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Effect of Cyclosporine in Nonshockable Out-of-Hospital Cardiac Arrest
The CYRUS Randomized Clinical Trial

Laurent Argaud, MD, PhD; Martin Cour, MD, PhD; Pierre-Yves Dubien, MD; François Giraud, MD; Claire Jossan, MSc; Benjamin Riche, PhD; Romain Hernu, MD; Michael Darmon, MD, PhD; Yves Poncelin, MD; Xavier Tchénio, MD; Jean-Pierre Quenot, MD, PhD; Marc Freysz, MD, PhD; Cyrille Kamga, MD; Pascal Beuret, MD; Pascal Usseglio, MD; Michel Badet, MD; Bastien Anette, MD; Kevin Chaulier, MD; Emel Alasan, MD; Sonia Sadoune, MD; Xavier Bobbia, MD; Fabrice Zéni, MD, PhD; Pierre-Yves Gueugniaud, MD, PhD; Dominique Robert, MD; Pascal Roy, MD, PhD; Michel Ovize, MD, PhD; for the CYRUS Study Group

IMPORTANCE Experimental evidence suggests that cyclosporine prevents postcardiac arrest syndrome by attenuating the systemic ischemia reperfusion response.

OBJECTIVE To determine whether early administration of cyclosporine at the time of resuscitation in patients with out-of-hospital cardiac arrest (OHCA) would prevent multiple organ failure.

DESIGN, SETTING, AND PARTICIPANTS A multicenter, single-blind, randomized clinical trial was conducted from June 22, 2010, to March 13, 2013 (Cyclosporine A in Out-of-Hospital Cardiac Arrest Resuscitation [CYRUS]). Sixteen intensive care units in 7 university-affiliated hospitals and 9 general hospitals in France participated. A total of 6758 patients who experienced nonshockable OHCA (ie, asystole or pulseless electrical activity) were assessed for eligibility. Analyses were performed according to the intention-to-treat analysis.

INTERVENTIONS Patients received an intravenous bolus injection of cyclosporine, 2.5 mg/kg, at the onset of advanced cardiovascular life support (cyclosporine group) or no additional intervention (control group).

MAIN OUTCOMES AND MEASURES The primary end point was the Sequential Organ Failure Assessment (SOFA) score, assessed 24 hours after hospital admission, which ranges from 0 to 24 (with higher scores indicating more severe organ failure). Secondary end points included survival at 24 hours, hospital discharge, and favorable neurologic outcome at discharge.

RESULTS Of the 6758 patients screened, 794 were included in intention-to-treat analysis (cyclosporine, 400; control, 394). The median (interquartile range [IQR]) ages were 63.0 (54.0-71.8) years for the cyclosporine group and 66.0 (57.0-74.0) years for the control group. The cohorts included 293 men (73.3%) in the treatment group and 288 men (73.1%) in the control group. At 24 hours after hospital admission, the SOFA score was not significantly different between the cyclosporine (median, 10.0; IQR, 7.0-13.0) and the control (median, 11.0; IQR, 7.0-15.0) groups. Survival was not significantly different between the 98 (24.5%) cyclosporine vs 101 (25.6%) control patients at hospital admission (adjusted odds ratio [aOR], 0.94; 95% CI, 0.66-1.34), at 24 hours for 67 (16.8%) vs 62 (15.7%) patients (aOR, 1.08; 95% CI, 0.71-1.63), and at hospital discharge for 10 (2.5%) vs 5 (1.3%) patients (aOR, 2.00; 95% CI, 0.61-6.52). Favorable neurologic outcome at discharge was comparable between the cyclosporine and control groups: 7 (1.8%) vs 5 (1.3%) patients (aOR, 1.39; 95% CI, 0.39-4.91).

CONCLUSION AND RELEVANCE In patients presenting with nonshockable cardiac rhythm after OHCA, cyclosporine does not prevent early multiple organ failure.

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The CYRUS study investigators are listed at the end of the article.

Corresponding Author: Laurent Argaud, MD, PhD, Hospices Civils de Lyon, Hôpital Edouard Herriot, Service de Réanimation Médicale, 5, place d'Arsonval, 69437 Lyon Cedex 03, France (laurent.argaud@chu-lyon.fr).

With an annual incidence that can exceed 100 cases per 100 000 persons, out-of-hospital cardiac arrest (OHCA) remains a major health issue in industrialized countries.[1] Among all OHCAs treated by emergency medical services, a nonshockable cardiac rhythm (ie, asystole or pulseless electrical activity) is the most frequent and has the worst prognosis.[2] Most successfully resuscitated patients develop a postcardiac arrest syndrome consisting of brain injury, myocardial dysfunction, and a systemic ischemia reperfusion response that often leads to multiple organ failure.[3,4]

Although resumption of blood circulation is the primary therapeutic objective of cardiac resuscitation, reflow after whole-body ischemia might cause reperfusion injury that significantly contributes to the severity of the postcardiac arrest syndrome.[3] Opening of the mitochondrial permeability transition pore (PTP) at the time of reperfusion has been reported[5-8] to be involved in damage to various organs (eg, heart, brain, liver, and kidney) after regional ischemia. Experimental evidence[7-15] suggests that, through mitochondrial determinants, reperfusion injury might also contribute to multiple organ failure following a global ischemic insult, including postcardiac arrest syndrome.

Cyclosporine, apart from its immunosuppressive activity, can prevent the opening of the PTP that occurs in the early minutes of reflow and attenuate single organ damage.[5,6,16,17] We and others[11-14] have reported that cyclosporine administered early after the onset of resuscitation in a nonshockable cardiac arrest may decrease tissue lesions and blunt postcardiac arrest organ dysfunctions using in vivo experimental preparations. The objective of the present study was to determine whether early administration of cyclosporine during advanced life support in patients with OHCA would prevent postcardiac arrest multiple organ dysfunction syndrome.

Key Points

Question Is cyclosporine able to prevent, as in preclinical studies, the postcardiac arrest syndrome?

Findings In this randomized clinical trial of 794 patients with nonshockable out-of-hospital cardiac arrest, 2.5 mg/kg of cyclosporine administered at resuscitation did not prevent early multiple organ failure.

Meaning The present results do not support the use of early administration of cyclosporine to prevent multiple organ failure after out-of-hospital cardiac arrest.

Methods

Study Design

The Cyclosporine A in Out-of-Hospital Cardiac Arrest Resuscitation (CYRUS) trial was a multicenter, single-blind, randomized clinical trial conducted in 16 centers in France and coordinated by the Hospices Civils de Lyon (protocol available in the Supplement). This trial was performed in accordance with the principles of the Declaration of Helsinki[18] and the European Guidelines for Good Clinical Practice. In accordance with French laws, the protocol was approved by the ethics committee (Comité de Protection des Personnes Sud-Est IV) in Lyon, France. Waiver of informed consent was authorized by the ethics committee owing to the urgent need for treatment of OHCA. The patients' relatives were informed about the trial; written informed consent for further participation in the trial was obtained from a family member or from patients who were capable of giving consent. There was no financial compensation.

Patients

The French emergency medical system has been described elsewhere.[19] Ambulances staffed by physicians and based at major hospitals provided advanced cardiovascular life support (ACLS). Consecutive adults with witnessed OHCA presenting with nonshockable cardiac rhythm upon the arrival of the ACLS team were considered eligible for the study. The exclusion criteria were age younger than 18 years or older than 80 years, duration of untreated cardiac arrest of more than 30 minutes, rapidly fatal underlying disease, evidence of trauma, evidence of pregnancy, and allergy to cyclosporine.

Randomization and Trial Intervention

Eligible patients were randomly assigned by the physician dispatcher (using a "scratch-off" randomization list) using a 1:1 ratio either to the cyclosporine or control group. Randomization was stratified on the center. A permuted block design with a computer-generated random number was used. Because of the open design of the trial, blocks of various sizes were used. As soon as possible after the onset of ACLS, patients assigned to the cyclosporine group received a single intravenous bolus injection of cyclosporine, 2.5 mg/kg (Sandimmun, Novartis Pharma SAS). This dose was chosen arbitrarily based on the dose used in previous clinical trials.[20,21] Patients assigned to the control group did not receive any additional intervention.

According to the single-blind design of the trial, investigators from the ACLS team were aware of the intervention assignment. However, all physicians involved in the trial after hospital admission were unaware of the treatment assignment.

Data Collection and End Points

For each patient, demographics, comorbidities, and characteristics of the OHCA and data on resuscitation, based on the Utstein style,[22] were recorded. The use of targeted temperature management (ie, therapeutic hypothermia) and the Simplified Acute Physiology Score II[23] (range, 0-164, with higher scores indicating greater severity of illness) were also documented at the time of admission to the intensive care unit.

The primary end point was the Sequential Organ Failure Assessment (SOFA) score, as recorded 24 hours after hospital admission by a physician unaware of the randomization group. SOFA assesses multiple organ failure in intensive care units, including the setting of postcardiac arrest syndrome.[4,24-27] The SOFA score ranges from 0 to 24 (higher scores indicate more severe organ failure), with 0 to 4 points assigned for each of 6 organ dysfunctions (ie, central nervous system, cardiovascular, respiratory, renal, coagulation, and liver). As previously described,[25] *organ failure* was defined as a score of 3 or 4 points for the affected organ.

Secondary end points included criteria related to the severity of early organ dysfunction at intensive care unit admission and at 24 hours as well as outcomes. Thus, the SOFA score was recorded on admission to the intensive care unit. The Glasgow Coma Score[28] (range, 3-15; lower scores indicate reduced levels of consciousness) and the need for organ support were documented. In all participating centers, a physician who was unaware of the assigned group performed the neurologic evaluation from 72 hours after hospital admission. All clinical decisions for withdrawal of life-sustaining therapy remained at the discretion of the treating team, according to an international statement.[3] The probabilities of a return of spontaneous circulation and admission to the hospital alive; survival to 24 hours, 7 days, and 28 days; and discharge from the hospital alive were also recorded. Neurologic performance was assessed at hospital discharge using the Cerebral Performance Categories scale,[29] which ranges from 1 to 5 (1, good cerebral performance or minor disability; 2, moderate disability; 3, severe disability; 4, coma or vegetative state; and 5, brain death or dead). *Favorable neurologic outcome* was defined as a Cerebral Performance Categories level of 1 or 2 at discharge.

The safety of cyclosporine administration was assessed by recording all adverse effects. *Major adverse events* were defined as in-hospital death, need for renal replacement therapy, or postanoxic vegetative state.

Statistical Analysis

Under the alternative hypothesis of an expected difference of half the SD (effect size, 0.5) of the mean SOFA score at 24 hours, at least 128 patients had to be alive at 24 hours in the 2 arms to reject the null hypothesis of a similar mean SOFA score in both arms in 80% of the studies (β = 20%), with type 1 error at α = 5% (2-tailed). With an expected 24-hour mortality rate of 80%, at least 640 patients had to be randomized. Inclusions continued until the primary end point was analyzable in 128 patients. The sample size was calculated with the use of nQuery Advisor, version 5.0 (Statistical Solutions).

Variables were expressed as median and interquartile range (IQR) or number and proportion, as appropriate. Wilcoxon rank sum, χ^2, or Fisher exact tests were performed on the baseline characteristics of patients to detect a differential selection of patients after randomization. Analyses of both primary and secondary end points were performed according to the random assignment of patients (intention-to-treat analysis).

The main analysis of the primary end point, the SOFA score at 24 hours, was performed by fitting a mixed-effects linear model with a fixed effect for the assigned treatment and a random center effect. A non-Gaussian distribution of the SOFA score was anticipated, leading to the application of a Box-Cox transformation of the SOFA score at 24 hours, the power parameter being estimated by the profile likelihood. Analysis of the primary end point was conducted according to the treatment received (per-protocol analysis). Secondary analysis of the primary end point was performed with the same power parameter. A mixed-effects multivariate linear model was fitted systematically with a random center effect and fixed effects for treatment, sex, age, and duration of untreated cardiac arrest. In addition, bystander cardiopulmonary resuscitation, cardiac origin of the OHCA, and total duration of ACLS were included in multivariate modeling if the significance level of their association with the primary end point was smaller than 10% in the univariate analyses and were retained in the final model if the adjusted level of significance was smaller than 5%. The influence of in-hospital targeted temperature management on the treatment effect was estimated by introducing an interaction term into the model, with $P < .10$ considered significant for the interaction test. The involvement of each SOFA component was analyzed by fitting mixed-effects unconditional logistic regression models with a fixed effect for the assigned treatment and a random center effect.

The SOFA score at hospital admission was also analyzed by fitting a mixed-effects linear model with a fixed effect for the assigned treatment and a random center effect. Other secondary end points relating to early organ dysfunction were compared using Wilcoxon rank sum, χ^2, or Fisher exact tests. Outcomes were analyzed by fitting unconditional logistic regression models with a fixed effect for the assigned treatment and a random center effect.

Type I error rate was fixed at α = 5% in all tests (2 tailed) performed with SAS, version 9.3 (SAS Institute Inc) and R version, 2.15.1 (R Foundation).

Results

Study Population

From June 22, 2010, to March 13, 2013, a total of 6758 patients with OHCA were screened, and 794 were enrolled in the trial (**Figure 1**). Of these, 400 patients (50.4%) were randomly assigned to the cyclosporine group and 394 (49.6%) to the control group. The primary end point was assessed for 129 patients alive at 24 hours: 67 (51.9%) in the cyclosporine group and 62 (48.1%) in the control group. Two patients in the control group at 24 hours had received cyclosporine and were included in the primary analysis (Figure 1). Complete follow-up data were available for all 794 patients.

The characteristics of the patients, including resuscitation data, are presented in **Table 1** for both the randomized population and the patients included in the primary analysis. Asystole of cardiac origin was the leading cause of OHCA. No significant difference was seen between the groups at inclusion in the study except for age. The characteristics of the patients included in the intention-to-treat analysis were similar in the 2 groups.

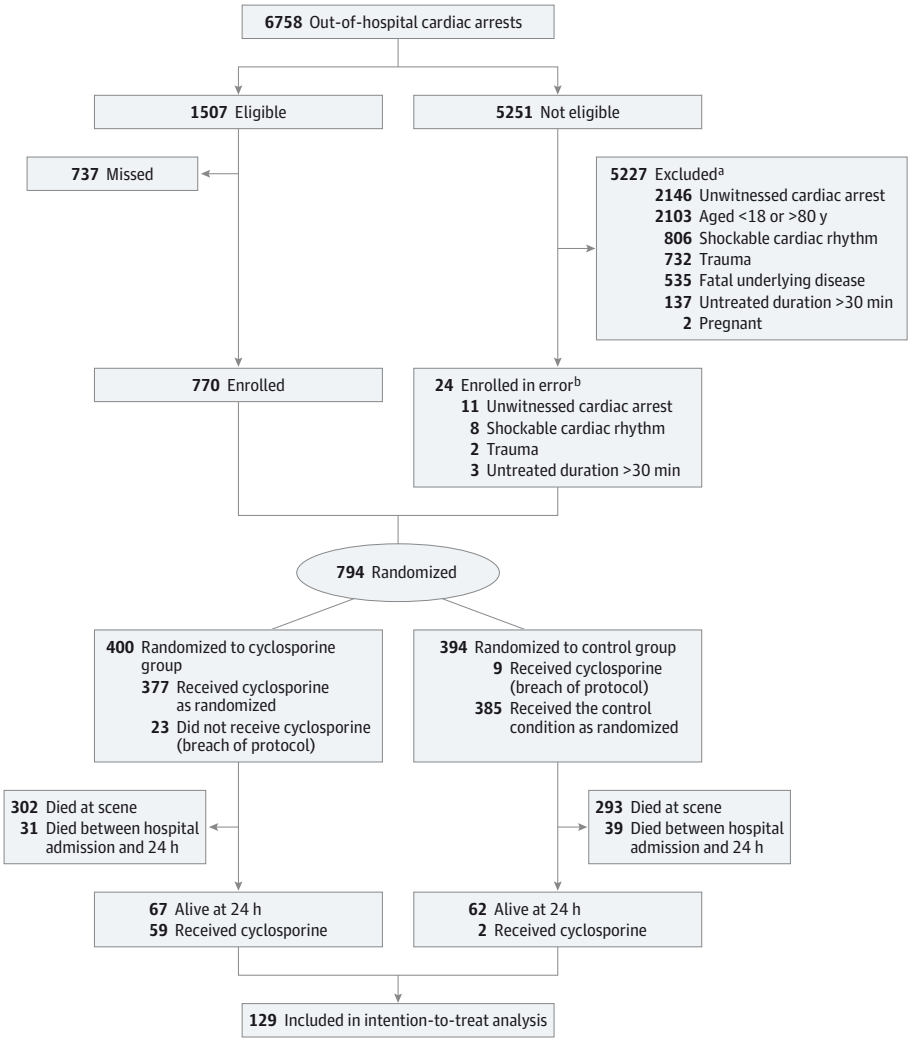
Intervention Group

In the intervention group, 377 patients received cyclosporine (Figure 1), with a median dose of 200 mg administered to 226 patients (59.9%). The median time from collapse to administration of cyclosporine was 29.0 (IQR, 21.0-35.0) minutes. Times from ACLS and from the first dose of epinephrine to the administration of cyclosporine were 8.0 (IQR, 5.0-13.0) minutes and 3.0 (IQR, 1.0-7.0) minutes, respectively.

Primary End Point

The median SOFA scores at 24 hours were 10.0 (IQR, 7.0-13.0) in the cyclosporine group and 11.0 (IQR, 7.0-15.0) in the

Figure 1. CONSORT Diagram



[a] A total of 1234 patients met more than 1 exclusion criterion.

[b] Five patients remained in the intention-to-treat analysis.

control group (**Figure 2**). The primary analysis of the SOFA score (Box-Cox transformation with power parameter = 0.46) did not detect a significant difference between the 2 groups (P = .45). The predicted mean was 10.1 (95% CI, 9.2-11.1) in the cyclosporine group and 10.7 (95% CI, 9.7-11.7) in the control group.

Per-protocol analysis did not show a significant difference in the primary end point (P = .51) when comparing 61 patients who received cyclosporine with 68 patients who did not receive the drug, with a predicted mean of the SOFA score at 24 hours of 10.1 (95% CI, 9.2-11.2) vs 10.6 (95% CI, 9.7-11.6), respectively. In addition, the primary end point was not significantly influenced by the delay of cyclosporine administration. Choosing a cutoff value of 29 minutes for the time from collapse to administration of cyclosporine, the SOFA score at 24 hours was not significantly different (P = .77) in the group with the shortest interval (n = 35; median, 10.0 [IQR, 7.0-14.0]) versus the group with the longest interval (n = 26; median, 10.0 [IQR, 8.0-13.0]).

In the secondary analysis of the primary end point, the variables sex (P = .72), age (P = .85), and duration of untreated cardiac arrest (P = .59) were not associated with the SOFA score at 24 hours after admission; however, a longer duration of ACLS was associated with a higher value of the SOFA score (P = .002). For a 60-year-old man with a 10-minute untreated cardiac arrest followed by 30 minutes of ACLS, the mean estimated SOFA score at 24 hours was 10.4 (95% CI, 9.3-11.5) in the cyclosporine group and 11.1 (95% CI, 10.0-12.3) in the control group (P = .29). In-hospital targeted temperature management had no interaction with the effects of cyclosporine (P = .36). Except for respiratory function, with an adjusted odds ratio of 0.41 (95% CI, 0.18-0.94; P = .04), cyclosporine had no significant effect to prevent other organ failure.

Secondary End Points

Identical medians of the SOFA score of 11.0 (IQR, 8.0-13.0) were observed in the 2 groups at admission without significant

Table 1. Patient Characteristics

Variable	Randomized Patients[a]			Patients Included in Primary Analysis[a]		
	Cyclosporine Group (n = 400)	Control Group (n = 394)	*P* Value	Cyclosporine Group (n = 67)	Control Group (n = 62)	*P* Value
Age, median (IQR), y	63.0 (54.0-71.8)	66.0 (57.0-74.0)	.003	62.1 (52.9-72.7)	63.5 (53.8-72.3)	.65
Male sex	293 (73.3)	288 (73.1)	>.99	45 (67.2)	47 (75.8)	.33
Medical history						
Coronary heart disease	82 (22.0) [372]	74 (20.3) [364]	.59			
Other cardiac disease	141 (37.9) [372]	155 (42.6) [364]	.20			
Respiratory disease	46 (12.4) [372]	34 (9.3) [364]	.19			
Other	178 (47.8) [372]	180 (49.5) [364]	.71			
No history of disease	101 (27.2) [372]	93 (25.5) [364]	.68			
Unknown	28 (7.0)	30 (7.6)	.79			
Location of cardiac arrest						
Place of residence	297 (74.3)	280 (71.1)	.43	40 (59.7)	46 (74.2)	.22
Public place	74 (18.5)	76 (19.3)		20 (29.9)	12 (19.4)	
Other	29 (7.3)	38 (9.6)		7 (10.4)	4 (6.5)	
Witnessed arrest	396 (99.0)	387 (98.2)	.38	67 (100)	61 (98.4)	.48
Bystander CPR	170 (42.6) [399]	168 (42.7) [393]	>.99	31 (46.3)	26 (41.9)	.72
Suspected cause of cardiac arrest						
Cardiac	134 (33.5)	142 (36.0)	.87	33 (49.3)	24 (38.7)	.28
Respiratory	94 (23.5)	90 (22.8)		22 (32.8)	22 (35.5)	
Other	50 (12.5)	44 (11.2)		7 (10.4)	5 (8.1)	
Unknown	122 (30.5)	118 (29.9)		5 (7.5)	11 (17.7)	
Initial recorded cardiac rhythm						
Asystole	336 (84.0)	343 (87.1)	.26	54 (80.6)	51 (82.3)	.44
Pulseless electrical activity	61 (15.3)	46 (11.7)		12 (17.9)	8 (12.9)	
Ventricular fibrillation or tachycardia	3 (0.8)	5 (1.3))		1 (1.5)	3 (4.8)	
Intervals, median (IQR), min						
Duration of untreated cardiac arrest	10.0 (5.0-15.0) [396]	10.0 (4.0-15.0) [390]	.20	8.0 (5.0-12.0)	10.0 (4.0-14.0)	.34
Time from collapse						
To emergency call	2.0 (0.0-5.0) [395]	1.0 (0.0-5.0) [386]	.99			
To ACLS	19.0 (13.0-25.0) [396]	19.0 (12.0-25.0) [387]	.19	15.0 (10.0-22.0)	16.0 (10.0-22.0)	.78
To first epinephrine injection	23.0 (17.0-30.0) [392]	22.0 (15.0-30.0) [386]	.09			
To return of spontaneous circulation	NA	NA		35.0 (27.0-46.0) [66]	32.0 (24.0-41.0) [58]	.36
To hospital admission	NA	NA		90.0 (70.0-105.0)	93.5 (75.0-120.0)	.24
Total duration of ACLS, median (IQR)	40.0 (30.0-50.0) [397]	40.0 (30.0-50.0) [393]	.35	23.0 (16.0-31.0)	21.0 (15.0-31.0)	.26
CPR initiated before arrival of ACLS	364 (91.0)	362 (91.9)	.70			
Dose of epinephrine administered, median (IQR), mg	8.0 (5.0-11.0) [397]	8.0 (5.0-10.0) [393]	.71	4.0 (2.0-6.0) [66]	4.0 (2.0-7.0)	.83
Route of administration of drugs						
Peripheral intravenous	370 (92.5)	367 (93.1)	.34			
Intraosseous infusion	15 (3.8)	8 (2.0)				
Central intravenous	8 (2.0)	13 (3.3)				
Other	7 (1.8)	6 (1.5)				

(continued)

Table 1. Patient Characteristics (continued)

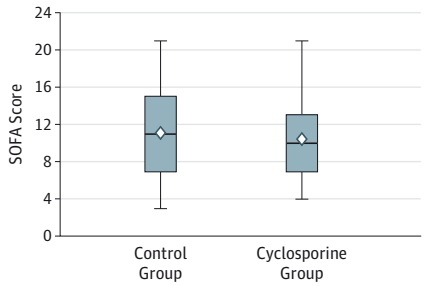
Variable	Randomized Patients[a]			Patients Included in Primary Analysis[a]		
	Cyclosporine Group (n = 400)	Control Group (n = 394)	*P* Value	Cyclosporine Group (n = 67)	Control Group (n = 62)	*P* Value
Defibrillation shocks applied						
No. of patients	137 (35.1) [390]	141 (36.2) [390]	.82			
No. of shocks, if given, median (IQR)	3.0 (1.0-5.0) [137]	3.0 (1.0-4.0) [141]	.83			
Cyclosporine		NA			NA	
Dose, median (IQR), mg				200 (150-200) [59]		
Time from collapse to administration				27.0 (19.0-32.0) [59]		
Target temperature management	NA	NA				
Prior to hospital arrival				21 (31.3)	21 (33.9)	.85
In-hospital				51 (76.1)	44 (71.0)	.55
SAPS II, median (IQR)[b]	NA	NA		72 (63-84)	76 (62-85)	.68

Abbreviations: ACLS, advanced cardiovascular life support; CPR, cardiopulmonary resuscitation; IQR, interquartile range; NA, not applicable; SAPS II, Simplified Acute Physiology Score II.

[a] Numbers in brackets indicate the number of patients available for analysis if it differs from the full sample size.

[b] Score ranges from 0 to 164, with higher scores indicating greater severity of illness.[23]

Figure 2. Sequential Organ Failure Assessment (SOFA) Score at 24 Hours After Admission



Cyclosporine administration resulted in no significant reduction in the SOFA score in the cyclosporine vs control group, with a median of 10.0 (IQR, 7.0-13.0) vs 11.0 (IQR, 7.0-15.0) (*P* = .45). The box plots indicate the median value and interquartile range (IQR) of the SOFA score in the cyclosporine and control groups; the white diamond indicates the mean. The box plot whiskers indicate the most extreme data points within 1.5 times the IQR from each edge of the box plot.

difference when a mixed linear model was fitted (*P* = .36). There was no significant difference between groups regarding the severity of the postcardiac arrest syndrome both at admission and at 24 hours (**Table 2**).

Survival rates were comparable in the cyclosporine and control groups (**Table 3**). In-hospital mortality was also similar in the 2 groups: 89.8% (88 of 98) and 95.0% (96 of 101) in the cyclosporine and control groups, respectively (adjusted odds ratio, 0.46; 95% CI, 0.14-1.56; *P* = .19). The most common causes of death for these 184 patients were postanoxic encephalopathy leading to treatment withdrawal (94 patients [51.1%]) and intractable shock after cardiac arrest (85 patients [46.2%]), with no significant difference between the 2 groups (*P* = .63).

Predefined major adverse events were not significantly different between the groups. No adverse effect was detected in patients who received cyclosporine.

Discussion

In this multicenter, randomized clinical trial, we examined whether the administration of cyclosporine early after resuscitation for a nonshockable OHCA might prevent multiple organ failure. We observed no significant reduction of the SOFA score in the treatment vs control patients 24 hours after hospital admission.

The rationale for using cyclosporine in the prevention of postcardiac arrest multiple organ failure was based on experimental data[5-9,11-17] suggesting that its powerful inhibition of mitochondrial permeability transition was able to prevent reperfusion injury in various conditions of tissue damage and organ failure. Under physiologic conditions, the inner mitochondrial membrane is impermeable to most metabolites and ions, and the PTP is in a closed conformation.[5,6] Following an ischemic insult, PTP opening occurs within the first minutes of reperfusion and can compromise cell function and viability.[5,6] Regardless of its immunosuppressive activity, cyclosporine inhibits PTP opening by binding to cyclophilin D, a mitochondrial chaperone protein.[5,6,17] Experimental studies, including those from our group,[11-14] have demonstrated that early administration of cyclosporine at the time of resuscitation after nonshockable cardiac arrest can inhibit PTP opening, attenuate tissue damage, and prevent failure of several organs.

The present study did not detect a significant difference between the cyclosporine and control groups with respect to the severity of postcardiac arrest, patients' outcomes, or their neurologic prognosis at hospital discharge. However, the study may have lacked statistical power to detect a moderate

Table 2. Postcardiac Arrest Syndrome–Induced Organ Dysfunction

Variable	At Admission[a]			At 24 h[a]		
	Cyclosporine Group (n = 98)	Control Group (n = 101)	*P* Value	Cyclosporine Group (n = 67)	Control Group (n = 62)	*P* Value
Clinical characteristics, median (IQR)						
Mean arterial pressure, mm Hg	80 (62-99) [94]	79 (63-100) [98]	.73	75 (64-91)	79 (63-89)	>.99
Heart rate, beats/min	90 (74-105) [96]	90 (76-104)	.82	95 (75-112)	91 (75-105)	.47
Body temperature, °C	34.8 (33.9-35.4) [85]	34.9 (33.8-35.8) [90]	.41	36.2 (34.3-37.4)	36.3 (34.2-37.3)	.99
Glasgow Coma Scale score[b]	3 (3-3)	3 (3-3)	.36	3 (3-3)	3 (3-3)	.98
Biological data, median (IQR)						
pH	7.16 (7.04-7.26) [92]	7.17 (7.09-7.27) [94]	.35	7.32 (7.24-7.41) [66]	7.36 (7.29-7.43) [60]	.12
Lactate, mg/dL	79.3 (52.3-124.3) [89]	82.0 (52.3-123.4) [89]	.75	25.2 (15.3-40.5) [66]	27.0 (17.1-45.9) [54]	.60
Pao_2/FiO_2, mm Hg	184 (118-296) [92]	213 (142-327) [91]	.13	255 (180-337) [66]	195 (129-312) [59]	.05
Troponin I, ng/mL	1.07 (0.10-11.00) [87]	0.39 (0.10-2.80) [89]	.23	3.32 (0.32-19.74) [55]	2.36 (0.29-66.50) [48]	.96
Organ failure						
No., median (IQR)	2.0 (2.0-3.0)	2.0 (2.0-3.0)	.55	2.0 (1.0-3.0)	2.0 (2.0-3.0)	.42
Type, No. (%)						
Central nervous system	98 (100)	101 (100)	NA	66 (98.5)	62 (100)	>.99
Cardiovascular	71 (72.4)	70 (69.3)	.64	43 (64.2)	39 (62.9)	>.99
Respiratory	55 (56.1)	47 (46.5)	.20	23 (34.3)	32 (51.6)	.05
Renal	16 (16.3)	20 (19.8)	.58	16 (23.9)	21 (33.9)	.25
Coagulation	6 (6.1)	4 (4.0)	.53	2 (3.0)	1 (1.6)	>.99
Liver	3 (3.1)	1 (1.0)	.36	0	1 (1.6)	.48
Organ support, No. (%)						
Mechanical ventilation	98 (100)	101 (100)	NA	67 (100)	62 (100)	NA
Catecholamines	69 (70.4)	71 (70.3)	>.99	43 (64.2)	39 (62.9)	>.99
Renal replacement therapy	NA	NA		5 (7.5)	9 (14.5)	.26

Abbreviations: IQR, interquartile range; NA, not applicable; Pao_2/FiO_2, ratio of arterial oxygen partial pressure to fractional inspired oxygen.

SI conversion factors: To convert lactate to millimoles per liter, multiply by 0.111; troponin I to micrograms per liter, multiply by 1.

[a] Numbers in brackets indicate the number of patients available for analysis if it differs from the full sample size.

[b] Score ranges from 3 to 15; lower scores indicate reduced levels of consciousness.[28]

Table 3. Patient Outcomes

Variable	No. (%)			
	Cyclosporine Group (n = 400)	Control Group (n = 394)	Adjusted OR (95% CI)	*P* Value
Died at scene	302 (75.5)	293 (74.4)	1.06 (0.75-1.52)	.71
Return of spontaneous circulation	140 (35.0)	156 (39.6)	0.82 (0.60-1.13)	.20
Admitted to hospital	98 (24.5)	101 (25.6)	0.94 (0.66-1.34)	.71
Survived to 24 h	67 (16.8)	62 (15.7)	1.08 (0.71-1.63)	.70
Survived to 7 d	22 (5.5)	21 (5.3)	1.03 (0.53-2.03)	.92
Survived to 28 d	13 (3.3)	8 (2.0)	1.62 (0.61-4.30)	.31
Discharged alive	10 (2.5)	5 (1.3)	2.00 (0.61-6.52)	.23
Favorable neurologic outcome at discharge[a]	7 (1.8)	5 (1.3)	1.39 (0.39-4.91)	.59

Abbreviation: OR, odds ratio.

[a] Defined as a Cerebral Performance Category score of 1 (good cerebral performance or minor disability) or 2 (moderate disability).[29]

benefit of cyclosporine to prevent early multiple organ failure or to improve survival. In addition, our study population represented cardiac arrest patients at the higher end of the injury spectrum, including a majority of patients with asystole and very high in-hospital mortality. Whether cyclosporine would benefit patients with a less severe injury (eg, a cohort of patients with shockable OHCA) remains to be evaluated.

Several effect modifiers might alter the impact of any protective intervention aimed at limiting the postcardiac arrest syndrome, including underlying diseases, cause of cardiac

arrest, initial cardiac rhythm, cardiopulmonary resuscitation quality (which was not measured in the study), and timing of ACLS. However, none of these factors can likely explain the absence of effect of cyclosporine since they were well balanced between the 2 groups. The main limitation of our study is probably the delay in administration of cyclosporine after the resumption of circulation. Indeed, strong evidence[5,6,12,30,31] indicates that reperfusion injury occurs immediately at reflow and that a few-minute delay in application of any protective intervention can abolish its benefit. Despite the recommendations to inject cyclosporine as soon as possible, the median delay for injection once the ACLS team was on site was 8 minutes. In addition, most patients had already undergone bystander cardiopulmonary resuscitation, suggesting that the delay from onset of reflow to cyclosporine injection was likely even longer. One might speculate that earlier administration of cyclosporine would result in better prevention of the postcardiac arrest syndrome. However, in an unpowered post hoc analysis, we did not find any influence of the delay of cyclosporine administration.

Additional aspects render the clinical settings different from our experimental model of asphyxial cardiac arrest.[11,14] In the present study, OHCA was suspected of respiratory origin in only 23.2% of the cases, while a cardiac cause was suspected in 34.8% with previous coronary artery disease present in 19.6%. One cannot rule out that untreated myocardial ischemia or underlying cardiac damage might have compromised the recovery of cardiac function and blunted a potential favorable impact of cyclosporine. In addition, nearly 75% of the patients received in-hospital targeted temperature management, which is often associated with the use of sedative drugs, with both known to be cytoprotective via mitochondrial mechanisms.[6,32-34] These interventions might have attenuated a putative protection afforded by cyclosporine. It can be hypothesized that a higher dose or more prolonged administration of cyclosporine would have been more efficient.

Finally, our results are in keeping with the recently published CIRCUS trial[35] that did not show any beneficial effect of cyclosporine administered immediately after reperfusion in patients with acute myocardial infarction. Because of its nonspecific effects on PTP or its nonmitochondrial effects, cyclosporine might not be the appropriate PTP inhibitor to prevent reperfusion injury and improve clinical outcome in patients with acute myocardial infarction and OHCA. In any event, our results do not call into question the concept of reperfusion injury in cardiac arrest. Given the current prognosis of OHCA, further trials investigating other protective interventions are required more than ever to prevent resuscitation injury in the setting of postcardiac arrest syndrome.

Conclusions

Among resuscitated patients with nonshockable OHCA, the present trial failed to demonstrate the benefits of 2.5 mg/kg of cyclosporine administered at resuscitation to prevent multiple organ failure as assessed by the SOFA score at 24 hours after hospital admission. Further studies are needed to investigate other approaches to prevent resuscitation injury in the future.

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Author Affiliations: Hospices Civils de Lyon, Hôpital Edouard Herriot, Service de Réanimation Médicale, Lyon, France (Argaud, Cour, Hernu, Robert); Institut National de la Santé et de la Recherche Médicale, Unité Mixte de Recherche 1060, Carmen, Equipe Cardioprotection, Lyon, France (Argaud, Cour, Ovize); Université de Lyon, Université Claude Bernard Lyon 1, Lyon, France (Argaud, Cour, Riche, Gueugniaud, Robert, Roy, Ovize); Hospices Civils de Lyon, Service d'Aide Médicale Urgente 69, Lyon, France (Dubien, Gueugniaud); Centre Hospitalier Universitaire de Saint-Etienne, Service d'Aide Médicale Urgente 42A, Saint-Etienne, France (Giraud, Zéni); Hospices Civils de Lyon, Hôpital Louis Pradel, Explorations Fonctionnelles Cardiovasculaires et Centre d'Investigation Clinique de Lyon, Lyon, France (Jossan, Ovize); Hospices Civils de Lyon, Centre Hospitalier Lyon-Sud, Service de Biostatistique, Lyon, France (Riche, Roy); Centre National de la Recherche Scientifique Unité Mixte de Recherche 5558, Laboratoire de Biométrie et Biologie Evolutive, Equipe Biostatistique-Santé, Villeurbanne, France (Riche, Roy); Centre Hospitalier Universitaire de Saint-Etienne, Hôpital Nord, Service de Réanimation Polyvalente, Saint-Etienne, France (Darmon, Zéni); Centre Hospitalier de Bourg-en-Bresse, Hôpital Fleyriat, Service d'Aide Médicale Urgente 01, Bourg-en-Bresse, France (Poncelin); Centre Hospitalier de Bourg-en-Bresse, Hôpital Fleyriat, Service de Réanimation Polyvalente, Bourg-en-Bresse, France (Tchénio); Centre Hospitalier Universitaire de Dijon, Hôpital François Mitterand, Service de Réanimation Médicale, Dijon, France (Quenot); Centre Hospitalier Universitaire de Dijon, Service d'Aide Médicale Urgente 21, Dijon, France (Freysz); Centre Hospitalier de Roanne, Service d'Aide Médicale Urgente 42B, Roanne, France (Kamga); Centre Hospitalier de Roanne, Service de Réanimation et Soins Continus, Roanne, France (Beuret); Centre Hospitalier Métropole Savoie, Service d'Aide Médicale Urgente 73, Chambéry, France (Usseglio); Centre Hospitalier Métropole Savoie, Service de Réanimation Polyvalente, Chambéry, France (Badet); Centre Hospitalier de Villefranche-sur-Saône, Service Mobile d'Urgence et de Réanimation de Villefranche-sur-Saône, Villefranche-sur-Saône, France (Anette); Centre Hospitalier de Villefranche-sur-Saône, Service de Réanimation, Villefranche-sur-Saône, France (Chaulier); Centre Hospitalier d'Ardèche Nord, Service Mobile d'Urgence et de Réanimation d'Annonay, Annonay, France (Alasan); Centre Hospitalier Régional Universitare, Service d'Aide Médicale Urgente 54, Nancy, France (Sadoune); Centre Hospitalier Universitaire de Nîmes, Pôle Anesthésie Réanimation Douleur Urgences, Nîmes, France (Bobbia).

Author Contributions: Dr Argaud had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Argaud, Cour, Ovize.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Argaud, Cour, Roy.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Argaud, Riche, Roy.
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Group information: Members of the CYRUS (Cyclosporine A in Out-of Hospital Cardiac Arrest Resuscitation) Study Group include *Hospices Civils*

de Lyon: Olivier Capel, MD, David Pinero, MD, Djamila Rerbal, MD, Jean-Michel Robert, MD, Julien Bohé, MD, PhD, Sylvie de La Salle, RN, Marielle Buisson, PharmD, and Christine Pivot, BPharm. *Centre Hospitalier Universitaire (CHU) de Saint-Etienne:* Nicolas Desseigne, MD, Fabrice Granjon, MD, Pierre Alban Guenier, MD, and Maud Coudrot, MD. *Centre Hospitalier de Bourg-en-Bresse:* Hélène Lovery, MD, and Adrien Robine, MD. *CHU de Dijon:* Jean-Michel Yeguiayan, MD, and Saber-David Barbar, MD. *Centre Hospitalier de Roanne*: Michael Vial, MD†. *Centre Hospitalier Métropole Savoie*: François Vitrat, MD, and Vincent Susset, MD. *Centre Hospitalier de Villefranche-sur -Saône*: Marc du Besset, MD, and Julien Illinger, MD. *Centre Hospitalier d'Ardèche Nord:* Irène Laval, MD, and Vincent Cadiergue, MD. *Centre Hospitalier Régional Universitaire de Nancy:* Damien Barraud, MD. *CHU de Nîmes:* Claire Roger, MD. *CHU de Grenoble*: Eric Fontaine, MD, PhD, and Xavier Leverve, MD, PhD†. *Centre Hospitalier Intercommunal de Toulon–La Seyne-sur-Mer:* Stéphane-Yannis Donati, MD, and Jacques Istria, MD. *Centre Hospitalier de Valence*: Claude Zamour, MD, and Quentin Blanc, MD. *CHU de Rouen*: Benoit Jardel, MD, and Fabienne Tamion, MD. *Hospices Civils de Beaune:* Bénédicte Vallet, MD. *Centre Hospitalier de Vienne*: Carlos El Khoury, MD. *Assistance Publique–Hôpitaux de Marseille*: Richard Toesca, MD, and Marc Gainnier, MD, PhD.

†Deceased.

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