Hemodynamic effects of nitric oxide synthase inhibition before and after cardiac arrest in infant piglets

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Schleien, Charles L., John W. Kuluž, and Barry Gelman. Hemodynamic effects of nitric oxide synthase inhibition before and after cardiac arrest in infant piglets. Am. J. Physiol. 274 (Heart Circ. Physiol. 43): H1378–H1385, 1998.—Using infant piglets, we studied the effects of nonspecific inhibition of nitric oxide (NO) synthase by Nω-nitro-L-arginine methyl ester (L-NAME; 3 mg/kg) on vascular pressures, regional blood flow, and cerebral metabolism before 8 min of cardiac arrest, during 6 min of cardiopulmonary resuscitation (CPR), and at 10 and 60 min of reperfusion. We tested the hypotheses that nonspecific NO synthase inhibition (1) will attenuate early postreperfusion hyperemia while still allowing for successful resuscitation after cardiac arrest, (2) will allow for normalization of blood flow to the kidneys and intestines after cardiac arrest, and (3) will maintain cerebral metabolism in the face of altered cerebral blood flow after reperfusion. Before cardiac arrest, L-NAME increased vascular pressures and cardiac output and decreased blood flow to brain (by 18%), heart (by 36%), kidney (by 46%), and intestine (by 52%) compared with placebo. During CPR, myocardial flow was maintained in all groups to successfully resuscitate 24 of 28 animals (P value not significant [NS]). Significantly, L-NAME attenuated postresuscitation hyperemia in cerebral, diencephalon, anterior cerebral, and anterior-middle watershed cortical brain regions and to the heart. Likewise, cerebral metabolic rates of glucose (CMRgluc) and of lactate production (CMRLac) were not elevated at 10 min of reperfusion. These cerebral blood flow and metabolic effects were reversed by L-arginine. Flows returned to baseline levels by 60 min of reperfusion. Kidney and intestinal flow, however, remained depressed throughout reperfusion in all three groups. Thus nonspecific inhibition of NO synthase did not adversely affect the rate of resuscitation from cardiac arrest while attenuating cerebral and myocardial hyperemia. Even though CMRgluc and CMRLac early after reperfusion were decreased, they were maintained at baseline levels. This may be clinically advantageous in protecting the brain and heart from the damaging effects of hyperemia, such as blood-brain barrier disruption.

This study is unique in that we are the first to study whole body physiological effects of nonselective NO synthase inhibition in a model of cardiac arrest and CPR, a clinically relevant animal model. Three reasons that NO synthase inhibition should be beneficial in the setting of cardiac arrest, CPR, and reperfusion include increased systemic vascular resistance, attenuation of cerebral hyperemia, and neuronal protection. Selective vasoconstriction of blood vessels supplying nonvital organs is essential during CPR for maintaining adequate blood flow to the brain and heart (27). The use of an NO synthase inhibitor, as with α-adrenergic agonists through their ability to vasoconstrict nonvital organs, should also result in a high rate of resuscitation. Postischemic hyperemia in brain and heart has been demonstrated in various models of ischemia and may, in part, be caused by high levels of NO produced during ischemia and early reperfusion (20). Hyperemia may be detrimental to cells especially in the brain parenchyma, by causing early disruption of the blood-brain barrier (BBB), which may ultimately worsen neurological injury (37). If our first hypothesis is correct, that NO synthase inhibition blocks early hyperemia after cardiac arrest, then we postulate that normal levels of cerebral oxygen and glucose utilization will be maintained. In addition, NO blockade during ischemia may protect neurons against excitotoxic injury. NO has been demonstrated to worsen outcome after focal ischemia (6). Thus the use of an NO synthase inhibitor may preserve vital organ function after an episode of global ischemia through any or all of these mechanisms.

In this study, we tested the hypotheses that nonspecific inhibition of NO synthase activity by Nω-nitro-L-arginine methyl ester (L-NAME) 1 attenuates postischemic hyperemia in the brain and heart and can be reversed with L-arginine, 2) has salutary vascular effects on other organs, kidney, and intestines, allowing for successful resuscitation and normalization of blood flow during reperfusion, and 3) will maintain the cerebral metabolic rate of oxygen (CMRO2) and glucose (CMRgluc) without altering the cerebral metabolic rate of lactate (CMRLac) production in the face of attenuating cerebral blood flow after resuscitation. In fact, we were able to maintain vital organ blood flow during CPR allowing for successful resuscitation with L-NAME while diminishing early postreperfusion hyperemia and maintaining CMRO2 and CMRgluc without increasing CMRLac.

MATERIALS AND METHODS
The Animal Care and Use Committee of the University of Miami School of Medicine approved the protocol for this study.
study. The care and handling of all animals were in accordance with National Institutes of Health guidelines.

General preparation. Infant piglets (2−4 wk old) weighing 3.5−6.0 kg were anesthetized with pentobarbital sodium (40 mg/kg ip) and thereafter with additional doses of 2−3 mg/kg iv as needed during surgical preparation. A tracheostomy was performed followed by ventilation with a volume-controlled ventilator (model 613, Harvard Apparatus, South Natick, MA) to maintain end-tidal Pco2 at 35−40 Torr (4.7−5.3 kPa). Supplemental oxygen using a fractional inspired oxygen of 0.3−0.4 was given to keep arterial Po2 >100 Torr. Saline-filled catheters were inserted in femoral and axillary vessels and the sagittal sinus, as in previous experiments, for blood sampling, fluid and drug administration, blood pressure monitoring, and microsphere injection and sampling (11). A 4-Fr bipolar pacing catheter was inserted into the femoral vein and advanced into the right heart for later induction of ventricular fibrillation. A 6-Fr sheath was inserted into the right external jugular vein, through which a 5.5-Fr balloon-tipped catheter was advanced into the pulmonary artery using pressure waveform analysis until the pulmonary capillary wedge pressure could be obtained with 0.5− to 0.7-ml balloon inflation. A temperature probe was placed in the rectum (YSI model 43 Telethermometer, Yellow Springs, OH). Saline (0.9%; 10 ml/kg iv bolus) was given initially after completion of surgery and then infused at a rate of 10 ml·kg⁻¹·h⁻¹ throughout the experiment to maintain adequate hydration.

Measurements. Aortic, right atrial, pulmonary artery, and sagittal sinus pressures were measured with Statham pressure transducers (model P23XL, Viggo-Spectramed, Oxnard, CA) calibrated before each experiment and zeroed at the level of the right atrium. Pressures were continuously recorded on a strip chart recorder (Gould series RS 3800). Cardiac output measured by thermodilution and pulmonary capillary wedge pressure were measured intermittently at baseline and after resuscitation. Cerebral perfusion pressure was calculated as the difference between mean aortic and sagittal sinus pressures; myocardial perfusion pressure was calculated as the difference between aortic diastolic and right atrial pressures. Rectal and pulmonary arterial blood temperatures were measured continuously and recorded intermittently. Rectal temperature was maintained at 37.5−38.5°C by the use of a heating blanket and overhead warmer; all animals remained normothermic. Rectal and pulmonary arterial blood temperatures were measured continuously and recorded intermittently. Rectal temperature was maintained at 37.5−38.5°C by the use of a heating blanket and overhead warmer; all animals remained normothermic.

Arterial, pulmonary artery, and sagittal sinus blood samples were obtained simultaneously for analysis of pH and blood gases (Radiometer ABL330, Copenhagen, Denmark) and oxygen content (OSM-2 hemoximeter, Radiometer). Glucose and lactate concentrations (arterial and sagittal sinus only) (YSI, model 2300 STAT) were measured from plasma. Blood gases were analyzed at 37°C and were corrected for blood temperature (pH stat).

Radiolabeled microspheres (15 ± 0.5 µm in diameter; New England Nuclear, Wilmington, DE) were injected into the left ventricle for measurement of regional blood flow. Five isotopes were used (141Ce, 114In, 105Ru, 99Tc, and 85Sr), the sequence of which was randomized for each experiment. The preparation and use of microspheres for regional blood flow measurements followed our previously validated protocol (14, 13). The blood withdrawn was replaced with 0.9% saline (1:3) after each microsphere injection. After each experiment, a postmortem examination was performed to confirm the position of vascular catheters. The brain and heart were removed, fixed in 10% buffered Formalin for 24−48 h, and then dissected into 0.5− to 2.5-g sections as described previously (11, 33) for measurement of regional blood flow. Samples of kidney, jejunum, skeletal muscle, facial muscle, and tongue were also obtained and weighed. CMRGluc was calculated as the product of the arterial minus sagittal sinus oxygen content difference and blood flow to the total cerebrum; cerebral glucose uptake (CMRGluc) and lactate efflux (CMRLac) were calculated similarly.

Experimental protocol. On completion of surgery, the animal was placed supine and secured to a U-shaped board designed to fit on the base of a pneumatic chest compressor (Thumper; Michigan Instruments, Grand Rapids, MI). Heparin sulfate (200 U/kg iv) was given just before ventricular fibrillation to avoid intravascular clotting during ischemia and CPR. Pancuronium (0.2 mg/kg) was given at this time to prevent spontaneous respirations during ventricular fibrillation and CPR. After baseline measurements, ventricular fibrillation was induced through the bipolar pacing catheter, and ventilation was stopped as done in previous CPR studies (11). After 8 min of cardiac arrest, CPR was started as performed previously (11). Epinephrine (10 µg/kg iv) was given just before CPR and an infusion of 4 µg·kg⁻¹·min⁻¹ was begun. This type of CPR and these doses of epinephrine have previously been shown to optimize cerebral and myocardial blood flow in pigs (10, 35). After 6 min of CPR, the heart was defibrillated (DC defibrillator, American Optical, Bedford, MA) with 30−40 J. If spontaneous circulation was not reestablished after four defibrillation attempts, the experiment was terminated. After return of spontaneous circulation, the epinephrine infusion rate was halved every 3 min if mean aortic pressure was ≥70 Torr. After 1 h of reperfusion, the animal was killed by ventricular fibrillation.

Blood gas samples, arterial and sagittal sinus glucose and lactate concentrations, and regional organ blood flows were measured at baseline (baseline 1), 15 min after drug or placebo was given (baseline 2), during CPR, and at 10 min (10R) and 60 min of reperfusion (60R).

The animals were randomly assigned to one of three groups after all physiological measurements were made at baseline. Piglets in group 1 (n = 8) received an equal volume of 0.9% saline as placebo; piglets in group 2 (n = 8) and group 3 (n = 8) received 3 mg/kg iv L-NAME over 2 min, prepared as a 3 mg/ml solution (pH 7.4). In group 3, immediately after successful resuscitation, a bolus (90 mg/kg iv) of L-arginine (pH 7.4) was given to piglets over 3 min followed by a continuous infusion of L-arginine (3 mg·kg⁻¹·min⁻¹) to reverse the effects of L-NAME.

Statistical analysis. Data were analyzed with CRUNCH statistical package (CRUNCH Software, Oakland, CA). All values are presented as means ± SE. Comparisons between groups were made using two-way analysis of variance with Bonferroni's post hoc correction. Comparisons within each group were made using repeated-measures analysis of variance with Dunnett's post hoc correction. Statistical significance was set at P ≤ 0.05. A χ²-analysis was used for comparing the rate of successful resuscitation. Because groups 2 and 3 were treated identically up to the point of defibrillation, data before cardiac arrest and during CPR from these groups were combined to increase the sensitivity of our analysis of the effect of L-NAME on measured hemodynamic variables.

RESULTS

Before cardiac arrest, after L-NAME, mean aortic pressure increased from 104 ± 5 to 124 ± 5 mmHg and pulmonary artery pressure increased from 19 ± 3 to 29 ± 3 mmHg, while cardiac index decreased from 198 ± 16 to 136 ± 14 ml·min⁻¹·kg⁻¹ (Table 1). These
vascular changes were accompanied by decreased blood flow to brain by 18% (Fig. 1), to heart by 36% (Fig. 2), to kidney by 46% (Fig. 3), and to jejunum by 52% (Fig. 4). Neither vascular pressures nor regional blood flow changed between the two baseline measurements in group 1.

During CPR, mean aortic pressure (mean 45–50 mmHg) and regional blood flows were not different between groups. Myocardial blood flow of 114 ± 14 ml·min\(^{-1}\)·100 g\(^{-1}\) and myocardial perfusion pressure of 23 ± 2 mmHg for the three groups during CPR were

<table>
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<td>199 ± 12</td>
<td>138 ± 13*†</td>
<td>102 ± 21*</td>
<td>119 ± 19*</td>
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</table>

Values are means ± SE; cardiopulmonary resuscitation (CPR) data that are not shown were not measured. PA, pulmonary arterial; PCW, pulmonary capillary wedge pressure. *P < 0.05 within group compared with baseline 1; †P < 0.05 between groups compared with group 1. See text for descriptions of groups and experimental protocol.

Fig. 1. A: total brain blood flow (ml·min\(^{-1}\)·100 g\(^{-1}\)). B: cerebral perfusion pressure (mmHg) calculated as mean aortic pressure minus sagittal sinus pressure. Filled bars, group 1; crosshatched bars, groups 2 and 3 combined; open bars, group 2; hatched bars, group 3. CPR, cardiopulmonary resuscitation; 10R and 60R, 10 and 60 min of reperfusion, respectively. See Experimental protocol for description of baseline 1 and baseline 2 groups. *P < 0.05 within groups compared with baseline 1.

Fig. 2. A: total heart blood flow (ml·min\(^{-1}\)·100 g\(^{-1}\)). B: myocardial perfusion pressure (mmHg) calculated as aortic diastolic pressure minus right atrial pressure. Filled bars, group 1; crosshatched bars, groups 2 and 3 combined; open bars, group 2; hatched bars, group 3. *P < 0.05 within groups compared with baseline 1; †P < 0.05 between groups compared with group 1.
well above the threshold for successful resuscitation in this model (20 ml·min⁻¹·100 g⁻¹ and 15–20 mmHg, respectively) (34) (Fig. 2). Renal and intestinal blood flow reached near-zero values during CPR, usually seen with maximal vasoconstriction due to epinephrine (33) (Figs. 3 and 4).

The rate of successful resuscitation was not affected by L-NAME: 8 of 9 animals in group 1, 8 of 10 animals in group 2, and 8 of 9 animals in group 3. When groups 2 and 3 were combined, the success of resuscitation was not different from group 1.

After resuscitation (10R), animals in group 2 were less hypertensive than those in groups 1 and 3 (Table 1). Mean pulmonary artery pressure remained elevated in group 2 compared with group 1 after defibrillation and throughout reperfusion. L-Arginine (group 3) partially reversed the elevation of pulmonary artery pressure. One hour after resuscitation cardiac index remained depressed in group 2 (73 ± 6 vs. 121 ± 13 and 129 ± 30 ml·kg⁻¹·min⁻¹ in groups 1 and 3, respectively). Myocardial blood flow also remained depressed at 57% of baseline in group 2 (baseline, 284 ± 41 ml·100 g⁻¹·min⁻¹; 10R, 162 ± 23 ml·100 g⁻¹·min⁻¹). Myocardial hyperemia at 10R, which occurred in group 1 (174% of baseline) and in group 3 (189% of baseline), was associated with higher myocardial perfusion pressure (Fig. 2).

Likewise, early cerebral hyperemia occurred at 10R with cerebral blood flow reaching 301 ± 81, 185 ± 36, and 269 ± 63% of baseline, respectively, in groups 1–3.

When the supratentorium was analyzed separately, no significant differences were detected between groups at 10R; however, the hyperemia was significantly reduced in the anterior-middle watershed and anterior cerebral cortexes and diencephalon in group 2 compared with groups 1 and 3. Likewise, in group 2, hyperemia at 10R was almost totally attenuated in the entire infratentorium (139 ± 19% compared with baseline vs. 298 ± 122 and 242 ± 61% compared with baseline in groups 1 and 3, respectively), with a significant reduction of flow to the cerebellum in group 2 compared with groups 1 and 3 (Fig. 5). Total cerebral vascular resistance was not different between groups at this time point (Table 2).

Cerebral perfusion pressure, although slightly increased at 10R in group 1 (P = NS), was higher than baseline only in group 3 (103 ± 5 vs. 125 ± 4 mmHg) because of an increase in mean aortic pressure and not because of a change in calculated resistance (Fig. 1).

Hyperemia did not occur in kidney or jejunum at 10R. In group 1, jejunal blood flow was not different from baseline; however, renal blood flow remained below baseline at 10R. In group 2, L-NAME did not affect jejunal or renal blood flow compared with group 1. L-Arginine did not reverse the hypoperfusion (Figs. 3 and 4).

By 30 min after reperfusion, cardiac index was similar in the three groups, although it remained at levels 40–50% below baseline. Mean arterial pressure returned to baseline by 30 min after reperfusion, but mild pulmonary hypertension persisted throughout the 60-min reperfusion period in all three groups. By 60R, myocardial blood flow returned to baseline in all three groups; however, the brain, kidneys, and intestine remained hypoperfused at 60R in all three groups.

Cerebral oxygen uptake was not different from baseline in any group at any time point during the experiment (Table 3). CMRGluc was unchanged during both baseline measurements and CPR. However, this value increased greatly, coincident with cerebral hyperemia at 10R in groups 1 and 3. In group 2, L-NAME completely prevented the increase of CMRGluc at 10R.

Arterial plasma glucose concentration, which increased two- to threefold in all groups at 10R (352 ± 18, 239 ±
remained elevated in groups 1 and 3 between groups at any time. In all groups, arterial PCO2 throughout the experiment.

Thase inhibitor L-NAME did not reduce cerebral or during and after cardiac arrest and CPR, a clinically 

tions regarding the effects of NO synthase inhibition 

Table 3. Cerebral substrate uptake

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline1</th>
<th>Baseline2</th>
<th>CPR</th>
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</table>

Values are means ± SE. *P < 0.05 within group compared with baseline 1.
sure seen in piglets at a higher dose (10 mg/kg) in our laboratory. Traystman et al. (38) found a more complete inhibition of NO activity with larger doses of L-NAME, although in their study, all animals had at least a 40% decrease in NO activity at a dose of 10 mg/kg, a dose only three times larger than the dose of L-NAME used in this study. Thus we used a dose of L-NAME that did not preclude successful resuscitation while allowing for a decrease in early cerebral hyperemia. The timing of administration of the drug may also play an important role in cerebral penetration. Irikura et al. (17) found that the maximal effect of L-NAME was not seen until 60 min after topical application through a closed cranial window. L-NAME resulted in at least a 70% inhibition of NO synthase activity by 30 min after its administration (38). We waited 30 min after L-NAME administration before commencing with CPR. The peak effect on cerebral blood flow of NO synthase inhibition probably was not reached by that time. However, we would not expect any lag time after L-NAME administration on other organ vascular effects. As mentioned, pharmacological species differences among NO synthase inhibitors have been seen. Pigs were more resistant to NO synthase inhibition by N^G-nitro-L-arginine but not with L-NAME (38). Alternatively, the constrictive effects of L-NAME may have been opposed by its antagonistic action on muscarinic receptors (4).

During CPR, total brain blood flow was reduced to 40, 53, and 49% of baseline, respectively, in groups 1–3, respectively. These values for cerebral blood flow during CPR are lower than those obtained in previous studies; however, in those studies, CPR was begun after only 15 s of cardiac arrest (33). Nevertheless, the level of cerebral blood flow produced during posts ischemic CPR in this study provides adequate oxygen delivery to the brain. Changes in regional cerebral blood flow were heterogeneous. For example, medullary blood flow was higher during CPR compared with baseline in the two L-NAME groups.

An interesting and important finding is that L-NAME did not cause a decrease in total cerebral blood flow during CPR compared with placebo-treated animals. Systemic vasoconstriction caused by NO synthase inhibition might compare favorably to that produced by a-adrenergic agonists during CPR. a-Agonists raise aortic diastolic pressure and increase myocardial and cerebral blood flow (42). Whether the vasoconstrictive effects of epinephrine can be achieved by NO synthase inhibition during CPR is presently unknown. These data suggest that L-NAME, at the dose used in combination with epinephrine, does not produce more vasoconstriction than with epinephrine alone in the brain and heart, holding open the possibility of a role for L-NAME in the pharmacological approach to the severely vasodilated patient with cardiac arrest.

After resuscitation, L-NAME reduced the magnitude of the early hyperemic response to ischemia-reperfusion in certain brain regions, most notably the brain stem. In addition, supratentorial brain regions such as diencephalon, anterior cerebral cortex, and anterior-middle watershed regions also had less hyperemia in group 2. The difference in regional blood flow could be attributed to differences in NO receptors in anatomic regions of pig brain (1). In group 3, L-arginine, at a dose 30 times that of L-NAME, completely reversed the effects of L-NAME on early cerebral hyperemia after cardiac arrest. Attenuation of cerebral hyperemia by L-NAME may protect the brain after ischemia-reperfusion injury. Previous investigators have measured similar effects of L-NAME on hyperemia (13, 16). Greenberg et al. (13) showed that 50 mg/kg of L-NAME, a dose 12 times higher than ours, decreased early postischemic cerebral vasodilation. Postischemic hyperemia can be attenuated by chronic trigeminal postganglionectomy, which reduces the release of vasodilating neuropeptides (30), all of which may come under the control of NO. In addition, a relationship between NO release and prostaglandin synthesis may result in cerebral hyperemia. Hyperemia was decreased in pigs anesthetized with isoflurane that received both L-NAME and a cyclooxygenase inhibitor, indomethacin (29).

Hyperemia, characteristically observed in dogs (30, 34) and piglets (16, 21) after global ischemia, if attenuated may reduce damage to the BBB. Early BBB injury has been documented by both quantitative analysis (35) and by morphological analysis (5) 4 h after CPR. However, earlier disruption of the BBB with vasogenic edema may occur (22). Systemic hypertension that occurs commonly during and after successful CPR results in increased cerebral blood flow. This hypertensive response, thought to be a major contributor to vasogenic edema seen after brain injury (5, 25), has been shown to worsen BBB injury. Thus attenuation of cerebral hyperemia may improve outcome after cardiac arrest and CPR.

Delayed cerebral hypoperfusion occurred in all three groups of animals. After 1 h of reperfusion, cerebral blood flow fell to 56–70% of baseline levels. We might have observed more severe hypoperfusion if we had measured blood flow later after resuscitation (12). Interestingly, tonic NO-mediated cerebral vasodilation persists after transient global cerebral ischemia despite delayed hypoperfusion in cats (8). Thus L-NAME probably further reduced cerebral blood flow during reperfusion in ischemic animals coincident with progressive hypoperfusion.

CMRO_2 was unchanged during CPR because of the high extraction rate of oxygen by the brain when blood flow is low. Early during reperfusion, CMRO_2 levels were also maintained at baseline values, resulting in greater blood flow compared with CMRO_2, even when hyperemia was diminished. No differences in CMRO_2 were observed between groups at any time point. Unlike CMRO_2, CMR_Lac and CMR_Gluc were directly correlated to cerebral blood flow at 10R in both group 1 and group 3. L-NAME, however, completely blocked the increase in CMR_Gluc and CMR_Lac at 10R, with levels unchanged from baseline. NO synthase inhibition may play a role in decreasing glial and neuronal metabolism. This inhibition has been shown to decrease neurotoxic effects of glutamate (9), whereas conditions associated with excitotoxicity and increased cerebral

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metabolism are associated with increased production of NO (2). NO has a variety of targets that modulate many metabolic processes. These include protein kinase C and its effects on phosphorylation (23), glyceroldehyde 3-phosphate dehydrogenase and effects on glycolysis (3), glutathione and its effects on the hexose monophosphate shunt (7), and DNA damage resulting in increased ATP production (43), all of which could contribute to an increase in glucose utilization. NO synthase blockade may therefore decrease glucose utilization. The effects of lactate utilization may parallel the effects on glucose metabolism.

NO synthase blockade decreased renal and jejunal blood flow before cardiac arrest. During CPR, blood flow to the kidneys and intestines approached zero, due to the α-adrenergic effects of the high doses of epinephrine used in this study (27). The renal vasculature contains both constitutive (37) and inducible NO synthase (31). NO has toxic effects on renal blood vessels (19, 32) and both beneficial and toxic effects on renal parenchymal cells (32). In addition, prolonged hypoperfusion of the kidneys likely resulted from severe ischemia-reperfusion injury.

Likewise, intestinal blood flow was reduced by one-half before ischemia in the two L-NAME groups. Intestinal blood flow did not return to baseline during reperfusion in either group 2 or group 3. This may be due to severe vasoconstriction seen in intestine associated with cardiac arrest and the use of high-dose epinephrine for resuscitation. NO production may be necessary for intestinal preservation (36), given that mediators such as cytokines, cyclooxygenase products, and vasoactive intestinal peptide may play a role in vasoconstricting mesenteric vessels after global ischemia. Alternatively, the vascular effect of L-NAME could be increasing to its peak during the reperfusion period.

Myocardial blood flow was reduced by L-NAME in a fashion similar to that for cerebral blood flow. Blood flow decreased more in heart than in brain, perhaps because of increased bioavailability. Myocardial blood flow during CPR compared favorably to previous studies in piglets (33, 34) and was sufficient to resuscitate the heart from ventricular fibrillation in the majority of animals. The absence of myocardial hyperemia in L-NAME-treated piglets at 10R is striking, an effect that was totally reversed by L-arginine. In contrast to that in intestine and kidney, myocardial blood flow continued to rise in group 2 animals to equal the blood flow in the other two groups by 60R. NO production or release is reduced significantly after ischemia-reperfusion of the heart (39, 41); thus the effect of NO synthase inhibitors after ischemia-reperfusion may be lessened if lower levels of NO are present.

The effect of L-NAME on myocardial function is difficult to assess on the basis of the measurements made in this study. Calculated systemic vascular resistance increased by 80% after L-NAME with an associated decrease of cardiac output by 31%. However, because of the increase in pulmonary capillary wedge pressure in L-NAME-treated piglets, we conclude that L-NAME has a negative inotropic effect.

In conclusion, the use of a nonselective NO synthase inhibitor, L-NAME, at a relatively low dose, attenuated the hyperemic response in brain and heart after cardiac arrest and CPR. Clinically, this may improve outcome particularly if it results in preservation of BBB function. L-NAME preserved myocardial and cerebral blood flow during CPR and allowed for a high rate of resuscitation after cardiac arrest and CPR. Caution is warranted, however, because of possible adverse effects of NO synthase inhibition on cerebral and myocardial function, blood flow to kidneys and intestine, and cellular metabolism including glycolysis.

We thank Morayma Barreto for flawless typing of the manuscript, Susan Li for technical support, and our fellows Drs. Alan Pinto and Eduardo Pino for help in preparation of experiments.

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Received 22 October 1997; accepted in final form 15 December 1997.

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