Effects of Blood Gases on the Pressure-Flow Relationships in Canine Cerebral Circulation

BY TAKAYUKI IWABUCHI, M.D., TAKASHI KUTSUZAWA, M.D., KYUHEI IKEDA, M.D., AND TAKASHI NAKAMURA, M.D.

Abstract: The effects of the arterial oxygen saturation and carbon dioxide pressure on the pressure-flow relationships in cerebral circulation were studied in 22 dogs. The cerebral blood flow was observed with stepwise lowering of the systemic arterial blood pressure by controlled bleeding in normoxic normocapnic, normoxic hypocapnic, normoxic hypercapnic, hypoxic hypocapnic and hypoxic normocapnic animals. The autoregulation of cerebral blood flow occurred in the animals in which the arterial oxygen saturation and carbon dioxide pressure were above 90%, and between 20 and 46 mm Hg, respectively.

When the arterial oxygen saturation and carbon dioxide pressure were maintained between 17% and 40%, and 34 and 47.5 mm Hg, or above 92%, and between 65 and 82 mm Hg, respectively, almost complete loss of autoregulation was observed. However, autoregulation revived in breathing air at about 30 minutes after autoregulation had been lost during severe hypoxia or hypercapnia, which was induced for about 30 minutes. This suggests that a hypoxic or hypercapnic situation for about 30 minutes does not irreversibly damage the autoregulatory mechanism.

Additional Key Words dorsal sagittal sinus autoregulation hypoxia hypercapnia hypocapnia oxygen saturation carbon dioxide

The ability to maintain constant blood flow in spite of changes in perfusion pressure has been observed in cerebral circulation by many investigators, and described as autoregulation of cerebral blood flow to perfusion pressure. The mechanism to which autoregulation is ascribed still remains obscure. The responses of cerebral vessels to changes of the arterial carbon dioxide and oxygen pressures are well known. The effects of blood gases on the pressure-flow relationships in cerebral circulation have been reported by several authors. Loss of autoregulation was observed in hypoxia, and in hypercapnia. However, the results are conflicting regarding the conditions in which autoregulation disappeared. This study was undertaken to determine the critical situations of the arterial blood gases which cause loss of autoregulation to perfusion pressure.

Methods
The experiments were performed on 22 mongrel dogs of both sexes, weighing 10 to 20 kg. They were anesthetized by intravenous injection of pentobarbital sodium (30 mg/kg body weight). The trachea was intubated and the dogs were artificially ventilated by a Harvard respirator to control the arterial carbon dioxide pressure constant after paralysis of the animals by intravenous administration of 2 mg/kg of gallamine triethiodide. Additional doses of gallamine triethiodide were injected as required. Expired CO₂ was continuously recorded by a capnograph (CG 119, Godart). The femoral arteries and one vein were cannulated with polyethylene tubes. One of the arterial tubes was connected to a pressure transducer (MP-4, Nihonkoden) and the other was prepared for sampling arterial blood and withdrawing or restoring blood. Drugs were administered through the venous tube. The animal was in the prone position and the head was fixed in a holder. The temporal muscles were widely reflected bilaterally with electric cautery, and the dorsal sagittal sinus was exposed about 3 cm rostral to the occipital protuberance removing the overlying skull. The cerebral venous outflow was measured by cannulating the posterior third of the dorsal sagittal sinus. The blood from the dorsal sagittal sinus was diverted to the jugular vein passing through a transducer probe of an electromagnetic flowmeter (MF-12, Nihonkoden) (fig. 1). The venous pressure was monitored just before the flow probe. During the experiments, the range of fluctuation of the venous pressure was from 0 to 50 mm H₂O. The systemic arterial blood pressure was considered as the perfusion pressure to the brain because the venous pressure was negligible. The mean
systemic arterial blood pressure was reduced stepwise by 10 or 20 mm Hg to the pressure of 35 to 10 mm Hg. Each pressure was maintained for about two minutes by removing or restoring the blood.

The arterial carbon dioxide pressure in the animal was changed by hyperventilation or inhalation of a mixture of 10% CO₂ in air, and the arterial oxygen saturation by breathing mixed gases of 10% O₂ or 6% to 4% O₂ in nitrogen. It must be said that during the experiments, the arterial carbon dioxide pressure was maintained as constant as possible by controlling a respirator. In most instances the arterial carbon dioxide pressure decreased significantly with reduction of the blood pressure below about 50 mm Hg despite artificial control of ventilation. The arterial oxygen pressure, carbon dioxide pressure and pH were measured by a pH/gas analyzer (Model 113-SI, Instrumentation Laboratory) and the arterial oxygen saturation was measured by a co-oximeter (Model 182, Instrumentation Laboratory). Blood gases and pH were measured at each pressure tested throughout the experiments. In nine animals, pressure-flow relationships were observed in two different situations of blood gases. In these cases, the second experiment was performed after the cerebral blood flow and blood gases had returned to the control state and confirming that autoregulation was not lost. Before the start of the experiment, it was ascertained that the response to carbon dioxide was not impaired by surgical procedures in all experiments.

Results
NORMOXIC AND NORMOCAPNIC GROUP
In seven dogs, the arterial oxygen saturation and carbon dioxide pressure were maintained by breathing air between 90% and 95%, and between 30 and 46 mm Hg, respectively. One of the seven dogs was the same one which had undergone a pressure-flow study in the normoxic hypercapnic situation. The variations of the arterial carbon dioxide pressure and oxygen saturation during the individual experiments were between 1.4 and 6.3 mm Hg (mean 4.9 mm Hg), and between 1.0% and 5% (mean 2.6%), respectively. The maximum values of the mean systemic arterial blood pressure of the animals ranged from 85 to 150 mm Hg at the start of the experiments. The mean systemic blood pressure was reduced stepwise from maximum pressures to pressures of 35 to 20 mm Hg and the pressure-flow relationships were observed.

As shown in figure 2, the cerebral blood flow remained almost unchanged in spite of reduction of the systemic blood pressure to about 40 mm Hg in all seven experiments, except for one case in which the blood flow decreased abruptly below 70 mm Hg. At lower blood pressures the blood flow declined pariri-passu with blood pressure.

EFFECTS OF ARTERIAL CARBON DIOXIDE PRESSURE ON THE PRESSURE-FLOW RELATIONSHIP
NORMOXIC HYPERCAPNIC GROUP
Five dogs were hyperventilated with air and the arterial oxygen saturation and carbon dioxide pressure were between 90% and 98%, and between 20 and 28.5 mm Hg, respectively. One of the five dogs had had a previous pressure-flow study in the normoxic normocapnic condition before hyperventilation was induced. The pressure-flow relationships were observed between 145 to 100 mm Hg and

FIGURE 1
Schematic illustration of experimental design. PT: pressure transducer. See text for explanation.
The pressure-flow relationships in seven normoxic normocapnic dogs. The arterial oxygen saturation and carbon dioxide pressure were between 90% and 95%, and between 30 and 46 mm Hg, respectively. The cerebral blood flow remained almost unchanged until the mean arterial blood pressure was reduced to about 40 mm Hg.

EFFECT OF HYPOXIA ON THE PRESSURE-FLOW RELATIONSHIP

Slightly or Moderately Hypoxic and Normocapnic Group
In five dogs, the arterial oxygen saturation and carbon dioxide pressure were kept between 51% and 78%, and between 30 and 41 mm Hg, respectively, by breathing 10% O₂ in nitrogen. The variations of the arterial oxygen saturation and carbon dioxide pressure during individual experiments were between 7% and 15% (mean 11.9%), and between 2 and 7 mm Hg (mean 4.3 mm Hg), respectively. Three of five dogs had been tested previously in normoxic normocapnic, normoxic hypocapnic or normoxic hypercapnic situations. The cerebral blood flow increased in all five dogs by inhalation of 10% O₂ in
The pressure-flow relationships in five normoxic hypocapnic dogs. The arterial oxygen saturation and carbon dioxide pressure were between 90% and 98%, and between 20 and 28.5 mm Hg, respectively. Autoregulation of cerebral blood flow occurred until the arterial blood pressure was lowered to about 40 mm Hg.

The pressure-flow relationships in six normoxic hypercapnic dogs. The arterial oxygen saturation and carbon dioxide pressure were above 92%, and between 65 and 82 mm Hg, respectively. The cerebral blood flow decreased linearly with lowering of the blood pressure.
Autoregulation of cerebral blood flow in normoxic normocapnic situation (dotted line) at 30 minutes after loss of autoregulation in hypercapnic situation (solid line).

Mean Arterial Blood Pressure mmHg

FIGURE 5

The pressure-flow relationships in slightly to moderately hypoxic and hypocapnic (dotted line) or normocapnic (solid line) dogs. Autoregulation was impaired in variable degrees in both groups. See text for further explanation.
nitrogen and became steady within three to ten minutes after the beginning of inhalation. Then the pressure-flow relationships were observed at mean blood pressures between 130 to 95 mm Hg and 30 to 15 mm Hg, as shown in figure 6. One dog showed almost constant blood flow despite changes in mean blood pressures from 95 to 65 mm Hg. At lower pressures the blood flow decreased passively with the perfusion pressure. The arterial oxygen saturation and carbon dioxide pressure of the dog were between 51% and 59%, and between 37 and 39 mm Hg, respectively. In the other four dogs, the cerebral blood flow changed with lowering of the blood pressure. The reduction of blood flow was more abrupt at the pressures below 60 to 45 mm Hg.

Slightly or Moderately Hypoxic and Hypocapnic Group
In three dogs, one of which had been tested previously in the normoxic hypocapnic situation, the arterial oxygen saturation and carbon dioxide pressure were maintained between 55% and 80%, and between 20 and 30 mm Hg, respectively. The individual variations of oxygen saturation and carbon dioxide pressure during the experiments were between 2% and 20% (mean 9.7%), and 3 and 8 mm Hg (mean 5.3 mm Hg). The cerebral blood flow increased more or less in all three dogs and became steady within five to ten minutes after the start of breathing 10% O₂ in nitrogen. One dog showed almost the same pressure-flow relationship as did the normoxic normocapnic or normoxic hypocapnic groups. The arterial oxygen saturation and carbon dioxide pressure of the dog were between 78% and 80%, and between 20 and 24 mm Hg, respectively. In another two dogs the cerebral blood flow reduced with lowering of the pressures. Reductions of blood flow were more marked at blood pressures below 70 to 40 mm Hg (fig. 6).

Severely Hypoxic and Normocapnic Group
This group consisted of five dogs, breathing 4% to 6% O₂ in nitrogen, in which the arterial oxygen saturation and carbon dioxide pressure were maintained between 17% and 40%, and between 34 and 47.5 mm Hg, respectively. Two dogs had been tested previously in normoxic normocapnic or normoxic hypocapnic states. The variations of oxygen saturation and carbon dioxide pressure during the individual experiments were between 3% and 11.9% (mean 6.9%), and between 0 and 5.9 mm Hg (mean 3.6 mm Hg).

The cerebral blood flow markedly increased by breathing 4% to 6% O₂ in nitrogen. It needed 10 to 16 minutes before the blood flow became steady. In

![Mean Arterial Blood Pressure and Blood Flow](attachment:image.png)

**FIGURE 7**
The pressure-flow relationships in severely hypoxic and normocapnic dogs. The arterial oxygen saturation and carbon dioxide pressure were between 17% and 40%, and between 34 and 47.5 mm Hg, respectively. The cerebral blood flow decreased concomitantly with reduction of blood pressure, showing loss of autoregulation.
all dogs the cerebral blood flow decreased almost linearly with fall of the blood pressures between 145 to 100 mm Hg and 45 to 20 mm Hg (fig. 7). In one dog of this group, pressure-flow relationship also was observed in arterial oxygen saturation of 90% and arterial carbon dioxide pressure of 42 mm Hg at 30 minutes after the pressure-flow study had been performed in the hypoxic state for about 30 minutes. As shown in figure 8, the cerebral blood flow was almost constant in spite of reduction of the pressures from 90 to 50 mm Hg.

Discussion

From anatomical studies it was reported that cerebral venous blood obtained from the posterior third of the dorsal sagittal sinus shows only a small and constant contamination by extracerebral blood, when the overlying skull was removed. The blood drained through the dorsal sagittal sinus is derived from both gray and white matter. Based on these observations, cerebral venous outflow was measured by cannulating the posterior third of the dorsal sagittal sinus, removing the overlying skull.

The term “autoregulation” of blood flow has been usually defined as “the intrinsic tendency of an organ to maintain constant blood flow despite changes in arterial perfusion pressure.” There have been many papers which showed the existence of autoregulation in the brain as mentioned above. However, autoregulation was not evidenced in isolated cerebral circulation. Therefore, it is uncertain whether the brain truly has the intrinsic tendency to regulate blood flow. In this study pressure-flow relationships were observed with lowering systemic blood pressures by removing arterial blood. The variations of the arterial carbon dioxide pressures were about 4 to 5 mm Hg during the individual experiments, though a respirator was controlled to keep the arterial carbon dioxide pressure constant. In most cases, marked decrease in the arterial carbon dioxide pressure occurred below 50 mm Hg of the mean arterial blood pressure. Above the blood pressure, variations of the arterial carbon dioxide pressure were almost negligible. Harper observed that at hypotension of about 50 mm Hg the cerebral blood flow did not respond to the changes of arterial carbon dioxide pressure. Therefore, it might be considered that the variations of arterial carbon dioxide pressure had no significant effects on the cerebral blood flow in these experiments.

When the arterial oxygen saturation and carbon dioxide pressure were maintained above 90%, and between 20 and 46 mm Hg, respectively, the cerebral blood flow was almost constant in spite of lowering of the arterial blood pressure in the range of the mean blood pressures from 150 to about 40 mm Hg. This result well agreed with previous reports regarding the pressure-flow relation by Rapela and Green, Hägrendal and Johansson, Harper and Ekström-Jodal, though in Harper’s observation the
range of blood pressure showing autoregulation was narrow (from 155 to about 80 mm Hg).

Harper\(^6\) reported that in hypercapnic animals, in which the arterial carbon dioxide pressure was between 70 and 90 mm Hg, blood flow decreased linearly with blood pressure. Similar results also were reported by Rapela and Green\(^3\) and Zwetnow.\(^8\)

However, in the experiments of Håggedal and Johansson,\(^4\) hypercapnic dogs in which the arterial carbon dioxide pressure was between 70 and 95 mm Hg showed autoregulation in the higher pressure range from 150 to about 80 mm Hg in all animals, except one which showed loss of autoregulation. In this study, the pressure-flow relationships were linear in all of the hypercapnic dogs in which the arterial carbon dioxide pressure was between 65 and 82 mm Hg. This finding is in agreement with the works of Harper\(^5\) and Zwetnow.\(^8\)

In severely hypoxic dogs the cerebral blood flow decreased concomitantly with lowering of the blood pressure, showing linear pressure-flow relation curves. In these dogs, the arterial oxygen saturation and oxygen pressure were between 17% and 40%, and 6.1 and 26 mm Hg, respectively. When the arterial oxygen saturation was maintained between 50% and 80%, the autoregulatory ability was diminished in variable degrees. Håggedal and Johansson\(^1\) observed almost complete loss of autoregulation during milder hypoxia of less than 60% of the arterial oxygen saturation. Kogure et al.\(^7\) reported that autoregulation was lost after the arterial oxygen pressure had been maintained below 15 mm Hg for four to six minutes, though autoregulation persisted even after the arterial oxygen pressure had remained at 25 mm Hg for four to six minutes. In their experiments the cerebral blood flow increased only during the first minutes. However, in this study the cerebral blood flow increased during about 8 to 16 minutes after inhalation of 5% to 10% O\(_2\) in nitrogen in most of the cases. Therefore, the pressure-flow relation could not be observed in a situation of less than ten minutes of hypoxia.

Autoregulation revived in breathing air at about 30 minutes after autoregulation had been lost during severe hypoxia or hypercapnia, which was induced for about 30 minutes. This suggests that a hypoxic or hypercapnic situation for about 30 minutes does not irreversibly damage the autoregulatory mechanism. The vasodilatory effect of carbon dioxide is explained by an increase in the intracellular hydrogen ion of smooth muscle fibers of cerebral arterioles,\(^14\) and the vasodilatation in hypoxia is considered as the consequence of parenchymatous acidosis in the brain.\(^15\) It seems, therefore, that loss of autoregulation in hypoxia or hypercapnia might be the consequence of acidosis in the brain.

---

**Acknowledgments**

The authors acknowledge the technical assistance of Miss Sachiko Susuga. Thanks also are due to Mr. Yozo Ito and Mr. Yoshitaka Hinuma for their assistance.

**References**

Effects of Blood Gases on the Pressure-Flow Relationships in Canine Cerebral Circulation
TAKAYUKI IWABUCHI, TAKASHI KUTSUZAWA, KYUHEI IKEDA and TAKASHI NAKAMURA

Stroke. 1973;4:65-72
doi: 10.1161/01.STR.4.1.65
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1973 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/4/1/65

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/