An Assessment of Dynamic Autoregulation from Spontaneous Fluctuations of Cerebral Blood Flow Velocity: A Comparison of Two Models, Index of Autoregulation and Mean Flow Index

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BACKGROUND: Various methods of assessment of cerebral autoregulation, using spontaneous slow fluctuations of blood flow velocity (FV), arterial blood pressure, and cerebral perfusion pressure, have been used in clinical practice. We studied the association between the dynamic index of autoregulation (ARI) and time correlation index (mean flow index, Mx) in a group of patients after head injury.

METHODS: Fifty head-injured patients of an average age of 31 yr, sedated, paralyzed, and ventilated (mild hypocapnia) with continuous monitoring of arterial blood pressure and intracranial pressure were studied. Cerebral blood FV was monitored daily for 3 days after injury during periods that were free from interventions (e.g., suctioning).

Digitally recorded data were analyzed retrospectively. ARI was calculated as a coefficient graded from 0 (absence of autoregulation) to 9 (strongest autoregulation), describing a dynamic model of autoregulation. Mx was calculated as the correlation coefficient between 40 consecutive 6-s averages of FV and cerebral perfusion pressure and then averaged over the whole recording period. ARI and Mx values, assessed during the first 3 days after injury, were averaged for each patient.

RESULTS: ARI and Mx showed moderately strong mutual linear relationship with correlation $r = -0.62$; $P = 0.0001$. Both indices correlated with outcome, indicating worse autoregulation in patients achieving unfavorable outcome.

CONCLUSION: ARI and Mx agree relatively well in head-injured patients. Autoregulation affects outcome after head injury.

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As long as cerebral autoregulation (CA) works efficiently, blood perfusion to the brain is protected against fluctuations in cerebral perfusion pressure (CPP). This reduces the possibility of ischemic brain insults[1] as long as CPP stays above the lower limit of CA. Assessment of CA after acute stroke, subarachnoid hemorrhage, or head injury has become an important element of brain monitoring systems.[2] Various modalities are used including direct cerebral blood flow (CBF) imaging using perfusion computed tomography (CT), xenon-enhanced CT (Xe-CT) or positron emission tomography, thermal dilution, tissue oxygenation, Doppler-ultrasound or laser Doppler techniques. The special role of transcranial Doppler ultrasonography (TCD) is its noninvasiveness and relatively low cost. However, there are some limitations to these techniques: monitoring requires fixing the TCD probes for a long time; blood flow velocity (FV) is not always proportional to CBF; and, finally, assessment of CA requires clearly defined changes in CPP. Many drugs used to alter arterial blood pressure (ABP) cross the blood–brain barrier, affecting cerebrovascular resistance (CVR). Release of leg-cuffs[3] may also alter CVR by washing-out of vasoactive metabolites, which may have accumulated in the peripheral circulation during inflation of cuffs. Compression of the common carotid artery[4] carries some risk of releasing embolisms and may also produce extra variability to ABP. Methods suitable for continuous monitoring are based on analysis of slow fluctuations of ABP (periods of 15 s or slower) and their relation to FV. A

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commonly disputed point is whether changes in FV are always a response to changes in ABP, or whether both modalities may change simultaneously in response to autonomic activation.

The methods based on an analysis of transfer function presume that fluctuations of ABP produce coherent responses in FV. Autoregulation can dynamically attenuate this response,[5] and effect characterized by the autoregulation index (ARI). ARI is a dimensionless index ranging from 0 to 9, describing the response of CBF to a step decrease in ABP. An ARI of 9 describes a system where CBF returns very quickly to baseline after a step decrease in ABP; an ARI value of 0 describes a system in which there is no compensatory change in CBF. The advantage of this method is that an ARI with release of a leg-cuff has been used in many studies investigating CA,[3] therefore making direct comparison of methods possible.

In the time correlation method, mean flow index (Mx) the time series of ABP and FV are two stochastic processes of short-term stationarity. An estimator of linear correlation coefficient between these two processes (after filtration of pulse and respiratory waves) hypothetically characterizes autoregulation. Strong and positive correlation indicates disturbed autoregulation and correlation close to zero or negative, and good autoregulatory reserve.[6]

As both methods, ARI and Mx, are used in different studies and have a long list of favorable references, we analyzed their agreements and differences in a group of head-injured patients.

METHODS

Daily assessment of CA is a routine clinical practice in the Neurocritical Care Unit (NCCU), Addenbrooke's Hospital, Cambridge, United Kingdom. Individual consent was not required at the time of data recording (1992–1998). Data were analyzed retrospectively and anonymously as part of the clinical audit. The NCCU Users Committee and IRB approved retrospective analysis and publication of the results.

Fifty patients admitted after head injury to Addenbrooke's Hospital (1992–1998) with a median Glasgow Coma Score (GCS) of 6 (range, 3–13; 10% of patients with initial GCS >9) were studied. Patients were selected from a larger database previously presented cases[7] containing material from daily clinical assessment of CA (n = 187). Criteria for selection were as follows: patients with closed head injury, examinations performed during the first 3 days after injury (to avoid the effects vasospasm or secondary intracranial hypertension), good quality of monitored signals, and waves in ABP and intracranial pressure (ICP) more than 5 mm Hg present in recordings.

The patients were paralyzed, sedated, and ventilated to achieve normocapnia. Decreases in ABP, which reduced CPP below 60 mm Hg, were managed with intravascular fluid administration and dopamine 2–15 $\mu g \cdot kg^{-1} \cdot min^{-1}$. If required, norepinephrine was also started at a rate of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. If ICP increased above 20 mm Hg, boluses of mannitol were administered (200 mL of 20%, over a period of 20 min or longer), and the ventilation rate was increased to achieve mild hypocapnia ($PAco_2$ range, 28–35 mm Hg).

Monitoring

IP was monitored continuously using microtransducers (Camino Direct Pressure Monitor, Camino Laboratories, San Diego, CA; or Codman MicroSensor, Johnson & Johnson Professional, Rynham, MA), inserted intraparenchymally into the frontal region. ABP was monitored directly from the radial or dorsalis pedis artery (System 8000, S&W Vickers Ltd, Sidcup, UK or Solar 6000 System, Marquette, USA). The middle cerebral artery (MCA) was insonated daily on the side of the ICP bolt for a period of 20 min to 2 h starting from the day of admission until day 3 after head injury, using the PCDop 842 Doppler Ultrasound Unit (Scimed, Bristol, UK) or Neuroguard (Medasonics, Fremona, CA).

The depth of insonation was from 4 to 6 cm. Signals were monitored during periods of stable respiratory variables, free from physiotherapy, tracheal suction, and other disturbances.

Data Capture

Analog output from the pressure monitors and the TCD unit (maximal frequency envelope) were connected to the analog-to-digital converter (DT 2814, Data Translation, Marlboro, USA) fitted into an IBM AT laptop computer (Amstrad ALT 386 SX, UK). Data were sampled, digitized, and stored on the hard disk using software specifically designed for waveform recording (WREC, W. Zabolotny, Warsaw University of Technology).

Calculation of ARI

For assessment of dynamic CA based on spontaneous fluctuations of ABP, more reliable values of ARI are obtained by fitting the models proposed by Tiecks et al.[8] to the CBF velocity (CBFV) step response, as described previously.[5,9] Transfer function analysis was used to quantify the dynamic relationship between mean ABP (input) and mean CBFV (output). A Fast Fourier transformation algorithm was applied to the time-series of beat-to-beat changes in mean ABP and mean CBFV; the auto- and cross-spectra were calculated with the Welch method, using eight segments of data, with 1024 samples each (204.8 s), and 40% superposition. The inverse Fourier transform was used to obtain the CBFV impulse response in the time domain, which was integrated to yield an estimate of the CBFV response to a hypothetic step change in ABP.[10] Each of the 10 models proposed by Tiecks et al.,[8] corresponding to ARI values from 0 (absence of autoregulation) to 9 (best autoregulation), was fitted to the first 10 s of the CBFV step response, as shown in Figure 1, and the best fit, as selected by the minimum squared error, was chosen as the representative value

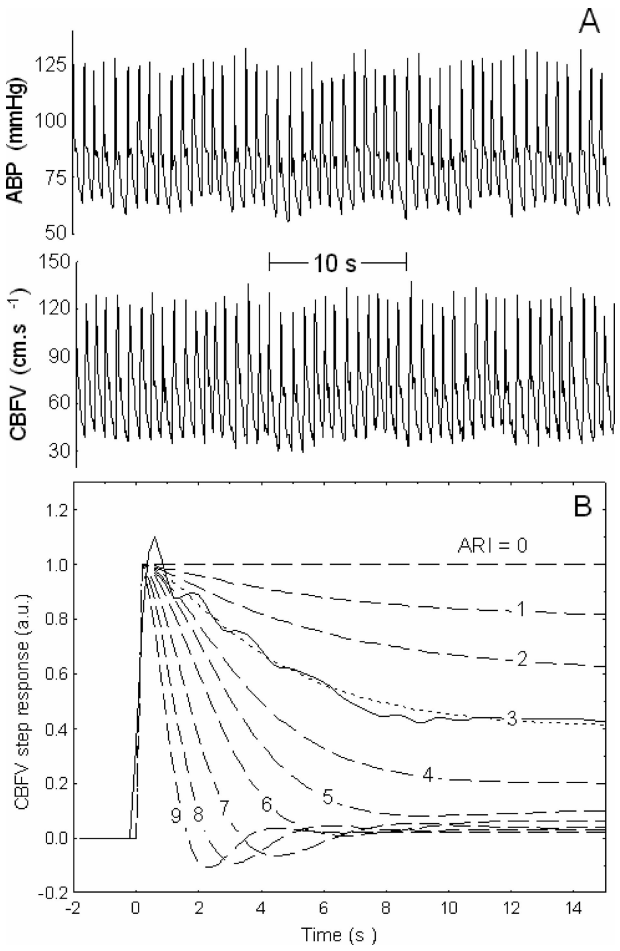

Figure 1. Estimation of index of autoregulation (ARI) from cerebral blood flow velocity (CBFV) step response. (A) Sample of the original arterial blood pressure (ABP) and CBFV recordings. (B) CBFV step response (solid line), superposed to the 10 model responses (interrupted line) predicted by Tiecks et al. model.[8] In this case, the best fit corresponded to a value of ARI = 3 (dashed line).

of ARI for that segment of data. Values of ARI were averaged for patients with more than one segment of data.

Calculation of Mx

Digital signals were then processed using software ICM+ developed in-house[11] (www.neurosurg.cam.ac.uk/icmplus). Time-averaged values of ICP, ABP, CPP (CPP = ABP − ICP) were calculated using waveform time integration for 6-s intervals. Time-averaged mean, systolic, and diastolic values of FV were calculated after spectral filtration to reduce an influence of noise, and averaged within the same 6 s periods.

A Mx was calculated as a Pearson's correlation coefficient of 40 consecutive samples of CPP and FVm, i.e., every 4 min. Positive association between CPP and FV (positive values of Mx) indicates passive dependence of blood flow on CPP, therefore defective autoregulation. Negative or zero value of Mx implies active cerebrovascular responses to changes in CPP, therefore autoregulation is preserved (Fig. 2).

Validation of Mx as an index of autoregulation has been highlighted in previous studies: Mx was significantly correlated with the leg-cuff test, $Paco_2$-reactivity[12] and the transient hyperemic response test.[4] Theoretically, Mx can indicate autoregulation if the magnitude of slow CPP fluctuations is reasonably large, to activate an autoregulatory response (>5 mm Hg). This was the case in all of our patients. Mx fluctuates in time according to changing ICP and ABP; some random fluctuations are also observed.[6] Mx was averaged for the whole window of recording (20 min to 2 h) and for final analysis, multiple recordings taken from the same patient were averaged to represent each patient by one data point (as ARI).

RESULTS

There were 16 women and 34 men, ages ranging from 17 to 75 yr (mean age, 31 yr). The median GCS at admission was 6, with three patients having initial GCS >8 but further deteriorating and requiring full intensive care. Fifteen percent had subdural hematomas on their initial CT of which 60% were evacuated surgically. Intracerebral hematomas were found in

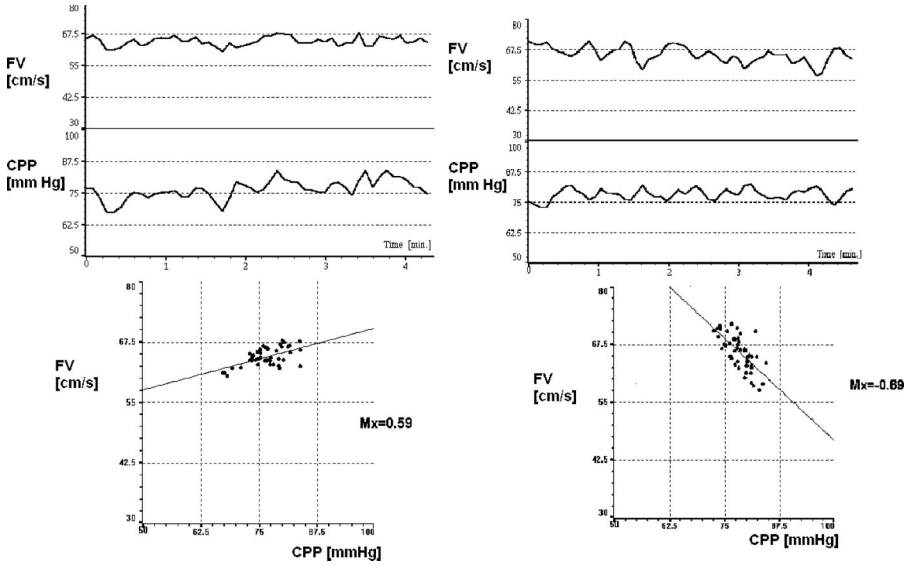

Figure 2. Principles of assessment index of autoregulation using the time correlation method (Mx). Averaged values of flow velocity and cerebral perfusion pressure (CPP) (window 6 s) are correlated within the time period of 4 min. Positive correlation (Mx is linear correlation coefficient) means passive dependence of blood flow on CPP and failing autoregulation. Zero or negative value autoregulation working properly (although negative Mx can be seen only in hyperventilated patients).

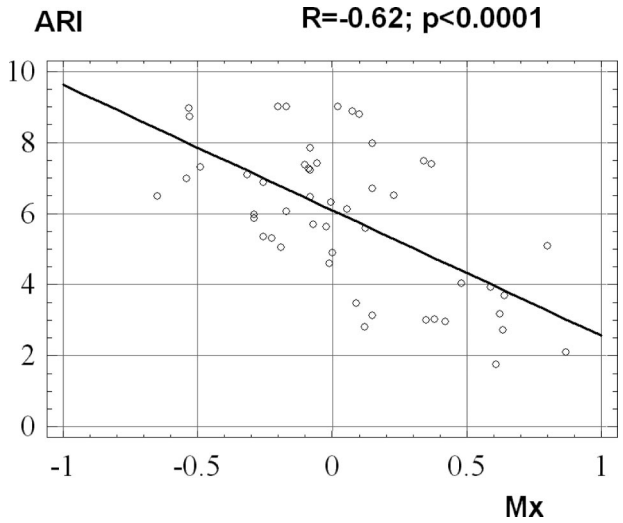

Figure 3. Relationship between index of autoregulation (ARI) and index of autoregulation assessed using the time correlation method (Mx).

20% (50% were removed surgically) and extradural hematomas in 10% of these patients. Ten percent had diffuse brain injury, 50% brain swelling, and 22% presented with a midline shift. Subarachnoid blood was found in 25% of patients, with no patient demonstrating mean flow velocity above 120 cm/s. The mean CPP was 64 mm Hg with no patient having CPP below 45 mm Hg. Mean blood FV was 62 (21 SD) cm/s. The mean ICP was 20 (11.8 SD) mm Hg and with only one patient having ICP above 40 mm Hg.

The correlation between ARI and Mx in patients examined from day 1 to 3 after head injury was −0.62 ($P = 0.0001$). The best model fit was linear (Fig. 3):

ARI = 6.01–3.53*Mx. Bland–Altman analysis of the residual of this model versus average of ARI and predictors revealed a bias 0.2 and standard deviation of residuals 1.6, indicating 95% interval of prediction of ARI using Mx equal to ±3.2.

Residuals did not correlate with any of the monitored variables, with the exception of heart rate ($r = 0.40$; $P = 0.0028$).

The average value of ARI differed between different outcome groups classified as favorable (good and moderate disability outcome) and unfavorable (severe disability, persistently vegetative and dead patients). In patients with unfavorable outcome ($n = 27$) ARI was 5.1 ± 2.36, and with favorable outcome ($n = 23$), it was 6.7 ± 1.68 ($P = 0.016$ – Fig. 4A). Mx also indicated on average better autoregulation in patients who achieved favorable (Mx = −0.12 ± 0.28) than those who had unfavorable outcome (Mx = 0.21 ± 0.35; $P = 0.0062$; Fig. 4B). This was independent of a slight worsening of autoregulation with age (Age: ARI—$r = -0.35$; $P = 0.012$ and Age: Mx—$r = 0.30$; $P = 0.034$). There was no correlation between autoregulation and severity of injury.

Mx correlated positively with mean ICP ($r = 0.31$; $P = 0.028$) and negatively with CPP ($r = -0.33$; $P = 0.016$), but ARI did not ($P = 0.26$ and 0.35).

DISCUSSION

Relevance of Intermethod Comparisons

After the seminal contribution of Aaslid et al.[3] describing the transient response of dynamic CA in humans, there has been a proliferation of methods of analysis, involving a diversity of protocols, measurement techniques, and data analysis approaches.[2] Under ideal conditions, each of these new proposals would be compared with a reference ("gold standard") technique to assess their merits in relation to different aspects, such as reliability, reproducibility, diagnostic, and prognostic value. The main problem with CA is that there is no such reference method.[2] Although some might regard "static" CA as a gold standard there are many reasons why this is not appropriate, especially when compared with techniques aimed at assessing dynamic CA.[2,13] First, because of the different time scales involved, it is still not clear if dynamic and static CA share the same underlying biochemical and cellular regulatory pathways. Second, it is extremely difficult to obtain rigorous static assessment of CA in humans, because of the need to change mean ABP, usually involving pharmacologic methods[2] and the need to maintain relatively stable levels of ABP for a reasonable length of time. Also, most previous work on the subject of static CA can be criticized for using only two ABP levels, thus leading to statistically unreliable estimates of slope.[2] Finally, it has been shown that dynamic methods can be more sensitive to deterioration of autoregulation than static ones.[14] Despite these limitations of static

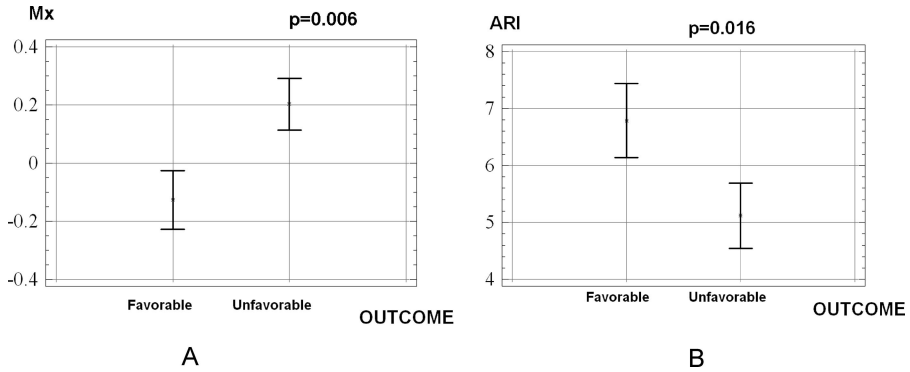

Figure 4. Mean values and 95% confidence intervals in patients who attained favorable and unfavorable outcome. (A) Index of autoregulation (ARI); (B) index of autoregulation assessed using the time correlation method (Mx).

autoregulation, some investigators have demonstrated good agreement between different dynamic autoregulation methods and the static approach.[8,16]

Because of the lack of a reliable reference, alternative approaches are needed for optimizing methods of dynamic CA modeling and assessment. Clinical and physiologic studies are important, since they can allow the identification of each method's sensitivity to physiologic covariates and also its sensitivity and specificity to different clinical conditions. Unfortunately, the general pattern of most previous studies is that only a single method of dynamic CA analysis is considered, and thus it is not possible to learn how other methods would have performed under similar circumstances. To be able to learn more about the advantages and limitations of different methods, intermethod comparison is an important strategy for achieving a convergent process of optimization.

Hitherto, the Mx was the approach that has had the largest number of comparative studies in the literature. Mx has been positively compared with static rate of autoregulation,[16] CO_2 reactivity,[13] transient hyperemic response test,[4] leg-cuff release,[12] phase shift between FV and ABP,[17] and pressure reactivity.[18] A comparison with the ARI, as proposed in this study, is important due to the large number of physiologic and clinical studies, which were based on the ARI.[2,5,10,15,20] As discussed below, the results of comparative studies do not always seek to advance knowledge in the direction of a comprehensive understanding of the properties and potential contribution of different methods.

Limitations of the Study

The common concern about changes in MCA diameter invalidating the assumption that CBFV can be used as an index of CBF does not apply to this study, since both the ARI and Mx were calculated from the same CBFV recording, and it is unlikely that any differences between the two indices could have been due to diameter changes taking place during relatively short recordings.

The conventional approach for assessing the agreement between physiologic measurements is to calculate the bias and precision; that is, the mean and SD of differences between numeric values given by the two methods as recommended by Bland and Altman.[21] In our case, this was not possible due to the different scales of measurement adopted for the ARI and Mx, which possibly also imply different statistical distributions. Bland–Altman analysis between residuals and average of ARI and predictors of ARI was included. Although the correlation coefficient can sometimes give a distorted picture of the association between two variables,[21] the highly significant value obtained in this case, and the clear association reflected by the scatter diagram in Figure 3, confirm a reasonable degree of agreement between the two indices. Moreover, the simultaneous agreement with outcome (Fig. 4) also suggests that both methods can be equally useful for clinical assessment of autoregulation from spontaneous fluctuations in ABP and CBFV.

Although the ARI was originally proposed to quantify CBFV responses to changes in ABP induced by the thigh cuff maneuver,[8] it has been shown that similar results are obtained when ABP is changed by other maneuvers or, indeed, when spontaneous fluctuations in ABP and CBFV are used to obtain estimates of this index.[22] It is difficult to assess CA using spontaneous fluctuations of ABP, ICP, and FV. First, useful waveforms should be present during the assessment periods. Second, we presume that extracranially induced fluctuations of ABP cause changes in FV and ICP and we then use any transmission from ABP or CPP to FV as an index carrying information regarding CA. But we usually do not consider the potential influence of autonomic regulation of CVR. This may produce changes in FV, ABP, and ICP, modifying our presumed model.

Mx is essentially a qualitative or, at best, semiquantitative assessment of CA, and generally not considered to be a gold standard, despite the numerous comparative studies we have performed. However, support for its validity comes from observed correlations between various other indices of autoregulation and correlation with potentially clinically relevant end points: outcome,[5,7] incidence of intracranial hypertension, vasospasm in subarachnoid hemorrhage,[23] and degree of carotid artery stenosis in patients with stenotic disease.[13,24] The assumption, though, that disturbed autoregulation predicts worsening of the clinical picture remains largely unverified.

Autoregulation, particularly after traumatic brain injury, is affected regionally. The value of ARI and Mx are that they grade autoregulation and can be understood as weighted spatial averages of autoregulation as seen from the aspect of the MCA. Autoregulation assessed with TCD cannot be treated as a yes-or-no phenomenon. It may be on average worse or better, but definitively good autoregulation and definitively impaired autoregulation is seen very seldom.

Multiple studies[25,26] indicate disruption of CBF-metabolic coupling after traumatic brain injury. In this study, the CBF-metabolic link was not assessed. We can only speculate that since worse autoregulation correlates with worse cerebral metabolic rate of oxygen[27] more patients with bad outcome were affected by metabolic depression.

CONCLUSIONS

The ARI and Mx correlate with each other quite well in patients with severe head injury. Further comparative studies are necessary to assess the simultaneous behavior of the two indices in other patient populations and to try to identify any patterns and discrepancies between the two approaches, which were not evident in this study.

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