


LETTER



Cyclosporine A prevents cardiac arrest-induced acute respiratory failure: a post-hoc analysis of the CYRUS trial

Louis Kreitmann^{1,2}, Laurent Argaud^{1,2,3}, Michel Ovize^{2,3,4}, Martin Cour^{1,2,3*}  and For the CYRUS Study Group

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Dear Editor,

Accumulating evidence suggests that hypoxemic acute respiratory failure (ARF) is independently associated with poor outcomes in patients successfully resuscitated after out-of-hospital cardiac arrest (OHCA) [1]. This finding opens new therapeutic perspectives, targeting lung injury, to improve the prognosis of OHCA patients. Experimentally, Cyclosporine A (CsA) has been shown to prevent systemic inflammation-induced ARF [2, 3]. To investigate the effect of CsA on ARF in the clinical setting, we conducted a post-hoc analysis of the prospective, multicenter, randomized CsA in OHCA resuscitation (CYRUS) trial (ClinicalTrials.gov identifier: NCT01595958).

The CYRUS trial failed to demonstrate a significant decrease in the sequential organ failure assessment (SOFA) score at 24 h after nonshockable OHCA in patients receiving a prehospital single injection of 2.5 mg/kg CsA [4]. All the 129 patients alive at 24 h included in the intention-to-treat analysis (67 in the CsA group and 62 in the control group) were analyzed in the present post-hoc analysis (without correction for multiple comparison), in which the primary endpoint was the occurrence of ARF at 24 h, as defined by a SOFA respiratory sub-score > 2. The CsA effect was adjusted for history of

respiratory disease, respiratory cause of OHCA and for relevant variables with $p < 0.1$ after univariate analysis.

Patient's and OHCA's characteristics were well matched between the two groups (Table 1). At admission, both the median (interquartile) ratio of the arterial partial pressure of oxygen to the fractional inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) and the percentage of patients with ARF did not significantly differ between the CsA and the control groups: 211 (133–319) versus 207 (131–318) mmHg and 34.3% versus 32.3%, respectively. At 24 h, ARF was significantly less frequent in the CsA group (29.8%) compared to the control group (54.8%) and median $\text{PaO}_2/\text{FiO}_2$ was 68 mmHg higher in the CsA group (Table 1). Patients treated with CsA were also less likely to fulfill criteria for acute respiratory distress syndrome (Table 1). Importantly, CsA was still independently associated with a lower risk for ARF after multivariate analysis (OR 0.33; 95%CI [0.16–0.70], $p < 0.01$) (Supplementary Table 1). This result was confirmed in the per-protocol population of the CYRUS trial (i.e. 61 patients who actually received CsA and 68 patients who did not) by both univariate analysis (ARF in 33% versus 50% of patients, respectively, $p < 0.05$) and multivariate analysis (OR 0.42; 95%CI [0.20–0.88], $p = 0.02$).

We report here the first clinical data suggesting that CsA might limit the severity of ARF at 24 h following OHCA. Even though this post-hoc analysis of the CYRUS trial does not provide mechanistic insight, our findings are in line with both experimental and clinical studies reporting potent protective effects of CsA against ischemia/reperfusion (I/R) injury [1, 2, 3, 5]. CsA may indeed limit I/R-induced cellular damages by inhibiting the cyclophilin D-dependent opening of the mitochondrial permeability transition pore and by

*Correspondence: martin.cour@chu-lyon.fr

¹ Service de Médecine Intensive - Réanimation, Hospices Civils de Lyon, Hôpital Edouard Herriot, 5, place d'Arsonval, 69437 Lyon Cedex 03, France
Full author information is available at the end of the article

Members of "For the CYRUS Study Group" are listed in Acknowledgement section.

preserving oxidative phosphorylation [5]. In acute lung injury models, cytoprotection was also attributed to a decrease in circulating mitochondrial pro-inflammatory and pro-apoptotic factors [2, 3]. Studies are now needed to examine the longer-term effects of CsA on

lung injury, which could not be done here due to high early mortality rate.

In conclusion, the present study identified CsA as a potential new therapeutic strategy to prevent cardiac arrest-induced ARF. This finding will need further confirmation.

Table 1 OHCA-induced acute respiratory failure

	Cyclosporine group (n = 67)	Control group (n = 62)	p-value
<i>Patients</i>			
Age (years)	62.1 (52.9–72.7)	63.5 (53.8–72.3)	0.651
Male	42 (67.2)	47 (75.8)	0.332
History of respiratory disease	10 (14.9)	8 (12.9)	0.741
History of cardiac disease	36 (53.7)	35 (56.4)	0.756
<i>OHCA</i>			
Arrest at place of residence	40 (59.7)	46 (74.2)	0.119
Respiratory cause	22 (32.8)	22 (35.5)	0.751
Cardiac cause	33 (49.3)	24 (38.7)	0.228
Bystander cardiopulmonary resuscitation	31 (46.3)	26 (41.9)	0.723
Duration of untreated cardiac arrest (min)	8 (5–12)	10 (4–14)	0.340
Time from collapse to ROSC (min)	35 (27–46)	32 (24–41)	0.358
Target temperature management	51 (76)	44 (71)	0.550
<i>Cardiovascular dysfunction at 24 h</i>			
Mean arterial pressure (mmHg)	75 (64–91)	79 (63–89)	> 0.99
Heart rate (beats per min)	95 (75–112)	91 (75–105)	0.464
Left ventricular ejection fraction (%)	50 (30–65)	55 (40–60)	0.899
Vasoactive drugs	43 (64.2)	39 (62.9)	0.880
<i>Respiratory dysfunction at 24 h</i>			
Mechanical ventilation	67 (100)	62 (100)	N/A
<i>Ventilator settings</i>			
FiO ₂ (%)	40 (35–60)	50 (40–70)	0.230
PEEP (cmH ₂ O)	5 (4–6)	5 (5–6)	0.278
Tidal volume (mL/kg)	6.6 (6.1–8.2)	6.4 (5.8–7.9)	0.593
Minute ventilation (L/min)	10.6 (8.5–12.6)	10.7 (7.8–12.8)	0.749
Sedation/curarization	42 (62.7)	30 (48.4)	0.102
Chest quadrants with infiltrates	2 (1–3)	2 (1–4)	0.522
<i>Arterial blood gases</i>			
pH	7.32 (7.24–7.41)	7.36 (7.29–7.43)	0.116
PaCO ₂ (mmHg)	36 (31–42)	35 (32–41)	0.914
PaO ₂ (mmHg)	104 (82–135)	91 (77–121)	0.103
PaO ₂ /FiO ₂ (mmHg)*	255 (180–337)	187 (125–304)	0.021
Lactate (mmol/L)	2.8 (1.7–4.5)	3.0 (1.9–5.1)	0.603
Acute respiratory failure [†]	20 (29.8)	34 (54.8)	0.019
Acute respiratory distress syndrome [‡]	5 (7.4%)	11 (17.7%)	0.108

Data are expressed as median (interquartile range) or number (%) and compared using Wilcoxon, chi-square or Fisher's exact tests, as appropriate

OHCA out-of-hospital cardiac arrest, ROSC restoration of spontaneous circulation, SOFA sequential organ failure assessment score, PEEP positive end-expiratory pressure, PaCO₂ arterial partial pressure of carbon dioxide, PaO₂/FiO₂ ratio of the arterial partial pressure of oxygen to the fractional inspired oxygen

*Imputed, if needed, using adjusted pulse saturation of oxygen (SpO₂) to FiO₂ ratio (n = 2 patients in the control group)

[†] Defined as PaO₂/FiO₂ ratio < 200 mmHg in mechanically ventilated patients

[‡] Defined according to Berlin criteria

Electronic supplementary material

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Author details

¹ Service de Médecine Intensive - Réanimation, Hospices Civils de Lyon, Hôpital Edouard Herriot, 5, place d'Arsonval, 69437 Lyon Cedex 03, France. ² Faculté de médecine Lyon Est, Université de Lyon, Université Claude Bernard Lyon 1, 69373 Lyon, France. ³ INSERM, U1060 CarMeN, 69373 Lyon, France. ⁴ Service d'Explorations Fonctionnelles Cardiovasculaire, Centre d'Investigations Cliniques, Hôpital Cardiologique Louis Pradel, Bron, France.

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Compliance with ethical standards

Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of our institutional research committee and with the 1964 Declaration of Helsinki and its later amendments. The study was approved by the institutional review board (Comité de Protection des Personnes Sud-Est IV, France), and written informed consent for participation in the study was obtained for all patients.

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