Desflurane Improves Neurologic Outcome after Low-flow Cardiopulmonary Bypass in Newborn Pigs

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**Background:** Despite improvements in neonatal heart surgery, neurologic complications continue to occur from low-flow cardiopulmonary bypass (LF-CPB) and deep hypothermic circulatory arrest (DHCA). Desflurane confers neuroprotection against ischemia at normothermia and for DHCA. This study compared neurologic outcome of a desflurane-based with a fentanyl-based anesthetic for LF-CPB.

**Methods:** Thirty piglets aged 1 week received either fentanyl-droperidol (F/D), desflurane 4.5% (Des4.5), or desflurane 9% (Des9) during surgical preparation and CPB. Cerebral blood gases, glucose, heart rate, arterial pressure, brain temperature, and cerebral blood flow (laser Doppler flowmetry) were recorded. After CPB cooling (22°C brain) using pH-stat strategy, LF-CPB was performed for 150 min followed by CPB rewarming, separation from CPB, and extubation. On postoperative day 2, functional and histologic outcomes were assessed.

**Results:** Cardiovascular variables were physiologically similar between groups before, during, and after LF-CPB. Cerebral blood flow during LF-CPB (13% of pre-CPB value) did not differ significantly between the groups. Functional disability was worse in F/D than in Des9 (P = 0.04) but not Des4.5 (P = 0.1). In neocortex, histopathologic damage was greater in F/D than in Des4.5 (P = 0.03) and Des9 (P = 0.009). In hippocampus, damage was worse in F/D than in Des9 (P = 0.01) but not Des4.5 (P = 0.08). The incidences of ventricular fibrillation during LF-CPB were 90, 60, and 10% for F/D, Des4.5 (P = 0.06), and Des9 (P = 0.0002), respectively.

**Conclusions:** Desflurane improved neurologic outcome following LF-CPB compared with F/D in piglets, indicated by less functional disability and less histologic damage, especially with Des9. Desflurane may have produced cardiac protection, suggested by a lower incidence of ventricular fibrillation.

**DESpite** the advances in cardiac surgical management, infants undergoing open-heart surgery frequently exhibit postoperative neurologic abnormalities.1,2 Among the neurologic abnormalities are alterations of muscle tone, seizures, movement disorders, impaired fine motor and language skills, and diminished cognition in up to 41% of survivors. Postoperative cardiac impairment can also increase neurologic abnormalities through episodes of hypoxia, hypotension, and cardiac arrest, as well as increase overall mortality.

Low-flow cardiopulmonary bypass (LF-CPB) and deep hypothermic circulatory arrest (DHCA) are used to perform complex surgical repairs in infants. During DHCA, CPB flow is discontinued, resulting in complete ischemia of all organs. During LF-CPB, CPB flow is markedly reduced, posing a risk of incomplete ischemia to vital organs. Because LF-CPB has been shown to improve postoperative outcome, it is becoming more popular than DHCA for infant cardiac surgery. However, abnormal postoperative cognitive performance, development, and motor skills following LF-CPB are still observed.3 Additional neuroprotective strategies are therefore needed for infant heart surgery.

Recent work indicates that volatile anesthetics confer neurologic and myocardial protection against ischemia–reperfusion injury. Halothane, isoflurane, sevoflurane, and desflurane protect during focal as well as global brain ischemia.4 They seem to protect by limiting excitotoxicity, decreasing metabolic demand, and increasing tissue oxygenation. However, the optimal dose for neuroprotection, as well as the potency of the protection, remains uncertain. *In vitro* studies found neuroprotection at or above 1 minimum alveolar concentration (MAC), although an *in vitro* study suggests neuroprotection below 1 MAC.5–7 Laboratory studies also suggest that inhalational anesthetics bestow myocardial protection against ischemia–reperfusion injury through preconditioning and pharmacologic mechanisms at doses around 1 MAC.8

Of the inhalational anesthetics, desflurane’s pharmacodynamic profile makes it particularly attractive for use in infant heart surgery. Desflurane’s low solubility ensures a rapid achievement of tissue concentrations for organ protection. Its preservation of cardiac output permits administration before and during CPB in this population with limited hemodynamic reserve. Desflurane is also a vasodilator, which promotes homogeneous CPB cooling. Desflurane has recently been shown to confer neurologic protection in a piglet DHCA model of infant heart surgery.9 The current study evaluates two doses of desflurane for neuroprotection in a piglet LF-CPB model.

**Methods**

After review by the Institutional Animal Care and Use Committee (Children’s Hospital of Philadelphia, Phila-
delphia, Pennsylvania), 30 piglets aged 1 week were randomly assigned to one of three regimens for surgical preparation and cardiopulmonary bypass: fentanyl–droperidol (F/D group), 4.5% desflurane (Des4.5), or 9% desflurane concentration (Des9), corresponding to 0.5 and 1 MAC. All animals received intramuscular ketamine (35 mg/kg) and acepromazine (3.3 mg/kg) for anesthetic induction followed by orotracheal intubation and mechanical ventilation. After intravenous catheter insertion, the F/D group received intravenous fentanyl (25 μg/kg bolus and then 10 μg · kg⁻¹ · h⁻¹) and droperidol (0.25 mg/kg bolus and then 0.25 mg · kg⁻¹ · h⁻¹), and the desflurane groups received only one intravenous dose of fentanyl (25 μg/kg) with 4.5% or 9% desflurane end-expired (Poet IQ; CSI, Waukesha, WI) lactated Ringer’s solution was infused at 4 ml · kg⁻¹ · h⁻¹. A femoral arterial catheter was placed to monitor pressure, blood gases, pH, and hemoglobin (iStat; iStat Co., East Windsor, NJ) and glucose concentrations (Surestep; Lifescan Inc., Milpitas, MN). Electrocardiogram (Hewlett-Packard, Andover, MA), arterial pressure ( Gould Instrument Systems, Valley View, OH), end-expired carbon dioxide (Poet IQ), and esophageal and rectal temperatures (Yellow Springs Instruments, Yellow Springs, OH) were monitored.

A scalp incision and a 3-mm skull hole were made over the right parietal region to accommodate an epidural thermistor and laser Doppler probe to monitor brain temperature (Yellow Springs Instruments) and cortical thermistor and laser Doppler probe to monitor brain temperature (Yellow Springs Instruments, Yellow Springs, OH) were monitored. View, OH), end-expired carbon dioxide (Poet IQ), and esophageal and rectal temperatures (Yellow Springs Instruments, Yellow Springs, OH) were monitored.

After a right neck incision, the carotid artery and the external jugular vein were cannulated (Biomedicus; Medtronic, Minneapolis, MN), and cannulae were advanced into the aortic arch and the right atrium for CPB, respectively. In piglets, ligation of one carotid artery has advanced into the aortic arch and the right atrium for CPB, and then the cannulae were removed, protamine (4 mg/kg intravenously) was administered, and the neck incision was closed.

Postoperatively, minute ventilation was adjusted to maintain an arterial partial pressure of carbon dioxide (Paco₂) of 35–45 mmHg, and blood was transfused to maintain a MAP greater than 50 mmHg. After retransfusion of the blood collected before CPB, 5% dextrose in lactated Ringer’s solution was infused intravenously at 4 ml · kg⁻¹ · h⁻¹. Brain temperature was maintained normothermic (38°C) until extubation, at which point the temperature probe was removed. After return of a regular breathing pattern, airway reflexes, and purposeful movement, the trachea was extubated. Animals were inspected hourly for the initial 4 h and then every 6–8 h. Piglets were allowed to feed at will; those unable to ambulate were bottle fed; those unable to bottle feed were administered intravenous fluids.

Heart rate, arterial pressure, cortical blood flow, and all temperatures were recorded every 5 min during CPB and every 15–30 min during LF-CPB and after separation from CPB. Arterial blood gases, pH, hemoglobin, and glucose concentrations were documented at baseline, after 15 min CPB cooling, every 30 min during LF-CPB, after 15 min CPB rewarming, and at 15 min and 120 min after separation from CPB.

Piglets were sacrificed 48 h postoperatively after receiving intramuscular ketamine (35 mg/kg), acepromazine (3.3 mg/kg), as well as intravenous heparin (300 U/kg) and pentobarbital (100 mg/kg). After infusion of 1 l chilled 0.9% NaCl solution followed by 4% paraformaldehyde in 1 l phosphate-buffered saline (pH, 7.4; 0.15 m Na₂HPO₄) into the carotid artery to fix the brain in situ, the brain was removed as a whole. A superficial cut was made along the undersurface of the right hemibrain to distinguish it from the left. Coronal cut 5-mm blocks of the whole brain were dehydrated in ethanol and xylene (Citadel 2000; Shandon-Lipshaw, Pitts-
Table 1. Physiologic Data in Fentanyl–Droperidol and Desflurane Groups

<table>
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<th></th>
<th>pH</th>
<th>pCO₂ (mmHg)</th>
<th>pO₂ (mmHg)</th>
<th>Hematocrit (%)</th>
<th>Glucose (mg/dl)</th>
<th>MAP (mmHg)</th>
<th>HR (beats/min)</th>
<th>CBF (% baseline)</th>
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<td>F/D</td>
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<td>33±5</td>
<td>492±105</td>
<td>25±3</td>
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<td>22±5</td>
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<td>154±18</td>
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<td>24±4</td>
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<tr>
<td>F/D</td>
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<tr>
<td>F/D</td>
<td>7.28±0.11</td>
<td>48±10</td>
<td>455±161</td>
<td>26±3</td>
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<td>196±72</td>
<td>59±11</td>
<td>207±33</td>
<td>ND</td>
<td>34.7±1.7</td>
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Mean ± SD; n = 10 per group; except for CBF: n = 7 in F/D, n = 6 in Des4.5, and n = 7 in Des9. F/D, Des4.5, and Des9 refer to fentanyl–dripredol, desflurane 4.5%, and desflurane 9%. cCPB, LF-CPB, rCPB, 15 min off, 2 h off indicate cooling, low flow-cardiopulmonary bypass, rewarming, 15 min, and 2 h after separation from CPB.

* Statistically significant difference from F/D and Des4.5, P < 0.01
ND = no data.

The table shows the physiologic data during the study. Of the physiologic parameters, only arterial partial pressure of oxygen (\( P_O₂ \)) during LF-CPB was statistically

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different between groups: Arterial $P_{O_2}$ was lower in the Des9 group than in the F/D and Des4.5 groups. Technical problems precluded measuring CBF in three animals in the F/D group, four in the Des4.5, and three in the Des9 group during CPB (bleeding around laser Doppler probe), and in all animals after separation from CPB (head movement). CPB cooling and reperfusion durations were not different between the groups. CPB cooling was $22 \pm 7$ min in F/D, $21 \pm 5$ min in Des4.5, and $25 \pm 7$ min in Des9. CPB reperfusion was $34 \pm 4$ min in F/D, $35 \pm 5$ min in Des4.5, $35 \pm 5$ min in Des9. The time to endotracheal extubation, marked from onset of CPB reperfusion, was significantly less ($P = 0.016$) in Des9 ($179 \pm 101$ min) than in F/D ($223 \pm 52$ min) but not in Des4.5 ($192 \pm 40$ min).

Heart rate, arterial pressure, and incidence of arrhythmias were not significantly different between the three study groups before CPB, during CPB cooling, or after separation from CPB. However, ventricular fibrillation during LF-CPB occurred significantly more often in the F/D (9 of 10) than in the Des9 (1 of 10, $P = 0.0005$) group, as displayed in figure 1. The prevalence of ventricular fibrillation in the Des4.5 group (6 of 10) did not differ statistically ($P = 0.15$) compared with the F/D group. The first onset of ventricular fibrillation occurred at 45 min of LF-CPB in both the F/D and the Des4.5 groups, whereas this rhythm disturbance did not start until 135 min of LF-CPB in the Des9 group.

Functional outcome as well as histopathologic outcome was better in the desflurane groups than in the F/D group. Figure 2 depicts functional outcome in the groups. In F/D, two animals died (one cardiovascular, one neurologic), before postoperative day 1. On postoperative day 2, 6 of 10 animals in F/D were disabled or dead compared with disability (but no deaths) in 3 of 10 in Des4.5 and 1 of 10 in Des9. Disability scores were significantly higher in F/D when compared with Des9 ($P = 0.044$). Figure 3 shows the neuronal damage score in neocortex and hippocampus, which was significantly worse in F/D animals than in both desflurane groups. All F/D animals had histologic evidence of damage in both regions, predominantly as selective neuronal necrosis and infarction. By comparison, in Des4.5 and Des9 groups, no damage was observed in the hippocampus in two (20%) and three (30%) animals, respectively. Although all animals in Des4.5 and Des9 had damage in the neocortex, the scores were significantly lower in both desflurane groups compared with the F/D group ($2.6 \pm 2.3$ vs $4.8 \pm 1.9$, $P = 0.001$).

Fig. 1. Prevalence of ventricular fibrillation during low-flow cardiopulmonary bypass. F/D, Des4.5, and Des9 refer to fentanyl–droperidol, 4.5% desflurane, and 9% desflurane, respectively; $n = 10$ per group.

Fig. 2. Disability score 48 h after low-flow cardiopulmonary bypass. F/D, Des4.5, and Des9 refer to fentanyl–droperidol, 4.5% desflurane, and 9% desflurane, respectively. Horizontal bars represent mean values; $n = 10$ per group.

Fig. 3. Neuronal damage score in neocortex and hippocampus 48 h after low-flow cardiopulmonary bypass. F/D, Des4.5, and Des9 refer to fentanyl–droperidol, 4.5% desflurane, and 9% desflurane, respectively. Horizontal bars represent mean values; $n = 8$ animals in the F/D group, and $n = 10$ for both desflurane groups.
1.1 for F/D vs. 1.5 ± 0.8 for Des4.5 vs. 1.3 ± 0.8 for Des9, *P = 0.024). Neuronal damage scores for the hippocampus were significantly lower in Des9 versus F/D (0.8 ± 0.7 vs. 2.4 ± 1.6, *P = 0.012). The damage score in the Des4.5 group (1.3 ± 1.1) was not statistically different from F/D (*P = 0.08). There were no differences in neuronal damage scores between desflurane groups. The histologic injury pattern did not differ between both hemispheres in any animal.

Discussion

Despite improvements in surgical management for congenital heart disease, neurologic and cardiac complications related to ischemia during CPB and DHCA continue to occur. Hypothermia remains the only routine modality for neurologic protection, although this protection is incomplete. In animal models of normothermic ischemia, concentrations of volatile anesthetics at or above 1 MAC have been shown to confer neurologic protection, whereas the neuroprotective potency less than 1 MAC remains uncertain. Desflurane, 9%, has been shown to confer neuroprotection in a piglet DHCA model. The current study found better functional and neuropathologic outcome in an LF-CPB piglet model with 4.5% and 9% desflurane, indicating protection for this surgical technique as well.

Deep hypothermic circulatory arrest and LF-CPB are commonly used to perform repairs of complex cardiovascular malformations in infants. During DHCA, CPB is discontinued affording a bloodless operative field at the risk of ischemic organ damage. LF-CPB continues to provide some blood flow, although operating conditions are not as good and total CPB and surgical duration can be increased, posing a risk of incomplete ischemia over a longer duration. Recent work indicates better functional and neuropathologic outcome with LF-CPB compared with DHCA for neonatal surgery. However, intelligence and motor and language skills in both DHCA and LF-CPB groups were significantly below the normal population. Blood acid–base, hematocrit, and cooling–rewarming management during CPB also appear to influence neurologic outcome. The pH-stat strategy and increased blood oxygenation have been found to improve neurologic outcome in neonatal animal models of DHCA. Animal and clinical studies also suggest nonrapid CPB cooling and rewarming promote homogenous brain hypothermia and maintenance of tissue oxygen supply-and-demand relations.

Our LF-CPB piglet model used a membrane oxygenator, pH-stat strategy, nonrapid cooling and rewarming, and increased hematocrit and arterial Po2 in an attempt to simulate conditions during infant cardiac surgery. However, CPB pump flow was less and duration of LF-CPB was greater than standard clinical practice in order to incur reproducible brain damage to perform a neuroprotection study. The advantage of the closed-chest model includes minimal bleeding, pulmonary dysfunction, or postoperative physical disability from surgery, simplifying postoperative care and neurologic assessment. Ligation of one carotid artery in piglets has been shown to have no effect on cerebral blood flow during normal or ischemic conditions, and in the current study, no differences in neuropathology were seen between the two brain hemispheres. The LF-CPB pump flow and duration were determined empirically in pilot studies: Longer duration and lower arterial pressures were not survivable, whereas shorter duration and higher MAP did not cause reproducible damage. The target parameter for LF-CPB was MAP, and not pump flow or CBF, because cerebral blood flow is influenced more by MAP than pump flow, and laser doppler flowmetry was not reliable during CPB.

Brain damage following LF-CPB is similar yet different from that following DHCA. DHCA represents complete cerebral ischemia, whereas LF-CPB corresponds to incomplete cerebral ischemia, with cerebral blood flow approximately 10% of that before CPB. In LF-CPB as well as DHCA, the vulnerable regions include the neocortex and hippocampus, in which selective neuronal death and less often infarction are observed optimally at 1–3 days after the event. The clinical recovery after LF-CPB and DHCA in piglets is rapid despite ongoing neuronal cell death. However, cell death in neocortex differs between techniques. In our observations, neuronal damage after DHCA appears predominantly in the superficial gray matter (layers 2 and 3), whereas it is located in the deeper gray matter (layers 4–6) after LF-CPB. Moreover, cell death after DHCA involves mainly apoptotic mechanisms, whereas it appears to involve necrotic mechanisms after LF-CPB.

The anesthetic regimens in the current study were based on good clinical practice. Fentanyl was added to the desflurane groups to provide postoperative analgesia; droperidol and fentanyl were used in the other group to provide anesthesia without neuroprotection. Fentanyl alone is not an anesthetic in piglets, and other supplements, like midazolam or propofol, have neuroprotective properties. Desflurane, 4.5% and 9%, were used because the latter dose corresponds to approximately 1 MAC and confers neuroprotection for DHCA, and the former dose corresponds to approximately 0.5 MAC and has been found to confer neuroprotection in in vitro studies. Use of a common anesthetic for all groups during surgical preparation and randomizing the anesthetics for CPB introduces other confounders, like drug interactions. Anesthesia is defined by unconsciousness, amnesia, and lack of movement to surgical stimulation, and not by “stress” or cardiovascular responses. Although the three anesthetic regimens may have had...
differences in stress responses, they appeared to be similar in the other aspects.

During steady state conditions, inspired and expired volatile anesthetic concentration reflects the brain anesthetic concentration. Anesthetic tissue concentration depends on the partial pressure and solubility coefficient of the volatile agent. Steady state is achieved more rapidly with less soluble anesthetic, like desflurane. Temperature influences the solubility coefficient: Lower temperatures increase the solubility of the gas in the blood or tissue, such that for a given partial pressure, the concentration in the blood or tissue will be increased at deep hypothermia compared with normothermia. In the current study, brain and blood temperature during LF-CPB were 22°C, while the inspiratory and expiratory concentrations in the desflurane groups were 9% and 4.5%. Recent data regarding tissue-gas solubility as a function of temperature indicate that desflurane’s solubility in brain tissue and blood increase by approximately 50% from 37°C to 22°C. Assuming steady state during LF-CPB, these data suggest desflurane brain tissue concentrations of approximately 6.25% and 13.5% (22°C) for the 4.5% and 9% desflurane groups, respectively. In the current study, arterial desflurane concentration measured in two piglets in the Des9 group was similar to the predicted value.

The mechanisms by which desflurane improved neurologic outcome following LF-CPB remain uncertain. One possibility is that CBF may have been greater in the desflurane groups than in the F/D group. CBF was measured by laser Doppler flowmetry relative to before CPB. Although the relative decrement in CBF was similar between groups during LF-CPB, pre-CPB CBF may have been higher in the desflurane group, because desflurane has been observed to increase CBF by 40% through cerebral vasodilation, provided arterial pressure is adequate, as was the case before CPB. However, during incomplete ischemia in which arterial pressure is inadequate, differences in CBF have not been observed between fentanyl- and isoflurane-based anesthetics. Technical difficulties associated with laser Doppler flowmetry include interference of larger surface vessels, bleeding, and motion artifacts. The latter two may have contributed to the increased variability and failure rate in the current study.

Another possibility for desflurane’s ability to improve neurologic outcome could be related to CBF during CPB rewarming after LF-CPB. Rewarm after cerebral ischemia is characterized by a phenomenon of delayed hypoperfusion. While controversial, the delayed hypoperfusion is thought to contribute to a second ischemic injury. Although inspired desflurane was discontinued at the onset of CPB rewarming, residual brain desflurane might have increased CBF and averted postischemic hypoperfusion, as suggested by higher CBF in the Des9 group. However, this increased CBF might also indicate no hypoperfusion because of neuroprotection during LF-CPB.

Other possibilities include group differences in brain temperature, arterial P O2, and glucose, although these were unlikely to account for the differences in neurologic outcome. Brain temperature was measured over the cerebral cortex, the region injured. Brain temperature was similar in all groups, yet brain damage score was significantly different. Although Pa O2 was statistically lower in the Des9 group, the magnitude was unlikely to have been physiologically important. The current study showed a trend to higher blood glucose in the F/D group compared with the desflurane groups. In the immature brain, the effect of blood glucose during ischemia on neurologic outcome remains controversial. However, higher glucose levels might indicate a more pronounced stress response, in which other factors might play a role in neuroprotection.

Cellular mechanisms might also play a role in volatile anesthetic neuroprotection. Isoflurane has been shown to decrease extracellular excitatory amino acid concentrations during global ischemia, to block a-amino-3-hydroxy-5-methyl-4-isoxazole prionate and N-methyl-D-aspartate receptors, and to inhibit voltage-gated calcium channels, limiting intracellular calcium, free radical generation, and activation of proteases, lipases, and DNAses. Like isoflurane, desflurane might confer neuroprotection during LF-CPB by blocking both receptor-gated and voltage-gated calcium channels.

The parameters to evaluate myocardial function were blood pressure, heart rate, and presence of arrhythmias. None of these parameters differed between the desflurane groups and the control group before CPB, during CPB cooling, or after separation from CPB. However, an incidental finding of the current study was that desflurane decreased the incidence of ventricular fibrillation during LF-CPB. Although this might have resulted from a direct antiarrhythmic effect of the drug, a more likely explanation is a myocardial protective effect of desflurane, in which ventricular fibrillation is a sign of myocardial oxygen insufficiency. Accordingly, Pagel et al. and Preckel et al. have found that desflurane improves left ventricular function during myocardial ischemia and decreases markers of myocardial cellular injury when used in conjunction with cardioplegia. The use of volatile anesthetics for infant heart surgery may have the benefit of both cerebral and cardiac protection.

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