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Sodium Nitroprusside Infusion Does Not Dilate Cerebral Resistance Vessels during Hypothermic Cardiopulmonary Bypass

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This study determined whether sodium nitroprusside (SNP) changes cerebral vascular resistance during stable, hypothermic cardiopulmonary bypass (CPB). Cerebral blood flow (CBF) was measured using Xenon clearance in 39 patients anesthetized with fentanyl. In 25 patients (group 1), CBF was measured before and during infusion of SNP at a rate sufficient to reduce mean arterial pressure (MAP) ~ 20%. In 14 other patients (group 2), CBF was measured before and during simultaneous infusion of SNP and phenylephrine; SNP was continued at a rate that had reduced MAP ~ 20% while phenylephrine was added in a dose sufficient to restore MAP to preinfusion levels. Patients within each group were randomized to maintenance of Pa_{CO_2} ~ 40 mmHg (groups 1a and 2a), uncorrected for body temperature, or to maintenance of Pa_{CO_2} ~ 50 mmHg (groups 1b and 2b). The following variables were maintained within a narrow range: nasopharyngeal temperature (26–29° C), pump oxygenator flow (1.7–2.5 $l \cdot min^{-1} \cdot m^{-2}$), Pa_{O_2} (150–300 mmHg), and Hct (22–28 vol%). In each patient, controlled variables varied no more than ±5% between measurements. In group 1a (Pa_{CO_2} ~ 40 mmHg), MAP was 86 ± 9 mmHg (mean ± SD) before and 65 ± 8 mmHg during SNP infusion ($P < 0.0001$). CBF was 12 ± 3 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ before and 10 ± 2 $ml \cdot 100^{-1} \cdot min^{-1}$ during SNP infusion ($P < 0.01$). In group 1b (Pa_{CO_2} ~ 55 mmHg), MAP was 86 ± 11 mmHg before and 66 ± 13 mmHg during SNP infusion ($P < 0.0001$). CBF changed from 22 ± 10 to 16 ± 6 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ ($P < 0.05$). In group 2a (Pa_{CO_2} ~ 40 mmHg), MAP was 71 ± 10 mmHg before and 73 ± 9 mmHg during the combined SNP–phenylephrine infusion (P = not significant). CBF was 12 ± 2 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ before and 10 ± 1 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ during the combined infusion ($P < 0.05$). In group 2b (Pa_{CO_2} ~ 50 mmHg), MAP was 74 ± 8 mmHg before and 71 ± 4 mmHg during the combined infusion (P = ns). CBF was 18 ± 5 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ before and 15 ± 5 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ during the combined infusion ($P < 0.01$). The decrease in CBF was statistically similar in each group and was comparable to that previously reported to occur as a function of the duration of stable hypothermic CPB. Restoration of MAP by phenylephrine during continued SNP infusion did not result in either a relative or absolute CBF increase. During nonpulsatile, hypothermic CPB, SNP does not produce primary cerebral vasodilation in humans anesthetized with fentanyl. (Key words: Anesthesia: cardiovascular. Anesthetic techniques: deliberate hypotension. Brain: cerebral blood flow; cerebral oxygen consumption. Cardiopulmonary bypass. Hypothermia: induced. Pharmacology: nitroprusside. Surgery: cardiac. Sympathetic nervous system, alpha-adrenergic agonists: phenylephrine.)

SODIUM NITROPRUSSIDE (SNP) is a systemic vasodilator commonly used to treat acute hypertension and to induce elective hypotension. Because SNP increases intracranial pressure (ICP) in animals and humans,[1–6] it is frequently described as a cerebral vasodilator. However, its effects on cerebrovascular resistance (CVR) remain controversial. When used to induce hypotension, even to profoundly reduced levels of mean arterial pressure (MAP), SNP induces either no change or a slight reduction in cerebral blood flow (CBF); CVR decreases sufficiently to preserve CBF, despite the reduction in cerebral perfusion pressure (CPP).[3,7–14] The effects appear to vary, depending on the anesthetic used. In animals receiving spinal anesthesia, CBF does not change during SNP-induced hypotension; however, CBF decreases during SNP infusion in animals anesthetized with isoflurane.[14] The mechanism by which CVR is reduced during SNP infusion has not been defined. One possibility is that SNP directly dilates cerebral resistance vessels; another possibility is that cerebral pressure autoregulation continues in the presence of SNP (*i.e.*, the physiologic cerebral vasodilatory response to decreasing MAP is preserved).

Two recent studies suggest that SNP may exert direct cerebral vasodilator effects if MAP is restored to normotensive levels. Pinaud *et al.* studied patients undergoing clipping of intracranial aneurysms and found that restoration of MAP to normotensive levels after termination of SNP-induced hypotension (MAP ~ 40 mmHg) resulted

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in a CBF increase to approximately 125% of baseline values.[8] Michenfelder and Milde demonstrated in isoflurane-anesthetized dogs that CBF increased to approximately 120% of baseline if aortic occlusion returned MAP to normotensive levels during SNP infusion.[14]

In patients receiving a high dose of fentanyl (75 $\mu g \cdot kg^{-1}$) and undergoing hypothermic, nonpulsatile cardiopulmonary bypass (CPB), we have previously shown that SNP-induced reductions in MAP of 20 mmHg were associated with reduced CBF in patients managed either at a temperature-uncorrected Pa_{CO_2} level of 42 ± 2 mmHg or a Pa_{CO_2} level of 60 ± 14 mmHg.[10] However, that CBF decrease was similar in magnitude to the decrease in cerebral perfusion previously reported to occur during hypothermic CPB in the absence of pharmacologic alteration of MAP.[15] Therefore, there appeared to be no additional direct SNP effect in patients managed at either lower or higher levels of Pa_{CO_2}. Because cerebral pressure autoregulation appears to be preserved during CPB when temperature-uncorrected Pa_{CO_2} levels are maintained near 40 mmHg,[15] the lack of any drug-induced change in CBF under those circumstances would be expected. However, at the higher Pa_{CO_2} level (54 ± 8 mmHg), CBF is pressure-passive in phenylephrine-treated patients.[15] In these patients with high carbon dioxide levels, the failure of CBF to decrease as predicted in a pressure-dependent fashion with SNP-induced reductions in MAP may be due to direct cerebrovasodilating properties of SNP. Restoration of MAP with phenylephrine (which is believed not to have any direct cerebral vasoconstricting properties[15]), while SNP infusion is continued, should unmask this phenomenon and result in increased CBF and a lower calculated CVR. This hypothesis forms the rationale for the current study.

Materials and Methods

After approval by the institutional Clinical Research Practices Committee, 39 patients scheduled to undergo elective coronary artery bypass grafting (CABG) gave informed, written consent to participate in the study. Exclusion criteria included a clinical history of cerebrovascular disease or uncontrolled hypertension. All subjects were screened with the use of carotid Doppler ultrasonography to exclude asymptomatic extracranial occlusive disease. After preanesthetic medication with lorazepam 50 $\mu g \cdot kg^{-1}$ orally and morphine 0.1 $mg \cdot kg^{-1}$ intramuscularly, subjects were given fentanyl 75 $\mu g \cdot kg^{-1}$ and they were paralyzed with a combination of nondepolarizing muscle relaxants (pancuronium/metocurine); after tracheal intubation, their lungs were ventilated with oxygen (fractional inspired oxygen concentration = 1.0) to maintain normocarbia. Other than heparin, SNP, or phenylephrine, no additional drugs were administered until all measurements had been completed.

In all patients, CPB was conducted through an ascending aortic cannula, using systemic hypothermia (26–29° C) and moderate hemodilution (Hct 22–28 vol%). A membrane oxygenator, arterial filter, and blood-free priming solution were used in each case. Two series of patients were studied. In the first series (group 1), subjects were randomly assigned to maintenance at a lower Pa_{CO_2} level near 40 mmHg (group 1a; n = 13) or to maintenance at a higher Pa_{CO_2} level (50–55 mmHg) (group 1b; n = 12). In the second series (group 2), patients were randomized to a lower Pa_{CO_2} level ~ 40 mmHg (group 2a; n = 8) or to a higher Pa_{CO_2} level (50–55 mmHg) (group 2b; n = 6). All Pa_{CO_2} values are uncorrected for body temperature. Nasopharyngeal temperature (NPT), Hct, Pa_{O_2}, systemic flow rate (Q), and Pa_{CO_2} were not permitted to change more than 5% in individual patients between measurement intervals. Pa_{CO_2} and Pa_{O_2} levels were monitored continuously during CPB with an in-line monitoring device (Bentley Gas-Stat®; CDI, Inc., Irvine, CA); however, data for statistical analysis were obtained by arterial blood-gas sampling (IL 813 Blood Gas Analyzer, Instrumentation Laboratory, Lexington, MA).

Baseline measurements of CBF were performed after aortic cross-clamping when NPT had been stable (±0.2° C) for 3 or more minutes (fig. 1). In group 1, MAP was then decreased 20% from baseline by infusion of SNP into the venous reservoir of the CPB circuit. When MAP had been stable for at least 3 min, the CBF measurement was repeated. In group 2, after baseline CBF measure-

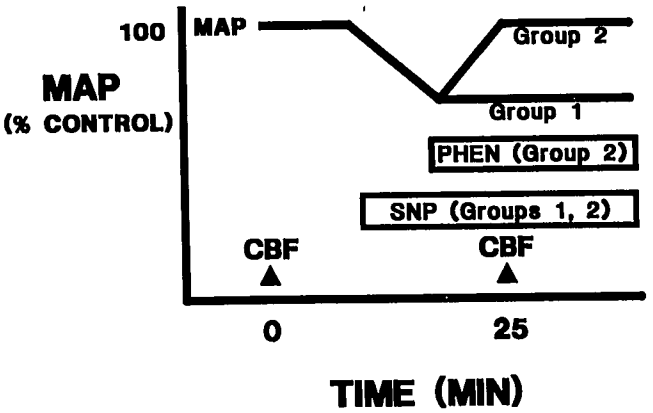

FIG. 1. Experimental design. After preinfusion measurements of cerebral blood flow (CBF), sodium nitroprusside (SNP) was infused until mean arterial pressure (MAP) had declined approximately 20%. In group 1, the second determination of CBF was performed at the lower MAP. In group 2, the SNP infusion was continued while phenylephrine (PHEN) was infused to restore MAP to its previous level. When MAP was stable at that level, the second determination of CBF was performed.

ments had been obtained and SNP had been infused to decrease MAP by 20%, SNP infusion was then continued at the same rate while phenylephrine was infused at a rate sufficient to restore MAP to pre-SNP levels. The measurements were then repeated. Randomization of the order of measurements was precluded because discontinuation of SNP infusion has been associated with rebound cerebral hyperemia lasting approximately 20 min.[7,8] The total time available to study each patient at a consistent body temperature rarely exceeded 40 min, the minimum time required to alter MAP and record two measurements. Had CBF been measured first during SNP or SNP–phenylephrine infusion, subsequent measurements after discontinuation of these agents could not have been considered drug-free control values.

Regional CBF was measured with the use of a helmet containing 16 cadmium telluride gamma detectors. ^{133}Xenon (^{133}Xe) washout was monitored after injection of 3–5 mCi ^{133}Xe (dissolved in saline) into the arterial inflow tubing of the CPB circuit, proximal to the arterial filter. Unlike direct intracarotid injection, this method permits simultaneous study of both cerebral hemispheres and avoids the risk of internal carotid puncture. Each patient was monitored for recirculation of ^{133}Xe by means of a separate detector placed over the arterial inflow tubing. On-line analysis and display of desaturation data from individual brain regions were accomplished with the use of a portable Microvax computer (Microvax I, Digital, Maynard, CA) with a color graphics terminal. Recirculation was not detected in any instance. The CBF_{15} calculation, a noncompartmental computation method originally developed by Obrist and Wilkinson,[16] was used to analyze the clearance curves. In CPB patients, the CBF_{15} method correlates highly with the classic stochastic or height/area (H/A) method, the reference standard for intraarterial injection.[17] ^{133}Xe clearance data were corrected for alterations in temperature and Hct by the formula of Chen *et al.*[18] The second set of measurements was performed approximately 25 min after the first, when MAP had been stabilized with the combined SNP–phenylephrine infusion for 3 or more minutes. This interval between studies ensures a background radioactivity level less than 2.5% of the peak of the first injection, reducing the likelihood of artifact affecting the second CBF measurement. Additionally, the ^{133}Xe dose for the second injection was increased by 50%. Use of the arterial inflow injection technique results in distribution of a small proportion of tracer to the extracerebral compartment. However, this source of error is minimal if the CBF_{15} method is used, because only the first 11 min of the washout curve are used in the calculation.[16] In comparison, clearance from the extracerebral compartment is comparatively slow (≈30–45 min during normothermia).[16] In normothermic patients, the error attributable to blood flow to extracerebral tissues has been calculated to be less than 5%.[19,20] Obrist and Wilkinson have shown, using computerized three-compartment models, that the extracerebral compartment involves a consistent error of less than 3% with the CBF_{15} method.[16]

The mean global CBF was determined for each patient at each measurement interval by averaging regional CBF (rCBF) values from all 16 detectors.

CVR was calculated as follows:

$$\text{CVR (mmHg} \cdot \text{ml}^{-1} \cdot 100\ \text{g} \cdot \text{min)} = \frac{\text{CPP (mmHg)}}{\text{global CBF (ml} \cdot 100\ \text{g}^{-1} \cdot \text{min}^{-1})}$$

where CPP = cerebral perfusion pressure, calculated as follows:

$$\text{CPP (mmHg)} = \text{MAP (mmHg)} - \text{JVP (mmHg)}$$

where JVP = pressure measured in the jugular bulb.

Jugular venous bulb pressure was measured with the use of a 20-G 15-cm jugular bulb catheter, inserted percutaneously and advanced retrograde through the right internal jugular vein before induction of anesthesia. Placement was assumed if patients complained of ear discomfort or if rapid injection of a small bolus of saline produced an ipsilateral roaring sensation. Retrograde passage was confirmed on postoperative chest roentgenograms.

In a subsidiary analysis, we estimated the potential effects of the time-related decrease in CBF reported during stable hypothermic CPB[15] to determine whether that factor might obscure pharmacologic effects. That calculation used the following formula:

$$CBF_{est} = CBF_{infusion} + (CBF_b \times 0.0087 \times \text{time difference})$$

where CBF_{est} = estimated CBF; $CBF_{infusion}$ = CBF during the SNP or the combined drug infusion; CBF_b = baseline CBF; 0.0087 = time correction coefficient; and the time difference between CBF measurements is expressed in minutes.[10,15] The same estimated correction factor was applied to groups 1 and 2.

Statistical Analysis

Controlled variables (NPT, Hct, Pa_{CO_2}, Pa_{O_2}, and Q) were compared within groups with the use of *t* tests to ensure that no differences had occurred between measurement intervals. MAP and the dependent variables (CBF and CVR) within groups were compared by repeated measures analysis of variance (ANOVA) to detect any significant change, defined as $P < 0.05$. An analysis of covariance (ANCOVA) was used to detect any significant

TABLE 1. SNP Infusion Only: Controlled Variables

	Group 1a (Lower Pa_{CO_2})		Group 1b (Higher Pa_{CO_2})	
	Baseline	SNP	Baseline	SNP
Pa_{CO_2} (mmHg)*	40.4 ± 3.4	40.4 ± 2.4	53.2 ± 8.3	55.1 ± 6.9
MAP (mmHg)	86 ± 9	65 ± 8†	86 ± 11	66 ± 13†
JVP (mmHg)	8 ± 4	9 ± 4	12 ± 5	12 ± 4
CPP (mmHg)	77 ± 11	56 ± 9†	74 ± 11	54 ± 15†
NPT (° C)	27.6 ± 1.0	27.7 ± 1.0	27.3 ± 0.7	27.3 ± 0.4
Hct (%)	25.3 ± 3.8	24.3 ± 3.9	25.7 ± 5.2	26.0 ± 4.6
Pa_{O_2} (mmHg)*	281 ± 54	271 ± 62	217 ± 61	276 ± 91
Q ($l \cdot min^{-1} \cdot m^{-2}$)	2.1 ± 0.4	2.1 ± 0.4	1.8 ± 0.3	1.8 ± 0.3

Means ± SD.
MAP = mean arterial pressure; JVP = jugular venous pressure; CPP = cerebral perfusion pressure; NPT = nasopharyngeal temperature; Hct = hematocrit; Q = pump flow.
* Uncorrected for body temperature.
† $P < 0.0001$ in comparison to baseline measurement.

change between groups 1 and 2. All values are expressed as mean ± standard deviation (SD).

Results

Tables 1 and 2 display values for controlled variables during both measurement intervals. In groups 1a and 1b, MAP and CPP declined during SNP infusion according to experimental design (table 1; $P < 0.0001$). In groups 2a and 2b, MAP and CPP were unchanged during the combined SNP–phenylephrine infusion as compared with preinfusion values (table 2). MAP and CPP were different at baseline between groups 1 and 2 ($P < 0.0001$), but not between groups 1a and 1b or between groups 2a and 2b. There were no baseline differences for other variables within or between groups. Within groups, JVP, NPT, Hct, Pa_{CO_2}, Pa_{O_2}, and Q were similar at both measurement intervals. There was no significant intergroup difference in CBF between groups 1a and 2a at baseline or between groups 1b and 2b at baseline (table 3). Table 3 shows that CBF declined in association with SNP infusion in groups 1a ($P < 0.01$) and 1b ($P < 0.05$) and during the combined SNP–phenylephrine infusion in groups 2a ($P < 0.05$) and 2b ($P < 0.01$). Comparison of CVR values for groups 1 and 2 shows that patients with a higher Pa_{CO_2} level had a lower CVR value, confirming previous observations that carbon dioxide is a potent cerebrovasodilator.[21] CVR decreased significantly within group 1a ($P < 0.05$), remained unchanged in group 1b, and increased in groups 2a and 2b during the combined SNP–phenylephrine infusion ($P < 0.01$ and $P < 0.05$, respectively). Subsidiary analysis of these data suggests that CBF would change in a similar manner in groups 1 and 2 if two measurements had been performed during stable hypothermic CPB in the absence of any pharmacologic intervention (table 4).

Discussion

Neurologic and neuropsychologic complications frequently follow CPB.[22–24] Although frank stroke occurs in only 5% of CABG patients and is severe in only 2%,[22] neuropsychologic testing demonstrates cognitive dysfunction in 79% of patients, 24% of whom show severe deficits.[23] Although diffuse microembolization may ex-

TABLE 2. Combined SNP/PHEN Infusion: Controlled Variables

	Group 2a (Lower Pa_{CO_2})		Group 2b (Higher Pa_{CO_2})	
	Baseline	SNP/PHEN	Baseline	SNP/PHEN
Pa_{CO_2} (mmHg)*	41.3 ± 2.7	40.5 ± 1.7	50.0 ± 5.1	50.3 ± 4.9
MAP (mmHg)	71 ± 10	73 ± 9 (NS)	74 ± 8	71 ± 4 (NS)
JVP (mmHg)	8 ± 3	8 ± 4	7 ± 6	9 ± 6
CPP (mmHg)	62 ± 10	65 ± 11 (NS)	67 ± 11	62 ± 8 (NS)
NPT (° C)	27.4 ± 0.6	27.1 ± 0.6	27.0 ± 1.6	26.8 ± 1.5
Hct (%)	24.9 ± 2.9	24.5 ± 3.0	25.8 ± 3.1	25.2 ± 3.3
Pa_{O_2} (mmHg)*	279 ± 57	274 ± 57	311 ± 122	298 ± 106
Q($l \cdot min^{-1} \cdot m^{-2}$)	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.3	2.0 ± 0.2

Means ± SD.
MAP = mean arterial pressure; JVP = jugular venous pressure; CPP = cerebral perfusion pressure; NPT = nasopharyngeal temperature; Hct = hematocrit; Q = pump flow rate; NS = no significant difference.
* Uncorrected for body temperature.

TABLE 3. Cerebral Blood Flow before and during Drug Infusion

	SNP only			
	Group 1a (Lower Pa_{CO_2})		Group 1b (Higher Pa_{CO_2})	
	Baseline	SNP	Baseline	SNP
CBF (ml · 100 g^{-1} · min^{-1})	12 ± 3	10 ± 2*	22 ± 10	16 ± 6‡
CVR (mmHg · ml^{-1} · 100 g · min)	6.8 ± 1.8	5.7 ± 1.5†	4.2 ± 2.4‡	4.3 ± 2.7 (NS)
	SNP/PHEN			
	Group 2a (Lower Pa_{CO_2})		Group 2b (Higher Pa_{CO_2})	
	Baseline	SNP/PHEN	Baseline	SNP/PHEN
CBF (ml · 100 g^{-1} · min^{-1})	12 ± 2	10 ± 1†	18 ± 5	15 ± 5*
CVR (mmHg · ml^{-1} · 100 g · min)	5.4 ± 1.1	6.5 ± 1.2*	4.0 ± 1.3§	4.5 ± 1.6†

Means ± SD.
CBF = cerebral blood flow; CVR = cerebrovascular resistance.
* $P < 0.01$, compared to corresponding baseline measurement.
† $P < 0.05$, compared to corresponding baseline measurement.
‡ $P < 0.05$ for 1a *versus* 1b.
§ $P < 0.01$ for 2a *versus* 2b.

plain some post-CPB deterioration,[25,26] the cause requires additional clarification. During cardiac surgery, the cerebral circulatory effects of physiologic alterations and pharmacologic interventions merit elucidation. If microembolization of debris produces postoperative deficits, cerebral hyperemia might distribute a disproportionate share of emboli to the cerebral circulation.[27] If global cerebral hypoperfusion is etiologic, avoidance of physiologic states or drugs that reduce CBF might also limit the frequency of deficits.[28]

The phenomenon of cerebral pressure autoregulation complicates interpretation of SNP-related changes in CBF and CVR (*i.e.*, if cerebral autoregulation is intact, CVR should decline to maintain CBF as CPP declines). The experimental challenge is to distinguish autoregulatory vasodilation from a direct cerebral vasodilatory effect of SNP. During hypothermic CPB, such studies are constrained by the limited time available during constant hypothermia before systemic rewarming. Nevertheless, the control of potentially confounding variables (*i.e.*, Pa_{CO_2}, systemic flow rate, MAP, and temperature) possible during CPB provides a unique opportunity to accurately characterize pharmacologic effects.

The current study produces, in humans, the experimental conditions necessary to distinguish whether SNP exerts a primary vasodilatory effect on CVR during non-

TABLE 4. Comparison Data to Estimate the Influence of CPB Duration

		Lower Pa_{CO_2} data		Higher Pa_{CO_2} data	
		Baseline	Repeat	Baseline	Repeat
No drug*	Pa_{CO_2} (mmHg)†	41 ± 3	40 ± 4	58 ± 4	60 ± 6
	TE (min)	—	30 ± 20	—	20 ± 4
	CBF (ml · 100 g^{-1} · min^{-1})	16 ± 4	13 ± 2‡	27 ± 7	21 ± 4‡
SNP only (group 1)	Pa_{CO_2} (mmHg)†	40 ± 3	40 ± 2	53 ± 8	55 ± 7
	TE (min)	—	22 ± 8	—	23 ± 7
	CBF (ml · 100 g^{-1} · min^{-1})	12 ± 3	10 ± 2‡	22 ± 10	16 ± 6‡
	CBF_{est} (ml · 100 g^{-1} · min^{-1})	—	13 ± 2 (NS)	—	21 ± 8 (NS)
SNP/PHEN (group 2)	Pa_{CO_2} (mmHg)†	41 ± 3	41 ± 2	50 ± 5	50 ± 5
	TE (min)	—	27 ± 8	—	27 ± 7
	CBF (ml · 100 g^{-1} · min^{-1})	12 ± 2	10 ± 1‡	18 ± 5	15 ± 5‡
	CBF_{est} (ml · 100 g^{-1} · min^{-1})	—	13 ± 2 (NS)	—	20 ± 8 (NS)

Means ± SD.
SNP = sodium nitroprusside; PHEN = phenylephrine; TE = time elapsed between first and second CBF measurements; CBF = cerebral blood flow; CBF_{est} = CBF estimate if duration of CPB had no influence on CBF; NS = no significant difference from baseline CBF value.
* Comparison data from a previously reported study in patients not given any vasoactive drug, and in whom MAP remained unchanged from baseline to the repeat CBF measurement.[15]
† Uncorrected for body temperature.
‡ Significant differene from baseline.

pulsatile, hypothermic CPB. Measurement of CBF during simultaneous SNP and phenylephrine infusion has never been reported in anesthetized humans during CPB. Our data are consistent with those reported by Gelman *et al.*, which demonstrated no change in CBF if SNP was used to offset hypertension induced by aortic cross-clamping.[29] Restoration of MAP with the use of phenylephrine is not directly comparable to aortic occlusion. However, previous data from this laboratory have demonstrated that phenylephrine infusion appears to exert no direct cerebrovascular effects during hypothermic CPB.[15]

Previous studies suggest that, if Pa_{CO_2} is maintained at a temperature-uncorrected level $\sim$ 40 mmHg during hypothermic CPB, cerebral pressure autoregulation is preserved.[15] However, the data at higher levels of Pa_{CO_2} defy simple interpretation. Based on our previous phenylephrine data,[15] autoregulation is impaired at a Pa_{CO_2} level of 55 ± 7 mmHg; *i.e.*, when MAP increases with phenylephrine infusion, CBF increases significantly. This is consistent with the contention that higher Pa_{CO_2} management induces cerebral vasodilation and impairs pressure autoregulation. Consequently, if SNP exerts no direct cerebrovascular effects at a higher Pa_{CO_2} level, SNP-induced decreases in MAP should be associated with pressure-passive decreases in CBF that exceed the decrease associated with the duration of CPB. Such significant decreases did not occur in our previous SNP study at a mean Pa_{CO_2} level $\sim$ 60 mmHg,[10] nor did they occur in the current study at a Pa_{CO_2} level of 50–55 mmHg. Therefore, one might conclude that SNP had a direct cerebral vasodilatory effect. However, that explanation is disproved by the current observation that CBF did not increase with MAP restoration by SNP–phenylephrine. Viewed together, these data suggest that SNP exerts no direct cerebral vasodilatory effect and preserves autoregulatory vasodilation during CPB even in patients managed at a Pa_{CO_2} level of 50 mmHg.

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