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# Remote ischemic conditioning in septic shock: the RECO-Sepsis randomized clinical trial

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## Abstract

**Purpose:** To determine whether remote ischemic conditioning (RECO), compared to standard care, limits the severity and the consequences of multiple organ failure in patients with septic shock.

**Methods:** The RECO-Sepsis trial, a prospective, multicenter, randomized, open-label, parallel group trial with blinded assessment of the outcome, was conducted at six intensive care units in France in adult patients with septic shock. Within 12 h after the onset of septic shock, patients were randomized (1:1 ratio) to receive either RECO applied by inflating/deflating (200/0 mmHg for 5/5 min) 4 times a cuff around an arm or a sham procedure every 12 h for 24 h. The primary endpoint was the severity of multiple organ failure assessed by the mean daily Sequential Organ Failure Assessment (SOFA) score from inclusion to the fourth day after inclusion (day 4). Patients were followed for 90 days.

**Results:** Among 180 randomized patients, 178 completed the trial (RECO group: 87; control group: 91) and were included in the intention-to-treat analysis (108 men [60.7%], median age 68 [59–75] years). There was no significant difference in the mean daily SOFA score between the intervention group and the control group (7.2 points [5.2–10.7] versus 7.6 points [4.9–10.7], respectively;  $p=0.919$ ). Cumulative mortality within 90 days was 27.6% in the RECO group and 39.6% control group (Log-rank test,  $p=0.10$ ; adjusted hazard ratio 0.59, 95% CI, 0.35 to 0.99;  $p=0.049$ ).

**Conclusions:** In patients with septic shock, RECO failed to reduce the severity of organ failures assessed by mean daily SOFA score from inclusion to day 4. Adequately powered trials are needed to assess potential delayed benefits of RECO.

**Keywords:** Remote ischemic conditioning, Septic shock, SOFA score, Organ failure

## Introduction

Septic shock, one of the most severe complications of any infection, affects millions of people each year [1, 2]. Approximately 10% of the patients admitted to the

intensive care unit (ICU) have septic shock in Europe and United States of America [2]. Despite significant improvements in early recognition and treatment of septic shock (based on regularly updated international guidelines), up to 50% of patients still die within days or weeks after diagnosis [1–3]. The number and severity of organ dysfunctions are both important predictors of patients' outcomes [4]. Therefore, new therapeutic approaches are urgently needed to limit the septic shock-induced multiple organ failure (MOF) and thereby to improve the prognosis in this disease [5].

The pathophysiology of septic shock-induced MOF involves uncontrolled immune response and

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ischemia–reperfusion (I/R) injury resulting from low arterial blood pressure, imbalance between systemic oxygen delivery and oxygen demand (with or without low cardiac output), compromised microcirculation and mitochondrial dysfunction, among others [3, 4, 6]. Remote ischemic conditioning (RECO), which usually consists of applying brief and repeated cycles of ischemia alternating with reperfusion by inflating and deflating a blood pressure cuff placed around a limb, is a promising strategy to protect organs against I/R injury [6–11]. Few clinical trials in cardiovascular disease even showed improvement in long-term survival with this intervention [12–14]. This non-invasive, low-cost intervention is thought to activate cell survival pathways, to modulate inflammatory response, prevent I/R-induced vascular dysfunction and improve mitochondrial functions [7–11]. Accumulating experimental evidence suggests that RECO might prevent MOF and improve survival in septic shock [6, 15–18]. Apart from its beneficial effects on microcirculation alterations in sepsis [19], the potential of RECO in septic shock has not been investigated in the clinical setting.

The Remote Conditioning in Septic Shock (RECO-Sepsis) trial examined whether RECO using a simple blood pressure cuff repeatedly inflated around an arm would limit the severity and the consequences of MOF in septic shock patients compared to standard care.

## Methods

### Study design

The RECO-Sepsis study is a prospective, multicenter, randomized, open-label, parallel group trial with blinded assessment of the outcome that was conducted at 6 centers in France. The rationale and design of the trial has been previously published [20]. The trial protocol and statistical analysis plan are available in the Supplemental material. The trial was authorized by the French national drug agency on 23 August 2017 and was also approved by an Ethics Committee (Comité de Protection des Personnes CCP Ile-de-France X) on 5 September 2017 (no. 2017-A01684-49) and was registered in ClinicalTrials before the start of the study (NCT03201575). The trial was conducted according to the requirements of the Declaration of Helsinki. Written informed consent was obtained from all participants or their closest relatives (in cases of impaired decision-making capacity) at the time of enrollment.

### Patients

All patients admitted at the participating centers were screened for eligibility criteria. Patients were eligible for inclusion if they were aged 18 years or older, hospitalized in ICU for less than 24 h, and had septic shock evolving

Remote ischemic conditioning compared to standard care did not significantly limit the severity and the consequences of multiple organ failure in patients with septic shock, as assessed by mean daily Sequential Organ Failure Assessment score over the first 4 days following inclusion.

Adequately powered trials are needed to assess potential delayed benefits of RECO in patients with septic shock

for less than 12 h. Septic shock was defined according to the 2016 revised consensus criteria (Sepsis-3): documented or suspected infection, lactatemia >2 mmol/l, and norepinephrine administration to maintain a mean arterial pressure (MAP) above 65 mmHg after adequate fluid resuscitation [1, 21]. Non-inclusion criteria were determined by the patient's wish not to be resuscitated, contraindication for the use of a brachial cuff on both arms, intercurrent disease with an expected life expectancy of less than 24 h, cardiac arrest, pregnancy or breast-feeding, participation in another interventional study, lack of French national health insurance coverage, and judicial protection.

### Randomization and trial intervention

After consent, eligible patients were randomly assigned to receive either the trial intervention (RECO group) or standard care with a sham procedure (control group). Randomization was stratified by center on a 1:1 basis; randomization codes were computer-generated and concealed from investigator. Randomization was performed using a secure web application for managing online data collection (ClinSight™ software, Ennov Clinical Software, Paris, France).

To target I/R injury, the first cycle of RECO had to be performed as soon as possible after the onset of septic shock. In the absence of data on optimal protocol of RECO in septic shock, the intervention was repeated at 12 h and 24 h after the first procedure to enhance potential protective effects. In all patients, immediately after randomization, a standard CE-approved blood pressure cuff (Tensiomètre Manopoire Duo Colson®, Drive DeVilbiss Healthcare, Frouard, France) was placed, deflated, around one of the patient's upper arms. In the RECO group, ischemic conditioning consisted of four cycles of cuff inflation to 200 mmHg for 5 min and then deflation to 0 mmHg for another 5 min (40 min total duration of the intervention). In the control group, the cuff was left in place deflated for 40 min (sham procedure). In line with the recommendations for non-invasive measurement of blood pressure, the size of the cuff was chosen to accommodate the patient's arm [22]. The procedure (RECO or sham)

was repeated at 12 and 24 h after the first procedure. Complete study treatment was defined as 4 consecutive cycles of inflation/deflation at inclusion, at 12 h and at 24 h after inclusion (or until death if it occurred before 24 h). Standard operation procedures (SOP) describing the interventions were available for all investigators. The intervention was provided by the physician in charge of the patient. With the exception of the tested intervention, patients received standard care, at the discretion of the investigators and in accordance with international guidelines [23].

### Data collection and endpoints

For each patient, demographics, concurrent medical conditions and comorbidities, sepsis diagnosis and treatment, vital signs and laboratory results, characteristics of the trial intervention procedure, life-sustaining therapies, and outcomes (follow-up: 90 days) were recorded. The Simplified Acute Physiology Score (SAPS) II (range, 0–164, with higher scores indicating greater severity of illness) was also documented at the time of admission to the ICU [24].

The primary endpoint was the severity of sepsis-induced MOF as assessed by the mean daily Sequential Organ Failure Assessment (SOFA) score from inclusion to the fourth day after inclusion (day 4) or to the day of death if it occurred before day 4. The SOFA score ranged from 0 to 24 (higher scores indicate more severe organ failure), with 0 to 4 points assigned for each of the six organ systems (i.e., cardiovascular, respiratory, renal, central nervous system, coagulation, and liver) [25]. As previously described, a daily SOFA score was calculated using the worst clinical and/or biological values within the latest 24 h (or from the start of the 24-h period to death) and organ failure was defined as a score of 3 or 4 points for the affected organ [25, 26]. The SOFA scores were assessed by physicians unaware of the randomization group. Predefined rules for dealing with potential missing data were established before the start of the trial.

Secondary endpoints related to the SOFA score were:

- (1) mean SOFA score from inclusion to day 4 after exclusion of the neurological sub-score,
- (2) daily SOFA sub-scores (for each organ/system) from day 1 to day 4,
- (3) peak SOFA score from day 1 to day 4,
- (4) daily SOFA scores from day 1 to day 4,
- (5) change in SOFA scores (delta-SOFA) from inclusion to days 1 to 4.

Predefined secondary endpoints unrelated to the SOFA score were:

- (1) number of days alive on day 28 without invasive mechanical ventilation, without renal replacement therapy, and/or without vasoactive drugs,
- (2) length of ICU and hospital stay and,
- (3) all-cause mortality in ICU, in hospital, on day 28 and on day 90 after inclusion.

### Statistical analysis

No a priori evidence suggested the magnitude of the effect of RECO on the severity of MOF in septic shock patients. Under the alternative hypothesis of an expected difference of half the standard deviation (effect size 2) of the mean daily SOFA score of the first 4 days after inclusion, at least 168 patients had to be enrolled to reject the null hypothesis of a similar mean SOFA score in both arms in 90% of the studies ( $\beta=10\%$ ), with type 1 error at  $\alpha=5\%$  (two-tailed). The sample size was calculated by means of nQuery Advisor, version 5.0 (Statistical Solutions). To further account for potential loss to follow-up and withdrawal of consent (7%), enrollment of 180 patients was planned.

All analyses were conducted in accordance with the statistical analysis plan drawn up by statistical officer of the Clinical Investigation Center (Hospices Civils de Lyon) before the trial database was locked and unblinded to treatment assignment (available in Supplement 2) [20]; all analyses reported herein were prespecified and included in the statistical analysis plan. Analyses were calculated using R software (version 3.3.3, R Foundation for Statistical Computing). A 2-sided  $P$  value of 0.05 or less was considered statistically significant. Patient data were analyzed according to their randomization group. Missing data were not imputed and the numbers of patients with available data were reported. Variables were expressed as median and interquartile range (IQR) or number and proportion, as appropriate. Logarithmic transformation was applied when necessary in order to achieve normality distribution for further parametric analysis. Continuous variables were compared using the Wilcoxon rank-sum test or the Student  $t$  test, and the Chi-2 or the Fisher exact test was used for proportions. Analyses of both primary and secondary endpoints were performed according to the random assignment of patients (intention-to-treat analysis). Because of a potential for type I error caused by multiple comparison, findings for analyses of secondary endpoints should be considered as exploratory. A per-protocol analysis was performed for the patients who complied with the inclusion criteria and did not have major protocol deviation.

The main analysis of the primary endpoint was adjusted for trial center (using mixed-effects linear model with a fixed effect for the assigned treatment and a random effect for the center). The effect (adjusted for trial

center) of RECO on the primary endpoint was explored in four prespecified subgroups: diabetes, SOFA score at inclusion superior or equal to the median value, invasive mechanical ventilation at inclusion, lactatemia superior or equal to the median value.

Unless otherwise specified, analyses of secondary outcomes were unadjusted. Mortality at day 90 was compared using Kaplan–Meier curves and the log-rank test. In addition, it was analyzed using Cox proportional hazards regression, with results reported as hazard ratios with 95% confidence intervals (CI). Prespecified variables adjusted in the Cox model were center, age, SOFA score at inclusion, nosocomial origin of septic shock and potential imbalanced variables at baseline with  $p$  value < 0.1.

## Results

### Study population

From November 15, 2017 to May 6, 2019, a total of 662 patients were screened and 180 were enrolled in the study. Of these, 88 (48.9%) were randomly assigned to the

RECO group and 92 (51.1%) to the control group (Fig. 1). In each arm, one patient was excluded because of invalid consent form. Thus, 178 patients were included in the intention-to-treat analysis. Complete follow-up was available for all these 178 patients.

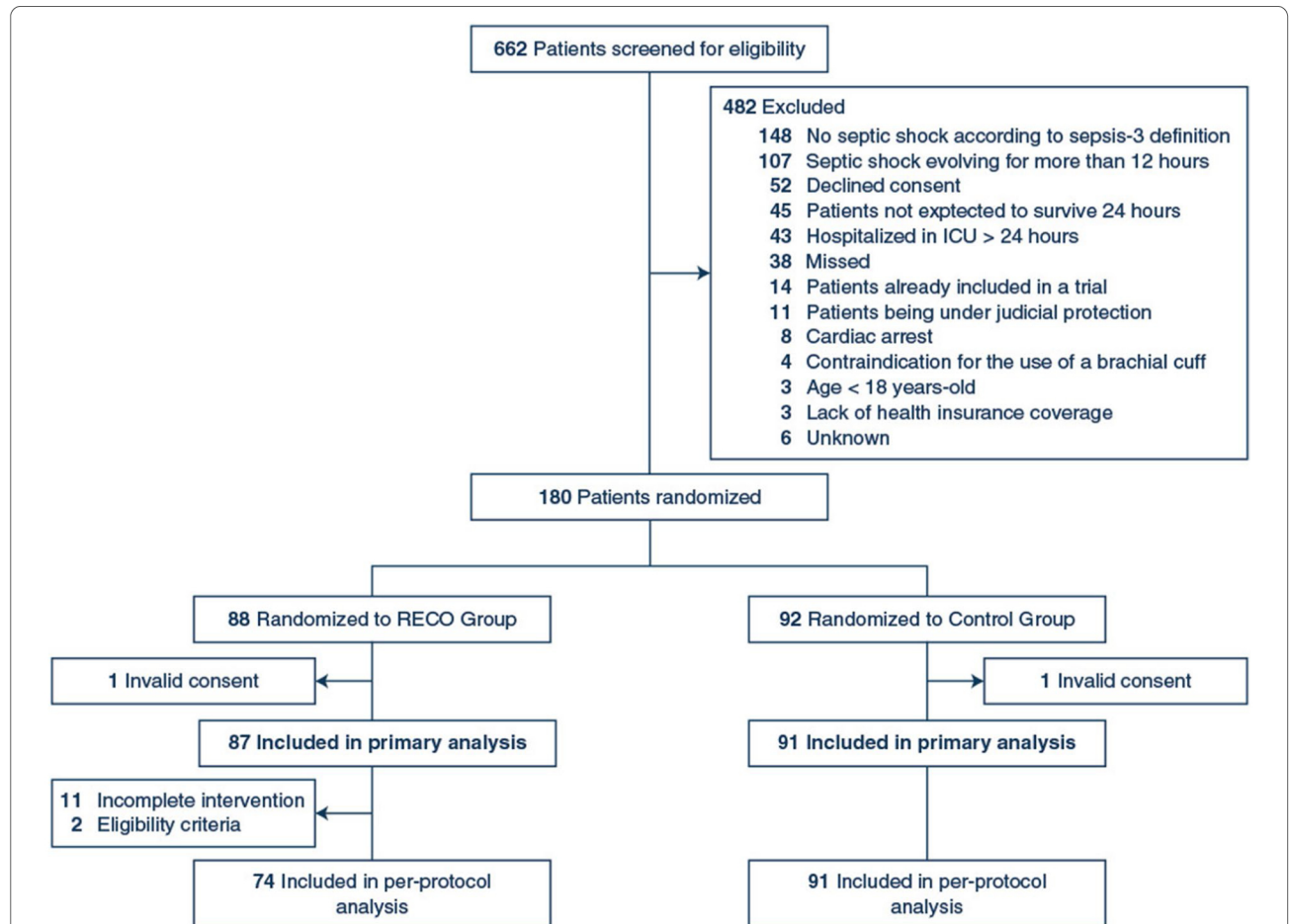
The characteristics of the patients (median age 68 years [IQR, 59–75 years], 108 men [60.7%]) are presented in Table 1 and were well matched between study arms.

### Intervention

In the RECO group, the pressure cuff was inflated according to the procedure at least once in all the 87 patients (100%). The median time from meeting the eligibility criteria to the first cuff inflation was 6 h (IQR 3–8 h). Seventy-five patients (86%) underwent the complete study treatment. There was no unexpected serious adverse event related to the RECO procedure.

### Primary endpoint

The mean daily SOFA scores from inclusion to day 4 were 7.2 points (IQR 5.2–9.7) in the RECO group and



**Fig. 1** CONSORT study flow diagram. ICU intensive care unit, RECO remote ischemic conditioning

**Table 1 Baseline patient characteristics**

Characteristic	RECO group (n = 87)	Control group (n = 91)
Age, median (IQR), y	68 (58.5–76.5)	67 (59.5–75)
Male, n. (%)	52 (59.8)	56 (61.5)
Body mass index, kg m <sup>-2</sup>	26 (22.8–31)	25 (22–30)
Comorbidities, n. (%)		
Hypertension	44 (50.6)	48 (52.7)
Diabetes	29 (33.3)	26 (28.6)
Chronic cardiac disease	21 (24.1)	24 (26.4)
Chronic kidney disease	14 (16.1)	13 (14.3)
Chronic respiratory disease	11 (12.6)	17 (18.7)
MacCabe and Jackson, No. (%)		
Non-fatal disease	49 (56.3)	59 (64.8)
Ultimately fatal disease (< 5 years)	21 (24.1)	22 (24.2)
Rapidly fatal disease (< 1 year)	17 (19.5)	10 (11)
Type of admission, n. (%)		
Medical	79 (90.8)	85 (93.4)
Surgery	8 (9.2)	6 (6.6)
Type of infection, n. (%)		
Community acquired	60 (69)	65 (71.4)
Hospital-acquired (nosocomial)	27 (31)	26 (28.6)
Source of primary infection, n. (%)		
Pneumonia	30 (34.5)	35 (38.5)
Intra-abdominal infection	13 (14.9)	19 (20.9)
Urinary tract	18 (20.7)	13 (14.3)
Other	24 (27.6)	20 (22)
Unknown	2 (2.3)	4 (4.4)
Positive microbiologic culture, n. (%)	66 (75.9)	65 (71.4)
Time to randomization, h		
From meeting inclusion criteria	5 (3–8)	4 (2–8)
From ICU admission	6 (4–9)	5 (3–11)
Physiological variables, median (IQR)		
Heart rate, beats/min	100 (89–116)	103 (91–118)
Mean arterial pressure, mmHg	72 (68–79)	70 (64–79)
Temperature, °C	37.2 (36.4–38)	37.2 (36.5–38)
Leucocytes count, G/L	16.9 (9.7–24.6) [81]	15 (9.1–23.7) [86]
C-reactive protein, mg/l	195 (93–273) [65]	157 (78–287) [69]
Lactates, mmol/L	3.1 (2.5–4.6)	3.1 (2.3–4.4)
SOFA score, median (IQR)	8 (7–10)	8 (7–10)
Organ failure type, n. (%)		
Cardiovascular	87 (100)	91 (100)
Respiration	15 (17.2)	18 (19.8)
Renal	12 (13.8)	11 (12.1)
Central nervous system	10 (11.5)	9 (9.9)
Coagulation	9 (10.3)	5 (5.5)
Liver	5 (5.7)	7 (7.7)
Number of organ failures, median (IQR)	2 (1–2)	1 (1–2)
Supportive therapy at inclusion, n. (%)		
Mechanical ventilation	30 (34.5)	37 (40.7)
Renal replacement therapy	7 (8)	2 (2.2)
Norepinephrine dose, µg/kg/min	0.38 (0.2–0.7)	0.40 (0.16–0.66)
Hydrocortisone at inclusion	29 (33.3)	23 (25.3)
SAPS II, median (IQR)	52 (43–67)	52 (43–68)

**Table 1 (continued)**

Numbers in brackets indicate the number of patients available for analysis if different from the full sample size

RECO, remote ischemic conditioning; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; SAPS II, Simplified Acute Physiology Score II

7.6 points (IQR, 4.9–10.6) in the control group (mean difference  $-0.199$ , 95% CI  $-1.298$  to  $0.899$ , unadjusted  $p=0.721$ ). No significant difference was found after adjustment for the trial center ( $p=0.919$ ). There was no statistically significant effect modification determined by diabetes, level of lactatemia at inclusion, invasive mechanical ventilation at inclusion or SOFA score at inclusion (Supplemental material Fig. 1). Per-protocol analysis comparing 74 patients in the RECO group and 91 patients in the control group (Fig. 1) did not show

a significant difference in the primary endpoint after adjustment for trial center ( $p=0.786$ ).

### Secondary endpoints

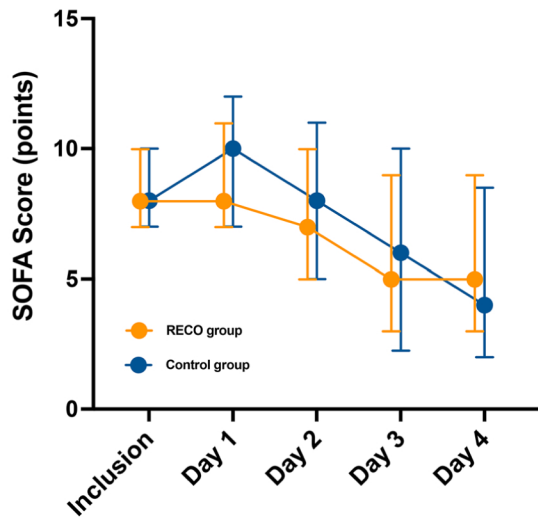
Secondary endpoints related to the SOFA score are reported in Table 2. Daily SOFA scores from inclusion to day 4 for both groups are presented in Fig. 2. Change in SOFA score from inclusion to day 1 was significantly different between the RECO and the control group: 0

**Table 2 Secondary endpoints**

Variable	RECO group (n = 87)	Control group (n = 91)	p value <sup>a</sup>
<b>SOFA score</b>			
Mean daily SOFA score from inclusion to day 4 after excluding neurological sub-score	6.4 (4.8–9)	7 (4.6–9.8)	0.650
Mean daily SOFA sub-scores from inclusion to day 4			
Cardiovascular	2.8 (2.1–4)	2.8 (2.1–4)	0.683
Respiration	1.6 (1–2.2)	1.8 (0.9–2.5)	0.546
Renal	0.4 (0–2.4)	1 (0–2.4)	0.571
Central nervous system	0.4 (0–1.4)	0 (0–1.2)	0.910
Coagulation	0.6 (0–1.9)	0.4 (0–1.8)	0.414
Liver	0 (0–0.5)	0 (0–0.8)	0.510
Peak SOFA score between inclusion and day 4	9 (8–12)	11 (8–13)	0.556
Variation of SOFA score			
From inclusion to day 1	0 (–1 to 2)	1 (0–2)	0.005
From inclusion to day 2	–1 (–3 to 1) [82]	–1 (–3 to 1) [83]	0.462
From inclusion to day 3	–3 (–4 to 0) [81]	–3 (–4 to 0) [80]	0.999
From inclusion to day 4	–3 (–5 to –1) [79]	–3 (–5 to –1) [77]	0.674
Organ supports			
Number of days alive at day 28			
Without vasoactive drugs	25 (21–26)	24 (10–26)	0.085
Without renal replacement therapy	28 (20–28)	28 (11–28)	0.375
Without mechanical ventilation	27 (11–28)	25 (4–28)	0.340
Without organ supports	24 (9–26)	23 (3–26)	0.185
<b>Outcomes</b>			
Length of stay			
In the ICU	4 (3–9)	5 (3–8)	0.698
In the hospital	18 (9–30)	15 (9–28)	0.387
Death			
At ICU discharge	17 (19.5)	23 (25.3)	0.376
At day 28	21 (24.1)	27 (29.7)	0.499
At hospital discharge	23 (26.4)	31 (34.8)	0.329
At day 90	24 (27.6)	36 (39.6)	0.110

RECO, remote ischemic conditioning; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit

<sup>a</sup> All the statistical analyses were unadjusted



**Fig. 2** Longitudinal plots of daily SOFA score over time. Median (circle) and interquartile ranges (error bars) values of Sequential Organ Failure Assessment (SOFA) scores at inclusion, at 24 h after inclusion (day 1), at day 2, day 3 and day 4 are presented for patients included in the control group (in blue) or in the remote ischemic conditioning group (RECO, in orange)

[IQR -1 to 2] versus 1 [IQR 0-2], unadjusted  $p=0.005$  (Table 2 and Supplemental material Fig. 2).

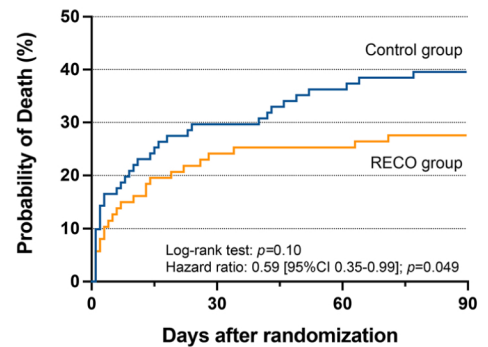
The number of days without organ support at day 28, as well as both the ICU and the hospital lengths of stay did not significantly differ between the 2 groups (Table 2).

Mortality did not significantly differ between the two groups at the different timepoints (Table 2). Sixty patients (34%) died within 90 days from enrollment. Cumulative mortality at day 90 was 27.6% ( $n=24/87$ ) in the RECO group and 39.6% ( $n=36/91$ ) in the control group ( $p=0.10$  by log-rank test; adjusted hazard ratio 0.59; 95% CI 0.35-0.99;  $p=0.049$ ) (Fig. 3).

## Discussion

In this multicenter, open-label, randomized clinical trial involving patients with septic shock, RECO via the cyclic inflation/deflation of a cuff, compared to standard care, did not significantly limit the severity of MOF as assessed mean daily SOFA score over the first 4 days following inclusion and did not significantly decrease mortality at day 90. In exploratory analyses, the intervention significantly limited the increase in the SOFA score during the first 24 h after inclusion and was associated with a significantly lower adjusted cumulative day-90 mortality.

RECO-Sepsis was the first randomized trial to assess the effects of RECO on MOF in septic shock. Therefore, it is difficult to compare our results with those obtained by others. Only one observational clinical study investigated RECO in sepsis; in comparison with an historical



No. at risk  
Control group 91 72 66 64 64 59 58 56 55 55  
RECO group 87 74 69 66 65 65 65 64 63 63

**Fig. 3** Kaplan-Meier estimates of cumulative mortality within 90 days. The unadjusted cumulative mortality at day 90 between the control group (blue line) and the remote ischemic conditioning group (RECO, orange line) did not significantly differ ( $p=0.10$  by log-rank test). Adjusted cumulative mortality at day 90 was assessed by a Cox proportional hazards model that included as predefined covariates center, age, Sequential Organ Failure Assessment (SOFA) score at inclusion, and nosocomial origin of septic shock

group, RECO significantly improved microcirculation but other potential benefits were not addressed [19]. In settings other than sepsis, randomized clinical trials mainly focused on a single organ of interest acutely exposed to I/R injury and aimed to determine whether RECO could limit the extent of cell death, reporting benefits, although inconsistently [6-10, 27-29]. Nevertheless, few randomized trials previously showed that RECO may prevent organ dysfunction and even MOF [27-29]. A significant decrease in the need for renal replacement therapy after cardiac surgery has even been observed with RECO compared to standard care [27]. In patients with rheumatic heart disease undergoing valve replacement, RECO allowed a reduction in the dose of inotropes and decreased both lung and liver injury within 48 h after cardiac surgery [28]. Another trial showed that RECO could enhance the early recovery of renal function, as assessed by creatinine and NGAL in recipients after kidney transplantation [29]. Even if assessed with different tools (i.e., SOFA sub-scores), these benefits of RECO on each organ dysfunction were not observed in the RECO-Sepsis study.

We chose the primary endpoint to be the mean daily SOFA score from inclusion to day 4 for several reasons. First, the SOFA score is the most validated score to assess organ dysfunction/failure in septic shock patients and is well-correlated with mortality [25, 26, 30]. For this reason, in recent years, the SOFA score (including mean daily SOFA score [31]) has been increasingly used as a primary endpoint instead of mortality for clinical trials



in sepsis [26, 30–33]. The choice of a surrogate endpoint was justified by the fact that benefit of RECO on mortality in sepsis was only supported by experimental studies [15–18]. Moreover, mortality has never been chosen as a stand-alone primary endpoint in clinical trials because RECO was tested in diseases associated with low mortality rates. Second, the primary endpoint (i.e., mean daily SOFA score) could be calculated for all patients. Indeed, as daily SOFA scores were calculated using the clinicobiological worst values for each 24-h period, at least 2 values of SOFA (SOFA at inclusion and SOFA at day 1) were available for all patients, allowing calculation of a mean daily SOFA score, even if they died before 24 h after inclusion. Third, the choice of this primary endpoint helps to minimize a survivorship bias which may paradoxically favor the study group with higher mortality. Fourth, as the ICU length of stay was expected to be 4–5 days, we chose to measure the SOFA for 4 days rather than a longer period of time to avoid both missing data and recording low-quality data after discharge from ICU. Despite all these considerations, the study failed to demonstrate benefits of RECO on early MOF as assessed by the mean daily SOFA score. Similar findings were observed in the predefined subgroups.

Recently, it has been recently pointed out that clinical trials on sepsis are unlikely to identify a difference in SOFA score of more than one point [30]. Herein, we found that RECO was associated with a significantly lower median delta-SOFA score of one point between inclusion and day 1. This was the only data related to the SOFA score that was not biased by early death or early discharge from ICU. This result is important because a strong association between mortality and early change in SOFA score after ICU admission is well-established [25, 26, 30]. Our proof-of-concept study was insufficiently powered to draw meaningful conclusions regarding the treatment effect on mortality. Nevertheless, it provides important data for designing future randomized trials with mortality as primary endpoint.

### Limitations

The trial has several limitations. First, the investigators were not blinded to the intervention. Nevertheless, the primary endpoint was assessed by physicians unaware of the randomization group and was based on objective criteria. Second, a single protocol of RECO was tested and the intervention was applied only during the first 24 h after inclusion. An increase in the number of inflation/deflation and/or the continuation of the intervention beyond 24 h might yield different results. Third, the first RECO was applied with a median delay of 6 h after the diagnosis of septic shock; earlier intervention

might also provide different results. It would be also the case in less severe patients, i.e., in sepsis. Fourth, many factors (e.g., diabetes, age, and sedation) are known to interfere with RECO. Given the limited number of patients, it was difficult to provide definitive conclusions on subgroups in whom RECO would be more effective.

### Conclusions

In patients with septic shock, RECO compared to standard care did not significantly limit organ dysfunction/failure as assessed by the mean daily SOFA score from inclusion to the fourth day after inclusion. Adequately powered trials are needed to assess potential delayed benefits of RECO.

### Author details

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### Author contributions

MC and LA had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. MC, MO, NM and LA performed the study conception and design. All the authors contributed to the acquisition, analysis and/or interpretation of data. The first draft of the manuscript was performed by MC, CA, and LA. All the authors critically revised the manuscript for important intellectual content. Statistical analysis was performed by MC, CA, NM and LA. All the authors read and approved the final version of the manuscript.

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## Declarations

## Conflict of interest

The authors declare they have no conflict of interest, including financial interests, activities, relationships, and affiliations in relation with the RECO-Sepsis trial.

## Ethical approval

The trial was authorized by the French national drug agency on 23 August 2017 and was also approved by an Ethics Committee (Comité de Protection des Personnes CCP Ile-de-France X) on 5 September 2017 (n°2017-A01684-49) and was registered in ClinicalTrials before the start of the study (NCT03201575). The trial was conducted according to the requirements of the Declaration of Helsinki. Written informed consent was obtained from all participants or their closest relatives (in cases of impaired decision-making capacity) at the time of enrollment.

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