Comparison of Static and Dynamic Cerebral Autoregulation Measurements

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Background and Purpose Cerebral autoregulation can be evaluated by measuring relative blood flow changes in response to a steady-state change in the blood pressure (static method) or during the response to a rapid change in blood pressure (dynamic method). The purpose of this study was to compare the results of the two methods in humans with both intact and impaired autoregulatory capacity.

Methods Using intraoperative transcranial Doppler sonography recordings from both middle cerebral arteries, we determined static and dynamic autoregulatory responses in 10 normal subjects undergoing elective surgical procedures. The changes in cerebrovascular resistance were estimated from the changes in cerebral blood flow velocity and arterial blood pressure in response to manipulations of blood pressure. Static autoregulation was determined by analyzing the response to a phenylephrine-induced rise in blood pressure, whereas rapid deflation of a blood pressure cuff around one thigh served as a stimulus for testing dynamic autoregulation. Both measurements were performed in patients with intact autoregulation during propofol anesthesia and again in the same patients after autoregulation had been impaired by administration of high-dose isoflurane.

Results There was a significant reduction in autoregulatory capacity after the administration of high-dose isoflurane, which could be demonstrated using static ($P<.0001$) and dynamic ($P<.0001$) methods. The correlation between static or steady-state and dynamic autoregulation measurements was highly significant ($r=.93$, $P<.0001$).

Conclusions These data show that in normal human subjects measurement of dynamic autoregulation yields similar results as static testing of intact and pharmacologically impaired autoregulation. (***Stroke.* 1995;26:1014-1019.**)

Key Words • autoregulation • blood flow velocity • cerebral blood flow • ultrasonics

Cerebral autoregulation (CA) refers to the ability in the brain to maintain constant blood flow despite changes in cerebral perfusion pressure.[1-3] In the past, evaluation of CA was performed under steady-state conditions: a measurement of cerebral blood flow (CBF) is obtained first at a constant baseline arterial blood pressure (ABP) and constant CBF, followed by another (steady-state) measurement that is taken after the autoregulatory response to a manipulation of ABP has been completed. We have termed this method "static" autoregulation testing. If the blood flow changes significantly with either an increase or a decrease in ABP, CA is said to be impaired. If blood flow is maintained at or near the baseline level, despite a change in ABP, CA is said to be intact.[1-3] This method to evaluate CA requires time-consuming and/or invasive procedures such as the Kety-Schmidt technique[4] or ^{133}Xe measurements[5] and manipulations of the blood pressure using vasoactive medications.

Aaslid et al[6] introduced a noninvasive method using transcranial Doppler ultrasonography (TCD) to evaluate CA in humans. This "dynamic" approach uses the rapid drops in ABP caused by the release of thigh blood pressure cuffs as an autoregulatory stimulus and compares ABP and CBF velocity (CBFV) during the autoregulatory process. The validity of this method was questioned at the time because of the use of CBFV instead of CBF,[7] but the method has subsequently been validated.[8-10] It has also been shown recently by comparison of TCD with CBF measurements according to the Fick principle that TCD is valid for static, or steady-state, measurements of CA.[11]

Static measurements evaluate the overall effect (efficiency) of the autoregulatory action, ie, the change in cerebrovascular resistance (CVR) in response to the manipulation of ABP, but they do not address the time in which this change in CVR is achieved (its "latency"). Measurement of the dynamic response, however, yields information about the latency as well, which may be relevant in certain clinical conditions including head injury. Preliminary data (Aaslid et al, unpublished data, 1994) suggest that progressive impairment in autoregulation first affects the latency and then the efficiency of the autoregulatory response. However, we are aware of no clinical study that systematically compares static and dynamic autoregulation in the same individuals.

Therefore, our study investigated whether both methods correlate in patients with normal autoregulation and whether they show differences if autoregulation is impaired. Using TCD and ABP recordings, we studied both dynamic and static autoregulatory responses with intact autoregulation during propofol anesthesia and then again during high-dose isoflurane anesthesia. Isoflurane is known to impair CA in a dose-dependent manner,[12-15] whereas intravenous agents like propofol have little or no effect on CA.[14,16] Static and dynamic measurements of intact and impaired autoregulation were performed and analyzed to compare the results of the two measurement techniques.

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TABLE 1. General Patient Data

Patient No.	Age, y	Weight, kg	HR, bpm	ABP, mm Hg	P_{CO_2}, mm Hg	Left CBFV, cm/s	Right CBFV, cm/s
1	35	50	53	79	37	39	33
2	40	75	59	100	38	30	34
3	20	85	71	71	40	60	62
4	41	100	84	81	38	32	26
5	27	69	68	70	38	31	29
6	54	95	72	80	39	24	22
7	46	115	61	76	36	20	18
8	36	85	86	81	37	44	47
9	28	97	59	63	36	18	23
10	27	74	82	86	31	53	47
Mean±SD	35±10	85±18	70±12	79±10	37±2	35±14	34±14

HR indicates heart rate; bpm, beats per minute; ABP, arterial blood pressure; P_{CO_2}, arterial carbon dioxide pressure; and CBFV, cerebral blood flow velocity.

Subjects and Methods

Ten adults (8 men and 2 women of physical status grade 1 or 2 according to the American Society of Anesthesiology) undergoing elective orthopedic surgery took part in the trial. The study was approved by the University of Washington Human Subject Review Committee, and written informed consent was obtained from each subject. A history or signs of cerebrovascular or cardiac disease and the use of psychoactive drugs were the exclusion criteria for the study. Anesthesia was induced with 2 to 2.5 mg/kg propofol, 3 μg/kg fentanyl, and 0.1 mg/kg vecuronium and was maintained with 50% nitrous oxide in oxygen and 2 μg/kg per hour of fentanyl infusion in addition to either propofol or isoflurane. Additional doses of vecuronium were given as needed.

After intubation of the trachea, ventilation was adjusted to provide constant normocapnia as determined by repeated blood gas sampling. A phenylephrine infusion was maintained and titrated to keep the mean blood pressure between 70 to 80 mm Hg before steady-state testing. The first series of tests was performed during infusion of 180 to 200 μg/kg per minute of propofol. Then propofol was stopped, and isoflurane was given to maintain a steady-state end-tidal concentration of 1.3% to 1.6%. At least 30 minutes was allowed to elapse after the propofol infusion had been discontinued, and 15 minutes of unchanged end-tidal isoflurane concentration was permitted before the second series of testing started.

In addition to routine monitoring including invasive ABP measurement, both middle cerebral arteries (MCAs) were identified by TCD according to standard criteria.[17] The transducers were then fixed in place with a custom-designed frame, and CBFV was continuously monitored at the depth of the best signal (44 to 50 mm) with TCD equipment (Multidop X, DWL) that provided simultaneous display and recording of ABP and CBFVs.

Static CA was tested by slow continuous infusion of phenylephrine to induce an increase in mean ABP of approximately 20 mm Hg (to not more than 110 mm Hg) while ABP and CBFV were continuously recorded. Static autoregulation (sCA) was calculated as the percentage change in estimated cerebrovascular resistance (CVR_e) in relation to the change in ABP over the entire period of time needed for an ABP increase from baseline (1) to the higher level (2). Estimating CVR_e as CVR_e=ABP/CBFV, we calculated static CA as sCA=(%ΔCVR_e/%ΔABP)×100% with %ΔCVR_e=(CVR_e2−CVR_e1)/CVR_e1 and %ΔABP=(ABP2−ABP1)/ABP1.

Thus, static CA values are expressed as a percentage of full autoregulatory capacity. A change in CVR that would fully compensate for the drop in ABP would yield a static CA of 100%, and no change in CVR would yield a static CA of 0%.

Dynamic CA was assessed as previously reported[6] with the induction of a rapid-step decrease in ABP and comparison of the temporal courses of the return of ABP and CBFV to baseline. The ABP drop was achieved with the sudden release of a large blood pressure cuff around one thigh, which had been inflated to 30 mm Hg above the systolic ABP for 3 minutes. To test dynamic CA at the same ABP range as static CA, phenylephrine was titrated to maintain ABP at the upper level of the previous steady-state measurement (ie, at 90 to 100 mm Hg). Only steep drops in ABP of more than 15 mm Hg from this level were considered to be a sufficient stimulus. ABP normally remains lowered for approximately 20 seconds before gradually returning to its initial level. CBFV, in contrast, returns more rapidly to its initial level, depending on the autoregulatory ability.[6]

The CBFV and ABP values after the cuff release are used to calculate an autoregulatory index that reflects the change in CVR per second in relation to the change in ABP. Triggered at the moment of the cuff release and based on the actual ABP curve of the following 30 seconds, a hypothetical CBFV curve without autoregulation is calculated by computer for this time span. This curve assumes that the CBFV passively follows the course of the ABP, ie, that the percentage changes in CBFV are equal to those of the ABP. If then, for example, the actual CBFV curve from a given test fit this computer model perfectly, the autoregulatory index would be 0. Nine other different computer models of possible CBFV curves are calculated as well, each assuming a higher degree of autoregulatory capacity (see "Appendix"). Each model curve is compared to the actual CBFV recordings for the best fit (ie, the lowest standard error of the mean of the differences between the actual and each hypothetical curve at each of the 30 seconds after the cuff release). The chosen model that best fits the actual CBFV curve is superimposed onto the actual CBFV curve on the screen for visual control of the fit (see Fig 2).

Higher autoregulatory values indicate increasingly better dynamic CA. For example, under resting conditions (light propofol anesthesia) our subjects had a mean autoregulatory index of about 5 (4.8±1.0, mean±SD).

All calculations were performed off-line using the time-averaged mean velocities of the maximum velocity outlines of the Doppler spectrum and mean ABP. Values for each MCA were analyzed separately. Data were analyzed using Student's *t* test and simple regression analysis and are shown as mean±SD.

Results

Demographic data and results for heart rate, P_{CO_2}, baseline ABP, and velocities after induction of anesthesia are presented in Table 1. Table 2 shows the ABP, CBFV, and autoregulatory data with intact autoregulation under propofol anesthesia (top) and impaired autoregulation under isoflurane anesthesia (bottom). No significant difference in baseline variables, including

TABLE 2. Changes During Autoregulatory Testing: Propofol and Isoflurane

Patient No.	ABP, mm Hg		CBFV, cm/s				Static CA, %		ABP Drop, mm Hg	Dynamic CA	
			Baseline		End						
	Baseline	End	Left	Right	Left	Right	Left	Right		Left	Right
Propofol											
1	79	96	41	33	38	32	100	100	15	6	5
2	98	118	25	28	24	27	100	100	24	5	4
3	72	93	58	60	61	63	85	86	20	4	5
4	82	113	38	30	38	31	96	94	15	6	5
5	81	111	34	34	40	39	44	52	17	3	3
6	80	109	24	21	27	24	58	53	20	4	3.5
7	82	115	24	21	24	20	100	100	18	6	6
8	81	109	44	47	45	50	91	74	24	6	5
9	87	106	26	34	24	32	100	100	28	5	5
10	89	109	60	51	60	53	100	61	24	4.5	4.5
Mean±SD	83±7	108±8*	37±13	36±13	38±14	37±14	87±20	82±10	21±4	4.9±1.0	4.6±0.9
Isoflurane											
1	70	94	44	34	68	51	22	27	15	1	2
2	103	121	29	33	31	36	57	44	24	3	2
3	71	87	72	74	75	77	78	79	17	3.5	3.5
4	83	112	59	51	83	68	0	3	17	2	2
5	77	105	58	61	78	83	4	0	16	1	0
6	64	100	33	28	48	43	13	3	16	1	1
7	79	99	34	30	39	34	36	42	25	2	2.5
8	78	98	60	62	70	74	30	21	19	2.5	2
9	85	104	32	46	38	54	22	23	18	1.5	1.5
10	82	102	103	98	110	104	65	67	24	4	4
Mean±SD	80±11	102±9*	52±23	52±23	64±25	62±23	33±26†	31±27†	19±4	2.2±1.1†	2.1±1.1†

ABP indicates arterial blood pressure; CBFV, cerebral blood flow velocity; CA, cerebral autoregulation; ABP drop, drop in ABP due to cuff release (from the level of ABP end); baseline, beginning of static testing; and End, end of static testing.

*Significant difference between beginning and end of static testing ($P<.05$ by Student's t test).

†Significant difference between isoflurane and propofol ($P<.05$ by Student's t test).

P_{CO_2}, was noted between the two test series other than a significant increase in CBFV from 38 cm/s under propofol anesthesia to 51 cm/s under isoflurane anesthesia ($P<.0001$).

Static Autoregulation

During testing of static CA, phenylephrine raised ABP in both series by a mean of 24±4 mm Hg, without a significant difference between the two test series. Typical examples of individual subjects for ABP and CBFV recordings during static testing with intact (propofol) and impaired (isoflurane) autoregulatory capacity are shown in Fig 1. Characteristically, with propofol the rise in ABP showed only little effect on CBFV, whereas high-dose isoflurane often produced a pressure-passive change in CBFV. The mean reduction in static CA from 85±20% to 37±30% was significant ($P<.0001$), although autoregulation was preserved to a variable degree in some individuals.

Dynamic Autoregulation

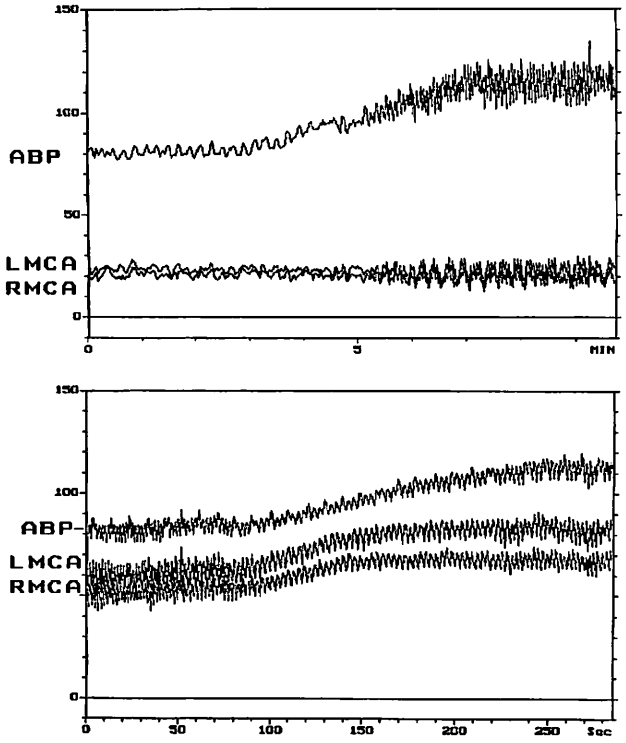
Typical recordings of dynamic autoregulation testings of individual subjects are displayed in Fig 2. The mean drop in ABP that was induced by the cuff release was 20±4 mm Hg (range, 15 to 28 mm Hg; a drop of less than 15 mm Hg was not acceptable and occurred in three subjects, all of whom demonstrated major drops after repetition of the test). Similar to static CA, the dynamic response showed a clear impairment with isoflurane. The autoregulatory index dropped from 4.8±1.0 with propofol to 2.3±1.3 with isoflurane ($P<.0001$). There were only two subjects (patients 3 and 10 in Tables 1 and 2) in whom dynamic CA was not markedly reduced by high-dose isoflurane. These individuals also demonstrated little or no impairment during static testing. Interestingly, those two subjects were the youngest. There was no other characteristic variable that distinguished these subjects from the others.

Simple regression analysis comparing all corresponding static and dynamic data shows a good correlation between static and dynamic CA ($r=.93$, $P<.0001$; Fig 3).

Discussion

We have shown that static, or steady-state, and dynamic tests of autoregulation yield similar results in normal anesthetized adults with intact or impaired autoregulation, thus demonstrating a good correlation between both methods.

Before we discuss the theoretical and clinical implications of our findings, several methodological aspects of the study require discussion. First, patient selection and concomitant drug administration, as well as the circumstances of surgery, may have had an influence on the results. We chose a sample of relatively young patients undergoing elective surgery without any evidence of cerebrovascular or cardiac disease to minimize the chance of preexisting abnormalities or possible inhomogeneity. We did not randomize the anesthesia sequence of the study because we wanted to verify that patients studied had intact autoregulation at the outset. We also tried to avoid testing during peaks of surgical stimulation; however, there still may have been differences in CBFV from surgical stimulation, since sensory stimulation in the periphery is associated with an increase in

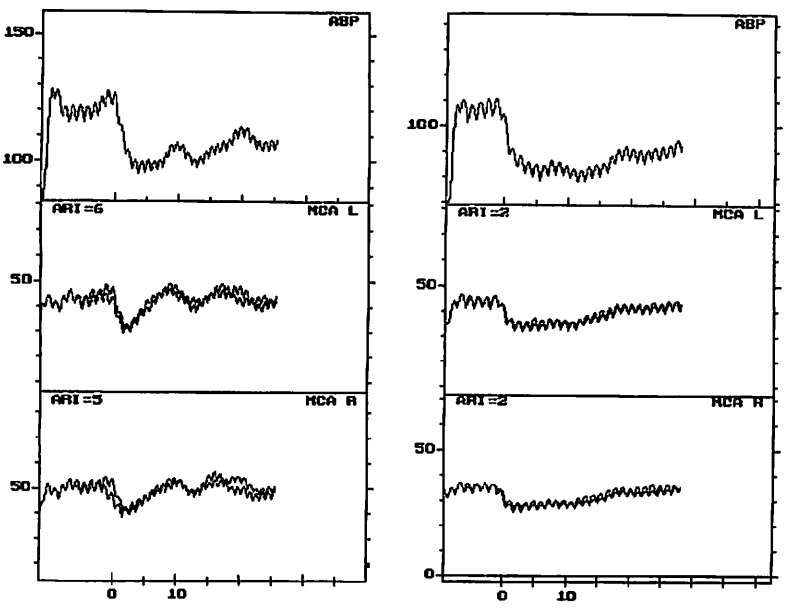


Static autoregulation tests from individual subjects with intact (top) and impaired (bottom) autoregulation. *Y* axis, mean arterial blood pressure (ABP) in millimeters of mercury and mean velocities in the left (LMCA) and right (RMCA) middle cerebral arteries in centimeters per second; *X* axis, time in minutes and seconds. Although with intact autoregulation (with propofol anesthesia) velocities remain constant during an increase in ABP (top), they passively follow the increase in ABP if autoregulation is impaired by isoflurane (bottom).

CBF in the contralateral hemisphere.[18] Data analysis from our bilateral recordings, however, did not reveal marked side-to-side differences. Moreover, we also allowed a period of stable velocity before proceeding with the study.

Second, the concomitant drugs that were used during the induction and maintenance of anesthesia and to maintain or raise ABP are very unlikely to affect any aspect of CA. Fentanyl[19] and nitrous oxide[12] are not known to cause impairment of autoregulation. Additionally, if these agents had an effect on CA, one would expect this to affect both static and dynamic CA, although a differential effect could theoretically occur. Phenylephrine, which was used not only to raise ABP for static testing but also to maintain it in the respective desired range, could interfere with CA measurements if it had a direct vasoconstrictive effect on cerebral resistance vessels or the MCA. It was shown, however, by ^{133}Xe CBF measurements that intracarotid application of epinephrine or norepinephrine does not influence regional CBF in humans, nor do these drugs change the diameter of the larger arteries as shown by angiography.[20] In another study it was demonstrated that phenylephrine is able to increase CBF after hemorrhage during isoflurane anesthesia in rats, again suggesting that there is no relevant vasoconstriction of cerebral resistance vessels.[21]

The use of TCD for CBF measurements also must be addressed. A constant diameter of the insonated vessel, ie, the MCA, is required during the autoregulation test to interpret relative changes in CBFV as relative CBF changes.[7] There is, however, considerable evidence that the MCA diameter remains practically constant during different autoregulation tests. It has been demonstrated by simultaneous comparison of CBFV measurements of cerebral arterial inflow and venous return[9] and also by direct correlation with electromagnetic flowmetry[8,10] that MCA velocity measurements during dynamic autoregulation reflect relative changes in blood flow. Moreover, it has been demonstrated recently that CBF measurements using xenon washout and the Fick principle[11] correlated closely with changes in CBFV. Additional evidence for this assumption is derived from experiments in which direct visualization of the MCA during craniotomy revealed no significant change in vessel caliber during changes in ABP.[22] The TCD method therefore appears to be a valid tool to evaluate both dynamic and static CA.



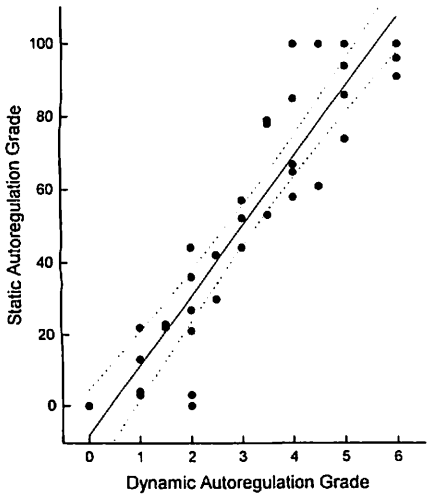
Dynamic autoregulation tests from individual subjects with intact (left) and impaired (right) autoregulation. *Y* axis, mean arterial blood pressure (ABP) in millimeters of mercury and mean velocities in the left (MCA L) and right (MCA R) middle cerebral arteries in centimeters per second; *X* axis, time in seconds. While the upper part of each figure presents the actual ABP recording during the cuff release (onset of time count), the two lower panels display the actual velocity recordings in each MCA with a superimposed curve. This curve represents a velocity course, which was fitted to the actual curve under the assumption of a certain autoregulatory capacity as quantified by the displayed autoregulatory index (ARI). In intact autoregulation (left), the velocities return to baseline considerably faster than the ABP, demonstrating ARIs of 5 and 6, whereas in impaired autoregulation (right) the response is slowed down (ARI of 2).

TABLE 3. Comparison of Autoregulation Index to Rate of Regulation

T, s	D	K	ARI	dROR, %/s
...	0.00	0	0	0 (No autoregulation)
2.00	1.60	0.20	1	2.5
2.00	1.50	0.40	2	5.0
2.00	1.15	0.60	3	10.0
2.00	0.90	0.80	4	15.0
1.90	0.75	0.90	5	20.0 ("Normal" autoregulation)
1.60	0.65	0.94	6	30.0
1.20	0.55	0.96	7	40.0
0.87	0.52	0.97	8	60.0
0.65	0.50	0.98	9	80.0 (Fastest autoregulation)

T indicates time constant; D, damping factor; K, autoregulatory dynamic gain; ARI, autoregulation index; and dROR, dynamic rate of regulation.

Static and dynamic testing of autoregulation may assess some different aspects of the cerebral response to changes in ABP. Autoregulation has been found to be a complex phenomenon, showing heterogeneity in its site and time course of action.[23-25] Since metabolic, myogenic, and possibly endothelium-related mechanisms may be involved,[2,3,24,26-28] several factors may vary depending on the challenging stimulus, the vessel tone, or the degree of impairment of CA. During static testing, our stimulus consisted of an increase in ABP, which should induce vasoconstriction of the resistance vessels to account for the autoregulatory response. During dynamic testing, ABP is lowered, which should lead to vasodilation of the arterioles. Vasoconstriction and vasodilation, however, could depend on different mechanisms of action, which could vary individually or could be affected to a different extent if autoregulation is impaired. Even if the underlying mechanism was the same, it could be hypothesized that the abilities to dilate or constrict the cerebral arterioles may show some normal variability within individuals, which could lead to a less exact correlation if the two methods were compared at intact autoregulation alone.



Graph shows correlation of static and dynamic autoregulation. The values of static and dynamic autoregulatory capacity for each middle cerebral artery are plotted for all measurements, showing a good correlation between static and dynamic measurements ($y=-8.65+19.37x$; $r=.93$, $P<.0001$). Dotted lines indicate 95% confidence intervals.

The vascular tone at the time of testing may affect the autoregulatory response. Aaslid et al[6] have shown that hypocapnia (leading to an increase in vascular tone) enhances dynamic CA, whereas hypercapnia (causing a decrease in vascular tone) reduces the autoregulatory response. Improvement of impaired static CA with hyperventilation has been reported in patients with focal brain lesions, suggesting that the efficiency of static CA also depends on vascular tone.[29] Isoflurane has some intrinsic vasodilatory effect on cerebral arterioles, whereas propofol has vasoconstrictive properties.[30-32] This is the reason for the significant difference in CBFV between the propofol and the isoflurane series. Therefore, it is likely that the vascular tone differed between both series.

The overall correlation between the two methods was good despite these considerations, suggesting that the different aspects of autoregulation respond similarly in intact as well as in severely pharmacologically impaired autoregulatory capacity. Autoregulation, however, is not an "all or none" phenomenon.[25,33-35] Since the ability to autoregulate was almost abolished by the selected dose of isoflurane in most of our patients, the possibility remains that some aspect of autoregulation is affected first if minor impairment occurs. It seems likely, for example, that dynamic CA is initially more reduced than static CA if impairment of the autoregulatory process affects first the latency of CA and then its efficiency. Furthermore, our study cannot answer whether different mechanisms of impairment of autoregulation (eg, intracranial pathology) would lead to different results or whether the correlation would be as close in elderly subjects.

For clinical purposes, however, it seems to be fair to assume that dynamic testing reflects most aspects of the autoregulatory response correctly. Thus, evaluation of dynamic CA by TCD may be useful for patient management. A variety of pathological conditions including brain trauma, subarachnoid hemorrhage, and focal ischemia affect the autoregulatory abilities to a variable extent.[25,33-35] Since in severely impaired CA the brain is obviously no longer protected from the effects of both hyperperfusion and hypotension, and the effect of important drugs (eg, mannitol[36]) might be dependent on intact CA, routine assessment of CA may add useful information in severe cerebral disease. Further studies are needed to determine the role of autoregulation testing in the clinical management of patients with conditions that lead to CA impairment.

Appendix

The effect of the cerebral autoregulation on mean velocity (mV) was approximated by a second-order linear differential equation set with state variables $x1$ and $x2$, which were assumed to be equal to 0 during the control period. After the step in ABP, these equations were solved by the computer in steps of 100 milliseconds (sampling rate, f=10 Hz) by the algorithm

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

$$x2=x2+(x1-2D\cdot x2)/(f\cdot T)$$

$$x1=x1+(dP-x2)/(f\cdot T)$$

$$mV=cVmca\cdot(1+dP-K\cdot x2)$$

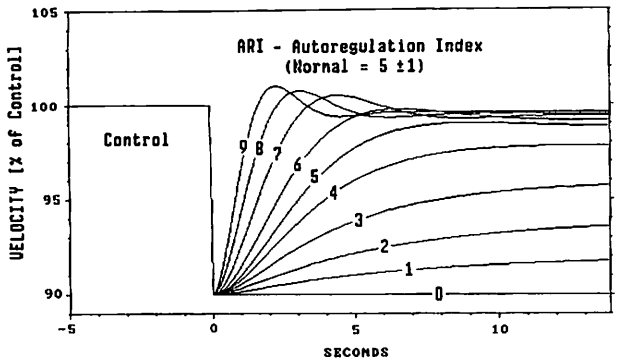


FIG 4. Responses of cerebral autoregulation model to a step change in blood pressure.

where dP is the normalized change in mean arterial blood pressure (MABP) from its control value (cABP), including the effect of the critical closing pressure (CCP), which was assumed to be constant at 12 mm Hg in the present study. (This parameter can later be estimated individually.) MABP was obtained by filtering the pulsatile ABP at 0.5 Hz. cVmca is control velocity in the MCA. The control values were obtained as explained in "Methods." 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 the dynamic autoregulatory index and to the dynamic rate of regulation as shown in Table 3. Figure 4 illustrates autoregulatory responses according to the model.

Acknowledgments

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