Effects of Isoflurane on Cerebral Autoregulation in Dogs

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The effect of decreased cerebral perfusion pressure (CPP) on regional cerebral blood flow (CBF) with radiolabeled microspheres in dogs receiving either 1.4% or 2.8% isoflurane following anesthesia induction with thiopental (12 mg/kg, iv bolus) was studied. Mean arterial blood pressure (MABP), cerebrospinal fluid pressure (PcSF), and sagittal sinus pressure (Pss) were measured. CPPs of 43, 33, and 23 mmHg were studied in three groups of animals. In group 1 (n = 6, isoflurane 1.4%) CPP was decreased by hemorrhage, in group 2 (n = 6, isoflurane 1.4%) CPP was decreased by increasing Pcss while MABP was maintained constant, and in group 3 (n = 6; isoflurane 2.8%) CPP was decreased by hemorrhage. Control total CBF in groups 1, 2, and 3 was 69 ± 8, 72 ± 7, and 150 ± 25 ml·min⁻¹·100 g⁻¹, respectively, at CPP of 84 ± 1 mmHg. Flow to both cerebral hemispheres and brain stem in animals receiving 2.8% isoflurane was approximately twice that found with 1.4% isoflurane while CMRO₂ was similar (about 3.5 ml·min⁻¹·100 g⁻¹). In groups 1 and 2 flow in all brain areas was maintained as CPP decreased to 43 mmHg and then flow decreased as CPP decreased further (P < 0.05). In group 3 flow to all brain areas decreased progressively as CPP decreased from 83 to 23 mmHg. At CPP of 43 mmHg and below, flow to cerebrum was similar in the three groups; however, flow to brain stem in group 3 animals remained elevated above groups 1 and 2 until CPP was decreased to 23 mmHg. Control cerebrovascular resistance (CVR) was 1.4 ± 0.2, 1.8 ± 0.2, and 0.8 ± 0.1 mmHg ml⁻¹·min⁻¹·100 g⁻¹ in groups 1, 2, and 3, respectively. In groups 1 and 2 CVR continuously declined as CPP decreased. In group 1 control CVR was less than groups 1 and 2 (P < 0.05) and was unchanged from control as CPP decreased from 83 to 23 mmHg. CMRO₂ was 3.5, 3.8, and 3.1 ml·min⁻¹·100 g⁻¹ in groups 1, 2, and 3, respectively and was unchanged as CPP decreased. Cerebral autoregulation to decreased CPP is preserved with 1.4% isoflurane, whereas autoregulation is eliminated by 2.8% isoflurane. The increased CBF produced by 2.8% isoflurane maintains cerebral O₂ delivery at or greater than that with 1.4% isoflurane as CPP is decreased. (Key words: Anesthetics, volatile; isoflurane. Brain: oxygen consumption. Brain, blood flow; autoregulation.)

CONSTANCY of cerebral blood flow (CBF) despite changes in blood pressure (autoregulation) maintains oxygen delivery to the brain. Cerebral autoregulation is preserved with iv drugs such as barbiturates and synthetic opiates (fentanyl), whereas volatile anesthetics such as halothane and enflurane obtund or abolish autoregulation. In circumstances of potential brain injury, isoflurane is recommended over halothane and enflurane because of less hyperemia and brain surface protrusion and protection during cerebral oxygen deprivation as indicated by preservation of ATP and phosphocreatine. Isoflurane is suggested as an agent of choice to induce hypotension in patients at risk for neurologic injury. Previous studies of the effects of isoflurane on cerebral autoregulation have been limited to single-step changes in mean arterial blood pressure (MABP) or increasing concentrations of isoflurane studied with only small changes in MABP and have failed to assess brain metabolism in the presence of isoflurane as blood pressure is altered. Within a narrow range of blood pressure (95–120 mmHg MABP), autoregulation remains intact with 1.4% isoflurane, whereas flow changes passively with pressure at isoflurane concentrations greater than 1 MAC.

Cerebral perfusion pressure (CPP) may be decreased by either arterial hypotension or intracranial hypertension. With barbiturate anesthesia, autoregulation remains intact in both conditions. However, because cerebral vasodilation has been described with isoflurane, it is unknown whether the two methods of decreasing CPP would have similar effects on CBF during isoflurane anesthesia.

We tested the hypothesis that clinically useful concentrations of isoflurane do not alter the ability of the brain to control CBF as CPP is altered. Because isoflurane may be used as both an anesthetic and hypotensive agent (in concentrations higher than that necessary to provide anesthesia), we studied the effect of 1 and 2 MAC isoflurane on CBF as CPP was altered.

Methods

This study was approved by the Johns Hopkins Medical Institutions Animal Care and Use Committee. Mongrel dogs (mixed sex; 20–25 kg) were initially anesthetized with thiopental (12 mg/kg, iv bolus). Following tracheal intubation the animals’ lungs were mechanically ventilated. Anesthesia was maintained with isoflurane 1.4% end-tidal in air supplemented with oxygen (FIO₂ = 0.3–0.5) during the insertion of catheters. In the dog MAC has been reported between 1.3% and 1.5%. We arbitrarily chose 1.4% to represent MAC. Isoflurane was administered via a vaporizer designed for isoflurane (Ohio Model TC-3, Madison, WI) and end-tidal isoflurane concentration was monitored using an infrared analyzer (Beckman LB-2, Fullerton, CA) calibrated with isoflurane containing calibration gas of 0.5, 1.0, and 3.0% (±0.01%) (Scott Medical Products, Plumsteadville, Pennsylvania). A catheter was inserted retrograde via a femoral artery into the left ventricle for radiolabeled microsphere injection. Catheters were inserted into each omocervical artery for measurement of MABP and microsphere reference.
withdrawal. In animals receiving 1.4% isoflurane a femoral artery was cannulated with a large catheter and connected to a reservoir containing heparinized saline in series with a large air containing reservoir, which buffered changes in MABP and allowed precise adjustment of CPP. In animals receiving 2.8% isoflurane a balloon-tipped catheter (Fogerty®, 10 ml balloon, American Edwards Laboratories, Irvine, CA) was inserted retrograde 40 cm via the femoral artery contralateral to the left ventricular catheter to facilitate raising MABP from control (about 63 mmHg) to that necessary to produce CPP of 83 mmHg. Balloon inflation with 3–5 ml of saline was sufficient to raise MABP to the desired level.

Following bone removal with a diamond-tipped drill a catheter was inserted into the sagittal sinus for withdrawal of cerebral venous blood and measurement of sagittal sinus pressure (Ps). A 16-gauge catheter was inserted into the cisterna magna to measure cerebrospinal fluid pressure (PcSF). In animals in which CPP was decreased by PcSF elevation, a 16-gauge blunt-tipped needle was inserted into a lateral cerebral ventricle and connected to a reservoir of mock cerebrospinal fluid, which could be elevated to raise PcSF. Free flow between the reservoir and the lateral ventricle reproducibly elevated Ps and maintained CPP constant. Rectal temperature was maintained at 38.0 ± 1.0°C by heating lamps. The arterial blood pressure transducer was placed at the level of the right atrium, and the transducers for Ps and PcSF were placed at the level of the external auditory meatus. All pressures were measured with Statham P23 dB transducers and recorded on a Gould-Brush Polygraph. Because the transducers were at slightly different levels (10 cmH2O; 7 mmHg), the reported CPP in text and tables reflects the correction of MABP for the difference in height between right atrial level and head level (external auditory meatus). Surgical preparation required approximately 1 h. A stabilization period of 30 min was allowed following completion of surgery during which time blood gases were adjusted.

**BLOOD GAS AND pH ANALYSIS**

Arterial blood samples were obtained from the omo-cervical artery and cerebral venous samples were obtained from the sagittal sinus. P02, PCO2, and pH were measured at 37°C immediately after the samples were obtained by use of Radiometer BMS-3 electrodes and analyzer. Oxygen saturation and hemoglobin concentration were measured with an Instrumentation Laboratories Co-oximeter (Model 282). Arterial and cerebral venous O2 content were calculated from the measured O2 saturation and hemoglobin concentration. Cerebral metabolic rate for oxygen (CMRO2) was calculated by multiplying hemispheric CBF times the arterial to cerebrovenous O2 content difference. Oxygen extraction fraction was computed as arterial minus cerebrovenous oxygen content divided by arterial oxygen content. Cerebral vascular resistance (CVR) was calculated by dividing CPP by total CBF. In each animal CPP was the difference between MABP and Psys or Pss, whichever was greater.

**CBF MEASUREMENT: TOTAL AND REGIONAL**

CBF was measured with radiolabeled microspheres (15 ± 1.5 μm diameter; Dupont-New England Nuclear) using the reference withdrawal method. Six radiolabels (155Gd, 114In, 115Sn, 103Ru, 95Nb, and 46Sc) were injected in random sequence. Prior to each injection the vial containing the spheres was shaken vigorously and sonicated for 20 min. Approximately 3 × 10⁶ spheres were injected for each measurement of flow. The microspheres were injected into the left ventricle over a 20-s period followed by a 20-s flush of 10 ml of saline. The reference blood sample was withdrawn from the omocervical artery using a Harvard withdrawal syringe pump set at 4.94 ml/min beginning 1 min prior to the injection and continuing for 3 min after the flush. At the end of the experiment the animal was killed with KCl, and the brain was removed and fixed in 10% buffered formalin for 4–7 days.

The brain was cut into the following areas: cervical spinal cord, cerebellum, medulla, caudate, periventricular white matter, and cerebrum (cerebral hemispheres). All tissue samples were weighed and placed in 15-ml poly Q vials and counted in a Packard multichannel autogamma scintillation spectrometer (model 9042) with a 3-inch through-hole NaI crystal. The energy levels of the window settings for the six isotopes were as follows: 155Gd, 70–174; 114In, 174-230; 115Sn, 370-430; 103Ru, 460-550; 95Nb, 710-820; and 46Sc, 840-1,200 keV. The overlap of activity among isotopes was subtracted to obtain corrected counts for each isotope by solving simultaneous equations using overlap coefficients from pure isotope standards. Blood flow (QT) was calculated from the equation QT = C T × Q R (C R × W), where C T is the corrected tissue counts, Q R is reference blood sample withdrawal rate in milliliters per minute, C R is total corrected counts in the reference arterial blood sample, and W is tissue weight in grams.

**EXPERIMENTAL PROTOCOLS**

In group 1 (n = 6; isoflurane 1.4%) MABP was manipulated to produce CPP of 83, 63, 53, 43, 33, and 23 mmHg. MABP was altered by pressurizing to the desired level a saline-filled reservoir connected to a catheter in the femoral artery. This reservoir allowed translocation of fluid between the reservoir and animal to minimize fluctuations in MABP. CPP was progressively decreased and each CPP was maintained for 10 min to allow correction of blood gases prior to determination of CBF.
In group 2 (n = 6; isoflurane 1.4%) MABP was maintained at control level (approximately 87 mmHg) while Pscf was elevated in increments to produce CPP of 83, 63, 53, 43, and 23 mmHg by use of a reservoir of mock CSF elevated to produce the desired decrease in CPP. Each CPP was maintained for 10 min to allow stabilization of blood gases prior to determination of CBF.

In group 3 (n = 6; isoflurane 2.8%) MABP was elevated to produce control CPP of 83 mmHg. This was accomplished by inflation of a midthoracic balloon-tipped catheter because control MABP was 53–63 mmHg. Thereafter MABP was decreased by deflation of the midthoracic aortic balloon and then controlled hemorrhage. CPP of 83, 63, 53, 43, and 23 mmHg were produced and each CPP was maintained for 10 min prior to determination of CBF.

**Statistical Analysis**

Analysis of variance (ANOVA) for between–within design was performed after logarithmic transformation to assess the effects of isoflurane concentration and CPP. A P < 0.05 was considered significant and Bonferroni's correction for multiple comparisons was used to compare data at different isoflurane concentrations and different CPP.

**Results**

Hemodynamic, blood gas, and arterial oxygen content data for groups 1, 2, and 3 as CPP was decreased from 83 to 23 mmHg are shown in table 1.

Control pH was approximately 7.38 in groups 1–3 and was maintained in all groups as CPP was decreased from 83 to 33 mmHg. Mild metabolic acidosis (pH approximately 7.31) developed in all groups as CPP was decreased to 23 mmHg. Control PaCO2 was approximately 120 mmHg in groups 1–3 and did not change as CPP was decreased. Control PaO2 was 34–36 mmHg in the three groups and was unchanged in each group as CPP was decreased from 83 to 23 mmHg. Arterial O2 content for groups 1, 2, and 3 at CPP of 83 mmHg was 16.4 ± 0.9, 19.4 ± 0.8, and 15.7 ± 1.0 ml/dl, respectively. Although the oxygen content was higher in group 2 than in groups 1 and 3 (P < 0.05), within each group oxygen content was unchanged as CPP was decreased from 83 to 23 mmHg.

Figure 1 shows total and regional CBF in groups 1–3 at the same CPP (83 ± 1 mmHg). Control total CBF in groups 1–3 were 72 ± 12, 67 ± 10, and 150 ± 25 ml·min⁻¹·100 g⁻¹, respectively. Total and regional flow in all brain areas was increased by 2.8% isoflurane compared with 1.4% isoflurane. This increase ranged from 158% in caudate to 900% in cerebellum.

Figure 2 shows total CBF, CVR, and oxygen extraction fraction in groups 1–3 as CPP was decreased from 83 to 23 mmHg. In groups 1 and 2 total CBF was maintained as CPP was decreased to 43 mmHg but decreased (P < 0.05) at CPP of 33 mmHg and further decreased at CPP of 23 mmHg. In group 3 (2.8% isoflurane) CBF was initially higher than in groups 1 and 2 (P < 0.05), but total CBF continuously declined as CPP was decreased from 83 to 23 mmHg. Total CBF in group 3 remained...
higher than in groups 1 and 2 until CPP was decreased to 23 mmHg. Control CVR was 1.4 ± 0.2, 1.6 ± 0.2, and 0.8 ± 0.1 mmHg ml⁻¹ min⁻¹ 100 g⁻¹ for groups 1, 2, and 3, respectively. In group 1 CVR was decreased at 63 mmHg (P < 0.05) and remained less than control level as CPP decreased further. In group 2 CVR decreased as CPP declined to 53 mmHg (P < 0.05) and remained less than control (P < 0.05) as CPP decreased to 23 mmHg. In group 3 control CVR was less than in groups 1 and 2 (P < 0.05) and was unchanged as CPP decreased from 83 to 23 mmHg. Control CMRO₂ was 3.5 ± 0.3, 3.8 ± 0.4, and 3.1 ± 0.4 ml·min⁻¹·100 g⁻¹ for groups 1, 2, and 3, respectively, and was maintained at the control level in each group as CPP decreased to 23 mmHg. Control oxygen extraction fraction was 0.52 ± 0.03, 0.33 ± 0.04, and 0.16 ± 0.03 in groups 1, 2, and 3, respectively. Control oxygen extraction fraction was less in group 3 than in groups 1 and 2 (P < 0.05). As CPP decreased, oxygen extraction fraction progressively increased to 0.59 ± 0.07, 0.54 ± 0.06, and 0.40 ± 0.04 for groups 1, 2, and 3, respectively, at CPP of 23 mmHg (P < 0.05). Oxygen extraction fraction was lower in group 3 than in groups 1 and 2 as CPP decreased to 33 mmHg (P < 0.05). At CPP of 23 mmHg oxygen extraction fraction was similar in animals receiving 1.4 and 2.8% isoflurane.

Figure 3 shows blood flow in cerebellum, medulla, caudate, white matter, and cerebrum in the groups 1–3 as CPP decreased from 83 to 23 mmHg. In group 1 flow to cerebrum, medulla, and cerebellum was maintained as CPP decreased to 43 mmHg, whereas flow to caudate and white matter was maintained as CPP decreased to 53 mmHg. Spinal cord flow was maintained at control level (42 ± 10 ml·min⁻¹·100 g⁻¹) as CPP was decreased to 43 mmHg. At CPP of 33 and 23 mmHg flow was 67% and 55% of control, respectively.

In group 2 control blood flow to the cerebrum, caudate,
cerebellum to 30% of control, and white matter to 26% of control. Control spinal cord flow was 97 ± 12 ml·min⁻¹·100 g⁻¹ and declined to 27% of control at CPP of 23 mmHg. Flow to white matter and caudate was similar with 1.4% and 2.8% isoflurane, whereas flow to cerebellum, medulla, and cerebrum was higher with 2.8% isoflurane until CPP decreased to 43 mmHg (fig. 3).

Discussion

The current study assessed the ability of the cerebral vasculature to control CBF in the presence of 1 and 2 MAC isoflurane. We found that with 1 MAC (1.4%) isoflurane cerebral autoregulation remained intact as CPP was decreased and the lower limit of autoregulation was similar to that reported for dogs anesthetized with barbiturates. However, 2.8% isoflurane caused hyperemia relative to 1.4% isoflurane and produced a pressure passive cerebral vasculature (abolished autoregulation). Because we measured CBF over a wide range of CPP (23–83 mmHg) in the presence of two isoflurane concentrations, our data are useful in reconciling results from previous studies of CBF in which increasing the isoflurane concentration has been used to lower MABP. In addition to information concerning regional CBF, we provide data on CMRO₂ and cerebral oxygen extraction as CPP is altered during isoflurane administration. We altered CPP mechanically to avoid confounding effects of vasoconstrictors. Because both intracranial hypertension and arterial hypotension may decrease CPP in patients at risk of neurologic injury, we studied cerebrovascular responsiveness during isoflurane anesthesia as CPP was decreased by each method.

Isoflurane is considered superior to halothane and enflurane in circumstances involving brain injury because of reports of impaired autoregulation with halothane and enflurane, whereas limited studies of cerebral autoregulation with isoflurane (i.e., single-step pressure changes) have suggested that autoregulation is preserved during ventilation with 1 MAC isoflurane. The impact of isoflurane on autoregulation in concentrations greater than 1 MAC is unclear because of reports of unchanged CBF or decreased CBF as MABP is decreased by increasing the isoflurane concentration. Our results are useful in reconciling those studies because we show that 2 MAC isoflurane produces a pressure passive cerebral vascular bed. Thus, increasing isoflurane concentration above 1 MAC can result in either no change or decreased CBF compared to lower concentrations, depending on the severity of decrease in MABP and CPP. Because MABP rather than CPP has generally been reported, direct comparison with previous studies is difficult. Our results demonstrate that CBF during 2 MAC (2.8%) isoflurane is greater than or equal to flow during 1.4% isoflurane as CPP is decreased to 23 mmHg. Our results differ from those of Gelman et al., who found no increase in CBF as isoflurane was increased from 1 to 2 MAC (123 ± 17 vs. 132 ± 28 ml·min⁻¹·100 g⁻¹) while MABP decreased from 100 ± 5 to 64 ± 6 mmHg. However, our study differs from that of Gelman et al. because we compared 1.4 and 2.8% isoflurane at a similar CPP. Inspection of figure 2 may provide insight into this apparent lack of change. Because intracranial pressure was not reported in that study, we can only speculate concerning the exact value of CPP. Our data (table 1) suggest that CPP with isoflurane is 5–6 mmHg less than MABP. Thus, changing from 1 MAC isoflurane at CPP about 95 mmHg to 2 MAC isoflurane at CPP about 58 mmHg would result in relatively small difference (if any depending on the exact...
CPP in CBF despite a complete absence of autoregulation with the higher isoflurane concentration. Todd and Drummond\textsuperscript{6} using a single 30-mmHg increase in MABP in the presence of 1 MAC isoflurane (plus nitrous oxide) found that autoregulation is intact. However, VanAken et al.\textsuperscript{7} found that a single 30-mmHg increase in MABP at 1.4% isoflurane increased CBF. These differences may be due to different species or ancillary anesthetic drugs present.

Manohar and Parks\textsuperscript{19} administered isoflurane to awake animals and found that 1 MAC isoflurane increased brain stem and cerebellar blood flow without increasing hemispheric CBF. With a higher dose of isoflurane (1.5 MAC), hemispheric flow increased, but the hyperemia in brain stem and cerebellum continued. Manohar and Parks\textsuperscript{19} speculated that because isoflurane increased CBF more in brain stem and cerebellum than in cerebral hemispheres, autoregulation might be more affected in those areas. We found the brain to be homogeneous with respect to the limit of autoregulation because flow to brain stem and cerebrum declined at the same CBF with 1 MAC isoflurane. These results differ from previous studies with iv anesthesia,\textsuperscript{17,18} which showed that, with decreasing CBF, flow to cerebrum decreased at a higher CPP than that required to decrease brain stem flow. Our data on flow to cerebrum suggests that the difference in MABP depression in previous studies\textsuperscript{8,19} in the presence of a pressure sensitive cerebral vasculature caused by isoflurane explains why CBF has been reported to be unchanged (MABP = 67 mmHg)\textsuperscript{19} or decreased (MABP = 51 mmHg).\textsuperscript{8}

Our results differ from those of a previous study, which showed that CMRO\textsubscript{2} decreased more with 2 MAC isoflurane than with 1 MAC\textsuperscript{20} because we found similar CMRO\textsubscript{2} in animals receiving 1 and 2 MAC isoflurane. In that study\textsuperscript{20} CMRO\textsubscript{2} was about 72% of control with 1 MAC isoflurane and 62% of control with 2 MAC isoflurane. Our value of CMRO\textsubscript{2} (3.1 ± 0.4 ml·min\textsuperscript{-1}·100 g\textsuperscript{-1}) found with 2.8% isoflurane is similar to a previous study with 2.9% isoflurane associated with a similar CBF.\textsuperscript{21} Cucchiara et al.\textsuperscript{22} found only a small difference in CMRO\textsubscript{2} with 1.4% and 2.4% isoflurane in dogs (76% and 70% of control, respectively). Our sample size may have been too small to detect such a small difference because of the relatively large interanimal variability of control CMRO\textsubscript{2}.

Figure 3 shows that if only CBF is considered, 2.8% isoflurane is preferable to 1.4% isoflurane during decreased CPP because cerebral O\textsubscript{2} delivery (CBF X arterial O\textsubscript{2} content) is higher with 2.8% until CPP decreases to 25 mmHg. At that CPP 1.4% and 2.8% isoflurane provide equal cerebral O\textsubscript{2} delivery. This is substantiated by preservation of CMRO\textsubscript{2} by an increase in oxygen extraction fraction in animals receiving both 1.4% and 2.8% isoflurane as CPP decreased to 25 mmHg. Thus, despite a failure of autoregulation with 2.8% isoflurane, the metabolic function of the brain is not impaired.

The mechanism of cerebral vasodilation by volatile anesthetic agents is unclear. Cerebral vasodilation by halothane appears to bear a relationship to effects on whole brain cyclic-AMP.\textsuperscript{23} In that study cyclic AMP was not increased until the halothane concentration was increased to 1.5%. In primates vasodilation produced by halothane does not occur\textsuperscript{24} until inspired concentrations are reached that elevate cyclic AMP.\textsuperscript{23} This threshold phenomenon for cyclic AMP-produced vasodilation\textsuperscript{23,24} is consistent with our data because one concentration of isoflurane (1.4%) increases flow but preserves autoregulation while a higher concentration (2.8%) further increases CBF and obviates autoregulation. This effect is consistent with a dose-dependent increase in cyclic AMP.

Extrapolation of our results to the clinical use of isoflurane requires caution. We have experimentally dissociated peripheral vascular effects from cerebrovascular effects of isoflurane by controlling CPP, thus allowing comparison of 1.4 and 2.8% isoflurane at a similar CPP. Because isoflurane has a dose-dependent effect on the cardiovascular and cerebrovascular systems, the interaction of these effects must be considered when the impact of isoflurane on oxygen delivery to the brain is considered. Our data show that with 1 MAC isoflurane, less attention needs to be paid to control of CPP, whereas at a high concentration (2 MAC) control of CPP may be important. However, even with 2 MAC isoflurane, cerebral O\textsubscript{2} delivery is not depressed below control levels at CPP as low as 23 mmHg.

In summary, CBF autoregulation is preserved by 1.4% isoflurane but not 2.8% isoflurane. Because 2.8% isoflurane produces hyperemia relative to 1.4%, regional CBF is greater than or equal to that found with isoflurane at the lower concentration even at a CPP of 23 mmHg. With both 1.4% and 2.8% isoflurane concentration, CMRO\textsubscript{2} is maintained to CPP of 23 mmHg. Both high concentrations of volatile anesthetics and extremely low perfusion pressure cause maximal vasodilation so that our finding of similar CBF at 1.4% and 2.8% isoflurane at low CPP simply reflects maximum cerebral vasodilation.

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