Anesthesiology
51:127–130, 1979

Hypertension during Anesthesia on Discontinuation of Sodium Nitroprusside-induced Hypotension

Hoshang J. Khambatta, M.D., J. Gilbert Stone, M.D.,* Emaduddin Khan, M.Sc.†*

The authors had observed that on intraoperative discontinuation of sodium nitroprusside being administered to induce hypotension, mean arterial pressure increased to above the prehypotension level. Twelve patients who received hypotensive anesthesia for surgical correction of cerebral aneurysms were studied to evaluate the role of the renin–angiotensin system in this phenomenon. In the awake state, mean arterial pressure was 100 ± 2 torr and plasma renin activity 3.0 ± 0.1 ng/ml/hr. Thirty minutes after the establishment of stable halothane–nitrous oxide anesthesia, mean arterial pressure decreased to 85 ± 1 torr and plasma renin activity increased to 4.4 ± 0.1 ng/ml/hr. No appreciable change in either occurred over the next two hours of operation. During sodium nitroprusside-induced hypotension, mean arterial pressure decreased to 49 ± 2 torr and plasma renin activity increased to 15.2 ± 0.2 ng/ml/hr. Thirty minutes after discontinuation of sodium nitroprusside administration, mean arterial pressure increased to 112 ± 2 torr, which was not only higher than the prehypotension level, but also significantly higher than that recorded in the awake state. Plasma renin activity at that time was 10.9 ± 0.1 ng/ml/hr. As the half-life of plasma renin is 15 min, the data suggest that the persistently increased plasma renin activity is probably responsible for the increase of arterial pressure following sodium nitroprusside-induced hypotension. (Key words: Anesthetic techniques, hypotension, induced: nitroprusside. Blood pressure: hypertension; hypotension. Polypeptides: renin–angiotensin.)

RUPTURE AND HEMORRHAGE from an intracranial aneurysm can occur any time in the perioperative period.[1] The control of blood pressure is therefore desirable even after repair.[2]

The use of sodium nitroprusside to induce hypotension during anesthesia for correction of intracranial aneurysms is now well established. However, after abrupt discontinuation of sodium nitroprusside, we have repeatedly observed a gradual increase in arterial pressure to a level exceeding that seen preoperatively. The etiologic factor governing this undesirable side effect of sodium nitroprusside-induced hypotension has not been determined, but we believe that the reinin–angiotensin system may play a role in this phenomenon. The purpose of this study was to determine plasma renin activity in patients with cerebral aneurysms undergoing hypotensive anesthesia with sodium nitroprusside and to correlate arterial blood pressure with changes in plasma renin activity.

Method

Twelve patients, average age 34 years (range 18–60 years), who received hypotensive anesthesia for surgical correction of cerebral aneurysms were studied, with their informed consent. They were all neurologically intact preoperatively and had no concomitant cardiovascular, respiratory or renal disease. None was receiving any medication other than phenobarbital for sedation. Plasma electrolyte values were normal. Premedication consisted of atropine, 0.5 mg, and secobarbital, 100 mg, given intramuscularly an hour prior to induction of anesthesia. Anesthesia was induced with sodium thiopental, 250 to 300 mg, and *d*-tubocurarine, 0.6 mg/kg, given intravenously. Anesthesia was maintained with halothane, 1.0 per cent, in nitrous oxide, 70 per cent, and oxygen, 30 per cent. Following tracheal intubation, mechanical ventilation was established to maintain Pa_{CO_2} at 30 torr. Arterial pressure was recorded from a 20-g Teflon cannula in a radial artery using a Bentley-Trentec 800 transducer and a Hewlett-Packard modular monitoring system. Hypotension was induced five hours into the operation by titrating an intravenous infusion of sodium nitroprusside, 0.04 per cent. Rate of infusion was controlled by a Holter pump, the rates ranging from 0.3 to 0.5 mg/kg/hr. Mean arterial pressure was decreased to about 40 per cent below the preinfusion level and the decrease maintained for an average duration of 75 min. The total dose of sodium nitroprusside used was between 0.4 and 0.7 mg/kg. The duration of anesthesia was about nine hours, during which the patients received an average of 2,800 ml of lactated Ringer's solution intravenously. Urinary output was 1,600 ml and estimated blood losses averaged 800 ml.

Five-milliliter samples of arterial blood were collected in prechilled Vacutainer® tubes (Becton-Dickinson No. 4770) containing sufficient disodium salt of ethylenediamine tetra-acetic acid (EDTA) to achieve a final concentration of 1.4 mg/ml in order to measure plasma renin activity by radioimmunoassay using the Gamma Coat ^{125}I Plasma Renin Activity Kit.‡

* Assistant Professor.

† Research Worker.

Received from the Department of Anesthesiology, College of Physicians and Surgeons, Columbia University, New York, New York 10032. Accepted for publication December 21, 1978. Supported in part by NIH Grant #5P01 GM 09069. Presented in part at the Fifth European Congress of Anaesthesia, September 1978, Paris, France.

Address reprint requests to Dr. Khambatta.

‡ Manufactured by Clinical Assays, Travenol Laboratories, Inc., Cambridge, Mass.

TABLE 1. Plasma Renin Activity, Mean Arterial Pressure, and Heart Rate at Various Stages of Anesthesia, Operation, and Hypotension with Sodium Nitroprusside

	Plasma Renin Activity (ng/ml/hr)	Mean Arterial Pressure (torr)	Heart Rate (Beats/Min)
Awake	3.0 ± 0.1	100 ± 2	72 ± 2
30 min after induction of anesthesia	4.4 ± 0.1*	85 ± 1*	69 ± 2
During operation	4.6 ± 0.2	86 ± 2	71 ± 1
Prior to hypotension	4.5 ± 0.1	84 ± 1	70 ± 2
30 min of hypotension with sodium nitroprusside	14.8 ± 0.2†	51 ± 1†	93 ± 2†
Prior to end of hypotension	15.2 ± 0.2†	49 ± 2†	96 ± 1†
30 min after discontinuation of sodium nitroprusside	10.8 ± 0.1‡	112 ± 2‡	83 ± 2‡

* $P < 0.001$, awake versus 30 min after induction of anesthesia.
† $P < 0.001$, 30 min after induction of anesthesia versus induced hypotension.
‡ $P < 0.001$, awake versus 30 min after discontinuation of sodium nitroprusside.

The method is an adaptation of that described by Haber *et al.*[3] Briefly, the plasma was separated immediately in a refrigerated centrifuge and kept at 4 C. Radioimmunoassay was performed within 24 hours of collection, but failing this, the specimen was stored at −20 C. The sensitivity of the Gamma Coat plasma renin activity determination, calculated as the amount of angiotensin I necessary to depress binding to a count level equivalent to maximum binding less two standard deviations from that point, is 17 pg. The interassay variability in our laboratory is 7 per cent.

The hemodynamic measurements were made and blood samples were collected at the following periods: awake; 30 min after induction of anesthesia; during operation when the patient's vital signs were stable; immediately prior to induction of hypotension; after 30 min of hypotension; just prior to discontinuation of hypotension; 30 min after the sodium nitroprusside infusion had been discontinued.

Results are expressed as means ± standard error of the mean (SE). Statistical evaluation was performed using the Student *t* test for paired data within groups; $P < 0.05$ was considered significant.

Results

During the awake state, mean arterial pressure was 100 ± 2 torr and plasma renin activity was 3.0 ± 1 ng/ml/hr (table 1). With the induction of anesthesia there was a significant decrease in mean arterial pressure to 85 torr and an increase in the plasma renin activity to 4.4 ng/ml/hr. There was no appreciable change in mean arterial pressure or plasma renin activity during the stable period of anesthesia and operation. During hypotension induced with sodium nitroprusside, mean arterial pressure was maintained at 49 torr and plasma renin activity increased to 15.2 ng/ml/hr. Thirty minutes after discontinuation of sodium nitroprusside administration, mean arterial pressure had gradually increased to 112 torr, thus overshooting not only the prehypotension value, but that of the awake state as well. At this time plasma renin activity was 10.8 ng/ml/hr. Plasma electrolyte values measured within an hour of completion of operation were: sodium, 135 ± 4 mEq/l; potassium, 3.6 ± 0.3 mEq/l; chloride, 102 ± 3 mEq/l, and were not different from those obtained the day before operation.

Discussion

In the present study induction of anesthesia with sodium thiopental and its maintenance with nitrous oxide and halothane resulted in both a statistically significant decrease in mean arterial pressure (15 per cent) and an increase in plasma renin activity (50 per cent). This is in agreement with the findings of Pettinger *et al.*, who have shown in rats that induction of a surgical plane of anesthesia results in a less-than-twofold increase in plasma renin activity.[4] Other reports in the literature demonstrate an increase in plasma renin activity in anesthetized dogs.[5,6] However, Miller and co-workers were unable to show an increase in plasma renin activity in rats with the induction of anesthesia, even though mean arterial pressure decreased 23 per cent.[7,8] This discrepancy remains unexplained, even though Miller and co-workers did report higher than average control values.[7,8]

During the next four hours, while the operation was in progress, there was no appreciable change in plasma renin activity in our patients. Robertson and Michelakis showed a significant increase in plasma renin activity in patients during anesthesia and operation, but most of these patients either were hypotensive or had sustained blood losses.[9] In our patients blood pressures did not fluctuate during this phase of the operation. The inspired anesthetic concentration remained constant, and fluid infusion matched urinary output and blood loss. No appreciable change in the plasma electrolyte values was observed after operation.

With the infusion of sodium nitroprusside, mean arterial pressure decreased 40 per cent and there was concomitant reflex tachycardia. A fivefold increase in plasma renin activity occurred during hypotensive anesthesia. Miller and colleagues have shown an increase in plasma renin activity in anesthetized rats that received sodium nitroprusside.[7] Kenko and co-workers also demonstrated an increase in plasma

renin activity in unanesthetized human subjects who received sodium nitroprusside.[10] Other vasodilating, hypotensive agents have also been shown to increase plasma renin activity in man[11-13] and rats.[14] There was no significant difference in the levels of plasma renin activity between the two sampling periods during hypotension. This corroborates the work of Miller *et al.*, who have shown that plasma renin activity reaches a pressure-dependent plateau with sodium nitroprusside and that continued administration, while maintaining the same level of arterial pressure, does not further increase plasma renin activity.[7]

The half-life of plasma renin activity is 15 min.[15] Thirty minutes after discontinuation of sodium nitroprusside in our patients, plasma renin activity declined to only 10.8 ng/ml/hr, compared with 15.2 ng/ml/hr just before discontinuation of the drug. Thus, the level of plasma renin activity was considerably higher than that expected on the basis of its half-life. We also found that during this final period, while the anesthetic concentration was not altered, mean arterial pressure gradually increased and reached a level higher than that in the awake period. This suggests that the high plasma renin activity was responsible for the increased pressure. The explanation for the high plasma renin activity during this period, however, is unknown.

Renin is not a vasoactive substance. This proteolytic enzyme acts in the general circulation to cleave its substrate on α_2-globulin to produce the decapeptide angiotensin I. Angiotensin I in turn is rapidly cleaved by the converting enzyme, primarily in the lungs, to octopeptide angiotensin II, which then is rapidly degraded into inactive polypeptide fragments by the enzyme angiotensinase. It has recently been suggested that the terminal heptopeptide of angiotensin II can act independently of angiotensin II and is appropriately designated angiotensin III.[16] Angiotensins I, II and III act both by a direct vasoconstrictor action on blood vessels and also by causing the release of catecholamines from the adrenal glands and central nervous system.[17] Pettinger and co-workers have shown the presence of a feedback mechanism; the catecholamines that are released in response to angiotensin stimulation in turn bring about further release of renin.[18,19] Thus, it is possible that this feedback mechanism may be responsible for the sustained high level of plasma renin activity seen in our patients.

The liver has a dual blood supply; about 70 per cent from the portal vein and the remainder via the hepatic artery. The liver is not an autoregulated organ,[20] hence a decrease in arterial pressure will result in a decrease in blood flow from that fraction supplied by the hepatic artery. The hepatic circulation has not been studied in man during hypotensive anesthesia with sodium nitroprusside. However, sodium nitroprusside has been shown to decrease mesenteric blood flow (hence portal flow) in the dog,[21] and in man nitroglycerin has been shown to decrease splanchnic blood flow, as estimated by the sulfobromophthalein method.[22] It is therefore possible that hepatic blood flow may be decreased during hypotensive anesthesia. In turn, inactivation of renin in the liver would be diminished[23] and be responsible for the increased half-life of plasma renin activity seen in our patients.

The cooperative study of cerebral aneurysms showed that 19 per cent of patients have two or more aneurysms.[24] Even when single aneurysms are identified, it may not be possible to clip them, and they may be wrapped in muslin or coated with plastic. Eighteen per cent of our patients are treated in this fashion. Even aneurysms that can be clipped may not be secure, as Selverstone has stated that "even a well designed, well chosen and well placed clip may be dislodged from the site postoperatively, presumably as a result of arterial pulsation, with immediate or subsequent fatal hemorrhage."[2] Therefore, it seems imprudent to allow the arterial pressure to increase beyond that which the patient had preoperatively,§ and we hope this report will draw attention to the phenomenon of hypertension following discontinuation of sodium nitroprusside administration. In the patients described here, the modest increases in mean arterial pressure had no ill effect. However, in our practice we prevent such modest increases in arterial pressure in patients with cerebral aneurysms by gradual withdrawal of sodium nitroprusside.

References

1. Skultety FM, Nishioka H: Report on the cooperative study of intracranial aneurysms and subarachnoid hemorrhage. Results of intracranial surgery in the treatment of aneurysms. J Neurosurg 25:683-704, 1966
2. Selverstone B: Coating intracranial aneurysms with nontoxic adherent plastics, Current Techniques in Operative Neurosurgery. Edited by HH Schmidek, WH Sweet. New York, Grune and Stratton, 1977, pp 31-40
3. Haber E, Koerner T, Page LB, et al: Application of radioimmunoassay for angiotensin I to the physiologic measurements of plasma renin activity in normal human subjects. J Clin Endocrinol 29:1349-1355, 1969

§ Mount LA, Emeritus Professor of Clinical Neurological Surgery, College of Physicians and Surgeons, Columbia University and the Neurological Institute, New York, New York: Personal communication.

4. Pettinger WA, Tanaka K, Keeton K, et al: Renin release, an artifact of anesthesia and its implications in rats. Proc Soc Exp Biol Med 148:625–630, 1975
5. Ganong F: Sympathetic effects on renin secretion: Mechanism and physiologic role. Adv Exp Med Biol 17:17–32, 1972
6. Johnson MD, Malvin RL: Plasma renin activity during pentobarbital anesthesia and graded hemorrhage in dogs. Am J Physiol 229:1098–1101, 1975
7. Miller ED, Ackerly JA, Vaughan D Jr, et al: The renin–angiotensin system during controlled hypotension with sodium nitroprusside. ANESTHESIOLOGY 47:257–262, 1977
8. Miller ED, Longnecker DE, Peach MJ: Regulatory function of the renin–angiotensin system during general anesthesia. ANESTHESIOLOGY 48:399–403, 1978
9. Robertson D, Michelakis AM: Effect of anesthesia and surgery on plasma renin activity in man. J Clin Endocrinol Metab 34:831–835, 1972
10. Kenko Y, Ikeda T, Takeda T, et al: Renin release during acute reduction of arterial pressure in normotensive subjects and in patients with renovascular hypertension. J Clin Invest 46:705–716, 1967
11. Küchel O, Fishman LM, Liddle GW, et al: Effect of diazoxide on plasma renin activity in hypertensive patients. Ann Intern Med 67:791–799, 1967
12. Winer N, Chokshi DS, Yoon MS, et al: Adrenergic receptor mediation of renin secretion. J Clin Endocrinol 29:1168–1175, 1969
13. Ueda H, Kaneko Y, Takeda T, et al: Observations on the mechanism of renin release by hydralazine in hypertensive patients. Circ Res (suppl II) 27:201–206, 1970
14. Pettinger WA, Campbell WR, Keeton K: Adrenergic component of renin release induced by vasodilating and hypertensive drugs in the rat. Circ Res 33:82–86, 1973
15. Douglas WW: Polypeptides—angiotensin, plasma kinins, and other vasoactive agents; prostaglandins, The Pharmacological Basis of Therapeutics. Edited by LS Goodman, A. Gilman. New York, Macmillan, 1975, pp 630–652
16. Blair-West JR, Coghlen JP, Denton DA, et al: The effect of heptapeptide (2–8) and hexapeptide (3–8) fragments of angiotensin II on aldosterone secretion. J Clin Endocrinol 32:575–578, 1971
17. Peach MJ: Renin–angiotensin system: Biochemistry and mechanism of action. Physiol Rev 57:313–370, 1977
18. Pettinger WA: Anesthetics and the renin–angiotensin–aldosterone axis. ANESTHESIOLOGY 48:393–396, 1978
19. Pettinger WA, Graham RA, Keeton TR: The role of β-adrenoreceptor in the mediation of renin release. Excerpta Med (in press)
20. Strunin L: Organ perfusion during controlled hypotension. Br J Anaesth 47:793–803, 1975
21. Wang HH, Liu LMP, Katz RL: A comparison of cardiovascular effects of sodium nitroprusside and trimethaphan. ANESTHESIOLOGY 46:40–48, 1977
22. Ferrer MI, Bradley SE, Wheeler HO, et al: Some effects of nitroglycerine upon the splanchnic, pulmonary and systemic circulation. Circulation 33:357–373, 1966
23. Davis JO, Freeman RH: Mechanisms regulating renin release. Physiol Rev 56:1–56, 1976
24. Locksley HB: Natural history of subarachnoid hemorrhage, intracranial aneurysms and arteriovenous malformations. Intracranial Aneurysm and Subarachnoid Hemorrhage: A Cooperative Study. Edited by AL Saks, GE Parret, HB Locksley et al. Philadelphia, Lippincott, 1969, pp 37–57