Ubiquitous protective effects of cyclosporine A in preventing cardiac arrest-induced multiple organ failure

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Cour M, Abrial M, Jahandiez V, Loufouat J, Belaydi E, Gharib A, Varennex A, Monneret G, Thibault H, Ovize M, Argaud L. Ubiquitous protective effects of cyclosporine A in preventing cardiac arrest-induced multiple organ failure. J Appl Physiol 117: 930–936, 2014. First published September 11, 2014; doi:10.1152/japplphysiol.00495.2014.—Opening of the mitochondrial permeability transition pore (mPTP) appears to be a pivotal event in myocardial ischemia-reperfusion (I/R) injury. Resuscitated cardiac arrest (CA) leads to the post-CA syndrome that encompasses, not only myocardial dysfunction, but also brain injury, failure of other organs (kidney, liver, or lung), and systemic response to I/R. We aimed to determine whether cyclosporine A (CsA) might prevent multiple organ failure following CA through a ubiquitous mPTP inhibition in each distant vital organ. Anesthetized New Zealand White rabbits were subjected to 15 min of CA and 120 min of reperfusion. At the onset of resuscitation, the rabbits received CsA, its non-immunosuppressive derivative NIM811, or vehicle (controls). Survival, hemodynamics, brain damage, organ injuries, and systemic I/R response were analyzed. Fresh mitochondria were isolated from the brain, heart, kidney, liver, and lung to assess both oxidative phosphorylation and permeability transition. CsA analogs significantly improved short-term survival and prevented multiple organ failure, including brain damage and myocardial dysfunction (P < 0.05 vs. controls). Susceptibility of mPTP opening was significantly increased in heart, brain, kidney, and liver mitochondria isolated from controls, while mitochondrial respiration was impaired (P < 0.05 vs. sham). CsA analogs prevented these mitochondrial dysfunctions (P < 0.05 vs. controls). These results suggest that CsA and NIM811 can prevent the post-CA syndrome through a ubiquitous mitochondrial protective effect at the level of each major distant organ.

AT LEAST 500,000 AMERICANS and almost as many Europeans suffer cardiac arrest (CA) each year with <10% of these patients surviving (5). Although current cardiopulmonary resuscitation performance can increase the rate of restoration of spontaneous circulation (ROSC), the prognosis remains poor, partly because a large majority of immediate survivors die of post-CA syndrome (22). Indeed, the whole body ischemia-reperfusion (I/R) response that occurs during resuscitated CA induces complex pathophysiological processes (named the post-CA syndrome), leading to irreversible brain damage, myocardial dysfunction, failure of other vital organs (e.g., kidney and liver), and, in most cases, death (22, 28).

Even if there is no doubt that limiting the duration of ischemia prevents irreversible cell injury, it has also been proposed that reperfusion by itself may damage the previously ischemic tissues (34). There is general agreement that mitochondria are important actors in these reperfusion-induced organ damage (14). As a result, mitochondria are emerging as targets of choice for therapeutic interventions in CA (4, 9, 11, 15). Growing evidence suggests that mitochondrial permeability transition pore (mPTP) opening, a cyclosporine A (CsA)-sensitive channel located in the inner membrane, mediates cell death at the onset of reperfusion, including in CA (6, 9, 10, 14, 15). The mPTP opening occurs in the first few minutes of reperfusion, when conditions that increase the probability of pore opening prevail: calcium overload, matrix corrected pH, ATP depletion, and a burst of reactive oxygen species (6, 10, 14). Accumulating data from our group and others supports the pharmacological inhibition of mPTP opening by CsA (independent of its immunosuppressive properties) as a potent strategy to prevent cellular injury after I/R, particularly in the heart and brain (3, 17, 26, 30, 34).

Using a rabbit model of CA, our laboratory has previously identified the central role of mPTP in preventing CA-induced myocardial dysfunction (9). The beneficial effects of CsA on cardiovascular failure have also recently been reported in a rodent model (15). However, it remains unclear whether permeability transition is also involved in the pathogenesis of remote organs failure (brain, kidney, liver, and lung). We hypothesized now that the post-CA syndrome was related to ubiquitous mitochondrial damages at a distance of the heart that might be prevented by local pharmacological mPTP inhibition.

MATERIALS AND METHODS

The investigation conformed to French laws and the revised Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council “Guide for the Care and Use of Laboratory Animals” National Academy Press, Washington, DC, 1996. All experiments were approved by the Lyon I Claude Bernard University Committee for Animal Research.
Animal Preparation

We used our established rabbit model of CA and resuscitation (9). Briefly, New Zealand White rabbits (2.5–3.5 kg) were anesthetized using xylazine and ketamine. A tracheotomy was performed, and animals underwent mechanical ventilation with 30% oxygen. A left thoracotomy was performed to expose the heart. Invasive arterial pressure, heart rate, end-tidal carbon dioxide concentration (a surrogate marker of cardiac output), and esophageal temperature were also continuously measured. A 15-min stabilization period was observed before experiments.

CA and Resuscitation

As previously described, rabbits were paralyzed with pancuronium bromide (9). CA was induced by the withdrawal of mechanical ventilation. After 15 min of untreated CA, resuscitation was started with the resumption of mechanical ventilation with 100% oxygen, cardiac massage (200 beats/min), and intravenous (iv) administration of epinephrine (20 μg/kg) every 3–5 min in the absence of ROSC or when the mean arterial pressure (MAP) was <15 mmHg. ROSC was defined as the return of an organized cardiac rhythm for at least 2 min, with MAP > 15 mmHg. The resuscitative efforts were stopped in the absence of ROSC after 30 min. The inspired oxygen fraction (FiO₂) was decreased to 30%, 30 min after CA.

Experimental Protocol

After the stabilization period, animals were randomly assigned to one of the four following groups: control (Ctrl) group (CA with 120 min of reperfusion following resuscitation); CsA group (iv bolus of CsA (5 mg/kg) at the onset of the resuscitation); NIM811 group (iv bolus of N-methyl-4-isoleucine-cyclosporine (NIM811, 2.5 mg/kg)); and sham-operated group. NIM811, originally developed as an anti-viral agent, is a non-immunosuppressive CsA derivative (an isobutyl group is replaced by a sec-butyl group at position 4), that specifically inhibits mPTP opening (29, 32).

Each of the five organ systems (cardiovascular, neurological, renal, hepatic, and respiratory) was extensively studied. To this end, heart, brain, kidney, liver, and lung were harvested. For experimental reasons, fresh mitochondria were isolated from a maximum of three vital organs from the same animal. All procedures were blinded to the group assignment.

Markers of Multiple Organ Injuries and/or Failures

Cardiac output and left ventricular surface shortening fraction were measured at baseline and after 120 min of reperfusion by echocardiography with a 7-MHz linear transducer (Vivid 7, GE Medical Systems, Milwaukee, WI).

Blood levels of neuron-specific enolase (NSE), a marker of neuronal damage was determined at the end of the protocol by using an ELISA test (Glory Science, Del Rio, TX) (21). Pupillary reactivity to light, a rough functional estimate of cerebral damage after CA, was defined as present when pupils constricted more than 1 mm (21).

Troponin Ic, creatinine, alanine aminotransferase concentrations, and arterial blood gases were measured at an off-site reference laboratory after 120 min of reperfusion to assess heart, kidney, liver, and lung damages, respectively. Lung dysfunction was also assessed by measuring edema. To this end, lungs were weighted and dried in an oven at a constant temperature of 80°C over 48 h and the wet-to-dry ratio was calculated (16). The ratio of the partial pressure of oxygen in arterial blood to the FiO₂, a widely used index of oxygen exchange, was calculated and expressed in millimeters of mercury.

Systemic Response to I/R

After 120 min of reperfusion, plasma levels of nitrate/nitrite, an indicator of nitric oxide synthesis, were determined by enzymatic reduction of nitrate and by the colorimetric Griess reaction, as previously described (16). Plasma levels of tumor necrosis factor (TNF)-α, a proinflammatory cytokine, were determined by using an ELISA test (R&D Systems). Lactate dehydrogenase (LDH) and arterial lactate concentrations were also determined at an off-site laboratory.

Mitochondrial Assays

Mitochondria from the left ventricle anterior wall of the heart, the left side of the cerebral cortex, the whole kidney, the liver, and the lungs were isolated by differential centrifugation (3, 9, 17). The cold isolation buffer contained either 70 mM sucrose, 210 mM mannitol, 1 mM EGTA in Tris-HCl, pH 7.4 for heart, brain, and lung, or 250 mM sucrose, 10 mM Tris, 0.5 mM EGTA, pH 7.4 for kidney and liver. Isolated mitochondria were resuspended in the same buffers devoid of calcium chelating agents and kept on ice before experiments.

As previously described, calcium retention capacity (CRC) was determined using spectrofluorimetry (9, 17). Briefly, CaCl₂ pulses were added every minute to a medium containing mitochondria until mPTP opening. CRC was used as an indicator of the susceptibility of mPTP opening in the presence of Ca²⁺ and was expressed as nanomoles of CaCl₂ per milligram of protein. Oxygen consumption was also determined as previously described (9, 17). State 3 (ADP-stimulated), state 4 (ADP-limited), and respiratory control index (RCI; state 3/state 4) were determined by oxygraphy (Oroboros Oxygraph, Pass, Austria). Electron donors to complex I (glutamate 5 mM and malate 5 mM) were used for both CRC and mitochondrial respiration assays.

Statistical Analysis

Data are expressed as means ± SE or number (%). Comparisons among categorical variables were performed using two-sided Fisher’s exact test. Comparisons among continuous variables were performed by use of one-way ANOVA. The Tukey’s test or the Kruskal-Wallis test were used for pairwise post hoc comparisons, as appropriate. The comparisons between time-based measurements within each group were performed with two-way ANOVA with repeated measures on one factor. Statistical significance was defined as a value of P < 0.05.

RESULTS

Seventy rabbits were used in this study. One animal was excluded before randomization because of a lung perforation. Results from the remaining 69 rabbits are presented (sham: n = 18; Ctrl: n = 24; CsA: n = 18; NIM811: n = 15).

CA, Resuscitation, and Outcomes

The duration of asphyxia before CA ranged from 5 to 7 min and did not differ among groups (Table 1). In the CsA and NIM811-treated groups, there was a trend toward a shorter cardiac massage, smaller amounts of epinephrine required to restore circulation, and higher rates of ROSC (Table 1). When pooling data of CsA and NIM811 groups, the survival was significantly improved in animals treated with mPTP inhibitors compared with Ctrl: 30/33 (91%) vs. 16/24 (67%) (P < 0.05).

The Post-CA Syndrome

Cardiovascular dysfunction. Hemodynamics and echocardiographic parameters were not significantly different among groups at baseline (Table 2). MAP was significantly impaired throughout reperfusion in all CA groups (P < 0.05 vs. baseline). At 120 min of reperfusion, cardiovascular function was...
significantly improved in the CsA and NIM811-treated groups ($P < 0.05$ vs. Ctrl).

Neurological damage. Among the 24 Ctrl rabbits included in the study, only 7 (29%) were alive with a pupillary reflex at the end of the protocol (Fig. 1A). This group also exhibited a significant increase in NSE, averaging $5.6 \pm 0.4$ vs. $2.7 \pm 0.3$ ng/ml in the sham group (Fig. 1B). Both CsA and NIM811 significantly prevented pupillary areflexia after CA and reduced NSE release ($P < 0.05$ vs. Ctrl) (Fig. 1).

Organ injuries and/or failures. As shown in Fig. 2, the Ctrl group displayed a significant increase in troponin, alanine aminotransferase, and creatinine at the end of the protocol compared with the sham group ($P < 0.05$). As expected, CsA and NIM811 prevented the increase in all three markers ($P < 0.05$ vs. Ctrl). In contrast, partial pressure of oxygen in arterial blood-to-$Fi_O_2$ ratio was comparable among groups (Fig. 2). Also, the wet-to-dry ratio of lung tissue did not significantly differ among groups (data not shown).

Pathophysiological Features

Markers of the systemic response to global I/R. At baseline, arterial blood gases were comparable among groups (data not shown). Thirty minutes after ROSC, there was a comparable severe acidosis in all groups (mean pH < 7.10 in all groups) ($P = $nonsignificant). At the end of the 120 min of reperfusion phase, the mean arterial blood pH remained very low in the Ctrl group (7.10 ± 0.03), whereas it was significantly improved in CsA (7.25 ± 0.04) and NIM811-treated (7.27 ± 0.03) groups ($P < 0.05$ vs. Ctrl). Similarly, CsA and NIM811 prevented LDH release, and the increase of both lactate and TNF-α (Fig. 3). By contrast, increase in nitrite/nitrate plasma levels was not mitigated by CsA and NIM811 (Fig. 3D).

Mitochondrial functions. After CA, ADP-stimulated respiration (state 3) was significantly impaired in mitochondria isolated from all organs except lung ($P < 0.05$ vs. sham) (Table 3). Heart and brain mitochondria prepared from Ctrl exhibited also a significant decrease in RCI ($P < 0.05$ vs. sham). In these two organs, both CsA and NIM811 restored oxidative phosphorylation ($P =$ nonsignificant vs. sham) compared with untreated animals (Table 3). Alteration of mitochondrial functions appeared less severe in liver and kidney than in heart and brain, as depicted by a lower decrease in state 3 and RCI.

In mitochondria isolated from organs with I/R injury, i.e., brain, heart, kidney, and liver (Figs. 1 and 2), the amount of $Ca^{2+}$ required to open the mPTP (i.e., the CRC) was significantly decreased after resuscitated CA (Fig. 4). The CRC was not modified in mitochondria isolated from the lungs. As expected, CRC was significantly enhanced by in vitro addition of CsA (1 μM in all groups and organs ($P < 0.01$; data not shown). In vivo treatment with CsA and NIM811 also restored the CRC in the injured tissues (Fig. 4).

DISCUSSION

In the present study, we demonstrated for the first time that post-CA syndrome is associated with mitochondrial dysfunction.

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Values are means ± SE; n, no. of animals. Ctrl, controls; CsA, cyclosporine A; NIM811, N-methyl-4-isoleucine-cyclosporine; ROSC, restoration of spontaneous circulation.

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<th>Table 2. Hemodynamics</th>
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Values are means ± SE; HR, heart rate; MAP, mean arterial pressure; ETCO₂, end-tidal CO₂; SSF, left ventricular surface shortening fraction; CO, cardiac output. $^*$P < 0.05 vs. baseline. $^+$P < 0.05 vs. sham. $^-$P < 0.05 vs. Ctrl.
tion in each distant major organ. Administration of mPTP inhibitors at resuscitation prevented mitochondrial dysfunction in all vital organs and attenuated the post-CA syndrome.

**Post-CA Syndrome and Dysfunction of Mitochondria**

Post-CA syndrome is the main cause of death after resuscitated CA (22). This postresuscitation disease includes brain injury, myocardial dysfunction, and a systemic I/R response to the global I/R insult, including a multiple organ failure (MOF) in the conditions of an inflammatory response and oxidative stress (22, 28). This pattern is comparable to that observed in septic shock (1, 22). Although the pathophysiology is poorly understood, both experimental and clinical evidence suggest that mitochondrial dysfunctions are central to the process that leads to MOF (8, 16). It has previously been shown that resuscitated CA induces severe mitochondrial damage, including permeability transition, oxidative phosphorylation impairments, and the release of pro-apoptotic agents, such as cytochrome c (4, 9, 15, 27, 31). Our laboratory previously showed that mPTP inhibition with CsA, used at the time of reflow, prevents dysfunction of cardiac mitochondria and attenuates the post-CA syndrome versus the local (organ-specific) reaction to I/R injury. We showed here that targeting mPTP opening had a favorable "clinical" impact, and that the markers of the local, but also of the global response, were modified. Although both CsA and NIM811 inhibit mPTP opening through modulation of the matrix cyclophilin D binding to core components of the pore, in both newborn piglet and rat models (12, 15). In the present work, by studying mitochondria isolated from brain, kidney, liver, and lung, we extended this demonstration to all injured organs.

We questioned whether mitochondrial dysfunction in each distant organ (brain, kidney, liver, and lung) might explain MOF and whether local inhibition of mPTP opening might contribute to attenuate the post-CA syndrome. In other words, an important pathophysiological question is the respective role of the adverse systemic response to the global cardio-circulatory arrest vs. the local (organ-specific) reaction to I/R injury. We showed here that targeting mPTP opening had a favorable "clinical" impact, and that the markers of the local, but also of the global response, were modified. Although both CsA and NIM811 inhibit mPTP opening through modulation of the matrix cyclophilin D binding to core components of the pore,
Recently, our group demonstrated that inhibition of cyclophilin D to a global mitochondria-driven bioenergetic breakdown. Re-alternative explanation to the adverse systemic response relates as the mitochondrial inner membrane integrity, was signifi-Meanwhile, we showed that oxidative phosphorylation, as well and the normal myocardial contraction-relaxation cycle (23).
dial depressant, presumably disrupting calcium homeostasis /H9251 served hemodynamic failure since TNF- injury following I/R. This effect may partly explain the ob- it might simply be secondary to the attenuation of distant organ /H9251 our model (16). Niemann et al. (23) recently reported that CsA and NIM811 failed to decrease nitric oxide synthesis in-contrast, as previously observed in experimental septic shock, CsA and NIM811 failed to decrease nitric oxide synthesis in our model (16). Niemann et al. (23) recently reported that direct pharmacological TNF-α blockade improves hemodynamics and survival following CA. How mPTP inhibitors might limit the circulating levels of TNF-α is unclear, although it might simply be secondary to the attenuation of distant organ injury following I/R. This effect may partly explain the ob-served hemodynamic failure since TNF-α is a known myocar-dial depressant, presumably disrupting calcium homeostasis and the normal myocardial contraction-relaxation cycle (23). Meanwhile, we showed that oxidative phosphorylation, as well as the mitochondrial inner membrane integrity, was signifi-cantly more preserved with CsA and NIM811 treatment. An alternative explanation to the adverse systemic response relates to a global mitochondria-driven bioenergetic breakdown. Re-cently, our group demonstrated that inhibition of cyclophilin D attenuates the calcium transfer from endoplasmic reticulum to the mitochondria upon I/R, hence limiting calcium overload of mitochondria on reperfusion (24). Because calcium is a major driver of the tricarboxylic acid cycle and energy production by mitochondria, one may speculate that, beyond inhibition of mPTP opening, CsA and NIM811 might help to improve the bioenergy status, thereby contributing to limit post-CA MOF.

Specific Organ Damage and Functional Failure

Limiting brain damage remains a challenge for improving the outcome of CA (5, 21, 22, 28). Mitochondria also play a key role in neuronal death processes after I/R, notably through the opening of the mPTP (15, 17, 30). Our data suggest that CsA analogs (i.e., CsA and NIM811), when administered at the time of resuscitation, protect against neurological dysfunction after CA. Indeed, mPTP inhibitors significantly prevent pupillary areflexia, a major clinical sign as it consistently predicts unfavorable neurological outcome (21). Pharmacological mPTP inhibition was also associated with a lesser NSE elevation, a rough marker of neuronal lysis that is routinely used in clinical practice to predict neurological outcome after CA (21). In the present study, brain oxidative phosphorylation was also significantly impaired after CA. Our results are in agreement with a recent report by Gong et al. (13) that showed quite similar abnormalities of oxidative phosphorylation in mitochondria isolated from pig brain 24 h after CA. In our work, both CsA and NIM811 prevented a decrease in ADP-stimulated respira-tion and RCI (i.e., a measure of mitochondrial coupling be-tween oxygen consumption and phosphorylation). As a de-crease in RCI generally indicates a misuse of oxygen that is known to produce oxidative stress, it might have favored mPTP opening and subsequent cell damages (13, 25). In agreement with non-CA studies, we also found that mPTP opening susceptibility was increased in brain after whole body I/R (6, 17, 30). This pattern was herein prevented by CsA and NIM811 administered at reflow. It has previously been shown that pharmacological mPTP inhibition could decrease brain infarct size in ischemic stroke models, provided that the drugs penetrate into the brain (6, 17, 30). Indeed, a major limiting factor in producing the therapeutic effect of CsA is its ability to cross the brain blood barrier (BBB) (30). It is well established that CA can lead to the disruption of the BBB (19). The fact that mPTP opening was inhibited in brain mitochondria after in vivo administration of CsA in our study strongly suggests that this is the case. Moreover, we used a single bolus of CsA, leading to high blood concentration, within the first minutes of reflow, which may have overpassed drug efflux mechanisms of the BBB.

The poor prognosis of CA is also driven by the failure of other organs (21, 22, 28). Functional impairments of peripheral vital organs, such as kidney, liver, or lung, are expected after CA, including in humans (1, 7, 21, 22, 28, 33). For example, ~40% of patients resuscitated from out-of-hospital CA de-velop renal dysfunction, while liver function test abnormalities have been observed in up to 25% of CA victims (7, 33). Although very frequent in clinical practice, there is only limited experimental data indicating that CA causes acute lung injury (7, 35). In the present work, we demonstrated, for the first time, the potent nephro- and hepatoprotective effect of pharmacological mPTP inhibition after CA. These findings are...
in accordance with studies reporting that low doses of CsA derivatives attenuate both renal and hepatic injury after transient focal ischemia (18, 31). By contrast, there was no evidence of significant CA-induced respiratory failure in our model, and CsA had no effect on both gas exchange or lung edema. Several hypotheses can be put forward to explain this absence of acute lung injury. First, rabbits were ventilated with positive pressure ventilation, a condition known to limit hydrostatic pulmonary edema. Second, the animals were tracheotomized, which prevented the risk of aspiration pneumonia (which is probably the main cause of acute lung injury in humans). Interestingly, the mitochondria from the lungs did not exhibit any alteration in susceptibility to mPTP opening, even after in vivo CsA administration, in contrast to those from damaged organs (i.e., heart, brain, kidney, and liver). This suggests that mitochondrial response to CA differs among organs, and that beneficial effects of CsA are limited solely to the organs injured by CA. Whether mPTP inhibitors prevent non-organ-specific cell damage (e.g., endothelial cells) in our model remains to be determined. We cannot rule out that the ubiquitous cytoprotection afforded by CsA derivatives we observed was, at least in part, related to a better preservation of endothelial function. In any case, our study opens up the possibility of translating basic research findings into effective intervention able to prevent CA-induced MOF in humans.

In summary, this study strongly suggests that the post-CA syndrome may be due to a ubiquitous mitochondrial dysfunction in each vital organ, and that CsA derivatives, administered at the time of resuscitation, may attenuate cell injury and MOF. Pharmacological modulation of mitochondrial dysfunction may be a new therapeutic approach to CA-induced MOF. Clinical trials are now required to determine whether these experimental results could be translated into humans.

GRANTS
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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

REFERENCES


