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Cerebral Blood Flow and Cerebral Oxygen Consumption during Nitroprusside-induced Hypotension to Less than 50 mmHg

Michel Pinaud, M.D., Ph.D., Rémi Souron, M.D.,† Jean-Noël Lelausque, M.D.,‡ Marie-France Gazeau, M.D.,‡ Youenn Lajat, M.D.,§ Bernard Dixneuf, M.D.†*

The authors determined the effect of profound induced hypotension (*i.e.*, mean arterial blood pressure < 50 mmHg) during craniotomy for cerebral aneurysm on cerebral blood flow and cerebral metabolic rate for oxygen before, during, and after (20 min and 40 min after) the hypotensive period. The study was performed on nine adults (mean age, 29.2 yr) who were awake and conscious without peripheral neurologic deficits at the time of surgery. The study was conducted with the dura open with the use of a radial artery cannula, a 7-Fr thermodilution flow-directed pulmonary artery catheter, and an internal jugular vein catheter. The ^{133}xenon intraarterial injection technique was used to determine regional cerebral blood flow (rCBF) in the nonoperated hemisphere. rCBF remained unchanged (from 22.8 ± 4.1 ml · 100 g^{-1} · min^{-1} to 23.8 ± 4.6 ml · 100 g^{-1} · min^{-1}) during the hypotensive period (MAP from 87.8 ± 10.4 mmHg to 40.0 ± 4.4 mmHg; $P < 0.001$) despite an increase in cardiac index since cerebral perfusion pressure and cerebrovascular resistance decreased to a similar degree. No gross cerebral metabolic disturbances were observed. A period of decreased cerebrovascular resistance and increased rCBF followed induced hypotension. rCBF increased from 23.8 ± 4.6 ml · 100 g^{-1} · min^{-1} to 30.0 ± 5.8 ml · 100 g^{-1} · min^{-1} ($P < 0.001$) 20 min after sodium nitroprusside (SNP) was stopped without rebound hypertension. These modifications disappeared 20 min later. Reduction of mean arterial blood pressure to 40 mmHg by SNP was apparently safe for the brain, although the possibility of low perfused regions and local brain and cerebrospinal fluid lactoacidosis, particularly in the retracted hemisphere, cannot be excluded. (Key words: Anesthesia: neurosurgical. Anesthetic techniques: hypotension. Brain: blood flow; oxygen consumption.)

DELIBERATE HYPOTENSION for ligation of cerebral aneurysms facilitates surgical dissection and minimizes the potential for aneurysmal rupture.[1] Unfortunately, this maneuver may interfere with cerebral circulation and metabolism by impairing circulation in peripheral regions of ischemic brain tissue, by increasing the likelihood of vasospasm, and by interfering with cerebral blood flow (CBF) autoregulation.[2] Based on CBF autoregulation thresholds and clinical experience, reduction of mean arterial pressure (MAP) to 50 mmHg is usually considered safe for the brain in the absence of cerebrovascular disease and arterial hypertension in normothermic patients.[3,4] In fact, CBF remains similar to baseline values, with reduction of MAP to 50 mmHg with sodium nitroprusside.[5–8] However, surgical conditions may require an extremely low arterial pressure of less than 50 mmHg.[9,10] A number of conflicting reports concerning the effects of nitroprusside on cerebral circulation in animals have been published,[11–16] but there are no data documenting the consequences of reduction of MAP to less than 50 mmHg on the human brain.

Accordingly, this study was undertaken to determine the effects of nitroprusside-induced hypotension—during craniotomy for cerebral aneurysm—on CBF and cerebral metabolic rate for oxygen (CMR_{O_2}) in the prehypotensive, intrahypotensive, and posthypotensive periods.

Materials and Methods

After approval by our local Subcommittee on Human Research, informed consent was obtained from the patients and from members of their families. The study was performed on nine patients subjected to surgery for the elective clipping of a cerebral aneurysm during nitroprusside-induced hypotension. Craniotomy was delayed 10–15 days after the initial subarachnoid hemorrhage had occurred from a ruptured congenital aneurysm, that is until neurologic function was optimal (asymptomatic patient or with minimal headache and nuchal rigidity), and no cerebral vasospasm was found on angiograms. The mean age of patients was 29.2 yr (range, 22–40 yr) and the mean weight 63.8 kg (range, 45–78 kg). In the preoperative phase, therapy to prevent aneurysm rerupture included sedation and arterial blood pressure control (*i.e.*, calcium entry blocking agent). At the time of surgery, all patients were awake and conscious without peripheral neurologic deficits (grade I or II in the Hunt and Hess classification[17]).

One hour before induction of anesthesia, droperidol (150 μg/kg) was administered im. Anesthesia was induced iv with thiopental (6 mg/kg) supplemented with phenoperidine (30 μg/kg). Succinylcholine (1 mg/kg iv) was administered to facilitate tracheal intubation. Ventilation

* Assistant Professor of Anesthesiology.
† Professor of Anesthesiology and Chairman.
‡ Staff Anesthesiologist.
§ Professor of Neurosurgery, Service de Neurochirurgie.

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Address reprint requests to Dr. Pinaud: Département d'Anesthésiologie, Hôtel-Dieu, 44035 Nantes Cédex 01, France.

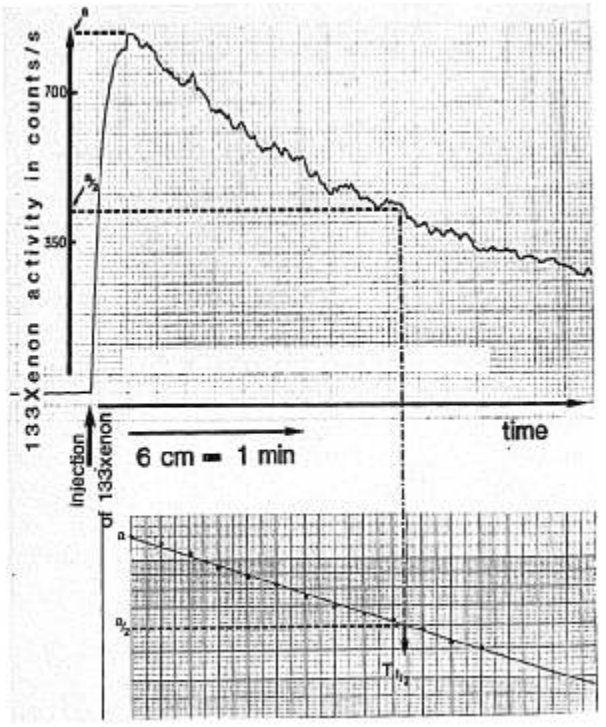

FIG. 1. *A* (upper). Clearance curve of hemispheric radioactivity following the injection of 1 mCi of ^{133}xenon in the internal carotid artery. *B* (lower). Determination of the time ($T_{1/2}$) required for the peak activity (a) to return to ½ peak activity (a/2) after semilogarithmic transform of the first 2 min of the clearance curve.

was controlled with nitrous oxide in oxygen (Fi_{O_2} = 0.5) and end-expiratory carbon dioxide concentration monitored to maintain FE_{CO_2} in the 30–35 mmHg range. Additional doses of phenoperidine (1–2 mg) and droperidol (5 mg) were administered every 30 min, and neuromuscular blockade was maintained with alcuronium. Glucose infusion was stopped during surgery before induced hypotension.[2] Mannitol was not used.

Heart rate (HR) was obtained from precordial electrodes. The following catheters were placed after induction of anesthesia: a radial artery cannula for blood sampling and arterial blood pressure measurement referenced to the level of Circle of Willis, and a 7-Fr thermodilution flow-directed pulmonary artery catheter was inserted into the pulmonary artery with the use of fluoroscopy to measure right atrial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure (PCWP), and cardiac output (CO). CO was determined with iced injectate in triplicate. Blood temperature in the pulmonary artery (θ) was obtained from the thermistance of the flow-directed pulmonary artery catheter. Derived hemodynamic values were calculated in the usual manner[18]: cardiac index (CI), stroke index (SI), and systemic vascular resistance index (SVRI). A polyethylene catheter was positioned in the internal jugular vein contralateral to the aneurysm to obtain jugular venous bulb pressure (Jug P) and blood samples. Blood–gas tensions, *p*H, HCO_3^-, hemoglobin, and hemoglobin saturation were measured in arterial blood and in jugular venous blood. Lactate concentrations were measured in jugular venous blood (Jug lact). Cerebral perfusion pressure (CPP) was calculated as MAP-Jug P.

Another small polyethylene catheter was placed *via* the common carotid artery to the internal carotid artery on the side contralateral to the aneurysm. The correct position of the catheter in the internal carotid artery was verified by fluoroscopy. The ^{133}xenon intraarterial injection technique was used to determine hemispheric regional cerebral blood flow (rCBF). A bolus of 1 mCi of ^{133}xenon dissolved in 1 ml sterile saline solution was quickly injected into the internal carotid artery (injection time: 1–2 s). The wash-out of radioactivity was measured by a portable detector (Mecaserto® Mo 141) placed over the ipsilateral temporoparietal area of the skull. Collimation was provided by a cylindric lead tube and a (1" × 1") NaI crystal. The detector was connected to a rate meter equipped with a linear writing potentiometer. rCBF was calculated from the slope of the logarithmically displayed first 2 min of the clearance curve,[19] according to the following equation: $rCBF = 100 \cdot \lambda \cdot 0.693 \cdot T_{1/2}^{-1}$, where $T_{1/2}$ is the time required for peak activity to return to ½ peak activity and λ is the average blood-to-tissue partition coefficient (fig. 1). Cerebrovascular resistance (CVR) was calculated as CPP/rCBF. CMR_{O_2} was obtained from the product of arteriojugular venous difference in oxygen contents and rCBF (CMR_{O_2} = rCBF × C [a-jug v]O_2).

Data were collected four times during anesthesia with the dura open: the first set of measurements was done just before starting infusion of nitroprusside (before); nitroprusside (concentration: 200 mg/l) was then infused to maintain MAP close to 40 mmHg from the time of aneurysm exposure to clipping. The second set of measurements was done 5 min after MAP had stabilized at the expected level (during). After clipping, the dose of nitroprusside was progressively diminished (during 3–5 min) to avoid hypertensive rebound. The last two sets of measurements were done 20 (after 20) and 40 min (after 40) after nitroprusside was discontinued.

The data are presented as mean ± SD. Data were analyzed by ANOVA and Scheffé's method. A P value < 0.05 was considered significant.

Results

The operative conditions were excellent. There was no evidence of brain herniation, and no cerebral dysfunction was apparent in the postoperative period.

TABLE 1. Systemic and Cerebral Hemodynamic and Metabolic Values

	Before SNP	During SNP	20 Minutes after Stopping SNP	40 Minutes after Stopping SNP	ANOVA *P* Value
HR (beats/min)	78.1 ± 10.0	96.6 ± 14.0*	82.3 ± 13.8†	82.6 ± 13.6†	<0.02
MAP (mmHg)	87.8 ± 10.4	40.0 ± 4.4*	92.3 ± 9.9†	90.2 ± 10.6†	<0.001
PCWP (mmHg)	5.1 ± 1.5	3.8 ± 1.6	4.3 ± 1.5	4.7 ± 1.9	NS
CI ($l \cdot min^{-1} \cdot m^{-2}$)	2.91 ± 0.49	3.90 ± 0.66*	2.86 ± 0.48†	2.89 ± 0.56†	<0.001
SVRI ($dyn \cdot s \cdot cm^{5} \cdot m^{2}$)	2280 ± 470	740 ± 280*	2470 ± 590†	2420 ± 560†	<0.001
CPP (mmHg)	84.4 ± 11.1	37.8 ± 4.5*	89.5 ± 10.1†	88.4 ± 10.6†	<0.001
rCBF ($ml \cdot 100\ g^{-1} \cdot min^{-1}$)	22.8 ± 4.1	23.8 ± 4.6	30.0 ± 5.8*†	22.2 ± 4.1¶	<0.01
CVR ($mmHg \cdot ml^{-1} \cdot min^{-1} \cdot 100\ g$)	3.85 ± 0.69	1.55 ± 0.53*	2.95 ± 0.66‡§	3.94 ± 0.68†**	<0.001
$CMRO_2$ ($ml\ O_2 \cdot 100\ g^{-1} \cdot min^{-1}$)	2.71 ± 0.48	2.50 ± 0.51	2.97 ± 0.57	2.69 ± 0.43	NS
Jug lact (mmol/l)	1.35 ± 0.26	1.42 ± 0.27	1.43 ± 0.26	1.40 ± 0.30	NS
Pa_{CO_2} (mmHg)	32.7 ± 2.9	32.5 ± 3.1	33.3 ± 2.8	33.0 ± 2.7	NS
Θ (°C)	36.1 ± 0.3	36.0 ± 0.3	36.0 ± 0.3	35.9 ± 0.4	NS

Abbreviations: HR = heart rate; MAP = mean arterial blood pressure; PCWP = pulmonary capillary wedge pressure; CI = cardiac index; SVRI = systemic vascular resistance index; CPP = cerebral perfusion pressure; rCBF = mean regional cerebral blood flow; CVR = cerebral vascular resistance; CMR_{O_2} = cerebral metabolic rate for oxygen; Jug lact = lactate concentration in jugular venous blood; Pa_{CO_2} = arterial carbon dioxide tension; Θ = blood temperature in the pulmonary artery; SNP = sodium nitroprusside.

Data (mean ± SD) were collected in nine patients subject to craniotomy for cerebral aneurysm during sodium nitroprusside- (SNP) induced hypotension; when compared with prehypotensive values: *$P < 0.001$; ‡$P < 0.01$; when compared with values during hypotension: †$P < 0.001$; §$P < 0.01$; when compared with values 20 min after stopping nitroprusside: ¶$P < 0.001$; **$P < 0.01$.

Data are summarized in table 1. Nitroprusside, infused at 10.1 ± 3.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during 21.8 min (range, 16–30 min), rapidly produced arterial hypotension, decreasing MAP from 89 mmHg on average to 40 mmHg on average in the nine patients studied. This 55% decrease in MAP was associated with a decrease in SVRI, whereas CI increased. Mean rCBF for the group remained unchanged (from 22.8 ± 4.1 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ to 23.8 ± 4.6 $ml \cdot 100\ g^{-1} \cdot min^{-1}$) during profound induced hypotension and decreased CPP (from 84.4 ± 11.1 mmHg to 37.8 ± 4.5 mmHg), despite the increase in CI, because CPP and CVR decreased to a similar degree. CMR_{O_2} was unchanged. The same pattern was found for all individual values (fig. 2).

Twenty minutes after nitroprusside was stopped and MAP and CPP were reestablished without rebound hypertension, a slight but significant increase in rCBF (from 23.8 ± 4.6 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ to 30.0 ± 5.8 $ml \cdot 100\ g^{-1} \cdot min^{-1}$) was observed, whereas CVR remained significantly lower in comparison with prehypotensive values. Forty minutes after nitroprusside was discontinued, systemic and cerebral data were unchanged in comparison with prehypotensive values.

Discussion

The rCBF results obtained in this study are approximately 40% lower than those in awake normal subjects. Although such low cerebral blood flow levels have been observed in patients with subarachnoid hemorrhage,[20–24] the absence of preoperative cerebral vasospasm on angiography and of neurologic deterioration would seem to exclude this possibility in our patients. The anesthetics used may have accounted for the low rCBF because thiopental, droperidol, and fentanyl decrease CBF in humans.[25–28] Such baseline values in the 18–35 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ range have been found by other investigators during thiopental–phenoperidine–pancuronium,[29] etomidate,[30] or Althesin®[31] anesthesia. The role of hypothermia and hypocapnia may be excluded because they were moderate. Finally, the ^{133}xenon intraarterial injection technique may have been a factor. The clearance of the isotope was followed by a single collimated scintillation detector measuring the CBF of gray matter in the tem-

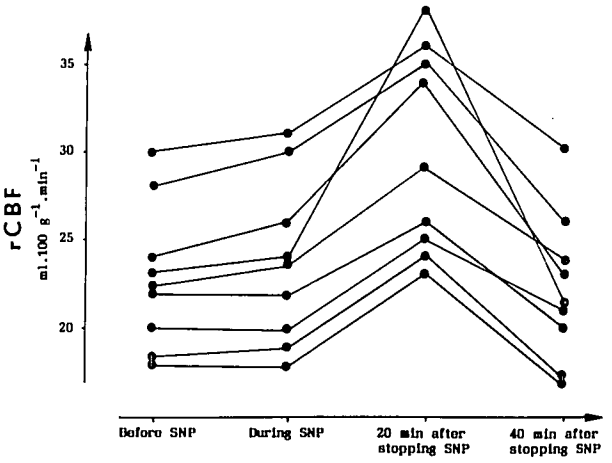

FIG. 2. The individual effect of sodium nitroprusside (SNP) infusion on cerebral blood flow (rCBF) in nine patients operated for cerebral aneurysms.

poroparietal region. Although such detected changes in radioactivity are considered representative of mean hemispheric blood flow in milliliters per 100 g of brain per minute,[5] we may suppose that the counting of radioactivity from brain tissue in the peripheral field of our single detector was less efficient than that of multiple collimated scintillation detectors. Hence, the measured radioactivity and consequently hemispheric blood flow may have been underestimated. However, inasmuch as anesthesia, arterial carbon dioxide tension, blood temperature, and the position of the detector on the skull remained unchanged throughout the procedure, and because no mannitol was infused,[32] the changes in rCBF can be accurately compared.

In our series, rCBF remained constant despite changing arterial blood pressure during profound nitroprusside-induced hypotension but increased after discontinuance of nitroprusside and reestablishment of MAP without rebound hypertension. Only four studies in humans have previously documented the effects of nitroprusside on cerebral blood flow and metabolism in anesthetized patients.[5-8] In these studies CBF appears to have been maintained at MAP of 50–65 mmHg in neurosurgical patients[5-7] or those having total hip replacement.[8] Despite the apparent safety margin between the generally accepted safe lower limit of MAP of 50–55 mmHg[33] and the well-tolerated one demonstrated in our study (MAP = 35–45 mmHg), the critical pressure below which CBF decreases significantly cannot always be predicted for a given patient.

The constant flow, despite increased CI, down to extremely low CPPs, is consistent with the findings of Fitch *et al.*[34] in baboons showing that sodium nitroprusside extended the lower range of autoregulation. Although nitroprusside acts directly on the cerebral vasculature[35] and stimulates the renin–angiotensin and sympathetic nervous systems,[36] it is difficult to differentiate autoregulation (passive effects mediated through changes in systemic blood pressure) from the direct and indirect effects of the drug. It would only seem that the combination of anesthesia and cerebrovascular dilatation resulting from nitroprusside preserves cerebral perfusion, so that a pronounced reduction in arterial blood pressure can be tolerated without any decrease in CBF. However, even if cerebrovascular resistance and cerebral perfusion decreased to a similar degree, to maintain rCBF, the possibility of low perfused regions cannot be excluded with the method used (single detector). Moreover, rCBF values were obtained on the side contralateral to the aneurysm and thus in the nonretracted hemisphere. The direct approach of aneurysms implies frontal and/or temporal retraction. Reductions in rCBF may also occur at the site of retraction because of reduced local cerebral perfusion pressure by retractor compression.[37,38]

The CMR_{O_2} was derived as the product of the fast component of the clearance curve (gray matter flow) and the difference in arteriojugular venous oxygen contents. Although jugular venous flow contains blood draining from gray and white matter, CMR_{O_2} is not a true value of gray matter use. However, this method is currently used for estimation of CMR_{O_2}.[5-8] The profound degree of hypotension used in our study did not produce a decrease in either rCBF or CMR_{O_2} or an increase in lactate concentration of jugular venous blood. These results, in agreement with previous human studies,[5-8] do not demonstrate any evidence of poor cerebral tissue oxygenation and cerebral ischemia. Finally, nitroprusside in our series reduced MAP but not cerebral metabolic activity, and the patients were not in as good a cerebral metabolic condition as those receiving isoflurane.[39,40]

After discontinuance of nitroprusside and reestablishment of MAP without rebound hypertension, we observed a significant (26%) increase in rCBF, whereas cerebrovascular resistance compared to the hypotensive period but remained lower than its prehypotensive values. CBF and cerebrovascular resistance returned to preinfusion levels 40 min after cessation of nitroprusside. A 13% increase in CBF was also found by Henriksen *et al.* 10–15 min after termination of nitroprusside in anesthetized neurosurgical patients[7]; however, these authors made no later measurements to determine when CBF returned to its prehypotensive values. All these results suggest prolonged direct nitroprusside-induced vasodilation in brain vessels compared with peripheral vessels and a redistribution of blood flow to the brain. Cerebral vasodilatation may occur without a decrease in systemic vascular resistance.[41] This displacement of a portion of blood volume into the cerebral circulation previously dilated by nitroprusside may indicate an impairment of cerebral autoregulation.[35] Consequently, sudden increases in arterial blood pressure must be avoided not only during the hypotensive period but also during the postinfusion period, because they may be associated with precipitous increases in CBF. A loss of autoregulation has also been demonstrated by Okuda *et al.* after halothane-induced hypotension to blood pressure below 50 mmHg.[42]

The hypothesis of a luxury–perfusion syndrome is an unlikely explanation[43] because CBF was not decreased and lactate jugular venous blood concentrations were not increased during the hypotensive period. However, the possibility of low perfused regions and local brain and cerebrospinal fluid lactoacidosis cannot be excluded.

We conclude that during aneurysm clipping in patients with good neurologic function (grade I or II in the Hunt

and Hess classification), mean regional cortical CBF in the nonoperated hemisphere remained unchanged despite a major nitroprusside-induced reduction in blood pressure (decrease in CPP from 84.4 ± 11.1 mmHg to 37.8 ± 4.5 mmHg).

Thus, under the conditions of our study, a reduction of MAP to 40 mmHg by nitroprusside was apparently safe for the brain. As indicated above, low perfused regions and local brain and cerebrospinal fluid lactoacidosis, especially in the retracted area, cannot be excluded.

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