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The Cerebral Pressure–Flow Relationship during 1.0 MAC Isoflurane Anesthesia in the Rabbit: The Effect of Different Vasopressors

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The influence of different vasopressors on the cerebral pressure–flow relationship during 1.0 MAC isoflurane anesthesia has been studied. Mean arterial pressure (MAP) was increased by one of three vasopressors [angiotensin II (AT), norepinephrine (NE), or phenylephrine (PE)] in three groups of New Zealand white rabbits (n = 11, 10, and 9, respectively). Regional cerebral blood flow (CBF) was measured at five intervals by the injection of radioactive microspheres at a stable 2.05% (1.0 MAC) end-tidal isoflurane concentration (baseline) and following elevation of mean arterial pressure (MAP) by 20%, 40%, 60%, and 80% above baseline MAP with either AT, NE, or PE. Baseline MAP was the same in all groups. No differences in MAP were seen between groups when MAP was elevated from 20% to 80% above baseline. Normocapnia (Pa_{CO_2} 35.8–38.2 mmHg) was maintained throughout. Total cerebral blood flow (tCBF), hemispheric CBF (hCBF), and posterior fossa (cerebellum and brain stem) CBF (pCBF) were determined. Baseline tCBF, hCBF, and pCBF was similar in all groups. For each experiment a pressure–flow curve was generated by curvilinear regression analysis. Mean slopes and intercepts were derived for each group. For all regions examined, the slope of the pressure–flow curve was significantly less steep when MAP was elevated with AT *versus* NE or PE ($P < 0.05$ Tukey's studentized range test). There was no difference in slope between the NE and PE groups for any region. These results indicate that either NE and PE result in indirect cerebral vasodilation or that AT has intrinsic cerebral vasoconstrictive effects during 1.0 MAC isoflurane anesthesia in the rabbit. Thus, in the rabbit choice of vasopressor critically influences the interpretation of whether cerebrovascular autoregulation is intact during isoflurane anesthesia. (Key words: Anesthetic, volatile: isoflurane. Animal model: rabbit. Brain: blood flow. Measurement technique: radioactive microspheres. Pharmacology: angiotensin II; norepinephrine; phenylephrine.)

TO STUDY THE EFFECT of anesthetics on cerebrovascular autoregulation, vasopressors are usually infused to increase mean arterial pressure (MAP). Such studies assume that vasopressors in themselves do not alter cerebrovascular resistance.[1,2] However, various studies have shown that cerebral blood flow (CBF) may be markedly different when MAP is raised to similar values with different vasopressors.[3–5] Thus, the interpretation of retained or impaired cerebrovascular autoregulation for an anesthetic agent in a given study may be critically dependent on the vasopressor used for the experiment. To rigorously assess this hypothesis, cerebral pressure–flow curves for each vasopressor should contain a number of data points to accurately delineate the nature of the curve over an extensive pressure range. In this fashion, differences between vasopressors may then become apparent.

In this study using radioactive microsphere methodology, with up to five regional CBF (rCBF) determinations per experiment, we have compared how each of three different vasopressors [angiotensin II (AT), norepinephrine (NE), or phenylephrine (PE)] influence the cerebral pressure–flow relationship during 1.0 MAC isoflurane anesthesia in the rabbit.

Methods

These experiments were approved by the Animal Care Committee of the University of Manitoba. Animals were allowed free access to food and water until the time of the experiment. New Zealand white rabbits (2.5–3.0 kg) were placed in a plexiglass box and anesthetized with a free flow of 5% isoflurane in oxygen at 6 l/min. The animals were then paralyzed with succinylcholine, 40 mg im, the trachea intubated, and the lungs ventilated at a respiratory rate of 30 breaths/min and a tidal volume of 15 ml/kg. Carbon dioxide was introduced into the inspiratory tubing, and end-tidal CO_2 was continuously monitored by a Puritan-Bennett 223 CO_2 monitor and maintained in the range of 35–40 mmHg. Anesthesia was maintained with 2.05% end-tidal isoflurane (1.0 MAC)[6] as measured continuously by an infrared anesthetic gas analyzer (Beckman LB-2). Isoflurane was delivered by a previously calibrated agent specific Ohio Medical Products vaporizer.

Rectal temperature was maintained at 38 ± 1° C by a servocontrolled heat lamp. PE-90 catheters were introduced into each femoral artery for continuous MAP monitoring, arterial blood sampling, and blood withdrawal. A PE-50 catheter was placed in the left femoral vein for fluid and drug administration. The right femoral vein was cannulated and a PE-50 catheter advanced into the thoracic inferior vena cava; its position was confirmed by inspection of the central venous pressure (CVP) trace and at post mortem. A left thoracotomy was performed and a left atrial (LA) catheter was inserted for radioactive microsphere injection. The animals were turned prone and the head secured in the sphinx position in a stereo-

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tactic head frame. Following a dorsal neck skin incision, a 22-G pediatric spinal needle was introduced into the cisterna magna by a micromanipulator for intracranial pressure (ICP) monitoring. Blood pressure and ICP were recorded at end-expiration using calibrated Gould P23 transducers referenced to the level of the cisterna magna; MAP and mean ICP were obtained by electronic integration.

Following surgical preparation, all wounds were infiltrated with 0.25% bupivicaine, and pancuronium 2 mg was administered intravenously for muscle paralysis. Except for the withdrawal of arterial blood samples for measurement and adjustment of Pa_{CO_2}, the animals were left undisturbed for a period of 1 h.

Data were recorded on paper by a Gould oscillograph and on hard disk using an IBM PC-AT computer-based data acquisition system (Dataq Instruments). Arterial blood gases (ABG) and hemoglobin concentration were measured with a blood gas analyzer (ABL 3, Radiometer, Copenhagen) immediately before and after radioactive microsphere injection.

Microsphere Preparation

Microspheres (15 μm diameter) of ^{46}Sc, ^{85}Sr, ^{141}Ce (3M Company), and ^{95}Nb and ^{113}Sn (New England Nuclear) were suspended in normal saline. Small samples of the microsphere suspensions were placed on graph paper, and the microspheres were counted through a microscope. These samples were then placed in a gamma counter (LKB Compugamma) and counts $\cdot$ min^{-1} $\cdot$ sphere^{-1} were obtained for each radionuclide. This information was subsequently used to determine the total number of microspheres injected and the number of microspheres present in the tissue and reference blood samples. Prior to use, the microspheres were ultrasonically agitated in a water bath for 20 min and then thoroughly agitated with a Deluxe Mixer (American Hospital Supply Corporation). Approximately 300,000–500,000 microspheres in a volume of 0.05–0.075 ml was drawn into separate syringes; the use of this number of microspheres resulted in the presence of at least 600–800 microspheres in the smallest tissue sample studied and about 1,200–1,500 microspheres in the reference blood sample.[17] Immediately prior to injection, the syringes were thoroughly agitated as above.

Experimental Protocol

CBF was determined with five separate microsphere injections in each animal. The first flow (baseline) was measured at baseline MAP and stable 1.0 MAC end-tidal isoflurane concentration. Subsequent flows (flows 2, 3, 4, and 5) were measured after increasing MAP to 20%, 40%, 60%, and 80% above baseline MAP with AT (20 μg/ml, Sigma Chemicals) in group AT animals, NE (32 μg/ml, Winthrop Laboratories) in group NE animals, and PE (120 μg/ml, Winthrop Laboratories) in group PE animals. Animals were randomly assigned to each of the three groups. The vasopressors were administered into the left femoral vein by Harvard infusion pump. The infusion rate of the vasopressor was slowly increased to gradually elevate MAP at a rate not exceeding 2–3 mmHg/min. The MAP was allowed to stabilize at the desired level for 5 min prior to the injection of the radioactive microspheres.

Regional blood flows were determined by LA injection of radioactive microspheres.[8,9] The selection of microspheres was randomized. The microspheres were flushed into the LA with a normal saline infusion by Harvard pump at a rate of 2.47 ml/min over a period of 20 s. Hemodynamic alterations and cardiac rhythm disturbances were not seen following microsphere injection. Using a Harvard pump, 3.0 ml of blood was withdrawn from the femoral artery over 120 s starting 20 s before injection of microspheres. Total counts/min in each syringe before and after injection were measured by gamma counter.

After the fifth microsphere injection, the ventilator was disconnected and the animal was decapitated. The brain was removed and the pia mater stripped away. Right and left frontal, parietal and occipital lobes, cerebellum, and brain stem were weighed in glass vials. The organ and reference blood samples were centrifuged to minimize gamma counting error[7] and placed in the gamma counter. Counts/min were converted to regional blood flow (ml $\cdot$ g^{-1} $\cdot$ min^{-1}) and cardiac output (CO) (ml/min) by computer as previously described.[10]

Total brain blood flow (tCBF) in ml $\cdot$ g^{-1} $\cdot$ min^{-1} was determined by the summation of weighted flows to all brain regions. Similarly, cerebral hemispheric CBF (hCBF) and posterior fossa CBF (pCBF) were determined by the summation of weighted flows to the cerebral hemispheres and posterior fossa, respectively.

Statistical Methods

Time-related changes for each group were evaluated by analysis of variance (ANOVA) for repeated measures. Within- and between-group comparisons were made using the least-squares means test. Bonferroni's correction was applied ($P \leq 0.05/n$; where n = number of comparisons) when multiple comparisons were made. The corrected P value was considered statistically significant.

For each experiment curvilinear regression analysis of the raw data relating pressure to flow yielded curves of the form $y = Ae^{Bx}$ (fig. 1). In all instances the data could be successfully fit to the equation shown. The correlation coefficient was higher for the majority of curves analyzed in this fashion than by linear regression analysis. The mean slope (B) and mean intercept (A) of tCBF *versus* MAP, hCBF *versus* MAP, and pCBF *versus* MAP were derived

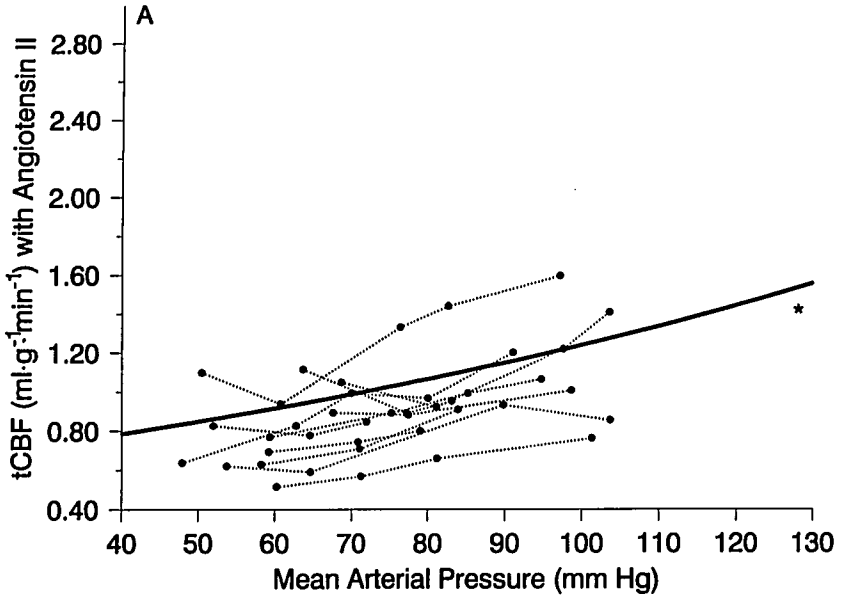

FIG. 1. *A.* Plot of tCBF *versus* MAP of the raw data for the 11 experiments in the AT group. The equation of the solid line is $y = 0.58e^{0.008x}$ as derived from curvilinear regression analysis of pressure–flow data from the 11 experiments. $*P \leq 0.05$ *versus* mean slopes in figure 1*B* and 1*C* (Tukey's studentized range test).

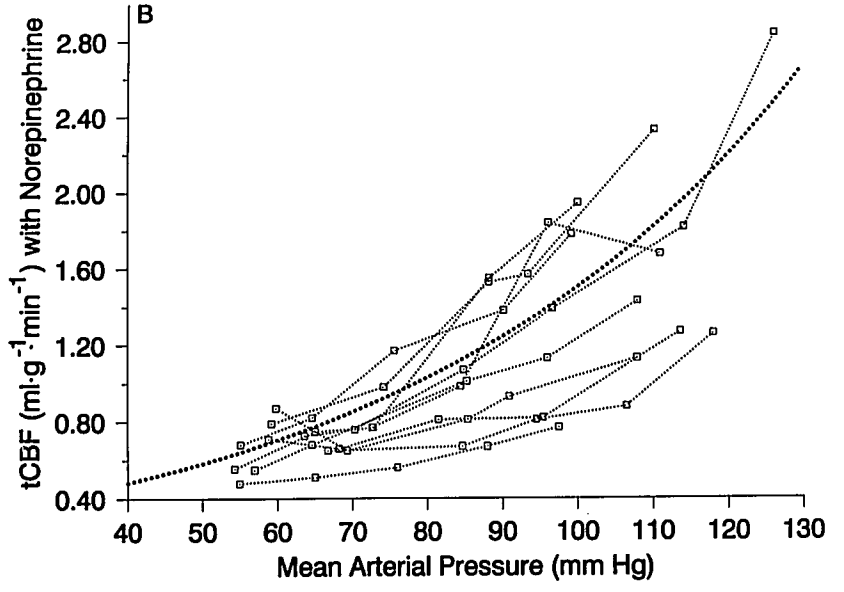

FIG. 1. *B.* Plot of tCBF *versus* MAP of the raw data for the ten experiments in the NE group. The equation of the dotted line is $y = 0.23e^{0.019x}$ as derived from curvilinear regression analysis of pressure–flow data from the ten experiments.

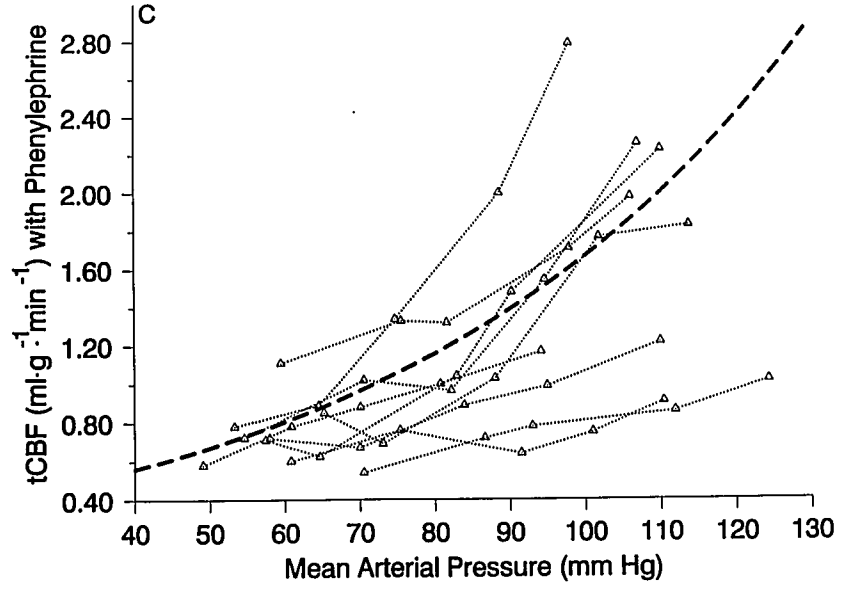

FIG. 1. *C.* Plot of tCBF *versus* MAP of the raw data for the nine experiments in the PE group. The equation of the dashed line is $y = 0.27e^{0.018x}$ as derived from curvilinear regression analysis of pressure–flow data from the nine experiments.

for each of the three vasopressor groups. Between-group comparisons of the mean slopes and mean intercepts were made by Tukey's studentized range test; $P \leq 0.05$ was considered significant.

Results

Physiologic Variables

The experimentally controlled variables are shown in table 1. Among the three groups, MAP at baseline and during flows 2, 3, 4, and 5 were not statistically different. ICP was significantly elevated above baseline in groups NE and PE at flow 5; there was no difference in ICP between groups at any time period. Statistically significant but minor differences were seen in left atrial and right atrial pressures between and within groups. With incremental elevations in MAP, CO decreased in groups AT and PE but was maintained in group NE.

Arterial hemoglobin concentration was significantly lower in group AT at baseline and during subsequent flows periods, although this difference was small (1.4 g/dl). Within each group there was a gradual decrease in hemoglobin concentration that reached statistical significance during flows 4 and 5. The animals were not given blood transfusions to compensate for the lower hemoglobin. Arterial CO_2 tensions were not different both within and between groups except for an elevation of 2.2 mmHg in group NE for the final two flows. A mild metabolic acidosis developed in all groups during the last two flow measurements; the decrease in *p*H was greatest in group PE. No attempts to correct the metabolic acidosis were made. Arterial O_2 tension was >250 mmHg for each injection period in all experiments.

Vasopressor Effects

All vasopressors were mixed in and diluted with normal saline. The total volumes of vasopressor solutions used during each flow measurement period were not different among the three groups.

At baseline tCBF and rCBF were similar in all three groups (table 2). The CBF was measured at five intervals in each animal in groups NE and PE. Despite the use of high doses of AT, we were unable to elevate the MAP to the desired level in all animals in group AT. Therefore, flows 4 and 5 were measured in only 6 and 3 animals, respectively, in this group.

To best assess the interaction between vasopressors, the raw pressure–flow data from each experiment were analyzed using curvilinear regression analysis to obtain a slope and intercept. The raw pressure–flow tCBF data for each experiment for the three vasopressor groups and the derived mean exponential curves are shown in figure 1. Figures 2 and 3 show the derived mean exponential curves for the three vasopressors for hCBF and pCBF, respectively. In all regions studied, the slope of the regression line in group AT was significantly less steep

TABLE 1. Hemodynamic Parameters and Arterial Blood Gas Data

	Vasopressor	Baseline	Flow 2	Flow 3	Flow 4	Flow 5
MAP	AT	59.6 ± 2.1	71.9 ± 2.0†	82.3 ± 2.7†	94.3 ± 3.5†	98.6 ± 3.6†
	NE	59.5 ± 1.6	70.6 ± 2.4†	83.2 ± 2.7†	94.9 ± 2.5†	108.1 ± 2.7†
	PE	59.0 ± 2.1	71.4 ± 2.5†	83.2 ± 2.5†	95.7 ± 3.0†	108.1 ± 2.9†
ICP	AT	2.7 ± 0.5	2.8 ± 0.5	3.0 ± 0.7	3.8 ± 0.7	3.2 ± 1.2
	NE	2.3 ± 0.4	2.2 ± 0.4	3.0 ± 0.4	3.4 ± 0.5†	3.8 ± 0.6†
	PE	2.7 ± 0.4	2.5 ± 0.6	2.6 ± 0.7	3.2 ± 0.5	4.1 ± 0.7†
LAP	AT	2.2 ± 0.3	2.7 ± 0.4	3.8 ± 0.9	4.7 ± 1.2†	2.4 ± 1.8
	NE	2.0 ± 0.2	2.2 ± 0.3	2.3 ± 0.4	3.0 ± 0.5	4.6 ± 1.4†
	PE	1.7 ± 0.2	1.7 ± 0.2	2.2 ± 0.2	2.6 ± 0.3	3.4 ± 0.5
RAP	AT	3.0 ± 0.3	3.1 ± 0.3	3.6 ± 0.4	3.0 ± 0.4	3.5 ± 1.3
	NE	2.1 ± 0.5*	2.1 ± 0.5*	2.7 ± 0.6	2.8 ± 0.7	3.1 ± 0.8
	PE	2.9 ± 0.6	2.5 ± 0.6	2.6 ± 0.5	2.6 ± 0.6	3.2 ± 0.5
CO	AT	445 ± 26	319 ± 16†	322 ± 23†	352 ± 23†	413 ± 162
	NE	358 ± 28*	308 ± 24	348 ± 22	395 ± 24	483 ± 30†
	PE	336 ± 48*	254 ± 43*†	222 ± 40*†	234 ± 40*†	264 ± 60*†
HGB	AT	12.2 ± 0.4*	12.1 ± 0.4*	12.2 ± 0.5*	12.0 ± 0.6*	12.3 ± 1.0*
	NE	13.0 ± 0.4	12.9 ± 0.4	12.8 ± 0.4	12.7 ± 0.4†	12.5 ± 0.4†
	PE	13.6 ± 0.3	13.2 ± 0.3	13.0 ± 0.2†	12.8 ± 0.2†	12.6 ± 0.2†
Pa_{CO_2}	AT	36.6 ± 0.2	37.3 ± 0.4	37.5 ± 0.5	37.3 ± 0.4	38.0 ± 1.6
	NE	35.8 ± 0.5	37.1 ± 0.4	37.2 ± 0.4	38.0 ± 0.6†	37.9 ± 0.5†
	PE	37.2 ± 0.5	37.2 ± 0.3	37.3 ± 0.3	37.9 ± 0.5	38.2 ± 0.6
*p*H	AT	7.36 ± 0.01	7.34 ± 0.01	7.32 ± 0.02	7.34 ± 0.02	7.34 ± 0.01†
	NE	7.37 ± 0.02	7.36 ± 0.02	7.36 ± 0.02	7.34 ± 0.02	7.31 ± 0.03†
	PE	7.35 ± 0.02	7.36 ± 0.02	7.34 ± 0.02	7.34 ± 0.02†	7.27 ± 0.03*†

All data are presented as mean ± SEM. All pressure measurements are shown in mmHg.

MAP = mean arterial pressure; ICP = intracranial pressure; LAP = left atrial pressure; RAP = right atrial pressure; CO = cardiac output (ml/min); HGB = hemoglobin concentration (g/dl); Pa_{CO_2} = arterial carbon dioxide tension (mmHg).

* $P < 0.05$ for between-group comparisons.

† $P < 0.05$ for within-group comparisons to baseline values.

TABLE 2. Baseline Regional Cerebral Blood Flows

Vasopressor	tCBF	hCBF	pCBF
AT (n = 11)	0.78 ± 0.07	0.75 ± 0.07	0.86 ± 0.06
NE (n = 10)	0.67 ± 0.04	0.65 ± 0.04	0.75 ± 0.05
PE (n = 9)	0.73 ± 0.06	0.70 ± 0.05	0.82 ± 0.07

All data are presented as mean ± SEM. All flows are in $ml \cdot g^{-1} \cdot min^{-1}$.

compared with the slopes of the regression lines in groups NE and PE ($P < 0.05$, Tukey's studentized range test), indicating that cerebrovascular resistance (CVR) was greater with AT during 1.0 MAC isoflurane anesthesia. There was no difference in slopes or intercepts between groups NE and PE. Differences in mean intercept were present for some comparisons between the AT group and the other two groups, but these differences are of doubtful physiologic significance because we did not investigate the pressure–flow relationship at low MAP and at baseline rCBF was not different between groups (table 2).

Discussion

In this study we examined the cerebral pressure–flow relationship that resulted when MAP was increased by one of three different vasopressors, AT, NE, and PE, at identical anesthetic depth (1.0 MAC isoflurane), MAP, and Pa_{CO_2}. Thus, differences in the pressure–flow relationship between vasopressors suggest an intrinsic cerebrovascular effect of at least one agent.

Our data show that for a given increase in MAP, AT results in lower CBF as evidenced by a significantly shallower slope for the pressure–flow curve; therefore, CVR was greater with AT than with either NE or PE. This difference in cerebrovascular effect was seen in all regions studied. There was no difference between the effects of NE and PE. The dissimilar effects of these agents on CBF and CVR could be due to either greater vasodilation by the α-agonists or more vasoconstriction by AT. Our study cannot differentiate between these two mechanisms. However, based on previous studies, we advance the following explanation. It is generally accepted that α-agonists do not produce cerebral vasodilation directly. However, in monkeys[11] and rats[12] when NE was infused intravenously following osmotic opening of the blood–brain barrier (BBB), CBF and CMR_{oxygen} were increased. That propranolol blocks this effect of NE suggests that it was mediated by a β-receptor mechanism.[13] The integrity of the BBB was not directly assessed in our study, but several factors argue against it being damaged: 1) the upper limit of cerebral autoregulation in the awake rabbit is 140 mmHg,[14] a pressure not exceeded in our study, 2) MAP was elevated gradually (2–3 mmHg/min) and abrupt increases in MAP are necessary to damage the BBB,[15] 3) in rabbits BBB disruption only occurred when MAP was increased by >80 mmHg[16]; the maximal increase in MAP in our experiments was 50 mmHg, 4) although the effect of isoflurane on the BBB is not known, halothane has been shown not to affect the BBB[17]; and 5) because the central stimulatory action of catecholamines is thought to be due to a β-receptor effect, we would expect to see a higher CBF with NE than with PE (PE has negligible β-agonist activity). That we did not find a difference between NE and PE suggests that the BBB in our experiments was intact. Hence, we suggest that the higher CBF seen with NE and PE administration is unlikely to be explained by indirect cerebral vasodilation secondary to BBB disruption.

Conversely, AT-induced increases in MAP resulted in

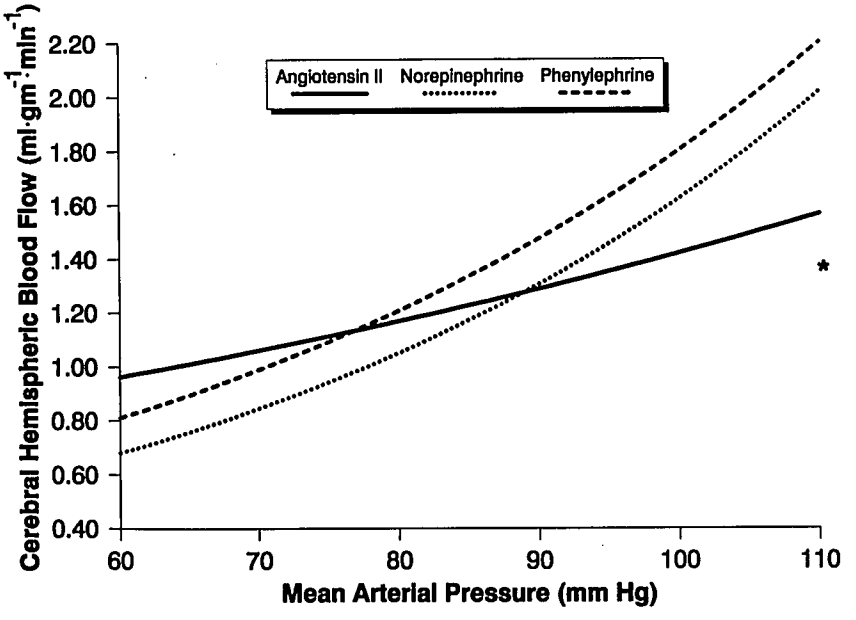

FIG. 2. Plot of hCBF *versus* MAP of the derived exponential equations for the three vasopressors. The equation for the AT group is $y = 0.53e^{0.010x}$, for the NE group is $y = 0.18e^{0.022x}$, and for the PE group is $y = 0.25e^{0.020x}$. *$P \leq 0.05$, AT *versus* NE and PE.

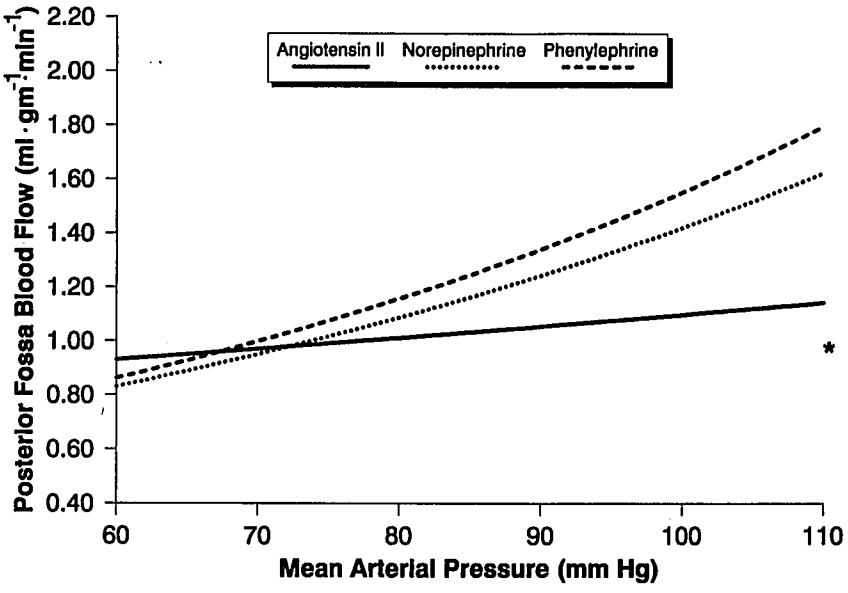

FIG. 3. Plot of pCBF *versus* MAP of the derived exponential equations for the three vasopressors. The equation for the AT group is $y = 0.72e^{0.004x}$, for the NE group is $y = 0.37e^{0.015x}$, and for the PE group is $y = 0.36e^{0.015x}$. *$P \leq 0.05$, AT *versus* NE and PE.

a significantly shallower slope for the pressure–flow relationship in all regions examined. It therefore appears that cerebrovascular autoregulation at 1.0 MAC isoflurane is better maintained with AT or that AT has an intrinsic cerebral vasoconstrictive effect in the rabbit. The first explanation seems implausible because anesthetic depth was identical for all three experimental groups, thus, the influence of isoflurane on cerebrovascular autoregulation should be constant. There is experimental data to support the second hypothesis. Reynier-Rebuffel *et al.* demonstrated generalized cerebral vasoconstriction following intracarotid injection of AT in the rabbit.[18] Also in support of this hypothesis, Haas *et al.* have reported an angiographically documented case of lethal cerebral vasoconstriction associated with a high level of plasma renin activity.[19]

Reynier-Rebuffel *et al.*[3] in a subsequent study in rabbits also demonstrated a dissimilar effect on CBF of NE and AT. These authors found a steeper slope for the CBF–MAP relationship with angiotensin II than with norepinephrine. These results are opposite to those of our study. Methodologic differences between the two studies probably account for these discrepancies. Reynier-Rebuffel *et al.*[3] used fixed doses of AT and NE to elevate MAP in awake and althesin-anesthetized rabbits; the elevations in MAP were variable between rabbits. In addition, in each experiment only a single CBF–MAP data point was generated. Autoregulatory curves were generated when the data points were pooled from individual experiments. Such an analysis assumes a linear relationship between CBF and MAP in different animals. In contrast, the animals in our study were anesthetized with isoflurane. Because the vasopressor infusions were titrated to a specific MAP, the MAP in all three groups were similar. Furthermore, we measured CBF at baseline and following four increments in MAP, thereby constructing true pressure–flow curves.

The conflicting reports of the effects of isoflurane on cerebral autoregulation may in part be clarified by our results. When AT is used to increase MAP, cerebral autoregulation is reported to be preserved.[20,21] This is compatible with our finding of a significantly shallower slope for tCBF *versus* MAP when MAP was increased with angiotensin. Similarly, a significantly steeper slope for tCBF *versus* MAP when PE was infused is compatible with the results of Bunegin *et al.*,[22] who showed that autoregulation was attenuated during 1.0 MAC and 2.0 MAC isoflurane anesthesia when PE was used to elevate MAP.

Several aspects of our study need further clarification. As described, pressure–flow slopes were generated for each experiment, and then mean slopes and intercepts were derived for each group. For the NE and PE groups there were five pressure–flow points for each experiment. For the AT group because of inability to elevate MAP to desired levels in all experiments, despite massive doses of AT, of the 11 experiments there were only three experiments with five pressure–flow points, six with four pressure–flow points, and in five experiments only three pressure–flow points could be obtained. Thus, the mean slope for this group could possibly be less steep than for the other two groups if the upper end of the autoregulatory curve for 1.0 MAC isoflurane was exceeded at higher MAP. However, we also examined our data in the fashion described but truncated to only the first three pressure–flow points for all three groups. The mean slope was still significantly less steep in group AT *versus* groups NE and PE for hCBF ($P = 0.025$; drug effect by ANOVA) and approached statistical significance for tCBF ($P = 0.065$). Arterial hemoglobin concentration was significantly lower in the AT group during all flow measurement periods.

Because the experiments were performed in random sequence, it is unlikely that the development of greater experimenter expertise during the latter experiments resulted in better experimental preparations for the NE and PE groups. The magnitude of the difference in hemoglobin concentration was small (maximum 1.4 g/dl) and probably did not significantly affect the results. Had the arterial hemoglobin concentration in the AT group been identical to that in the NE and PE groups, the CBF in the AT group would have been lower,[23] further strengthening our conclusions. A mild metabolic acidosis developed in most animals during the latter stages of the experiments. The cause of the metabolic acidosis was probably mild hypovolemia (blood withdrawal for blood gas analysis and measurement of CBF) as well as tissue hypoperfusion due to vasoconstriction. No attempt was made to correct the acidosis. Even though acidosis can increase CBF,[24] the *p*H was similar in all groups during each flow (with the exception of flow 5 in the PE group), making valid the comparison of CBF during each flow measurement period.

In conclusion, our data show that the cerebral pressure–flow relationship during 1.0 MAC isoflurane anesthesia is dependent on the vasopressor used to determine the relationship. The mean slope of this curve was significantly less steep when AT was used to increase MAP compared with NE- and PE-induced increases in MAP. These results indicate that NE and PE may indirectly result in cerebrovascular vasodilation or that AT had intrinsic cerebral vasoconstrictive effects during isoflurane anesthesia in the rabbit. The latter explanation is thought to be more plausible. Thus, in the rabbit choice of vasopressor can critically influence the interpretation of whether cerebrovascular autoregulation is intact during isoflurane anesthesia. In general, determination of cerebrovascular autoregulation for any anesthetic agent should ideally depend on generating pressure–flow curves from multiple data points over an extensive range of blood pressure. In addition, the vasopressor chosen for the study should be the one that results in the fewest cerebrovascular effects for that species.

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