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Asymmetric Dynamic Cerebral Autoregulatory Response to Cyclic Stimuli

Rune Aaslid, PhD; Martin Blaha, MD; Gill Sviri, MD;
Colleen M. Douville, BA, RVT; David W. Newell, MD

Background and Purpose—Dynamic cerebral autoregulation has been shown to be fast and effective, but it is not well known if the mechanism is symmetric, that is to say, it acts with equal compensatory action to upward as compared with downward abrupt changes in arterial blood pressure (ABP).

Methods—Fourteen patients with head injuries and 10 normal subjects had bilateral transcranial Doppler and continuous ABP recording. Cyclic ABP stimuli were generated by large thigh cuffs, which were rapidly inflated above systolic pressure for 15 seconds alternating with 15 seconds of deflation. At least 8 such cycles were ensemble-averaged and the dynamic autoregulatory gain (AG_{up} and AG_{dn}) was estimated separately for upward and downward changes in ABP. The results were compared with the autoregulation index using conventional leg cuff releases.

Results—In normal subjects, AG_{dn} was 0.74 ± 0.18 and AG_{up} was 0.77 ± 0.17 (mean$\pm$SD); the difference was insignificant. The correlation between AG_{dn} and AG_{up}, however, was weak ($r=0.24$). In the patients with head injury, AG_{dn} was 0.30 ± 0.21 and AG_{up} was 1.27 ± 0.76, the difference being highly significant ($P<0.001$). There was a negative relationship between AG_{dn} and AG_{up} ($r=-0.33$). Autoregulation index correlated well with AG_{dn} ($r=0.79$) and weakly negatively with AG_{up} ($r=-0.47$).

Conclusions—A strongly asymmetric dynamic response of the cerebral autoregulation was seen the majority of patients with head injury. It might also have been present, albeit to a lesser degree, in the normal subjects. The findings suggest that nonlinear effects may be present in the operation of the cerebral autoregulation mechanism. (*Stroke*. 2007;38:1465-1469.)

Key Words: cerebral autoregulation ■ head injury ■ transcranial Doppler

The cerebral autoregulation mechanism regulates cerebral vascular tone to maintain near-constant cerebral blood flow in response to fluctuations in arterial blood pressure (ABP). This physiological control system is remarkably effective, any deviations are rapidly compensated for,[1,2] and the steady-state cerebral blood flow is kept remarkably constant.[3] In patients recovering from head injuries, the cerebral autoregulation mechanism may become impaired, leaving the brain exposed to the vagaries of blood pressure fluctuations, possibly adding to the damage caused by the initial trauma. Increasing ABP may cause hyperperfusion with edema formation or even cerebral hemorrhage, whereas decreasing ABP may cause hypoperfusion and ischemia. It is not known if the cerebral autoregulation is equally effective in guarding the cerebral circulation in both directions. In other words, is the response of the cerebral autoregulation symmetric? If so, it should react with the same speed and effectiveness to a given upward change in ABP as to the same downward change. Two previous studies have suggested that there are nonlinear factors in cerebral hemodynamic.[4,5] In the first article,[4] nonlinearity was assumed attributable to poor fit of linear models to the observed data. In the second article,[5] the

nonlinear behavior was inferred from the shape of the coherence, phase, and amplitude characteristics. However, both of these approaches are indirect and therefore more suggestive than conclusive. The present study was designed to investigate directly the symmetry of the dynamic autoregulatory response in normal subjects and in patients recovering from closed head injury.

Absolute values of volume flow are not required for a study of autoregulatory linearity. Changes in cerebral blood flow are proportional to changes in the flow velocity (FV) in the feeding arteries.[6,7] Therefore, the transcranial Doppler technique, which measures blood flow velocity in the basal cerebral arteries, is well suited for assessment of upward–downward changes in cerebral blood flow. In this report, we propose a new method to investigate the dynamic aspects of cerebral autoregulation response. The method was designed to increase the signal-to-noise ratio by using repetitive stimuli combined with averaging techniques. Moreover, the stimulus sequence used was bipolar, meaning that dynamic autoregulation responses in both upward and downward directions could be directly quantified.

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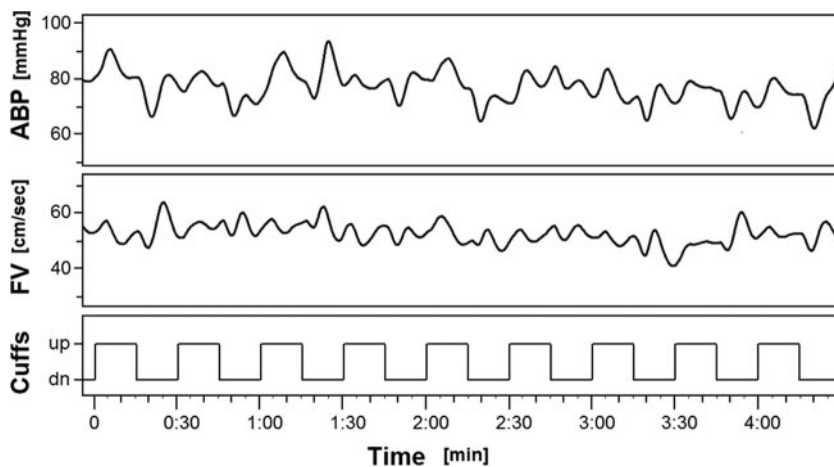
Figure 1. Recordings of ABP and middle cerebral artery FV during cycling of leg cuffs. The cuffs were rapidly inflated (up) above systolic pressure and deflated (dn) in 9 cycles each 30 seconds long. The ABP and FV tracings were low-pass filtered at 0.2 Hz to remove heartbeat pulsatility.

Subjects and Methods

The study was conducted in a series of 14 patients admitted to the neurosurgery intensive care unit with a diagnosis of closed head injury. Age range was 12 to 63 years (mean, 32 years), and there were 3 female and 11 males. Average Glasgow coma score was 6.7. Inclusion criteria were adequate transcranial Doppler insonation of at least one middle cerebral artery, placement of a radial artery catheter, and an intracranial pressure (ICP) probe. Moreover, because of the complex relationship between ABP and cerebral perfusion pressure in intracranial hypertension, only cases with ICP less than 25 mm Hg were included in this study. All patients were intubated and on artificial ventilation, and the $EtCO_2$ was recorded and maintained at slight hypocapnic (32 to 35 mm Hg) levels.

As normal control subjects, 10 subjects from the hospital staff aged 27 to 56 years (mean, 34 years) were recruited. None of the subjects had any record of cardiovascular or neurological disease and were not medicated at the time of study. The control subjects gave informed consent to the procedure, which involved only noninvasive measurements. Continuous ABP recordings in this group were obtained using radial artery tonometry (CBM-7000; Colin).

In both groups, bilateral transcranial Doppler recordings of FVs in the middle cerebral arteries were made using 2-MHz probes attached with a headband. In 2 of the patients, only unilateral transcranial Doppler insonation was possible. A dual-channel ultrasound pulsed Doppler instrument (Multi-Dop X2; DWL GmbH) was used to record the envelope of the FV spectra in the middle cerebral arteries. This instrument, running software version TCD-7.40X, was also used to digitize the analog signals from the ABP, ICP, $EtCO_2$, and leg cuff inflation devices. All signals were recorded to files on the hard drive at sampling rates of 28.5 or 57 Hz. The files were later transferred to a computer running Windows XP. The raw data were decoded from the proprietary TCD-7 file format into floating point arrays and analyzed as described subsequently using a custom Windows program written in Microsoft Visual Studio C++.

To create the stimuli for the cerebral autoregulation, leg cuffs (Model CC22; Hokanson) were wrapped around both thighs and connected to a rapid cuff inflator/deflator (Model E20; Hokanson). In comparison to "normal" leg cuffs, these extra large cuffs cause much less discomfort and pain. The stimulus system was used in 2 different modes: (1) the conventional leg cuff method mode,[2,8,9] in which the cuffs were rapidly deflated after being inflated for 2 to 3 minutes above systolic ABP. A minimum of 3 such tests were made in each subject; and (2) the new repetitive cyclic mode, which consisted of 15 seconds of leg cuff inflation above systolic ABP alternated with 15 seconds of deflation. A minimum of 8 such inflation/deflation cycles (4 minutes) were applied. A typical example of recordings from a normal subject during the cyclic mode is shown in Figure 1. The intended physiological effects of the new stimulus mode were: (1) a sudden increase in ABP after cuff inflation attributable to the increased total systemic resistance when the leg circulation was stopped; and (2) an abrupt decrease in ABP when the leg circulation was restored.

Data Analysis and Evaluation

The data from the conventional leg cuff deflation method were analyzed as described previously.[8] The release of the leg cuffs typically induced a sudden drop in ABP, which persisted until central cardiovascular compensatory reflexes stepped in to restore it after 6 to 10 seconds. The dynamic recovery of FV during this period was analyzed with the dynamic autoregulation index (ARI) model,[8,9] which classifies the response on a scale of 0 to 9. Zero is no autoregulation, whereas "normal" dynamic autoregulation is in the range from 3 to 7 with mean of 5. ARI values above 7 characterize very rapid autoregulatory responses.[10] The median ARI value of the tests performed in each individual was used in further data evaluation. In the present study, a time interval of 7 seconds after cuff release was used to estimate ARI. This is shorter than previously described[8] and results from the new findings in the present study and their implications as argued in the "Discussion" subsequently.

The unfiltered ABP and FV data from the 8 last complete heartbeats before starting the cyclic leg cuff stimulus sequence were used to estimate mean critical closing pressure (mCCP) based on the first harmonic Fourier component of the pulsatile waveforms.[11] The pulsatile data were also used to determine the time delay between the FV and the ABP waveforms.[11] The FV data were then shifted by this time delay (0.04 to 0.09 seconds) in the subsequent processing so that the effects of pulse transmission would be compensated for when calculating autoregulatory response.

The ABP and FV data from the cyclic stimulus mode were low-pass filtered at 0.2Hz (fourth-order filter) to remove heartbeat pulsatility and other high-frequency fluctuations and noise. This filtering preserved the main components of the autoregulatory response, which are found at frequencies around and lower than 0.1 Hz.[12,13] Eight recorded cycles were then averaged using the cuff inflation signal (tracing labeled cuffs in Figure 1) as time reference. Figure 2 shows an example of averaged ABP and FV in a normal subject. In the middle tracing, the calculated response of the cerebral autoregulation is shown assuming that cerebral blood flow is regulated by changes in the CCP. Because the changes in flow are relatively small, such linearization should be permissible. We also attempted to use changes in the slope of the pressure-flow velocity relationship (instead of CCP) to quantify autoregulatory response. The results were practically identical, and we therefore chose to present the data based on CCP being the regulating parameter. Moreover, assuming regulation is generated by variations in CCP makes this cyclic model linear corresponding to the model used for determining ARI.[8,9]

The first step in estimating the autoregulatory gains is to determine the slope (S) between velocity and pressure. Because we could use
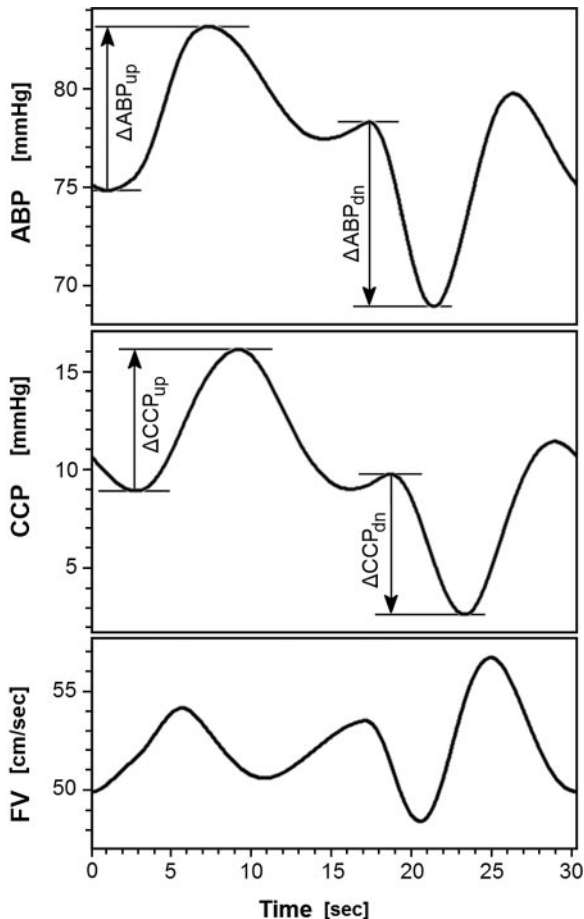
Figure 2. Time-averaged representations of response to cyclic leg cuff stimulation calculated from the recordings shown in Figure 1. The sudden increase in cuff pressure was used as time reference for averaging. The CCP tracing was calculated from the ABP (blood pressure) and middle cerebral artery FV tracings using equations 1 and 2 as described in "Methods." The figure illustrates how the ΔABP_{up}, ΔABP_{dn}, ΔCCP_{up}, and ΔCCP_{dn} values were measured. These were used for calculating the dynamic autoregulatory gains AG_{up} and AG_{dn} using equations 3 and 4. In some of the patients with highly asymmetric autoregulatory responses, a clear reference for defining the start of the ΔCCP_{dn} response could not be determined. In these cases, the value of the CCP at 18 seconds was used.

the pulsatile data to determine the mCCP, this slope is given by the following equation assuming a linear relationship:

$$S = mFV/(mABP - mCCP)$$

In these equations, mABP is mean blood pressure and mFV is mean flow velocity. The slope is assumed to remain constant during the cyclic variations and can therefore be regarded as a static parameter. The changes in pressure ($\Delta ABP = ABP - mABP$) and flow velocity ($\Delta FV = FV - mFV$) can then be combined to estimate ΔCCP, which is assumed to be related to the regulatory response of the cerebral autoregulation:

$$\Delta CCP = \Delta ABP - \Delta FV/S$$

Note that the critical closing pressure trace ($CCP = \Delta CCP + mCCP$) in Figure 2 is determined on the basis of filtered data in which the pulsatility had been removed. In the figure, it is also shown how the measurements of up/down stimuli and corresponding responses were made. The upward regulatory action, ΔCCP_{up}, is assumed to be the response to the upward peak in blood pressure, ΔABP_{up}, caused by cuff inflation. Likewise, the downward regulatory action, ΔCCP_{dn}, is

assumed to be the response to the downward peak in blood pressure, ΔABP_{dn}, caused by cuff deflation.

If cerebral autoregulation response to increases in blood pressure was perfect, with no change in FV, ΔCCP_{up}, would have to be equal to ΔABP_{up}. The same reasoning would apply to decreases in blood pressure. Such balanced autoregulatory response would be characterized by a gain of one. For "less than perfect" responses, we can calculate the dynamic autoregulatory gains AG_{up} to upward and AG_{dn} to downward stimuli as:

$$AG_{up} = \Delta CCP_{up}/\Delta ABP_{up}$$

$$AG_{dn} = \Delta CCP_{dn}/\Delta ABP_{dn}$$

In a hypothetical case in which there was no autoregulatory compensatory response, the gains should both have been zero. If the compensatory response was perfectly symmetrical, both gains should have the same value. Using this algorithm, we calculated the dynamic autoregulatory gains for both upward and downward stimuli in both subject groups. In addition, we determined the time delay of the response as the time distance between the traces when passing through 50% of ΔABP and ΔCCP. Two-tailed t tests were used to determine statistical significance in the results. All results are presented as mean$\pm$SD. Conventional linear regression was used to determine correlation coefficient and relationships.
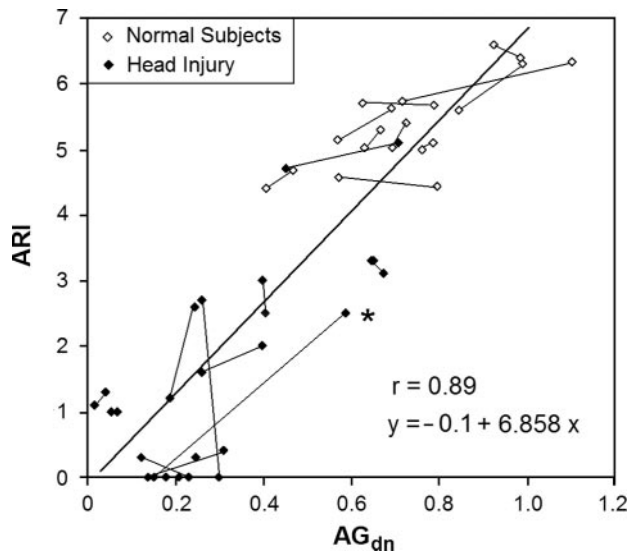
Results

The cyclic leg cuff autoregulation test was well tolerated in all subjects. In 3 of the patients, the standard leg cuff deflation led to transient increases in the ICP by more than 15 mm Hg, whereas the ICP during cyclic stimuli remained near the prestimulus level. The fluctuations in ICP during cycling were small compared with the fluctuations in ABP. In the patient group, the ABP was 96.2$\pm$9.0 mm Hg and the ICP was 15.7$\pm$4.1 mm Hg.

The cyclic stimulus produced sufficient variations in ABP to determine the autoregulatory gains. In the normal subjects, ΔABP_{up} and ΔABP_{dn} were 7.8$\pm$2.8 mm Hg and 9.5$\pm$4.3 mm Hg, respectively; in patients, the corresponding values were 8.2$\pm$4.3 mm Hg and 7.2$\pm$3.8 mm Hg. Statistically, there was no significant difference between up and down excursions of the ABP and no differences between the groups in the ΔABP values. Moreover, in all cases, there was an immediate and abrupt change in ABP in both directions.

In the normal subjects, the dynamic autoregulation index ARI was 5.4$\pm$0.65. The downward gain (AG_{dn}) was 0.74$\pm$0.18 and the upward (AG_{up}) 0.77$\pm$0.17, the difference not being statistically significant ($P > 0.5$). The correlation between AG_{dn} and AG_{up} was weak ($r=0.24$). There was a weak correlation ($r=0.47$) between AG_{dn} and ARI and no correlation ($r=0.24$) between AG_{up} and ARI. However, it should be noted that the range of ARIs in normal subjects was low (SD$=0.65$). In the normal subjects, only one determination resulted in an AG_{up} slightly above 1.

In the patients with head injury, the results were quite different. The ARI was 1.6$\pm$1.51, which would indicate that the majority of the subjects had impaired dynamic autoregulation. This was also reflected in a reduced downward gain (AG_{dn}) of 0.30$\pm$0.21. In contrast, the upward gain (AG_{up}) was augmented to 1.27$\pm$0.76. This value was significantly higher than the downward gain ($P < 0.001$). There was a negative relationship between AG_{dn} and AG_{up} ($r=-0.33$). In this group, 15 of the 25 AG_{up} determinations were higher than 1, indicating an overcompensating dynamic autoregulatory re-

Figure 3. Relationship between the downward AG_{dn} to cyclic stimuli and the dynamic ARI to conventional leg cuff releases. Data from the same individual are connected by lines. The results of linear regression are shown in the figure, and the findings indicate that these 2 approaches to estimate dynamic cerebral autoregulation (to different types of downward ABP challenges) correlate well. In the patient marked by an asterisk, the trauma was on the side with very impaired dynamic autoregulation.
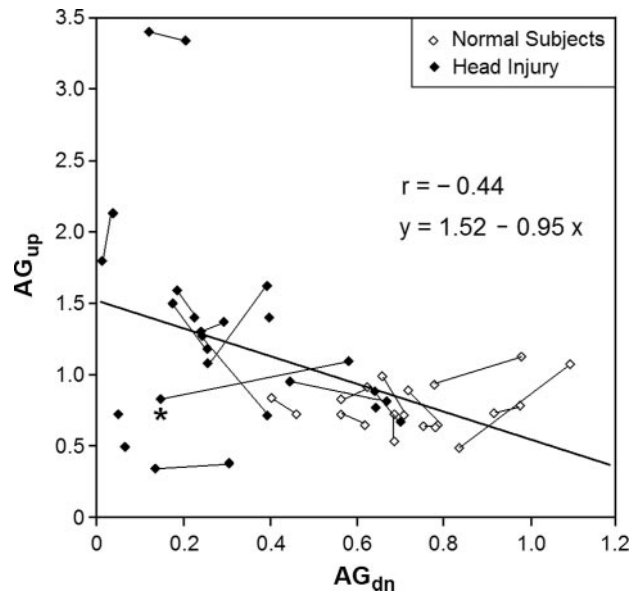

Figure 4. Relationship between the AG_{dn} and the AG_{up} to cyclic stimuli. Data from the same individual are connected by lines. A relatively weak negative correlation was found as shown by the linear regression line in the figure. Note the wide range of AG_{up} values for patients with impaired AG_{dn} (<0.5). The asterisk marks the same patient as in Figure 3.

sponse. The correlations of AG_{dn} and the AG_{up} to mABP in the patient group were only weakly positive ($r=0.37$ and $r=0.32$, respectively) and not statistically significant.

Figure 3 shows the relationship between AG_{dn} and ARI. For the entire series (normal subjects and patients), the results of these 2 different methods correlated well ($r=0.89$; the linear regression line is shown in the figure). The correlation between AG_{up} and ARI was weakly negative ($r=-0.47$). Figure 4 shows that there was a weak negative relationship between AG_{dn} and AG_{up} for the entire series; this is probably the result of highly asymmetric or nonlinear dynamic autoregulatory responses in the majority of the patients with head injury.

The half response downward delays were quite similar, 1.72 ± 0.36 seconds in normal subjects and 1.88 ± 1.78 seconds in patients. The upward response delays were 2.10 ± 0.95 and 2.24 ± 1.01 seconds, respectively.

Discussion

The results of the present study were unexpected and indicate that the cerebral autoregulatory mechanism may respond with asymmetric reactions. In most of the head injury cases, the autoregulation mechanism dynamically overreacted to increases in blood pressure, whereas it had a diminished response to falling levels. Moreover, in normal subjects, the poor correlation between AG_{dn} and AG_{up} indicates that asymmetric responses could also be present, although not as prominently, within the normal physiological regime. The findings support a hypothesis that cerebral autoregulation reacts more efficiently against the dangers of "breakthrough" and hyperperfusion than against hypoperfusion. A study in apes, using sharp induced upward ABP stimuli, also found such very

strong and rapid autoregulatory responses.[1] The dynamic cerebral autoregulation seems to prioritize protection against the imminent danger of cerebral hemorrhage that may accompany upward spike ABP. Ischemia and infarctions, which are the primary dangers of hypoperfusion, would develop over a longer time scale, and more time would be available for compensatory action.

As for the mechanism(s) causing the asymmetric response, the most likely hypothesis is that in addition to a relatively symmetrical (linear) steady-state regulation, a different mechanism may be active in response to rapidly rising blood pressure. If this is the case, one could hypothesize that the cerebral autoregulation is nonlinear. The possible explanation that the nonlinearity is attributable to the ABP being close to the lower limit of autoregulation[14] is not likely. Such a hypothesis simply cannot explain the augmented response seen in most patients to upward spikes in the ABP. No further clarification of these mechanisms is possible in light of the findings of the present study design.

The algorithm used in the present study is based on the assumption that the CCP is the regulating parameter of the cerebral circulation pressure–flow relationship. The other possibilities would be regulation by the slope (S in equations 1 and 2) or a combination of the 2. One study has shown that CCP and S were both approximately equally active in regulation of flow during cerebral hyperemia after cardiac arrest.[11] In the present study, assuming that both parameters were regulated would make the algorithms and their implementation more complex. Moreover, additional assumptions of the precise relative contribution of each would have to be made. Because the present study used relatively small stimuli, linearization was assumed to be permissible and therefore avoiding the added complexity of assuming dual parameter regulation.

The present findings may have ramifications for studies of cerebral autoregulation dynamics. First, when random fluctuations,[12,13] or periodic bipolar stimuli[15] are used to study autoregulation, linear transfer function analysis may not be an appropriate technique to use because the system itself may be highly nonlinear. Second, when using time-domain analysis, the responses should be analyzed separately for upward and downward stimuli. Third, if the cuff release method is used, the interval used for autoregulatory parameter estimation[8,9] should be limited to approximately 6 to 10 seconds after cuff release because the ABP typically starts recovering after this period and the downward stimulus is followed by an upward stimulus. In a previous publication,[8] a longer interval (30 seconds) was recommended.

The study underscores the difficulty of analyzing the response of the cerebral autoregulation. The method used for determining the AGs is not ideal because it depends on low-pass filtering and graphic determination of the different peaks. This determination was somewhat problematic in the patients with high degrees of asymmetry in which the strong responses to upward stimuli could mask the response to downward stimuli. However, the approach as described was the best we could think of at this stage. It is hoped that future development of more precise mathematical model techniques such as used for the ARI determination will give more insight into the complex dynamic response.

The new cyclic stimuli sequence method appears better suited for clinical use than the hyperemic leg cuff step release method described earlier.[2] A sequence of 8 cycles requires only about the same time as one ARI determination. The new stimulus sequence is also less taxing on the cerebral circulation because the induced changes in ABP are shorter and smaller, and possible increases in ICP are avoided. Normally, the smaller responses would add uncertainty to the estimates. This was compensated for by using signal averaging; and the accuracy and consistency of the method was corroborated by the good correlation found between the AG_{dn} and the conventional cuff release step response ARI. The clinical significance of "normal" or even markedly augmented autoregulatory gain to sudden upward changes in ABP while, in the same individuals, regulation to downward changes was impaired, is not yet known. More data and new studies are needed to determine under which circumstances such highly nonlinear autoregulatory responses occur.

Disclosures

None.

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