The stress response to induced hypotension for cerebral aneurysm surgery: a comparison of two hypotensive techniques

Margery S.P. Macnab MBChB FRCPC,
Pirjo H. Manninen MD FRCPC, Arthur M. Lam MD FRCPC,
Adrian W. Gelb MBChB FRCPC

Plasma epinephrine (PE), plasma norepinephrine (PNE), plasma renin activity (PRA), mean arterial pressure (MAP) and heart rate (HR) were measured before, during and after induced hypotension in two groups of patients undergoing cerebral aneurysm surgery. In Group I isoflurane was used to maintain anaesthesia and induce hypotension. Mean PE fell significantly during hypotension and remained reduced after hypotension, mean PNE remained unchanged, while mean PRA rose slightly but not significantly during hypotension, falling again after hypotension. In Group II halothane was used to maintain anaesthesia and sodium nitroprusside to induce hypotension. During anaesthesia and surgical stimulation PNE and PRA were significantly greater compared to Group I. Mean PE, PNE and PRA all rose during hypotension and remained elevated after hypotension. The rise in PNE and PRA was statistically significant. After hypotension the MAP in Group II was significantly higher when compared to Group I. There was no significant change in HR during the study in either group. In conclusion, isoflurane-induced hypotension with isoflurane anaesthesia unlike sodium nitroprusside-induced hypotension with halothane anaesthesia attenuated the stress response.

Key words

ANAESTHETIC TECHNIQUES: induced hypotension;
ANAESTHESIA: neurosurgical; PHARMACOLOGY:
isoflurane, sodium nitroprusside; SYMPATHETIC NERVOUS
SYSTEM: catecholamines, renin.

From the Department of Anaesthesia, University Hospital, University of Western Ontario, London, Ontario.

Address correspondence to: Dr. P.H. Manninen, Department of Anaesthesia, University Hospital, P.O. Box 5339, Station "A," London, Ontario, N6A 5A5.

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Induced hypotension is widely used during anaesthesia for cerebral aneurysm surgery to reduce the risk of rupture and to facilitate the clipping of the aneurysm. Siegel *et al.* in 1971 first described the use of intravenous sodium nitroprusside (SNP) to induce arterial hypotension during cerebral aneurysm surgery.¹ Several studies have reported transient increases in arterial pressure over basal arterial pressure after discontinuing the SNP, and have associated this rebound hypertension with increased catecholamine and renin activity both during and after SNP-induced hypotension.²⁻⁵ Rebound hypertension can be especially hazardous in cerebral aneurysm surgery where 19 per cent of patients may have more than one aneurysm and some aneurysms cannot be clipped or the clip may be dislodged.⁶ Recently, deep isoflurane anaesthesia has been used with success to induce hypotension in neurosurgery.⁷

The aim of this study was to compare the catecholamine and renin responses to induced hypotension in two groups of patients during cerebral aneurysm surgery. One group received isoflurane anaesthesia with a higher concentration of isoflurane to induce hypotension. The other group received halothane anaesthesia with SNP to induce hypotension.

Methods

Sixteen patients presenting for cerebral aneurysm surgery requiring induced hypotension were studied. The study was approved by the Health Sciences Standing Committee for Human Research of the University of Western Ontario and each patient gave informed consent. No patient had concomitant cardiac, respiratory or renal disease. Patients receiving beta blocking drugs were excluded from the study. All patients had normal pre-operative serum electrolytes. All patients were unpremedicated and had anaesthesia induced in a standardized manner with thiopentone 5-6 mg·kg⁻¹, fentanyl 2-3 µg·kg⁻¹, lidocaine 1.5 mg·kg⁻¹ and succinylcholine 1 mg·kg⁻¹. An additional dose of fentanyl (1-2 µg·kg⁻¹)

was administered just prior to the insertion of head pins. Mechanical ventilation was employed to maintain end-tidal CO_2 between 25–30 mmHg. A lead II electrocardiogram was monitored continuously. A 20-gauge cannula was inserted in a dorsalis pedis or radial artery for continuous blood pressure monitoring. The transducer was placed level with the base of skull. Other routine monitors included a central venous pressure catheter, urinary catheter, oropharyngeal temperature probe and end-tidal capnometer. A lumbar subarachnoid catheter was inserted for drainage of cerebral spinal fluid. During craniotomy all patients received $1\text{--}2 \text{ g}\cdot\text{kg}^{-1}$ 20 per cent mannitol.

Patients were divided into two groups. In Group I anaesthesia was maintained with isoflurane one per cent inspired, nitrous oxide (66 per cent), oxygen (33 per cent) and pancuronium $0.1 \text{ mg}\cdot\text{kg}^{-1}$. Hypotension was induced by increasing the inspired concentration of isoflurane to 3–4 per cent until the desired mean arterial pressure (MAP) of 50 mmHg was achieved. Thereafter, the inspired concentration of isoflurane was reduced to 2–2.5 per cent to maintain this level. When hypotension was no longer required, the inspired concentration of isoflurane was adjusted to the prehypotensive level. In Group II anaesthesia was maintained with halothane one per cent inspired, nitrous oxide (66 per cent), and oxygen (33 per cent) and pancuronium $0.1 \text{ mg}\cdot\text{kg}^{-1}$. An intravenous infusion of 0.1 per cent SNP in five per cent dextrose was used to induce hypotension to a MAP of 50 mmHg.

Blood samples were withdrawn from the peripheral artery for plasma epinephrine (PE) and plasma norepinephrine (PNE) concentrations and plasma renin activity (PRA) after dural opening (stable anaesthesia and surgery), 15 minutes after the onset of stable induced hypotension and 30 minutes after recovery of blood pressure. The blood was collected into prechilled vacuum tubes. Plasma was separated immediately in a refrigerated centrifuge and stored at -20°C until analyzed. PE and PNE concentrations were measured by radio enzymatic assay based on the method described by Peuler *et al.*⁸ PRA was measured using the Rianen™ Angiotensin I (^{125}I) Radio Immunoassay Kit. This method is an adaptation of that described by Haber *et al.*⁹ All samples were analyzed within 48 hours of collection. MAP and heart rate (HR) were recorded preoperatively and at all times of blood sampling and continuously for 30 minutes after induced hypotension. For comparison between measurement periods within each group the Friedman analysis of variance was used. Where statistical significance was found, the Wilcoxon signed rank test with Bonferroni's modification was used to delineate the differences. Comparison of the data within a measurement period between two groups was done using the Mann-Whitney

test. A *p* value of less than 0.05 was considered significant.

Results

Clinical details of the patients and their surgical procedures are shown in Table I. Patient characteristics and surgical procedures were similar in both groups. With respect to their clinical status following subarachnoid haemorrhage, all patients were classified as Botterell Grade I with the exception of one patient in Group II who was classified as Grade II. There were no intraoperative complications in any of the patients studied. Postoperative outcome was similar in both groups. In Group I, four patients had a good outcome, three were fair, that is, patients had neurological deficits but were showing recovery at time of discharge, and one patient was poor with major neurological deficits. In Group II, five patients had a good outcome, two fair and one poor. Table II summarizes the MAP and HR data and Table III, the PE and PNE concentrations and PRA at times of sampling.

Group I (isoflurane)

Mean PE concentrations fell significantly during hypotension and remained significantly lower after hypotension. Mean PNE concentrations were essentially unchanged throughout the study. Mean PRA rose during hypotension but not significantly. MAP after induced hypotension returned to prehypotensive levels. Rebound hypertension was not observed at any time after induced hypotension. Mean HR was unchanged throughout the measurement periods.

Group II (halothane and SNP)

Mean PE and PNE concentrations and PRA all rose during hypotension and remained elevated after hypotension. The increase in PNE and PRA was statistically significant. MAP after hypotension was elevated when compared with prehypotensive values. Mean HR was essentially unchanged throughout the study. Mean ($\pm$ SEM) SNP dose was $0.20 \pm 0.08 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$.

Between group comparison

Mean PE concentrations before hypotension were similar, but during and after hypotension mean PE concentrations were higher in Group II. This difference did not, however, reach statistical significance. Mean PNE concentrations and PRA were significantly higher in Group II before, during and after hypotension. MAP after hypotension was significantly higher in Group II. As the plasma catecholamines and PRA values exhibited a very large range, it was considered appropriate to calculate and compare the percentage changes in mean PE, PNE concentrations and PRA from before hypotension to during

FIGURE Percentage change from control (before induced hypotension) of catecholamines and renin activity during induced hypotension. Values are mean $\pm$ SEM.

hypotension in both groups. The percentage changes in mean PE and PNE concentrations were significantly greater in Group II (Figure). However, the percentage change in mean PRA was not significantly different.

Discussion

The results of this study show that during cerebral aneurysm surgery, isoflurane anaesthesia with isoflurane-induced hypotension attenuates the catecholamine and renin response to induced hypotension better than the technique of halothane anaesthesia with SNP-induced hypotension. There was absence of rebound hypertension in the isoflurane group, whereas the MAP and catecholamine levels were significantly elevated following SNP-induced hypotension with halothane anaesthesia.

Our results obtained for halothane anaesthesia with

TABLE II Haemodynamic data. Mean $\pm$ SEM

	Heart rate (beats·min ⁻¹)	Mean arterial pressure (mmHg)
Group I (isoflurane)		
Before hypotension	80 $\pm$ 3	75 $\pm$ 2
During hypotension	84 $\pm$ 3	50 $\pm$ 1*
After hypotension	78 $\pm$ 3	74 $\pm$ 2
Group II (halothane & SNP)		
Before hypotension	71 $\pm$ 4	80 $\pm$ 3
During hypotension	76 $\pm$ 5	50 $\pm$ 1*
After hypotension	76 $\pm$ 3	93 $\pm$ 5†

* = $p < 0.05$ compared to before hypotension.

† = $p < 0.05$ between Groups I and II.

SNP-induced hypotension are similar to those documented by Khambatta and his colleagues.³⁻⁵ However, we did not find as great an elevation of PE, PNE and PRA during and after SNP-induced hypotension or as great a rise in MAP after hypotension. These discrepancies between the two studies may be accounted for by the differences in methodology. In our study, fentanyl was given as part of the anaesthetic technique, surgery and induced hypotension were of much shorter duration, and more fluid was given intraoperatively with careful monitoring of central venous pressure and fluid losses.

A mechanism whereby drug-induced hypotension causes an increase in PRA was demonstrated by Keeton in rats¹⁰ and subsequently by Khambatta's studies in humans using SNP-induced hypotension.³⁻⁵ These studies concluded that the observed increase in PRA during drug-induced hypotension was almost entirely due to stimulation of the carotid baroreceptor reflex resulting in activation of the renal sympathetic nerves. The increased renin then generates angiotensin I, II and III. These substances are not only direct vasoconstrictors, but they also act on the adrenal gland and central nervous system to stimulate further catecholamine release giving a further increase in renin.¹¹

The inhalation agents, halothane and isoflurane, have both been shown to depress the carotid baroreceptor reflex mechanism in man in a dose-related manner.^{12,13} Thus, it could be postulated that during isoflurane-induced hypotension in which high inspired concentrations of isoflurane were employed that the carotid baroreceptor reflex mechanism would be more depressed than in Group II where smaller concentrations of halothane were used. The mean PE, PNE and PRA found in our study during and after isoflurane-induced hypotension are consistent with this hypothesis. Alternatively, isoflurane may have a more direct depressant effect on the catecholamine response to induced hypotension.

We did not observe in either of our two study groups the

TABLE I Clinical data. Mean $\pm$ SEM

	Group I (isoflurane) (n = 8)	Group II (halothane & SNP) (n = 8)
Age (yr)	52 $\pm$ 4	46 $\pm$ 3
Weight (kg)	70 $\pm$ 5	67 $\pm$ 7
Sex (M:F)	1:7	2:6
Length of surgery (min)	315 $\pm$ 30	330 $\pm$ 30
Length of hypotension (min)	40 $\pm$ 10	45 $\pm$ 6
Fluids in (L)	3.6 $\pm$ 0.3	3.7 $\pm$ 0.4
Fluids out (L)	2.2 $\pm$ 0.2	2.2 $\pm$ 0.4

TABLE III Plasma catecholamine and renin results. Mean $\pm$ SEM

	Plasma epinephrine concentrations ($\text{pmol} \cdot \text{L}^{-1}$)	Plasma norepinephrine concentrations ($\text{pmol} \cdot \text{L}^{-1}$)	Plasma renin activity ($\text{ng} \cdot \text{L}^{-1} \cdot \text{sec}^{-1}$)
Group I (isoflurane)			
Before hypotension	301 $\pm$ 102	1201 $\pm$ 264	0.97 $\pm$ 0.13
During hypotension	189 $\pm$ 63*	1260 $\pm$ 345	1.33 $\pm$ 0.20
After hypotension	166 $\pm$ 49*	1209 $\pm$ 205	0.99 $\pm$ 0.13
Group II (halothane & SNP)			
Before hypotension	231 $\pm$ 63	1988 $\pm$ 267†	1.89 $\pm$ 0.42†
During hypotension	376 $\pm$ 150	3131 $\pm$ 566*†	2.79 $\pm$ 0.59*†
After hypotension	313 $\pm$ 164	2803 $\pm$ 564*†	2.33 $\pm$ 0.47*†

* = $p < 0.05$ compared to before hypotension.† = $p < 0.05$ between Groups I and II.

reflex tachycardia noted in Khambatta's studies during induced hypotension.³⁻⁵ Again, this could be due to the differences in methodology mentioned above. Fentanyl has been reported to depress the carotid baroreceptor reflex mechanism which is thought to be responsible for the tachycardia.¹⁴ As well, the addition of fentanyl to inhalation anaesthesia (both isoflurane and halothane) has been shown to decrease heart rate.¹⁵

We did not use minimum alveolar concentration (MAC) equivalents of isoflurane and halothane in the two groups because it was not our aim to determine the stress response to MAC values of anaesthetic agents, but rather to determine and compare during clinical conditions the stress response to two hypotensive techniques employed for cerebral aneurysm surgery.

In summary, our study suggests that isoflurane anaesthesia with isoflurane-induced hypotension, unlike halothane anaesthesia with SNP-induced hypotension, attenuates the stress response to induced hypotension allowing good control of MAP and HR without rebound hypertension.

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Résumé

On a mesuré avant, pendant et après l'hypotension induite chez les patients divisés en deux groupes devant subir une anévrismectomie cérébrale l'épinéphrine plasmatique (PE), la norépinéphrine (PNE), l'activité de la rénine (PRA), la pression artérielle moyenne (MAP) et la fréquence cardiaque (HR). Dans le groupe I l'isoflurane a été utilisé afin de maintenir une anesthésie et d'induire l'hypotension. La PE moyenne diminua significativement pendant l'hypotension et demeura diminuée après l'hypotension, la PNE moyenne demeura inchangée, alors que la PRA moyenne s'éleva légèrement et non d'une façon significative durant l'hypotension pour diminuer par la suite après l'hypotension. Dans le groupe II l'halothane a été utilisé afin de maintenir l'anesthésie et le nitroprussiate de soude afin d'induire l'hypotension. Durant l'anesthésie la stimulation chirurgicale, la PNE et la PRA étaient significativement plus grands comparativement au groupe I. Les valeurs moyennes de PE, PNE et PRA augmentèrent durant l'hypotension et restèrent élevées après l'hypotension. L'augmentation du PNE et PRA était statistiquement significative. Après l'hypotension la MAP du groupe II était significativement plus élevée comparativement au groupe I. Il n'y avait aucun changement significatif du IIR durant l'étude dans les deux groupes. En conclusion l'hypotension induite par l'isoflurane lors d'une anesthésie à l'isoflurane contrairement à celle induite par le nitroprussiate de soude lors d'une anesthésie à l'halothane atténue la réponse au stress.