

Effects of Hemorrhagic and Pharmacologic Hypotension on Cerebral Oxygen Utilization and Blood Flow

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Cerebral oxygen utilization and blood flow were measured by the washout of oxygen-15 isotopes injected into the internal carotid artery in baboons during hypotension produced by acute hemorrhage, trimethaphan, and sodium nitroprusside. Acute hemorrhage, trimethaphan, and sodium nitroprusside lowered the mean arterial blood pressure to 52 per cent, 55 per cent, and 47 per cent, respectively, of control values. There were corresponding decreases in cerebral blood flow to 76 per cent ($P < 0.01$), 81 per cent ($P < 0.05$), and 79 per cent ($P < 0.01$) of control values. When the mean arterial blood pressure was decreased 11 per cent with hemorrhage, autoregulation of the cerebral vasculature was preserved and cerebral oxygen utilization increased 10 per cent ($P < 0.01$). When cerebral autoregulation was lost with acute hemorrhage, cerebral oxygen utilization declined 17 per cent ($P < 0.05$). When cerebral autoregulation was lost with pharmacologic hypotension, cerebral oxygen utilization was preserved with trimethaphan and increased 17 per cent ($P < 0.05$) with sodium nitroprusside. The increase in cerebral oxygen utilization seen with sodium nitroprusside and hemorrhagic (autoregulation preserved) hypotension may be due to stimulation of the sympathetic nervous system with release of circulating catecholamines. However, the mechanism by which circulating catecholamines mediate an increase in cerebral oxygen metabolism during hypotension is not clear. (Key words: Anesthetic techniques: hypotension, induced. Blood pressure: hypotension. Brain: blood flow; oxygen consumption. Hemorrhage. Sympathetic nervous system: catecholamines.)

CONTROLLED HYPOTENSION is used extensively in surgical practice to reduce bleeding and in neurosurgery to facilitate the clipping of intracranial aneurysms. Sodium nitroprusside and trimethaphan are two agents widely used to induce arterial hypotension. Sodium nitroprusside is a short-acting, vascular smooth muscle relaxant, whose effects are caused by peripheral vasodilation by a direct action on blood vessels¹ including those to the brain.² In contrast, trimethaphan produces peripheral vasodilation primarily by blocking the transmission of impulses in autonomic ganglia even though it also has a direct dilating effect on arterioles.¹ The effect of sodium nitroprusside and trimethaphan on cerebral blood flow (CBF) has been investigated by others and compared

with changes in CBF produced by controlled hemorrhagic hypotension.³⁻⁵ Only a limited amount of information exists, however, about the effect of hemorrhagic and pharmacologic hypotension upon cerebral oxygen metabolism (CMR_{O_2}).^{4,6-8} These data^{4,6-8} suggest that changes in the CMR_{O_2} with controlled hypotension may be a function of the manner in which hypotension is produced (*i.e.*, hemorrhage *vs.* pharmacologic agents) as well as the level of the cerebral perfusion pressure (CPP) achieved. A clear understanding of the effect of controlled hypotension on the CMR_{O_2} is important for its safe application. If differences do exist between the effect of sodium nitroprusside and trimethaphan on the CMR_{O_2} , it is important to document them and, if possible, seek an explanation. We have, therefore, measured CMR_{O_2} and CBF in baboons during hypotension produced by acute hemorrhage, trimethaphan, and sodium nitroprusside.

Methods

CBF and CMR_{O_2} were determined by the injection of 0.2 ml whole blood labeled with $H_2^{15}O$ and ^{15}O -oxy-hemoglobin, respectively, into the internal carotid artery of baboons.

To facilitate the injection of the radioisotope into the internal carotid artery, all branches of the right external carotid artery were ligated under phencyclidine anesthesia (2 mg/kg), a minimum of two weeks prior to the experiments. The radioisotopes were then injected into the common carotid artery through a small (0.021-cm) catheter positioned under fluoroscopic control from the femoral artery. To prevent the development of clots in the catheter system, the animals underwent full hepatic resection during the procedure.

The baboons were initially anesthetized with a single dose of ketamine (15 mg/kg), given at least two hours prior to making any measurements to avoid the known pharmacologic effects of the agent.^{9,10} They were paralyzed with gallamine and then passively ventilated with a mixture of 65 per cent nitrous oxide and 35 per cent oxygen throughout the study. The end-tidal P_{CO_2} (PET_{CO_2}), arterial blood pressure, and rectal temperature were monitored continuously. The rectal temperature was maintained between 37°C and 38°C with a heating pad. Arterial pH , P_{CO_2} , and P_{O_2} were measured during each set of injections. During the experiments, the arterial P_{CO_2} was kept constant by adjusting the respirator to keep PET_{CO_2} stable.

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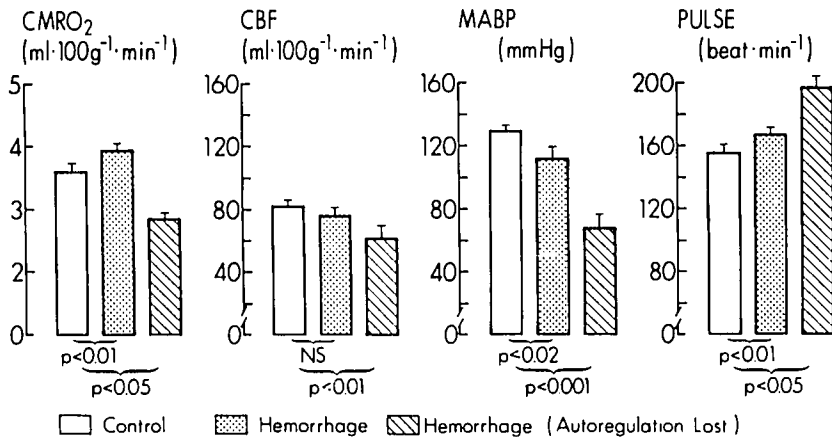


FIG. 1. The effect of hemorrhage on CMRO₂, CBF, MABP, and pulse rate in baboons anesthetized with nitrous oxide. The standard error of averaged values is shown by the vertical bars.

Radioactive oxygen-15 was prepared in the Washington University cyclotron by the irradiation of nitrogen gas containing oxygen carrier with 7 MeV deuterons.¹¹

The time course of each tracer through the injected hemisphere was monitored by means of a 3 × 2-inch NaI(Tl) scintillation detector appropriately collimated and positioned to ensure essentially uniform detection efficiency of the hemisphere. The signal from the detector was processed by a pulse height analyzer with an energy window of acceptance adjusted symmetrically around the 511 keV photopeak (481 to 541 keV) to eliminate scattered radiation. There would, of course, be no difference in the responses arising from the use of the two different radionuclides H₂¹⁵O and ¹⁵O-oxyhemoglobin, since both are positron emitters and are counted with identical detection efficiencies for the same counting geometry.

The accepted events (counts) per time frame were stored in the memory of a small laboratory computer. Appropriate data processing, including corrections of the count rate for electronic dead time loss, physical decay and background, and conversion to count rate (counts/s) as a function of time were performed by the computer. Routine data retrieval was in the form of processed count rate as a function of time plotted by an X-Y plotter. Optimal temporal resolution was achieved in the initial portion of each recording by using sampling integration times of 0.1 s. Statistically smooth recordings were ensured by injection of sufficient ¹⁵O-oxyhemoglobin and H₂¹⁵O to achieve a peak counting rate of 2,000 to 5,000 counts/s for the first tracer and 10,000 to 20,000 counts/s for the second.

DATA ANALYSIS

Cerebral blood flow was determined by residue detection of the injected bolus of labeled water.¹²⁻¹⁴ A 75-s index from the clearance curve was used to calculate CBF. This index has been shown to have an excellent correlation with the compartmental analysis of the clearance curve.¹³

An analysis of the washout curve obtained by the injection of ¹⁵O-oxyhemoglobin, combined with the arterial oxygen content and CBF, were used to calculate CMRO₂.^{15,16}

The observed changes in CBF, CMRO₂, and vital signs from control values were tested for significance by Student's paired *t* test.

EXPERIMENTAL DESIGN

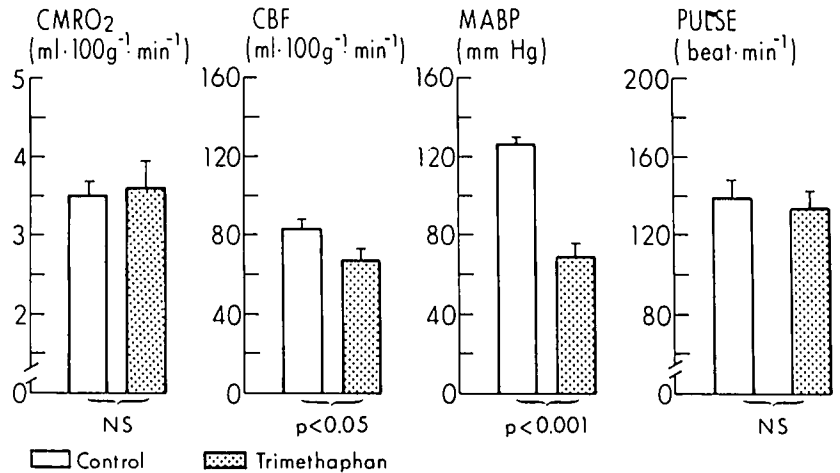
In six animals, hypotension was created by steady withdrawal of blood from a catheter positioned in the inferior vena cava. Control values of CBF and CMRO₂ were obtained. The arterial blood pressure was mildly reduced and stabilized at a lower level. CBF and CMRO₂ were again measured. Further blood was then removed from the inferior vena cava so that the mean arterial blood pressure (MABP) was stabilized at approximately one half the control value. The MABP was held at this level for approximately 10 min while measurements of CBF and CMRO₂ were repeated. The blood pressure was allowed to return to normal levels and remain at these levels for 1 h before repeating the experimental protocol.

Hypotension was produced in six animals by the intravenous infusion of trimethaphan (0.1 mg/ml) and in seven animals by the intravenous infusion of sodium nitroprusside (0.2 mg/ml). In both groups of animals after control values of CBF and CMRO₂ were obtained, the MABP was lowered to approximately one half the control value, stabilized, and held at this level for approximately 10 min. CBF and CMRO₂ were measured during the period of hypotension. The MABP was returned to normal levels for 1 h before repeating the experimental protocol.

Results

Figure 1 depicts the results obtained in the animals made hypotensive by acute hemorrhage. A moderate decrease in MABP to 89 per cent of control values, which

FIG. 2. The effect of intravenous trimethaphan on $CMRO_2$, CBF, MABP, and pulse rate in baboons anesthetized with nitrous oxide. The standard error of averaged values is shown by the vertical bars.



did not affect the autoregulation of the cerebral vasculature, produced a small, but significant 10 per cent increase of $CMRO_2$ ($P < 0.01$). A decrease in MABP to 52 per cent of control values caused a significant 17 per cent decline from control values of $CMRO_2$ ($P < 0.05$), and a significant decrease of 24 per cent in CBF ($P < 0.01$). The Pa_{CO_2} did not change significantly from control values ($45 \text{ mmHg} \pm 1 \text{ SEM}$). With increasing hypotension, there was a corresponding rise in the pulse rate.

The results seen with intravenous trimethaphan are shown in fig. 2. A decrease in MABP to 55 per cent of control values produced no change in $CMRO_2$, a significant decline of 19 per cent in CBF ($P < 0.05$), and no change in Pa_{CO_2} (control: $45 \text{ mmHg} \pm 1 \text{ SEM}$) or pulse rate during hypotension.

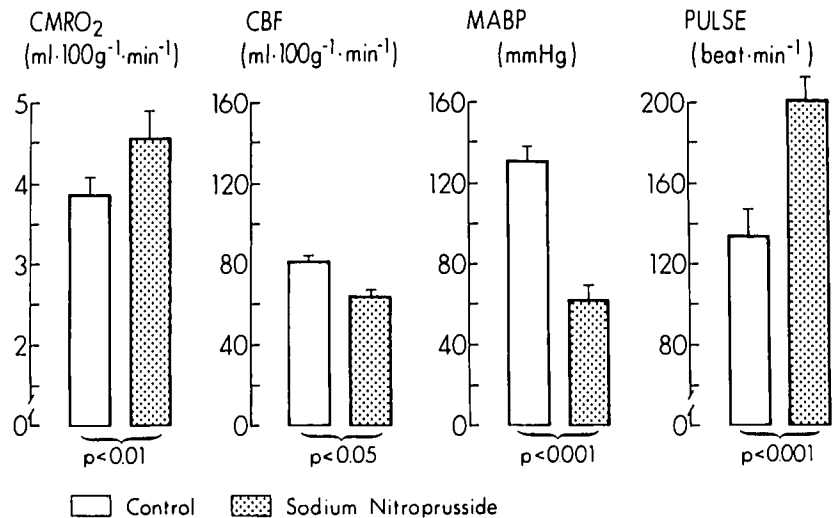
Figure 3 presents the results obtained with intravenous sodium nitroprusside. When MABP was reduced to 47 per cent of control values, there was a significant decrease of 21 per cent in CBF ($P < 0.01$). However, during hypotension, there was a significant 17 per cent increase

in $CMRO_2$ ($P < 0.05$). There was no significant change in Pa_{CO_2} from control values ($43 \text{ mmHg} \pm 1 \text{ SEM}$) during the period of hypotension. There was a large rise in the pulse rate during the period of low MABP. CBF and $CMRO_2$ returned to control values after the MABP was restored to normal levels with all three methods of producing hypotension.

Discussion

Changes in CBF during both hemorrhagic and pharmacologic hypotension have been extensively studied and used to define the lower limit of cerebral vascular autoregulation, a concept that implies a constant CBF over a wide range of perfusion pressures.^{5,17-21} The reported effects of trimethaphan, sodium nitroprusside, and hemorrhagic hypotension on CBF are not entirely uniform, with the reported lower limit of autoregulation varying somewhat in different species and, within the same species, depending on the methods used to measure CBF and lower the MABP. For example, Fitch and co-work-

FIG. 3. The effect of intravenous sodium nitroprusside on $CMRO_2$, CBF, MABP, and pulse rate in baboons anesthetized with nitrous oxide. The standard error of averaged values is shown by the vertical bars.



ers⁵ found pharmacologic hypotension better tolerated than hemorrhagic hypotension in baboons. Cerebral autoregulation was maintained until the MABP had decreased to 65 per cent of control (MABP of 80 mmHg) with hemorrhagic hypotension, while in animals subjected to hypotension produced by either trimethaphan or sodium nitroprusside, cerebral autoregulation was maintained until the MABP was 35–40 per cent of control (MABP of 40–50 mmHg). In contrast, hemorrhage, trimethaphan, and sodium nitroprusside all produced large decreases in CBF at a CPP of 30 and 40 mmHg in dogs studied by Michenfelder and Theye,⁴ with the largest declines in CBF occurring during trimethaphan hypotension. During severe hypotension (MABP of 30–35 mmHg) produced by trimethaphan and hemorrhage in cats, Maekawa and co-authors⁶ demonstrated large decreases in CBF. However, at the same hypotensive level of MABP induced with sodium nitroprusside, there was only a small decline in CBF.

Changes in CBF seen with sodium nitroprusside-induced hypotension have been especially inconsistent. Cerebral autoregulation during sodium nitroprusside hypotension has been found to be intact to a MABP of 40 mmHg in dogs²² and baboons,⁵ 50 mmHg in goats,² and 65–70 mmHg in humans.²³ However, other studies have shown that cerebral autoregulation failed with only small decreases in MABP.^{24,25}

In our studies, CBF autoregulation was lost to approximately the same degree with all three forms of hypotension at a MABP of approximately 65 mmHg (figs. 1–3). Although we did not attempt to determine the exact perfusion pressure at which CBF was no longer maintained (*i.e.*, so-called lower limit of autoregulation), it seems reasonable to suggest that no dramatic differences would have been found among the effects of sodium nitroprusside, trimethaphan, and hemorrhage. Extant data simply do not allow us to explain the diversity of results obtained by others as detailed in this report. Of more immediate interest to us, however, was the difference in the CMR_{O_2} produced by each form of hypotension.

Hypotension, sufficient to cause a reduction in CBF, had an effect on the CMR_{O_2} which was clearly dependent upon the manner in which the blood pressure was lowered in our experiments. Hemorrhagic hypotension to approximately 50 per cent of control caused a significant fall in the CMR_{O_2} (fig. 1), trimethaphan caused no change in the CMR_{O_2} (fig. 2), and sodium nitroprusside caused a significant increase in the CMR_{O_2} (fig. 3). It should be emphasized that these differences occurred despite almost identical changes in the MABP and CBF.

Work by others on the effect of hemorrhagic and pharmacologic hypotension on the CMR_{O_2} are generally consistent with these observations although the differences are less distinct. Hamar and associates⁸ found that baboons made hypotensive (MABP of 56 mmHg) by hem-

orrhage had a moderate fall in CMR_{O_2} . Michenfelder and Theye⁴ observed no change in CMR_{O_2} during hemorrhagic and trimethaphan hypotension, and a small, but statistically insignificant, increase in CMR_{O_2} during sodium nitroprusside hypotension in dogs (CPP of 40 mmHg). In this same study,⁴ further reduction of CPP to 30 mmHg by hemorrhage, as well as by sodium nitroprusside and trimethaphan, produced a moderate decline in CMR_{O_2} , a finding confirmed by Maekawa *et al.*⁶ Stoyka and Schutz,²² studying dogs under ketamine anesthesia, observed a 25 per cent decrease in CMR_{O_2} at a CPP reduced to 50 mmHg with trimethaphan, a change they considered "borderline." Further reduction of the CPP with trimethaphan produced further and more significant reduction in the CMR_{O_2} . Sodium nitroprusside produced no significant change in the CMR_{O_2} down to a CPP of 40 mmHg. At a CPP of 30 mmHg induced by sodium nitroprusside, their data²² show an actual increase in the CMR_{O_2} which, from their lack of comment, we must conclude did not achieve statistical significance.

These three forms of induced hypotension have some distinguishing features which may permit a limited insight into the possible reason for the differences observed in the CMR_{O_2} . The material reviewed in the next section has led us to the working hypothesis that catecholamines may play a role in the observed changes.

Hemorrhagic and sodium nitroprusside hypotension both stimulate the sympathetic nervous system. This is clearly evident in our data in the significant tachycardia produced by each (figs. 1 and 3). Trimethaphan, on the other hand, usually abolishes peripheral sympathetic activity through its ganglionic blocking actions.¹ Appropriately, no tachycardia is observed with trimethaphan hypotension (fig. 2). Furthermore, levels of circulating catecholamines (both epinephrine and norepinephrine) are elevated in dogs during hemorrhagic and sodium nitroprusside hypotension but not during trimethaphan-induced hypotension.⁴ Because of these data, it is attractive to ascribe the increase in CMR_{O_2} observed with sodium nitroprusside and hemorrhagic (autoregulation preserved) hypotension to the action of the sympathetic nervous system. Support for this hypothesis comes from a variety of studies in laboratory animals and man.^{26–32} Norepinephrine applied directly to brain³¹ or gaining access through an "open" blood-brain barrier³² causes an increase in cerebral metabolism. Less direct data come from studies of immobilization stress in small laboratory animals.²⁶ The remarkable increases in CBF and CMR_{O_2} produced by immobilization stress are abolished by prior adrenalectomy or the administration of the beta adrenergic blocker propranolol. Studies in man have likewise suggested that circulating levels of epinephrine have a direct effect on CBF and CMR_{O_2} .³⁰

The mechanism by which circulating catecholamines

might mediate an increase in CMR_{O_2} during sodium nitroprusside or hemorrhagic (autoregulation preserved) hypotension is not clear. Catecholamines do not readily cross the blood-brain barrier.³³ In one canine study in which an intravenous infusion of norepinephrine increased CBF and CMR_{O_2} , it was even suggested that norepinephrine might produce its effects via carotid and aortic chemoreceptors.²⁸ Alternatively, changes in central catecholamine levels, which parallel those in the periphery, could be responsible for the change observed in CMR_{O_2} during sodium nitroprusside hypotension. In support of this are the observations³⁴⁻³⁶ that immobilization stress causes an increase in the activity of central monoamine neurons and the turnover of central catecholamines. At this time it seems reasonable to conclude that catecholamines could play a role in mediating the increase in CMR_{O_2} observed with sodium nitroprusside hypotension and hemorrhagic (autoregulation preserved), but the exact role played by peripheral and central catecholamine systems in this response is not clear.

The role of catecholamines in the observed changes in the CMR_{O_2} in hemorrhagic hypotension is confused, somewhat, by the fact that the CMR_{O_2} increases significantly only as long as autoregulation is effective in preserving CBF. When the autoregulatory capacity of the cerebral vasculature is exceeded, CBF and CMR_{O_2} decrease in parallel (fig. 1). Two related pieces of evidence seem relevant to an understanding of this problem. First, Maekawa and associates,⁶ measuring brain surface oxygen tension (PB_{O_2}) in cats, observed a marked hypoxic shift of PB_{O_2} with hemorrhagic hypotension, an intermediate shift with trimethaphan hypotension, and no shift from control values with sodium nitroprusside. These observations were made at MABP in the range of 30-35 mmHg. Second, it has been clearly demonstrated that an acute reduction in brain oxygen tension is associated with corresponding changes in brain catecholamine synthesis and metabolism.³⁷⁻³⁹ From these two pieces of evidence, it seems reasonable to suggest that hemorrhagic hypotension can only be expected to produce a catecholamine-induced increase in CMR_{O_2} as long as CBF is maintained (*i.e.*, autoregulation is preserved). Below the level of CPP consistent with preserved autoregulation, brain hypoxia will attenuate or eliminate altogether such a response. We must conclude, further, on the basis of the work of others^{4,6-8} that below a certain CPP, which may vary according to the species studied and other experimental variables, all forms of controlled hypotension lead to a reduction in the CMR_{O_2} due to cerebral ischemia.

The potential problem of stimulating cerebral metabolism while reducing blood flow should be kept in mind when sodium nitroprusside is used to achieve controlled hypotension in the clinical setting. Clearly the increase in CMR_{O_2} seen with sodium nitroprusside-induced hy-

potension does not indicate that hypotension produced by this agent is superior to other forms of controlled hypotension.

References

1. Koch-Weser J: Hypertensive emergencies. *N Engl J Med* 290:211-214, 1974
2. Ivankovich AD, Miletich DJ, Albrecht RF, et al: Sodium nitroprusside and cerebral blood flow in the anesthetized and unanesthetized goat. *ANESTHESIOLOGY* 44:21-26, 1976
3. Fitch W: Editorial: Sodium nitroprusside and the cerebral circulation. *Br J Anaesth* 49:399-400, 1977
4. Michenfelder JD, Theye RA: Canine systemic and cerebral effects of hypotension induced by hemorrhage, trimethaphan, halothane, or nitroprusside. *ANESTHESIOLOGY* 46:188-196, 1977
5. Fitch W, Ferguson GG, Sengupta D, et al: Autoregulation of cerebral blood flow during controlled hypotension in baboons. *J Neurol Neurosurg Psychiatry* 39:1014-1022, 1976
6. Maekawa T, McDowall DG, Okuda Y: Brain-surface oxygen tension and cerebral cortical blood flow during hemorrhagic and drug induced hypotension in the cat. *ANESTHESIOLOGY* 51:313-320, 1979
7. Gypax P, Wiernsperger N: Oligemic hypotension-induced changes in EEG, CBF, and PO_2 and their pharmacological modifications. *Acta Neurol Scand (Suppl)* 56:5.10-5.11, 1977
8. Hamar J, Kovach AGB, Reivich M, et al: Effect of phenoxymethamine on cerebral blood flow and metabolism in the baboon during hemorrhagic shock. *Stroke* 10:401-407, 1979
9. Appel E, Dudziak R, Palm D, et al: Sympathoneuronal and sympathoadrenal activation during ketamine anesthesia. *Eur J Clin Pharmacol* 16:91-95, 1979
10. Dawson B, Michenfelder J, Theye RA: Effects of ketamine on canine cerebral blood flow and metabolism: Modification by prior administration of thiopental. *Anesth Analg (Cleve)* 50:443-447, 1971
11. Welch MJ, Ter-Pogossian MM: Preparation of short half-lived radioactive gases for medical studies. *Radiat Res* 36:580-587, 1968
12. Ter-Pogossian MM, Eichling JO, Davis DO, et al: The determination of regional cerebral blood flow by means of water labeled with radioactive oxygen-15. *Radiology* 93:31-40, 1969
13. Eichling JO, Raichle ME, Grubb RL, et al: Evidence of the limitations of water as a freely diffusible tracer in the brain of rhesus monkey. *Circ Res* 35:358-364, 1974
14. Raichle ME, Eichling JO, Straatmann MG, et al: Blood-brain barrier permeability of ^{14}C -labeled alcohols and ^{18}O -labeled water. *Am J Physiol* 230:543-552, 1976
15. Ter-Pogossian MM, Eichling JO, Davis DO, et al: The measure in vivo of regional cerebral oxygen utilization by means of oxyhemoglobin labeled with radioactive oxygen-15. *J Clin Invest* 49:381-391, 1970
16. Raichle ME, Grubb RL Jr, Eichling JO, et al: Measurement of brain oxygen utilization with radioactive oxygen-15: Experimental verification. *J Appl Physiol* 40:638-640, 1976
17. Harper AM: Autoregulation of cerebral blood flow: Influence of the arterial blood pressure on the blood flow through the cerebral cortex. *J Neurol Neurosurg Psychiatry* 29:398-403, 1966
18. Lassen NA: Autoregulation of cerebral blood flow. *Circ Res* 15 (suppl 1): 201-204, 1964
19. Lassen NA: Cerebral blood flow and oxygen consumption in man. *Physiol Rev* 39:183-238, 1959
20. Rapela CE, Green HD: Autoregulation of canine cerebral blood flow. *Circ Res* 15 (suppl 1):205-212, 1964
21. MacKenzie ET, Farrar JK, Fitch W, et al: Effects of hemorrhagic hypotension on the cerebral circulation. I. Cerebral blood flow and pial arterial caliber. *Stroke* 10:711-718, 1979
22. Stoyka WW, Schutz H: The cerebral response to sodium nitroprusside and trimethaphan controlled hypotension. *Can Anaesth Soc J* 22:275-283, 1975
23. Griffiths DPG, Cummins BH, Greenbaum R, et al: Cerebral blood

- flow and metabolism during hypotension induced with sodium nitroprusside. *Br J Anaesth* 46:671-679, 1974
24. Brown FD, Crockard HA, Johns LM, et al: The effect of sodium nitroprusside and trimethaphan camsylate on cerebral blood flow in rhesus monkeys. *Neurosurgery* 2:31-34, 1978
 25. Carter LP, Atkinson JR: Cortical blood flow in controlled hypotension as measured by thermal diffusion. *J Neurol Neurosurg Psychiatry* 36:906-913, 1973
 26. Carlsson C, Hagerdal M, Kaasik AE, et al: A catecholamine-mediated increase in cerebral oxygen uptake during immobilisation stress in rats. *Brain Res* 119:223-231, 1977
 27. Dahlgren N, Rosen I, Sakabe T, et al: Cerebral functional, metabolic and circulatory effects of intravenous infusion of adrenaline in the rat. *Brain Res* 184:143-152, 1980
 28. James IM, MacDonnell L: Factors affecting the cerebrovascular response to noradrenaline in the dog. *Br J Pharmacol* 54:129-143, 1975
 29. Kety SS: Circulation and metabolism of the human brain in health and disease. *Am J Med* 8:205-217, 1950
 30. King BD, Sokoloff L, Wechsler RL: The effects of L-epinephrine and L-norepinephrine upon cerebral circulation and metabolism in man. *J Clin Invest* 31:273-279, 1952
 31. MacKenzie ET, McCulloch J, Harper AM: Influence of endogenous norepinephrine on cerebral blood flow and metabolism. *Am J Physiol* 231:489-494, 1976
 32. MacKenzie ET, McCulloch J, O'Keane M, et al: Cerebral circulation and norepinephrine. *Am J Physiol* 231:483-488, 1976
 33. Oldendorf WH: Brain uptake of radiolabeled amino acids, amines and hexoses after arterial injection. *Am J Physiol* 221:1629-1639, 1971
 34. Corrodi H, Fuxe H, Hokfelt T: The effect of immobilisation stress on the activity of central monoamine neurons. *Life Sci* 7:107-112, 1968
 35. Thierry AM, Javoy F, Glowinski J, et al: Effects of stress on the metabolism of norepinephrine, dopamine, and serotonin in the central nervous system of the rat. I. Modification of norepinephrine turnover. *J Pharmacol Exp Ther* 163:163-171, 1968
 36. Saavedra JM, Kvetnansky R, Kopin IJ: Adrenaline, noradrenaline and dopamine levels in specific brain stem areas in acutely immobilized rats. *Brain Res* 160:271-280, 1979
 37. Davis JM, Carlsson A: The effect of hypoxia on monoamine synthesis, levels and metabolism in rat brain. *J Neurochem* 21:783-790, 1973
 38. Davis JM: Adaptation of brain monoamine synthesis to hypoxia in the rat. *J Appl Physiol* 39:215-220, 1975
 39. Prioux-Guyonneau M, Cretet E, Jacquot C, et al: The effect of various simulated attitudes on the turnover of norepinephrine and dopamine in the central nervous system of rats. *Pflügers Arch* 380:127-132, 1979