

# Rapid Hypothermic Aortic Flush Can Achieve Survival without Brain Damage after 30 Minutes Cardiac Arrest in Dogs

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**Background:** Neither exsanguination to pulselessness nor cardiac arrest of 30 min duration can be reversed with complete neurologic recovery using conventional resuscitation methods. Techniques that might buy time for transport, surgical hemostasis, and initiation of cardiopulmonary bypass or other resuscitation methods would be valuable. We hypothesized that an aortic flush with high-volume cold normal saline solution at the start of exsanguination cardiac arrest could rapidly preserve cerebral viability during 30 min of complete global ischemia and achieve good outcome.

**Methods:** Sixteen dogs weighing 20–25 kg were exsanguinated to pulselessness over 5 min, and circulatory arrest was maintained for another 30 min. They were then resuscitated using closed-chest cardiopulmonary bypass and had assisted circulation for 2 h, mild hypothermia (34°C) for 12 h, controlled ventilation for 20 h, and intensive care to outcome evaluation at 72 h. Two minutes after the onset of circulatory arrest, the dogs received a flush of normal saline solution at 4°C into the aorta (cephalad) via a balloon catheter. Group I (n = 6) received a flush of 25 ml/kg saline with the balloon in the thoracic aorta; group II (n = 7) received a flush of 100 ml/kg saline with the balloon in the abdominal aorta.

**Results:** The aortic flush decreased mean tympanic membrane temperature (Tty) in group I from 37.6 ± 0.1 to 33.3 ± 1.6°C and in group II from 37.5 ± 0.1 to 28.3 ± 2.4°C (P = 0.001). In group I, four dogs achieved overall performance category (OPC) 4 (coma), and 2 dogs achieved OPC 5 (brain death). In group II, 4 dogs achieved OPC 1 (normal), and 3 dogs achieved OPC 2 (moderate disability). Median (interquartile range [IQR]) neurologic deficit scores (NDS 0–10% = normal; NDS 100% = brain death) were 69% (56–99%) in group I versus 4% (0–15%) in group II (P = 0.003). Median total brain histologic damage scores (HDS 0 = no damage; >100 = extensive damage; 1,064 = maximal damage) were 144 (74–168) in group I versus 18 (3–36) in group II (P = 0.004); in three dogs from group II, the brain was histologically normal (HDS 0–5).

**Conclusions:** A single high-volume flush of cold saline (4°C) into the abdominal aorta given 2 min after the onset of cardiac arrest rapidly induces moderate-to-deep cerebral hypothermia

and can result in survival without functional or histologic brain damage, even after 30 min of no blood flow. (Key words: Cardiopulmonary bypass; cerebral preservation; hemorrhage; ischemia; resuscitation.)

NORMOTHERMIC cardiac arrest (CA; *i.e.*, temporary complete global brain ischemia) lasting 5 min or longer and reversed by standard resuscitation is almost invariably followed by brain damage.<sup>1–5</sup> Hypothermia induced before arrest (protection) is more likely to mitigate postischemic brain damage than when induced after arrest (resuscitation).<sup>2,4,6</sup> This study explored hypothermia induced during arrest (preservation). After normothermic CA of longer than 10 min in dogs, restoration of spontaneous circulation requires emergency cardiopulmonary bypass (CPB).<sup>7</sup> We suspect that many military or civilian victims of traumatic exsanguination<sup>8</sup> and presently unresuscitable patients with normovolemic sudden cardiac death<sup>9</sup> could be saved with rapid preservation of brain and heart to buy time for transport, repair, and resuscitation with CPB. About one half of out-of-hospital cardiopulmonary–cerebral resuscitation attempts for normovolemic CA fail to restore heartbeat,<sup>9</sup> and many long-term survivors suffer permanent brain damage.<sup>2</sup> For sudden cerebral ischemia, the rapid loss of energy, disappointing pharmacologic cerebral resuscitation trials,<sup>2,4</sup> and the benefits from even mild preservative and resuscitative cerebral hypothermia<sup>2,3,6,10–12</sup> have been reported.

In 1984, Bellamy and Safar,<sup>8</sup> considering combat casualties killed in action, recommended research into rapid induction of preservation of the organism for transport and surgical hemostasis without pulse, to be followed by delayed resuscitation to survival without brain damage. Using dog outcome models of exsanguination CA and CPB for the induction of profound hypothermia (5–10°C), we achieved cerebral preservation during complete circulatory arrest of 60 min,<sup>13</sup> but not 120 min.<sup>14</sup> We have recently documented effective rapid induction of cerebral hypothermia without CPB, using aortic arch cold flush to induce hypothermic preservation within 5 min of no blood flow for CA 15 min<sup>15,16</sup> or CA 20 min.<sup>17</sup>

We hypothesized<sup>18</sup> that flushing the aorta (and, hence, the brain) with normal saline at 4°C immediately after the onset of CA of 30 min can achieve survival without brain damage, and that the cold flush must include the spinal cord and abdominal viscera, which cannot tolerate normothermic ischemia of longer than 20 min.<sup>17</sup>

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## Materials and Methods

This study was approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh, Pittsburgh, Pennsylvania, and followed United States national guidelines for the treatment of animals. Sixteen male custom-bred hunting dogs, 8–12 months of age and with a body weight of 20–25 kg, were used. All experiments were performed by the same team within 1 y in mixed sequence without systematic randomization.

### Preparation

The dogs were fasted overnight with free access to water. After premedication with 10 mg/kg ketamine intramuscularly, anesthesia was induced with 50%:50% N<sub>2</sub>O:O<sub>2</sub> and 2–4% halothane *via* mask. After tracheal intubation, the dogs were mechanically ventilated with tidal volumes of 15 ml/kg and positive end-expiratory pressure of 5 cmH<sub>2</sub>O, without paralysis. Anesthesia was continued with nitrous oxide and 0.5–1.5% halothane titrated to sustain normotension. The ventilatory rate was adjusted to achieve normocapnia (arterial partial pressure of carbon dioxide [Paco<sub>2</sub>], 35–40 mmHg), with an end-tidal carbon dioxide level of 4–5%. Electrocardiogram electrodes were attached to the extremities, and a pulse oximeter probe was placed on the tongue. Gastric and bladder catheters were inserted. Temperature probes were inserted for measuring tympanic membrane (Tty), esophageal (Tes), and rectal temperatures (Tr). Dextrose, 5%, in 5 ml · kg<sup>-1</sup> · h<sup>-1</sup> NaCl, 0.45%, was administered *via* a peripheral intravenous line to maintain central venous pressure at a level higher than 3 mmHg.

A PE 90 catheter (Becton, Dickinson Co., Parsippany, NJ) was surgically inserted into the left femoral artery for monitoring of arterial pressure and blood sampling. A 7.5-French balloon catheter (Intellith Continuous Cardiac Output Thermodilution Catheter; Baxter Co., Irvine, CA) was inserted *via* the left femoral vein into the pulmonary artery for pressure monitoring, continuous cardiac output determination (Vigilance Monitor software 4.42, Baxter Co., Irvine, CA), temperature measurements (Tpa), and blood sampling. The right femoral artery was cannulated with a prototype 8-French catheter with one hole at the distal end (Cardeon Corp., Cupertino, CA) and an inflatable balloon 1 cm from the tip which, when inflated with 1.0–1.5 ml saline, occluded the aorta (as determined by disappearance of femoral artery pressure). The catheter had an internal diameter of 2.24 mm. To verify that the balloon was placed in the abdominal or descending thoracic aorta, the length was marked prior to insertion. The right external jugular vein was cannulated with a multiple-holed, spiral-reinforced, 18-French plastic cannula which was advanced to the level of the right atrium. This

was used for venous bleeding and for venous return to the CPB system.

Arterial and central venous pressures and electrocardiography were continuously recorded on a polygraph (Grass Model 7D Polygraph; Astro-Med Inc., West Warwick, RI). Pulmonary artery pressure, pulmonary artery occlusion pressure, cardiac output, arterial and mixed venous blood gases, hemoglobin, hematocrit, sodium, potassium, glucose, and lactate were measured at regular intervals. Blood gases were measured at 37.5°C without correction for body temperature. Just before start of the insult, Tty was controlled at 37.5 ± 0.1°C using a heating blanket and lamp.

### Cardiac Arrest

After two baseline measurements, heating devices, intravenous fluids, and halothane were discontinued while the dogs were weaned to spontaneous breathing on N<sub>2</sub>O:O<sub>2</sub> 75%:25% *via* an endotracheal tube. When the canthal reflex returned, hemorrhage was initiated. Over a 5-min period the dogs were bled *via* the arterial and venous cannulae into bags containing citrate. The hemorrhage was controlled to achieve mean arterial pressure (MAP) of 40 mmHg at 2 min, 30 mmHg at 3 min, and 20 mmHg at 4 min. At 5 min, ventricular fibrillation (VF) was induced with a transthoracic shock of 95–105 V alternating current at 60 Hz for 2 s, repeated as needed. Total no-flow time was 30 min.

### Preservation by Aortic Flush

The flush strategies chosen were based on previous results<sup>15–17</sup> and pilot experiments (see Discussion). Two min after the onset of VF, the balloon of the aortic catheter was inflated with 1.0–1.5 ml saline to occlude the aorta. The aorta was flushed with normal saline solution using a roller pump. In group I, with the balloon in the thoracic aorta, 25 ml/kg of 4°C saline was infused over 1 min. In group II, with the balloon in the lower abdominal aorta, 100 ml/kg of 4°C saline was infused over 4 min. (We had found in a pilot experiment that mean carotid artery pressure during this kind of aortic arch flush is about 100 mmHg). The venae cavae were allowed to drain into bags during the aortic flush. After the flush, during CA, the aortic catheter was replaced by a short, 7- to 8-gauge arterial CPB cannula to optimize flow for later resuscitation by CPB.

### Resuscitation

After CA 30 min, reperfusion was achieved with CPB.<sup>3,7</sup> The CPB system included a centrifugal pump (Biomedicus, Eden Prairie, MN), a hollow-fiber membrane oxygenator, and a heat exchanger (Medtronic, Anaheim, CA). The circuit was primed with 400 ml of Dextran 40 10% in saline plus Ringer's solution, 50%:50%. Sodium bicarbonate, 2 mEq/kg, and 1500 U heparin were added. Just before start of CPB, an additional

1500 U of heparin and 2 mEq/kg sodium bicarbonate were injected into the circuit. The dogs were paralyzed with 0.1 mg/kg intravenous pancuronium. CPB was started with a flow of  $100 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , and enough shed blood was reinfused to achieve a central venous pressure of 10–15 mmHg. Repetitive doses of 0.01 mg/kg epinephrine were given into the femoral artery, if necessary, to increase the CBP-generated MAP to 100 mmHg. After CPB of 2–5 min with vigorous VF, defibrillation was attempted with an external direct-current counter-shock of 150 J. If necessary, shocks were repeated at 200 J, and a maximum of 300 J. Gas flow through the oxygenator was adjusted to keep  $\text{Paco}_2$  at 30–35 mmHg and arterial partial pressure of oxygen ( $\text{PaO}_2$ ) greater than or equal to 100 mmHg. Controlled ventilation at a rate of 8–10 breaths/min was resumed to prevent atelectasis. CPB controlled Tty at  $34^\circ\text{C}$  from reperfusion to 12 h. The intravenous fluids were restarted at 100 ml/h. A base deficit of more than 6 mEq/l was corrected with sodium bicarbonate. When restoration of spontaneous circulation was established, CPB was continued for assisted circulation to 120 min, with  $100 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  for 60 min,  $75 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  for 30 min, and  $50 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  for 30 min. During CPB, the activated clotting time was maintained at greater than 300 s with additional heparin if needed. After restoration of circulation, norepinephrine by intravenous drip was titrated to achieve initially a brief hypertension with MAP greater than or equal to 150 mmHg, followed by MAP controlled at 90–150 mmHg. The remaining shed blood was gradually reinfused, avoiding central venous pressure higher than 15 mmHg.

#### Intensive Care

Controlled ventilation was continued to 20 h with  $\text{N}_2\text{O}:\text{O}_2$  50%:50%. The dogs remained paralyzed with pancuronium until 20 h to assure a steady state of cardiovascular-pulmonary variables. For analgesia in case of suspected “stress” (mydriasis, tachycardia, hypertension), fentanyl boluses of 50 or 100  $\mu\text{g}$  per dog were titrated intravenously to maintain the pupils at small size and to help reverse severe hypertension ( $\text{MAP} \geq 150 \text{ mmHg}$ ) and tachycardia. More potent anesthesia was avoided because it can influence ischemic brain damage. In the dogs of this study, there were no painful stimuli during the 20 h paralysis after CA. There was also residual postischemic cerebral depression evident in all dogs at 20 h (evident after stopping all anesthesia and paralysis). Nevertheless, to be certain that this anesthetic regimen was sufficient,<sup>19</sup> two dogs without ischemia and without paralysis were intubated under brief, light halothane and were then ventilated with  $\text{N}_2\text{O}:\text{O}_2$  50:50%. Whenever movement, reaction to the endotracheal tube, or widening of pupils occurred, intravenous boluses of 100  $\mu\text{g}$  fentanyl were given. As expected, the required doses were greater in normal dogs than in the post-CA

dogs: namely, 100  $\mu\text{g}/\text{dog}$  about every 15 min. The canthal reflex also remained active. Nevertheless, there was no purposeful escape behavior and no movement on paw pinch.

After resuscitation, hypotension ( $\text{MAP} < 90 \text{ mmHg}$ ) was treated with intravenous Ringer’s solution or titrated norepinephrine. After analgesia was assured by the presence of small pupils, severe hypertension ( $\text{MAP} > 150 \text{ mmHg}$ ) was also controlled with boluses of 0.25–0.5 mg/kg labetalol or 0.5–1.0 mg/kg hydralazine. For infection prophylaxis, the dogs received 250 mg cefazolin intravenously every 8 h. Respiratory care included rotation, suctioning, and “sighing” at regular intervals. At 20–24 h after resuscitation, paralysis was reversed with 0.05 mg/kg neostigmine plus 0.025 mg/kg atropine administered intravenously. Weaning to spontaneous breathing was accomplished *via* endotracheal tube. The dogs were extubated when they were able to maintain normal  $\text{PaO}_2$  and  $\text{Paco}_2$  with spontaneous breathing, upper airway reflexes had returned, and circulation was stable. When dogs appeared awake, the catheters were removed under brief, light nitrous oxide-halothane anesthesia by mask, and the dogs were transferred to a stepdown area in the intensive care unit for continuous monitoring and life support by technician and critical care physicians. Suspected discomfort (howling, restlessness), seizures, running movements, or opisthotonos were controlled with titrated intravenous 0.2- to 0.3-mg/kg boluses of diazepam. For diazepam requirements, see Results. Tty was controlled with external cooling and warming at  $34^\circ\text{C}$  to 12 h<sup>12</sup> and at  $37.5^\circ\text{C}$  from 12–72 h.

#### Outcome Evaluation

**Function.** The methods used for the evaluation of outcome in terms of function until 72 h and morphology at 72 h have been described elsewhere.<sup>20–23</sup> Performance was evaluated according to overall performance categories (OPC) 1–5, where OPC 1 = normal; 2 = moderate disability; 3 = severe disability; 4 = coma; and 5 = brain death or death. Neurologic function was evaluated as neurologic deficit scores (NDS) 0–100%, where NDS 0–10% = normal and 100% = brain death. NDS included level of consciousness, breathing pattern, cranial nerve function, sensory and motor function, and behavior. Beginning 24 h after resuscitation, OPC and NDS were evaluated in dogs weaned from paralysis and fentanyl, and evaluation was continued every 8 h. The final evaluations at 72 h were independently recorded and agreed upon by two team members. Attempts were made to discontinue any sedation at least 4 h prior to final evaluation. If necessary, diazepam effect was reversed with 0.1 mg flumazenil intravenously, repeated as needed.

**Morphology.** After functional outcome evaluation, the dogs were reanesthetized in the same manner as

initially. The left hemithorax was opened, and the proximal descending aorta was ligated. A large-bore cannula was inserted proximal to the ligature. The dogs were then euthanized by infusing approximately 2 l of paraformaldehyde 3% (pH 7.4) with a roller pump with the right atrium opened, until clear fluid returned from the vena cava. A complete necropsy was performed. Macroscopic damage in gut and heart was estimated (dark hemorrhages, pale necroses), and samples of extracerebral organs were taken for histologic examination. After 1 h of brain fixation *in situ*, the skull was sawed open and the brain was removed.<sup>23</sup> Each brain was cut into 3-mm-thick coronal sections, which were immersed in paraformaldehyde for further fixation. Six selected slices were paraffin-embedded, cut into sections 4  $\mu$ m thick, and stained with hematoxylin-eosin-phloxine. Using light microscopy, the same pathologist (Dr. Radovsky), who was unaware of treatment assignments, scored 19 distinct anatomic brain regions (see Results) for severity and extent of ischemic neuronal changes (shrunken, eosinophilic neuron with pyknotic nucleus), infarcts, and edema.<sup>23</sup> For each region examined, the severity and extent of these lesions were assessed as HDS on a four-point scale, where minimal = 1+; moderate = 2+; severe = 3+; and maximal = 4+. The points were then multiplied by a weighting factor depending on the type of lesion (infarction 4 $\times$ , neuronal necrosis 2 $\times$ , and edema 1 $\times$ ). A maximal HDS of 56 per region was obtained if all three types of lesions occurred with maximal extent. Total HDS for the entire brain were obtained with a maximal possible score of 1,064 for all 19 regions combined. A total HDS of more than 100 represented extensive damage and had previously correlated with severe final NDS.<sup>10-12,14,20-23</sup> In two pilot experiments (see Discussion), the spinal cord was also removed and macroscopically abnormal sections were processed, stained with hematoxylin-eosin, and evaluated by light microscopy.

#### Statistical Analysis

Dogs that did not follow protocol or that died from extracerebral causes were excluded from analysis. Brain death was included as a cerebral outcome. Data are given as mean  $\pm$  SD or the median and IQR (the difference between the 25th and 75th percentiles) unless otherwise specified. We used the independent-samples *t* test or the Mann-Whitney U test for the comparison of continuous variables (physiologic variables, final NDS, and final HDS). We used the chi-square test for trend to determine group differences of final OPC. Since our endpoint was final outcome (at 72 h), changes in OPC, NDS, and HDS over time were not statistically analyzed. To account for the change in temperature over time during arrest, we calculated the area under the temperature curve. All data were computed using SPSS for

Windows, release 8.0 (SPSS Inc., Chicago, IL). A *P* value less than 0.05 was considered statistically significant.

## Results

Of the 16 dogs exsanguinated to CA, three had to be excluded from outcome evaluation: in group I, one of the eight dogs died 9 h after restoration of spontaneous circulation as a result of unrecognized airway obstruction, and one died 36 h after restoration of spontaneous circulation with heart failure caused by heartworms. This left six dogs in the protocol. In group II, one of the eight dogs developed severe oropharyngeal edema of unknown cause post-CA, which made extubation and evaluation of OPC and NDS impossible. This left seven dogs in the protocol. In group I, three of the six dogs included in the protocol developed an increasing need for large doses of norepinephrine; to obtain their brains for histologic evaluation, their OPC and NDS were determined after brief weaning from controlled ventilation prior to anticipated severe hypotension, with MAP still within protocol parameters. They were then reanesthetized at 42 h, 52 h, and 60 h, respectively, for perfusion fixation and morphologic evaluation. In group II, all seven dogs survived to 72 h.

There were no group differences in extracerebral variables important for cerebral recovery (table 1) at baseline and at 6 h after resuscitation, with the exception of central venous pressure, which was higher in group II at 6 h; lactate, which was higher in group I at 6 h; and O<sub>2</sub> extraction ratio, which was higher in group II at 6 h. Hematocrit immediately after resuscitation showed no significant intergroup difference (table 2).

There was no difference between groups in the required number and energy of defibrillating counter-shocks, total epinephrine doses, and bicarbonate requirement (table 2). The time to achieve restoration of spontaneous circulation was significantly longer and total norepinephrine requirements significantly higher in group I. The beginning of the induced brief hypertension was significantly earlier and the peak MAP significantly higher in group II *versus* group I (table 2). The duration of the hypertension (time with MAP >150 mmHg) varied greatly without intergroup difference.

Tty (fig. 1) just prior to the insult was  $37.6 \pm 0.1^\circ\text{C}$  in group I *versus*  $37.5 \pm 0.1^\circ\text{C}$  in group II ( $P = 0.1$ ). Saline flush rapidly decreased Tty during CA to a minimum of  $33.3 \pm 1.6^\circ\text{C}$  in group I *versus*  $28.3 \pm 2.4^\circ\text{C}$  in group II ( $P = 0.001$ ). Tty change over time (area under the curve) during CA was significantly different between the two groups (fig. 1). The lowest Tpa during CA was  $28.2 \pm 1.4^\circ\text{C}$  in group I *versus*  $20.9 \pm 2.8^\circ\text{C}$  in group II ( $P < 0.001$ ). The lowest Tes was  $32.9 \pm 4.2^\circ\text{C}$  in group I *versus*  $21.1 \pm 5.5^\circ\text{C}$  in group II ( $P = 0.002$ ). Tr remained

**Table 1. Physiologic Variables at Baseline and 6 h after Resuscitation**

	Baseline		6 h after ROSC	
	Group I	Group II	Group I	Group II
Heart rate (beats/min)	110 (108–141)	130 (120–130)	145 (120–153)	105 (90–140)
Mean arterial pressure (mmHg)	95 (94–96)	100 (90–115)	138 (125–141)	140 (130–155)
Blood glucose (mg/dl)	181 (123–288)	210 (178–221)	179 (156–298)	173 (171–195)
PaO <sub>2</sub> (mmHg), F <sub>IO<sub>2</sub></sub> 0.5	270 (249–286)	279 (272–286)	309 (288–511)*	280 (218–293)
Paco <sub>2</sub> (mmHg)	36 (34–40)	34 (33–38)	37 (34–39)	38 (35–40)
Arterial pH	7.35 (7.34–7.38)	7.34 (7.31–7.37)	7.35 (7.30–7.39)	7.35 (7.34–7.39)
Blood lactate (mM)	4.1 (2.1–4.3)	3.2 (2.6–3.8)	5.9 (4.5–7.5)†	3.4 (3.0–4.3)†
Base excess (mEq/l)	-4.0 (-5.1--2.8)	-5.2 (-5.9--4.7)	-4.5 (-6.1--2.8)	-2.9 (-3.9--1.5)
Serum sodium (mM)	144 (143–147)	145 (144–147)	153 (148–157)	153 (149–164)
Serum potassium (mM)	3.5 (3.1–3.7)	3.5 (3.3–3.6)	3.0 (2.9–3.2)	2.9 (2.7–3.2)
Hematocrit (%)	37 (34–42)	34 (33–37)	43 (31–47)	34 (27–35)
Cardiac index (l · min <sup>-1</sup> · m <sup>-2</sup> )	4.5 (3.3–6.9)	3.4 (3.0–5.6)	3.1 (2.6–5.2)	2.3 (3.0–3.1)
Oxygen extraction ratio (%)	15 (9–19)	20 (16–27)	15 (11–22)†	28 (21–32)†

Aortic flush at the start of the arrest was in group I with 25 ml/kg saline at 4°C (n = 6) and in group II with 100 ml/kg saline at 4°C (n = 7). Data are given as median and interquartile range.

\* This high 75th-percentile arterial oxygen tension (PaO<sub>2</sub>) value, above the expected value for a fractional inspired oxygen tension (F<sub>IO<sub>2</sub></sub>) of 0.5, was caused by measuring the value for one dog by error under an F<sub>IO<sub>2</sub></sub> of 1.0. † P < 0.05 comparing group I versus group II.

ROSC = restoration of spontaneous circulation; Paco<sub>2</sub> = arterial carbon dioxide tension.

normothermic and did not differ from baseline values during CA.

**Outcome**

OPC and NDS between 24 and 72 h improved less in group I than in group II. Final OPCs were better in group II, with 100 ml/kg low aortic flush, than in group I, with 25 ml/kg high aortic flush (P = 0.001; table 3).

Final NDS (table 3) was 69% (IQR, 56–99%) in group I (including the three dogs that had to be killed before 72 h) versus 4% (IQR, 0–15%) in group II (P = 0.003). Four dogs in group II with OPC 1 had NDS 0–10% (i.e., were normal). The slightly higher NDS in the other three dogs in group II reflected hind leg weakness and difficulty in walking or standing; however, they showed normal cerebral function and behavior.

The total dose of diazepam administered in each dog is shown in table 3. Dogs 1, 2, and 3 of group I received

0.2 mg flumazenil intravenously before evaluation of final OPC and NDS. Dogs 4, 5, and 6 of group I remained intubated under fentanyl and hence received no diazepam. In these dogs, fentanyl was reversed with naloxone shortly before euthanasia for evaluation of final OPC and NDS.

At necropsy, all dogs in group II were macroscopically normal. In group I, all dogs had moderate to severe (widespread) hemorrhagic areas in the gut mucosa and over the epicardium and endocardium.

On brain histology at 72 h, total brain HDS was 144 (IQR, 74–168) in group I versus 18 (IQR, 3–36) in group II (P = 0.004). Two dogs in group II had essentially normal brains on light microscopic examination, with total HDS of 0 and 4, respectively (table 3). Regional brain HDS (fig. 2) in frontal, parietal, occipital, and temporal cortices, hippocampus, dentate gyrus, putamen, amygdala, and thalamus were higher in group I than in group II (P < 0.05; fig. 2). In group II, no ischemic

**Table 2. Resuscitation and Restoration of Spontaneous Circulation**

	Group I	Group II	P Value
Countershocks, total number	1 (1–3)	3 (2–3)	0.2
Countershocks, total energy (J)	150 (150–550)	500 (300–500)	0.2
ROSC (min after start of CPB)	5 (5–7)	4 (3–4)	0.02
Total bicarbonate (mEq)	210 (158–295)	170 (130–215)	0.3
Total epinephrine (mg)	0.9 (0.5–1.7)	0.7 (0.6–1.2)	0.8
Total norepinephrine (mg)	39.3 (12.1–105.3)	1.3 (1.3–1.6)	0.004
Brief hypertension			
Start (min)*	9 (6–15)	4 (3–4)	0.005
Duration (min)†	4 (2–25)	8 (3–8)	0.6
Peak MAP (mmHg)	179 (167–194)	210 (205–220)	0.003
Hematocrit immediately after start of CPB (%)	19 (17–21)	15 (14–19)	0.08

Aortic flush at start of arrest was in group I with 25 ml/kg saline at 4°C (n = 6) and in group II with 100 ml/kg saline at 4°C (n = 7). Data are given as median and interquartile range.

\* Start of hypertensive bout = time after start CPB. † Duration of hypertensive bout = time with mean arterial pressure (MAP) greater than 150 mmHg.

ROSC = restoration of spontaneous circulation; CPB = cardiopulmonary bypass.

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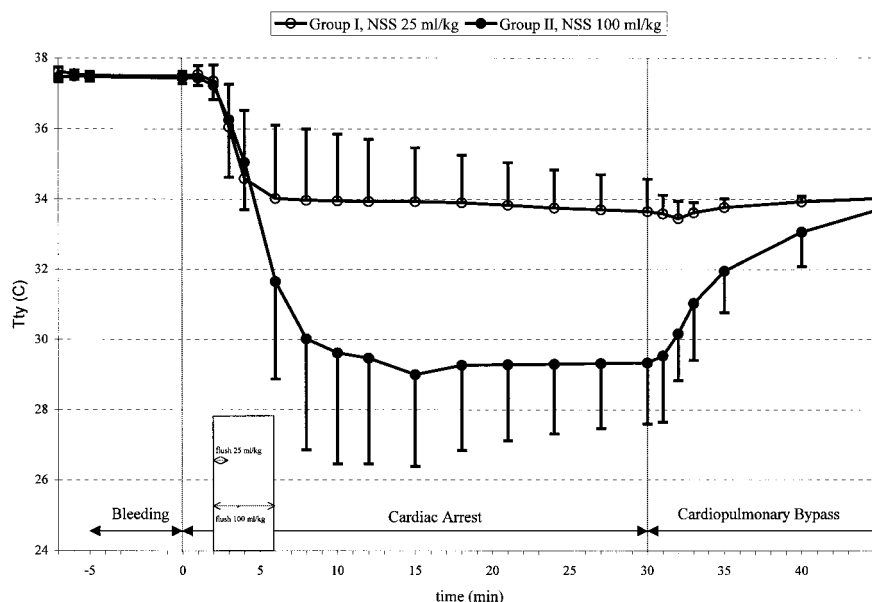


Fig. 1. Tympanic membrane temperatures ( $T_{ty}$ ) during exsanguination cardiac arrest of 30 min no-flow and resuscitation with cardiopulmonary bypass. Aortic flush with balloon catheter was with 25 ml/kg saline into the aortic arch in group I and with 100 ml/kg saline into the abdominal aorta in group II; in both cases, the saline was at a temperature of 4°C. Temperature areas under the curve during arrest were significantly different between groups ( $P = 0.003$ ). NSS = normal saline solution.

changes were found in the most vulnerable neurons, *i.e.*, in the hippocampus (three dogs) and in the cerebellar Purkinje neurons (four dogs). In group I, the insular cortex was damaged in one dog, and the midbrain and substantia nigra were damaged in another dog. The medulla and dentate nucleus did not show any histologic damage in either group (these regions are not shown in

fig. 2). Two dogs in group I and one dog in group II showed small infarcts. Spinal cord lesions in two pilot experiments are discussed later (see Discussion).

**Table 3. Final 72-h Outcomes after Exsanguination and No Flow of 30 min for Each Dog**

Dog No.	$T_{ty}^*$ (°C)	Diazepam (mg)	OPC*	NDS† (%)	HDS‡
<b>Group I</b>					
1	33.7	50	4	54	68
2	34.7	20	4	56	160
3	33.9	45	4	60	192
4	33.4	0§	4 (60 h)	78	132
5	30.1	0§	5 (52 h)	97	76
6	33.9	0§	5 (42 h)	100	156
<b>Group II</b>					
1	26.5	0	1	0	NA
2	25.8	0	1	0	16
3	31.3	0	1	1	4
4	29.6	2.5	1	4	0
5	25.2	10	2	14	46
6	30.2	0	2	15	20
7	29.6	0	2	18	32

Exceptions were dogs 4, 5, and 6 of group I, which had to be terminated at 60, 52, and 42 h (see text). Dog 1 of group II was allowed to survive, was adopted, and is normal at 1 yr. Aortic flush at start of arrest was in group I with 25 ml/kg saline at 4°C ( $n = 6$ ), with the tip of the balloon catheter in the thoracic aorta, and in group II with 100 ml/kg saline at 4°C ( $n = 7$ ), with the tip of the balloon catheter in the abdominal aorta.

\*  $P = 0.001$ . †  $P = 0.003$ .  $P = 0.004$ . § No diazepam required because anesthetized with fentanyl until final evaluation (overall performance category [OPC; 1 = normal, 5 = brain death] and neurologic deficit score [NDS; 0–100%] after fentanyl was reversed). || Weakness of the hind legs (cerebral performance was normal).

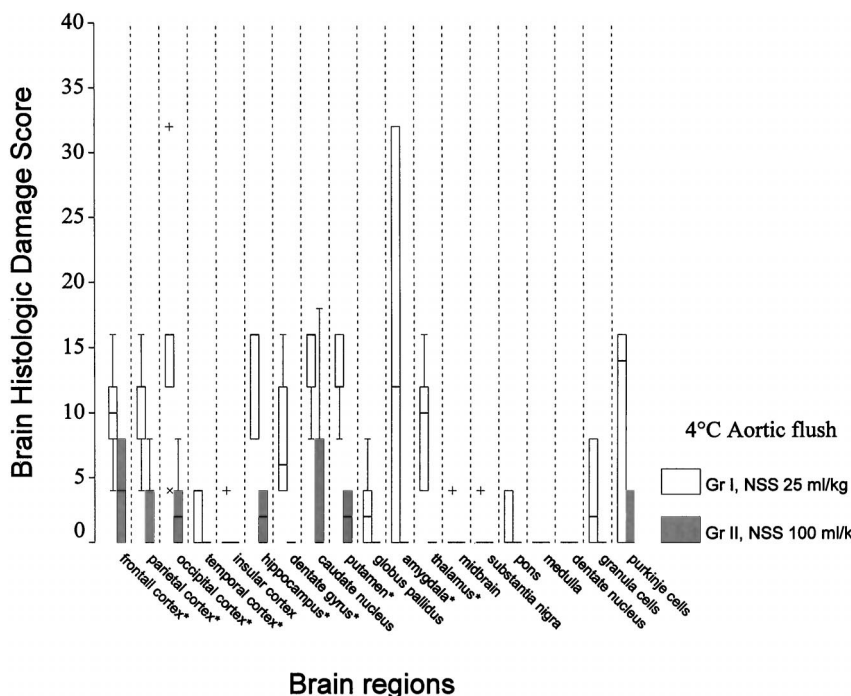
$T_{ty}$  = lowest tympanic membrane temperature during cardiac arrest; diazepam = total dose required; HDS = total brain histologic damage score; NA = not available.

## Discussion

This study documents that a single flush of 100 ml/kg cold saline (4°C) into the abdominal aorta (not into the thoracic aorta) *via* balloon catheter at the start of 30 min CA can allow survival without brain damage. To achieve similar results in a human, about 7 l of cold saline would be required. The mechanism is presumably related to the rapid induction of moderate to deep cerebral hypothermia (group II) at a rate much faster than could be achieved with surface cooling. This study also documents that in CA of 30 min, from which the healthy dog heart is unresuscitable under normothermia,<sup>3,24,25</sup> mild hypothermia (group I) is sufficient to preserve the heart's ability to beat, although severely damaged, but is insufficient for cerebral preservation. Aortic arch flush in group I left the nonflushed normothermic spinal cord and the viscera damaged.

Elective, slow, protective, pre-CA cooling has been practiced since the 1950s.<sup>26,27</sup> This study provides the first documentation of rapid preservative cooling during arrest. The degree of cerebral preservation seemed better than that seen previously with cooling to mild<sup>2,3</sup> or moderate hypothermia<sup>26–28</sup> induced before normovolemic CA. Normothermic aortic arch flush provided no significant preservation in dogs using the same model.<sup>15</sup> After normothermic VF-CA of 12.5 min, deep hypothermia by CPB does not result in better outcome than mild post-CA cooling.<sup>10</sup>

Fig. 2. Regional histologic damage scores (HDS). The box represents the interquartile range. The line across each box indicates the median. The whiskers indicate the highest and lowest values. The x indicates outliers (values between 1.5 and 3 box-lengths from the upper or lower edge of the box). The + indicates extremes (values >3 box-lengths from the upper or lower edge of the box). \**P* < 0.05. Gr = group; NSS = normal saline solution.



*Pilot Experiments on Flush*

This study was preceded by five pilot experiments in dogs to explore flush volume and catheter balloon position at start of CA 30 min to outcome at 72 h. Aortic arch flush with 50 ml/kg saline at 4°C resulted in one dog at 72 h with OPC 3, NDS 50%, and HDS 172 and with severe hemorrhagic areas in the duodenal mucosa, and in two dogs with normal cerebral function but with OPC 2 because of spastic paralysis of the hind legs (NDS 32% and 29%; HDS 20 and 40, respectively). Hearts and intestines were macroscopically normal. Two other dogs, flushed with 100 ml/kg saline at 4°C with the balloon at the level of the diaphragm, achieved normal cerebral function but with OPC 2 because of spastic paralysis of the hind legs (NDS 29% and 29%; HDS 16 and 12, respectively). Hearts and intestines were macroscopically normal. In these two dogs, the lumbar spinal cords showed histologic evidence of extensive degenerative changes, primarily in the ventral gray columns. This was characterized by neuronal degeneration with swelling and chromatolysis, neuronophagia, and prominent gliosis, including occasional glial nodule formation. Because of these pilot experiments, we decided for the final study group II to place the tip of the balloon catheter into the lower abdominal aorta.

*Adjunctive Study of DNA Damage*

All dog brains in the study were also stained using the TUNEL method.<sup>29</sup> Evidence of DNA fragmentation was found predominantly in neurons which, on regular staining, appeared shrunken and had condensed nuclei. A new DNA damage scoring method was developed and revealed that these scores correlated with HDS.

Dietrich *et al.*,<sup>30</sup> had shown that brief (4 h) postarrest mild hypothermia after normothermic incomplete forebrain ischemia in rats postpones but does not permanently salvage hippocampal neurons at 2 months. This is not relevant for our study, which produced moderate intraischemic (preservative) hypothermia, which in the Dietrich study gave lasting salvage of neurons at 2 months. Additionally, we used prolonged (12 h) post-CA mild hypothermia which, in a forebrain ischemia rat study by Colbourne *et al.*,<sup>31</sup> gave permanent benefit. Our dog 1 from group II (table 3) is functionally normal 1 year after CA.

Attempts at cerebral resuscitation with drugs have so far been disappointing.<sup>2,4,32</sup> In the mid-1980s we resumed research on resuscitative moderate hypothermia (30°C) after normothermic CA.<sup>2,33</sup> Breakthrough effects in dogs on outcome, however, were documented only when mild hypothermia (34–36°C), which is simple and safer than moderate hypothermia, was discovered to improve cerebral outcome when induced before VF-CA up to 15 min,<sup>2,3,7</sup> and even when induced after normothermic VF-CA of 10–12.5 min.<sup>2,10–12</sup> Mild resuscitative hypothermia essentially normalized cerebral outcome after VF-CA of 11 min when combined with cerebral blood flow-promoting measures.<sup>12</sup> Thus, protective-preservative hypothermia, induced and reversed by CPB, has been shown to preserve the brain and whole organism for VF-CA up to 15 min at about 35°C,<sup>3,7</sup> for CA up to 20 min at about 30°C,<sup>2,7,26</sup> for CA up to 30 min at about 20°C (deep hypothermia),<sup>28</sup> and for CA up to 60 min at about 10°C (profound hypothermia).<sup>13</sup> For transport and repair in exsanguinated trauma victims, it

is assumed that at least 30 min of preservation is needed until CPB can be initiated.

In a steady state, brain tissue temperature seems well reflected in Tty.<sup>34</sup> However, when deep hypothermia was rapidly induced during CPB, large temperature gradients between brain temperature and Tty were found.<sup>35</sup> In pilot experiments with the same dog model, we found that brain tissue may have been transiently 4–10°C below Tty. This might explain the unexpected complete cerebral preservation achieved in group II during CA of 30 min at Tty 28°C.

With CA of 30 min or longer, the heart needs to be protected to enable restoration of stable circulation.<sup>24,25</sup> With aortic arch flush of 25 ml/kg saline (group I), all six dogs had macroscopically severe hemorrhagic damage of the heart. In contrast, with flush of 100 ml/kg saline (group II), all seven dogs had macroscopically normal hearts. In group I, with the low-volume flush and high balloon position, the intestines also showed severe hemorrhagic damage. There was also a greater need for norepinephrine after return of spontaneous circulation to maintain normotension. In group II, abdominal mild hypothermia seemed to have protected the abdominal viscera and spinal cord; this was for tissue supplied by the superior mesenteric artery. Rectal temperature did not deviate from baseline during CA in both groups. The protection of intestines by flush into the abdominal aorta in group II could also have been the result of lower norepinephrine requirement and better overall hemodynamics.

For group I, we debated whether to exclude from outcome evaluation the three of six dogs that had cardiovascular failure requiring increasing amounts of norepinephrine postarrest. To obtain brain tissue, these three dogs were weaned from paralysis and fentanyl early to determine OPC and NDS; they were then euthanized for brain histologic examination at 42, 52, and 60 h rather than at 72 h (table 3, group I, dogs 4, 5, and 6). With comparable damage, earlier HDS would show fewer ischemic neurons than at 72 h. Our exclusion criteria of extracerebral organ failure with cardiovascular-pulmonary variables out of protocol did not apply, because we could maintain normotension, normoxia, and other critical variables until euthanasia. A deleterious effect on the histologic damage by norepinephrine cannot be ruled out. The two dogs that developed brain death (with dilated, fixed pupils) did so despite normotension; they could not be weaned to spontaneous breathing. Group I results confirm that CA 30 min, even with mild cardiac hypothermia, is too severe an insult to expect cardiovascular resuscitability.<sup>3,7,24,25</sup>

The broader objectives of this preservation study include: (1) Helping to save victims of temporarily uncontrollable (internal) traumatic exsanguination, such as combat casualties and civilian trauma victims without severe brain trauma<sup>8</sup>; (2) helping emergency medical

services save some nontraumatic cases of normovolemic, normothermic, sudden cardiac death who are unresuscitatable by standard cardiopulmonary resuscitation<sup>2,9</sup>; and (3) enabling selected elective surgical procedures that are feasible only during a prolonged state of no blood flow.<sup>36</sup> The last example would not require high-speed preservative cooling. With large fluid volumes and CPB, profound hypothermic asanguinous trickle flow could extend the tolerated preservation time to longer than 3 h.<sup>36</sup>

Various clinically feasible methods for the induction of cerebral hypothermia have been tested in animals and patients since the 1950s.<sup>2,26</sup> None is as rapidly effective as aortic cold flush<sup>15–18</sup> or CPB with heat exchanger.<sup>10–14</sup> Initiation of CPB, however, takes more time than the brain can tolerate under normothermic CA. The percutaneous Seldinger technique, with or without minor cutdown, available for femoral vessels and other vessels, has been shown to be feasible and rapid<sup>37</sup> but has not been explored for empty vessels in exsanguination. Almost as rapid as CPB cooling would be intracardiac rotid cooling.<sup>38,39</sup>

For civilian emergency care, the methods described in this report should be feasible now, in the hands of physician-staffed teams of mobile intensive care units, ambulances and in hospital emergency departments. There, CPB should be available to continue with profound hypothermic total circulatory arrest<sup>13</sup> or trickle flow<sup>36</sup> to achieve preservation of at least 60 min. We are exploring novel methods for access to the aorta with and without thoracotomy.<sup>2</sup> For field resuscitation by combat medics, rapid access to the aorta without thoracotomy, without CPB, and with small fluid volume at ambient temperature are needed. We therefore systematically explored the preservation achievable in the same dog model with six pharmacologic strategies, using aortic arch flush of 25 ml/kg saline at 24°C, which achieved a Tty of 36°C.<sup>32</sup> Thus far, moderate-to-deep hypothermia<sup>15–18</sup> proved much more preservative than any of the 14 drugs tested.<sup>32</sup>

We conclude that, in dogs, a single high-volume flush of cold saline (4°C) into the abdominal aorta at the start of exsanguination CA of 30 min rapidly induces moderate-to-deep cerebral hypothermia and can allow survival without functional or histologic brain damage. Future research should explore flush preservation for even longer arrest times, using profound hypothermia plus pharmacologic adjuncts.

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