

## Intracranial Pressure in the Cat during Nitroglycerin-induced Hypotension

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Intracranial pressure measurements were made during nitroglycerin-induced hypotension in the cat anesthetized with halothane. A total of 48 individual observations were made in eight animals. The administration of sufficient nitroglycerin to decrease mean arterial pressure from a control value of  $87 \pm 7$  torr by  $12 \pm 4$  torr resulted in an increase in mean intracranial pressure from a control value of  $7 \pm 2$  torr to  $12 \pm 2$  torr. Larger decreases in mean blood pressure were associated with larger increases in intracranial pressure. The increase in intracranial pressure was similar to that previously reported for nitroprusside, and greater as well as more reproducible than that reported for trimethaphan. Thus, nitroglycerin may produce significant increases in intracranial pressure, and this may be a limiting factor in its clinical use. (Key words: Anesthetic techniques, hypotension, induced: nitroglycerin. Blood pressure, hypotension. Cerebrospinal fluid: pressure.)

IT HAS BEEN REPORTED that sodium nitroprusside and trimethaphan increase intracranial pressure (ICP) when administered for purposes of inducing controlled hypotension.<sup>1-3</sup> Nitroglycerin has recently been advocated as a clinically useful vasodilator drug for inducing controlled hypotension during anesthesia,<sup>4</sup> and specifically during neurosurgical procedures.<sup>5</sup> Whether this agent is capable of provoking increased intracranial pressure during induced hypotension, however, had not been investigated. This paper reports the results of our study of this possibility.

### Methods

Male cats weighing 3–5 kg were used in the experiments. The animals were anesthetized by placing them in a specially designed closed-hood cage to facilitate anesthetic induction with halothane, 4 per cent, and oxygen, 30 per cent. When asleep, each cat was removed, the trachea intubated with a 2.5-mm endotracheal tube, and the lungs ventilated via a Harvard 607 respirator with halothane, 1 per cent, in oxygen-enriched air (oxygen concentration 30 per cent). A femoral artery was catheterized and another catheter

inserted into a femoral vein and threaded to the right atrium. These catheters permitted frequent sampling of arterial blood for blood-gas analyses, as well as continuous monitoring of blood pressure and central venous pressure with Statham® pressure transducers (p23Db) and Model 150 recorder. The animal was then paralyzed with a continuous infusion of pancuronium bromide, 23  $\mu\text{g}/\text{kg}/\text{hour}$ , and the ventilator adjusted to maintain  $\text{Pa}_{\text{O}_2} > 90$  torr,  $\text{Pa}_{\text{CO}_2} 40 \pm 3$  torr, and  $\text{pH} 7.42 \pm .04$ . Supplemental sodium bicarbonate was infused as necessary at the rate of 1.25 mEq/hour to maintain a base deficit of  $\pm 2$ . Rectal temperature was continuously monitored and maintained at  $37 \pm 0.5$  C with the use of a heating blanket and lamp as needed.

The animal was then placed in a "sphinx" position in a stereotactic frame. Muscle and connective tissue were retracted to expose the atlanto-occipital membrane. The dura was punctured and a 17-gauge catheter inserted into the cisterna magna to a depth of 1 mm. Care was taken to avoid introduction of air bubbles into the cisterna. The catheter was secured and connected to a Statham pressure transducer for continuous measuring of ICP. The experiment was initiated once the monitored physiologic variables were stable.

Nitroglycerin (Lilly) was diluted in physiologic saline solution and standardized as a 3-ml injection over 15 sec. The doses given ranged from 5 to 20  $\mu\text{g}/\text{kg}$ , and were known from earlier experiments to be sufficient to produce decreases in mean arterial blood pressure of 10 to 30 torr. Subsequent injections were not made until the blood pressure had been stable at the pre-drug level for at least 10 min. Comparisons between changes in blood pressure and ICP were made using mean pressure values. Mean systemic blood pressure was calculated as diastolic blood pressure plus  $0.33 \times$  pulse pressure, and mean ICP was calculated as diastolic pressure plus  $0.50 \times$  intracranial pulse pressure.<sup>2</sup> Statistical comparisons were made by use of the Student *t* test, and  $P < 0.05$  was considered significant.

### Results

A total of 48 individual observations were made in eight cats. The injection of sufficient nitroglycerin to

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TABLE 1. Relationships of Small, Moderate, and Large Decreases in Mean Systemic Blood Pressure to Increases in Mean Intracranial Pressure (Mean  $\pm$  SEM)

	Control $\overline{BP}$ (torr)	Decrease of $\overline{BP}$ (torr)	Control $\overline{ICP}$ (torr)	Maximum $\overline{ICP}$ after Nitroglycerin
Group I (n = 15)	87 $\pm$ 7	12 $\pm$ 4	7 $\pm$ 2	12 $\pm$ 2*
Group II (n = 14)	92 $\pm$ 10	21 $\pm$ 7	8 $\pm$ 3	18 $\pm$ 4*
Group III (n = 17)	90 $\pm$ 6	30 $\pm$ 7	8 $\pm$ 3	20 $\pm$ 5*

$\overline{BP}$  = mean systemic blood pressure;  $\overline{ICP}$  = mean intracranial pressure.

\* $P < .05$  compared with  $\overline{ICP}$ .

produce hypotension resulted in an increase in intracranial pressure in each observation in every animal (table 1). In two animals, the injection of nitroglycerin, 5  $\mu\text{g}/\text{kg}$ , failed to produce either significant hypotension or a significant increase in intracranial pressure, but the higher (10  $\mu\text{g}/\text{kg}$ ) doses produced both hypotension and increases in intracranial pressure. Each decrease in blood pressure and increase in intracranial pressure occurred within 2–3 sec of injection, and gradually disappeared over 30–120 sec (fig. 1). The increases in intracranial pressure often persisted for 15–60 sec after the return of blood pressure to control values.

## Discussion

The hemodynamic effects of nitroglycerin differ from those of other agents used for controlled hypotension, such as trimethaphan and nitroprusside. While nitroglycerin is a potent direct vasodilator of both arterial and venous vascular smooth muscle,<sup>6</sup> it does not consistently decrease arteriolar resistance.<sup>7</sup> The decreases in ventricular systolic and diastolic volumes,<sup>8</sup> as well as decreased pulmonary capillary wedge pressure<sup>8,9</sup> produced by this agent are due primarily to pooling of blood in large systemic veins and decrease in venous return.<sup>9,10</sup> Furthermore, when the effects of nitroglycerin on the blood supplies to specific organ systems are analyzed, it is apparent that nitroglycerin produces disparate responses in different vascular beds. Ferrer<sup>10</sup> even reported that nitroglycerin had a vasoconstrictive effect on the splanchnic circulation.

With disparate effects on different vascular beds and only preliminary observations on cerebral vasculature,<sup>5,11</sup> the effects of nitroglycerin on ICP could not be predicted with certainty. While the fact that nitroglycerin increases ICP is not a surprise, it cannot be assumed that all agents used for the production of hypotension will increase ICP. Trimethaphan, for example, is a ganglionic blocking agent that clearly produces systemic vasodilatation, depressed cardiac

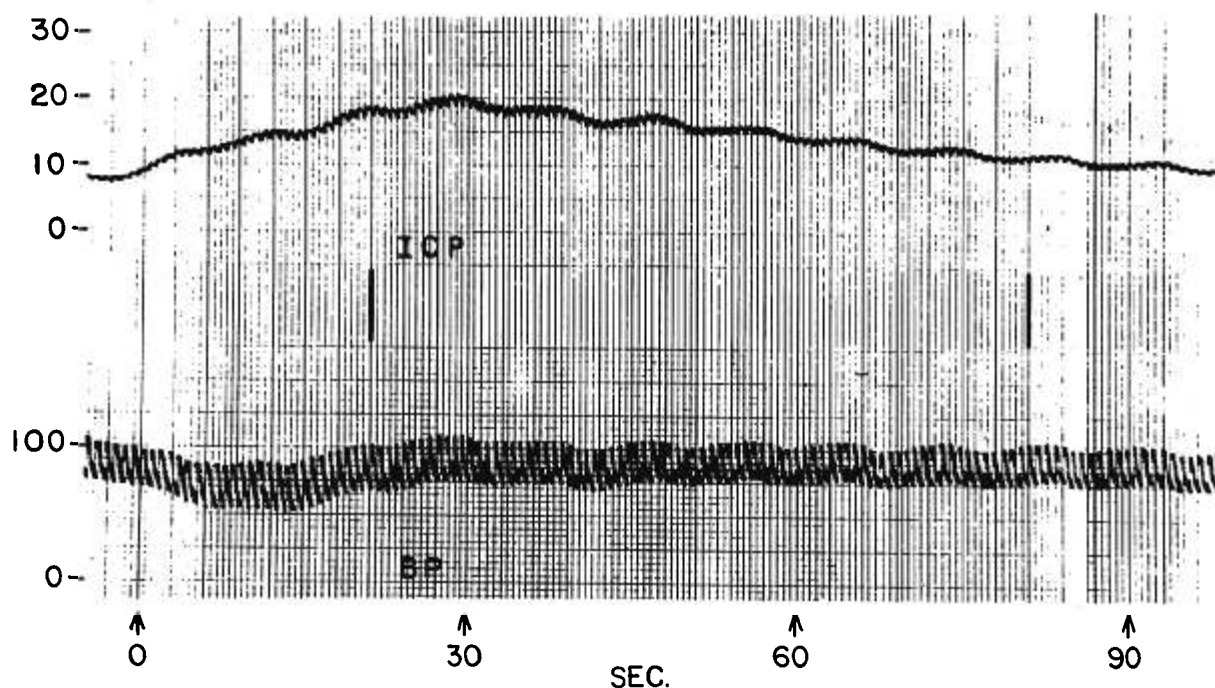


FIG. 1. Time course of changes in systemic blood pressure and intracranial pressure in the cat. Arrow indicates administration of nitroglycerin. BP = blood pressure; ICP = intracranial pressure.

output, and variable changes in ICP.<sup>2,3,12-14</sup> On the other hand, nitroprusside, a direct relaxant of vascular smooth muscle, has been shown to decrease systemic vascular resistance and clearly increase ICP.<sup>2,3,12-14</sup> As a result, it appears that it is necessary to evaluate the effect on ICP of each agent used for the production of controlled hypotension.

Our data clearly establish that nitroglycerin results in a prompt, significant increase in ICP. In fact, it is possible with small doses of nitroglycerin to increase intracranial pressure with only minor systemic blood pressure effects. Of interest is the fact that nitroglycerin appears to be more potent in provoking an increase in intracranial pressure for a given decrease in mean systemic pressure than has previously been reported for trimethaphan.<sup>2,3</sup> This effect, however, was similar in magnitude to that reported for nitroprusside, an agent that also relaxes vascular smooth muscle.<sup>1,2</sup> The increase in ICP produced by nitroglycerin occurred in animals with normal intracranial pressure and intracranial compliance, and the magnitude of intracranial pressure changes would probably be exaggerated in a patient with intracranial disease and decreased intracranial compliance.

We deliberately chose to give nitroglycerin as a rapid injection, as previously described by Stullken and Sokoll<sup>3</sup> in their studies of nitroprusside and trimethaphan. The use of this technique permits study not only of the ICP changes associated with hypotension but also of any change occurring during the recovery period. It does not, however, elucidate the relationship between sustained systemic hypotension and ICP changes produced by continuous nitroglycerin infusion. While it is likely that the ability of nitroglycerin to increase ICP persists during prolonged infusion, as already demonstrated for nitroprusside, this cannot be confirmed until direct measurements of ICP are made during continuous infusion of nitroglycerin.

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