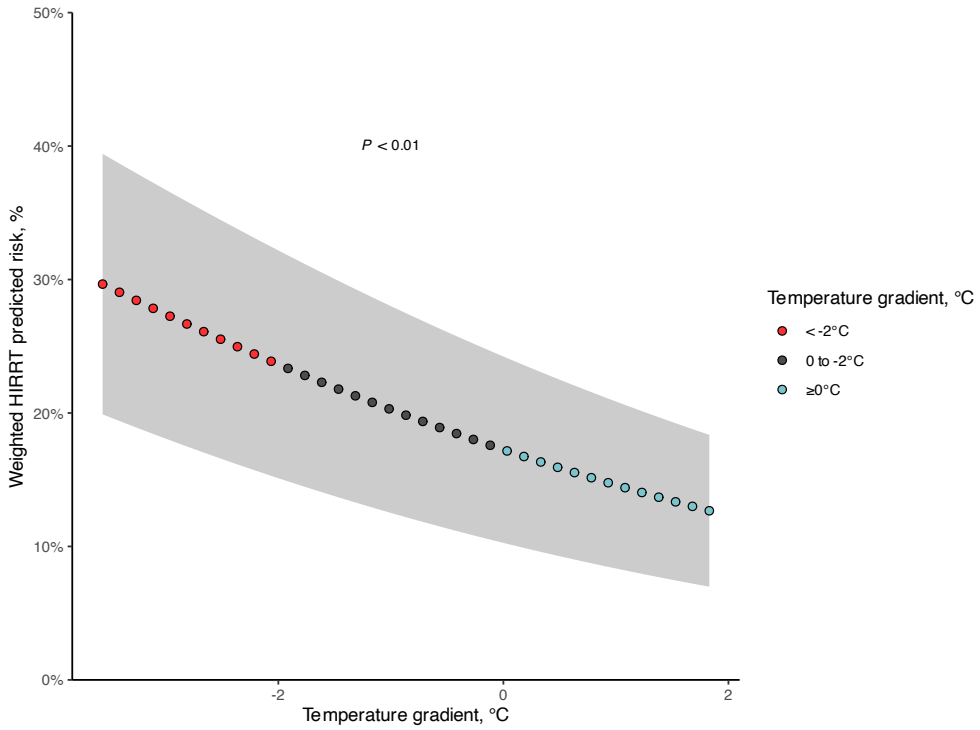
#: $P$<0.05 between gradient category < -2°C (red) and >0°C (blue) in post-hoc pairwise analysis; &: $P$<0.05 between gradient category -2°C to 0°C (grey) and >0°C (blue) in post-hoc pairwise analysis.

CCI: continuous cardiac index by pulse contour analysis.

### *HIRRT risk and temperature gradient*

The overall number of HIRRT episodes was 214, with a median number of episodes per patient of 4 [3–8] during follow-up and was significantly more frequent in the $\Delta T° < -2°C$ group (**Supplemental table S5**). In univariate analysis, HIRRT risk significantly decreased with increasing temperature gradient (**Figure 3**), which was also confirmed in normothermic observations (**Supplemental figure S6**)**.** In multivariate analysis (which included adjustments with the hemodynamic mediators), $\Delta T°$ was not significantly associated with HIRRT longitudinal risk (**Table 2**, univariate analyses presented in **Supplemental table S6**). Of note, no significant interaction existed between MAP and cardiac output with HIRRT risk prediction.

**Figure 3. Association of temperature gradient with longitudinal HIRRT risk during follow-up.**




The figure shows the predicted risk of HIRRT associated with temperature gradient during follow-up (*P*=0.01). Gradient categories are also represented. The grey shade represents the standard deviation of the prediction. Prediction was performed using a generalized linear regression mixed effects model, with HIRRT as the dependent variable, temperature gradient as the explanatory variable, and applied to 10 imputed datasets. Models' random effects were a random slope of visit number nested in a random intercept corresponding to the patient identification number. Model was weighted for the core temperature, using the CBPS method. Model coefficients were then pooled, and applied to a synthetic dataset with temperature gradient varying between the lowest and highest value observed in the cohort. For each imputed datasets, the C-statistics (and its 95% confidence interval, Delong's method) and the Hosmer-Lemeshow goodness-of-fit test was performed, and their results pooled. Final model's C-statistics: AUC: 0.59 [95% confidence interval: 0.57–0.61]; Hosmer-Lemeshow goodness-of-fit test: *P*=0.02.

**Table 2. Multivariate analysis of variables associated with longitudinal HIRRT risk**

| Variables (4-hourly observations) | HIRRT risk in the following 4h<br>Odd ratio [95% c.i.] | P value |
|---|---|---|
| Mean arterial pressure, per 10 mmHg increase* | | <0.01 |
| First degree component | 0.08 [0.02–0.38] | |
| Second degree component | 1.01 [1.00–1.02] | |
| Cardiac index, per 0.1 $L.min^{-1}.m^{-2}$ increase | 0.99 [0.96–1.02] | $ |
| Relative change in CCI during postural maneuver, per 1% increase | 1.15 [1.06–1.24] | $ |
| Relative change in CCI × cardiac index (*interaction term*) | 1.00 [0.99–1.00] | $ |
| Norepinephrine dose (tartrate), per 0.1 $\mu g.kg^{-1}.min^{-1}$ increase | - | - |
| Temperature gradient, per 0.1°C increase (unweighted) | 0.99 [0.98–1.01] | 0.33 |
| **Post treatment confounders** | | |
| Non-cardiovascular SOFA score, per 1 point increase | 0.94 [0.90–0.98] | <0.01 |
| Delay since last HIRRT < 8h (reference is ≥ 8h) | - | - |
| Daily lactate, per 1 mmol. $L^{-1}$ increase | 2.40 [1.23–4.69] | 0.02 |

*: quadratic polynomial factor in the model; ||: not retained in the model after backward stepwise selection; $$: significant interaction term between cardiac index and relative change in CCI ($P$<0.05).

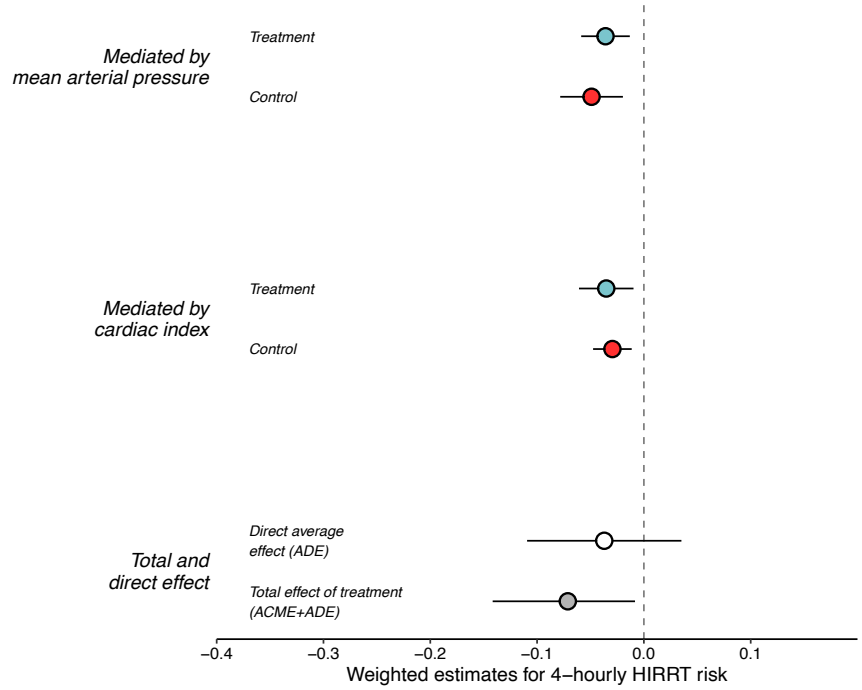
The mixed effects generalized linear regression model were run on 10 imputed datasets (N=970 observations in each dataset, due to the absence of follow-up in the next 4h regarding HIRRT at that time point), with the variables of interest as the fixed effects, HIRRT as the dependent variable, visit number as the random slope nested in a random intercept corresponding to the patient identification number. Variables inserted in the initial model were those with a P value < 0.20 in univariate analysis and deemed physiologically relevant to predict HIRRT risk. Variables were scaled and centered prior to regression (norepinephrine required additional transformation using the Box-Cox method due to leftward skewness). Backwards stepwise model selection was performed using Akaike's information criterion. Variables retained in the final model were those retained in at least 8 of the 10 imputed datasets (delay since last HIRRT < 8h: 4 votes, norepinephrine dose: 4 votes). Fixed effects were then pooled using Rubin's rule and descaled to the original hemodynamic parameter scale. No weighting was applied. For each imputed datasets, the C-statistics (and its 95% confidence interval, Delong's method) and the Hosmer-Lemeshow goodness-of-fit test was performed, and their results pooled. Final model's C-statistics: 0.78 (95% confidence interval: 0.75–0.82), Hosmer-Lemeshow goodness-of-fit test: $P$=0.35.

95% c.i: 95% confidence interval; CCI: continuous cardiac index by pulse contour analysis; HIRRT: hemodynamic instability related to renal replacement therapy; SOFA= sepsis-related organ failure assessment.

***Causal mediation***

Causal mediation analysis (**Figure 4**) showed that a ∆T° ≥ 0°C significantly decreased HIRRT risk, compared to a gradient < 0°C, mediated through both an increase in MAP and cardiac output (proportion mediated: 55% and 38% of the total effect of ∆T° on HIRRT risk, respectively). No significant direct (unmediated) effect of ∆T° in HIRRT risk was identified. The analysis also showed that a higher MAP or cardiac output would nevertheless lead to a decreased HIRRT risk in observations with a ∆T° < 0°C. **Supplemental figures S7**, **S8** and **S9** shows the results of the prespecified sensitivity mediation analyses.

**Figure 4. Mediation analysis**




The figure shows the weighted estimates associated with a temperature gradient ≥ 0° (in blue, treated), compared to a temperature gradient < 0°C (in red, control), mediated by mean arterial pressure and cardiac index (ACME, average causal mediated effect). The label "treatment" denotes the effect of the mediator (increasing MAP or CI) on HIRRT risk in observations with a gradient > 0°C (compared to ≤ 0°C), while the label "control" indicates the mediator's effect (increasing MAP or CI) on HIRRT risk if the gradient was ≤ 0°C (compared to > 0°C). The figure also shows the average direct (white dots) and total effect (sum of direct and indirect effects, in grey) of temperature gradient on HIRRT longitudinal risk. The mediation model was designed using the methodology developed by Imai and Yamamoto (2013), which allows the incorporation of alternative mediators when performing multiple causal analysis. Hence, 2 models were designed: one with the mean arterial pressure as the main mediator, and cardiac index as the alternative mediator. The second model did the opposite (cardiac index as the main mediator and mean arterial pressure as the alternative mediator). An interaction term between the treatment (temperature gradient) and the mediator (mean arterial pressure or cardiac index) was also included. The mediation model incorporated the following post-treatment confounders: non cardiovascular SOFA, norepinephrine dose, and daily arterial lactate concentration. The models were also weighted for pre-treatment cofounders (weights determined using the CBPS method). Models were evaluated on 10 imputed datasets, and their results pooled using Rubin's rule. Nonparametric confidence intervals were bootstrapped over 600 replicate datasets. Sensitivity analyses showed that the models were potentially susceptible to potential unaccounted-for confounders ($R^{2*}$ and $\tilde{R}^2 = 0.1$).

## DISCUSSION

### *Main results*

In this prospective, observational, single center study of a cohort of patients treated with CRRT and receiving advanced hemodynamic monitoring, we found that an increasing ΔT° was significantly associated with higher cardiac output and MAP, as well as with a lower HIRRT risk. A cooling temperature gradient (ΔT° ≥ 0°C, i.e. a CRRT temperature setting equal or inferior to core temperature) significantly decreased HIRRT risk, compared to a ΔT° < 0°C, mediated through both an increase in MAP and cardiac output.

### *Relationship to previous studies*

A cool dialysate strategy (usually 1 or 2°C below body temperature) is effective in patients with end-stage kidney disease undergoing intermittent hemodialysis on preventing intradialytic hypotension (8)(9). A systemic review and meta-analysis conducted in 2016 supported the evidence of using a cool dialysate to enhance hemodynamic tolerance during renal replacement therapy on chronic end-stage kidney disease patients undergoing hemodialysis (10).

In the context of critical illness, *Schortgen and al.* demonstrated that cooling the dialysate to lower body temperature reduced the risk of intradialytic hypotension in critically ill patients undergoing intermittent hemodialysis, along with other interventions(11). *Edrees and al.* also observed in a prospective randomized cross-over pilot study of patients receiving sustained low-efficiency dialysis (SLED) that a cool dialysate strategy led to significantly less HIRRT compared with dialysate temperature of 37°C(3). Finally, during CRRT, *Robert and al.* reported that cooling the replacement fluids to 36°C had no impact on body temperature but led to increased MAP and decreased catecholamine infusion dosage, in line with our results, although they reported no cardiac output data and could not conclude regarding HIRRT risk prevention (4).

Although the effect of cooling on MAP and norepinephrine dosage has been described before, the effect of a positive ΔT° gradient on heart rate and cardiac output, and subsequent protective effect on HIRRT risk, are less documented. External cooling

(applied to the peripheral/cutaneous envelope) is known to generate an increase in cardiac output, energy expenditure and oxygen consumption ($VO_2$) in exercising healthy subjects, in relation with the increase in muscle mass activity (shivering) and hypothalamus-driven neurohormonal activation aiming to maintain core temperature constant. On the other hand, intensive therapeutic cooling of septic and febrile patients with invasive mechanical ventilation has repeatedly shown a marked decrease in cardiac output (12), $VO_2$ and energy expenditure (13,14), especially in sedated, paralyzed patients. Among those, *Rokyta et al.* observed that cooling patients undergoing CRRT (using a replacement fluid temperature of 20°C), with septic shock and mild hyperthermia (> 37.5°C) led to decreased $VO_2$, cardiac output and heart rate (15). These contrasting results, contrary to our observations (where cardiac output increased), are related to the fact that these studies applied intensive cooling to generate a drastic fall in body core temperature (by cooling the dialysate down to 20°C or by turning off the heater, implying a $\Delta T°$ of 17°C or more). These conditions are in stark contrast with the condition met by our population exposed to an absolute difference between CRRT temperature and core temperature of a maximum of ±2°C, and in which the counteracting, core heating, response may not have been antagonized.

***Implications of study findings***

Our results showed that during CRRT, increasing the $\Delta T°$ between $T°_{CORE}$ and $T°_{CRRT}$ led to a lower risk of HIRRT, through an improvement in both MAP and cardiac output. These elements suggest that modifying the $\Delta T°$ by setting the $T°_{CRRT}$ below $T°_{CORE}$ might contribute to improve hemodynamic management and resuscitation. Furthermore, setting $T°_{CRRT}$ should probably account for the starting core temperature, to limit inadequate or excessive hypothermia, or on the contrary deleterious over-heating. Consequently, lower dialysate temperature might be a potential RRT-related interventions to limit HIRRT by promoting vasoconstriction and cardiac output.

Hypothermia is known to contribute to coagulopathy in trauma patient (16), and cooling patients undergoing CRRT could lead to the same complication by inhibiting the initiation phase of thrombin generation and fibrinogen synthesis. However, a critical temperature of 34°C was identified (17), below which platelet function is significantly impaired, a temperature that was not observed in our cohort. Furthermore, if mild or

relative hypothermia does alter coagulation, a potential benefit would be prolonged filter lifespan, although we are unable to conclude regarding this matter.

Furthermore, exposure to cold temperatures affects cellular and molecular defenses against pathogens in both humans and animals and causes secretion of norepinephrine, cortisol and decreased lymphoproliferative responses because of stress state induction. Indeed, hypothermia had significant effects on the immune system by suppressing the innate immune function, reducing monocyte HLA-DR expression and altering cytokine production and may be associated with increased septic complications and mortality (18,19). Further studies are needed to explore these potential adverse effects.

***Strengths and limitations***

Strengths of the study included the high number of HIRRT episodes collected that represented many situations. Secondly, the prospective nature of the study minimized the occurrence of missing values, which were nevertheless considered during statistical analysis. Thirdly, we used advanced statistical methodology including causal mediation analysis, multiple imputation and sensitivity analyses to stress the robustness of our results.

This study has several limits that must be addressed. First, because of the single-center study design, extrapolation of our results to other ICUs may be questionable. Second, there is no standardized definition of HIRRT, and our chosen definition may be debatable. Nevertheless, we used a straight-forward definition that can easily and commonly be used in ICUs. Third, we did not report skin temperature (a potent mediator of core temperature control) and effective CRRT circuit temperature, which limits the physiological interpretation of the tested interventions. In addition, although advanced hemodynamic monitoring was in place, we lack the data to estimate $VO_2$ and further describe the effect of $\Delta T°$ on energy expenditure and gas exchange. However, given the significant effect of the $\Delta T°$ on heart rate and cardiac output, this physiological response to mild cooling appears to be the more plausible explanation. Finally, it would have been interesting to quantify the impact of $\Delta T°$ on microcirculatory parameters such as mottles extension or capillary refilling time.

## CONCLUSIONS

In this single-center, prospective, causal mediation study, setting the CRRT temperature lower than body temperature significantly reduced the risk of HIRRT during CRRT, due to its beneficial effects on MAP and cardiac output.

## DECLARATIONS


### *Acknowledgements*

The authors are grateful to patients and families who allowed this study to be performed.


### *Statement of ethics*

The study was conducted in accordance with the Declaration of Helsinki and with local regulations. The study protocol was reviewed and approved by the Comité de Protection des Personnes Ile de France IV, ID-RCB 2017-A00483-50.

### *Competing interest*

The authors declare no competing interest in relation with the work.


### *Funding source*

None


### *Authors' contributions*

JCR, CG, LB and LF collected the data, interpreted the results and drafted the manuscript. JCR, LB and LF accessed and verified the underlying data. LB designed the study and performed the statistical analysis. TK, MC, GD, GC, MM, LC, HY and JCR interpreted the results, and revised the manuscript for important intellectual content. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors approved the final version to be published and agree to be accountable for all aspects of the work.

### *Data availability statement*

Source datasets are not publicly available due to ethical reasons. Further enquiries can be directed to the corresponding author at laurent.bitker@chu-lyon.fr. The authors vouch for the accuracy and completeness of the data.

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## APPENDIX

**Table S1. Baseline characteristics of the cohort**

| Variable | All patients | ΔT° < -2°C | ΔT° -2 to 0°C | ΔT° ≥ 0°C | P value |
|---|---|---|---|---|---|
| | N=42 | N=16 | N=12 | N=14 | |
| Age, years | 68 [58–76] | 70 [64–82] | 73 [61–78] | 58 [49–68] | 0.02 |
| Sex (male), N (%) | 26 (62%) | 11 (69%) | 7 (58%) | 8 (57%) | 0.78 |
| Body mass index, $kg.m^{-2}$ | 26 [22–31] | 25 [21–28] | 27 [24–32] | 26 [21–30] | 0.47 |
| Body weight at inclusion, kg | 74 [69–86] | 74 [66–80] | 75 [71–84] | 72 [68–89] | 0.71 |
| SAPS-2 score | 64 [49–76] | 66 [60–81] | 52 [46–72] | 68 [56–76] | 0.35 |
| SOFA score | 12 [8–15] | 12 [8–14] | 10 [8–12] | 14 [11–16] | 0.12 |
| Non cardiovascular SOFA | 8 [5–11] | 8 [4–11] | 6 [5–8] | 10 [7–12] | 0.12 |
| Non-renal SOFA score | 9 [6–12] | 9 [3–11] | 7 [6–8] | 12 [9–12] | 0.05 |
| Medical admission context, N (%) | 42 (100%) | 16 (100%) | 12 (100%) | 14 (100%) | NA |
| *Comorbidities* | | | | | |
| Diabetes, N (%) | 12 (29%) | 4 (25%) | 4 (33%) | 4 (29%) | 0.91 |
| Chronic respiratory disease, N (%) | 4 (10%) | 0 (0%) | 3 (25%) | 1 (7%) | 0.06 |
| Chronic heart failure, N (%) | 10 (24%) | 3 (19%) | 5 (42%) | 2 (14%) | 0.26 |
| Coronary artery disease, N (%) | 12 (29%) | 4 (25%) | 4 (33%) | 4 (29%) | 0.91 |
| Cirrhosis, N (%) | 6 (14%) | 4 (25%) | 2 (17%) | 0 (0%) | 0.15 |
| *Acute circulatory failure mechanism* | | | | | 0.05 |
| Cardiogenic shock, N (%) | 8 (19%) | 1 (6%) | 5 (42%) | 2 (14%) | |
| Septic shock, N (%) | 22 (52%) | 9 (56%) | 3 (25%) | 10 (71%) | |
| Vasoplegic non-septic shock, N (%) | 8 (19%) | 3 (19%) | 4 (33%) | 1 (7%) | |
| Post-cardiac arrest syndrome, N (%) | 4 (10%) | 3 (19%) | 0 (0%) | 1 (7%) | |
| Sepsis, N (%) | 33 (79%) | 14 (88%) | 6 (50%) | 13 (93%) | 0.03 |
| Septic shock, N (%) | 24 (57%) | 11 (69%) | 3 (25%) | 10 (71%) | 0.04 |
| Invasive mechanical ventilation, N (%) | 35 (83%) | 13 (81%) | 8 (67%) | 14 (100%) | 0.06 |
| RASS score, N (%) | -5 [-5–-4] | -5 [-5–-1] | -5 [-5–0] | -5 [-5–-5] | 0.04 |
| Neuromuscular blockade agonist, N (%) | 18 (43%) | 4 (25%) | 4 (33%) | 10 (71%) | 0.03 |

Data is median [interquartile range] or count (percentage)
Longitudinal groups of temperature gradient categories (columns 2 to 4) were defined as fraction of time spent <-2°C or ≥0°C over 30% of total follow-up.
Comparison between groups were performed using Fisher's test or the Kruskal-Wallis test
ΔT°: temperature gradient; RASS: Richmond analgesia and sedation scale; SAPS-2: simplified acute physiology score 2; SOFA: sequential organ failure assessment

**Table S2. CRRT settings at baseline**

| Variable | All patients | ΔT° < -2°C | ΔT° -2 to 0°C | ΔT° ≥ 0°C | P value |
|---|---|---|---|---|---|
| | N=42 | N=16 | N=12 | N=14 | |
| Delay between ICU admission and CRRT start, h | 1 [0–3] | 1 [0–3] | 2 [0–3] | 1 [0–4] | 0.78 |
| Delay between CRRT start and inclusion, h | 6 [1–15] | 8 [3–14] | 5 [1–16] | 4 [1–17] | 0.92 |
| Fluid balance at inclusion, kg | 3 [0–8] | 4 [0–8] | 2 [-3–4] | 4 [1–10] | 0.14 |
| *CRRT technique* | | | | | 0.77 |
| CVVH, N (%) | 39 (93%) | 14 (88%) | 12 (100%) | 13 (93%) | |
| CVVHD, N (%) | 3 (7%) | 2 (12%) | 0 (0%) | 1 (7%) | |
| *CRRT anticoagulation technique* | | | | | 0.77 |
| Regional citrate anticoagulation, N (%) | 3 (7%) | 2 (12%) | 0 (0%) | 1 (7%) | |
| Systemic heparin, N (%) | 39 (93%) | 14 (88%) | 12 (100%) | 13 (93%) | |
| *CRRT settings* | | | | | |
| Blood flow, $ml.min^{-1}$ | 250 [200–250] | 250 [200–250] | 250 [250–250] | 250 [200–288] | 0.66 |
| Effluent flow rate, $ml.kg^{-1}.h^{-1}$ | 29 [26–32] | 29 [24–32] | 29 [26–31] | 29 [27–34] | 0.74 |
| Net ultrafiltration flow rate, $ml.h^{-1}$ | 0 [0–200] | 44 [0–300] | 50 [0–162] | 0 [0–188] | 0.78 |
| Net ultrafiltration flow rate, $ml.h^{-1}.kg^{-1}$ | 0 [0–2.9] | 0.7 [0–4.5] | 0.6 [0–2.9] | 0 [0–2.7] | 0.83 |

Data is median [interquartile range] or count (percentage)
Longitudinal groups of temperature gradient categories (columns) were defined as fraction of time spent <-2°C or ≥0°C over 30% of total follow-up.
Comparison between groups were performed using Fisher's test or the Kruskal-Wallis test
CVVHD: continuous veno-venous hemodialysis; CVVH: continuous veno-venous hemofiltration; CRRT: continuous renal replacement therapy; ΔT°: temperature gradient; ICU: intensive care unit

**Table S3. Hemodynamic parameters at baseline**

| Variable | All patients | ΔT° < -2°C | ΔT° -2 to 0°C | ΔT° ≥ 0°C | P value |
|---|---|---|---|---|---|
| | N=42 | N=16 | N=12 | N=14 | |
| Duration of follow-up, h | 119 [57–143] | 140 [23–145] | 69 [43–108] | 131 [79–144] | 0.15 |
| Mean arterial pressure, mmHg | 70 [62–75] | 71 [65–75] | 68 [64–76] | 70 [57–75] | 0.81 |
| Systolic arterial pressure, mmHg | 110 [97–124] | 114 [103–121] | 106 [102–134] | 106 [80–122] | 0.59 |
| Diastolic arterial pressure, mmHg | 52 [45–58] | 50 [44–56] | 56 [48–61] | 52 [46–56] | 0.26 |
| Cardiac index, $L.min^{-1}.m^{-2}$ | 2.8 [2.1–3.3] | 2.7 [2.4–3.3] | 2.8 [2.1–3.4] | 2.8 [2.1–3.2] | 0.74 |
| Heart rate, $min^{-1}$ | 96 [74–113] | 82 [72–97] | 95 [72–109] | 107 [96–119] | 0.03 |
| Stroke volume index, $ml.m^{-2}$ | 29 [24–38] | 32 [25–45] | 26 [22–41] | 27 [20–33] | 0.23 |
| Preload dependent status, N (%) | 22 (52%) | 9 (56%) | 4 (33%) | 9 (64%) | 0.30 |
| Central venous pressure, mmHg | 8 [6–10] | 10 [5–10] | 8 [7–9] | 8 [6–10] | 0.97 |
| Extravascular lung water index, $ml.kg^{-1}$ | 11 [8.1–13.7] | 10.4 [9–13.7] | 13.3 [10.1–14.8] | 11.5 [7.5–13] | 0.59 |
| Pulmonary vascular permeability index | 2.2 [1.9–3] | 2.2 [1.7–2.6] | 2.4 [1.9–2.8] | 2.4 [1.9–3.3] | 0.33 |
| Global end-diastolic volume index, $ml.m^{-2}$ | 664 [593–843] | 765 [683–932] | 732 [567–950] | 597 [538–622] | <0.01 |
| Norepinephrine administration, N (%) | 40 (95%) | 15 (94%) | 11 (92%) | 14 (100%) | 0.74 |
| Norepinephrine dose (tartrate), $\mu g.kg^{-1}.min^{-1}$ | 0.54 [0.21–1.41] | 0.56 [0.15–1.09] | 0.3 [0.2–1.12] | 0.76 [0.34–2.62] | 0.35 |
| Arterial lactate, $mmol.L^{-1}$ | 2.9 [1.5–5] | 3 [1.9–4.7] | 1.9 [1.4–3.3] | 3.4 [1.6–6.8] | 0.60 |

Data is median [interquartile range] or count (percentage)
Longitudinal groups of temperature gradient categories (columns) were defined as fraction of time spent <-2°C or ≥0°C over 30% of total follow-up.
Comparison between groups were performed using Fisher's test or the Kruskal-Wallis test
ΔT°: temperature gradient

**Table S4. Temperature gradient and core temperature at baseline**

| Variable | All patients | ΔT° < -2°C | ΔT° -2 to 0°C | ΔT° ≥ 0°C | P value |
|---|---|---|---|---|---|
| | N=42 | N=16 | N=12 | N=14 | |
| *Core temperature* | | | | | |
| Before CRRT start, °C | 36.7 [36.3–37.4] | 36.6 [36–37.1] | 37 [36.5–37.5] | 36.9 [36.4–37.3] | 0.43 |
| At inclusion, °C | 36.5 [35.8–36.9] | 35.8 [35.6–36.3] | 36.7 [36–36.8] | 37 [36.3–37.4] | 0.01 |
| *Core temperature category* | | | | | 0.06 |
| < 36°C, N (%) | 15 (36%) | 9 (56%) | 3 (25%) | 3 (21%) | |
| 36 to 37.5°C, N (%) | 24 (57%) | 7 (44%) | 9 (75%) | 8 (57%) | |
| >37.5°C, N (%) | 3 (7%) | 0 (0%) | 0 (0%) | 3 (21%) | |
| Temperature gradient at inclusion, °C | -1.3 [-2.9–-0.5] | -2.9 [-3.3–-1.2] | -1.3 [-2–-1.1] | -0.6 [-2–0.4] | <0.01 |
| *Temperature gradient category at inclusion* | | | | | <0.01 |
| < -2°C, N (%) | 15 (36%) | 9 (56%) | 2 (17%) | 4 (29%) | |
| -2 to 0°C, N (%) | 20 (48%) | 7 (44%) | 10 (83%) | 3 (21%) | |
| ≥ 0°C, N (%) | 7 (17%) | 0 (0%) | 0 (0%) | 7 (50%) | |
| *Core temperature during follow-up* | | | | | |
| Fraction of time between 36 and 37.5°C | 0.78 [0.61–0.9] | 0.74 [0.48–0.79] | 0.82 [0.78–1] | 0.73 [0.58–0.9] | 0.07 |
| Fraction of time below 36°C | 0.08 [0–0.22] | 0.25 [0.17–0.52] | 0.08 [0–0.13] | 0 [0–0.06] | <0.01 |
| Fraction of time above 37.5°C | 0.01 [0–0.13] | 0 [0–0.01] | 0 [0–0.08] | 0.17 [0.09–0.41] | <0.01 |
| *Temperature gradient during follow-up* | | | | | |
| Fraction of time with gradient ≥ 0°C | 0.05 [0–0.48] | 0 [0–0] | 0.01 [0–0.13] | 0.57 [0.5–0.8] | <0.01 |
| Fraction of time with gradient between -2°C and 0°C | 0.29 [0.12–0.58] | 0.13 [0.04–0.29] | 0.74 [0.68–0.82] | 0.18 [0.12–0.4] | <0.01 |
| Fraction of time with gradient < -2°C | 0.24 [0.03–0.65] | 0.77 [0.61–0.94] | 0.09 [0–0.14] | 0.08 [0–0.21] | <0.01 |

Data is median [interquartile range] or count (percentage)
Longitudinal groups of temperature gradient categories (columns) were defined as fraction of time spent <-2°C or ≥0°C over 30% of total follow-up.
Comparison between groups were performed using Fisher's test or the Kruskal-Wallis test
CRRT: continuous renal replacement therapy ; ΔT°: temperature gradient

**Table S5. Clinical outcomes**

| Variable | All patients | ΔT° < -2°C | ΔT° -2 to 0°C | ΔT° ≥ 0°C | P value |
|---|---|---|---|---|---|
| | N=42 | N=16 | N=12 | N=14 | |
| Total number of HIRRT episodes | 214 | 92 | 54 | 68 | 0.03 |
| Number of HIRRT episodes per patient | 4 [3–8] | 6 [3–10] | 4 [3–4] | 6 [3–8] | 0.38 |
| Death at day-90, N (%) | 26 (62%) | 13 (81%) | 8 (67%) | 5 (36%) | 0.04 |
| RRT dependence at day-90, N (%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | >0.99 |
| RRT-free days at day-90 | 0 [0–74] | 0 [0–0] | 0 [0–52] | 63 [0–80] | 0.06 |

Data is median [interquartile range] or count (percentage)
Longitudinal groups of temperature gradient categories (columns) were defined as fraction of time spent <-2°C or ≥0°C over 30% of total follow-up.
Comparison between groups were performed using Fisher's test or the Kruskal-Wallis test
ΔT°: temperature gradient ; HIRRT: hemodynamic instability related to RRT; RRT: renal replacement therapy

**Table S6. Association of hemodynamics and suspected confounders with longitudinal HIRRT risk (univariate analysis)**

| Variables (4-hourly observations) | HIRRT risk in the following 4h<br>Odd ratio [95% c.i.] | P value |
|---|---|---|
| Mean arterial pressure, per 10 mmHg increase* | | <0.01 |
| First degree | 0.09 [0.02–0.43] | |
| Second degree | 1.01 [1.00–1.02] | |
| Cardiac index, per 0.1 $L.min^{-1}.m^{-2}$ increase | 0.93 [0.91–0.96] | <0.01 |
| Heart rate, per 10 $min^{-1}$ increase* | | <0.01 |
| First degree | 0.18 [0.09–0.35] | |
| Second degree | 1.01 [1.01–1.01] | |
| Stroke volume index, per 10 $ml.m^{-2}$ increase | 0.68 [0.54–0.86] | <0.01 |
| Relative change in CCI during postural maneuver, per 1% increase | 1.02 [1.01–1.04] | 0.01 |
| Preload dependent status (reference is preload independence)[‖] | 1.60 [1.11–2.29] | 0.01 |
| Norepinephrine dose (tartrate), per 0.1 $\mu g.kg^{-1}.min^{-1}$ increase | 1.00 [0.98–1.02] | 0.50 |
| Temperature gradient, per 0.1°C increase | 0.98 [0.97–0.99] | <0.01 |
| Weighted temperature gradient, per 0.1°C increase | 0.97 [0.95–0.99] | <0.01 |
| **Pre-treatment confounders** | | |
| Age, per 1 year increase | 1.01 [0.99–1.03] | 0.30 |
| Sepsis (reference is no sepsis) | 0.78 [0.46–1.33] | 0.37 |
| Invasive mechanical ventilation (reference is no invasive mechanical ventilation) | 0.74 [0.39–1.41] | 0.37 |
| RASS score ≤ -4 (reference is > -4) | 0.70 [0.41–1.22] | 0.23 |
| Core temperature, per 1°C increase | 1.00 [1.00–1.00] | 0.01 |
| CRRT modality is CVVHD (CVVH is the reference) | 0.58 [0.31–1.11] | 0.09 |
| **Post-treatment confounders** | | |
| Non-cardiovascular SOFA score, per 1 point increase | 0.94 [0.89–0.98] | 0.01 |
| Delay since last HIRRT < 8h (reference is ≥ 8h) | 1.55 [1.07–2.24] | 0.02 |
| Daily lactate, per 1 $mmol.L^{-1}$ increase | 2.27 [1.09–4.72] | 0.04 |

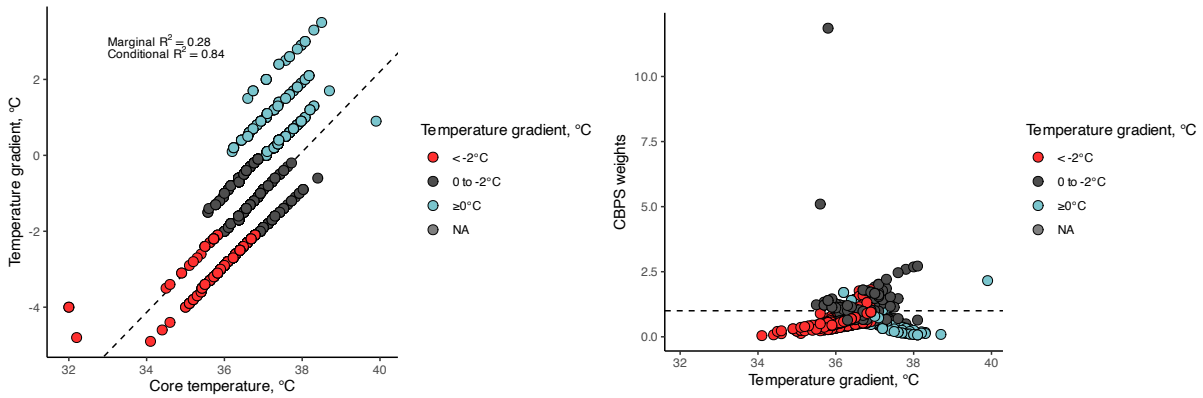
*: quadratic factor in the model

[‖]: defined as a CCI increase > 10% during the postural maneuver

Mixed effects generalized linear regression models were run on 10 imputed datasets (N=970 observations in each dataset, due to the absence of follow-up in the next 4h regarding HIRRT at that time point), with the variable of interest as the fixed effect, HIRRT as the dependent variable, visit number as the random slope nested in a random intercept corresponding to the patient identification number. Variables were scaled and centered prior to regression (norepinephrine required additional transformation using the Box-Cox method due to leftward skewness). Models' goodness-of-fit were checked using Hartig et al. method (package *DHARMa*). Fixed effects were then pooled using Rubin's rule and descaled to the original hemodynamic parameter scale. Weighting of temperature gradient was performed using the CBPS method to adjust for the effects of pre-treatment confounders on temperature gradient. P values were bootstrapped over 500 replicate datasets.

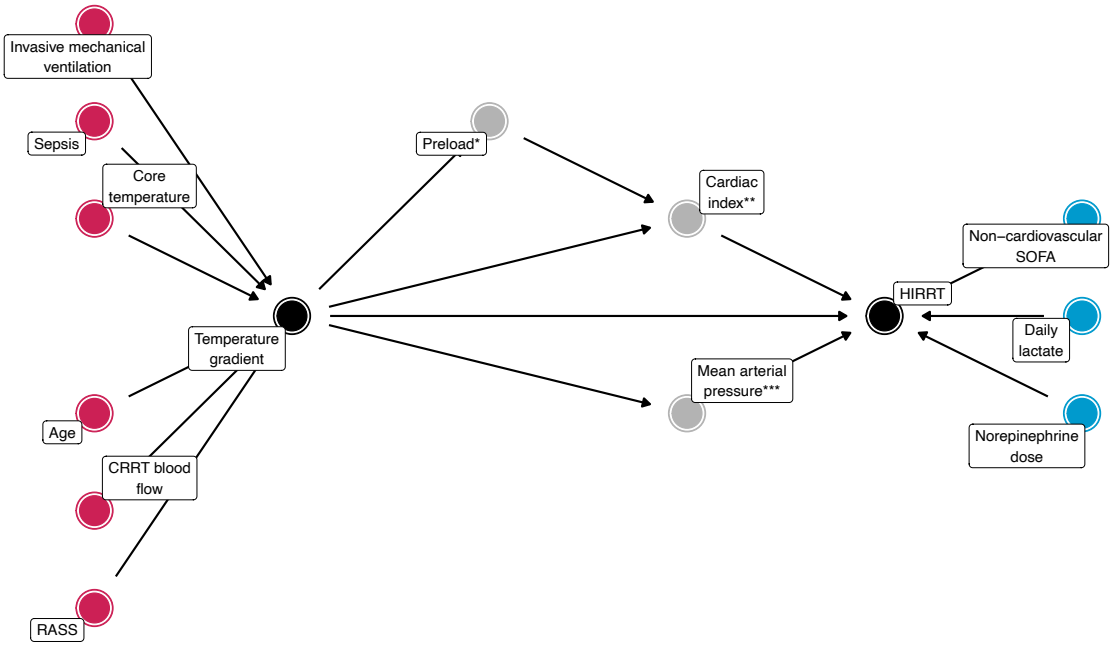
95% c.i.: 95% confidence interval; CCI: continuous cardiac index by pulse contour analysis; HIRRT: hemodynamic instability related to renal replacement therapy; RASS: Richmond's analgesia and sedation scale; SOFA= sepsis-related organ failure assessment.

**Supplemental figure 1. Correlation between core temperature and temperature gradient, and estimated weights applied to temperature gradient as a function of pre-treatment cofounders**




The figure shows the correlation between core temperatures and temperature gradients in panel A, and the weight values applied to temperature gradient in models to correct for the confounding effect of pre-treatment cofounders (core temperature, age, sepsis, RASS, invasive mechanical ventilation, CRRT modality). Data points are also categorized based on the temperature gradient category (< -2°C in red, between -2°C and 0°C in green, and ≥0°C in blue). Weights were determined using the covariate balancing propensity score methods for continuous treatments (Fong et al., 2018). The figure shows that in an observation with hyperthermia (> 37.5°C), a higher weigh will be given to observations with a gradient below 0°C. CRRT: continuous renal replacement therapy; RASS: Richmond analgesia and sedation scale.

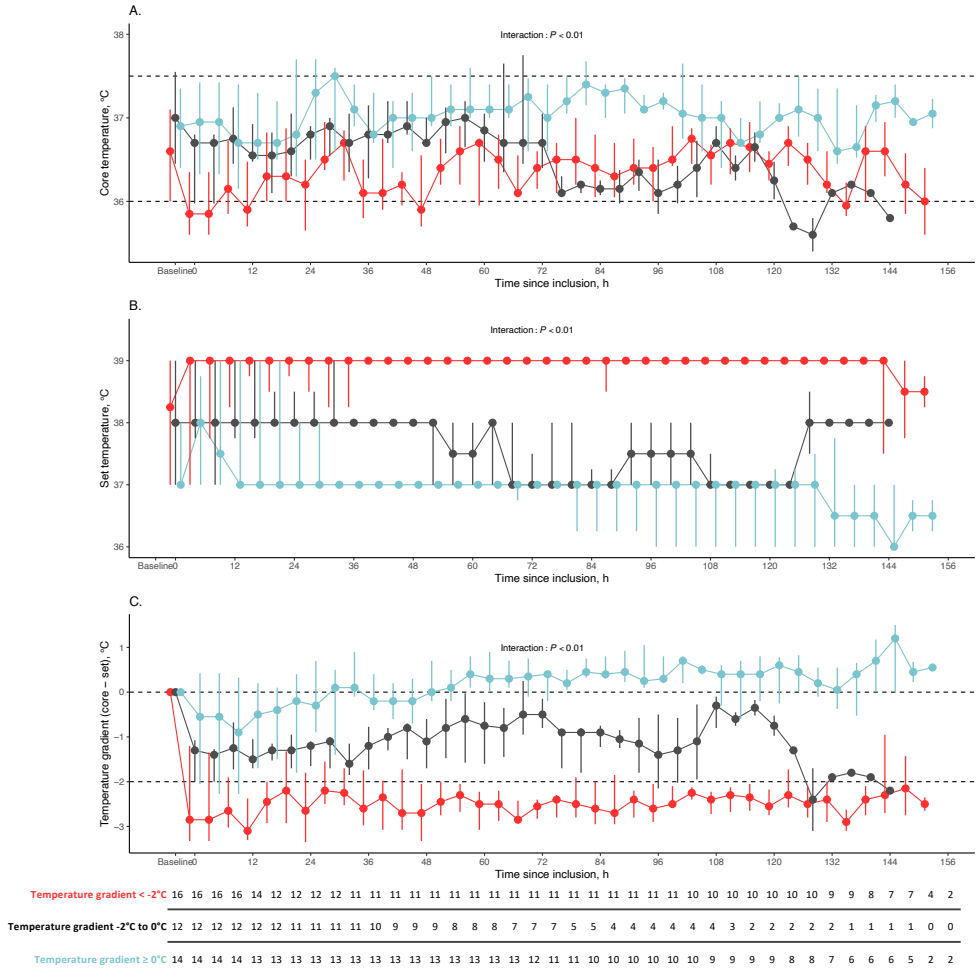
**Supplemental figure 2. Directed acyclic graph**




The figure shows the hypothesized causal relation between temperature gradient set on the CRRT monitor and the HIRRT risk, mediated through mean arterial pressure and cardiac index. In mediation models (** and ***), both mediators acted as the main mediator, while the other acted as the alternate mediator. Preload (*) was also included given the theoretical impact of temperature gradient on venous vasomotor tone and venous return. Core temperature and other covariates acted as a potential pre-treatment confounder (in red), while norepinephrine dose, non-cardiovascular SOFA score and arterial lactate concentration acted as post-treatment confounders, interacting with both the outcome and mediators (in blue). Interactions between mediators and treatment were also accounted for.

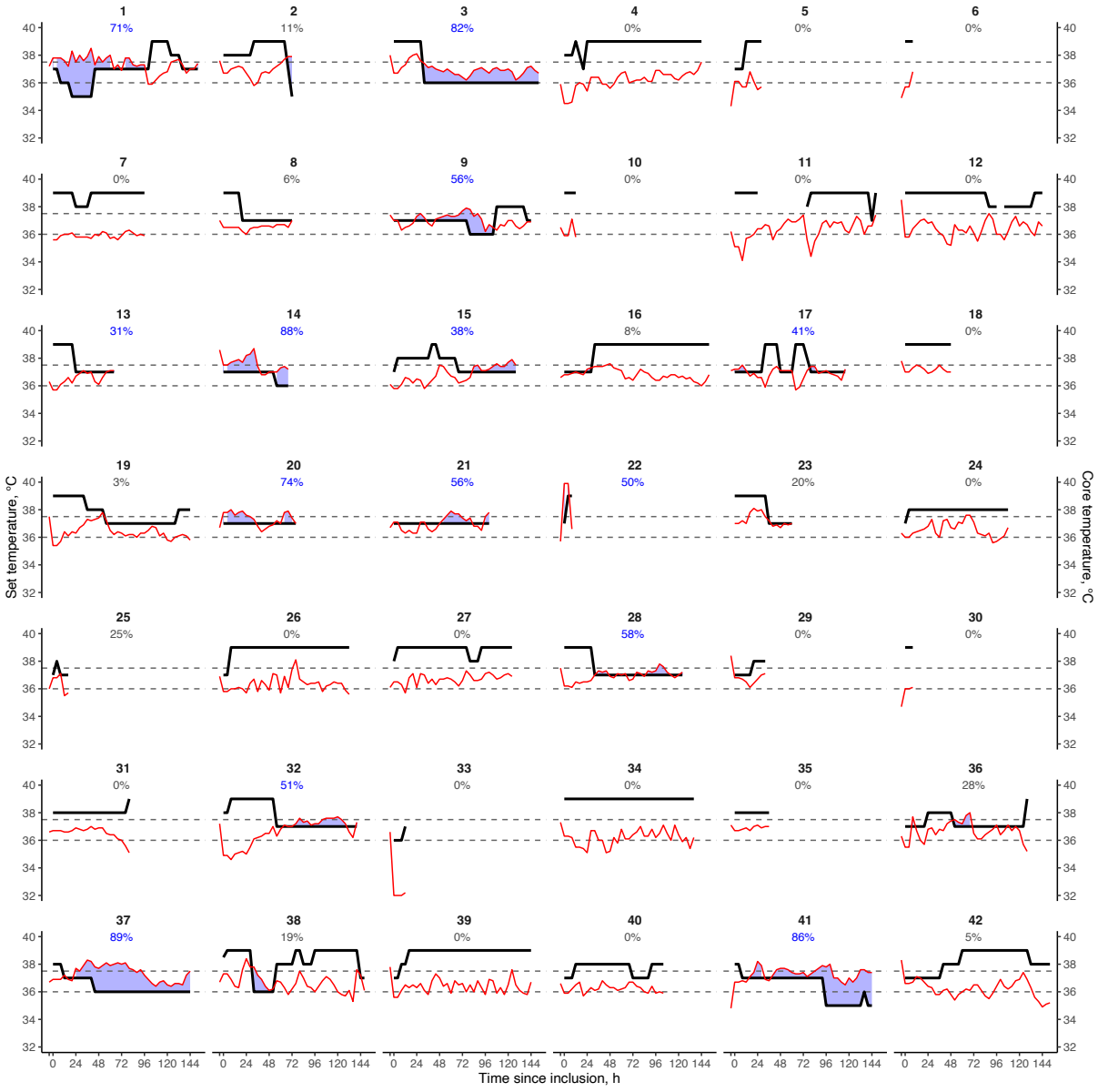
SOFA: sepsis-related organ failure assessment

**Supplemental figure 3. Core temperature, CRRT set temperature and temperature gradient over time**



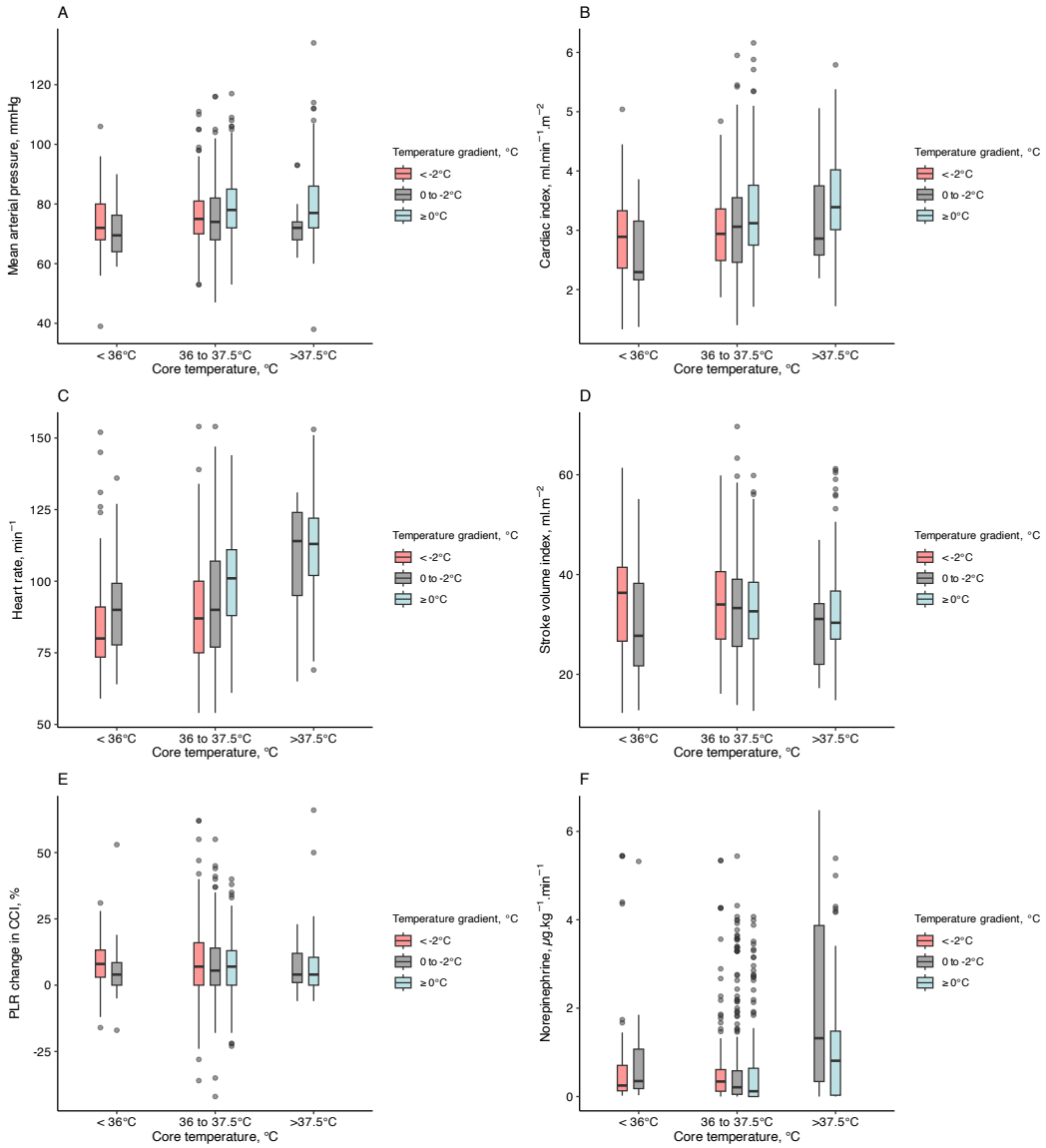

The figure shows the median value and first and third quartile value of core temperature (A), CRRT set temperature (B) and temperature gradient (C) over time in the cohort, categorized by the fraction of time spent in a temperature gradient category (>30% of time with temperature gradient ≥ 0°C in blue, >30% of time with temperature gradient < -2°C in red, the remaining observations in grey). Below the panels are the number of patients at risk in each category over time. In each panel, the *P* value examines the association of the interaction existing between elapsed time since inclusion (categorical) and the gradient category with the variable of interest, using a linear mixed effects model, with the patient identification number as the random intercept and the elapsed time as a random effect (continuous). An offset for the core temperature measured before inclusion was also included. CRRT: continuous renal replacement therapy.

**Supplemental figure 4. Core temperature, CRRT set temperature and temperature gradient over time in the 42 patients of the cohort.**




The figure shows the longitudinal evolution of core temperature (in red), set temperature (in black), and the gradient (the difference between the two latter) in patients included in the study. Positive gradients are represented with a blue shade, and the fraction (%) of time spent with a gradient >0°C is given for each individual. CRRT: continuous renal replacement therapy.

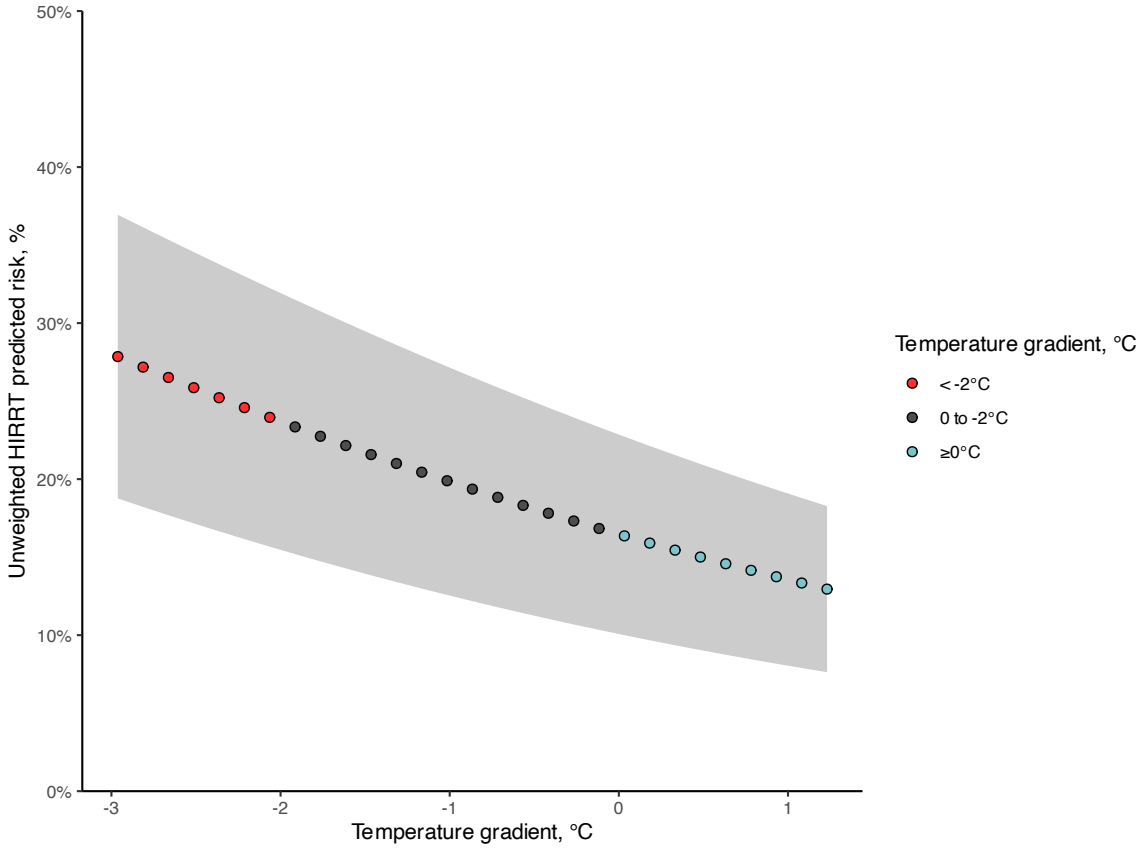
**Supplemental figure 5. Observed hemodynamic values based on the temperature gradient and core temperature categories.**




The figure shows the observed median value of mean arterial pressure (A), cardiac index (B), heart rate (C), stroke volume index (D), relative change in CCI during a postural maneuver (E) and norepinephrine dose (F) as a function of the core temperature category (x axis) and the temperature gradient (< -2°C in red, between -2 and 0°C in grey, and ≥ 0°C in blue) during longitudinal follow-up (4-hourly observations, N=1012).

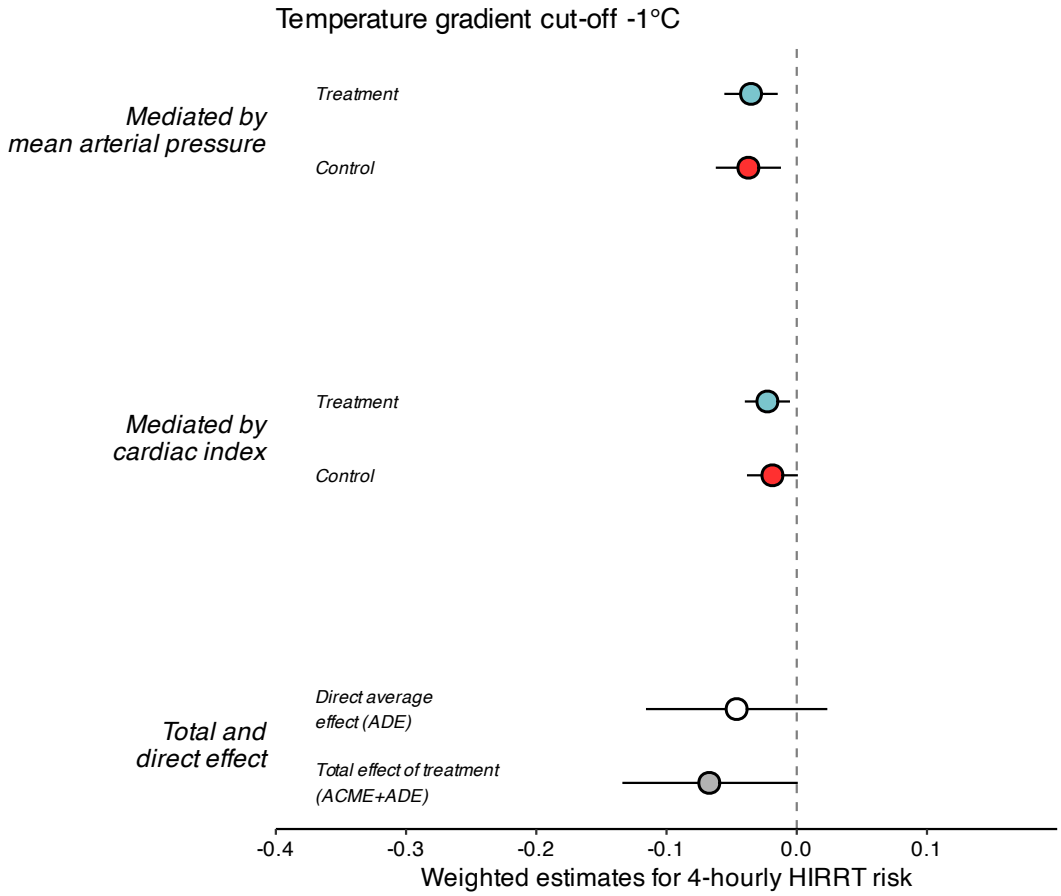
CCI: continuous cardiac index by pulse contour analysis.

**Supplemental figure 6. Association of temperature gradient with longitudinal HIRRT risk during follow-up (unweighted analysis in observations with normal core temperature)**



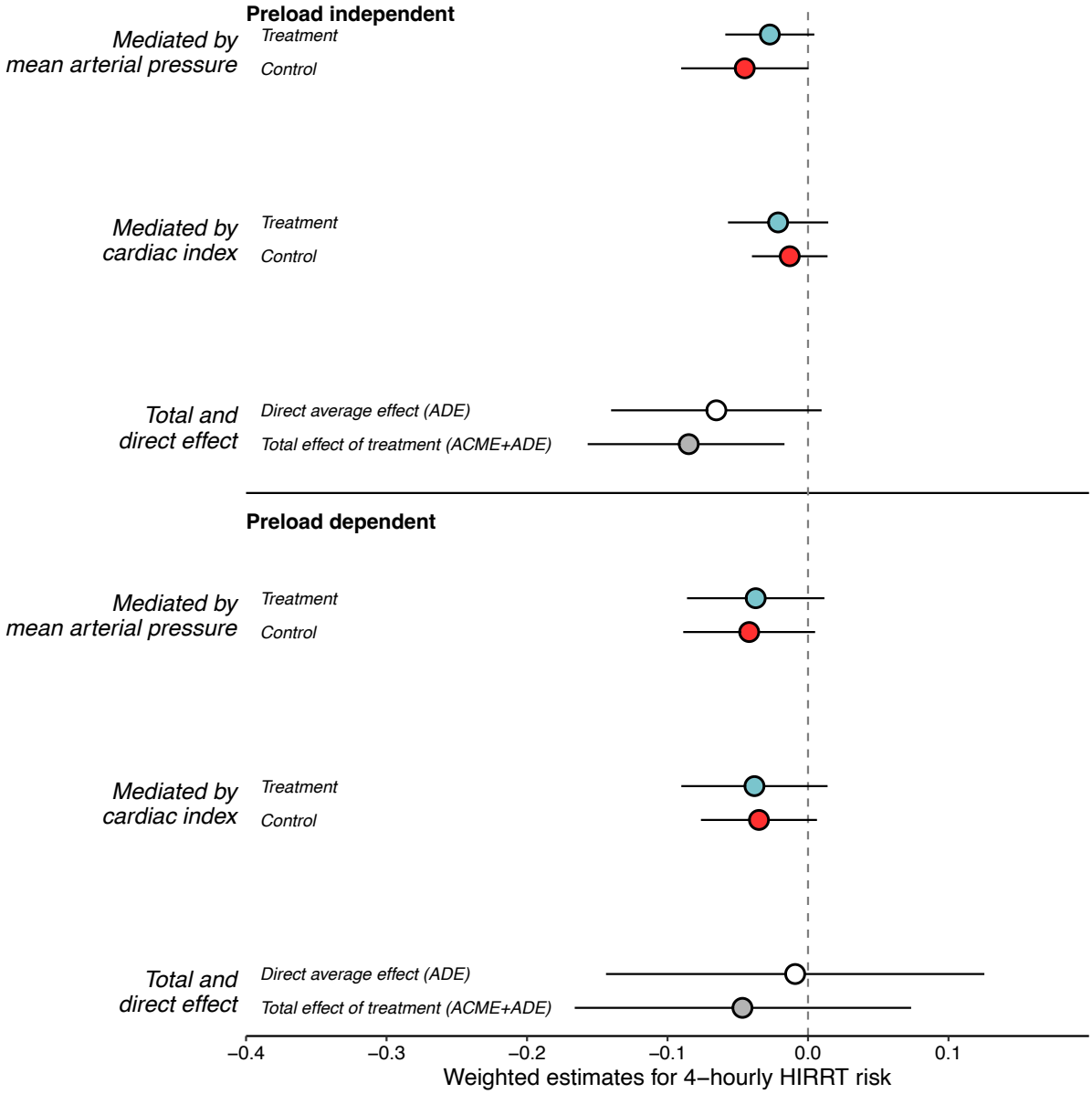

The figure shows the predicted risk of HIRRT associated with temperature gradient during follow-up in observations with a normal core temperature (*P*=0.02). Gradient categories are also represented. The grey shade represents the standard deviation of the prediction. Prediction was performed using a generalized linear regression mixed effects model, with HIRRT as the dependent variable, temperature gradient as the explanatory variable, and applied to 10 imputed datasets. Models' random effects were a random slope of visit number nested in a random intercept corresponding to the patient identification number. Model coefficients were not weighted for core temperature. Model coefficients were then pooled and applied to a synthetic dataset with temperature gradient varying between the lowest and highest value observed in the cohort. For each imputed datasets, the C-statistics (and its 95% confidence interval, Delong's method) and the Hosmer-Lemeshow goodness-of-fit test was performed, and their results pooled. Final model's C-statistics: 0.56 [95% confidence interval: 0.53–0.59], Hosmer-Lemeshow goodness-of-fit test: *P*=0.01.

**Supplemental figure 7. Mediation analysis in 4-hourly observations using a temperature gradient cut-off value ≥ -1°C o < -1°C**



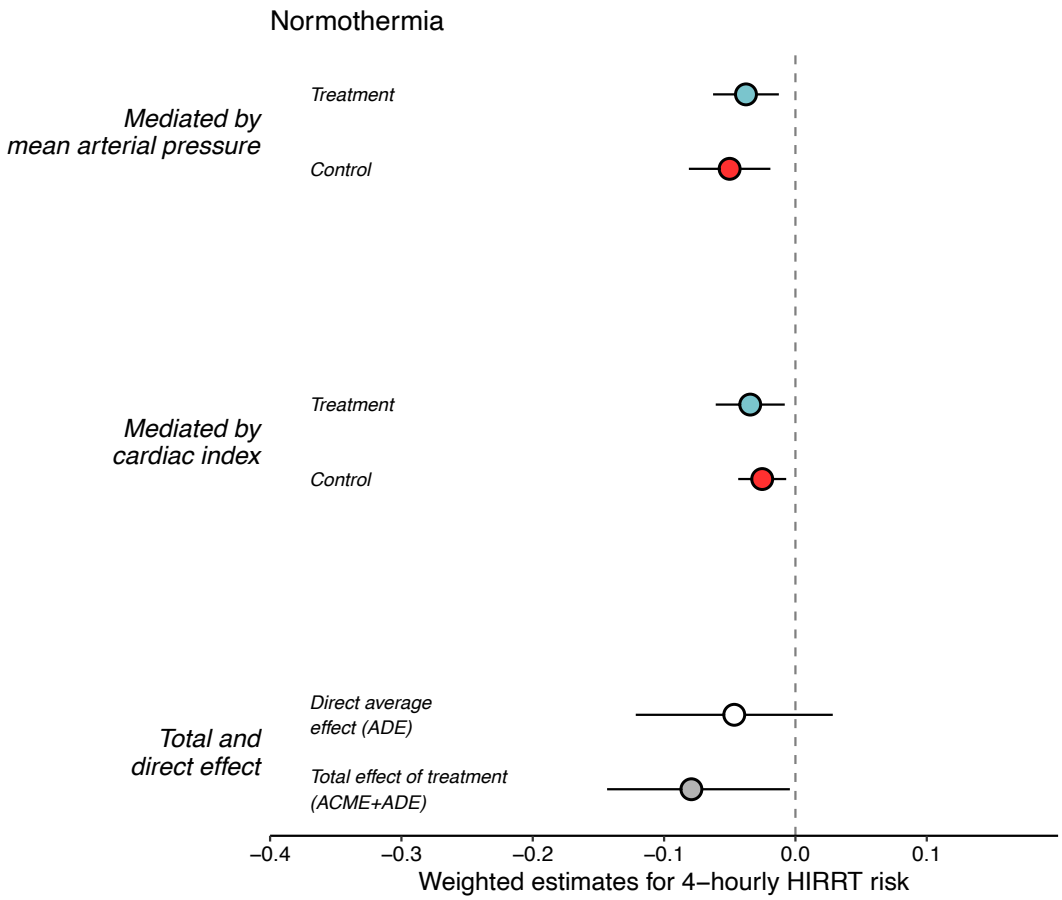

The methodology follows exactly that presented in the main analysis, except for the modification of the cutoff value used to define treatment (in blue) and controls (in red), modified to -1°C.

**Supplemental figure 8. Mediation analysis in 4-hourly observations with or without preload dependence.**




Given the fact that a potential interaction existed between preload dependence and cardiac index in HIRRT risk prediction, a sensitivity analysis was performed in the subgroup of 4-hourly observations with preload dependence (N=360) and those without (N=617, 35 imputed missing observations in the original datasets). Preload dependence was defined as relative change in continuous cardiac index > 10% during a postural maneuver performed at time of observation. The methodology follows exactly that presented in the main analysis.

**Supplemental figure 9. Mediation analysis in 4-hourly observations with normothermia.**




The figure shows the sensitivity analysis performed in the subset of observations with normothermia (N=753, core temperature between 36°C and 37.5°C). The methodology used follows exactly that presented in the main analysis.

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# CONCLUSIONS

L'instabilité hémodynamique liée à l'épuration extra rénale (HIRRT, pour hemodynamic instability associated with renal replacement therapy) est une complication sévère, observée avec toutes les techniques de l'épuration extra-rénale (EER) couramment utilisées, et est associé à une augmentation de la morbi-mortalité en réanimation. Les mécanismes physiopathologiques et réversibles associés à l'HIRRT impliquent l'application de réglages adéquats des paramètres de l'EER afin de prévenir cet événement indésirable. Parmi ceux-ci, le réglage d'une température du circuit extracorporel adaptée à la température corporelle du patient pourrait permettre, grâce à un transfert calorique favorable, une amélioration de la stabilité hémodynamique.

Nous avons, en conséquence, émis l'hypothèse qu'un réglage de la température du circuit extracorporel ($T°_{EERc}$) en dessous de la température centrale ($T°_{core}$) pendant l'épuration extra rénale continue (EERc) pourrait réduire le risque d'HIRRT grâce aux effets de l'hypothermie relative sur le débit cardiaque et le tonus vasomoteur artériel. L'objectif principal de l'étude était d'étudier la relation causale entre le gradient de température ($\Delta T°$, correspondant à la différence entre $T°_{core}$ et $T°_{EERc}$) et le risque longitudinal d'HIRRT chez les patients de réanimation traités par EERc.

Il s'agit d'une analyse ancillaire d'une étude prospective, observationnelle et monocentrique, portant sur des patients de réanimation présentant une insuffisance rénale aiguë de stade 3 sous EERc depuis moins de 24 heures, et porteurs d'une technique de surveillance continue de l'index cardiaque calibré (PiCCO®, Pulsion Medical, Allemagne).

Le $\Delta T°$ correspondait à $T°_{core} - T°_{EERc}$ (i.e. une valeur positive indique une $T°_{EERc}$ inférieure à $T°_{core}$). La $T°_{EERc}$ et la $T°_{core}$ (cette dernière mesurée par le dispositif PiCCO®), les paramètres hémodynamiques (pression artérielle moyenne [PAM], fréquence cardiaque, index cardiaque [IC], et la dose de noradrénaline) et les épisodes d'HIRRT nécessitant une intervention thérapeutique (définie par PAM < 65 mmHg) étaient recueillis toutes les 4 heures entre l'inclusion et J7 (ou la fin du suivi). Les données étaient exprimées sous forme de médiane [intervalle interquartile].

L'analyse principale a été réalisée en médiation causale à co-médiateurs multiples pour évaluer l'effet du $\Delta T°$ sur le risque longitudinal d'HIRRT pendant le suivi, en tenant compte des rôles conjoints de l'IC et de la PAM, et en ajustant pour les covariables pré-traitement (température corporelle) et les cofacteurs associés au risque d'HIRRT (score de gravité clinique SOFA, dose de noradrénaline, lactate artériel).

Quarante-deux patients ont été inclus (âge : 68 [58–76] ans, score SOFA à l'inclusion : 12 [8–15]) et suivis pendant 119 [57–143] heures (N = 1012 observations par 4 heures). Le ΔT° médian durant le suivi était de -1,3 [-2,4 – +0,1] °C. Le nombre médian d'épisodes de HIRRT par patient était de 4 [3–8].

Une augmentation du ΔT° était significativement associée à une augmentation de la fréquence cardiaque, une augmentation de l'IC et de la PAM, ainsi qu'à une réduction de la dose de noradrénaline. Par ailleurs, une augmentation du ΔT° était significativement associée à une diminution du risque de HIRRT en analyse univariée (0,97 [0,95–0,99] par augmentation de 0,1°C, P < 0,01).

L'analyse de médiation causale a démontré qu'un ΔT° ≥ 0°C réduisait significativement le risque de HIRRT par rapport à un gradient < 0°C, via une augmentation de la PAM et de l'IC (proportion médiée : 55 % et 38 % de l'effet total du ΔT° sur le risque de HIRRT, respectivement). Aucun effet direct (non médié) du ΔT° sur le risque de HIRRT n'a été identifié.

En conclusion, malgré des limites inerrantes au design de l'étude (monocentrique et observationnelle), notre travail a permis de montrer que le réglage d'une température du circuit extracorporel inférieure à la température corporelle réduisait significativement le risque d'HIRRT au cours du traitement par EERc. Cet effet protecteur d'un ΔT° positif était principalement médié par les conséquences hémodynamiques favorables d'une perte de chaleur, possiblement responsable d'une augmentation de la PAM et de l'index cardiaque.

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Professeur Philippe PAPAREL

Vu et permis d'imprimer
Lyon, le 10/03/2025

## Le Serment d'Hippocrate

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Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine. Je respecterai toutes les personnes, leur autonomie et leur volonté, sans discrimination.

J'interviendrai pour les protéger si elles sont vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance.

Je donnerai mes soins à l'indigent et je n'exigerai pas un salaire au-dessus de mon travail. Admis dans l'intimité des personnes, je tairai les secrets qui me seront confiés et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement la vie ni ne provoquerai délibérément la mort.

Je préserverai l'indépendance nécessaire et je n'entreprendrai rien qui dépasse mes compétences.  Je perfectionnerai mes connaissances pour assurer au mieux ma mission.
Que les hommes m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert d'opprobre et méprisé si j'y manque.

Faculté de Médecine et de Maïeutique
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# Effet du gradient de température sur le risque d'instabilité hémodynamique pendant l'épuration extra rénale continue en réanimation : une analyse de médiation causale.

FRAIRE Lorna - Thèse Médecine spécialisée clinique : Lyon 2025 ; n°39

**Introduction** : Abaisser la température du circuit extracorporel (T°CRRT) en dessous de la température centrale (T°core) lors de l'épuration extra rénale continue (EERc) pourrait réduire l'instabilité hémodynamique (HIRRT pour *hemodynamic instability related to renal replacement therapy*) en modifiant le débit cardiaque et le tonus vasomoteur. Cette étude visait à évaluer la relation causale entre le gradient de température (ΔT°) existant entre T°core et T°CRRT et le risque longitudinal de HIRRT. **Méthodes** : Cette analyse ancillaire d'une étude prospective monocentrique (NCT03139123) a inclus des patients présentant une insuffisance rénale aiguë de stade 3 (KDIGO), sous EERc depuis moins de 24 heures et bénéficiant d'une surveillance continue de l'index cardiaque. T°CRRT et T°core étaient mesurées toutes les 4 heures entre l'inclusion et le jour 7. Le ΔT° (T°core – T°CRRT) a été calculé, et les paramètres hémodynamiques ainsi que les épisodes de HIRRT (définis par une pression artérielle moyenne < 65 mmHg nécessitant une intervention thérapeutique) ont été recueillis. Une analyse de médiation a évalué l'effet de ΔT° sur le risque longitudinal de HIRRT via l'index cardiaque et la pression artérielle moyenne. **Résultats** : 42 patients ont été inclus (âge 68 [58–76] ans, SOFA 12 [8–15], 33 (79 %) atteints de sepsis) et suivis pendant 119 [57–143] heures (N=1012 observations). Une augmentation de ΔT° était significativement associée à une augmentation de la fréquence cardiaque, de l'index cardiaque et de la pression artérielle moyenne, ainsi qu'à une diminution de la dose de noradrénaline et du risque de HIRRT en analyse univariée (0,97 [0,95–0,99] par augmentation de 0,1°C, P<0,01). L'analyse de médiation causale a montré qu'un ΔT° ≥ 0°C réduisait significativement le risque de HIRRT par l'amélioration de la pression artérielle moyenne et de l'index cardiaque (effet médié : 55 % et 38 % de l'effet total, respectivement). **Conclusions** : Lors de l'EERc, une augmentation de ΔT° réduit le risque de d'instabilité hémodynamique, en améliorant la pression artérielle moyenne et le débit cardiaque.

***Effect of temperature gradient on hemodynamic instability risk during continuous renal replacement therapy: a causal mediation analysis***

**Introduction**: Lowering extracorporeal circuit temperature ($T°_{CRRT}$) below core temperature ($T°_{core}$) during continuous renal replacement therapy (CRRT) may decrease hemodynamic instability (HIRRT) by affecting cardiac output and vasomotor tone. This study aimed to evaluate the causal relationship between core-to-CRRT temperature gradient and HIRRT longitudinal risk. **Methods**: This ancillary analysis of a prospective, single-center study (NCT03139123) included patients with stage 3 acute kidney injury, who received CRRT for <24h and had continuous cardiac index monitoring. $T°_{CRRT}$ and $T°_{core}$ were measure every 4-hourly between inclusion and day 7. Temperature gradient ($T°_{core}$ - $T°_{CRRT}$) was calculated and, hemodynamics parameters and HIRRT (defined as a mean arterial pressure < 65 mmHg requiring therapeutic intervention) were collected. Mediation analysis evaluated the effect of ΔT° on HIRRT longitudinal risk during follow-up, mediated through cardiac index and mean arterial pressure. **Results**: 42 patients were enrolled in this ancillary analysis (age 68 [58–76], SOFA 12 [8–15] and 33 (79%) had sepsis), and were followed over 119 [57–143] hours (N=1012 observations). Increasing ΔT° was significantly associated with higher heart rate, CI and MAP, and lower norepinephrine dose, and reduced HIRRT risk in univariate analysis (0.97 [0.95–0.99] per 0.1°C increase, *P*<0.01). Causal mediation analysis showed that ΔT° ≥ 0°C significantly decreased HIRRT risk through improved MAP and CI (mediated: 55% and 38% of the total effect, respectively). **Conclusions**: During CRRT, increasing ΔT° between led to a lower risk of HIRRT, through an improvement in both MAP and CI.

MOTS CLÉS : Epuration extra rénale continue ; Température ; Hémodynamique ; Index cardiaque ; Pression artérielle moyenne

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Monsieur le Professeur Martin Cour
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