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Variability of time-domain indices of dynamic cerebral autoregulation

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Abstract

The intra- and inter-subject variabilities of the cerebral dynamic autoregulatory index (ARI) were studied in a group of 14 healthy subjects aged 23–51 years. An alternative index, derived from autoregressive-moving average (ARMA) modelling of the arterial blood pressure (ABP)–cerebral blood flow velocity (CBFV) dynamic relationship, named ARMA-ARI, is also proposed. The susceptibility of both indices to physiological sources of variability was studied by performing measurements during spontaneous respiration (SR), and controlled breathing at 6, 10 and 15 breaths min^{-1}. ABP was measured non-invasively (Finapres), CBFV was recorded with Doppler ultrasound in both middle cerebral arteries and end-tidal CO_2 ($EtCO_2$) was estimated with an infrared capnograph. ARI and ARMA-ARI were calculated as a summary measure for the whole of each recording period, and also continuously, using a 60 s moving data window. Respiration did not have an effect on either of these indices, despite significant, but relatively small, reductions in $EtCO_2$ at 10 and 15 bpm, compared to SR. Very significant differences were observed between ARI and ARMA-ARI in relation to their stability, variability and sensitivity to discriminate between subjects. For continuous estimates the coefficient of variation of ARI was $30 \pm 21\%$ compared to $15 \pm 8\%$ for ARMA-ARI ($p < 0.000$). The cumulative probability distributions were also significantly different for the two indices for each of the respiratory manoeuvres. The greater stability and reduced variability of ARMA-ARI, in relation to the classic ARI, suggest that the former should be used in future studies of dynamic autoregulation, mainly in situations where an improved temporal resolution might be required, such as the investigation of vaso-vagal syncope or the physiology of exercise.

Keywords: transcranial Doppler ultrasound, cerebral blood flow, respiration, physiological modelling

1. Introduction

Studies of cerebral blood flow (CBF) in humans have been traditionally based on indicator methods, using as tracers inert gases such as nitrous oxide or ^{133}Xe (Lassen 1959). These methods were useful to establish fundamental knowledge about the physiology of CBF, such as the mechanism of cerebral pressure-autoregulation (Lassen 1959, Paulson *et al* 1990, Panerai 1998). Blood flow to the brain tends to remain relatively constant despite changes in cerebral perfusion pressure in the range of 50–170 mmHg (Paulson *et al* 1990). The more recent introduction of noninvasive methods of measurement, particularly Doppler ultrasound, has allowed greater insight into the dynamic properties of cerebral pressure autoregulation, and has also facilitated clinical investigations in this area. It is now well known that, following a sudden change in mean arterial blood pressure (ABP), CBF velocity (CBFV) is also disturbed, but within a few seconds returns to its original level thus showing the transient or dynamic response of cerebral pressure-autoregulation.

Both time- and frequency-domain approaches have been proposed to quantify the transient CBFV response (Giller 1990, Tiecks *et al* 1995, Panerai 1998, Panerai *et al* 1998, 2001). Although these techniques have been able to identify failure or impairment of dynamic autoregulation in a wide range of clinical conditions (Czosnyka *et al* 1997, Panerai 1998, White and Markus 1997, Dawson *et al* 2000, Lang *et al* 2001, Panerai *et al* 2002), there are still concerns about their accuracy and reproducibility. One major difficulty in this area is the absence of measurement standards (Panerai 1998). Aaslid *et al* (1989) introduced the thigh cuff test to induce CBF transient responses, and later, a mathematical model to quantify the efficiency of dynamic autoregulation (Tiecks *et al* 1995). The model yields an autoregulatory index (ARI) ranging from 0 (absence of autoregulation) to 9 (best autoregulation). The ARI index has been frequently applied to clinical investigations, but only limited information is available about its reproducibility (Dawson 2000, Mahony *et al* 2000). In order to obtain a better understanding of the variability of ARI, and its susceptibility to physiological interference, we set out to investigate its behaviour during controlled respiration at different breathing rates. The initial results of the study have prompted us to propose an alternative formulation for the dynamic autoregulation index, which is also presented and compared to the classical ARI.

2. Methods

2.1. Subjects and measurements

Fifteen volunteers were recruited from the Leicester University Departments of Medicine for the Elderly and Medical Physics. None of the volunteers had a history of cardiovascular or neurological disease or were taking any medication known to affect cardiovascular or cerebrovascular responses, and all participants gave written informed consent. The local Leicestershire ethical committee approved the study.

Subjects avoided caffeine containing products, nicotine and alcohol for at least 12 h prior to the study. They wore loose comfortable clothing and were studied at least 2 h post-prandial. Measurements were performed in a quiet, dimly lit room at constant ambient

temperature (23 °C) with subjects lying supine on a couch with their heads supported by two pillows and their left arm supported at atrial height. After lying supine for 10 min, three semi-automated ABP readings were taken 1 min apart (Omron 711, Japan). The mean of the last two readings, providing pressures differed by less than 10 mmHg, was taken as the baseline casual ABP measurement. A surface 3 lead ECG was fitted and ABP was measured continuously and non-invasively from the middle finger of the left hand using a servo-controlled plethysmograph (Finapres 2300, Ohmeda), which has been extensively used in previous studies of dynamic autoregulation (Birch *et al* 1995, Zhang *et al* 1998, Panerai *et al* 1999, Dawson *et al* 2000, Mahony *et al* 2000, Lang *et al* 2001, Reinhard *et al* 2003). End-tidal carbon dioxide ($EtCO_2$) was measured via a closely fitting facemask and an infrared capnograph (Capnogard, Novametrix). CBFV was measured by insonating the middle cerebral artery (MCA) bilaterally using 2 MHz transcranial Doppler ultrasound (SciMed QVL 842X). Both Doppler probes were held in place using a custom-designed adjustable head frame and the velocity waveform spectra were visually displayed to aid positioning.

Once the subjects had rested supine for a minimum of 30 min and the Finapres and CO_2 traces had stabilized (<10% variation over 5 min), recording was started. Subjects were asked to lie still and to refrain from talking during the recordings. In random order, measurements consisted of a 10 min recording with subjects breathing spontaneously and three 5 min recordings made at respiratory rates of 6, 10 or 15 breaths per minute (bpm), guided by a light indicator. Subjects were instructed to breathe as normally as possible. A 5 min interval was allowed between measurements to avoid any lasting effects from previous respiratory manoeuvres. The ABP, dual-channel CBFV Doppler shift signals, end-tidal CO_2 and ECG were continuously recorded on digital tape for subsequent analysis (Sony PC 108M).

2.2. Data analysis

Data were downloaded in real time onto a dedicated personal computer. An FFT was used to convert the Doppler signals into maximum frequency velocity envelopes with a 5 ms window resolution. The ABP, $EtCO_2$ and ECG signals were sampled at 200 samples/s per channel. Data were visually inspected, the ABP trace was calibrated and artefactual data spikes on the CBFV signals were removed by linear interpolation. The five signals were low-pass filtered with a zero-phase eighth-order Butterworth digital filter with a cut-off frequency of 20 Hz. Each cardiac cycle was automatically marked to determine the R–R interval from the ECG tracing, and the mean ABP, mean CBFV and mean $EtCO_2$ were calculated for each cycle. Spline interpolation was used to resample the data with a time interval $\Delta t = 0.6$ s to create a uniform time base.

Calculation of the autoregulation index (ARI) followed the formulation proposed by Tiecks *et al* (1995). The time varying mean ABP signal, $P(t)$, was initially normalized as

$$\mathrm{d}P(t) = \frac{P(t) - P_M}{P_M - CrCP} \tag{1}$$

where P_M is the mean value of $P(t)$ for the data window. $CrCP$ is the critical closing pressure and was chosen as 12 mmHg (Tiecks *et al* 1995). The model predicted velocity, $V_T(t)$, is given by

$$V_T(t) = V_M(1 + \mathrm{d}P(t) - Kx_2(t)) \tag{2}$$

where K is a parameter reflecting autoregulatory gain and V_M is the mean velocity for the entire record. $x_1(t)$ and $x_2(t)$ are intermediate variables given by

$$x_1(t) = x_1(t-1) + \frac{\mathrm{d}P(t) - x_2(t-1)}{fT} \tag{3}$$

$$x_2(t) = x_2(t-1) + \frac{x_1(t) - 2Dx_2(t-1)}{fT} \tag{4}$$

f, D and T represent the sampling frequency, damping factor and time constant parameters, respectively. Specific combinations of values of K, D and T were used to generate ten grades of dynamic autoregulation, expressed by the ARI, ranging from 0 (absence of autoregulation) to 9 (best autoregulation) (Tiecks *et al* 1995).

Aaslid's model was initially proposed to represent the CBFV response to a negative step change in ABP, but it has been shown that it can also fit the CBFV–ABP dynamic relationship during spontaneous fluctuations in ABP or other challenges such as the Valsalva manoeuvre or lower body negative pressure (Panerai *et al* 2001). The model was fitted to each segment of data by selecting the value of ARI leading to the maximum correlation between $V_T(t)$ and the measured CBFV time series, $V(t)$. Unlike the least-squares error technique used by Tiecks *et al* (1995), this method does not rely on a specific value of $CrCP$ to select the closest match. Once a best-fit curve was selected, a parabolic interpolation was performed to estimate the value of ARI to one decimal place.

An alternative calculation of ARI was obtained by first modelling the dynamic relationship between $P(t)$ and $V(t)$ with an autoregressive-moving average model (ARMA) (Ljung and Soderstrom 1983). The general structure of these models is

$$V(t) = \sum_{i=1}^{M} a_i V(t-i) + \sum_{j=0}^{Q-1} b_j P(t-j) \tag{5}$$

where a_i and b_j are real coefficients and $[M, Q]$ are the model orders (Ljung and Soderstrom 1983). For each data segment, the model coefficients were estimated by the least-square method. To determine suitable values of M and Q, the Akaike information criterion (AIC) and final prediction errors (FPE) were calculated for all combinations of model orders ranging from [1, 1] to [7, 7], and AIC and FPE were averaged for all available data segments. This analysis indicated that a [2, 3] model was the most suitable for the dataset.

After obtaining the best fit for each data window, the impulse and step responses were calculated from a_i and b_j, and the velocity step response generated by the ARMA was matched to the most appropriate of the ten step responses given by Aaslid's model, also using the correlation coefficient, but taking into account only the first 6 s of the step response. This resulted in an alternative procedure to estimate the autoregulation index, which in this case is termed ARMA-ARI.

Values of ARI and ARMA-ARI were obtained for the entire data segments of the 10 min recordings at rest (spontaneous breathing) and the three 5 min recordings with controlled breathing at 6, 10 and 15 bpm. To explore the longitudinal variability of these indices, a 60 s sliding window was used and sequential estimates were obtained at 0.6 s intervals, except for the first and last 30 s of each record. The corresponding time series will be referred to as 'continuous ARI' and 'continuous ARMA-ARI'.

2.3. Statistics

The similarity between the beat-to-beat values of mean CBFV from the right and left MCA was assessed by the correlation coefficient. Probability distributions of ARI and ARMA-ARI were estimated from their histograms, using 20 bins in the interval 0–9. Differences between distributions were tested with χ^2. The agreement between the right and left side values of ARI and ARMA-ARI was assessed by the bias and confidence limits of differences (Bland and Altman 1986). A two-way ANOVA was used to test for the combined effects of subject and breathing pattern. Differences between dependent samples were tested by the

Table 1. Mean ± SD values of physiological parameters and CBFV correlation coefficients for right and left MCA for the four conditions studied.

	Spontaneous respiration	6 bpm	10 bpm	15 bpm
Mean ABP (mmHg)	84 ± 9	83 ± 9	85 ± 11	87 ± 10
CBFV (cm s^{-1})	62 ± 13	58 ± 14	58 ± 15	54 ± 13
Heart rate (beats min^{-1})	64 ± 9	64 ± 8	67 ± 9	66 ± 12
$EtCO_2$ (mmHg)	40.6 ± 5.0	41.3 ± 6.2	37.8 ± 8.1	36.4 ± 6.8
CBFV right/left correlation	0.85 ± 0.13	0.88 ± 0.07	0.87 ± 0.06	0.84 ± 0.10

Table 2. Mean ± SD values of ARI and ARMA-ARI for the right and left MCA.

Index	MCA	Rest	6 bpm	10 bpm	15 bpm
ARI (mean ± SD)	Right	5.81 ± 2.12	5.20 ± 2.60	5.14 ± 3.31	6.80 ± 2.21
ARI (mean ± SD)	Left	5.72 ± 2.20	5.28 ± 2.54	5.31 ± 3.51	6.82 ± 2.20
ARI bias (R-L)	–	0.085	−0.073	−0.169	−0.014
ARI limits of agreement	–	[−1.05, 1.23]	[−1.77, 1.63]	[−2.03, 1.69]	[−0.61, 0.58]
ARMA-ARI (mean ± SD)	Right	7.12 ± 0.76	6.59 ± 0.85	7.13 ± 1.45	6.85 ± 1.40
ARMA-ARI (mean ± SD)	Left	7.10 ± 0.82	6.32 ± 1.00	7.24 ± 1.31	6.72 ± 1.65
ARMA-ARI bias (R-L)	–	0.029	0.269	−0.103	0.129
ARMA-ARI limits of agreement	–	[−0.92, 0.98]	[−1.04, 1.58]	[−0.94, 0.74]	[−1.47, 1.73]

Wilcoxon matched pairs test. Bonferroni correction was performed for multiple inter-group comparisons. The longitudinal variability of the continuous estimates of ARI and ARMA-ARI was expressed by the per cent coefficient of variation. A value of $p < 0.05$ was considered significant.

3. Results

All subjects were capable of controlling their respiratory rate at the desired frequency as confirmed by inspection of the corresponding oscillations in the mean ABP signal. One subject was removed from the study due to persistent vibration of the face mask inducing noise in the CBFV signals. Problems with the left channel of the Doppler recordings were also encountered in two other subjects. In one case the left side could not be properly insonated in all recordings and in another there was excessive noise, but only during controlled breathing at 15 bpm. As a result, 14 complete sets of recordings were available for the right MCA and 12 for the left. The 14 subjects (7 male) aged 32 ± 9 years (range 23–51 years) had casual systolic ABP 114 ± 10 mmHg, diastolic ABP 71 ± 8 mmHg and mean ABP 86 ± 8 mmHg.

Table 1 presents the mean ± SD of physiological parameters at rest and for the three different breathing frequencies. Two-way ANOVA showed that $EtCO_2$ differed significantly between the four respiratory rates, although the pCO_2 differences are relatively small. The correlation coefficients included in table 1 confirm a high degree of similarity between the mean beat-to-beat CBFV signals of both sides. The CBFV mean values were also significantly different for the four conditions studied, following the changes in $EtCO_2$.

3.1. ARI and ARMA-ARI for entire records

The mean ± SD of the two autoregulation indices is given in table 2, for the two MCA sides, together with the bias and confidence limits for the analysis of agreement. No significant

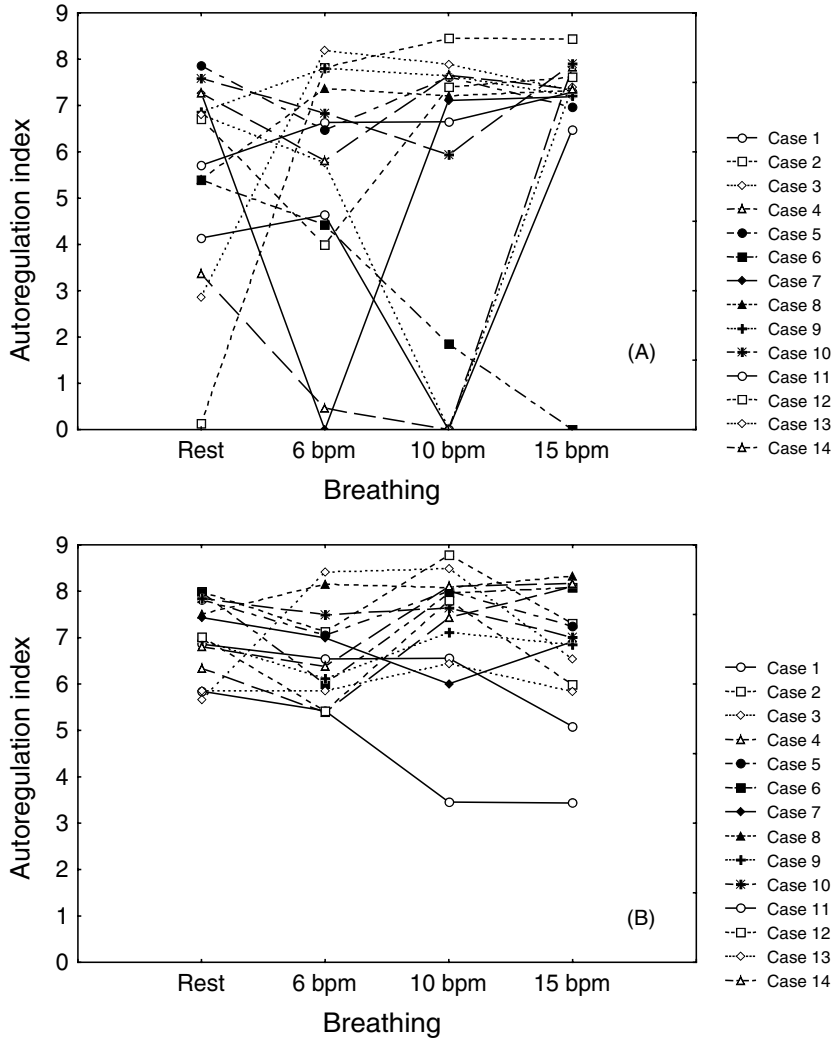

Figure 1. Individual values of ARI (A) and ARMA-ARI (B) estimated from 10 min recordings during spontaneous respiration (rest) and 5 min recordings of controlled respiration at 6, 10 and 15 breaths min^{-1}.

differences were found between the two sides for any of the breathing conditions studied. For this reason, data for the two sides were averaged for subsequent analyses, with the exception of the records where the left side recording was missing. The much higher variability of ARI in relation to ARMA-ARI (table 2) becomes clearer when the data for individual subjects are plotted as in figure 1(A). In every breathing mode there is at least one subject with ARI $= 0$, and there are very large swings from one breathing modality to another. On the other hand, the values for ARMA-ARI (figure 1(B)) are much more stable and differences between breathing modes suggest a gradual variation rather than the abrupt changes observed in figure 1(A).

Two-way ANOVA indicated that there were no significant effects of breathing mode or individuals to explain the scatter of ARI values in figure 1(A). On the other hand, the ARMA-ARI is strongly influenced by individual effects ($p = 0.0004$), although it is not

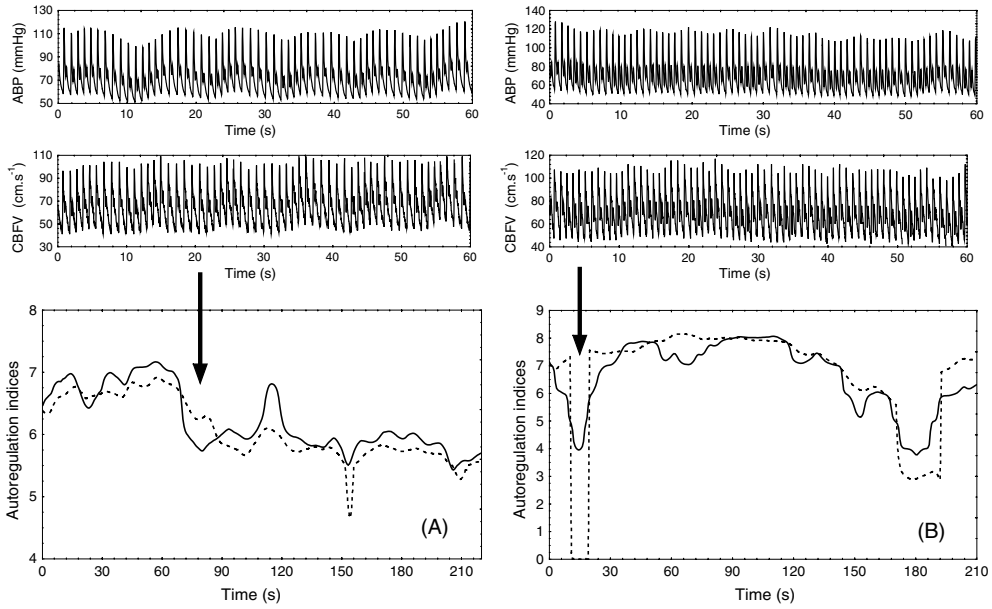

Figure 2. Representative tracings of continuous ARI (dashed line) and ARMA-ARI (solid line) during controlled breathing at 6 bpm (A) and 10 bpm (B). The ABP and CBFV signals above each plot represent the 60 s window segment of data used to obtain the ARI estimates at the point indicated by the arrow.

Table 3. Mean ± SD of correlation coefficients for fitting ARI and ARMA-ARI models with a 60 s sliding window. n is the total number of recordings entering into the mean, including data from both the right and left MCA.

Correlation coefficient	Rest ($n = 27$)	6 bpm ($n = 27$)	10 bpm ($n = 27$)	15 bpm ($n = 26$)
ARI model	0.691 ± 0.075	0.711 ± 0.125	0.713 ± 0.076	0.612 ± 0.101
ARMA model	0.987 ± 0.005	0.989 ± 0.004	0.984 ± 0.007	0.982 ± 0.009
Fitting ARI responses to ARMA	0.954 ± 0.022	0.949 ± 0.028	0.946 ± 0.032	0.944 ± 0.035

significantly affected by the different breathing patterns ($p = 0.51$). This result suggests that the ARMA-ARI has a high sensitivity to discriminate between the way individuals respond to the controlled breathing protocol.

3.2. Continuous ARI and ARMA-ARI

Fitting the CBFV–ABP relationship with a 60 s moving window resulted in the model correlation coefficients represented in table 3. The correlation coefficients for fitting the ARMA model are significantly greater than the corresponding values for fitting the ARI. The same is true for fitting the ARI responses to the ARMA step response. A two-way ANOVA showed that the correlations for both the ARI and ARMA models are significantly influenced by the mode of breathing, with the 15 bpm rate leading to the worst correlation coefficients in both cases.

Figure 2 depicts the longitudinal variability of the continuous estimates of ARI and ARMA-ARI, obtained with a 60 s moving window, for two representative subjects. On the

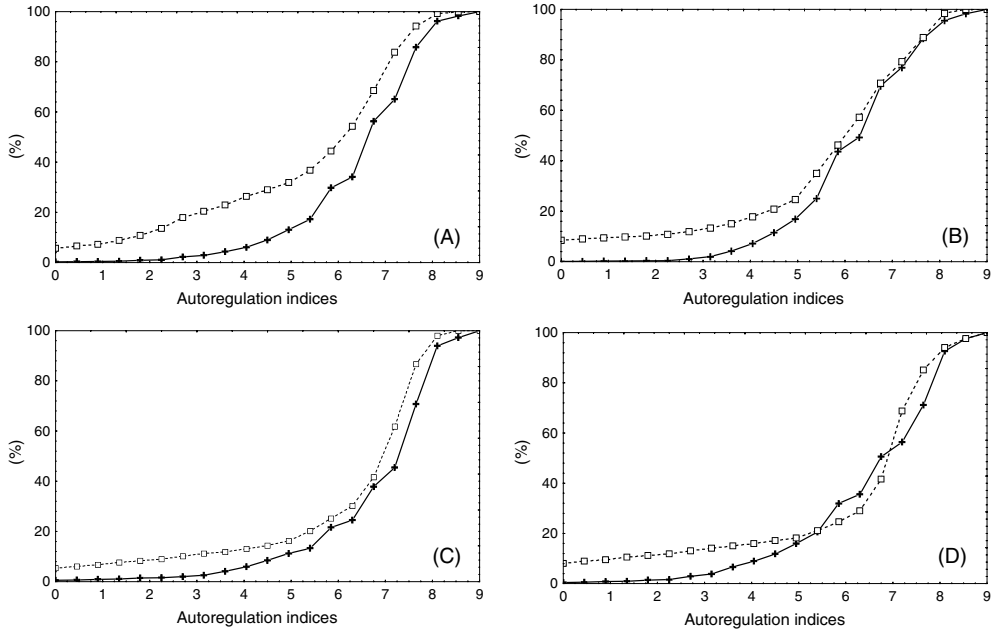

Figure 3. Cumulative probability distribution for continuous ARI (open squares, dashed line) and ARMA-ARI (crosses, continuous line) for the population studied. Spontaneous respiration is represented in (A). The other plots correspond to controlled breathing at 6 (B), 10 (C) and 15 (D) breaths min^{-1}.

left (figure 2(A)), the ARI and ARMA-ARI follow a roughly similar time course, whilst the right plot (figure 2(B)) shows sudden drops in ARI to zero, coinciding with periods in which the ARMA-ARI is reduced. A similar pattern was observed in a large number of recordings.

To characterize the distribution of the two indices, histograms were assembled separately for the right and left MCA for each breathing modality. The χ^2 test showed no significant differences between the distributions, and hence estimates from the left and right MCA were averaged for subsequent analyses. Figure 3 shows the cumulative distributions for ARI and ARMA-ARI for the spontaneous respiration and controlled breathing at 6, 10 and 15 bpm. In the four cases χ^2 points to very significant differences (largest $p = 0.008$, for 6 bpm). The distributions in figure 3 reflect the tendency of the continuous ARI to present a much higher incidence of values around zero as exemplified by figure 2(B). On the other hand, the ARMA-ARI distributions have medians between 6.2 and 7.2 and are not significantly different for the four breathing modalities considered. For visualization, the four distributions are superimposed in figure 4.

When the sequential values of ARI and ARMA-ARI are averaged for each recording, it leads to the distribution represented in figure 5, which can be compared to the corresponding values obtained when a single index was extracted from each segment of data (figure 1). The main difference observed between the two situations is for the ARI (figure 5(A)) which is less variable and does not show the ARI $= 0$ values observed in figure 1(A). The two-way ANOVA of these values confirmed a lack of effect of the breathing modality, but in this case both the ARI and ARMA-ARI showed a significant effect of the subject, with values of $p = 0.019$ and $p = 0.00014$, respectively.

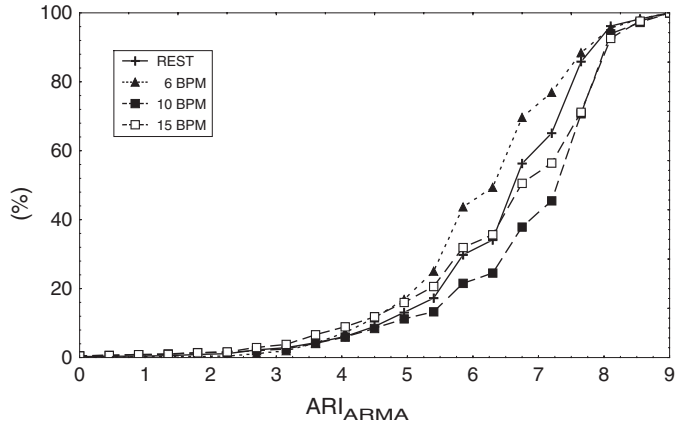

Figure 4. Population cumulative probability distributions for the continuous ARMA-ARI. REST corresponds to recordings performed during spontaneous respiration.

Despite the more stable values of ARI observed in figure 5(A), its longitudinal variability was still significantly greater than that obtained with the ARMA-ARI. For the continuous ARI the mean $\pm$ SD coefficient of variation (CV) was $30.0 \pm 21.2\%$, and for the ARMA-ARI it was $14.8 \pm 8.3\%$ (Wilcoxon $p < 10^{-6}$). The only significant effect revealed by the two-way ANOVA for the CV values is again for the subjects and only for the ARMA-ARI ($p = 0.0045$). Multiple Wilcoxon tests were also non-significant after the Bonferroni correction. Figure 6 represents the median and scatter of the CV for the four breathing modalities, showing that the median CV is at the lowest for the 10 bpm breathing rate, but larger scatter at this frequency, and at 15 bpm, probably led to this effect being missed by the two-way ANOVA.

4. Discussion

An exploration of the variability of time-domain indices of dynamic cerebral autoregulation, and their susceptibility to different modalities of breathing, has provided some objective results, but also raised a number of questions. Many of these questions are beyond the scope of the present study and will have to be addressed by future investigations. This discussion will concentrate on the main findings and limitations of the study.

4.1. Intra-subject variability

A previous study of the reproducibility of ARI has shown considerable intra-subject variation when the thigh cuff test was repeated up to six times in each subject (Mahony *et al* 2000). A more recent investigation has also found large variations in the strength of dynamic autoregulation, as reflected by the CBFV response to relatively large, but spontaneous ABP transients (Panerai *et al* 2003). Surprisingly, the majority of the healthy individuals studied have shown at least one spontaneous ABP transient where the corresponding CBFV transient response suggested the momentary absence of cerebral autoregulation (Panerai *et al* 2003). Using a sliding data window to obtain an approximately continuous estimate of ARI represents an alternative approach to study this short-term, intra-subject variability, without the need to locate specific occurrences of spontaneous transients in ABP. The results presented in figures 1–3, from an entirely different population of normal subjects, confirm those previous

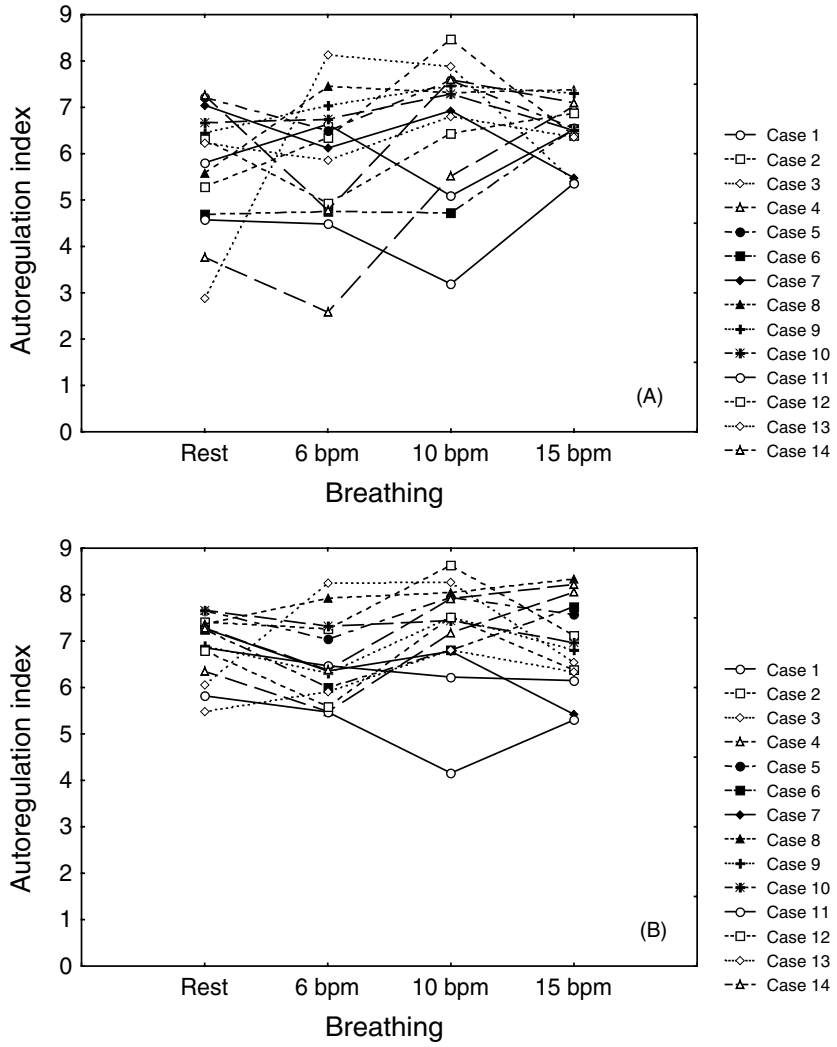

Figure 5. Mean values of continuous estimates of ARI (A) and ARMA-ARI (B) extracted from 10 min recordings during spontaneous respiration (rest) and 5 min recordings of controlled respiration at 6, 10 and 15 breaths min^{-1}.

observations of instances when ARI approached very low values, including zero. Concerns about the stability of ARI, and the sudden drops to zero (figure 2), have prompted us to explore other alternatives, such as the ARMA modelling that provided much more stable results. Fitting the pre-selected CBFV step responses predicted by Aaslid's model (Tiecks *et al* 1995), to the ARMA step response, has the advantage of maintaining a similar scale of measurement that has been used by other investigators. Further work will be necessary to clarify the reasons why the ARI presents such sudden drops to zero. One strong possibility is the limitation imposed by restricting the three main parameters to a single set of ten combinations (Tiecks *et al* 1995). Even if these sudden drops are dismissed as artefacts, the parallel changes in ARMA-ARI, shown in figure 2, also suggest a significant longitudinal, short-term variability in cerebral autoregulation indices. Care must be taken to interpret this finding though. From the observed

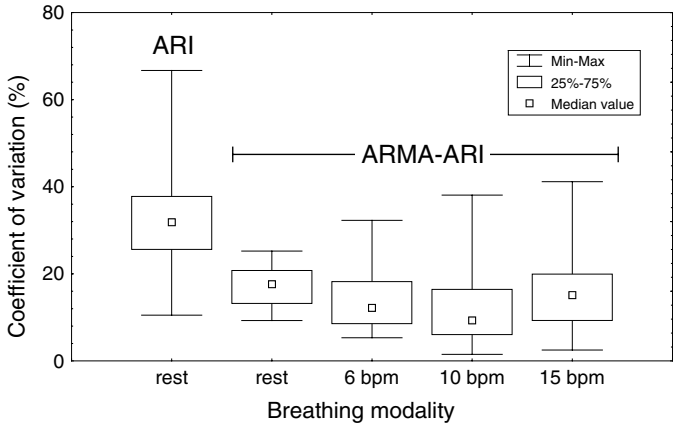

Figure 6. Median, percentile and range of longitudinal coefficient of variation (CV) of continuous estimates of ARMA-ARI for the four breathing modalities studied. For comparison, the CV for ARI during spontaneous respiration (rest) is also depicted.

temporal variations in these indices, it is not possible to conclude that the physiological mechanisms responsible for the regulation of CBF were momentarily 'switched off'. These indices only take into account the CBFV–ABP dynamic relationship, and it is possible that the interference of other physiological variables, that can also influence CBF, could cause these apparent lapses in dynamic autoregulation. A more detailed discussion of this topic has been provided by Panerai *et al* (2003). Future clinical studies should be able to provide an indication of whether the higher precision offered by ARMA-ARI, as indicated by the coefficients of variation in figure 6, will be able to provide an increased diagnostic sensitivity for cerebrovascular diseases.

4.2. Influence of respiration on dynamic autoregulation indices

One possible source of variability, that could explain the fluctuations in time-domain indices of autoregulation, is respiration. Changes in intrathoracic pressure are well known to have a strong influence on cardiac function. Neural efferent activity is also modulated by CNS mechanisms synchronous with respiration (Malpas 2002). Respiration can modulate venous cerebral pressure and hence influence cerebral perfusion pressure and CBF (Ursino and Lodi 1998). In particular, the Valsalva and Mueller manoeuvres have been shown to have a strong effect on the CBFV–ABP relationship (Tiecks *et al* 1996, Dawson *et al* 1999, Reinhard *et al* 2000). Previous studies of dynamic autoregulation have used controlled breathing at 6 bpm to measure the phase lead of CBFV in relation to ABP (Diehl *et al* 1995). Recently, Reinhard *et al* (2003) have also studied the effects of controlled breathing at 6 bpm on spectral estimates of dynamic autoregulation in patients with carotid artery disease. These authors concluded that controlled breathing at 6 bpm led to significant differences in the phase spectra, when compared to spontaneous breathing, and also had better reproducibility. From these results, they suggested that controlled breathing should be adopted as the standard protocol for studies of dynamic autoregulation. We are not aware of any other investigations adopting breathing rates of 10 and 15 bpm to assess dynamic autoregulation. What we have observed is that controlled breathing, at 6 bpm and at these two other frequencies, does not seem to affect the mean values of ARI or ARMA-ARI, or the intra-subject variability of these indices (figure 6). Therefore, we have not been able to confirm the results of Reinhard *et al*, or to demonstrate that respiration has any

influence on time-domain indices of dynamic autoregulation. Despite the significant changes in $EtCO_2$ and mean CBFV caused by controlled breathing at 10 and 15 bpm (table 1), the two-way ANOVA did not show a corresponding effect of respiration for the autoregulation indices. However, the reductions in $EtCO_2$ that we observed were relatively small, compared to other studies that have shown an improvement of dynamic autoregulation following hypocapnia (Aaslid *et al* 1989, Birch *et al* 1995).

4.3. Time-domain indices and models

From the results in figures 5 and 6, it is clear that ARMA-ARI shows a significantly smaller longitudinal variability than ARI. Undoubtedly, the sudden drops in ARI to very low values contribute to increase its variability. The major difference between the two approaches is that the ARMA of order [2, 3] has five 'free' parameters, whilst the classical ARI has only three parameters, and these are constrained by the fixed pre-established set of responses proposed by Tiecks *et al* (1995). When the ARI is calculated directly from the ABP and CBFV time series, it can lead to inappropriate solutions simply because the model parameters cannot be optimized. Sato *et al* (2001) fitted Aaslid's model to a sequence of up tilt and down tilt manoeuvres, by recalculating its three parameters. In eight normal subjects, the time constant parameter (T) varied between 2.0 and 3.0 (mean 2.55), whilst the value proposed by Tiecks *et al* (1995) is 1.90 for ARI $= 5$ and its maximum value is $T = 2.0$ for ARI $= 0$. If the CBFV–ABP signals from normal subjects require values of $T > 2.0$ for optimal fitting, as observed by Sato *et al* (2001), this would push the solution towards ARI $= 0$, and may explain why this is occasionally the case in healthy subjects (figure 1).

For the ARMA, the possibility of obtaining a better least-squares fit normally leads to robust step responses in the first place, and these can then be approximated to one of the 10 pre-determined step responses proposed by Tiecks *et al* (1995), with a reduced possibility of unstable results. The difference between the two approaches is exemplified by the mean correlation coefficients for fitting the two different models, given in table 3. For the ARMA, the values are around 0.98 whilst for the ARI, they are always less than 0.71. In addition, when the ARMA step response is fitted by one of the CBFV responses predicted by Aaslid's model, the correlations are still very high ($\approx$0.94).

4.4. Inter-subject variability

The mean value of ARI in normal individuals, as reported in the literature, is around 5. This value is not substantially different when the ARI was extracted from thigh cuff tests (Tiecks *et al* 1995, Junger *et al* 1997, White and Markus 1997, Dawson 2000, Dawson *et al* 2000, Panerai *et al* 2001, Vavilala *et al* 2002), spontaneous fluctuations (Panerai *et al* 2001), Valsalva manoeuvres (Dawson 2000, Panerai *et al* 2001), spontaneous transients (Panerai *et al* 2001) or other manoeuvres (Panerai *et al* 2001). Since these previous investigations have not used a sliding window, it is more appropriate to make comparisons with the results for the entire data record, given in figure 1 and table 2. With the exception of controlled breathing at 15 bpm, the other three conditions yielded mean values of ARI which are in reasonable agreement with previous reports. On the other hand, comparing inter-subject variability is more difficult, because of insufficient information about the number of repeated measurements performed by other investigators, which could be as many as eight thigh cuff manoeuvres in some cases (Junger *et al* 1997, Panerai 1998). From figure 1, it is clear that the much higher SD of ARI, when compared to ARMA-ARI, is due to the occurrence of outliers around ARI $= 0$. This is not a new finding though. Using six repeated thigh cuff tests, Mahony *et al* (2000)

have also reported the occurrence of very low values of ARI in normal subjects. Unfortunately, published results from other groups only give the ARI averaged for several repeated measurements, which precludes an assessment of its true dispersion.

As an alternative to ARI, the ARMA-ARI index showed a much smaller inter-subject variability (figure 1 and table 2), for all the breathing modalities under consideration. Despite its narrower distribution, the ARMA-ARI was influenced by the effect of subject in the two-way ANOVA, suggesting a higher sensitivity to individual differences. Table 2 and figure 4 also show that the mean values of ARMA-ARI tend to concentrate around 7 and thus cannot be directly compared to values of ARI from other studies. Future research, involving the application of ARMA-ARI to specific clinical conditions, will be important to assess its sensitivity to patho-physiological impairment of cerebral autoregulation.

4.5. Limitations of the study

Measurements of CBFV with Doppler ultrasound can only be assumed to reflect changes in CBF if the diameter of the middle cerebral artery (MCA) remains relatively constant for the duration of the measurement. Most studies addressing this issue have failed to demonstrate a significant change in MCA diameter, despite considerable changes in pCO_2, ABP and posture (Giller *et al* 1993, Newell *et al* 1994, Serrador *et al* 2000). Despite the lack of evidence about changes in MCA diameter, this possibility has to be kept in mind though, mainly regarding the significant longitudinal variability of the autoregulation indices demonstrated by estimates of continuous ARI and ARMA-ARI. However, as discussed previously, it is unlikely that diameter changes could explain the patterns of ARI and ARMA-ARI longitudinal variability observed in normal subjects (Panerai *et al* 2003). The use of noninvasive measurements of ABP, with the Finapres device, is also a limitation, since ABP fluctuations in the finger could be different from corresponding changes in the MCA. The Finapres device has been used in a large number of studies of cerebral autoregulation, with consistent results, both in time- and frequency-domain analyses. The latter have been particularly useful to demonstrate that coherence functions, between Finapres measurements of ABP and Doppler measurements of CBFV, have very elevated values for frequencies above 0.1 Hz. This is an indication that the finger measurements are strongly correlated to the true ABP fluctuations in the MCA.

The ARI and ARMA-ARI are only two of a large number of possible models that could be used to represent the dynamic relationship between CBFV and ABP in the time domain. Recently, Liu and Allen (2002) have used an ARMA model for this purpose, and analysed its performance and noise-sensitivity using simulated data. Neither the ARI nor the ARMA can provide further insight on the complex physiology of cerebral blood flow autoregulation. Both are formal empirical models that fit the CBFV–ABP relationship and can yield parameters that reflect autoregulatory performance. Moreover, both models are linear whilst autoregulation is an intrinsically non-linear phenomenon. One advantage of fitting these models to spontaneous fluctuations in CBFV and ABP though is the fact that the smaller amplitude of the ABP changes make the linear approximation more acceptable (Panerai 1998, Panerai *et al* 1998).

Despite the instability and variability of the ARI, as observed in figures 1 and 2, this parameter has been shown to reflect impairment of autoregulation during anaesthesia (Tiecks *et al* 1995), carotid artery disease (White and Markus 1997), head injury (Junger *et al* 1997), stroke (Dawson *et al* 2000) and hyperthermia (Doering *et al* 1999). Although the ARMA step response could be used on its own merits (Liu and Allen 2002), its approximation by the corresponding value of ARI provided a good compromise to achieve more stability whilst maintaining the same scale of measurement. It could also be argued that the use of only 60 s of data for the sliding window is insufficient to lead to stable and reliable estimates.

This argument does not hold for three main reasons. First, estimates using the entire 10 min or 5 min recording (figure 1) also led to outliers for ARI, whilst providing a distribution for ARMA-ARI that is very similar to what was obtained by the sliding window method (figure 5). Second, we have demonstrated previously that single estimates of ARI and the Wiener–Laguerre moving average model can be obtained successfully for 60 s segments of data from a number of different manoeuvres, as well as from spontaneous ABP and CBFV fluctuations (Panerai *et al* 2001). Third, and finally, data segments as short as 30 s have been used when estimating the ARI from thigh cuff manoeuvres.

Although the significant, and somewhat surprising, longitudinal variability of ARI and ARMA-ARI are reported in this study, no attempt was made to perform a formal pattern analysis as this should be the subject of future investigations. The segments of data leading to sudden reductions in ARI and ARMA-ARI (figure 2) were visually compared to the time series of $EtCO_2$, but no correlation could be established. Similarly, there were no indications that these changes could be explained by poor model fitting, as reflected by the corresponding time series of sequential correlation coefficients.

As mentioned above, one of the main limitations for research into dynamic cerebral autoregulation is the lack of a 'gold standard'. This has been true for classical methods, where several minutes of data are used to obtain time- or frequency-domain estimates of dynamic autoregulation. For sequential, or continuous estimates, the problem becomes even more acute, and it will take a considerable research effort, possibly involving many laboratories, to be able to obtain patho-physiological correlates for this novel approach.

5. Conclusions

We have demonstrated that an alternative procedure to estimate the autoregulatory index, called the ARMA-ARI, showed significantly lower variabilities than the classical ARI, for single estimates extracted from recordings lasting several minutes, and from sequential estimates using a 60 s sliding data window. Both time-domain indices were not influenced by controlled breathing at rates of 6, 10 or 15 breaths min^{-1}, when compared to spontaneous respiration. Future research should assess the diagnostic potential of ARMA-ARI and the physiological significance of the observed temporal fluctuations in dynamic autoregulation.

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