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Letter to the Editor

Cyclosporine A prevents ischemia-reperfusion-induced lymphopenia after out-of-hospital cardiac arrest: A predefined sub-study of the CYRUS trial

Sir,

Resuscitated cardiac arrest (CA) leads severe immune dysfunction, including low monocyte HLA-DR (mHLA-DR) expression and lymphopenia, similar to that observed in septic shock patients.[1] Low lymphocyte count has been described as an independent risk factor for death after CA while accumulating data suggest that preventing lymphopenia may dramatically improve outcomes in critically ill patients.[2] To our knowledge, no treatment has been shown to alter post-CA immune and/or inflammatory response.

Cyclosporine A (CsA), independently of its immunosuppressive properties, has potent anti-necrotic and anti-apoptotic properties (via mitochondrial effects) in the context of ischemia-reperfusion (I/R) injury.[3] We recently tested in the Cyclosporine in CA resuscitation (CYRUS) trial, whether CsA could limit the severity of organ failures after non-shockable witnessed CA.[4] Here, we aimed to analyze the effect of CsA on CA-induced immune dysfunction in a predefined sub-study of the CYRUS trial (ClinicalTrials.gov Identifier: NCT01595958).

In the CYRUS trial, patients with non-shockable out-of-hospital CA randomly received either CsA (2.5 mg/kg) at the onset of cardiopulmonary resuscitation (Cyclosporine group) or no additional intervention (Control group).[4] Among those included in the coordinating center of the trial, 33 patients (Cyclosporine group: n = 17; Control group: n = 16) had blood samples to evaluate the post-CA immune/inflammatory response.

The patients' characteristics, as well as the severity of multiple organ failure, did not significantly differ between the two groups (Table 1). All patients but one died before discharge (p = 0.48 between groups). Neuron specific enolase (NSE) levels were significantly lower in the Cyclosporine group than in the Control group at 24 h: 123 (40–151) ng/ml versus 230 (80–478) ng/ml, respectively (p = 0.02). At admission and 24 h, we observed in both groups an increase in neutrophils and a marked decrease in mHLA-DR compared to normal values (Table 1). CsA significantly reduced the CA-induced drop in total lymphocyte count and prevented CD4+ lymphopenia at 24 h (Table 1). Except for IL-10 at admission, the systemic response to I/R was similar between the two groups (Table 1).

In the setting of critical care, apoptosis, which occurs in response to acute inflammation, is the prevailing mechanism leading to the loss of lymphocytes.[2] In the present study, CsA altered neither the blood levels of pro-inflammatory markers nor the cytokine storm-mediated decrease in mHLA-DR expression. Consequently, prevention of lymphopenia in the CsA treated-group is unlikely to be explained by the anti-inflammatory effects of the drug. Thus, the most probable hypothesis is that CsA prevents CA-induced lymphocyte apoptosis via direct mitochondrial effects, as has been previously described in experimental conditions.[5] This assumption is also supported by the abundant literature reporting that CsA, independently of its immunosuppressive properties, prevents I/R-induced cell death by inhibiting the mitochondrial permeability transition pore (mPTP).[3] Taken together, our results suggest a new role for the mPTP in the pathophysiology of post-CA adaptive immune dysfunction, which deserves further research.

In summary, CsA protected against lymphopenia following non-shockable out-of-hospital CA, while limiting increase in blood NSE levels. CsA may represent the first therapeutic approach to prevent CA-induced immune dysfunction. The clinical impact of these findings, particularly on the prevention of post-CA nosocomial infection and long-term neurological outcomes, remains to be determined in less severe patients.

Table 1 – Patients' characteristics and systemic ischemia-reperfusion response.

	Cyclosporine group (n = 17)	Control group (n = 16)	p
Demographics			
Age (years)	64 (59–72)	67 (58–76)	0.53
Male	11 (65)	9 (56)	0.73
Cardiac arrest and resuscitation			
Arrest at home	12 (71)	12 (75)	>0.99
Duration of untreated cardiac arrest (min)	10 (6–14)	12 (5–15)	0.51
Time from collapse to ROSC (min)	43 (27–63)	32 (20–56)	0.41
Bystander CPR	8 (47)	5 (31)	0.48
Dose of epinephrine (mg)	4 (3–9)	3 (2–6)	0.37
Targeted temperature management	16 (94)	13 (81)	0.34
Organ failures			
SOFA score at admission	10 (9–11)	10 (5–12)	0.63
SOFA score at 24 h	11 (8–13)	9 (7–13)	0.66
Systemic I/R response at admission			
Neutrophils (G/l)	12.3 (7.9–20.8)	9.2 (5.7–13.0)	0.14
Lymphocytes (G/l)	3.3 (1.4–5.4)	3.7 (1.5–5.3)	0.72
mHLA-DR expression ($\times 10^3$ AB/C)	11.4 (7.2–16.9)	14.2 (9.4–18.6)	0.52
Interleukin-6 (pg/l)	152 (128–233)	146 (99–239)	0.88
Tumor Necrosis Factor-α (pg/l)	0.79 (0.32–0.87)	1.18 (0.52–3.07)	0.30
Interleukin-10 (pg/l)	45 (36–70)	143 (101–187)	0.04
C-Reactive Protein (mg)	42 (28–68)	16 (5–33)	0.06
Systemic I/R response at 24 h			
Neutrophils (G/l)	13.4 (9.0–15.4)	10.8 (7.0–13.7)	0.41
Lymphocytes (G/l)	1.3 (0.8–1.8)	0.8 (0.4–1.2)	0.03
CD4+ T lymphocytes (cells/μl)	557 (384–874)	233 (157–615)	0.01
mHLA-DR expression ($\times 10^3$ AB/C)	6.9 (4.5–12.5)	9.1 (6,1–12,9)	0.62
Interleukin-6 (pg/l)	100 (35–220)	225 (48–228)	0.96
Tumor Necrosis Factor-α (pg/l)	0.67 (0.13–1.19)	0.52 (0.36–1.05)	0.82
Interleukin-10 (pg/l)	48 (12–160)	33 (9–64)	0.36
C-Reactive Protein (mg))	77 (73–90)	61 (21–106)	0.42

ROSC: restoration of spontaneous circulation; CPR: cardiopulmonary resuscitation; SOFA: Sequential organ failure assessment; I/R: ischemia-reperfusion; mHLA-DR: Monocyte Human Leucocyte Antigen - antigen D Related; AB/C: Antibodies Bound per Cell.
Normal values: neutrophils: 1.8–7.5 G/l; lymphocytes: 1.0–4.0 G/l; CD4 + T lymphocytes: 500–1250 cells/μl; mHLA-DR expression: $>20.10^3$ AB/C.
Data are expressed as median (interquartile range) or number (%).

Conflicts of interest

The authors declare they have no conflict of interest.

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REFERENCES

1. Venet F, Cour M, Demaret J, Monneret G, Argaud L. Decreased monocyte HLA-DR expression in patients after non-shockable out-of-hospital cardiac arrest. Shock 2016;46:33–6.
2. Hotchkiss RS, Monneret G, Payen D. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. Nat Rev Immunol 2014;13:862–74.
3. Hausenloy DJ, Boston-Griffiths EA, Yellon DM. Cyclosporin A and cardioprotection: from investigate tool to therapeutic agent. Br J Pharmacol 2012;165:1235–45.
4. Argaud L, Cour M, Dubien PY, et al. Effect of cyclosporine in non-shockable out-ofhospital cardiac arrest: the CYRUS randomized clinical trial. JAMA Cardiol 2016;1:557–65.
5. Zamzani N, Marchetti P, Castedo M, et al. Inhibitors of permeability transition interfere with the disruption of mitochondrial transmembrane potential during apoptosis. FEBS Lett 1996;384:53–7.

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