■ LABORATORY INVESTIGATIONS

Intercellular Adhesion Molecule-1 Inhibition Attenuates Neurologic and Hepatic Damage after Resuscitation in Mice

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Background: Cardiac arrest and cardiopulmonary resuscitation may result in multiorgan damage after global hypoxia due to neutrophil recruitment. Patients display all signs of a systemic inflammatory response syndrome. Reducing neutrophil recruitment may thus preserve organ function.

Methods: Mice were subjected to cardiac arrest and resuscitation. CD18/CD11b expression on circulating neutrophils was assessed by flow cytometry. Intercellular adhesion molecule-1 expression was analyzed by Western blot and immunofluorescence. Neutrophil recruitment was quantified by immunohistochemistry. Neurologic function was assessed by a balance test. For liver and kidney function, plasma alanine aminotransferase activity and creatinine concentrations were determined. To reduce neutrophil recruitment, mice received 100 μg anti–intercellular adhesion molecule-1 antibody intraperitoneally.

Results: Resuscitation led to severe hypoxia, acidosis, and hypercarbia. Adhesion molecule expression and neutrophil recruitment were increased in the liver, kidney, and brain. Neurologic performance was impaired 24 h after cardiac arrest. Creatinine and alanine aminotransferase concentrations were significantly increased. Immunoneutralization of intercellular adhesion molecule-1 attenuated neutrophil influx in the liver along with alanine aminotransferase activity, whereas creatinine concentrations and neutrophil influx in the kidney remained unchanged. Neurologic function was improved in the treatment group.

Conclusions: Global hypoxia induces activation of the endothelium in the brain, liver, and kidney. The resulting damage to the brain and liver are due to infiltration of neutrophils, whereas kidney damage is not, because reduction of neutrophil recruitment after cardiopulmonary resuscitation improves recovery of neurologic and hepatic but not renal function. Inhibition of intercellular adhesion molecule-1 after global hypoxia may be beneficial in patients experiencing cardiac arrest and resuscitation.

□ Additional material related to this article can be found on the ANESTHESIOLOGY Web site. Go to http://www.anesthesiology. org, click on Enhancements Index, and then scroll down to find the appropriate article and link. Supplementary material can also be accessed on the Web by clicking on the "ArticlePlus" link either in the Table of Contents or at the top of the Abstract or HTML version of the article.

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ANNUALLY, approximately 750,000 Americans require cardiopulmonary resuscitation (CPR) after cardiac arrest.[1] Thirty percent of these patients reach the hospital, whereas only 14% are eventually discharged.[1] A large proportion of deaths are associated with the "postresuscitation" syndrome, characterized by multiorgan damage due to global hypoxia and ensuing reperfusion injury.[1] During and after CPR, activation of the plasmatic coagulation system, platelets, leukocytes, and endothelial cells occurs.[2–4] The activation of platelets is in part due to the direct hypoxic injury and thought to be related to formation of thromboxane A and the surface expression of adhesion molecules.[4] Soluble E-selectin and P-selectin concentrations are increased.[3,5,6] Recently, the syndrome occurring after cardiac arrest in humans was recognized to resemble a systemic inflammatory response syndrome.[7] Polymorphonuclear neutrophils (PMNs) play a pivotal role in tissue damage after ischemia–reperfusion.[7–10] Blocking or modulating recruitment of PMNs to ischemic tissue is an attractive strategy for therapeutic interventions. Intercellular adhesion molecule-1 (ICAM-1), presented by activated endothelial cells, is the major ligand for the leukocyte integrins MAC-1 (CD18/CD11b) and LFA-1 (CD18/CD11a) and is required for transendothelial migration of PMNs and monocytes.[11] Inhibition of ICAM-1–MAC-1 or ICAM-1–LFA-1 interactions with immunoneutralizing therapy in experimental animal studies has been shown to be efficacious in ameliorating myocardial ischemia–reperfusion injury by reducing PMN recruitment to damaged and necrotic heart tissue.[8,9,12–15] We hypothesized that a reduction of PMN-related inflammation due to CPR could preserve organ function. Therefore, we used a murine model of cardiac arrest and resuscitation to elucidate the therapeutic potential of inhibiting the interactions of ICAM-1 with its ligands during the post-CPR syndrome. Some of the results of these studies have been previously reported in the form of an abstract.

Materials and Methods

Animal Preparation

With approval of the institutional review board (Tierschutzkommission Münster, Münster, Germany), male swiss mice (mean body weight, 39 ± 5 g) were anesthetized using an intravenous injection of 100 μl propofol, 1%. After intubation of the trachea, the lungs were mechanically ventilated at a rate of 100 breaths/min and a stroke volume of 200 μl using a mouse ventilator (HSE-Harvard MiniVent Ventilator; Hugo Sachs Elektronik, March-Hugstetten, Germany). Anesthesia was maintained with 2% isoflurane in 100% oxygen. Saline-filled femoral artery and femoral vein catheters were inserted for continuous blood pressure monitoring and drug administration. Electrocardiographic and mean arterial pressure recordings were performed (PowerLab® System; ADInstruments, Spechbach, Germany).

Experimental Protocol

Cardiocirculatory arrest, verified on electrocardiogram by ventricular fibrillation and by a sudden decrease of blood pressure below 15 mmHg, was induced electrically using alternating current (10 V, 50 Hz) *via* an esophageal electrode with a presternally placed subcutaneous electrode, adapted from the model described by Böttiger *et al.*[16] To avoid spontaneous defibrillation, which is common in mice, the fibrillation current was maintained at 10 V for the first 120 s and then reduced to 2 V for another 120 s to minimize electrical trauma. This phase of cardiac arrest lasted 5 min. CPR procedures including mechanical ventilation (100% oxygen), closed chest cardiac massage, intravenous administration of epinephrine, and external defibrillation (1 J) if spontaneous defibrillation did not occur were initiated. Successful resuscitation was defined as the return of spontaneous circulation (ROSC) that was assumed with return of a regular electrocardiogram with a mean arterial pressure greater than 40 mmHg. If CPR lasted more than 5 min without ROSC, measures were stopped, and CPR was considered unsuccessful. Duration of successful CPR until ROSC was 24 s minimally and 214 s maximally, with a median of 47 s. There were no differences in duration of cardiac arrest or CPR or rate of ROSC between groups. After ROSC, isoflurane anesthesia was resumed, catheters were removed, animals were weaned from mechanical ventilation, and the trachea was extubated. Ventilation time and mode were not different in the sham group. Mice received 1 ml Ringer's solution subcutaneously after extubation. Sham-operated animals to control for surgical trauma received the same procedure except cardiac arrest and mechanical and pharmacologic resuscitation. Blood gas was drawn in a subgroup *via* the arterial line (ABL 500; Radiometer Copenhagen, Copenhagen, Denmark). Renal and hepatic cell death were determined over time as creatinine

and activity of alanine aminotransferase as described in the manufacturers instructions (Sigma, Taufkirchen, Germany). The blood was drawn in subgroups on different time points (baseline: before surgery; day 1: 24 h after surgery; day 2: 48 h after surgery; day 3: 72 h after surgery) from the retrobulbar plexus, and total blood was drawn through the inferior vena cava when mice were killed. On the previously set day of death, mice were reanesthetized, exsanguinated, and perfused with saline from the apex of the left ventricle until no blood return from a right atriotomy was observable before organs were harvested for histology and Western blot analysis.

Flow Cytometric Analysis of PMN Activation

Heparin-anticoagulated whole blood was processed as described previously.[17] Briefly, cells in whole blood were first double stained with phycoerythrin-conjugated monoclonal anti-GR1 antibody and fluorescein-coupled monoclonal anti-CD11b antibody (Pharmingen, Heidelberg, Germany) at saturating concentrations for 30 min at room temperature, then fixed, and erythrocytes were lysed. Blood samples were preincubated with monoclonal anti-FcγRII/III antibody (5 μg/ml; Pharmingen, Heidelberg, Germany) for 5 min at room temperature. Five thousand PMNs were analyzed using a flow cytometer (FACScan; Becton Dickinson, Heidelberg, Germany). Specific binding of monoclonal antibodies was calculated by subtracting nonspecific binding as determined with fluorochrome-labeled rat isotype–specific rat immunoglobulin G (IgG). Data are presented as the mean of linear fluorescence intensity.

Sensorimotor Testing

To assess the effect of CPR on neurologic performance, we used a modified balance test. Mice had to balance three times for 30 s on 3-, 2-, and 1-cm bars. This test allows for assessment of global sensorimotor performance. Rodents strive to hold themselves on a bar to avoid falling. Healthy animals easily pass this test to 100% on 1-cm round bars. Animals were subjected to the test once on the day before surgery (baseline) and every 24 h thereafter until death.

Immunohistochemistry

Quantification of PMN recruitment to the brain, liver, and kidney after CPR was performed on paraffin sections of embedded organs stained with anti-PMN monoclonal antibodies, clone MCA771G (Serotec, Oxford, England), and quantified using morphometry software (analysis; SIS, Münster, Germany). Three serial sections per mouse were used to quantify PMNs per high power field 24 and 48 h after surgery. Additional information regarding this

is available on the ANESTHESIOLOGY Web site at http://www. anesthesiology.org.‡‡

Western Blot

Tissue extracts were subjected to polyacrylamide gel electrophoresis, transferred to membranes, and probed with goat anti–ICAM-1 IgG (Santa Cruz Biotechnology, Heidelberg, Germany) and secondary peroxidase-labeled antibody. Blots were developed with Super Signal West Pico chemiluminescent substrate (Pierce Biotechnology, Rockford, IL). Additional information regarding this is available on the ANESTHESIOLOGY Web site at http://www. anesthesiology.org.

Antibody Treatment

Animals received intraperitoneal injections of 100 μg control IgG or 100 μg anti–ICAM-1 antibodies, clone E2 (BD Biosciences, San Jose, CA), diluted in phosphate-buffered saline by a blinded investigator.

Statistical Analysis

Data were analyzed with a commercial statistics software package (InStat; Graphpad, San Diego, CA), using Kruskal–Wallis testing with consecutive Mann–Whitney U testing to identify differences between individual groups. Comparison between group performance in sensomotor tests was conducted using the chi-square test. A P value less than 0.05 was considered significant.

Results

Blood Gas Analysis

Ventricular fibrillation caused hypoxemia (partial oxygen tension [Po_2]: 628 $\pm$ 20 vs. 33 $\pm$ 9 mmHg, before vs. after ventricular fibrillation, n = 8/7; $P < 0.05$) and acidemia (pH: 7.43 $\pm$ 0.02 vs. 6.81 $\pm$ 0.03, before vs. after ventricular fibrillation, n = 8/7; $P < 0.05$), with lactate concentrations increased up to 10 mM (table 1). Five minutes of cardiac arrest caused a mortality of 42%. In total, 89 mice were used. Twenty-nine animals received antibodies or vehicle upon ROSC, of which 16 survived to day 2 and entered analysis. Mice with ROSC still exhibited mild acidemia (pH: 7.32 $\pm$ 0.25, n = 4) but were no longer hypoxemic (Po_2: 115 $\pm$ 52 mmHg, n = 4) or hypotensive (mean arterial pressure: 58 $\pm$ 10 mmHg, n = 11).

Cardiac Arrest Activates Circulating PMNs

Flow cytometry revealed an increase in circulating PMN MAC-1 expression in CPR mice compared with

‡‡ The on-line materials contain details about immunohistochemical and Western blot methodology as well as colour micrographs documenting changes in intercellular adhesion molecule-1 expression and neutrophil recruitment in response to cardiopulmonary resuscitation compared to sham animals.

Table 1. Blood Gas Analysis of CPR Mice before Surgery, at Cardiac Arrest, and after Restoration of Spontaneous Circulation

	Baseline ($F_{IO_2} = 1$)	Cardiac Arrest	ROSC ($F_{IO_2} = 1$)
Po_2, mmHg	628 $\pm$ 20 (n=8)	33 $\pm$ 9 (n=7)	115 $\pm$ 52 (n=4)
Pco_2, mmHg	27 $\pm$ 2 (n=8)	110 $\pm$ 8 (n=7)	50 $\pm$ 23 (n=4)
pH	7.43 $\pm$ 0.02 (n=8)	6.81 $\pm$ 0.03 (n=7)	7.32 $\pm$ 0.25 (n=4)

Mice experience hypoxemia, hypercapnia, and acidemia during cardiac arrest. After restoration of spontaneous circulation (ROSC), blood gases significantly improve toward baseline values.

CPR = cardiopulmonary resuscitation; F_{IO_2} = fraction of inspired oxygen; Pco_2 = partial carbon dioxide tension; Po_2 = partial oxygen tension.

sham mice (21 $\pm$ 7 vs. 32 $\pm$ 8 [mean fluorescence], n = 5; $P < 0.05$), indicating an activation of circulating PMN by global ischemia and reperfusion.

Cardiac Arrest Leads to Activation of the Endothelium

Enhanced presentation of ICAM-1 due to CPR was confirmed by Western blots. Extracts of kidney, brain, and liver demonstrated an induction of ICAM-1 24 h after CPR (fig. 1). Immunofluorescent staining with antibodies directed against ICAM-1 demonstrated that CPR led to increased expression of ICAM-1 on endothelial cells of the brain, liver, and kidney, indicating activation of the endothelium. Additional information regarding this is available on the ANESTHESIOLOGY Web site at http://www. anesthesiology.org.

### Global Hypoxia Induces PMN Recruitment to the Brain, Kidney, and Liver

Forty-eight hours after CPR, recruitment of PMNs to the liver and kidney was significantly increased compared with that of sham mice. Additional information regarding this is available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org. Density of PMNs in livers of CPR mice were almost 18-fold increased (5 $\pm$ 1 vs. 88 $\pm$ 23 PMNs/mm^2, n = 7; $P < 0.05$) compared with that of sham mice (fig. 2A). In kidneys, after 48 h, recruitment of PMNs is 1.7-fold (23 $\pm$ 7 vs. 39 $\pm$ 22
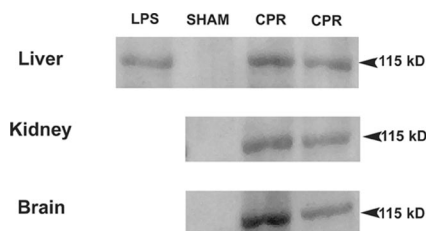
Fig. 1. Cardiac arrest and cardiopulmonary resuscitation (CPR) in mice induces expression of intercellular adhesion molecule-1 (ICAM-1) on endothelial cells. Liver total protein from endotoxin-treated mice (LPS) served as positive control (*lane 1*). Compared with sham-operated animals (*lane 2*), Western blot analysis revealed a strong increase in ICAM-1 expression in extracts of liver, kidney, and brain of CPR mice (*lanes 3* and *4*). The molecular weight of mouse ICAM-1 varies from 90 to 115 kd. Here, the anti-ICAM antibody detected a 110-kd protein.

**a.** liver- 48h

b. kidney - 48h

c. brain - 24h
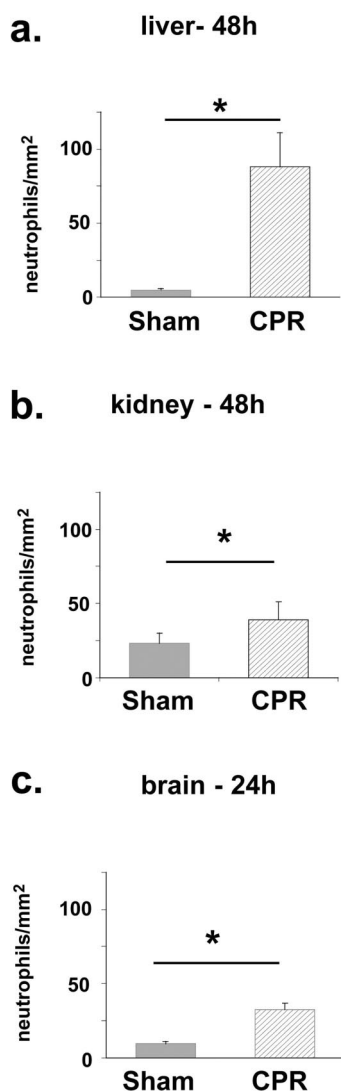
Fig. 2. Global hypoxemia due to cardiopulmonary resuscitation (CPR) induces neutrophil recruitment to liver, kidney, and brain. In CPR mice, density of neutrophils increased almost 18-fold in the liver after 48 h (*A*), 1.7-fold in the kidneys after 48 h (*B*), and 4-fold in the brain after 24 h (*C*) compared with sham mice.

PMNs/mm², n = 9; $P = 0.05$) increased in CPR animals compared with sham animals (fig. 2B). At this time, we observed only very sparse PMN infiltration in the brain. After 24 h, we were able to demonstrate a significantly increased but still sparse infiltration of the brain by PMNs in mice subjected to CPR compared with sham animals (9.4 ± 1.7 *vs.* 32.3 ± 4.4 PMNs/mm², sham *vs.* CPR, n = 5; $P < 0.05$) (fig. 2C).

Neurologic, Hepatic, and Renal Damage after CPR
Compared with baseline, CPR mice displayed increased plasma alanine aminotransferase concentrations at 48 h after ROSC (17 ± 2 *vs.* 140 ± 64 U/l, baseline *vs.* 48 h after CPR, n = 7; $P < 0.01$), whereas sham mice showed no increase (17 ± 1 *vs.* 17 ± 2 U/l, baseline *vs.* 48 h, n = 7). Plasma creatinine doubled after 48 h (0.2

a

b

c
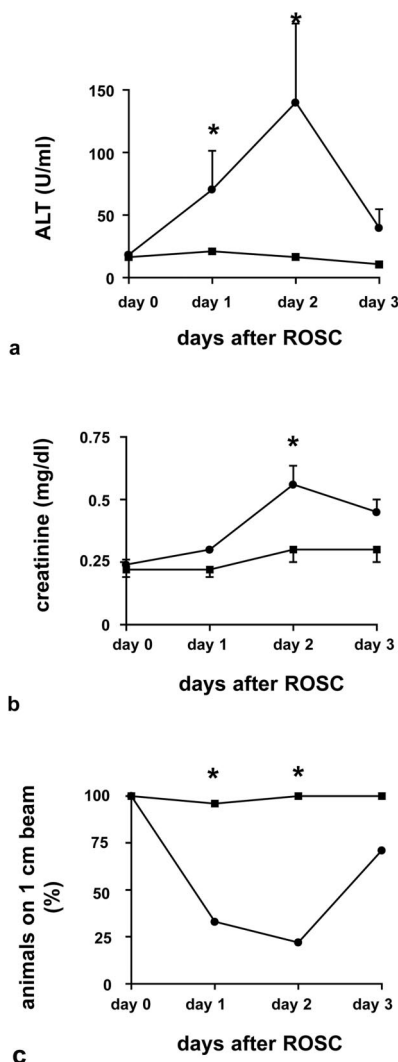
Fig. 3. Cardiopulmonary resuscitation (CPR) causes neurologic, hepatic, and renal damage. (*A*) Plasma alanine aminotransferase (ALT) and (*B*) plasma creatinine concentrations of CPR mice increase compared with pre-CPR values until 48 h after return of spontaneous circulation (ROSC), whereas sham mice displayed no increase. Seventy-two hours after CPR, the values of renal and hepatic damage returned toward baseline. (*C*) Neurologic performance was analyzed by having the mice balance on bars of decreasing width. Shown are the data for a 1-cm rectangular stick, thickness 1 cm. All sham animals (*rectangles*) passed the test, whereas only 28% of the CPR mice passed the test after 24 h, and 24% passed after 48 h. Three days after surgery, neurologic function started to recover in CPR animals (*circles*). * $P < 0.05$ *vs.* sham; n > 5 for each point.

± 0.03 *vs.* 0.5 ± 0.08, baseline *vs.* 48 h after CPR, n = 7/4; $P < 0.01$), whereas the sham group remained stable (0.2 ± 0.1 *vs.* 0.3 ± 0.05, baseline *vs.* 48 h after CPR, n = 7) (figs. 3A and B). Therefore, the increased serum creatinine and alanine aminotransferase concentrations indicate renal and hepatic cellular damage due to global ischemia. In addition, CPR animals revealed a marked neurologic deficit compared with sham mice. The day before and 1, 2, and 3 days after surgery, mice were subjected to sensorimotor testing by assessing their ability to balance on beams of different widths. Performance

Fig. 4. Immunoneutralization of intercellular adhesion molecule-1 (ICAM-1) with anti–ICAM-1 antibodies (aICAM) in cardiopulmonary resuscitated (CPR) mice reduces neutrophil (PMN) infiltration and renal and hepatic damage. (*A*) Compared with control antibody treatment (immunoglobulin G [IgG]), ICAM-1 inhibition reduced PMNs in the liver of CPR mice. (*B*) This translated into decreased alanine aminotransferase (ALT) concentrations. (*C*) Despite a slight reduction in PMN densities in the kidney, (*D*) plasma creatinine was unchanged by blocking ICAM-1.
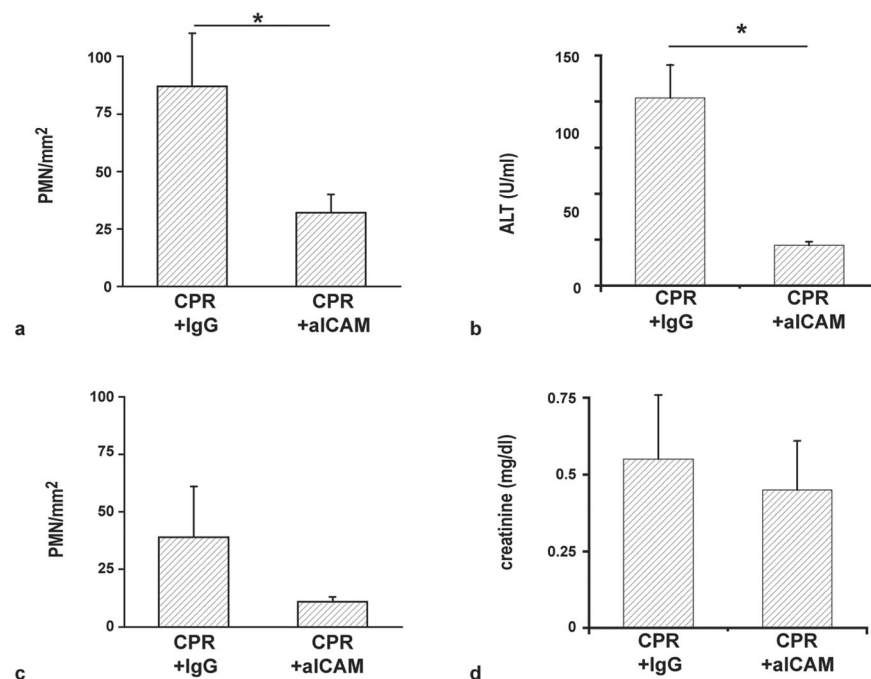
of CPR mice was significantly impaired after 1 and 2 days in comparison with sham animals. (fig. 3C). Three days after surgery, neurologic function recovered in CPR animals.

### Inhibition of ICAM-1 Ameliorates Outcome after CPR

Forty-eight hours after ROSC, functional blockade of ICAM-1 with monoclonal antibodies immediately after ROSC had significantly reduced PMN recruitment to the liver (32 ± 8 *vs.* 87 ± 23 PMNs/mm^2, anti–ICAM-1 antibodies *vs.* IgG, n = 7/7; $P < 0.05$) (fig. 4A), not quite reaching sham levels (compare fig. 2A). Alanine aminotransferase concentrations were also significantly decreased (26 ± 2 *vs.* 126 ± 21 U/l, anti–ICAM-1 antibodies *vs.* IgG, n = 5/7; $P < 0.05$) (fig. 4B), and PMN recruitment to the kidney showed a nonsignificant trend for a reduction (11 ± 2 *vs.* 39 ± 22 PMNs/mm^2, anti–ICAM-1 antibodies *vs.* IgG, n = 5/9; $P > 0.05$) (fig. 4C; compare fig. 2 for sham levels). Consequently, plasma creatinine did not change (0.45 ± 0.1 *vs.* 0.55 ± 0.21 mg/dl, anti–ICAM-1 antibodies *vs.* IgG, n = 6/11; P = not significant) (fig. 4D). Neurologic function was significantly improved 2 days after ROSC with ICAM inhibition compared with control IgG treatment (fig. 5). Nearly 80% of mice treated with blocking ICAM-1 antibodies were able to pass the balance test on a 1-cm beam, indicating a recovery of neurologic performance due to ICAM blocking.

Discussion

Survivors of cardiac arrest face a grave prognosis. Only little more than 10% of them ultimately survive to hos-

pital discharge.[1] A large proportion of the associated mortality is not directly related to the cause for cardiac arrest but derives from multiorgan failure secondary to global hypoxia.[1] Although reperfusion after global ischemia is essential for tissue repair, it may induce further injury. Activation of complement and PMN along with microcirculatory reperfusion disorders has been demonstrated to occur in resuscitated patients.[2-6] It was recently postulated that in humans, systemic inflammatory response syndrome occurs after resuscitation and is related to the poor outcome of patients experiencing cardiac arrest.[7]

The salient findings of our study are that mice mount a generalized inflammatory reaction after a 5-min period of cardiac arrest with global hypoxia. Hypoxia induces activation of endothelial cells and of circulating leukocytes as evidenced by induction of adhesion molecule expres-
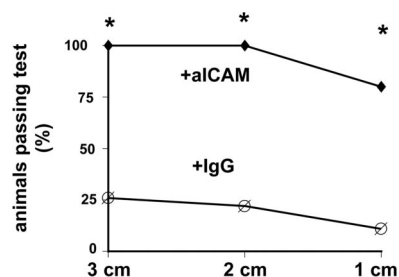
Fig. 5. Intercellular adhesion molecule-1 (ICAM-1) neutralization (aICAM) improves neurologic function after cardiopulmonary resuscitation. Mice that received ICAM-1–neutralizing antibodies displayed only mild neurologic deficits. Nearly 80% of cardiopulmonary resuscitated mice treated with blocking ICAM-1 antibodies were able to pass the balance test on a 1-cm beam, whereas only approximately 25% of the control immunoglobulin G (IgG)–treated animals balanced on any bar, indicating a significant improvement of neurologic performance due to ICAM blocking.

sion. Reperfusion injury aggravated neurologic dysfunction and liver but not kidney damage, because inhibition of PMN recruitment by ICAM-1–blocking antibodies prevented damage to the former but not to the latter.

We adapted a murine model of cardiac arrest and resuscitation that leads to apoptosis of neurons in the hippocampal CA1 region.[16,18] Neurologic dysfunction after resuscitation from cardiac arrest is one of the most important determinants of cardiac arrest mortality and morbidity. We were able to demonstrate that mice subjected to global hypoxia for 5 min exhibit a neurologic deficit detectable by a relatively simple battery of balancing tests compared with sham-operated mice. Failure in this test correlates with neurologic pathology seen in patients after CPR and resuscitation.[16,19–21] We also detected apoptotic cells in the brain (data not shown), although we deem the functional endpoint of sensorimotor testing more useful for our purposes. As in a clinical setting, the neurologic deficit occurred early after global hypoxia, but neurologic function returned to sham level at day 3 after ROSC, indicating a relatively mild hypoxic injury.

In addition to previously published findings,[16] we observed damage to the hepatic and renal systems. As in the brain, the extent of organ damage was mild but clearly detectable by routine parameters for renal and hepatic cell damage and function. Because of the small blood volume, it was not possible to assess a multitude of parameters to more closely characterize the extent of functional limitations.

Hypoxia has been shown to activate a specific subset of genes through altering the stability of hypoxia-inducible factor 1α, a transcription factor.[22–24] Increases in nuclear hypoxia-inducible factor 1α concentrations lead to the expression of proinflammatory proteins, among others ICAM-1, as we demonstrate in the endothelial cells of brain, liver, and kidney 24 h after the hypoxic injury.

MAC-1 expression on the surface of circulating PMNs was concomitantly increased, reflecting observations by others and ourselves that pathophysiologic conditions that cause activation of endothelial cells likewise induce activation of circulating blood cells such as PMNs, monocytes, and platelets.[25]

To establish whether a reduction of PMN recruitment would reduce organ damage, we used monoclonal blocking antibodies raised against murine ICAM-1. Blocking ICAM-1 is a strong and specific intervention that would allow testing of whether PMN-dependent inflammation contributes to organ damage after CPR.

Interestingly, renal damage was associated with increased PMN recruitment but was not dependent on it, because the reduction of PMN in the kidney did not significantly decrease creatinine. Cell death occurs in the proximal tubule in response to short ischemic injuries, but to induce PMN-dependent renal damage, much

longer periods of ischemia are needed in regional ischemia models.[26–28] It is therefore conceivable that although a trend for decreased creatinine concentrations was observed, renal failure was not dependent on inflammation in this particular setting.

On the contrary was the increase in alanine aminotransferase activity as a measure of impaired hepatocyte integrity after global hypoxia completely prevented by ICAM-1 blockade. This effect coincides with the repression of PMN recruitment to the liver 48 h after ROSC. ICAM-1 blockade has previously been shown to ameliorate reperfusion injury after regional ischemia in humans and in animal models.[13,25,29–31] We therefore postulate that hepatic damage and dysfunction after global hypoxia is dependent on PMN recruitment to the liver, because it is preventable if PMN recruitment is reduced or modulated.

Damage to the central nervous system that has a very low tolerance for hypoxia was also significantly reduced by ICAM-1 inhibition. The reduction did not quite reach sham neurologic function but accounted for approximately 80% of the neurologic deficit. This is in contrast to the very small numbers of PMN recruited to the brain 24 h after CPR. One may have predicted a more profound contribution of cerebral hypoxia to the damage rather than a major contribution of reperfusion to cerebral injury. However, apparently, inflammation in the brain occurs earlier than in the liver or the kidney and does play an important role for the severity of a neurologic deficit. Because organ dysfunction in all organs studied was mild and returned to baseline within 72 h, we can not predict how neurologic deficits that result from longer and more profound hypoxia would be influenced by inhibition of leukocyte recruitment. These findings are in accord with the data of Conolly *et al.*,[32] who demonstrated a marked up-regulation of ICAM-1 in the brain 22 h after induction of regional ischemia by clamping of the middle cerebral artery. In patients, ICAM-1 expression in the brain as well as circulating adhesion molecules correlates negatively with outcome after CPR, linking neurologic deficits after CPR to an inflammatory response in the brain.[3]

In conclusion, this study confirms that induction of cardiac arrest in mice is feasible and leads to a generalized cellular inflammatory reaction. Inhibition of ICAM-1 reduces PMN recruitment and organ damage in the liver and the brain. We propose that investigation of anti-PMN strategies may lead to novel therapeutic options for patients experiencing cardiac arrest.

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