

Phenylephrine Increases Cerebral Blood Flow during Low-flow Hypothermic Cardiopulmonary Bypass in Baboons

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Background: Although low-flow cardiopulmonary bypass (CPB) has become a preferred technique for the surgical repair of complex cardiac lesions in children, the relative hypotension and decrease in cerebral blood flow (CBF) associated with low flow may contribute to the occurrence of postoperative neurologic injury. Therefore, it was determined whether phenylephrine administered to increase arterial blood pressure during low-flow CPB increases CBF.

Methods: Cardiopulmonary bypass was initiated in seven baboons during fentanyl, midazolam, and isoflurane anesthesia. Animals were cooled at a pump flow rate of 2.5 l · min⁻¹ · m⁻² until esophageal temperature decreased to 20°C. Cardiopulmonary bypass flow was then reduced to 0.5 l · min⁻¹ · m⁻² (low flow). During low-flow CPB, arterial partial pressure of carbon dioxide (P_{CO₂}) and blood pressure were varied in random sequence to three conditions: (1) P_{CO₂} 30–39 mmHg (uncorrected for temperature), control blood pressure; (2) P_{CO₂} 50–60 mmHg, control blood pressure; and (3) P_{CO₂} 30–39 mmHg, blood pressure raised to twice control by phenylephrine infusion. Thereafter, CPB flow was increased to 2.5 l · min⁻¹ · m⁻², and baboons were rewarmed to normal temperature. Cerebral blood flow was measured by washout of intraarterial ¹³³Xe before and during CPB.

Results: Phenylephrine administered to increase mean blood pressure from 23 ± 3 to 46 ± 3 mmHg during low-flow CPB increased CBF from 14 ± 3 to 31 ± 9 ml · min⁻¹ · 100 g⁻¹, *P* < 0.05. Changes in arterial P_{CO₂} alone during low flow bypass produced no changes in CBF.

Conclusion: Although low-flow CPB resulted in a marked decrease in CBF compared with prebypass and full-flow bypass, phenylephrine administered to double arterial pressure during low-flow bypass produced a proportional increase in CBF. (Key words: Anesthesia: cardiovascular. Brain: blood flow; hypothermia. Surgery, cardiac: cardiopulmonary bypass. Sympathetic nervous system, α-adrenoceptor agonists: phenylephrine.)

LOW-FLOW hypothermic cardiopulmonary bypass (CPB) has become a preferred technique for the surgical repair of complex cardiac lesions in infants and children.^{1,2} By reducing pump flow to 20% of full flow, blood return to the surgical field is minimized, thus improving visibility. However, low-flow CPB results in a substantial decrease in cerebral blood flow (CBF) when compared to full flow.³ Because decreased cerebral perfusion has been implicated as an important etiologic factor in the relatively high incidence of neurologic complications after pediatric cardiac surgery,⁴ an intervention to increase CBF might improve outcome in these patients. Therefore, this study was designed to determine if deliberate elevation of arterial pressure with phenylephrine during low-flow hypothermic CPB would increase CBF.

Materials and Methods

After obtaining approval of the Institutional Animal Care and Use Committee of Columbia University, seven baboons (weighing 6–14 kg) of either sex were studied. Anesthesia was induced with 10 mg/kg intramuscular ketamine. Tracheas were intubated and ventilation was controlled with oxygen and isoflurane, 0.25% end-tidal concentration. Femoral arterial and venous

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catheters were placed. Fentanyl (50–100 $\mu\text{g}/\text{kg}$) and midazolam (0.2 mg/kg) were administered intravenously. Vecuronium was administered for neuromuscular block. Electrocardiogram, femoral arterial pressure, and esophageal and rectal temperature were continuously recorded. End-tidal carbon dioxide tension and isoflurane concentration were continuously recorded (CapnoMac, Datex, Helsinki, Finland).

The right common carotid artery was surgically exposed and a 19-mm 24-G polytetrafluoroethylene catheter was inserted and pressures transduced. A 24-G catheter was inserted into the right jugular vein and advanced to the jugular bulb (confirmed at autopsy in some animals). After median sternotomy, the right atrium and aorta were cannulated (DLP, Grand Rapids, MI). Heparin was administered (300 units/kg) to maintain an activated clotting time greater than 480 s. Cardiopulmonary bypass was initiated at a flow rate of $2.5 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^2$ (full flow) with α -stat management of arterial blood gases during full flow. Body surface area was estimated by the formula $A = (12.7) M^{2/3}$.⁵ The bypass circuit consisted of a membrane oxygenator (Cobe, Denver, CO), a roller pump, and 0.25-inch tubing. The system was primed with 175 ml Normosol-R and 175 ml 6% Hespán (DuPont, Wilmington, DE). Surgical blood loss was collected and processed with a Cell Saver 1 (Haemometrics, Braintree, MA) and then added to the bypass circuit. Baboons were cooled at a rate of $0.8\text{--}1.5^\circ\text{C}/\text{min}$ until esophageal temperature decreased to 20°C . Perfusate was cooled by water bath, the temperature of which was lowered to 10°C over 3 min. Once the perfusate reached 20°C , the water bath was maintained at $19\text{--}20^\circ\text{C}$. Once the temperature was stable at 20°C , pump flow rate was decreased to $0.5 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^2$ (low flow).

Arterial blood pressure and arterial partial pressure of carbon dioxide (P_{CO_2}) were altered to achieve each of three conditions during low-flow CPB in random sequence:

1. normocarbia (P_{CO_2} 31–39 α -stat) and control blood pressure
2. hypercarbia (P_{CO_2} 50–60 α -stat) and control blood pressure
3. normocarbia and blood pressure two times control pressure

Blood pressure was increased to twice control by infusion of 160 $\mu\text{g}/\text{ml}$ phenylephrine into the bypass circuit. Changes in arterial P_{CO_2} were made by adjusting oxygenator gas flow by flowmeter.

Thereafter, pump flow rate was increased to $2.5 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^2$ and baboons were rewarmed to greater than 34°C . Cardiopulmonary bypass was terminated when mean blood pressure was stable above 40 mmHg without bypass pump flow.

Cerebral blood flow was measured before CPB, after initiation of full-flow CPB, during the three conditions of low-flow CPB, and after rewarming during full-flow CPB. Each measurement was made after 20 min of unchanged physiologic conditions. For each determination 700 μCi ^{133}Xe in 0.8 ml saline was injected into the common carotid artery with its external branches occluded, and flushed with 2 ml normal saline. Single collimators directed at the superior parietal cortex detected radioactive washout with a Cerebrograph 10a (Novo Diagnostics Systems, Bagsvaard, Denmark). Additional detectors were positioned over the aortic cannula to confirm the absence of recirculating isotope. Clearance was recorded for at least 13 min and CBF was determined by the initial slope,⁶ fitting a mono-exponential decay curve to activity recorded from the scalp for 60 s beginning 3 s after obtaining its peak value.⁷ Values for the blood-tissue partition coefficient for ^{133}Xe were corrected for hematocrit and temperature.⁸

Arterial and jugular venous samples were drawn and analyzed at 37°C in a blood-gas analyzer and CO-Oximeter (Instrumentation Laboratory, Lexington, MA). Arterial and venous oxygen content were calculated by standard formulas.⁹ Cerebral metabolic rate for oxygen was calculated as the product of CBF and the arteriovenous oxygen content difference.

Values for CBF, arteriovenous oxygen content difference, cerebral metabolic rate for oxygen, blood pressure, hematocrit, carbon dioxide tension, and temperature were compared by repeated-measures analysis of variance. Multiple comparisons were made with Fisher's protected least significant difference testing. $P < 0.05$ was considered significant.

Results

Full-flow CPB resulted in a decrease in hematocrit from 33 ± 4 (mean \pm SD) to 18 ± 5 , and an increase in CBF from 27 ± 7 to $50 \pm 17 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$, $P \leq 0.05$ compared to prebypass (table 1). Low-flow CPB of $0.5 \text{ l} \cdot \text{min}^{-1} \cdot \text{M}^2$ was $19 \pm 4 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Low-flow CPB without phenylephrine decreased CBF to 14 ± 3 and $13 \pm 2 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ without and with hypercarbia, respectively ($P < 0.05$). Increasing mean

Table 1. Low-flow Hypothermic Cardiopulmonary Bypass

	Prebypass	Full Flow	Low Flow			Rewarm Full Flow
			Control	Hypercarbia	Phenylephrine	
CBF (ml · min ⁻¹ · 100 g ⁻¹)	27 ± 7*	50 ± 17†	14 ± 3‡	13 ± 2‡	31 ± 9§	46 ± 10
A-VO ₂ (ml/100 ml)	4.5 ± 3.4	3.5 ± 1.5	2.4 ± 0.6	2.0 ± 0.7†	1.2 ± 0.2**	4.1 ± 1.6
CMRO ₂ (ml · min ⁻¹ · 100 g ⁻¹)	1.2 ± 0.5	1.5 ± 0.3	0.4 ± 0.1‡	0.2 ± 0.1‡	0.4 ± 0.1‡	1.9 ± 1.2
MABP (mmHg)	67 ± 10	49 ± 15	23 ± 3	24 ± 2	46 ± 3	71 ± 17
Temperature (°C)	35.3 ± 1.2	35.5 ± 1.2	20.2 ± 1.2	20.6 ± 1.2	20.5 ± 1.1	36 ± 1
Pa _{CO₂} (mmHg)	31 ± 6	33 ± 5	34 ± 3	56 ± 5	34 ± 8	31 ± 5
pH	7.4 ± 1	7.4 ± 0.04	7.38 ± 0.02	7.26 ± 0.02	7.37 ± 0.08	7.4 ± 0.6
Pa _{O₂} (mmHg)	451 ± 82	406 ± 91	360 ± 66	400 ± 77	340 ± 58	324 ± 73
Hematocrit	33 ± 4	18 ± 5	18 ± 5	18 ± 5	18 ± 5	18 ± 5
JVP (mmHg)	8 ± 4	11 ± 5	7 ± 4	7 ± 4	8 ± 4	10 ± 5

Values are mean ± SD; n = 7. Arterial blood gas analysis was performed at 37°C.

CBF = cerebral blood flow; A-VO₂ = cerebral arteriovenous oxygen content difference; CMRO₂ = cerebral oxygen metabolic rate; MABP = mean arterial blood pressure; Pa_{CO₂} = arterial carbon dioxide partial pressure; Pa_{O₂} = arterial oxygen partial pressure; JVP = jugular venous pressure.

* P < 0.05 versus others, except phenylephrine low flow.

† P < 0.05 versus others, except rewarm full flow.

‡ P < 0.05 versus values without ‡.

§ P < 0.05 versus others, except prebypass.

¶ P < 0.05 versus prebypass and full flow.

** P < 0.05 versus others, except low flow control and hypercarbia low flow.

arterial pressure from 23 ± 3 to 46 ± 3 mmHg by infusion of phenylephrine increased CBF to 31 ± 9 ml · min⁻¹ · 100 g⁻¹, P < 0.05. The dose of phenylephrine administered to achieve this was 24 ± 13 μg · kg⁻¹ · min⁻¹. Cerebral metabolic rates for oxygen during hypothermic low-flow CPB were lower than values at higher temperatures. Changes in arterial P_{CO₂} during low-flow CPB did not alter CBF.

All animals were successfully separated from CPB without inotropic drugs. Two animals received 1 mg/kg lidocaine for treatment of ventricular fibrillation during rewarming.

Discussion

This study demonstrates that increasing arterial blood pressure by using phenylephrine markedly increases CBF during hypothermic low-flow CPB. This agrees with our earlier work showing that CBF during CPB is determined by arterial blood pressure.¹⁰ In that study, however, systemic pressure was increased by variable constriction of the descending aorta by snare. Here we report that a clinically applicable pharmacologic intervention will increase CBF while preserving the low-flow state and its surgical advantages.

Our results agree also with the findings of Greeley *et al.*,¹¹ who observed that CBF during deep hypothermic (18–22°C) bypass in pediatric patients correlated with mean arterial pressure (10–70 mmHg; r = 0.74). In that study, however, no intervention was made to control blood pressure. In contrast, van der Linden and colleagues reported that middle cerebral artery blood flow velocity, measured by transcranial Doppler, did not correlate with perfusion pressure (20–42 mmHg; r = 0.14), but did correlate with pump flow rate (r = 0.73) in children during deep hypothermic low-flow CPB.¹² In that study, as well, no intervention was made to control blood pressure.

Clinical evidence has indicated that even the modest cerebral perfusion of low-flow CPB results in improved neurologic outcome when compared to the complete absence of flow during total circulatory arrest.¹ In this clinical trial, children undergoing heart surgery predominantly managed with low-flow CPB demonstrated fewer postoperative clinical seizures and decreased concentrations of the brain isoenzyme of creatine kinase compared to patients managed with total circulatory arrest. Furthermore, at 1 yr of age, children treated with low-flow bypass had superior motor development and fewer neurologic abnormalities compared to those who had had circulatory arrest.² While

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these reports clearly imply that some CBF is superior to no flow at all, it remains to be investigated whether additionally increased CBF will further reduce neurologic injury in these patients.

Neurologic injury during CPB has been postulated to result from inadequate perfusion, embolization, inflammatory intermediates, or altered cerebral vasomotion. It is reasonable to assume, however, that whatever the mechanism of insult, the ultimate end point of injury is cerebral ischemia. Deliberate support of arterial pressure by phenylephrine has been shown to improve outcome from cerebral ischemic insults of various causes,¹³⁻¹⁵ and may prove beneficial for ischemic injury during CPB. This hypothesis that deliberate hypertension during CPB improves neurologic outcome was supported by a large clinical trial in adult surgical patients.¹⁶

Rogers *et al.*¹⁷ reported that phenylephrine administration, to increase mean arterial pressure from 56 ± 7 to 84 ± 8 mmHg (mean \pm SD) in patients during full-flow CPB at 28°C, produced no increase in CBF during α -stat blood gas management ($P_{CO_2} = 41$, uncorrected for temperature). This contrasts with our results, which demonstrate a marked CBF response to phenylephrine. This is almost surely owing to the difference in blood pressure ranges over which CBF was measured by these investigators. Cerebral autoregulation to arterial pressure is likely to apply within the range tested by Rogers *et al.*, whereas our results indicate that arterial pressures of 23–46 mmHg are beyond the cerebral autoregulatory range. The difference in CBF response to changes in blood pressure between these studies also may be caused by differences in temperature. Hypothermic rats at 30.5°C showed no evidence of autoregulation to hemorrhagic hypotension compared to rats at 36.5°C, for whom autoregulation was preserved until mean blood pressure decreased to 75% of baseline.¹⁸ Similarly, during CPB, Greeley *et al.* reported a positive correlation between CBF and mean arterial pressure in pediatric cardiac surgery patients at 18–22°C, but no correlation between blood pressure and CBF in a comparable group at 25–32°C.¹¹ However, Newman *et al.*¹⁹ reported that in elderly patients even moderate changes in arterial pressure resulted in small but significant changes in CBF during CPB within this same temperature range.

In our study, increasing arterial carbon dioxide tension during low-flow CPB resulted in no change in blood flow. This contrasts with the results of clinical

studies performed at higher blood pressures. Gravlee *et al.*²⁰ increased arterial P_{CO_2} from 46 ± 8 to 71 ± 12 mmHg in nine patients during full-flow bypass at a mean blood pressure of 68 mmHg and reported an increase in CBF from 15 ± 3 to 25 ± 6 ml \cdot min⁻¹ \cdot 100 g⁻¹. The difference in response to P_{CO_2} between these studies also can be attributed to the lower blood pressures achieved by us during low flow, where cerebral resistance vessels may be maximally dilated and unresponsive to hypercarbia. This is supported by the work of Okuda *et al.*,²¹ who demonstrated the loss of CBF reactivity to changes in carbon dioxide in baboons during hypotension below the normal limits of autoregulation. In our study, hypercarbia did not significantly alter cerebral metabolic rate for oxygen as has been previously reported in humans.²² This agrees with the results of other clinical and laboratory investigators reporting no discernible effect of P_{CO_2} on brain metabolism during CPB.²³⁻²⁵

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