Simultaneous Laser-Doppler Flowmetry of Canine Spinal Cord and Cerebral Blood Flow: Responses to Pa_{CO_2} and Blood Pressure Changes

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We observed the relative changes of both spinal cord blood flow (local SCBF) and local cerebral blood flow (local CBF) using independent laser-Doppler flowmeters (LDF) in 12 dogs under N_2O(50%)-O_2-enflurane(1.0%) anesthesia. The dorsal surface of the lumbar spinal cord and the parietal surface of the brain were partially exposed. Two fine LDF probes were placed between the exposed surfaces and the dura maters at each site. Both local SCBF and local CBF decreased simultaneously with hyperventilation and incresed with hypoventilation within several seconds. The local SCBF responses to Pa_{CO_2} changes were similar in direction and degree as those of the local CBF. Autoregulation of local SCBF to arterial blood pressure (ABP) changes was abolished, though that of the local CBF was still recognized in a blunted fashion within a mean ABP range of 50 to 150 mmHg. (Key words: spinal cord blood flow, cerebral blood flow, laser-Doppler flowmetry, autoregulation, carbon dioxide)

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Laser-Doppler flowmetry (LDF) permits noninvasive, continuous and real time measurement of relative blood flow changes on the surface of various organs[1]. Intraoperative monitoring of local cerebral blood flow (CBF) with LDF has been used clinically during craniotomy[2]. Recently, Lindsberg et al.[3] compared LDF with the established microsphere method for measurement of local spinal cord blood flow (SCBF) in anesthetized rabbits, and confirmed its validity in estimating local SCBF changes.

The present investigation was designed to simultaneously measure local SCBF and local CBF under enflurane anesthesia using independent laser-Doppler flowmeters, and to compare local SCBF responses to Pa_{CO_2} and arterial blood pressure (ABP) changes with those of local CBF.

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Materials and Methods

After approval of the protocol by our institutional Animal Investigation Committee, 12 adult mongrel dogs, weighing 11.2 ± 1.3 kg (mean ± SD), were randomly divided into two groups; group I (n=4) for Pa_{CO_2} changes and group II (n=8) for ABP changes. The animals were anesthetized with pentobarbital 30 $mg \cdot kg^{-1}$ i.v. and were endotracheally intubated. Subsequent surgical preparations and blood flow measurements were carried out under N_2O(50%)-O_2-enflurane(1.0%) anesthesia. The end-expired concentrations of the inhalation anesthetics were monitored with a Normac® (Datex Corp., U.S.A.) throughout the experiments. Under intermittent administration of pancuronium, respiration was mechanically controlled to maintain Pa_{CO_2} at around 35 mmHg, except during and following the hyper- and hypoventilation tests. A cutaneous forelimb vein was cannulated for the administration of fluids and drugs. Lactated Ringer's solution was continuously infused at a rate of 5 $ml \cdot kg^{-1} \cdot h^{-1}$. A femoral artery was also cannulated for continuous ABP monitoring and blood sampling. Arterial blood gas and hemograms were evaluated intermittently. Electrocardiogram leads were attached to the chest, and a balloon catheter was inserted into the bladder. Esophageal temperature was monitored and maintained at 37 ± 0.5°C with a heating-cooling pad. Following these preparations, the dogs were placed in a prone position. A burr hole, with a diameter of approximately 1.5 cm, was drilled into the exposed parietal bone. Partial laminectomy through the L_1 to L_3 spine was then performed. After completion of the surgical preparations, 1 $g \cdot kg^{-1}$ of 20% mannitol was intravenously given in order to ensure space under the cerebral and spinal dura mater. Then, the exposed cerebral and spinal dura mater were carefully opened, and the parietal cerebral surface and the dorsal cord surface were irrigated with warmed 0.9% saline solution before placement of laser-Doppler probes.

The laser-Doppler flowmeters (ALF 2100, Advance Corp., Japan) were used for simultaneous measurements of local SCBF and local CBF. The instrument utilizes a He-Ne laser light (wavelength 632.8 nm), which is delivered through a flexible fiber optic probe (2 mW output at the tip).

The digital output signal is expressed conventionally as $ml \cdot 100g^{-1}$ $tissue \cdot min^{-1}$. The analogue signals from the output terminal of each instrument were recorded on a heat pen recorded (LINEACORDER MARK 7, GRAPHTEC Corp., Japan) and simultaneously recorded on different channels. Two thin square type LDF probes (7 × 4 × 1.5 mm) were used. Both were inserted 1–2 cm through the incision in the dura and placed carefully on a surface devoid of any visible large blood vessels; one between the cerebral dura and the exposed cerebral surface to the frontal or temporal side, and the other between the spinal dura and the dorsal cord surface to the rostral side. After placement of the two probes, the dura mater at both sites was closed with sutures so that the probes would not move. Muscles, subcutaneous tissues and the skin were also closed in order to maintain the temmperature at the site of measurement. Meassurements of the CBF and SCBF started about 60 min after the infusion of mannitol. The mean ABP (MAP), arterial blood gas and body temperature were confirmed to be within the expected normal range at least for the previous 10 min, and then the blood flow (BF) at that time was taken as the baseline BF.

In group I, several minutes of

Table 1. Variations of physiological parameters during measurements of local SCBF and CBF

A. Ventilatory volume changes in group I (n=4)

		Normocapnia	Hypocapnia max	Normocapnia	Hypercapnia max
Pa_{CO_2}	mmHg	37.4 ± 2.3	18.3 ± 4.3	37.1 ± 2.8	54.5 ± 4.6
Esoph Temp	°C	37.3 ± 0.3	36.7 ± 0.5	36.6 ± 0.6	36.2 ± 0.3
Hematocrit	%	38.6 ± 6.4	39.3 ± 4.8	39.0 ± 7.1	38.5 ± 7.4
MAP	mmHg	127 ± 17	122 ± 20	127 ± 10	135 ± 24

mean ± SD

B. Drug-induced hyper- and hypotension in group II (n=8)

		Normotension	Hypertension max	Normotension	Hypotension max
MAP	mmHg	139 ± 24	173 ± 27	125 ± 17	48 ± 7
Esoph Temp	°C	37.6 ± 0.5	37.3 ± 0.8	37.0 ± 1.1	36.5 ± 0.6
Hematocrit	%	35.6 ± 5.0	36.9 ± 7.1	36.6 ± 6.6	37.1 ± 6.4
Pa_{CO_2}	mmHg	36.8 ± 2.8	36.7 ± 4.4	37.5 ± 3.8	35.5 ± 3.1

mean ± SD

max: maximum, Esoph Temp: esophageal temperature,
MAP: mean arterial pressure

hypocapnia or hypercapnia was first induced alternatively by manual control of the squeezing rate of a respiratory bag under an end-tidal CO_2 monitoring. The local CBF and SCBF responses to the ventilatory changes were simultaneously observed.

Next, hypocapnia or hypercapnia was induced gradually by altering the minute volume setting every 3 min under mechanical ventilation. The minute volume was increased or decreased at a rate of about 400 ml·3 min^{-1} so as to shift the Pa_{CO_2} down to 15 or up to 55 mmHg. Arterial blood gas and the values of both the BF's were determined at the end of each 3 min period.

In group II, MAP was increasd to near 180 mmHg at a rate of about 10 mmHg·min^{-1} by adjusting an intravenous drip infusion of noradrenaline (NA). Then, discontinuing the infusion of NA and confirming that both the BF's returned to nearly the basline BF's and were stable, MAP was decreased to near 40 mmHg by an intravenous drip infusuion of trimethaphan at the same rate of 10 mmHg·min^{-1}. Both BF values were recorded at every 10 mmHg of MAP change on the LDF recordings.

For all data, the stable baseline BF, just before ventilatory volume or MAP changes, was taken as 100%, and subsequent BF values were expressed as a percent change of the baseline BF. Results are given as the mean ± SD. Values between the groups were compared using Student's t-test. Significance was defined as $P < 0.05$. Linear regression anaysis was also performed and the correlation coefficient was calculated.

Results

There were no significant changes in the esophageal temperature, hema-

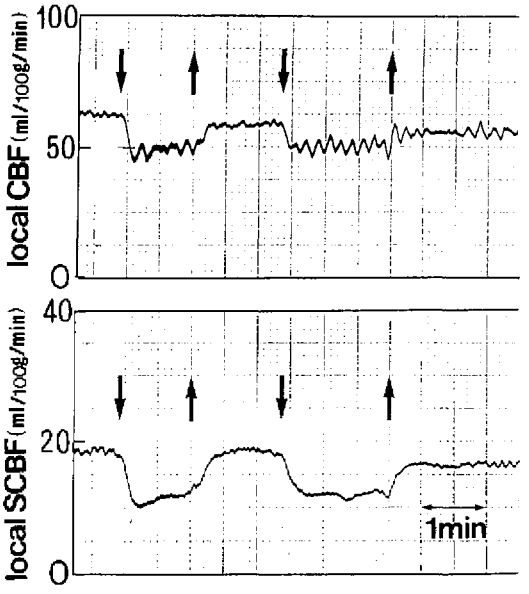


Fig. 1. Typical responses of local CBF and local SCBF to manual hyper- and hypoventilation in a dog in group I.
Downward arrows indicate initiations of manual hyperventilation and upward arrows indicate those of manual hypoventilation. These responses occurred simultaneously within several seconds.

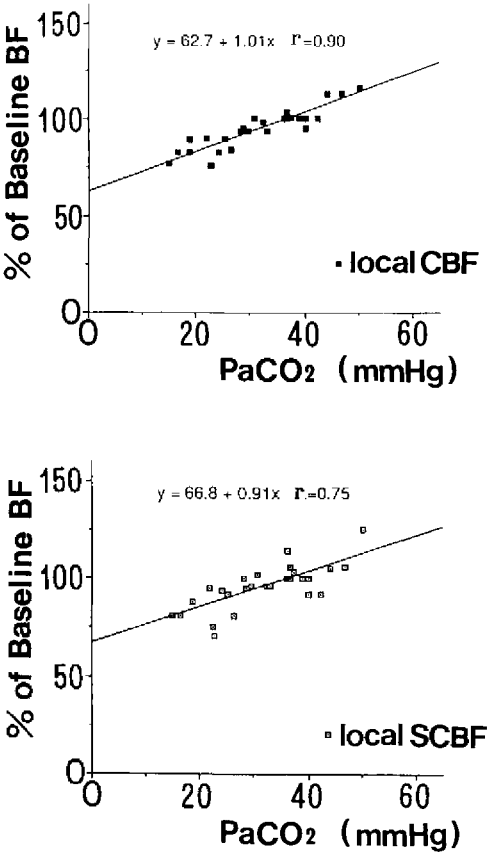
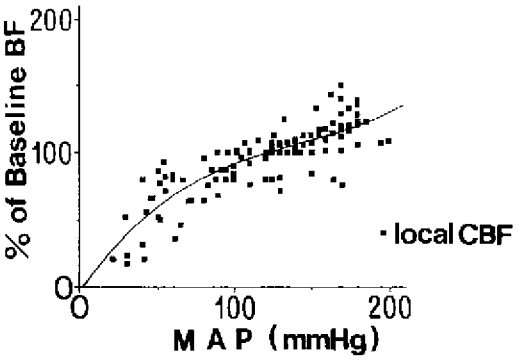


Fig. 2. Overall responses of local CBF and SCBF to Pa_{CO_2} changes in group I.

tocrit or MAP during the ventilatory volume changes in group I, nor in the esophageal temperature, hematocrit or Pa_{CO_2} during drug-induced hyper- and hypotension (table 1).

In group I, about 1 min of manual hyperventilation caused a decrease in local CBF and SCBF to 77 ± 8% and 71 ± 13% of the baseline, respectively. Subsequent manual hypoventilation caused an increase in local CBF and SCBF to 103 ± 7% and 104 ± 9% of the baseline, respectively. The rates of both decrease and increase were not significantly different. The local CBF and SCBF responses to manual hyper- and hypoventilation occurred within several seconds of each other. A typical case is shown in figure 1. In the Pa_{CO_2} range of 15–55 mmHg induced by changing a minute volume under mechanical ventilation, there were positive correlations between Pa_{CO_2} and local CBF and SCBF. The increasing and decreasing rates under $N_2O(50\%)$-O_2-enflurane(1%) anesthesia were 1.01%·mmHg^{-1} Pa_{CO_2} for the CBF and 0.91%·mmHg^{-1} Pa_{CO_2} for the SCBF (fig. 2). There was no significant difference between the two.

Figure 3 shows the local CBF and SCBF responses to drug-induced ABP changes in group II. Under $N_2(50\%)$-O_2-enflurane(1%) anesthesia, autoregulation of SCBF was almost abolished, though that of CBF was blunted within the MAP range of 50–150 mmHg. In one dog, in which autoregulation of CBF was well maintained under the same nitrous oxide-enflurane



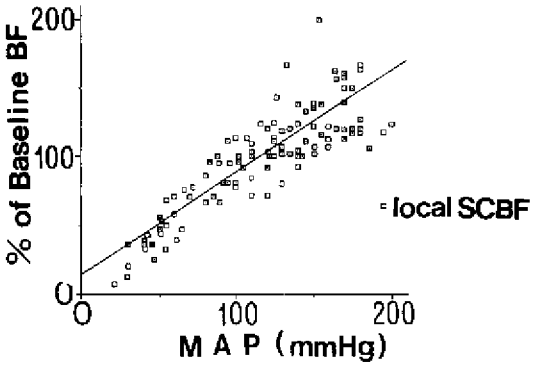
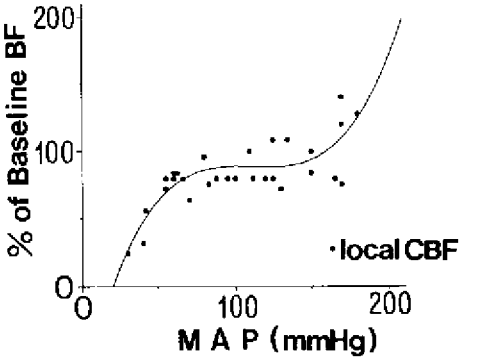


Fig. 3. Overall responses of local CBF and SCBF to MAP changes in group II.



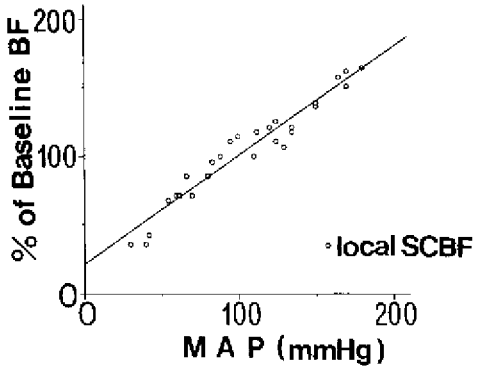


Fig. 4. Intact local CBF autoregulation in contrast with impaired local SCBF autoregulation in a dog in group II.

anesthesia, while SCBF increased or decreased proportionally to the MAP rise or fall. CBF decreased suddenly when the MAP dropped below 50 mmHg (fig. 4).

Discussion

The present investigation evaluated sequential and simultaneous responses of CBF and SCBF to two major modulating factors, e.g., Pa_{CO_2} and ABP. We confirmed that the microcirculatory CBF and SCBF responses to Pa_{CO_2} changes existed even under N_2O(50%)-O_2-enflurane(1%) anesthesia. Both BF's were almost the same in both direction and degree. Later, we used these responses as evidence of proper placement of the LDF probe. The majority of previous animal experiments have demonstrated a linear relationship between the Pa_{CO_2} and SCBF[4–6], although there has been some disagreement at lower values of Pa_{CO_2}[7]. According to those reports, the absolute sensitivity of SCBF to Pa_{CO_2} was in the range of 0.2–1.2 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ tissue per mmHg Pa_{CO_2}[4–7] and was lower than that of CBF[8]. The sensitivity of SCBF to Pa_{CO_2} in our study, though it was expressed as a percent change of the baseline BF, was somewhat low, compared with the above noted SCBF sensitivity. The discrepancy may reflect the problems involved in the regions measured and methodology employed. As we placed the probe for SCBF on the dorsal surface of the lumbar spinal cord, it is likely that we may have mainly measured white matter BF of the cord dorsum. Scremin et al.[9] ob-

served that the sensitivity of white matter BF to Pa_{CO_2} was less than one-fifth of that of gray matter BF.

In the present study, autoregulation of CBF was maintained in dogs under 1.1 MAC (0.5 MAC N_2O and 0.6 MAC enflurane) inhalation anesthesia, though it was impaired to some degree. However, autoregulation of SCBF was absent. The spinal cord may be a more primitive tissue than the cerebrum in terms of autoregulation. However, it has been confirmed by several investigators that SCBF manifests autoregulation to blood pressure changes similar to that of CBF[10–13]. With respect to the effects of inhalation anesthetics, Jacobs et al.[6] reported that autoregulation of canine SCBF was well maintained during nitroprusside-induced hypotension under 1.0–1.5% (1.3–2.0 MAC) halothane anesthesia. On the other hand, Hoffman et al.[8] observed that SCBF was increased threefold by anesthetizing rats with 1 MAC isoflurane, and that of autoregualtion of SCBF for trimetaphan-induced hypotension and phenylephrine-induced hypertension was severely impaired under the anesthesia. Further investigation is needed to determine the effects of inhalation anesthetics on SCBF.

We used trimetaphan to decrease blood pressure and norepinephrine to increase blood pressure. Wilton et al.[14] reported that hypotension induced by trimetaphan decreased SCBF to a great extent than that by nitroprusside, nitroglycerin or exsanguination, despite the same blood presure level. Kobrine et al.[15,16] postulated that sympathetic activity plays an important role in the autoregulation of SCBF, by showing the loss of SCBF autoregulation under administration of an α-adrenergic blocking agent in monkeys. We cannot exclude the possibility that the impairment of SCBF autoregulation is partly due to the indirect or direct effects of those drugs on peripheral circulation.

Continuous real-time monitoring of BF without injuring the tissue measured is an outstanding advantage of LDF. This enabled us to determine if autoregulation requires some time to respond to a sudden change of blood pressure. Therefore, we slowly changed the MAP at a rate of 10 $mmHg \cdot min^{-1}$. If we had changed it more slowly, autoregulation might have been better maintained. The greatest disadvantage of LDF is the introduction of artifacts associated with improper contact of the LDF probe or its slipping out of place. We inserted and fixed specially-made thin, light probes between the dura mater and cerebral or spinal cord tissue. Prior to placement of the probes, we administered mannitol to decrease the bulk of the cerebrum and spinal cord and to avoid capillary injuries on the surface of the measured tissue. In this way, we minimized the creation and effects of artifacts. Conventional methods for the measurement of SCBF have their own problems. Autoradioactive techniques using ^{14}C-antipyrine have the disadvantage that only a single BF measurement can be made in the same animal[17]. The xenon washout[11] or hydrogen clearance technique[15,16] is disadvantageous in that it requires invasion of the spinal cord. The recent microsphere technique[6,8,13,14] allows repeated, noninvasive BF measurements in the same animal. However, BF depends on the size of radionuclide-labeled particles which are trapped in the tissue after injection.

In summary, the microcirculatory CBF and SCBF responses to Pa_{CO_2} changes were maintained in a similar fashion even under $N_2O(50\%)$-O_2-enflurane(1%) anesthesia. Autoregulation of CBF continued to operate, though it was bluntd to some degree. Autoregulation of SCBF was abolished

under the same nitrous oxide-enflurane anesthesia.

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