Cerebral Blood Flow and Intracranial Pressure in the Dog During Intravenous Infusion of Nitroglycerin Alone and in Combination with Dopamine

CLAES VON ESSEN, M.D., J. PHILIP KISTLER, M.D., ROBERT S. LEES, M.D., AND NICHOLAS T. ZERVAS, M.D.

SUMMARY Nitroglycerin, long known as a safe and effective dilator of the large coronary arteries, has recently been shown to dilate the basilar artery of the dog after experimentally induced vasospasm. In this study we have evaluated the effects of intravenous nitroglycerin on local cerebral blood flow (H2 clearance technique) and intracranial pressure (intracisternal needle monitor) in normal beagle dogs (Group 1). In each of 7 dogs, infusion of nitroglycerin at rates of 3.5, and 10 μg/kg/min did not change blood flow in the right and left caudate nucleus, thalamus, frontal and parietal cortex. Autoregulation of cerebral blood flow remained unimpaired and intracranial pressure remained stable during nitroglycerin infusion.

The effects of a combination of intravenous nitroglycerin and dopamine on local cerebral blood flow was evaluated in another group of normal beagle dogs (Group 2). Local cerebral blood flow decreased or remained unchanged in response to intravenous infusion of dopamine at low rates, increased in response to moderate rates and again decreased in response to high infusion rates. These dopamine induced changes in blood flow occurred whether or not nitroglycerin was infused simultaneously. When the vasoconstrictor activity of dopamine was blocked by phentolamine or methysergide, local cerebral blood flow increased at moderate and high infusion rates, again whether or not nitroglycerin was infused simultaneously.

Our data suggest that nitroglycerin affects mainly the extracerebral capacitance arteries while dopamine affects the smaller intraparenchymal resistance vessels. Nitroglycerin has little effect on cerebral blood flow even when used in combination with dopamine.

NITROGLYCERIN has long been known to be a safe and effective coronary vasodilator.1, 2 Initially, nitroglycerin was used in the management of angina and, more recently, it has become an accepted therapy in the management of acute cardiac ischemia.3-4 Intravenous nitroglycerin improves circulation in ischemic myocardium and this effect is thought to occur because nitroglycerin has its major effect on the capacitance rather than on the resistance vessels.5-8 Despite the wide use of nitroglycerin in cardiac disease, little is known about its effects on cerebral hemodynamics. There is increasing evidence that nitroglycerin dilates the cerebral vessels.9-11 Intravenous bolus injections of nitroglycerin, large enough to cause a transient reduction in mean arterial blood pressure, may, however, also transiently increase intracranial pressure.12

Dopamine is widely used to increase blood pressure and cardiac output in patients with ischemic heart disease and in patients in circulatory shock. Dopamine has dose-dependent effects on the cerebral vasculature. Small doses usually decrease cerebral blood flow; moderate doses increase blood flow; large doses usually decrease cerebral blood flow.13-16 The increase in cerebral blood flow is believed to result from activation of specific vascular dopamine receptors14-16 with a resulting dilatation of the resistance vessels. Dopamine is sometimes used in the treatment of cerebral vasospasm following subarachnoid hemorrhage, either alone or in combination with other drugs,17-18 and is also used with nitroglycerin in the management of ischemic heart disease.

The effects of dopamine on cerebral blood flow have been studied previously.14, 16 We report here the results from experiments designed to analyze the effects of nitroglycerin on cerebral blood flow and intracranial pressure in the normal dog (Group 1). In addition, we report the results of experiments designed to analyze the effect of nitroglycerin on variations in cerebral blood flow already induced by dopamine (Group 2).

Methods

Local cerebral blood flow was measured in beagle dogs with body weights of 7 to 15 kg. The animals were premedicated with ketamine, 10 mg/kg. Anesthesia was induced with pentobarbital, 20 mg/kg intravenously, and maintained with nitrous oxide in a 65-70 percent mixture with oxygen. Muscle relaxation was achieved by repeated intravenous injections of gallamine triethiodide. A Harvard respirator (Model 607, Harvard Apparatus Company, Millis, MA) was used for ventilation through an endotracheal tube. Eight platinum electrodes were implanted stereotactically in the frontal and parietal cortex, caudate nucleus and thalamus bilaterally in each

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animal. The uninsulated tip of each electrode was 0.3 mm in diameter and 0.2 mm in length and was sharpened to a point. The electrodes were inserted through separate small burr holes. Four stainless steel screws in the skull were connected with a stainless wire that encircled the area of electrode implantation and acted as the reference electrode. The electrodes, burr holes, screws and wire were then secured and covered with acrylic cement so that only the connectors were bare. The muscles and skin flap were closed and the animals returned to their cages. All the dogs appeared to behave normally after electrode implantation. Five to 8 days later, the animals were again premedicated with ketamine and anesthetized with pentobarbital, intubated, paralyzed and ventilated with nitrous oxide and oxygen, as above. One brachial artery and vein were catheterized. The arterial catheter was connected to a pressure transducer (Model T23AC, Statham Laboratories Inc., Hato Rey, Puerto Rico) and the blood pressure recorded with a Grass polygraph (Model 7WC16PA, Grass Instruments Co., Quincy, MA). Mean arterial blood pressure was calculated as diastolic pressure plus 1/3 of the pulse pressure. One femoral vein was catheterized and a saline infusion begun at a rate of 1/2 ml per min. In Group 1 six of the dogs were immobilized in a stereotactic frame and the cisterna magna was punctured percutaneously with an 18 gauge needle which was connected to a water manometer. Cerebrospinal fluid pressure was measured at periodic intervals throughout the experiment using the level of the external auditory meatus as reference point.

Local cerebral blood flow was measured by the hydrogen clearance method of Aukland et al. as modified by Haining et al. and Willis et al. Clearance data from all 8 electrodes were obtained simultaneously with an 8 channel circuit. Hydrogen was administered by inhalation. The amount of nitrous oxide was diminished and an equivalent amount of hydrogen was given during the saturation phase which usually lasted 8 minutes. Blood gas analysis showed no change in arterial oxygen or carbon dioxide tension during this period. The clearance curves which followed cessation of hydrogen administration were recorded and displayed through an oscilloscope using computer assisted data acquisition (Micro Nova, Data General Corporation, Westboro, MA) according to the method of Brown. The first 40 sec of the initial curves were excluded from analysis and only values from the remainder of the clearance curves were analyzed. In most instances the remainder of the clearance curves were monoeponential, but occasionally multieponential curves were present. When this occurred the final blood flow measurement for any one curve represented a weighted average of all the values.

Arterial blood was regularly examined for oxygen tension, carbon dioxide tension and pH with micro-electrodes (Radiometer, Copenhagen). Arterial carbon dioxide tension was kept stable throughout the entire experiment.

In Group 1 a continuous intravenous infusion either of nitroglycerin or of normal saline was given through the brachial venous line using a Harvard infusion pump (Model 918, Harvard Apparatus Company). Three different infusion rates were used for nitroglycerin; 3, 5 and 10 µg/ml/min.

In Group 2 dopamine was administered at a concentration of 400 µg/ml in saline and given as a continuous intravenous infusion for at least 30 min before cerebral blood flow was measured. When the dose of dopamine was changed, 30 min were allowed to elapse before the next flow measurement. Nitroglycerin was administered at a concentration of 300 µg/ml in normal saline solution by the use of continuous intravenous infusion.

Autoregulation of cerebral blood flow was measured after changes in mean arterial blood pressure produced by bleeding and retransfusion. In most animals graded clamping of the thoracic aorta was required to increase blood pressure sufficiently. At the completion of the experiments the skull was removed and the brain and skull fixed in situ in formalin. The electrodes were later localized by microdissection of the brain.

General Procedure

When the skin flap had been turned down and the arterial and venous lines inserted, the electrodes were connected to the computer. A period of 45 min was allowed for stabilization. Cerebral blood flow reactivity to changes in arterial carbon dioxide tension was then tested and thereafter at least 3, and in most cases 5, control measurements of local cerebral blood flow, cerebrospinal fluid pressure (when performed) and arterial blood gases were taken before the nitroglycerin or the dopamine infusion was started. Arterial blood pressure was recorded continuously.

Measurements of local cerebral blood flow, cerebrospinal fluid pressure and arterial blood gases were then made 20 min after beginning each of the 3 infusion rates of nitroglycerin in Group 1. At least 2 recordings were made at each infusion rate before changing to the next.

Results

Group 1 — Effects of Nitroglycerin Alone on Cerebral Blood Flow and Intracranial Pressure

The effects of continuous intravenous infusion of nitroglycerin at 3, 5, and 10 µg/kg/min on local cerebral blood flow, mean arterial blood pressure, and intracranial pressure, are shown in the table. In each of the 7 animals studied, at least 2 recordings were made of the blood flow at each site (frontal, cortex, parietal cortex, caudate nucleus and thalamus) and a mean value was taken at each dosage. In each of the 7 dogs, cerebral blood flow did not vary appreciably from control values during nitroglycerin infusion. This was true even at the highest dose, i.e., 10 µg/kg/min (table). Throughout the experiment the arterial carbon dioxide tension did not vary more than 7 mm Hg in any one dog.
The effect of increasing infusion rates of nitroglycerin on mean arterial blood pressure is also seen in the table. In all but one dog, No. 4, the mean arterial blood pressure fell a modest but significant amount as higher doses of nitroglycerin were used. Despite this fall in mean arterial blood pressure, local cerebral blood flow remained stable.

The effect of nitroglycerin on intracranial pressure, recorded as cerebrospinal fluid pressure in the cisterna magna, was studied in 6 dogs. At infusion rates of 3, 5, and 10 μg/kg/min in each of the 6 dogs in the table, the intracranial pressure did not change significantly from its control value. In 2 experiments, an initial intravenous bolus of 500 μg/kg/min of nitroglycerin was given for 2 minutes after which the infusion rate was reduced to 3 μg/kg/min. This induced a sudden fall in the mean arterial blood pressure and also a sudden rise in the intracranial pressure in the range of 7 cm of water. However, the intracranial pressure returned to control values within 2 minutes.

To study autoregulation, mean arterial blood pressure was lowered or raised by bleeding, retransfusion or ligation of the thoracic aorta in 5 dogs. Mean arterial blood pressure (MAP) and arterial carbon dioxide tension (PaCO2) are given in mm Hg. Cerebrospinal fluid pressure (Psf) was measured in cm of water.

<table>
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<tr>
<th>Dog</th>
<th>Cerebrospinal fluid pressure (cm H2O)</th>
<th>Thalamus</th>
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<th>Frontal cortex</th>
<th>Frontal cortex</th>
<th>MABP (mm Hg)</th>
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*Cerebral blood flow (ml/100 g/min) was measured at the locations given in the table. Each value represents the mean of 2 or 3 measurements ± one standard deviation. Nitroglycerin (TNG) was infused at 3, 5 and 10 μg/kg/min. Mean arterial blood pressure (MABP) and arterial carbon dioxide tension (PaCO2) were given in mm Hg. Cerebrospinal fluid pressure (Psf) was measured in cm of water.
Figure 1. Local cerebral blood flow, expressed as percent of control, in response to continuous intravenous infusion of nitroglycerin (10 µg/kg/min) and varying doses of dopamine. Each black dot represents the mean value of 2 or 3 flow measurements at the tip of one electrode in either the right or left caudate nucleus, thalamus, frontal or parietal cortex. The data for each electrode at the above recording sites in each of the 6 dogs studied is represented by a line. In some instances, where the flow at more than one electrode was identical, the lines are superimposed. The infusion rate of dopamine was varied as shown on the abscissa.

Initial nitroglycerin infusion did not change cerebral blood flow. Addition of intravenous dopamine had highly unpredictable variable effects, similar to those known to occur in the absence of nitroglycerin\textsuperscript{14, 19} i.e., blood flow at a given dose might increase, decrease or remain unchanged.

In 2 dogs dopamine was infused first (fig. 2). When the effects of dopamine on local cerebral blood flow were established, the addition of nitroglycerin 10 µg/kg/min failed to change flow. Nitroglycerin was then stopped while the dopamine was maintained; one hour later the alpha-adrenergic antagonist phentolamine\textsuperscript{27} was given to one animal (Dog A, fig. 2) and the serotonin antagonist methysergide\textsuperscript{28} to the other (Dog G, fig. 2). In both animals local cerebral blood flow increased in all regions after administration of the antagonists during continuous infusion of dopamine.

Methysergide 10 mg/kg was given initially to 2 dogs (fig. 3). Methysergide alone had no effect on cerebral blood flow although it decreased mean arterial pressure substantially. The addition of nitroglycerin to the methysergide did not change flow, but when dopamine was added there was an increase in local cerebral blood flow at all the electrode sites. During those experiments small additional doses of methysergide had to be given intermittently as the effects of each dose on the arterial blood pressure decreased with time.

The effects of the combination of nitroglycerin, dopamine and methysergide on local cerebral blood flow are further illustrated in figure 4. After establishing control flows, dopamine infusion was started in 8 dogs at a constant rate which differed for each dog. Then, an infusion of nitroglycerin was added and, lastly, methysergide was given. Values from cortical electrodes are missing in some of the dogs because it was difficult in every case to obtain proper electrode

Figure 2. Local cerebral blood flow, expressed as percent of control, in response to continuous infusion of dopamine alone and in combination with other agents in 2 dogs. Each point is the mean value of 2 or 3 flow measurements at a given dose of drugs in a specific location (see key). In both dogs an infusion of nitroglycerin was given after the dopamine effect was established. Nitroglycerin was then discontinued and followed one hour later by phentolamine injection in dog A and methysergide in dog B.
position and thus proper clearance curves in the thin cortex of the dog. The figure shows that when the effect of dopamine on local cerebral blood flow was established, the addition of nitroglycerin did not change the flow further. This was true at the decreased flow generally induced by small and large doses of dopamine as well as at the increased flow induced by intermediate doses. When methysergide was added there was an increase in local cerebral blood flow in all regions in the 4 dogs that received dopamine doses of 7 \( \mu g/kg/min \) or higher.

The dose of methysergide needed to block the reduction in blood flow caused by the vasoconstrictive effect of high doses of dopamine (7 \( \mu g/kg/min \)) was established as follows. Ten additional dogs were given a constant infusion of dopamine at 7 \( \mu g/kg/min \) and nitroglycerin at 10 \( \mu g/kg/min \). In each dog increasing doses of methysergide were added until an increase in cerebral blood flow in all functioning electrodes occurred. This occurred in each dog at dosages of methysergide between 6 and 8 \( mg/kg \). We therefore chose the methysergide dose of 10 \( mg/kg \).

As a prelude to each experiment, arterial carbon dioxide tension was increased and decreased 10 mm Hg from control value. This induced a corresponding change in local cerebral blood flow between 25 to 55 percent of control depending on the control value of carbon dioxide tension.

Discussion

The data show that continuous infusion of nitroglycerin in the normal dog at doses of either 3, 5, or 10 \( \mu g/kg/min \) has little effect on local cerebral blood flow in the caudate nucleus, thalamus, frontal and parietal cortex. This is true in spite of a modest but definite decrease in mean arterial blood pressure. In addition, at infusion rates of nitroglycerin of 10 \( \mu g/kg/min \) there was no change in blood flow when mean arterial blood pressure was lowered by venesecction or aortic ligation, showing that autoregulation of cerebral blood flow was un influenced by nitroglycerin.

Our data also suggest that nitroglycerin has no effect on the changes in cerebral blood flow induced by dopamine (figs. 2, 4, 5). When the effects of a continuous intravenous infusion of dopamine on local cerebral blood flow were established, the additional infusion of nitroglycerin did not change them. When the nitroglycerin infusion was started first, the subsequent addition of dopamine produces the same effects as dopamine alone.14,19

Decrease in blood flow induced by dopamine indicating vasoconstriction of the small intraparenchymal resistance vessels did not occur as frequently in this study (fig. 1) as might have been expected from previous studies.14-18 Any modification by nitroglycerin of the vasoconstrictor activity of dopamine, however, seems to be ruled out by our results in these animals where an initial dopamine infusion caused a decrease in flow that was unaltered by subsequent addition of nitroglycerin (figs. 2, 4).

When the vasoconstrictor activity of dopamine was blocked by phentolamine (alpha receptor antagonist) there was an increase in local cerebral blood flow (fig. 2) similar to that shown in a previous study on global cerebral blood flow.14 Edvinson et al.18 recently demonstrated that the constrictor activity of dopamine on cerebral blood vessels could be blocked by serotonin antagonists as well as alpha receptor antagonists and suggested that serotonin receptors, as well as alpha-adrenergic receptors, mediate the vasoconstrictor effect of dopamine. Our results agree with those of Edvinson et al.19 in that the vasoconstrictor activity of dopamine could be blocked by the serotonin antagonist methysergide in the same way as by phentolamine (fig. 2). The increase in local cerebral blood flow induced by dopamine and methysergide (figs. 2, 4) indicated that vasodilation of the small resistance vessels was unchanged by the addition of nitroglycerin. This suggests that nitroglycerin does not effect the vasodilation induced by dopamine.
We have used the hydrogen clearance method to study local cerebral blood flow because it allows repeated measurements in a single area and, therefore, lends itself to the study of drug effects. Halsey et al. and Brown have pointed out potential problems with this method which offset some of its advantages. Errors may be introduced by intercompartmental diffusion of hydrogen. Pasztor et al., Halsey et al. and Brown have pointed out the necessity of prolonged hydrogen clearance in order to avoid distorted and abnormal clearance curves. To try to overcome these problems we allowed 8 minutes for hydrogen inhalation and have excluded the initial 40 sec of the clearance curves. In addition, carbon dioxide reactivity was measured to verify the sensitivity of the system to changes in local perfusion. Halsey et al. have also shown that the tip of the hydrogen electrode can "see" tissue at a distance of 2 millimeters. This may explain why most of our cortical electrodes show flow values that are lower than would be expected from xenon studies in the dog, since cortical thickness in our dogs did not exceed 2 millimeters, and therefore, some white matter flow was probably included. Our blood flow values from the electrodes in
the caudate nucleus and thalamus were also somewhat lower in most dogs than would be expected from hydrogen clearance method studies in other species; they nevertheless are in accordance with those discussed by Halsey. All our electrode tips were found to be well into the grey matter of the deep structures studied. Our methods of data analysis, particularly eliminating the first 40 sec of the flow curve and then taking a weighted average of the remainder of the curve if they were multiexponential, may also contribute to the low flow values. However, our experiments have been mainly concerned with relative change in blood flow caused by nitroglycerin rather than with absolute flow values.

Intracranial pressure in our normal dogs did not show any consistent change during the continuous infusion of nitroglycerin. Rogers showed that bolus doses of intravenous nitroglycerin increased intracranial pressure, especially when the blood pressure was transiently lowered by the drug. Our findings in 2 dogs, where bolus injections were given, are consistent with that observation. We suggest that when nitroglycerin is given in large bolus doses the immediate generalized cerebral vasodilatation may cause a sudden rise in intracranial pressure. There is then a short time delay while the normal mechanisms for intracranial pressure regulation occur, i.e., outflow of blood and cerebrospinal fluid. Patients who have elevated intracranial pressure secondary to mass effect or obstruction of outflow of cerebrospinal fluid are in a state of high pressure elastance on the cerebrospinal fluid pressure volume curve. In this setting, vasodilatation induced by nitroglycerin may have a more profound effect on intracranial pressure.

In summary, intravenous nitroglycerin results in dilatation of the large intracranial extracerebral arteries of the dog and monkey. Our present results suggest that in the brain, nitroglycerin primarily dilates these capacitance arteries with relatively little effect on the smaller intraparenchymal resistance arteries that control cerebral blood flow. These data are in keeping with experimental evidence concerning the effect of nitroglycerin on the coronary circulation.

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CARDIOVASCULAR EFFECTS OF CEREBRAL AIR EMBOLISM

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P. K. WEAVERSBY, PH.D., AND M. E. BRADLEY, M.D.

SUMMARY This study was conducted to determine whether air distributed to the cerebral circulation alone could cause acute cardiovascular dysfunction and thus be a potential mechanism for sudden death following arterial air embolism. Cardiovascular measurements were made in anesthetized, ventilated cats during infusion of air into a vertebral artery. Cerebral air embolism was found to induce an acute hypertensive response accompanied by severe cardiac arrhythmias. Interruption of the autonomic nervous system was found to abolish the cardiac arrhythmias but not to affect significantly the acute hypertensive response following cerebral air embolism. These results suggest that potentially lethal cardiac arrhythmias can occur from air distributed solely to the cerebral circulation, and that these arrhythmias are mediated by the autonomic nervous system. The results also indicate that acute hypertension can occur from cerebral air embolism, but that this response is not solely mediated by the autonomic nervous system.

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ARTERIAL air embolism can occur in 2 diverse settings. One is in the diving environment when, during rapid ascent from exposure to increased pressure, expansion of intra-alveolar gas may rupture the lung with escape of air into the systemic circulation. Air embolism from this cause has been termed "dysbaric" air embolism. In contrast, arterial air embolism may occur in the clinical setting as a result of various diagnostic and surgical procedures when air is accidentally trapped or infused into the systemic circulation. Regardless of the underlying cause, arterial air embolism may result in a wide variety of symptoms ranging in severity from mild neurological disturbances to unconsciousness, cardiovascular collapse, and sudden death. Despite past case reports and experimental studies, it is not known whether sudden death results from embolization of the coronary circulation, from respiratory arrest secondary to cerebral embolization, or from some other mechanism.

In previous investigations of the acute cardiovascular response to arterial air embolism, we had observed in upright, ventilated cats that air infused into the left ventricle produced either one of 2 distinct responses. Approximately half of the animals developed a response characterized by acute increases in blood pressure, heart rate, left ventricular contractile force, and by a wide variety of severe cardiac arrhythmias. In contrast, half of the animals developed few arrhythmias but showed an immediate depression of arterial blood pressure and left ventricular contractile force. The evidence obtained suggested that the arrhythmias and the acute hypertensive response resulted from cerebral air embolism, whereas the acute hypotensive response resulted from air in the coronary circulation.

The present study was made to determine whether air distributed to the cerebral circulation alone could cause acute cardiovascular dysfunction. To investigate this possible mechanism, we measured the cardiovascular response of anesthetized, ventilated cats during infusion of air into a vertebral artery. In a separate group of animals, the role of the autonomic nervous system in mediating the cardiovascular response was assessed by disruption of the autonomic neural systems before inducing air embolism.

METHODS

Male and female adult cats ranging in weight from 2.5 to 4.0 kg were used for these experiments. Anesthesia was induced by an i.m. injection of ketamine HCL (0.15 mg/kg). Anesthesia was maintained for the duration of the experiment by an intravenous injection of alpha-chloralose (80-100 mg/kg) dissolved in warm saline. After tracheal intubation, ventilation was controlled by a small animal respirator. At frequent intervals throughout the experiment, arterial Po2, Paco2, and pH were determined and maintained within normal physiological limits by adjusting rate and tidal volume of the respirator. Esophageal temperature was monitored and kept at 37-38°C by intermittent use of a heating pad.

A right femoral cut-down was performed and
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