Anesthesiology
V 42, No 4, Apr 1975

Intracranial Pressure during Hypotension and Subsequent Vasopressor Therapy in Anesthetized Cats

Edward H. Stullken, Jr., M.D., and Martin D. Sokoll, M.D.†*

The effects of vasopressor therapy on intracranial pressure (ICP) during hypotension were evaluated in 45 adult cats anesthetized with pentobarbital and hyperventilated via an endotracheal tube with nitrous oxide, 70 per cent, and oxygen, 30 per cent, to maintain Pa_{CO_2} 25 ± 5 torr. Hypotension was induced by intravenous administration of trimethaphan camsylate or sodium nitroferricyanide and by hemorrhage. Vasopressor (norepinephrine, ephedrine, or isoproterenol) administration in the absence of hypotension caused slight transient increases in ICP. Trimethaphan produced increases in ICP averaging 4.3 mm Hg, while sodium nitroferricyanide caused no change and hemorrhage decreased ICP by 3.9 mm Hg. After hypotension was established, vasopressors caused increases in ICP of 1–21 mm Hg. The greatest increase was seen with norepinephrine administration during sodium nitroferricyanide-induced hypotension. Increases in ICP were pronounced in absolute magnitude and rapidity of rise but were of short duration (2 to 5 minutes). The elevation of pressure might be of clinical significance in patients who have pre-existing intracranial hypertension or space-occupying lesions. (Key words: Anesthetic techniques, induced hypotension; Cerebrospinal fluid, pressure; Brain, intracranial pressure.)

THE FLUCTUATIONS of intracranial pressure (ICP) in relationship to various anesthetic techniques have been well studied in animals and man. However, the effects on ICP of other ancillary techniques common to neurosurgery have not been well studied. For example, to reduce bleeding and brain bulk during craniotomy, hypotension may be induced by sodium nitroferricyanide[1,2] or trimethaphan camsylate[3,4] administration and by deep halothane anesthesia.[5] The effects of induced hypotension and the use of vasopressors during hypotension on ICP have not been measured. When hypotensive agents are used, profound hypotension (systolic pressure <60 mm Hg) may occur. Although this is most often treated by discontinuance of the hypotensive agent, occasions may arise when the use of a vasopressor is considered indicated. Hypotension induced by surgical hemorrhage is also frequently treated with vasopressors when hemorrhage is rapid and blood replacement is not immediately available.[6]

This study examined the relationships between ICP, arterial hypotension, and vasopressor administration.

Methods and Materials

Forty-five adult cats weighing 2 to 6 kg were anesthetized by intraperitoneal injection of sodium pentobarbital, 30 mg/kg. The tracheas were intubated and the cats ventilated with N_2O–O_2 (FI_{O_2} = 0.30) to maintain Pa_{CO_2} 25 ± 5 torr. Rectal temperatures were maintained at 35–38 C. Arterial and venous iliac cannulations were performed. A 4-mm hollow threaded bolt was inserted through a temporoparietal burr hole of slightly smaller diameter than the bolt with the tip of the bolt resting in the subarachnoid space. A Luer-lok adapter soldered to the head of the bolt was attached to a Statham P23Db transducer by vinyl tubing. The entire system was filled with saline solution, and pressures from the subarachnoid space were recorded on a Beckman Dynograph.[7] Arterial and intracranial pressures and EEG were recorded continuously. Venous cannulas were used for infusion of 5 per cent dextrose in water; all drugs were administered in 30-second infusions.

After each cat was prepared and an hour had been allowed for stabilization, control arterial

* Resident.

† Professor.

Received from the Department of Anesthesia, University of Iowa School of Medicine, Iowa City, Iowa 52242. Accepted for publication September 3, 1974. Supported by the Department of Anesthesia Trust Fund.

Address reprint requests to Dr. Stullken.

TABLE 1. Arterial and Intracranial Pressure Changes with Vasopressors and Hypotensive Agents Alone (Means ± SD)

	Control Blood Pressure (mm Hg)	Blood Pressure after Agent (mm Hg)	Blood Pressure Change (mm Hg)	Control Intracranial Pressure (mm Hg)	Intracranial Pressure after Agent (mm Hg)	Intracranial Pressure Change (mm Hg)
Norepinephrine	85.7 ± 23.8	176.9 ± 25.6	91.3 ± 39.5 $P < 0.001$	7.4 ± 2.8	11.8 ± 4.0	+4.3 ± 2.0 $P < 0.001$
Ephedrine sulfate	107.7 ± 27.0	173.8 ± 26.4	66.1 ± 30.7 $P < 0.001$	6.5 ± 2.4	9.7 ± 4.0	+3.1 ± 2.2 $P < 0.001$
Isoproterenol	119.0 ± 23.7	66.9 ± 25.3	−52.1 ± 36.5 $P < 0.001$	7.3 ± 3.0	11.4 ± 3.9	+4.0 ± 2.3 $P < 0.001$
Trimethaphan camsylate	102.9 ± 24.8	40.6 ± 10.0	−62.3 ± 24.3 $P < 0.001$	7.6 ± 3.2	11.9 ± 5.8	+4.3 ± 3.6 $P < 0.001$
Sodium nitroferricyanide	116.6 ± 24.5	37.0 ± 13.0	−79.6 ± 24.9 $P < 0.001$	7.5 ± 2.8	8.4 ± 2.8	+0.9 ± 2.1 NS
8 per cent body weight hemorrhage	117.7 ± 35.6	50.0 ± 17.8	−67.7 ± 33.3 $P < 0.005$	7.7 ± 1.9	2.3 ± 3.0	−5.3 ± 1.7 $P < 0.001$

TABLE 2. Arterial and Intracranial Pressure Changes after Hypotension and Vasopressors (Means ± SD)

	Blood Pressure after Hypotension and Vasopressor (mm Hg)	Change in Blood Pressure from Control (mm Hg)	Change in Blood Pressure from Hypotension (mm Hg)	Intracranial Pressure after Hypotension and Vasopressor (mm Hg)	Change in Intracranial Pressure from Control (mm Hg)	Change in Intracranial Pressure from Hypotension (mm Hg)
Group 1	117.6 ± 21.9	22.6 ± 28.6 NS	88.6 ± 18.3 $P < 0.001$	25.4 ± 3.0	+15.8 ± 4.7 $P < 0.001$	+10.2 ± 2.8 $P < 0.005$
Group 2	146.4 ± 28.7	48.4 ± 43.3 NS	103.6 ± 24.4 $P < 0.001$	29.9 ± 9.7	+21.9 ± 6.8 $P < 0.005$	+21.1 ± 5.9 $P < 0.005$
Group 3	145.5 ± 34.1	73.4 ± 39.8 $P < 0.020$	101.6 ± 26.3 $P < 0.001$	2.7 ± 2.4	−2.9 ± 2.9 NS	+2.5 ± 1.7 $P < 0.050$
Group 4	119.4 ± 39.8	15.6 ± 23.8 NS	71.3 ± 39.4 $P < 0.020$	13.7 ± 1.7	+8.0 ± 2.7 $P < 0.005$	+4.7 ± 5.1 NS
Group 5	153.2 ± 44.2	34.6 ± 38.0 NS	123.4 ± 46.2 $P < 0.001$	23.6 ± 6.6	+16.4 ± 3.8 $P < 0.001$	+15.5 ± 6.3 $P < 0.010$
Group 6	115.6 ± 36.6	−13.8 ± 54.0 NS	67.2 ± 27.0 $P < 0.010$	18.4 ± 8.5	+10.1 ± 7.7 $P < 0.050$	+14.1 ± 9.8 $P < 0.050$
Group 7	51.2 ± 9.4	−58.6 ± 25.8 $P < 0.010$	9.4 ± 9.0 NS	11.5 ± 7.1	+4.0 ± 4.2 NS	+0.0 ± 4.4 NS
Group 8	140.6 ± 7.0	7.4 ± 7.8 NS	102.2 ± 8.5 $P < 0.001$	14.5 ± 2.6	+7.2 ± 3.0 $P < 0.010$	+6.2 ± 2.0 $P < 0.005$
Group 9	124.2 ± 41.3	−3.2 ± 28.6 NS	38.2 ± 22.2 $P < 0.020$	9.6 ± 1.3	+1.0 ± 1.7 NS	+3.3 ± 0.6 $P < 0.001$

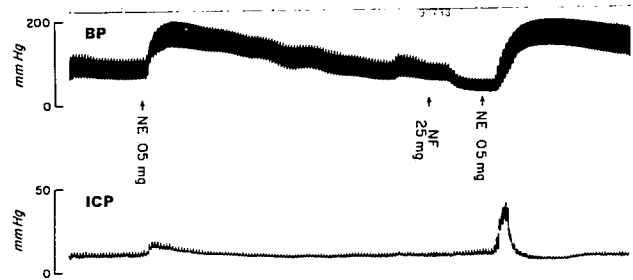

FIG. 1. Effects of norepinephrine alone and norepinephrine following sodium nitroferricyanide on intracranial pressure and arterial blood pressure. Time = 1 mark/min.

pressure and ICP measurements were recorded. Mean arterial pressure was calculated as the diastolic pressure plus one third of the pulse pressure. Each cat served as its own control during the experiment. Three representative vasopressors, norepinephrine, isoproterenol, and ephedrine, were chosen for study. Hypotension was produced using sodium nitroferricyanide, trimethaphan camsylate, and hemorrhage accomplished with 2-minute periods of exsanguination. Dose of hypotensive agent and amount of hemorrhage (approximately 8 per cent of body weight) were chosen to produce a systolic blood pressure of 45 ± 8 mm Hg.

The cats were divided into nine groups of five each. Each received one type of vasopressor and one type of hypotensive agent, according to the following schedule:

	Norepinephrine	Ephedrine	Isoproterenol
Trimethaphan camsylate	Group 1	Group 4	Group 7
Sodium nitroferricyanide	Group 2	Group 5	Group 8
Hemorrhage (8 per cent body weight)	Group 3	Group 6	Group 9

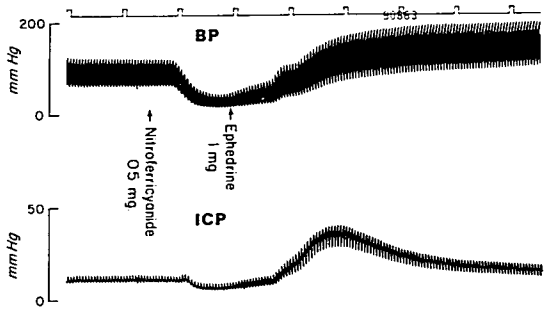

FIG. 2. Effects of sodium nitroferricyanide followed by ephedrine on intracranial pressure and arterial blood pressure. Time = 1 mark/min.

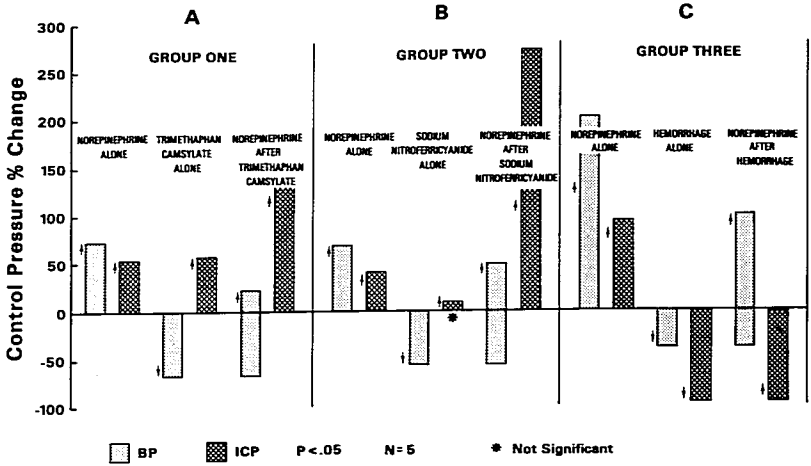

FIG. 3. Percentage changes in arterial and intracranial pressures from control—induced hypotensive episodes treated with norepinephrine. Arrow indicates direction of change.

After control measurements were obtained, a vasopressor was administered and mean pressures were again recorded. One hour was then allowed for restabilization. Hypotension was induced and the animal allowed to recover spontaneously to examine the effect of untreated hypotension on ICP. Following a second one-hour restabilization period, hypotension was again induced to the same extent and the vasopressor immediately administered. The duration of the hypotensive period was 1–3 minutes. Pressures were then recorded continuously for four hours.

Student's t test was used to determine the significance of arterial and intracranial pressure changes. $P < 0.05$ was considered significant.

Results

Norepinephrine, ephedrine, and isoproterenol increased ICP transiently and only slightly when administered to previously normotensive animals. Arterial and intracranial pressure changes occurred concurrently, but arterial pressure changes were of much longer duration (10–45 minutes as opposed to 0.5–3 minutes for ICP) (table 1; figs. 1 and 2). All three methods of inducing hypotension effectively lowered mean arterial pressure. ICP was increased by trimethaphan, unchanged by sodium nitroferricyanide, and decreased by hemorrhage. These ICP changes were also transient (1–3 min) (table 1). When vasopressors were administered after induced hypotension, ICP elevations, when present, lasted 2–5 minutes. The increases in ICP were rapid in onset. Peak pressures were sustained for 20 seconds to 2 minutes, with a gradual return to normal.

The effects on ICP of a vasopressor administered to hypotensive animals were different from the action of either the vasopressor or the hypotensive agent alone (table 2). In Groups 1 and 2 (norepinephrine after trimethaphan and norepinephrine after sodium nitroferricyanide), ICP's increased

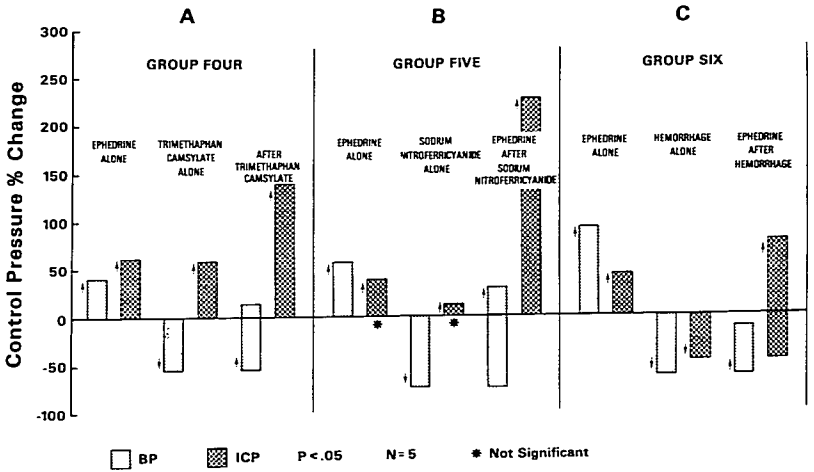

FIG. 4. Percentage changes in arterial and intracranial pressures from control—induced hypotensive episodes treated with ephedrine sulfate. Arrow indicates direction of change.

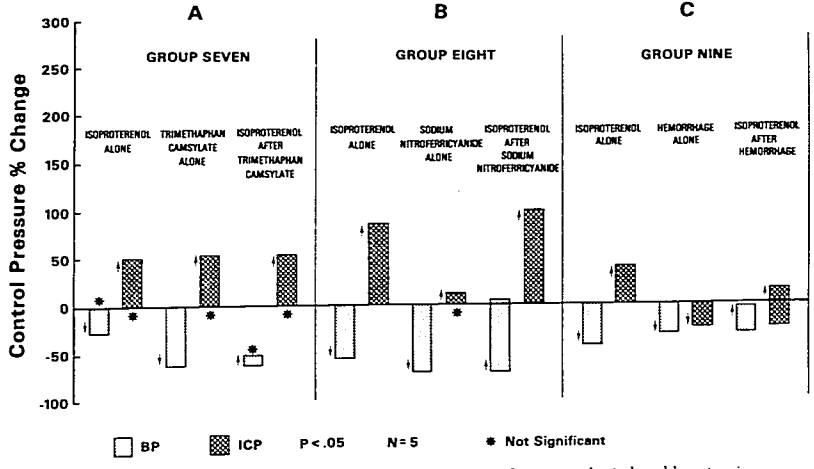

FIG. 5. Percentage changes in arterial and intracranial pressures from control—induced hypotensive episodes treated with isoproterenol. Arrow indicates direction of change.

165 ($P < 0.001$) and 264 per cent ($P < 0.005$), respectively, while arterial pressures did not significantly exceed control values (fig. 3, *A* and *B*). In Group 3, hemorrhage decreased ICP and subsequent norepinephrine administration returned it to near control (fig. 3*C*).

In Groups 1 and 2, the increases in ICP after norepinephrine was given to hypotensive animals exceeded the increases seen with either norepinephrine alone or hypotensive agents alone. In Group 3, norepinephrine brought ICP to its control level after the hemorrhage-induced decrease.

The administration of ephedrine after trimethaphan-induced hypotension (Group 4) increased ICP to 140 per cent ($P < 0.005$) above the control value (Fig. 4*A*), while ICP increased 228 per cent ($P < 0.001$) with ephedrine following sodium nitroferricyanide administration (Group 5) (fig. 4*B*). In Group 6 (ephedrine after hemorrhage), an increase in ICP to 122 per cent ($P < 0.05$) above control occurred (fig. 4*C*).

In Groups 4, 5, and 6, mean arterial pressures increased significantly from their hypotensive levels but did not significantly increase over prehypotensive control levels. In these groups, increases in ICP again exceeded the sum of the ICP changes resulting from ephedrine alone and hypotensive agents alone.

Isoproterenol administration did not increase ICP in animals in which hypotension was induced with trimethaphan (Group 7) (fig. 5*A*), but did cause a significant increase (99 per cent, $P < 0.01$) after sodium nitroferricyanide (Group 8) (fig. 5*B*). Mean arterial pressure did not exceed the control value. In Group 9 (isoproterenol after hemorrhagic hypotension) ICP failed to increase significantly above control (fig. 5*C*). Isoproterenol also did not significantly change mean arterial pressure.

In all nine groups, EEG activity appeared to be influenced by blood pressure alone. Depression occurred at mean arterial pressures < 50 mm Hg; EEG activity reverted to normal as arterial pressure returned to control levels.

Discussion

The results of our study indicate that in the cat, vasopressors, hypotensive agents, and particularly their combinations, significantly affect ICP. Vasopressors alone increased ICP transiently and slightly.[5] Autoregulatory processes returned ICP to control levels within 0.5–3 minutes, long before arterial pressure returned to normal. The transient increases in ICP seen with these drugs alone should not be deleterious in the clinical situation where ICP is normal. However, in pathologic states, where ICP is already elevated or compensatory mechanisms are maximally active, these small changes might be significant.

ICP was increased by trimethaphan, unchanged by sodium nitroferricyanide, and reduced by hemorrhage. Volle and Koelle[8] described a direct arteriolar vasodilating action of trimethaphan that reinforces the effects of ganglionic blockade. This direct vasodilating action may occur in CNS vasculature, causing a transient increase in ICP in the face of moderate systemic hypotension. Although it has not been proven, the increase in ICP seen with trimethaphan might also indicate some autonomic control of cerebral blood volume. Hemorrhage reduced ICP, probably by reducing the amount of blood in the cerebrovascular bed.[9] The decrease in ICP persisted as long as the decrease in arterial pressure. The short increase in ICP seen with trimethaphan was, like the increases seen with vasopressors, insufficient to be clinically deleterious unless ICP were initially elevated or compensatory mechanisms overwhelmed.

Norepinephrine, ephedrine, and isoproterenol, administered to already hypotensive cats, had an effect on ICP that differed from their effect when administered to normotensive cats. The greater increases in ICP after hypotension and subsequent vasopressor therapy cannot be explained by the higher arterial pressures, since mean arterial pressures in hypotensive cats given ephedrine sulfate and norepinephrine never exceeded the pressures resulting from administration of the same doses of drugs to

normotensive cats. Hypotensive cats given isoproterenol never regained their control arterial pressures, although arterial pressures did increase from hypotensive levels. It appears that trimethaphan, sodium nitroferricyanide, and hemorrhage interfere with mechanisms controlling ICP, permitting subsequent vasopressor therapy to elevate ICP more than the sum of the increases seen with vasopressor or hypotensive agent alone. These increases were also of somewhat longer duration than increases seen with hypotensive agents or vasopressor alone.

One possible explanation for the increased magnitude and duration of ICP elevation after hypotensive agent followed by vasopressor may be in the cerebral metabolic effects of the hypotension. With the decreased cerebral blood flow during hypotension, acid metabolites may have accumulated. Acidosis alone can cause cerebral vasodilatation.[10] This vasodilatation, followed by a marked increase in blood pressure, might give rise to these changes.

Our results show that, in the cat, norepinephrine or ephedrine following either trimethaphan or sodium nitroferricyanide can cause marked elevations of ICP. Increases of ICP were also seen with isoproterenol following sodium nitroferricyanide. Increases were not seen with isoproterenol following trimethaphan or hemorrhage. Although not examined in this study, the same increases may occur in man.

The results seen in this study may have been influenced by the anesthetic technique used. Both barbiturate administration[11] and hypocarbia are known to decrease elevated intracranial pressures. Although it is possible that the anesthetic technique used may have decreased the magnitude of the pressure changes seen, the actual effect remains uncertain.

The results also suggest that norepinephrine would be preferable to ephedrine as a vasopressor for patients in hemorrhagic shock with concomitant head injuries because of the increased ICP seen with the latter agent when administered to hypovolemic cats. Further study is needed to correlate our results in the cat with effects in human subjects and to elucidate the mechanisms of autoregulatory disruption following induced hypotension.

Drugs Used: Norepinephrine (Levophed bitartrate), Winthrop Laboratories; ephedrine sulfate, Abbott Laboratories; isoproterenol (Isuprel hydrochloride), Winthrop Laboratories; trimethaphan camsylate (Arfonad), Roche Laboratories; sodium nitroferricyanide, sodium nitroprusside, University of Iowa Hospital Pharmacy; sodium pentobarbital (Nembutal), Abbott Laboratories.

References

1. Corkill G: Hypotension with sodium nitroprusside in surgery of cerebral aneurysms. Anesthesia 28:191–194, 1974
2. Bodman RI: Controlled hypotension, Recent Advances in Anesthesia and Analgesia. Tenth edition. Edited by C Langton Hewer. London, J. and A. Churchill, 1967, p 90
3. McComish PB, Bodley PO: Anesthesia for Neurological Surgery. Chicago, Year Book Medical Publishers, 1971
4. Bodman RI: Controlled hypotension, Recent Advances in Anesthesia and Analgesia. Tenth edition. Edited by C Langton Hewer. London, J. and A. Churchill, 1967
5. Keaney NP, Pickerodt VW, McDowall DG, et al: Cerebral circulatory and metabolic effects of hypotension produced by deep halothane anesthesia. J Neurol Neurosurg Psychiatry 36:898–905, 1973
6. Brown AS: Pre-operative exsanguination in intracranial surgery. Anaesthesia 9:17, 1954
7. Vries JK, Becker, DP, Young HF: A subarachnoid screw for monitoring intracranial pressure. J Neurosurg 39:416–419, 1973
8. Volle RL, Koelle GB: Ganglionic stimulating and blocking agents, The Pharmacological Basis of Therapeutics. Third edition. Edited by LS Goodman, A Gilman. New York, MacMillan, 1965, pp 592–599
9. Freeman J, Ingvar DH: Elimination by hypoxia of cerebral blood flow autoregulation and EEG relationship. Exp Brain Res 5:61, 1968
10. Pannier JL, Wayne J, Leusen I: Effects of changes in acid–base composition in the cerebral ventricles on local and general cerebral blood flow. Eur Neurol 6:123–126, 1971/1972
11. Shapiro HM, Galindo A, Wyte SR, et al: Rapid intraoperative reduction of intracranial pressure with thiopentone. J Anaesth 45:1057–1062, 1973