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Stroke 2002;33:837-843

DOI: 10.1161/hs0302.104198

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ISSN: 1524-4628

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Dependence of Early Cerebral Reperfusion and Long-Term Outcome on Resuscitation Efficiency After Cardiac Arrest in Rats

Yan Xu, PhD; Serguei Liachenko, MD, PhD; Pei Tang, PhD

Background and Purpose—While it is well known that longer duration of cardiac arrest (CA) is often associated with poorer long-term outcome, the influence of resuscitation efficacy on postischemia recovery is less clear. The objective of the present study is to investigate whether an inadequate and prolonged resuscitation after a shorter CA can lead to worse long-term outcomes than an effective resuscitation after a longer CA, provided that the total time from the onset of CA to the return of spontaneous circulation is comparable.

Methods—Thirty-eight rats were randomized into 2 groups with nominal 9 minutes (group 1) and 15 minutes (group 2) of normothermic asphyxial CA. Each group was further divided into 2 subgroups on the basis of the duration of resuscitation efforts (labeled as S and L for short and long, respectively). Thus, the asphyxia and nominal resuscitation times were 8 and 1 minute, respectively, for group 1S, 5 and 4 minutes for group 1L, 14 and 1 minute for group 2S, and 11 and 4 minutes for group 2L. Cerebral perfusion was measured continuously at the dorsal hippocampus level before, during, and after the CA, with the use of the arterial spin labeling MRI technique. The survival time, histological damage, and neurological deficit were evaluated 5 days after resuscitation.

Results—Groups 1S and 1L had nearly the same duration of CA (9.02 ± 0.17 minutes, $n=6$ versus 8.58 ± 0.80 minutes, $n=6$). The same is true for groups 2S and 2L (15.51 ± 0.59 minutes, $n=11$ versus 15.65 ± 1.25 minutes, $n=15$). Despite longer asphyxia, shorter and more effective resuscitation was associated with significantly improved long-term outcomes and higher cerebral perfusion at the early stage of reperfusion.

Conclusions—Effective resuscitation increased early reperfusion and improved survival after CA. The clinical implication is that inadequate and prolonged resuscitation may have detrimental effects on the recovery of CA patients. (*Stroke*. 2002;33:837-843.)

Key Words: cerebral blood flow ■ heart arrest ■ ischemia, global ■ magnetic resonance imaging ■ reperfusion injury ■ rats

Despite constant improvement of cardiopulmonary resuscitation (CPR) guidelines,¹ the CPR success rate judged by long-term outcome has remained at the same low level for the past decade. The chance of survival after cardiac arrest (CA) declines by 7% to 10% for every minute of no-flow status.² For CA >12 minutes, only 2% to 5% of patients can achieve long-term survival.^{1,3-5} Good neurological outcomes are even less frequent.³ The main problem is not related to the CPR guidelines but to a delayed, suboptimal application of CPR.^{6,7} It is believed that CPR after 6 minutes of CA must generate a cerebral perfusion pressure >35 mm Hg to significantly restore cerebral energy metabolism and improve cerebral perfusion.⁷ Blood flow promotion during CPR can improve functional recovery after prolonged CA.⁸

Because the pathophysiology of early reperfusion during and immediately after the resuscitation and the influence of early

reperfusion on posts ischemic recovery remain poorly understood, we have set forth in this study to determine whether an inadequate and prolonged resuscitation after shorter duration of CA can lead to poorer long-term outcome than an effective resuscitation after longer duration of CA, provided that the total time from the onset of CA to the return of spontaneous circulation (ROSC) is similar. By comparing cerebral perfusion soon after resuscitation using the noninvasive MRI technique with arterial spin labeling, we hope to establish the correlation between early cerebral reperfusion and long-term outcome, as measured by survival time, neurological deficit scores (NDS), and histological damage scores (HDS).

Materials and Methods

Animal Preparation

Thirty-eight male Sprague-Dawley rats (weight, 199 ± 22 g; Charles River Laboratories, Inc, and Harlan Sprague-Dawley, Inc) were used

Received August 14, 2001; final revision received December 5, 2001; accepted December 6, 2001.

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TABLE 1. Parameters of CA and Resuscitation

Group	Subgroup	n	Apnea, min	Time to CA, s	Resuscitation, min	Arrest Time, min	Epinephrine, $\mu\text{g}/\text{kg}$
1	S	6	8	21 \pm 8	1.38 \pm 0.23*	9.02 \pm 0.17	85 \pm 13*
1	L	6	5	22 \pm 3	3.96 \pm 0.78*	8.58 \pm 0.80	116 \pm 15*
2	S	11	14	24 \pm 5	1.92 \pm 0.59†	15.51 \pm 0.59	52 \pm 13†
2	L	15	11	20 \pm 2	4.86 \pm 1.20†	15.65 \pm 1.25	84 \pm 14†

*†Significant difference between subgroups ($P<0.05$).

in this study. Animals were prepared according to an approved protocol, as described previously.^{9,10} Briefly, under 1.5% isoflurane general anesthesia, both femoral arteries and one of the femoral veins were cannulated. The arterial blood pressure and heart rate (HR) were monitored continuously. Rats were placed snugly in a birdcage probe,¹¹ with rectal temperature maintained at 36.2 \pm 0.3°C with a feedback-controlled air-heating blanket.

Rats were anesthetized (isoflurane 1%), paralyzed (pancuronium 2 mg/kg per hour), and mechanically ventilated with controlled physiological blood gases, which were analyzed frequently with a Ciba-Corning 278 Blood Gas Analyzer (Bayer, Inc) throughout the MRI experiments, as described previously.^{9,10}

CA and Resuscitation

As detailed previously,¹⁰ CA was induced by apnea and a rapid intravenous injection of esmolol (6.5 mg per rat). Rats were randomized into 2 experimental groups with nominal 9 (group 1) and 15 (group 2) minutes of CA. Each group consisted of 2 subgroups with distinctly different resuscitation times, designated as short (S, nominally 1 minute) and long (L, nominally 4 minutes) resuscitation (Table 1). The apnea time and the resuscitation time for subgroups 1S, 1L, 2S, and 2L were 8 and 1 minute, 5 and 4 minutes, 14 and 1 minute, and 11 and 4 minutes, respectively.

Resuscitation began with restoration of ventilation and infusion into the femoral artery of donor arterial blood mixed with epinephrine (8 $\mu\text{g}/\text{mL}$), sodium bicarbonate (0.05 mEq/mL), and heparin (5 U/mL).^{9,10} Heating of the animals was discontinued during CA and reinstated on resuscitation. The fundamental difference that resulted in short and long resuscitation was the effectiveness of the resuscitation efforts controlled by the intensity of retrograde intra-arterial infusion. Short resuscitation for subgroups 1S and 2S (Table 1) was achieved by maintaining mean arterial blood pressure (MABP) >20 mm Hg during a manual blood infusion, whereas long resuscitation for subgroups 1L and 2L was performed by constant infusion at a rate of 0.4 to 0.8 mL/min with the use of an automatic infusion pump (KD Scientific, Inc). The latter can only generate a system MABP of approximately 10 mm Hg. Blood infusion was stopped at the first sign of mechanical cardiac activity, which was followed shortly by ROSC. The rats were then continually ventilated, with anesthesia reinstated in steps between 20 and 90 minutes after ROSC from 0.25% to 1% isoflurane. At least 2.5 hours after resuscitation, rats were removed from the MRI magnet and detached from all catheters and the ventilator, as described previously.^{9,10}

Outcome Evaluation

Animals were closely observed for 5 days after resuscitation. The NDS was evaluated by the same investigator using the criteria proposed by Neumar and coworkers.¹² In this system, a score of 500 is considered neurologically normal, whereas a score of 0 is considered brain dead. After the final NDS evaluation on the fifth day after CA, rats were anesthetized with isoflurane and their brains were perfused with buffered 10% formalin.⁹ After decapitation, the heads were stored in the same fixative for at least 1 day. The brains were then removed from the skull, and 6- μm coronal slices at the level of dorsal hippocampus were prepared for hematoxylin-eosin staining. Histological damage was evaluated blindly by counting the total and the ischemia-injured neurons in the CA1 region of the hippocampus on digital microphotographs with the use of Adobe

Photoshop software (Adobe, Inc). HDS values were assigned as follows by a semiquantitative scale ranging from 0 to 5 according to the percentage of injured neurons in CA1 region: 0, <5%; 1, 5% to 20%; 2, 20% to 40%; 3, 40% to 60%; 4, 60% to 80%; and 5, >80%.

MRI Perfusion Measurement

The MRI experiments were performed with a Varian/Chemagnetics CMXW-400SLI imager, equipped with a 9.4-T, 111-mm vertical bore magnet. Noninvasive measurements of cerebral blood flow (CBF) before, during, and after CA were made with the use of the arterial spin labeling technique^{10,13} with imaging acquisition parameters of echo time=14 ms, repetition time=1 second, number of acquisition =2, slice thickness=3 mm, matrix size=128 \times 64, and field of view=44 \times 44 mm². The perfusion imaging plane was set at the dorsal hippocampus level, corresponding to brain level 30 to 32 in the Swanson rat brain atlas.¹⁴ The arterial spin tagging planes were \pm 14 mm away from the imaging plane for control and tagged images. To avoid overheating of the rat brain by the long radiofrequency tagging pulses during the no-flow period, the power of tagging pulses was purposely lowered. The degree of spin inversion (the α value) at the reduced tagging power was 0.48 \pm 0.01 (mean \pm SD). Perfusion images were calculated pixel by pixel as described before.¹⁰ The temporal resolution for perfusion images was 2.5 minutes per image.

Data Analysis

Perfusions in all visually identifiable regions of the brain (cortex, hippocampus, thalamus, hypothalamus, and amygdala) were averaged to reflect perfusion differences due to the two resuscitation procedures. Pixel values in a given region of perfusion maps were normalized against the averaged perfusion in that region in the same animal before CA. For regional average, an anatomic mask was generated for each individual rat from the rat brain atlas.¹⁴ The masks were digitally scaled to fit spin-echo images (128 \times 128 resolution) of individual brains according to their positions and sizes.¹⁰ Statistical analysis was performed with the use of the SPSS program (SPSS Inc). Independent samples *t* test was used to compare between-group means of various parameters. To compare dose of epinephrine received by the rats among groups, one-way ANOVA was used with Bonferroni post hoc multiple comparisons. If the assumption of normal distribution was violated (eg, HDS and NDS variable), nonparametric Mann-Whitney *U* test and Kruskal-Wallis test were used instead of *t* test and one-way ANOVA. Repeated-measures ANOVA was used to determine between-group differences of perfusion and blood pressure over time. Mean survival time of animals was analyzed by the Kaplan-Meier method and log rank test, with censored values set at 120 hours for surviving rats. The relation between the number of surviving rats and the method of resuscitation was tested with 2-tailed Fisher's exact test. Correlation analysis of CBF, Pco_2 , and mean survival time was performed with the use of the Pearson correlation coefficient. All data are reported as mean \pm SD except for nonparametric NDS, HDS, weight loss, and mean survival time, which are mean \pm SEM.

Results

All animals were successfully resuscitated. The times for CA onset, apnea, resuscitation effort, and total CA are listed in

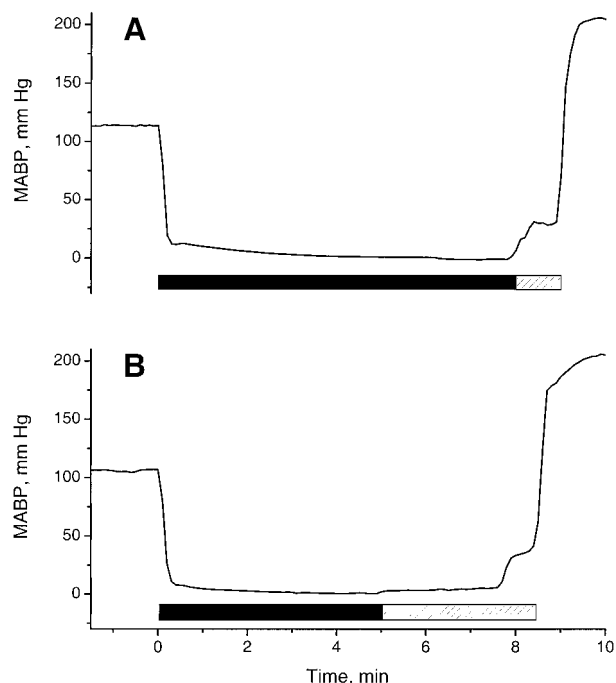


Figure 1. Representative tracings of MABP of 2 rats from group 1 (nominal 9 minutes of CA) with short (A) and long (B) resuscitation procedures. Black and cross-hatched horizontal bars indicate apnea and resuscitation periods, respectively. Note the great similarity between MABP recordings in these animals.

Table 1. For the same resuscitation procedure, the duration of resuscitation depended slightly on the no-flow time: ROSC was achieved in 1.38 ± 0.23 and 1.92 ± 0.59 minutes ($t=2.134$, $P=0.050$) in groups 1S and 2S, respectively, and in 3.96 ± 0.78 and 4.86 ± 1.20 minutes ($t=2.037$, $P=0.060$) in groups 1L and 2L, respectively. Systemic cardiac response during CA and resuscitation was comparable within each group, as exemplified in Figure 1. The duration of CA was not significantly different between subgroups of group 1 ($t=1.458$, $P=0.199$) and group 2 ($t=0.351$, $P=0.729$). The arterial PCO_2 level was controlled tightly to 40.1 ± 3.4 mm Hg ($n=38$) before CA by individually adjusting the ventilation. After ROSC, ventilation was given with the same parameters as before CA. Because arterial CO_2 is a powerful regulator of CBF under normal physiological conditions, we studied the influence of different resuscitation protocols on the arterial PCO_2 immediately after ROSC in a series of bench-top experiments, which are otherwise identical to those in groups 1S and 1L. Figure 2 shows the comparison of PCO_2 level from these experiments for short ($n=4$) and long ($n=3$) resuscitation. No significant differences in PCO_2 were detected between groups. The PCO_2 values were stabilized at the prearrest level approximately 10 minutes after ROSC. In the regular (in-magnet) experiments, the postresuscitation arterial PCO_2 was measured at 30, 60, and 120 minutes after ROSC and was at the level of 34.8 ± 8.0 mm Hg, with no significant differences between groups and over time. The epinephrine dose received by animals depended on the resuscitation procedure ($F=29.238$, $P<0.001$ by one-way ANOVA); subgroups with short resuscitation received significantly less epinephrine than subgroups with long resuscitation ($P<0.01$). In sub-

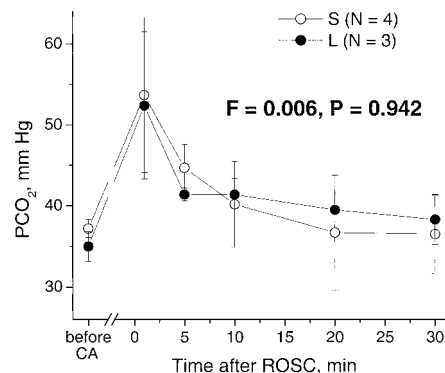


Figure 2. Detailed changes in arterial PCO_2 immediately after ROSC in rats with nominal 9 minutes of CA from bench-top experiments parallel to group 1. The F statistic was calculated by repeated-measures ANOVA to determine the significance of difference between groups. Data are mean \pm SD.

groups of the same resuscitation procedures, animals with longer CA received more epinephrine ($P<0.001$ for both groups). Figure 3 compares the MABP and HR between subgroups of different resuscitation procedures. In group 1, animals with short resuscitation showed more rapid recovery of HR. In group 2, no significant differences in MABP and HR between subgroups were detected.

Postarrest CBF strongly depended on the resuscitation procedures, especially in group 1. Figure 4 shows representative sets of perfusion maps from 2 rats in group 1 with different resuscitation procedures. The rat with short resuscitation (Figure 4A) exhibited significant hyperemia shortly after ROSC. The hyperemic phase was less apparent in the rat with long resuscitation (Figure 4B). The time dependence of the region-averaged CBF in cortex, hippocampus, thalamus, hypothalamus, and amygdala is shown in Figure 5 for all 4 subgroups. Significantly higher reperfusion immediately after ROSC is found in all brain regions of animals with short resuscitation. This is more profound in group 1. It is also noteworthy that the initial levels of reperfusion in the cortex follow the duration of CA and respiratory arrest time in the order of groups $2S>2L>1S>1L$. At approximately 40 minutes after ROSC, when MABP and HR were approaching the prearrest levels (Figure 3), all animals showed severe decline in CBF, which is marked as the development of protracted hypoperfusion. Note that during hypoperfusion subgroup 1S showed better perfusion recovery in the thalamus and hypothalamus regions than subgroup 1L (Figure 5). There were no significant differences between subgroups 2S and 2L in most brain regions during hypoperfusion. To confirm the late recovery of CBF, rats that were alive on the fifth day after CA were returned to the magnet for CBF measurements. All surviving rats showed normal levels of CBF.

The long-term survival was significantly different between subgroups of different resuscitation procedures (Table 2). All animals with short resuscitation survived for the entire observation period of 5 days. Animals with long resuscitation, however, showed significantly worse survival in both groups. Only 1 rat in group 1L (17%, compared with 100% in group 1S; $P=0.015$) and 3 rats in group 2L (20%, compared with 74% in group 2S; $P=0.019$ by Fisher's exact test) were

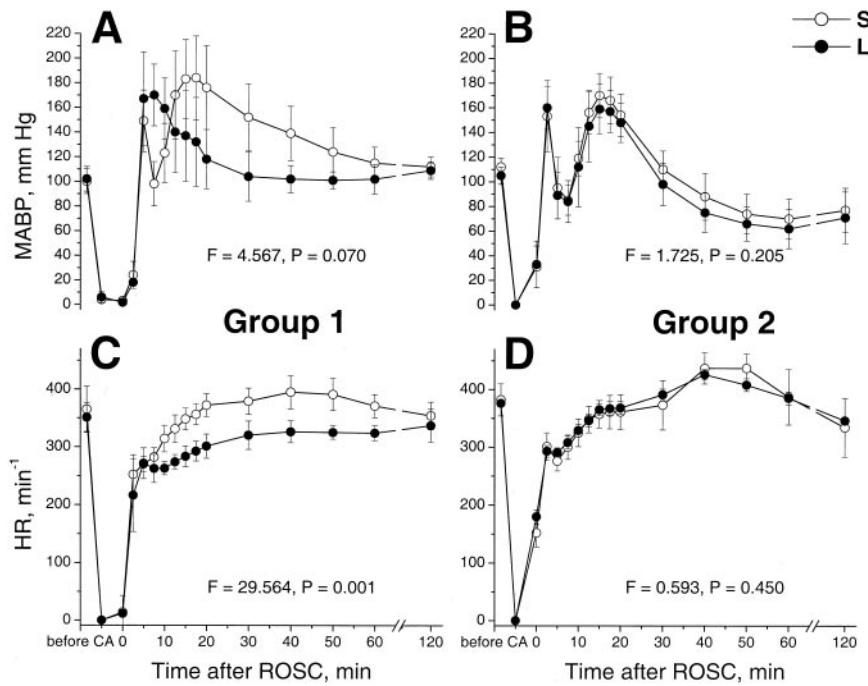


Figure 3. Dynamics of MABP and HR in response to nominal 9 minutes (group 1) and 15 minutes (group 2) of CA with short and long resuscitation procedures. F statistic by ANOVA and exact probability (P) are indicated for the time period between 7 and 50 minutes after ROSC.

alive 5 days after CA. With exclusion of the dead rats, all surviving animals had almost normal neurological appearance at the end of observation (NDS=468±10), with no significant difference between groups. Rats that became morbid and had to be killed before the end of observation according to the animal care and use protocol had an average NDS of 315±27, which is significantly different from the NDS of the surviving animals ($P<0.001$).

To determine the cerebral reperfusion on long-term outcome, the total CBF during the hyperemia stage (the first 25 minutes in group 1 and the first 15 minutes in group 2) was integrated and correlated to the mean survival time in different groups and subgroups. A strong positive correlation was found between the survival time and the brain-integrated early reperfusion in group 1 ($R=0.88$, $P<0.001$). In group 2, this correlation was not as strong but was statistically significant ($R=0.41$, $P=0.038$). No significant correlation was found between postresuscitation arterial PCO_2 level and CBF ($R=0.153$, $P=0.367$), which is consistent with the finding

that the reactivity of cerebral vessels to both hypocapnia and hypercapnia is noticeably decreased or even eliminated after global ischemia.¹⁵

Despite the significant difference in the survival time between subgroups S and L, the resuscitation time had no significant effect on histology damage scores. As shown in Table 2, all rats, except for the only surviving rat in subgroup 1L, showed similar values of HDS. No significant differences were found ($\chi^2=4.981$, $P=0.173$ by Kruskal-Wallis test).

Discussion

The clinical significance of resuscitation time, which is a strong indicator of resuscitation efficacy, has not been fully investigated. In the Brain Resuscitation Clinical Trial I,¹⁶ a subset of 131 patients suffering from 0 to 35 minutes (with a mean of 5.6 minutes) of CA showed significantly different recovery depending on the CPR time. CPR <15 minutes resulted in 42% recovery, whereas CPR >15 minutes had only 19% recovery. Similarly, among 257 patients with CA

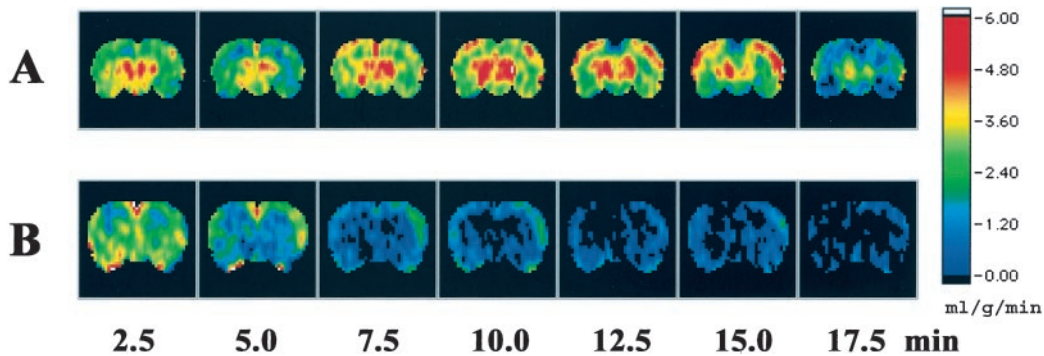


Figure 4. Perfusion maps of 2 rats with nominal 9 minutes of CA (group 1) with short (A) and long (B) resuscitation. Displayed images were acquired immediately after ROSC with temporal resolution of 2.5 minutes. Prominent early reperfusion was detected in cortical and thalamic regions of rats with short but not long resuscitation. The perfusion maps are color coded (expressed as milliliter per gram per minute) according to the color scale shown on right.

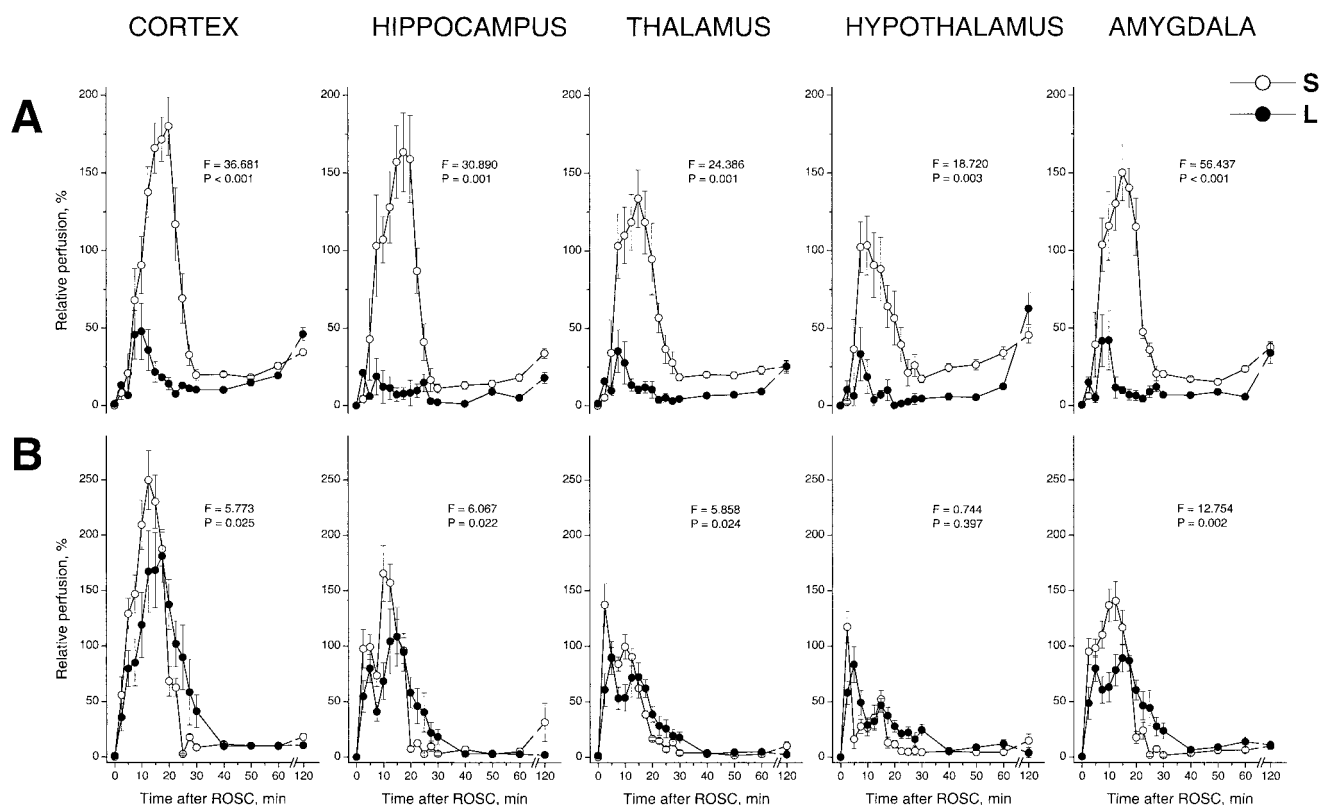


Figure 5. Relative changes of averaged perfusion in different brain structures after ROSC. A and B show rats in groups 1 and 2 with nominal 9 and 15 minutes of CA, respectively. The F statistic was calculated by repeated-measures ANOVA to determine the significance of differences between subgroups S and L during the first 25 and 15 minutes of reperfusion for groups 1 and 2, respectively. Data are mean±SEM.

of 1 to 23 minutes (mean=4.6 minutes) in the Brain Resuscitation Clinical Trial II,¹⁷ 31% of those resuscitated in <20 minutes achieved good cerebral recovery compared with only 14% when CPR was >20 minutes. However, because the no-flow time and resuscitation time varied widely in these clinical trials, the dependence of long-term outcomes on resuscitation efficacy could not be quantified.

In the present study we combined the use of a highly reproducible outcome model of CA in rats with noninvasive MRI measurements of CBF to investigate the effects of resuscitation on postarrest cerebral reperfusion and long-term recovery. With the no-flow and resuscitation times precisely controlled, we clearly demonstrate that an effective resuscitation, even after a longer no-flow time, can lead to better

recovery. In contrast, inadequate resuscitation, even after shorter arrest, can be detrimental to postresuscitation survival. A comparison of the results from subgroups 1S and 1L or from 2S and 2L indicates that when the total CA time is kept constant (9 or 15 minutes in group 1 or 2, respectively), a longer no-flow time does not necessarily result in worse outcome. The effects of resuscitation efficacy become even more apparent when the results from subgroups 1L (5 minutes of no-flow status plus 4 minutes of resuscitation) and 2S (14 minutes of no-flow status plus 1 minute of resuscitation) are compared. The apnea time and the absolute no-flow time in subgroup 2S are more than twice as long as those of subgroup 1L, yet the long-term survival is significantly better in subgroup 2S because of more effective resuscitation, as

TABLE 2. Long-Term Outcome After CA and Resuscitation

Group	Subgroup	Survival, %	Survival Time,* h	NDS†	HDS	Weight Loss, g
1	S	100‡	>120‡	500±0	4.4±0.6	21±10
1	L	17‡	24±18‡	500	2	3
2	S	73§	94±12§	421±19	3.7±0.4	30±9
2	L	20§	54±12§	470±21	4.3±0.3	25±10

Values are mean±SEM.

*Survival time was calculated by Kaplan-Meier survival analysis with censored values (survived animals) set to 120 hours.

†NDS of rats that did not survive for 5 days after CA were excluded.

‡§Significant difference between subgroups (P<0.05).

||Only 1 rat in this subgroup was alive 5 days after CA.

shown by the CBF images of the initial cerebral hyperperfusion. Because prolonging the no-flow time in humans is often associated with increasing difficulties in resuscitation by means of conventional CPR, a legitimate question is whether it is the long duration of no-flow time per se or the difficulty and thus the longer duration of resuscitation after a prolonged no-flow time that determines the long-term outcome of CA patients. Currently, the generally accepted upper limit for good outcomes after out-of-hospital CA and resuscitation is 5 minutes. Is this the limit of no-flow time or the limit for conventional CPR to produce sufficient cerebral perfusion pressure? Our results seem to imply that within a rather flexible time window of no-flow status, resuscitation efficiency is the determinant of long-term survival. If this is true, then the clinical implication will be that a suboptimal application of CPR may have detrimental effects on CA patients, even when the no-flow time is short. The benefit of waiting for more effective resuscitation may outweigh the risk of premature and suboptimal administration of CPR by untrained bystanders.

The potential for the brain tissue to recover after prolonged global ischemia is higher than previously realized. In animals with normothermic global ischemia, it has been shown that good neurological recovery occurs even after a complete interruption of CBF lasting up to 1 hour.¹⁸ It is also known that rat brain tissue can preserve its electrophysiological activity after >1 hour of CA.¹⁹ The pathophysiological consequences of no-flow and low-flow states, as well as the distinction between the two, deserve further investigation. Although the duration of the no-flow time is undoubtedly an important factor, resuscitation efficacy is probably equally or even more important in predicting long-term outcome. During resuscitation, especially by out-of-hospital CPR, a period of low-flow or trickle-flow reperfusion is created. It is well known that trickle blood flow during incomplete ischemia can be more damaging than complete absence of blood flow.²⁰ The low-flow states after a prolonged CA have been shown to aggravate early cerebral microcirculatory reperfusion disorders such as the no-reflow phenomenon.²¹

Promotion of initial postresuscitation reperfusion can improve long-term outcome.²² Standard CPR with low perfusion pressure before ROSC has been shown to produce no-reflow regions in rats, whereas immediate ROSC with higher blood pressure can substantially decrease no-reflow status.²¹ Pharmacological treatment of decreased postarrest CBF with vasodilators, such as endothelin receptor antagonists, also showed some beneficial effect on long-term recovery.^{23,24}

The correlation between brain-integrated reperfusion after ROSC and long-term survival suggests that the extent of the postresuscitative hyperemia immediately after ROSC might be important. High-pressure flush of the brain after CA may help to decrease the extent of initial no-reflow state caused by increased blood viscosity and perivascular edema.^{25–27} Blood flow promotion therapy has been used successfully to improve cerebral resuscitation after CA.^{3,8,28,29} The prevailing method of blood flow promotion during resuscitation remains the use of epinephrine because of its ability to increase coronary perfusion pressure and cardiac output.^{1,12,30} We used

a constant concentration of epinephrine in the resuscitation mixture (8 µg/mL). Because the use of resuscitation mixture was stopped at the time of ROSC, the animals in the short and long resuscitation groups received different epinephrine doses. It should be noted that the amount of epinephrine (and resuscitation mixture) received by the animals in the long resuscitation groups (1L and 2L) was significantly more than that received by the rats in the short resuscitation groups (Table 1). Interestingly, a higher dose of epinephrine in groups 1L and 2L did not lead to higher systemic blood pressure (Figure 3) and did not improve recovery after CA. The experiments with high doses of epinephrine during resuscitation in an asphyxial CA model also showed no beneficial effect on long-term outcome.^{12,30}

In conclusion, using noninvasive CBF MRI, we demonstrated that sufficient early reperfusion immediately after ROSC and before the development of protracted hypoperfusion is associated with significantly better survival after CA. Effective and proficient resuscitation ensures early reperfusion even after a prolonged no-flow period. Although the causal relation of neuronal cell responses to resuscitation protocol requires further investigation, it seems clear that suboptimal administration of resuscitation, even after a short no-flow period, may be detrimental to long-term survival.

Acknowledgments

This study was supported by grants from the National Institute of Neurological Disorders and Stroke (1R01NS36124) and the National Heart, Lung, and Blood Institute (1F32HL09784), National Institutes of Health. We thank Dr Ronald L. Hamilton for stimulating discussions and Martha Zegarra for technical assistance.

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