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Dynamic and Static Cerebral Autoregulation during Isoflurane, Desflurane, and Propofol Anesthesia

Stephan Strebel, M.D., Arthur M. Lam, M.D., F.R.C.P.C.,† Basil Matta, M.B., F.R.C.A.,‡ Teresa S. Mayberg, M.D.,§ Rune Aaslid, Ph.D.,‖ David W. Newell, M.D.#*

Background: **Although inhalation anesthetic agents are thought to impair cerebral autoregulation more than intravenous agents, there are few controlled studies in humans.**

Methods: **In the first group (n = 24), dynamic autoregulation was assessed from the response of middle cerebral artery blood flow velocity (Vmca) to a transient step decrease in mean arterial blood pressure (MABP). The transient hypotension was induced by rapid deflation of thigh cuffs after inflation for 3 min. In the second group (n = 18), static autoregulation was studied by observing Vmca in response to a phenylephrine-induced increase in MABP. All patients were studied during fentanyl (3 $\mu g \cdot kg^{-1} \cdot h^{-1}$)/nitrous oxide (70%) anesthesia, followed by, in a randomized manner, isoflurane, desflurane, or propofol in a low dose (0.5 MAC or 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and a high dose (1.5 MAC or 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$). The dynamic rate of regulation (dROR) was assessed from the rate of change in cerebrovascular resistance (MABP/Vmca) with the blood pressure decreases using computer modeling, whereas the static rate of regulation (sROR) was assessed from the change in Vmca with the change in MABP.**

Results: **Low-dose isoflurane delayed (dROR decreased) but did not reduce the autoregulatory response (sROR intact). Low-dose desflurane decreased both dROR and sROR. During 1.5 MAC isoflurane or desflurane, autoregulation was ablated (both dROR and sROR impaired). Neither dROR nor sROR changed with low- or high-dose propofol.**

Conclusions: **At 1.5 MAC, isoflurane and desflurane impaired autoregulation whereas propofol (200 $\mu g \cdot kg^{-1} \cdot min^{-1}$) preserved it. (Key words: Anesthetics, intravenous: propofol. Anesthetics, volatile: desflurane; isoflurane. Brain: autoregulation; cerebral blood flow velocity. Equipment: transcranial Doppler ultrasonography. Sympathetic nervous system, pharmacology: phenylephrine.)**

CEREBRAL autoregulation minimizes changes in cerebral blood flow (CBF) when cerebral perfusion pressure changes.[1,2] The capacity for the human brain to regulate its blood flow independent of blood pressure was first demonstrated by performing repeated static measurements of brain perfusion at different blood pressures, thereby establishing the range of blood pressure in which this mechanism was effective.[3] In clinical and experimental studies, the ability of this physiologic system to maintain relatively constant CBF within a cerebral perfusion pressure of 50–170 mmHg has been documented.[4,5] However, cerebral autoregulation is a sensitive mechanism and has been observed to be impaired by pathologic process and by general anesthesia.[6,7]

There are few controlled studies addressing the influence of anesthetics on cerebral autoregulation. Animal investigations suggest that volatile anesthetics lead to an impairment of cerebral autoregulation, whereas intravenous anesthetics preserve cerebral autoregulation.[8–12] Most human data available are derived indirectly from studies in which cerebral autoregulation was not the primary study interest.[13,14] There are several reasons for this lack of autoregulatory data in humans. First, assessment of cerebral autoregulation requires measurement of CBF during a period of hypotension or hypertension. Deliberate hypo- or hypertension, however, present ethical and strategic problems in patients. Second, measurement of CBF often requires bulky equipment and/or radioactive material, it is time-consuming, and only a limited number of measurements can be obtained. Third, drugs used to induce hypertension and/or hypotension may have direct effects on cerebral vessels and thus may influence autoregulation.[2]

* Visiting Professor of Anesthesiology. Current position: Department of Anesthesia, University Hospital, Basel, Switzerland.

† Professor of Anesthesiology and Neurological Surgery.

‡ Acting Assistant Professor of Anesthesiology.

§ Assistant Professor of Anesthesiology and Neurological Surgery.

‖ Research Professor of Neurological Surgery.

Associate Professor of Neurological Surgery.

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Address correspondence to Dr. Lam: Department of Anesthesiology, ZA-14, Harborview Medical Center, 325 Ninth Avenue, Seattle, Washington 98104.

We have studied the influence of isoflurane, desflurane, and propofol in a dose-related manner on cerebral autoregulation in healthy patients. Isoflurane, generally thought to have less cerebral vasodilatory properties (at least in the cortex) than other halogenated anesthetics at equipotent concentrations, is considered the ideal volatile anesthetic for neurosurgical procedures.[15] On the other hand, the cerebral vasoconstricting property of propofol makes this intravenous anesthetic an attractive alternative to isoflurane for neurosurgical procedures in patients with reduced intracranial compliance or increased cerebral elastance.[16] Finally, the qualities of the recently introduced inhalation anesthetic desflurane, a low blood-gas solubility and similar cerebral effects to isoflurane, make this anesthetic a suitable alternative for use in neuroanesthesia.[17]

Methods and Materials

The study was approved by the University of Washington Human Subjects Review Committee. Forty-four adults, ASA physical status 1 or 2, scheduled for elective orthopedic surgery were recruited, and 42 were included in the study. Written informed consent was obtained from each subject. Patients who had neurologic or cardiovascular diseases or who were medicated with psychoactive drugs were excluded. The study was performed in two parts: In the first, dynamic aspects of cerebral autoregulation were investigated in 24 patients. In the second, the static aspects of cerebral autoregulation were investigated in 18 patients.

Determination of Mean Middle Cerebral Artery Blood Flow Velocity

Both middle cerebral arteries (MCA) were insonated at a depth providing the best signal (45–50 mm) through the temporal window using a TCD ultrasonography monitor (MCD-TCD7, DWL Elektronische, Sipplingen, Germany). The technique used to locate the MCA had been described previously.[18] A custom-made bilateral probe arrangement strapped onto the patient's head and locked in position permitting continuous middle cerebral artery blood flow velocity (Vmca) measurements was used. The shifts in the frequency spectra of the Doppler signals were converted into velocity (cm/s) and calculated as mean Vmca. The bilateral Vmca and mean arterial blood pressure (MABP) obtained from direct invasive monitoring were displayed simultaneously on a video screen and recorded using the standard algorithm implemented on the instrument.

Determination of Dynamic Cerebral Autoregulation

The dynamic autoregulation tests were induced by a rapid transient change in MABP to activate the autoregulatory mechanism.[19] Large cuffs modified with larger tubings were placed around one or both thighs of the patient. The cuffs were inflated to 30 mmHg above the patient's systolic blood pressure. After 3 min of inflation, the cuffs were (<0.5 s) deflated rapidly. This process was repeated until a decrease of at least 10 mmHg in MABP and a duration of 10–20 s or longer was achieved.

As a method of determining the dynamic rate of regulation (dROR), the instrument used a special algorithm with several refinements compared to the one used by Aaslid *et al.*[19,20,**] This algorithm was developed to study autoregulation during microgravity experiments. The new algorithm compensated for the lack of consistent step change in MABP during microgravity by using a mathematical model and simple parameter estimation techniques.

The details of the mathematical model are outlined in the appendix. This method examines how quickly Vmca returns to baseline while the MABP remains lowered for a short period. The mathematical model fits the change in cerebral vascular resistance as derived from MABP/Vmca to a family of curves for the best fit. The descriptor of dynamic autoregulation, dROR, describes the rate of restoration of Vmca (m%/s) with respect to the decrease in MABP. Previous studies by Aaslid *et al.* showed that the autoregulation process normally is complete within 5 s. Thus, the normal dROR is 100%/5 s = 20%/s (0.2/s). All data, MABP, and the Vmca during the autoregulation tests were stored on the hard disk of the computer for subsequent analysis.

Determination of Static Cerebral Autoregulation

The static autoregulation was tested with an increase of 20 mmHg in MABP by infusion of phenylephrine. The initial (i) and final (f) Vmca and MABP were recorded for subsequent calculation of cerebrovascular resistance (CVR = MABP/Vmca) and analysis. To avoid

** Aaslid R, Bondar RL, Kassam MS, Stein F, Dunphy P: Cerebral autoregulation in microgravity. Proceedings, Spacebound 91, Ottawa, Ontario, 224:227, 1991.

overshoot, MABP was increased gradually with a slow infusion of phenylephrine. Analogous to the dROR for the dynamic autoregulatory test, an index of static autoregulation (although not a rate of regulation), static rate of regulation (sROR), was defined, and calculated from the MABP and Vmca values as follows:

$$\text{sROR}(\%) = 100(\%\Delta\text{CVR} \div \%\Delta\text{MABP}),$$

where ΔCVR = change in CVR, and ΔMABP = change in MABP.

Alternatively, sROR can be calculated as:

$$\text{sROR}(\%) = 100([\text{i}]\text{Vmca}/[\text{f}]\text{Vmca} - [\text{i}]\text{MABP}/[\text{f}]\text{MABP}/(1 - [\text{i}]\text{MABP}/[\text{f}]\text{MABP}).$$

Accordingly, an sROR of 1 or 100% implies a Vmca independent of MABP or perfect cerebral autoregulation; whereas, in a purely passive, nonregulating cerebrovascular bed, Vmca varies proportionally with MABP resulting in an sROR of 0.

Experimental Protocol

In both study parts, the patients were randomly allocated to one of three groups: isoflurane, desflurane, or propofol anesthesia. Patients were not premedicated. Physiologic variables monitored included invasive blood pressure, electrocardiogram, heart rate, end-tidal measurement of carbon dioxide and volatile anesthetics, and pulse oximetry (Spacelabs, Redmond, WA). The end-tidal concentration of desflurane was not measured; the inspired concentration from a regularly calibrated vaporizer was used instead. This was considered acceptable in view of the low blood-gas solubility. Anesthesia was induced with 4–6 mg/kg thiopental, 3 μg/kg fentanyl, and 0.1 mg/kg vecuronium. After the trachea was intubated, the lungs were mechanically ventilated to achieve normocapnia (Pa_{CO_2} of 38–40 mmHg). Anesthesia was maintained with 70% N_2O in oxygen and a fentanyl infusion of 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$. When necessary, an additional bolus of fentanyl was administered to maintain an adequate depth of anesthesia as judged by clinical signs, *i.e.,* presence of tachycardia and/or hypertension. Body temperature was maintained higher than 36.0°C in all patients using warmed intravenous infusion and thermal blankets. Maintenance infusion of Plasma-Lyte (Baxter, Deerfield, IL) was given at 150 ml/h after an initial bolus of 1,000 ml.

Cerebral autoregulatory tests were performed three times in each patient. Initially, during stable fentanyl/nitrous oxide anesthesia (a minimum of 15–20 min), baseline measurements were obtained. Next, the patient was randomly allocated to receive either low- or high-dose isoflurane, desflurane, or propofol, and the measurements were repeated. Final measurements were made during the same allocated anesthetic regimen but equilibrated to a different dose (*i.e.,* low dose reequilibrated to high dose or high dose reequilibrated to low dose). Low dose was defined as 0.5 MAC of volatile anesthetic or 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of propofol infusion after a bolus of 1.5 mg/kg, and high dose as 1.5 MAC of volatile anesthetic or 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of propofol. The intravenous bolus of propofol was given once, just before the first infusion of propofol. The minimum alveolar concentration of isoflurane was considered to be 1.15%,[21] and the minimum alveolar concentration of desflurane was considered to be 7.3%.[22] For the purpose of this study, the contribution of nitrous oxide to minimum alveolar concentration was ignored. Cerebral autoregulatory tests were not performed until at least 15 min of steady-state unchanged end-tidal isoflurane concentration or 20 min of unchanged inspired desflurane concentration had been reached (or 30 min after propofol infusion). During high-dose anesthetics, MABP was maintained within 5–10% of the baseline value during fentanyl/nitrous oxide anesthesia using a phenylephrine infusion.

Analysis of Data

Results from bilateral recordings were averaged before statistical analysis. All results are expressed as mean ± SE when not otherwise indicated. A two-way analysis of variance for repeated measures was used for intergroup comparisons. Intragroup comparisons were evaluated using one-way analysis of variance for repeated measures. When significance was found, Fisher's protected least significant difference test was used as a *post hoc* multiple comparison procedure. A *P* value of less than 0.05 was considered statistically significant.

Results

Demographic data of the three patient groups studied in both autoregulatory tests are summarized in table 1.

Two patients demonstrating no cerebral vascular autoregulation during baseline tests were replaced. In both patients, subsequent review of their medical history revealed a mild head injury with concussion, which excluded them from participation in the study. There were no complications from the study. No patient re-

DYNAMIC AND STATIC CEREBR

Table 1. Characteristics of Patients Stud

	Isoflurane	
	Dynamic (n = 8)	S
Age (yr)	30 ± 11	
Weight (kg)	78 ± 19	
Sex (M/F)	5/3	

Values are mean ± SD. There were no intergroup

quired blood transfusion before th
study, and there was no significant c
during the study.

Dynamic Autoregulatory Tests

There was no significant change
and Pa_{CO_2} during the study procedu
rate, MABP, Vmca, and Pa_{CO_2} are p
CBF velocity decreased significant
high-dose propofol infusion ($P <$
baseline (fentanyl/nitrous oxide a
significantly lower ($P < 0.001$) co
atile anesthetics. The dose-relate

Table 2. Physiologic Variables during I
Autoregulatory Tests

	Isoflurane (n = 8)
Baseline	
MABP (mmHg)	89 ± 2
Pa_{CO_2} (mmHg)	38 ± 1
Vmca (cm·s⁻¹)	68 ± 6
Decrease in MABP (mmHg)	19 ± 2
Low dose	
MABP (mmHg)	89 ± 4
Pa_{CO_2} (mmHg)	36 ± 2
Vmca (cm·s⁻¹)	61 ± 3
Decrease in MABP (mmHg)	21 ± 1
High dose	
MABP (mmHg)	86 ± 5
Pa_{CO_2} (mmHg)	37 ± 1
Vmca (cm·s⁻¹)	75 ± 10
Decrease in MABP (mmHg)	17 ± 2

Values are mean ± SE. Baseline = nitrous oxide
MAC for volatile anesthetics, 100 μg·kg·min⁻¹ fo
MAC for volatile anesthetics, 200 μg·kg·min⁻¹ fo
MABP = mean arterial blood pressure; Pa_{CO_2} =
cerebral blood flow velocity in the middle cerebral
* Significantly different *versus* baseline, $P < 0.01$.
† Significantly different *versus* the other two anest

Table 1. Characteristics of Patients Studied during Cerebral Autoregulatory Tests

	Isoflurane		Desflurane		Propofol	
	Dynamic (n = 8)	Static (n = 6)	Dynamic (n = 8)	Static (n = 6)	Dynamic (n = 8)	Static (n = 6)
Age (yr)	30 ± 11	37 ± 4	35 ± 16	31 ± 7	33 ± 16	32 ± 9
Weight (kg)	78 ± 19	73 ± 7	78 ± 8	70 ± 20	72 ± 19	91 ± 15
Sex (M/F)	5/3	5/1	7/1	4/2	4/4	6/0

Values are mean ± SD. There were no intergroup differences.

quired blood transfusion before the completion of the study, and there was no significant change in hematocrit during the study.

Dynamic Autoregulatory Tests

There was no significant change in heart rate, MABP, and Pa_{CO_2} during the study procedure. Changes in heart rate, MABP, Vmca, and Pa_{CO_2} are presented in table 2. CBF velocity decreased significantly during low- and high-dose propofol infusion ($P < 0.01$) compared to baseline (fentanyl/nitrous oxide anesthesia) and was significantly lower ($P < 0.001$) compared to both volatile anesthetics. The dose-related increase in Vmca with volatile anesthetics did not reach statistical significance. Illustrative recordings demonstrating preservation and impairment of dynamic autoregulation are displayed in figure 1. Deflation of the thigh cuffs resulted in an abrupt decrease of MABP and Vmca. During fentanyl/nitrous oxide anesthesia, Vmca returned rapidly to baseline level, whereas MABP remained low for approximately 10–20 s before it was gradually restored almost to the control value. There were no differences in baseline dROR among the three groups, and the dROR was similar to reported values for awake individuals.[19] The maximum decrease in MABP with cuff deflations was similar between and within groups. Both isoflurane and desflurane produce a dose-related delay in the return of Vmca to baseline with a significant reduction of dROR, whereas propofol had no effect

Table 2. Physiologic Variables during Dynamic Cerebral Autoregulatory Tests

	Isoflurane (n = 8)	Desflurane (n = 8)	Propofol (n = 8)
Baseline			
MABP (mmHg)	89 ± 2	83 ± 3	92 ± 6
Pa_{CO_2} (mmHg)	38 ± 1	38 ± 1	39 ± 1
Vmca ($cm \cdot s^{-1}$)	68 ± 6	67 ± 7	65 ± 7
Decrease in MABP (mmHg)	19 ± 2	19 ± 1	17 ± 1
Low dose			
MABP (mmHg)	89 ± 4	86 ± 7	83 ± 4
Pa_{CO_2} (mmHg)	36 ± 2	37 ± 1	38 ± 1
Vmca ($cm \cdot s^{-1}$)	61 ± 3	64 ± 9	45 ± 5*†
Decrease in MABP (mmHg)	21 ± 1	17 ± 1	16 ± 2
High dose			
MABP (mmHg)	86 ± 5	83 ± 5	82 ± 5
Pa_{CO_2} (mmHg)	37 ± 1	38 ± 1	37 ± 1
Vmca ($cm \cdot s^{-1}$)	75 ± 10	74 ± 9	39 ± 4*†
Decrease in MABP (mmHg)	17 ± 2	18 ± 1	17 ± 1

Values are mean ± SE. Baseline = nitrous oxide + fentanyl; Low dose = 0.5 MAC for volatile anesthetics, 100 $\mu g \cdot kg \cdot min^{-1}$ for propofol; High dose = 1.5 MAC for volatile anesthetics, 200 $\mu g \cdot kg \cdot min^{-1}$ for propofol; HR = heart rate; MABP = mean arterial blood pressure; Pa_{CO^2} = arterial CO_2; Vmca = mean cerebral blood flow velocity in the middle cerebral artery.

* Significantly different *versus* baseline, $P < 0.01$.

† Significantly different *versus* the other two anesthetics, $P < 0.001$.

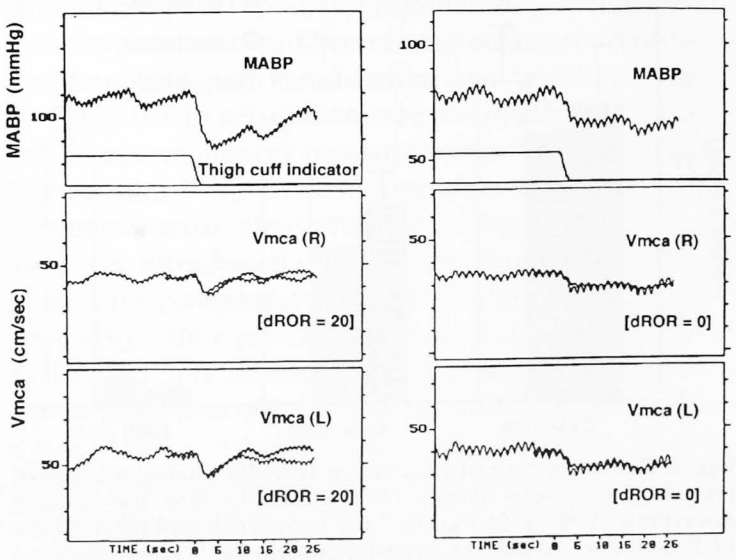

Fig. 1. Recordings from the study of dynamic autoregulation. (*Top*) The abrupt change in mean arterial blood pressure with cuff deflation. (*Bottom*) The corresponding change in right and left middle cerebral artery blood flow velocity. (*Left*) Normal dynamic autoregulation. (*Right*) Abolished autoregulation. The computer modeling for calculation of the dynamic rate of regulation is depicted by the dark lines on the bottom graphs.

(fig. 2). Compared to baseline, the decrease in dROR at low dose was significant ($P < 0.05$) for isoflurane and highly significant for desflurane ($P < 0.001$), whereas at high dose, the decrease in dROR was highly significant for both anesthetics ($P < 0.001$).

Static Autoregulatory Tests

No significant changes in heart rate, MABP, and Pa_{CO_2} occurred between baseline and increased anesthetic doses (table 3). All Vmca data reported are values recorded before elevation of MABP. The dose-related decrease in CBF velocity during propofol anesthesia was similar to the changes observed in the dynamic autoregulatory study in part one. There was no change in CBF velocity during low-dose inhaled anesthetics, but the flow velocity during high-dose desflurane anesthesia was significantly higher than baseline ($P < 0.001$).

The illustrative recordings for a static autoregulation testing demonstrating preserved and abolished autoregulation, respectively, are shown in figure 3. During fentanyl/nitrous oxide anesthesia, the increase in MABP resulted in little or no change in Vmca, and no difference in sROR among the three study groups (fig. 4). In contrast to the observations made during the dynamic autoregulatory test, low-dose isoflurane and desflurane caused only a small decrease in sROR, which reached statistical significance only in the desflurane group. However, during 1.5 MAC isoflurane and desflurane, the static autoregulatory response was impaired, as indicated by a corresponding increase in Vmca with the increase in MABP and a significantly reduced sROR ($P < 0.001$; fig. 4). During propofol anesthesia, Vmca did not change with the increase in MABP at either low dose or high dose, resulting in no significant sROR changes throughout the study (fig. 4).

Table 3. Physiologic Parameters during Static Cerebral Autoregulatory Tests

	Isoflurane (n = 6)	Desflurane (n = 6)	Propofol (n = 6)
Baseline			
MABP (mmHg)	80 ± 6	87 ± 6	75 ± 2
Pa_{CO_2} (mmHg)	39 ± 1	38 ± 2	37 ± 1
Vmca ($cm \cdot s^{-1}$)	61 ± 10	66 ± 9	47 ± 3
Low dose			
MABP (mmHg)	81 ± 2	86 ± 6	75 ± 2
Pa_{CO_2} (mmHg)	39 ± 1	37 ± 1	36 ± 1
Vmca ($cm \cdot s^{-1}$)	69 ± 12	72 ± 10	37 ± 5*†
High dose			
MABP (mmHg)	80 ± 4	89 ± 6	76 ± 2
Pa_{CO_2} (mmHg)	38 ± 1	35 ± 1	36 ± 1
Vmca ($cm \cdot s^{-1}$)	71 ± 15	84 ± 10*	33 ± 3*†

Values are mean ± SE. Baseline = nitrous oxide + fentanyl; Low dose = 0.5 MAC for volatile anesthetics, 100 $\mu g \cdot kg \cdot min^{-1}$ for propofol; High dose = 1.5 MAC for volatile anesthetics, 200 $\mu g \cdot kg \cdot min^{-1}$ for propofol; HR = heart rate; MABP = mean arterial blood pressure; Pa_{CO_2} = arterial CO_2; Vmca = mean cerebral blood flow velocity in the middle cerebral artery.

* Significantly different *versus* baseline (for high dose desflurane and propofol Vmca $P < 0.001$, low dose propofol Vmca $P < 0.01$).

† Significantly different *versus* the other two anesthetics (low dose propofol Vmca *vs.* isoflurane and desflurane $P < 0.01$, high dose propofol Vmca *vs.* isoflurane and desflurane $P < 0.001$).

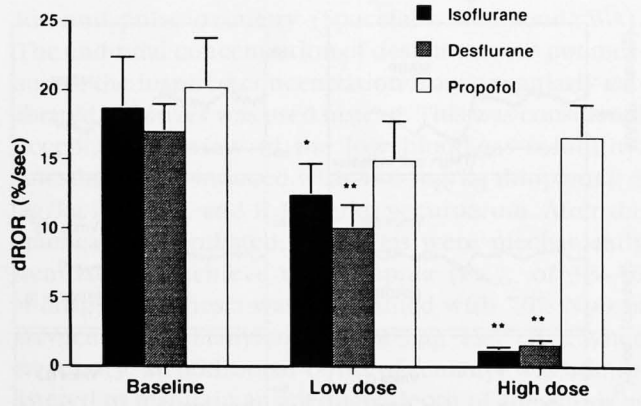

Fig. 2. Dynamic rate of regulation (dROR) during BASELINE (fentanyl + nitrous oxide), LOW DOSE (0.5 MAC for volatile anesthetic, 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for propofol), and HIGH DOSE (1.5 MAC for volatile anesthetic, 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for propofol) anesthetics. Values are mean ± SE. *$P < 0.05$ *versus* baseline. **$P < 0.001$ *versus* baseline. Values of dROR observed in all three groups during fentanyl/nitrous oxide anesthetic were similar to previously awake values.[19] Both volatile anesthetics decreased dROR in a dose-related manner, with almost complete absence of dynamic autoregulation during 1.5 MAC. In contrast, propofol had no significant effect on dROR with either dose.

Discussion

We demonstrated in this study that anesthetic agents may influence the cerebral autoregulatory capacity; inhaled agents such as isoflurane and desflurane preserve autoregulation at 0.5 MAC but not 1.5 MAC, whereas the intravenous anesthetic propofol had no effect on autoregulation.

The cerebral autoregulatory mechanism is likely to be a homeostatic control system based on feedback.[23] Such systems can be characterized by both dynamic and static performance criteria. For dynamic testing, it is necessary to induce a rapid change in MABP so that

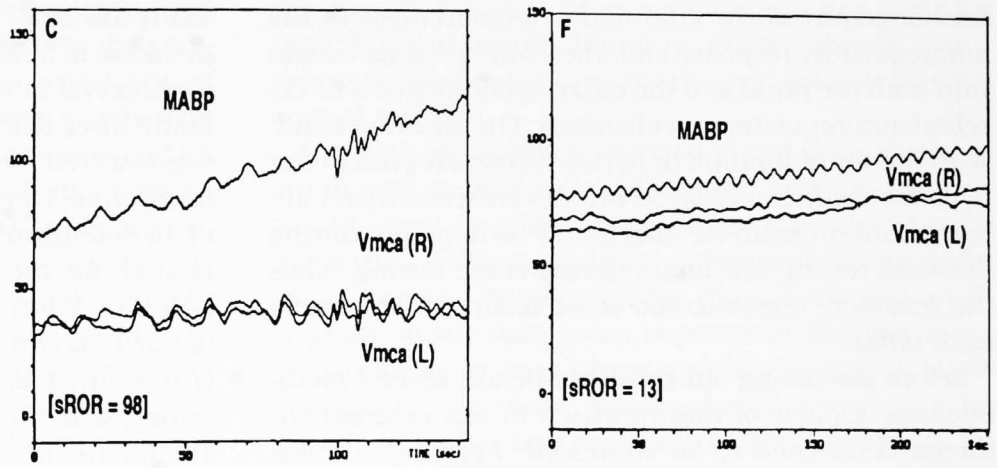

Fig. 3. Recordings of the study of static autoregulation. Simultaneous change in mean arterial blood pressure (MABP) and bilateral middle cerebral artery blood flow velocity with infusion of phenylephrine are shown. (*Left*) Normal static autoregulation with unchanged Vmca during the MABP increase. (*Right*) Impaired autoregulation.

the transient response can be seen. Drug-induced changes in MABP are too slow to be used for such tests; therefore, we employed a direct mechanical method of lowering the MABP. In contrast, for a static test, the ability to correct for a disturbance is measured after the dynamics have settled. For such a test, it is necessary to have a relatively prolonged change in MABP, which in practical clinical testing, only can be achieved by the administration of a drug without direct cerebral effects, such as phenylephrine.

Cerebral autoregulation traditionally has been assessed by repeated static measurements of CBF. Various indicator methods have been used to obtain these measurements at different blood pressure levels.[1,24] The methodology and techniques, because of the poor temporal resolution, can measure static changes only after a steady-state has been achieved, usually in minutes rather than seconds. Cerebral autoregulation, however, is a complex process composed of several physiologic mechanisms operating possibly at different rates.[25–27] Observations on the reaction of the CBF to different levels of perfusion pressure suggest that pressure-induced changes of CVR consist of two components; a rapid response sensitive to pressure pulsations followed by a slow response to changes in mean pressure.[28] There is considerable experimental evidence of the initial fast component of cerebral autoregulation.[28–31] In cats, 2–3 s of hypotension had been found sufficient to initiate compensatory pial vasodilation, and within 3–7 s, a 10% increase in vessel diameter was observed.[29] In rabbits, an autoregulatory plateau was reached 3–13 s after hypotension.[30] In humans, intraoperative CBF measurements with electromagnetic flowmeters placed round the intracranial carotid artery recorded an almost immediate compensatory vasodilation from collateral circulation after proximal carotid artery occlusion.[31] In addition, a rapid autoregulatory response to sudden hypotension was noted, with reestablishment of flow in less than 5 s.[32] Transcranial Doppler ultrasonography studies have confirmed the presence of these fast autoregulatory responses; CBF velocity as an index of CBF was fully restored to the baseline value as early as after 5–8 s after a step decrease in MABP.[19] Conventional CBF measurement techniques with the inability to record instantaneous changes probably would miss these initial fast components and, therefore, at best can be characterized as an incomplete assessment of the cerebral autoregulatory response. Studies with TCD ul-

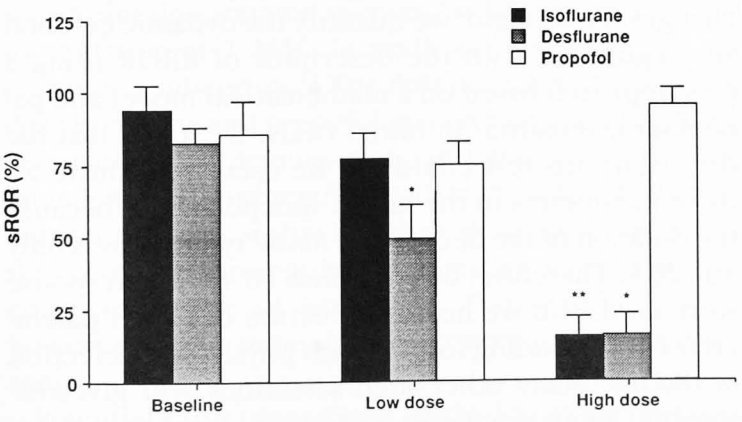

Fig. 4. Index of static rate of regulation (sROR) during BASELINE (fentanyl + nitrous oxide), LOW DOSE (0.5 MAC for volatile anesthetic, 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for propofol), and HIGH DOSE (1.5 MAC for volatile anesthetic, 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for propofol) anesthetics. Values are mean ± SE. *$P < 0.05$ *versus* baseline. **$P < 0.001$ *versus* baseline. Values of sROR ranged between 85% and 95% during baseline fentanyl/nitrous oxide anesthesia, and there were no intergroup differences. Low-dose desflurane resulted in a slight decrease in sROR, whereas in high doses of both isoflurane and desflurane significantly decreased sROR.

trasonography allow continuous measurement of the autoregulatory response and, therefore, provide insight into both the rapid and the delayed components of cerebral autoregulatory mechanisms. On the other hand, with the short duration of hypotension achieved in our dynamic testing, a delayed but nevertheless intact autoregulation would be interpreted as impaired during dynamic testing but intact during static testing. Thus the results of dynamic and static testing complement each other.

Before discussing our results in detail, several methodologic aspects of this approach to test cerebral autoregulation need to be addressed: (1) TCD ultrasonography provides a rapid and noninvasive assessment of cerebral hemodynamics in which flow velocity in large intracranial vessels can be measured with ultrasound signals transmitted through the skull.[33] However, TCD ultrasonography cannot provide absolute measures of CBF but rather offers an accurate assessment of relative changes in CBF.[34] Flow velocity is proportional to flow provided the diameter of the vessel does not change and, therefore, can serve as a continuous index of blood flow through the insonated vessel. (2) The validity of the assumption that CBF is proportional to Vmca depends on the premise that the cross-sectional area of the MCA does not significantly change during induced MABP changes. Studies using TCD ultrasonography for dynamic autoregulation analysis demonstrated no difference in percentage change between Vmca and CBF (based on simultaneous venous outflow or internal carotid artery blood flow) during step-wise changes in MABP.[20,35] Additionally, these findings are consistent with comparison studies using electromagnetic flowmetry as a reference in which a close linear correlation was found between flow velocity and volume flow during moderate changes in arterial blood pressure.[36] Direct observation of the MCA during craniotomy has indicated that the diameter of this artery changes only slightly (2.5%) during moderate MABP changes, a degree of change that probably will not cause an appreciable discrepancy between velocity and flow for most TCD applications.[37] (3) The ideal stimulus to test cerebral autoregulation is with an abrupt change in cerebral perfusion pressure and not MABP. However, in subjects without intracranial pathology, changes in MABP should approximate changes in cerebral perfusion pressure. Similarly, in our study, changes in jugular or central venous pressure with cuff deflation are ignored. This is considered acceptable because the potential decrease in venous pressure is likely too small to affect the vasodilating stimulus. The decrease in MABP should be maintained during the entire interval in which autoregulation study takes place. MABP after deflation of the thigh cuffs in our studies was lowered for only 10–20 s before it began to return to baseline. During normocapnia, however, this period of hypotension was observed to be sufficiently long enough for the brain to autoregulate with full restoration of Vmca to baseline.[19,20] The built-in software of our TCD equipment accordingly analyzed the period (from 1 to 10 s after the decrease in blood pressure) during which the step decrease in MABP occurs. (4) The relatively carbon dioxide-rich blood from the legs after cuff deflation, with its potential influence on the cerebrovascular tone, is a possible source of error in our experimental design. However, it is estimated that the transport time from the legs to the cerebrovascular system is approximately 15 s, by which time the data for analysis would have been collected.[19] The duration of ischemia (3 min) is insufficient to raise the systemic carbon dioxide after reperfusion. (5) Various authors have given different criteria to assess cerebral autoregulation. In almost all cases, the ability of the brain to autoregulate CBF was qualified as being either absent or present based on an arbitrarily defined value of the equation $\Delta CBF/\Delta MABP$. Cerebral autoregulation, however, probably is not an all-or-none phenomenon and can exhibit incremental impairments in both magnitude and rate of response. The key issue in autoregulation is whether CVR changes in response to pressure changes. To this end, we quantify the dynamic cerebral autoregulation with the descriptor of dROR using a new approach based on a mathematical model and parameter estimation. In initial trials, we found that the data from this test could not be used to estimate all three parameters in the model independently because the duration of the decrease in MABP typically was only 10–20 s. Therefore, only the first 10 s of the response were used, and we made a selection of model parameters corresponding to a relevant physiologic selection of dRORs. Many other such selections will give reasonably good predictions of the autoregulatory response. However, only one dROR will match the observed response, and this is the reason we selected the dROR to express the dynamic characteristics and not the parameters themselves. A decreased dROR can result from a delayed (because the hypotension is not sustained) or an abolished autoregulatory response. Correspondingly, we defined the descriptor of static cerebral autoregulation sROR as $\%\Delta CVR/\%\Delta MABP$. Al-

though we only used two points (at the beginning and the end of a 20-mmHg increase in MABP) for the computation of sROR, the continuous measurement of Vmca verifies the presence of a relatively steady-state of surgical stimulation, because fluctuation in the intensity of surgical stimulation might lead to corresponding fluctuation in Vmca. Thus TCD ultrasonography may provide a more accurate assessment of cerebral autoregulation than do conventional methods. The two derived parameters allow us to assess the dynamic time-related change and the static response of the cerebral autoregulatory mechanism. The normalization inherent in these derivations allow an accurate intragroup and intergroup comparison independent of the baseline Vmca variability. (6) We did not study cerebral autoregulation while the subjects were awake, thus true control values were lacking. However, fentanyl/nitrous oxide anesthesia is an acceptable substitute for control as dROR and sROR approached expected awake values of 0.2 and 1.0, respectively (figs. 2 and 4).

Our static autoregulatory results agree with previous data for isoflurane in different animal models, indicating preserved autoregulation at low dose and lost autoregulation at high dose. In dogs, cerebral autoregulation has been reported to be maintained during administration of 1 MAC but not 2 MAC isoflurane anesthesia.[10] Similar results have been reported in humans.[38] Cerebral autoregulation measured in isoflurane-anesthetized rats within different blood pressure ranges produced a significant dose-related increase in CBF and loss of autoregulation at 1 MAC in midbrain and at 2 MAC in cortex and subcortex.[11] The differential effects of high-dose isoflurane and propofol on cerebral autoregulation also have been demonstrated in baboons.[9,12] To our knowledge, no autoregulatory data exist for desflurane. Our results suggest that low-dose desflurane may affect the cerebral autoregulatory capacity more than an equipotent dose of isoflurane. The overall results, however, appear to be similar between the two inhaled agents.

Potential criticisms of our study design include the use of fentanyl/nitrous oxide-anesthetized patients as the control group, and the choice of the anesthetic doses. Nitrous oxide and opioids, however, are assumed not to influence cerebral autoregulation. In humans, cerebral autoregulation was found to be preserved during 70% N_2O.[7] In animals anesthetized with alfentanil, cerebral autoregulation was similar to that in animals anesthetized without opioids.[39] As mentioned above, our dynamic autoregulatory results at baseline compare favorably with results found in awake subjects,[19] and the static autoregulatory results are consistent with normal values.

Although blood levels of fentanyl and propofol were not drawn, we had assumed that the infusion regimen would result in relatively steady-state levels. Because our results indicate that neither fentanyl nor propofol affects cerebral autoregulation, the maintenance of an absolute steady-state is not imperative. The use of the vasoconstrictive drug phenylephrine to induce MABP changes in the static autoregulatory tests might be questioned. Although vasopressor agents generally are considered to have limited vasoconstrictive effect on the cerebral vasculature, their effect on intracerebral dynamics is not consistent, although the difference may be due to *in vivo*[40] *versus in vitro*[41] experimental settings. In animal experiments, cerebral vasoconstriction after phenylephrine infusion has been demonstrated.[42,43] However, our findings demonstrated no relevant cerebrovascular effect of phenylephrine. Any cerebral vasoconstrictive effect would have reduced Vmca unless the cross-sectional area of the Vmca is reduced by a proportional amount. However, direct intraoperative measurement of Vmca diameter has reported a negligible effect from phenylephrine.[37] The fact that an equivalent increase in MABP induced with phenylephrine caused no change in Vmca during propofol anesthesia and an increase in Vmca during volatile anesthetics (with 1.5 MAC) suggests that a relevant cerebral vasoconstrictive effect of phenylephrine does not exist, and the results reflect autoregulation changes.

It is possible that dynamic and static autoregulation, as tested in the current study, using different stimuli (transient hypotension *vs.* static hypertension) and different limbs of the autoregulatory curves (decrease *vs.* increase in MABP), do not measure the same regulatory mechanism. This possibility is not supported by the reasonably good concordance of results observed. However, the difference observed between dynamic and static autoregulation during 0.5 MAC inhaled anesthetic suggests that the dynamic process is impaired before the static process.

Our data provide no insight into the mechanisms by which anesthetics influence cerebral autoregulation. Cerebral autoregulation is known to be easily influenced by physiologically and pharmacologically induced changes in vasomotor tone: cerebral autoregulation was found to be perturbed during hypercapnia and restored after normalization of Pa_{CO_2}.[44] Because all

volatile anesthetics have some cerebral vasodilating properties (in high doses) in contrast to intravenous anesthetics, which generally have vasoconstrictive capabilities (with the exception of ketamine), this difference in vasomotor tone might explain the impaired autoregulation during high-dose volatile anesthesia. Our data do not reveal which of several proposed mechanisms of cerebral autoregulation may be operative. However, the similarity in the time response between metabolic mediated responses and autoregulatory responses suggests a metabolic mechanism.

In summary, cerebral autoregulation is significantly influenced by anesthetics. During 0.5 MAC isoflurane and desflurane anesthesia, dynamic cerebral autoregulation is reduced, and static autoregulation is only minimally affected, suggesting that the autoregulatory process is delayed but preserved; whereas, during 1.5 MAC, cerebral autoregulation is absent. In contrast, during propofol anesthesia, cerebral autoregulation is not affected. Although we studied only neurologically normal patients, these findings may have relevant clinical implications in patients with neurologic disorders.

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Appendix

The normal autoregulatory response is accomplished during 5–7 s with a smooth transition directly back to control flow.[20] However, if the test is performed during hyperventilation, the response is faster and may overshoot. A damped oscillatory transition back to control values is seen.[19,20] The simplest dynamic mathematical model to describe such responses is a linear second-order differential equation. We used data from earlier investigations[19,20] to determine a set of parameters (see below) that would provide dROR values to cover the physiologic range from no autoregulation to the fastest response seen to date in more than 500 measurements.

The response of this mathematical model is shown for various such sets of parameters in figure 5. The model is driven by an ideal 100% step in MABP. The dROR is the steepest slope of the response. The slope expresses the rate of regulation (%/s) during the period of maximal change in cerebrovascular resistance or tone. The procedure for determining dROR using this model is as follows:

1. Both the MABP and Vmca tracings were filtered by a fourth-order low-pass filter at 0.5 Hz to remove pulsatility and determine the respective time courses of the means (MABP and Vmca). The relative amplitude and phase relationships between the measurements were not changed by this procedure.
2. Control MABP and control Vmca were determined during the 5–10-s interval immediately before cuff release.
3. We used the MABP time-course as input to the mathematical model for all ten parameter sets. The error of the prediction was determined by subtracting Vmca from the model velocity (mV). The root-mean square of the error (RMSe) was calculated for the interval from 1 to 10 s after the blood pressure step decrease. The dROR, with its corresponding set of parameters, that gave the least RMSe was assigned to this test. Typical differences between measurement and model predictions are illustrated in figure 2. In most cases, this model predicted Vmca accurately (RMSe < 2.5%).

The effect of the cerebral autoregulation on mean velocity (mV) was approximated by a second-order linear differential equation set

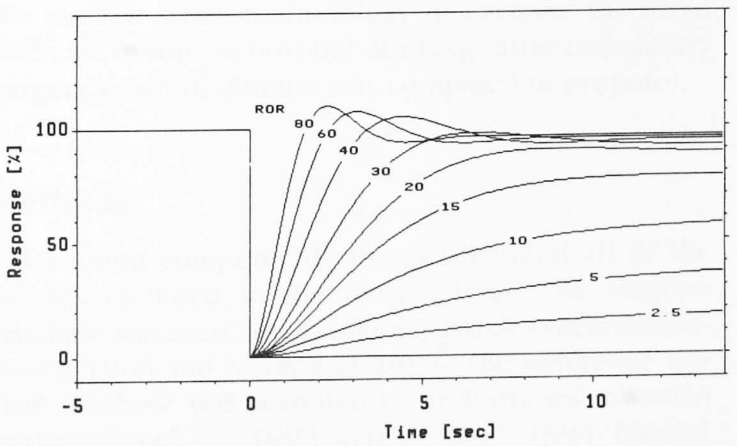

Fig. 5. Responses of the mathematical model of the cerebral autoregulation to an ideal step in arterial blood pressure at time 0. Ten parameter sets (Appendix) were selected to give responses with rates of regulation from 0 to 80, with 20 being the "normal" response.

with state variables x_1 and x_2, which were assumed to be equal to zero during the control period. After the step change in MABP, these equations were solved by the computer in time interval steps of 100 ms (corresponding to a sampling rate f = 10Hz) by the following algorithm:

$$dP = (MABP - cABP)/(cABP - CCP)$$

$$x_2 = x_2 \div (x_1 \cdot 2D \cdot x_2)/(f \cdot T)$$

$$x_1 = x_1 \div (dP - x_2)/(f \cdot T)$$

$$mV = cVmca \cdot (1 \div dP - K \cdot x_2).$$

dP is the normalized change in MABP from its control value (cABP) including the effect of the critical closing pressure (CCP), which was assumed to be constant at 12 mmHg in the current study. This parameter later can be estimated individually. MABP was obtained by filtering the pulsatile MABP at 0.5 Hz. cVmca was control velocity in the MCA. The control values were obtained as explained in the Methods section. This mathematical model was characterized by three parameters: T, the time constant; D, the damping factor; and K, the autoregulatory dynamic gain. These parameters were related to dROR as in the following table:

ROR	T (s)	D	K
0.0	—	—	0.00*
2.5	2.00	1.60	0.20
5.0	2.00	1.50	0.40
10.0	2.00	1.15	0.60
15.0	2.00	0.90	0.80
20.0	1.90	0.75	0.90†
30.0	1.60	0.65	0.94
40.0	1.20	0.55	0.96
60.0	0.87	0.52	0.97
80.0	0.65	0.50	0.98‡

* No autoregulation.

† "Normal" autoregulation.

‡ Fastest autoregulation.

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Comparisons betu Propofol on Time to Discharge

A Metaanalysis

Franklin Dexter, M.D., Ph.D.,* John H.

Background: Anesthesiologists can b use desflurane based on the magnitudes to other general anesthetics. The goa estimate the mean decrease in times t when desflurane was being used instea pofol. The mean decrease in time to h ambulatory surgery when desflurane w pofol also was examined.

Methods: Published studies that met lected up to November 1994. Include patients were randomly assigned to g planned at the end of surgery, and g induced with an intravenous agent. W metaanalysis to calculate confidence int differences.

Results: Six studies (with 229 patien flurane to propofol met the inclusion (with 316 patients) compared desflura tistically significant difference in the mands after discontinuation of desfl (mean difference 0.7 min (propofol confidence interval − 0.2 to 1.7 min) who received propofol were discharg 17 min (4–30 min) more quickly than desflurane. Patients who received des mands a mean of 4.4 min (3.3–5.4 min) patients who received isoflurane.

Conclusions: There are only minor c ferences between desflurane and isofl respect to time to following commands
(Key words: Anesthesia recovery peri

* Assistant Professor.

† Professor; Head.

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Address correspondence to Dr. Dexter: D University of Iowa, College of Medicine, City, Iowa 52242-1079.

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