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2005 Physiol. Meas. 26 725

(http://iopscience.iop.org/0967-3334/26/5/012)

INSTITUTE OF PHYSICS PUBLISHING PHYSIOLOGICAL MEASUREMENT

Physiol. Meas. **26** (2005) 725–741 doi:10.1088/0967-3334/26/5/012

High spontaneous fluctuation in arterial blood pressure improves the assessment of cerebral autoregulation

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Received 10 February 2005, accepted for publication 7 June 2005
Published 27 June 2005
Online at stacks.iop.org/PM/26/725

Abstract

Cerebral autoregulation maintains a relatively constant blood flow despite changes of blood pressure in the brain. Linear models have been extensively applied to identify this mechanism, using spontaneous arterial blood pressure (ABP) fluctuation as input and cerebral blood flow velocity (CBFV) change as output. Although valuable measurements have been achieved by these models, accuracy and consistency are of great concern due to the large variability of results. We therefore investigated whether more reliable measurements can be achieved by selecting only those recordings (or parts of recordings) with relatively high spontaneous variability of ABP. Twenty-four recordings, 7 from hypercapnia and 17 from normocapnia, of ABP and CBFV from 9 healthy adults were analyzed. Two conventional autoregulatory parameters were used to assess cerebral autoregulation. In the absence of a 'gold' standard for the study of dynamic cerebral autoregulation, lower variability of the parameters and higher correlation with pCO_2 were considered as criteria for identifying improved measures of autoregulation. Both significantly lower variability of the parameters, and higher correlation between the parameters and pCO_2 were achieved from the data with higher variability of blood pressure. We therefore conclude that ABP with high variability may effectively stimulate regulatory response in blood flow resulting in improved assessment of cerebral autoregulation.

Keywords: cerebral autoregulation, inter- and intra-subject variability, variability of blood pressure, end-tidal CO_2

Abbreviations

ABP	Arterial blood pressure
CBFV	Cerebral blood flow velocity
CPP	Cerebral perfusion pressure
ICP	Intracranial pressure
pCO_2	End-expiratory CO_2 partial pressure
ARI	Autoregulation index
ARMA	Autoregressive moving average
nRMSE	Normalized root mean square error
Pstd	Predicted standard deviation
$Pstd_{impulse}$	Predicted standard deviation of impulse response
$Pstd_{step}$	Predicted standard deviation of step response
CoC	Correlation coefficient
$CoC_{pco_2\text{-para}}$	Correlation coefficient between pCO_2 levels and autoregulatory parameters (phase-lead and ARI)

1. Introduction

During changes of blood pressure, blood flow to the brain is normally automatically regulated to maintain nearly constant levels by the dilation or constriction of arterioles through a mechanism known as cerebral autoregulation. In early studies of autoregulation, 133 xenon, a radioactive isotope, as well as some intra-arterial techniques were used to measure blood flow and blood pressure in order to determine the status of autoregulation (Lassen 1959, Paulson *et al* 1990). These measurements have been called 'static' methods for assessing autoregulation (Panerai *et al* 1998), as they deal with an approximately steady-state response. More recently, the advent of non-invasive methods of measuring blood flow velocity by transcranial Doppler ultrasound, and blood pressure with the FINAPRES (servo-controlled finger photoplethysmography), have provided continuous recordings of the signals, which has allowed further research on the dynamic aspects of cerebral autoregulation (Newell and Aaslid 1992, Newell *et al* 1994, Imholz 1998). In order to investigate the dynamic regulatory control, a variety of manoeuvres, such as the release of an inflated thigh-cuff, lower-body negative pressure, periodic breathing, body-tilt, the Valsalva manoeuvre and a hand-grip test, have been developed to induce relatively rapid changes of blood pressure (Panerai *et al* 1998). The response of the blood flow following these interventions can reflect the status of cerebral autoregulation. However, most of these experimental tests are not suitable for clinical examination in patients who are hemodynamically vulnerable, or for continuous monitoring. Alternatively, by means of signal processing techniques, spontaneous fluctuation of the cerebral blood flow velocity and arterial blood pressure have been studied, and suggested as useful for the assessment of cerebral autoregulation, without the need to provoke large changes in blood pressure (Giller 1990, Zhang *et al* 1998, Panerai *et al* 1995, 1998). Methods that allow the continuous monitoring of cerebral autoregulation have also been developed, and used in patients following head injury (Czosnyka *et al* 1997, 2001).

Currently most of the studies of autoregulation focus on linear methods to reveal the relationship between the different physiological variables (Zhang *et al* 1998, Birch *et al* 1995, Panerai *et al* 2000, 2001, Simpson *et al* 2001). Parameters, such as phase-lead at 1/12 Hz (Birch *et al* 1995) and autoregulation index (ARI) (Tiecks *et al* 1989), acquired from time- and frequency-domain analysis have been proposed to represent the status of

cerebral autoregulation. These parameters are usually extracted from estimated impulse, step or frequency responses. However, these parameters suffer from considerable inter- or intra-subject variability and may show very large fluctuations over short periods of time (Panerai *et al* 2003a). As an alternative, segments of recordings with spontaneously occurring ABP transients have been selected explicitly (Panerai *et al* 2003b) to identify autoregulation, using coherent averaging to improve signal-to-noise ratios. It has also been found (Simpson *et al* 2004) that the random error in estimating the ARI in neonates is inversely proportional to the variability of the ABP. We therefore hypothesize that the data with high spontaneous variability of ABP might provide clearer evidence of the autoregulation response, and that those recordings with low variability of ABP may be unsuitable for measuring autoregulation. This issue does not appear to have previously received much attention in the literature. Thus, we set out to investigate if significant improvement in assessing autoregulation can be achieved by selectively analyzing data with high variability of blood pressure.

Before describing the methodology in detail, we will outline the approach applied in this study. As mentioned above, an inverse relationship between the random error in ARI and the variability of ABP was observed in neonates (Simpson *et al* 2004). In the current paper, we will first check if a similar relationship holds in an independently collected data-set from adult subjects. Secondly, we will test if the analysis of only those recordings with high variability of blood pressure can improve the detection of the impairment of autoregulation known to be induced by inhaling CO_2. Thirdly, we will investigate if it is beneficial to restrict analysis to those segments within recordings which show relatively high variability in ABP. Alternative criteria for selecting signals (goodness of fit of linear model, and predicted variance of impulse and step-responses) will also be considered.

2. Methods

2.1. Subjects and measurement

The data employed have already been independently studied in other research of cerebral autoregulation (Liu and Allen 2002). ABP and CBFV signals were recorded from nine healthy adult subjects, who were free from known cerebrovascular or cardiovascular diseases. To ensure stability of cerebral autoregulation, measurements were completed within 4 h. The measurements were undertaken with subjects lying supine. ABP was measured non-invasively by a servo-controlled finger plethysmograph (Ohmeda Finapres 2300) from a finger resting at the heart level. CBFV was recorded using 2 MHz transcranial Doppler ultrasound (DWL MultiDopT) to insonate the middle cerebral artery. Data were recorded at rest (with only spontaneous changes in ABP) during normocapnia and hypercapnia. In order to induce hypercapnia, subjects inhaled a mixture of 5% CO_2, 30% O_2 and 65% N_2 through a face mask. End-expiratory CO_2 partial pressure (pCO_2) was measured simultaneously using a capnograph (Hewlett Packard 47210A) connected to the face mask, and provided an estimate of arterial pCO_2.

2.2. Signal pre-processing

A computer with a 12-bit analog-to-digital converter was used to record the analog signals from the Doppler system, Finapres and capnograph using a sampling rate of 50 Hz. The digital signals from the converter were simultaneously recorded by a microcomputer. In total, 27 recordings, varying from 2 to 5 min in duration for normocapnia and 3 to 5 min for hypercapnia, were acquired. For six of the subjects, two recordings were made during normocapnia. Spikes

in ABP and CBFV were detected and removed by linear interpolation. The beginning and end points of each cardiac cycle was marked from the recordings of ABP, and mean values of ABP and CBFV were calculated for each heart beat. Piecewise polynomial cubic spline data interpolation was then applied to interpolate the beat-to-beat time series of mean CBFV and ABP, followed by resampling at 1 sample s^{-1}, to produce signals with a uniform time base. These recordings were normalized by their mean values, and the mean values of the resultant signals were then removed. By this means, the relative change in each signal was obtained, and will be denoted by ΔABP and ΔCBFV, respectively. By visual inspection, three recordings with evidently large artifacts were eliminated from further analysis. A sliding window with a length of 60 s was shifted by 1 sample at a time, to give overlapping segments from the recordings of ABP and CBFV (Panerai *et al* 2003a), and for each of these segments, the autoregulatory parameters were estimated, as described below.

After signal pre-processing, three recordings were eliminated due to large artifacts and noise. Twenty-four recordings were thus used in further analysis; 7 recordings from 6 subjects were from hypercapnia, and 17 recordings from 9 subjects were from normocapnia.

2.3. Computation of the parameters and criteria

Two parameters (phase-lead and ARI) were chosen to grade cerebral autoregulation. These parameters were both derived from the coefficients of a linear filter fitted to the recorded signals, with ABP as the input and CBFV as the output. ARI was derived from a second-order difference equation (Tiecks' model) which may be expressed as a z-domain transfer function:

$$G[z] = \frac{\left(1 - \frac{K}{(fT)^2}\right) + \left(\frac{1}{(fT)^2} + \frac{2D}{fT} - 2\right)z^{-1} + \left(1 - \frac{2D}{fT}\right)z^{-2}}{1 + \left(\frac{1}{(fT)^2} + \frac{2D}{fT} - 2\right)z^{-1} + \left(1 - \frac{2D}{fT}\right)z^{-2}}, \tag{1}$$

where f is the sampling rate of the data and D, T and K are the damping factor, the time constant and the autoregulation gain, respectively (Tiecks *et al* 1995). This model was proposed by Tiecks *et al* (1995) to grade the levels of cerebral autoregulation by defining ten specific combinations of values of D, T and K, corresponding to the ARI ranging from 0 (absent autoregulation) to 9 (excellent autoregulation). The ARI is then chosen by selecting the filter whose transfer function best matches the relationship between the recorded ABP and CBFV signals. In addition to ARI, we also used phase-lead to assess autoregulation. Diehl *et al* (1995) first showed the significance of phase-lead of CBFV over ABP for the study of cerebral autoregulation. In their work, large positive phase-lead was observed from normal subjects while significant reduction of the phase-lead was noted in patients with impaired cerebral autoregulation. The phase difference between CBFV and ABP at 1/12 Hz was found to be very sensitive to the status of cerebral autoregulation (Birch *et al* 1995).

In order to calculate both the ARI and phase-lead, first an FIR model (Wiener filter) was fitted to each segment:

$$y[n] = h_0 u[n] + h_1 u[n-1] + \cdots + h_{M-1} u[n-M+1] + e[n], \tag{2}$$

where $y[n]$ is the output (CBFV), $u[n]$ is the input (ABP), $h_0, \ldots, h_{M-1}$ are the coefficients of the impulse response, M is the length of the impulse response and $e[n]$ denotes the error between predicted and measured outputs.

Equation (2) can be expressed in matrix form as

$$y[n] = \varphi^{\mathrm{T}}[n]\theta + e[n], \tag{3}$$

where

$$\varphi^{\mathrm{T}}[n] = (u[n], \ldots, u[n-M+1]), \tag{4}$$

and

$$\theta = (h_0, \ldots, h_{M-1})^{\mathrm{T}}. \tag{5}$$

By minimizing the mean-square value of the error, $e[n]$, the estimated impulse response, $\hat{\theta}$, can be calculated as

$$\hat{\theta} = (\Phi^{\mathrm{T}}\Phi)^{-1}\Phi^{\mathrm{T}}Y, \tag{6}$$

where

$$\Phi = (\varphi[1], \ldots, \varphi[N])^{\mathrm{T}}, \tag{7}$$

and

$$Y = (y[1], \ldots, y[N])^{\mathrm{T}}. \tag{8}$$

For an FIR model, $(\Phi^{\mathrm{T}}\Phi)^{-1}$ is the autocorrelation matrix of the input and $\Phi^{\mathrm{T}}Y$ is the cross-correlation between the input and output. Panerai *et al* (2003a) used the first 6 s of the impulse response from an autoregressive moving average (ARMA) model as the autoregulatory response is largely complete during this time. We therefore choose a sixth-order FIR model (6 s impulse response). The step response was then calculated from the cumulative sum of the impulse response. In order to avoid the large random errors that accumulate in the tail of the step response (Liu *et al* 2004), we only used the first 4 s of the step response to estimate the ARI. The mean-square error between this step-response and each of the ten step-responses defined according to Tiecks' model (Tiecks *et al* 1995) is then calculated. The ARI corresponding to the best fit is then selected. As an alternative measure of autoregulation, the phase at 1/12 Hz was obtained by Fourier analysis of the impulse response (Birch *et al* 1995). Since phase-lead is calculated from the impulse response rather than the step-response (i.e. we do not use the cumulative sum of filter parameters), the response was not truncated at 4 s, but the full 6 s duration was analyzed. This was then also zero-padded to provide the spectral resolution required for calculating the phase.

The two autoregulation parameters (ARI and phase-lead) were calculated for each of the overlapping 1 min long data segments, in each of the 24 recordings. The standard deviation of the parameters obtained from within one recording was considered as the intra-subject variability. In order to quantify the variability of blood pressure, we calculated the normalized root-mean-square (denoted as σ_{ABP}) value of ΔABP for each segment. Since ΔABP is the relative change of ABP, σ_{ABP} is given as a percentage. In addition to σ_{ABP}, two other criteria that might be helpful in selecting data were investigated. (1) The normalized root-mean-square error (nRMSE) was calculated from the error, $e[n]$, in equation (3), for each segment. This criterion quantifies how well the FIR model fits the data. (2) The standard deviation of impulse response ($\mathrm{Pstd}_{\mathrm{impulse}}$) or step response ($\mathrm{Pstd}_{\mathrm{step}}$) can also be predicted from theory (Soderstrom and Stoica 1989):

$$\mathrm{cov}(\hat{\theta}) = (\Phi^{\mathrm{T}}\Phi)^{-1}\Phi^{\mathrm{T}}R\Phi(\Phi^{\mathrm{T}}\Phi)^{-1}, \tag{9}$$

where $\mathrm{cov}(\hat{\theta})$ is the covariance matrix of the estimated impulse response, and

$$R = E\{ee^{\mathrm{T}}\}. \tag{10}$$

$\mathrm{Pstd}_{\mathrm{impulse}}$ was found as the root of the mean of the diagonal of the matrix $\mathrm{cov}(\hat{\theta})$. $\mathrm{Pstd}_{\mathrm{step}}$ can be found by a cumulative sum of terms in $\mathrm{cov}(\hat{\theta})$.

Thus, we have three criteria, variability of blood pressure (quantified by σ_{ABP}), nRMSE and Pstd to select data, and two parameters (ARI and phase-lead) to assess the status of cerebral autoregulation. These were then used firstly to assess if the variability (standard deviation) of autoregulatory parameters (ARI and phase-lead) is correlated with σ_{ABP}, nRMSE, $\mathrm{Pstd}_{\mathrm{step}}$ or $\mathrm{Pstd}_{\mathrm{impulse}}$. However, since reduced variability may be at the cost of reduced sensitivity to

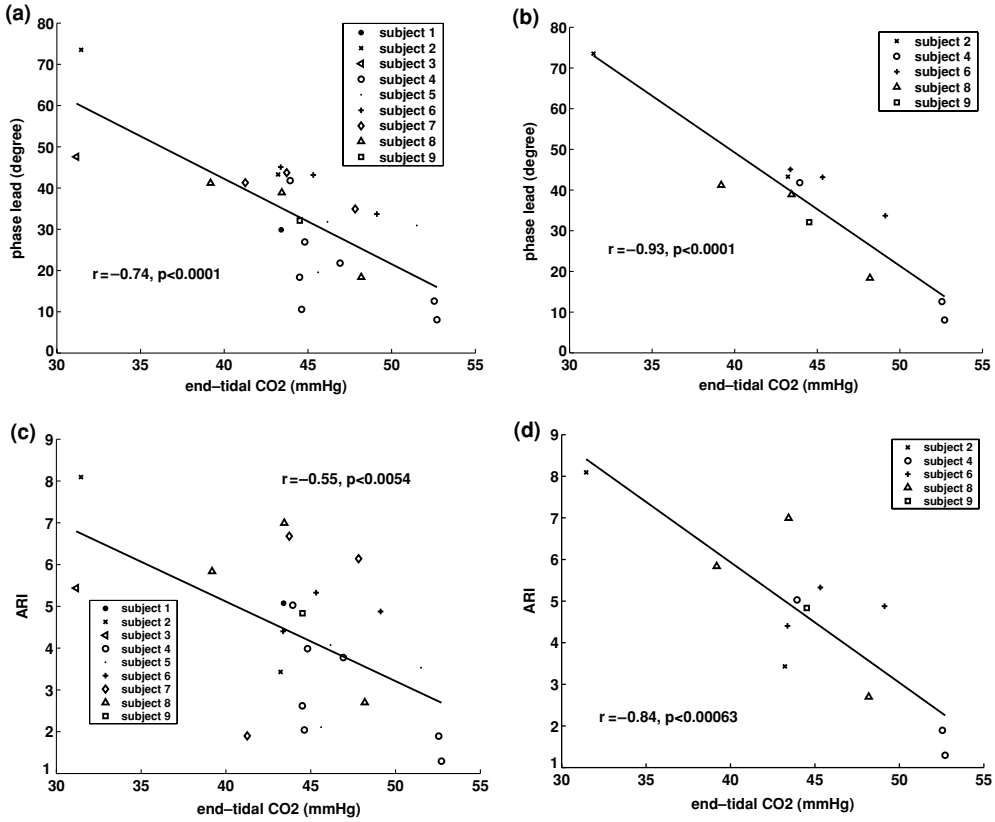

Figure 1. An example of using σ_{ABP} to select recordings. The correlation between the pCO_2 level (measured by end-tidal CO_2) and the parameters (phase-lead shown in (a) and (b), ARI shown in (c) and (d)) were plotted out. Parameters estimated from all 24 recordings were plotted in (a) and (c) using 9 symbols to denote the 24 recordings from 9 subjects. After the selection of the 'best' recordings according to σ_{ABP}, higher correlation coefficients were achieved, as indicated in (b) and (d).

change in autoregulatory status, in a second stage we also computed the correlation coefficient between the autoregulation parameters and the pCO_2 levels. It is well known that the pCO_2 level in cerebral arteries is correlated with the status of cerebral autoregulation (Paulson *et al* 1990). Since there is no generally accepted gold-standard for assessing dynamic autoregulation under a broad range of clinical conditions (Panerai *et al* 1998), we used the correlation with pCO_2 to test whether selected signal segments and recordings provide more robust measures of autoregulation. The methods applied for these calculations will be described and explained in more detail below.

2.4. Select recordings and significance tests

As illustrated in figures 1(a) and (c), we calculated the correlation coefficient between pCO_2 and ARI, and phase-lead, respectively. The correlation coefficient between pCO_2 and autoregulatory parameters will be abbreviated as $CoC_{pco_2\text{-para}}$, where the *para* stands for the parameters (ARI or phase-lead). We then repeated this calculation for only the recordings selected according to the criterion of highest σ_{ABP} (figures 1(b) and (d), where only the nine 'best' recordings are included).

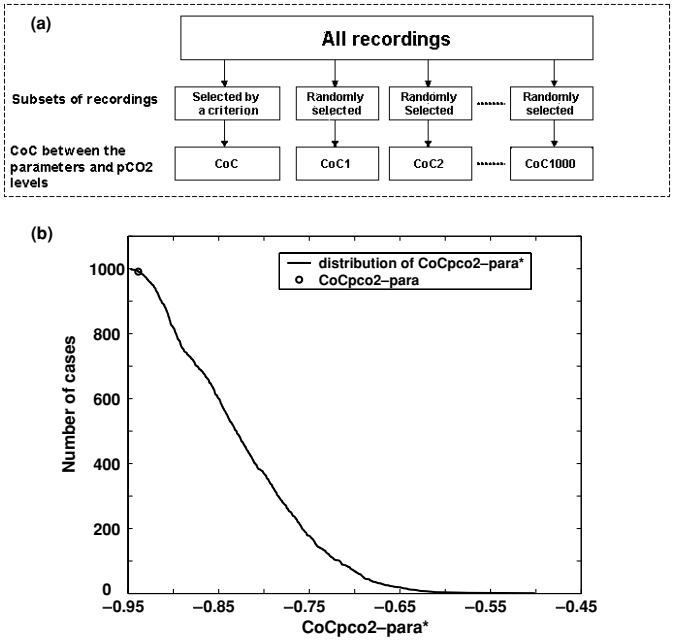

Figure 2. (a) A block diagram showing the calculation of the correlation coefficients (CoC) first from the data selected according to the chosen criterion, and the data by random resampling (CoC1 ··· CoC1000). (b) An example of the distribution function for $\mathrm{CoC}_{\mathrm{pco_2\text{-}para}}{}^{*}$, the ordinate gives the number of resamples (out of 1000) that were larger than or equal to any given value of CoC (abscissa). The circle indicates the $\mathrm{CoC}_{\mathrm{pco_2\text{-}para}}$ obtained from the five recordings with the highest σ_{ABP}. In this case, only 34 of the 1000 randomly selected samples were more strongly correlated with $\mathrm{pCO_2}$ ($\mathrm{CoC}_{\mathrm{pco_2\text{-}para}}{}^{*}$) than the sample with highest σ_{ABP} ($|\mathrm{CoC}_{\mathrm{pco_2\text{-}para}}| > |\mathrm{CoC}_{\mathrm{pco_2\text{-}para}}{}^{*}|$), giving $p = 0.034$, and indicating that the $\mathrm{CoC}_{\mathrm{pco_2\text{-}para}}$ is significantly lower than expected under $\mathrm{H_0}$, at a significance level of $\alpha = 0.05$.

In order to test if the recordings selected according to the chosen criteria provide statistically significant improvements in $\mathrm{CoC}_{\mathrm{pco_2\text{-}para}}$, we use an approach based on resampling the data (see figure 2(a)). The purpose is to test if the $\mathrm{CoC}_{\mathrm{pco_2\text{-}para}}$ from the selected recordings is greater than that obtained from a random set of recordings. To this end we first selected the five recordings with the highest mean σ_{ABP}, and calculated the correlation coefficient between $\mathrm{CO_2}$ and ARI, or phase-lead, respectively, for this set of recordings ($\mathrm{CoC}_{\mathrm{pco_2\text{-}para}}$). We then randomly selected (without replacement) five recordings from the set of 24, and again found the $\mathrm{CoC}_{\mathrm{pco_2\text{-}para}}$ (denoted by $\mathrm{CoC}_{\mathrm{pco_2\text{-}para}}{}^{*}$). The latter step was repeated $N = 1000$ times, providing an estimate of the distribution of $\mathrm{CoC}_{\mathrm{pco_2\text{-}para}}{}^{*}$, under the null hypothesis ($\mathrm{H_0}$) of no effect arising from the selection of recordings. An example of such an estimated probability distribution function is plotted in figure 2(b) (note the negative correlation coefficients). We then recorded the fraction of $\mathrm{CoC}_{\mathrm{pco_2\text{-}para}}{}^{*}$ that were less (higher in absolute value) or equal to the $\mathrm{CoC}_{\mathrm{pco_2\text{-}para}}$ (as found for the five recordings with the highest σ_{ABP}). This provides an estimate of the significance level (p value) for $\mathrm{H_0}$: if $p < 0.05$, we consider that $\mathrm{CoC}_{\mathrm{pco_2\text{-}para}}$ for our selected recordings is unusually (and statistically significantly) low. Finally, we repeated this test but selecting the $6, 7, \ldots, 20$ recordings with the highest σ_{ABP} out of the total of 24 recordings. The range of recordings selected (5–20) was based on a Monte Carlo simulation, in which we confirmed the effectiveness of this resampling methodology.

2.5. Selecting segments and testing for significant change

After the investigation into selecting whole recordings, we considered whether shorter segments within each recording should be selected. We thus tested again (1) if these 1 min long segments with higher σ_{ABP} provide lower standard deviation of autoregulation parameter estimates and (2) if these segments lead to improved correlation with pCO_2. To this end, the 60 s long segments in each recording were split into two subsets, with high and low σ_{ABP}. The level for group membership was set at a fixed percentage, above and below the mean σ_{ABP} for each recording (values between 1% and 5% were investigated). For instance, when the level was set to 1%, the σ_{ABP} of the segments in the group of high σ_{ABP} would be at least 1% higher than the mean σ_{ABP} for that recording, and those in the group of low σ_{ABP} would be at least 1% lower than the mean σ_{ABP}; segments with σ_{ABP} between these levels were neglected in further analysis. If less than five segments remained in either of the groups, the recording would be eliminated from further investigation. This was the case for one recording, and then only at the 5% σ_{ABP} level. In a further stage of the study, segments were then also selected using Pstd and nRMSE as alternative criteria, following a similar approach.

We compared the dispersion of the step responses estimated from the two subsets of segments (high and low σ_{ABP}) to show if higher variability of blood pressure leads to more consistent step responses. Figure 3 shows an example. The step responses from the subsets of the segments were averaged for each subject in both hypercapnia and normocapnia. Less dispersion of the step response was therefore expected from the subsets with high σ_{ABP}. In order to confirm this statistically, a test was also applied to show the relationship between the σ_{ABP} and the variability of the parameters (ARI and phase-lead). For this test, the standard deviation of the autoregulatory parameters and the mean value of the σ_{ABP} were calculated for each subset of segments at different threshold levels. Then we correlated these two resultant values to show their relationship.

In order to compare $CoC_{pco_2\text{-para}}$ from the two subsets (with high and low σ_{ABP}), conventional significance tests are not appropriate, since the segments overlap with consequently correlated data, leading to unknown degrees of freedom for say a *t*-test. Therefore, a resampling method was again employed. The procedure was as follows:

(1) Randomly select one segment from each group (high and low σ_{ABP}) in each recording. Thus, for 24 recordings, 48 segments were selected.
(2) Calculate autoregulation parameters (phase-lead and ARI) from these segments.
(3) For each group, calculate $CoC_{pco_2\text{-para}}$ using the parameters estimated, and the pCO_2 levels.
(4) Repeat steps (1) to (3) 500 times. Thus 500 pairs of $CoC_{pco_2\text{-para}}$ were obtained. The significance of the difference between these two sets of data was evaluated using the Mann–Whitney *U*-test. The same method was also applied using the criteria of Pstd and nRMSE for selecting segments of recordings.

In all statistical tests, the results were considered significant if $p < 0.05$.

3. Results

3.1. Relationship between the parameters, estimates and variables

Following visual inspection of the data, σ_{ABP} was log-transformed prior to correlating in order to linearize the linear relationship between σ_{ABP} and the standard deviation of the autoregulatory parameters. σ_{ABP} is significantly correlated with the standard deviation of

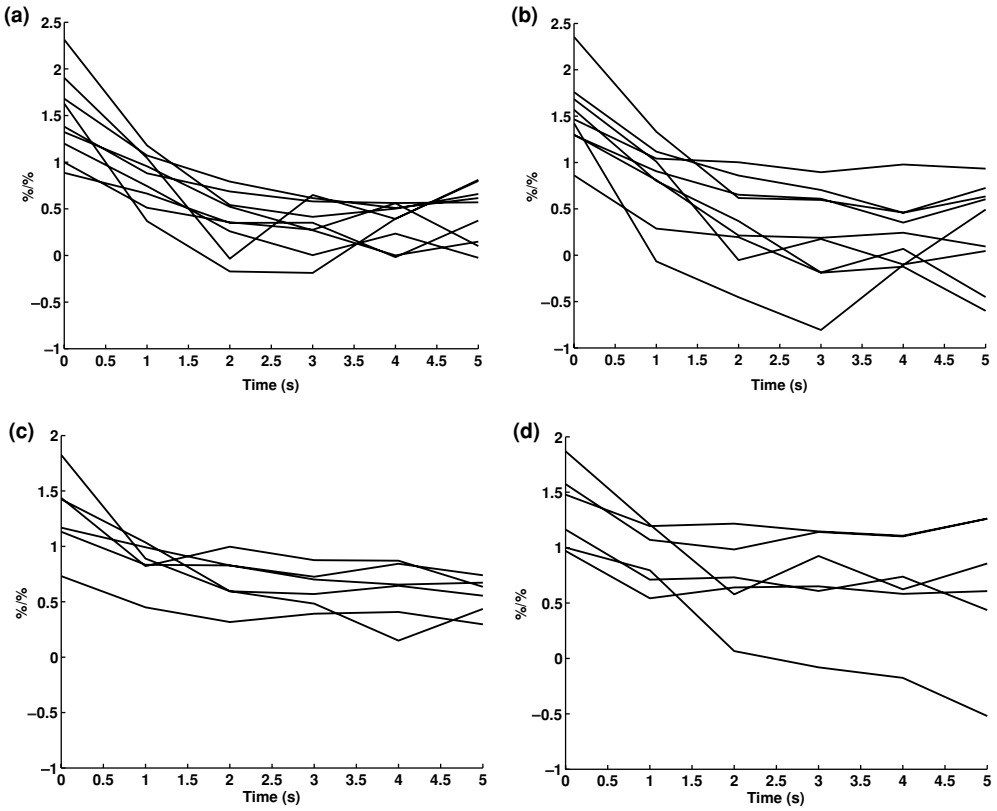

Figure 3. The step responses estimated from segments with high ((a), (c)) and low ((b), (d)) σ_{ABP}. The step responses from the selected segments were averaged for each subject. Each line in these plots is the mean value of the step responses from the segments selected by σ_{ABP} from one subject. Step responses in (a) and (b) (from seven subjects) are from normocapnia and those in (c) and (d) (from six subjects) are from hypercapnia. The step responses were obtained at 1% threshold level of σ_{ABP}.

Table 1. Correlation coefficients between the standard deviation of the parameters and values of different criteria.

STD of the parameters	σ_{ABP} (in log scale)	$Pstd_{impulse}$	$Pstd_{step}$	nRMSE
Phase-lead	-0.44^{*}	0.44^{*}	0.56^{**}	0.42^{*}
ARI	-0.44^{*}	0.42^{*}	0.56^{**}	0.38

$^{*}p < 0.05$.
$^{**}p < 0.01$.

the phase-lead and ARI (table 1, $p = 0.031$ for both phase-lead and ARI). As expected, the standard deviation of the parameters decreases when the σ_{ABP} of the recordings increases. The correlations between the standard deviation of the parameters and other criteria ($Pstd_{impulse}$, $Pstd_{step}$ and nRMSE) are also given in table 1. Note that we first calculated the predicted standard deviation of each coefficient of the impulse and step responses for each segment of each recording according to (8). $Pstd_{impulse}$ and $Pstd_{step}$ were then found by averaging the predicted standard deviation of all coefficients for that recording. These Pstd were also found to be highly correlated with the standard deviation of the estimates which were calculated

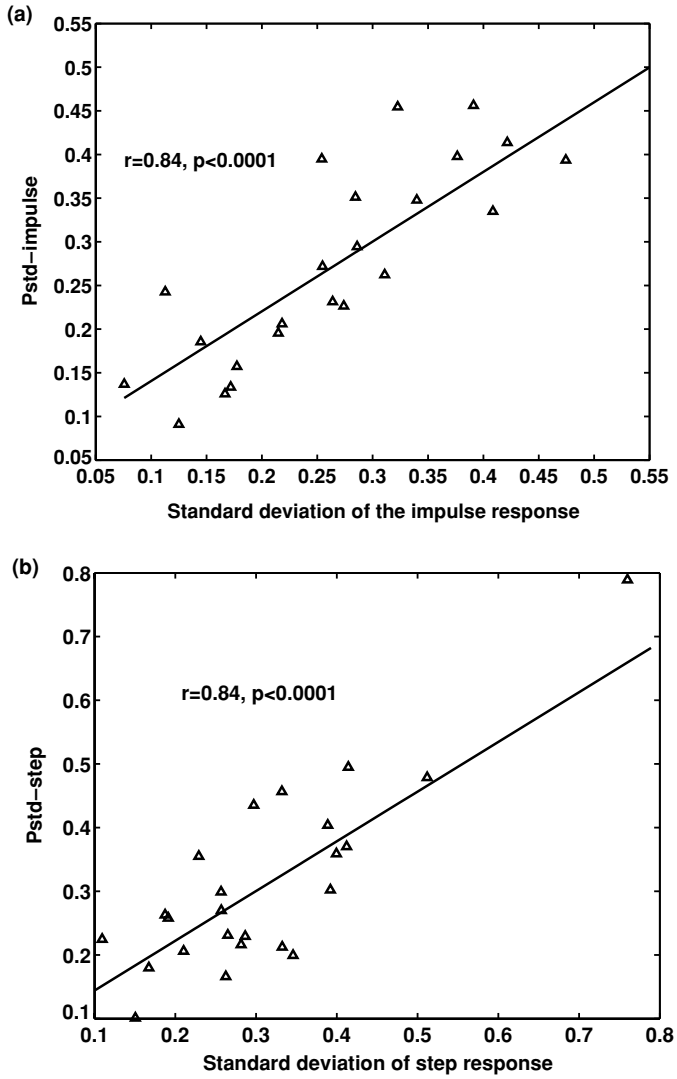

Figure 4. Predicted standard deviation of impulse and step responses (Pstdi and Pstds) against standard deviations of impulse (a) and step (b) responses as estimated from the overlapped segments. Each triangle represents one recording. The solid lines in the two plots are the regression lines.

from the successive segments in each recording ($r = 0.84$, $p < 0.0001$ for both $\text{Pstd}_{\text{impulse}}$ and $\text{Pstd}_{\text{step}}$), as illustrated in figure 4.

From table 1 it is evident that the standard deviations of the parameters ARI and phase-lead were most strongly correlated with $\text{Pstd}_{\text{step}}$. This may at first suggest that $\text{Pstd}_{\text{step}}$ might be the best criterion for selecting data. However, as discussed above, correlation with CO_2 should also be considered. This is carried out in the next section.

3.2. Results for selecting recordings

Figure 1 shows an example of how $\text{CoC}_{\text{pco}_2\text{-para}}$ was improved when using the σ_{ABP} to select recordings. In this figure, 12 (figure 1(b)) and 10 recordings (figure 1(d)) were selected for

Table 2. The correlation coefficients between the parameters (phase-lead and ARI) and pCO_2. The correlation was calculated for an increasing number of recordings (first column), which are the 'best' according to each of the four criteria.

Number of the recordings	$CoC_{pco_2\text{-para}}$							
	Phase-lead				ARI			
	σ_{ABP}	$Pstd_{impulse}$	$Pstd_{step}$	nRMSE	σ_{ABP}	$Pstd_{impulse}$	$Pstd_{step}$	nRMSE
5	−0.95*	−0.82	−0.97	−0.73	−0.86*	−0.54	−0.41	−0.26
6	−0.94*	−0.85	−0.80	−0.78	−0.86*	−0.63	−0.25	−0.33
7	−0.93*	−0.85	−0.77	−0.83	−0.86*	−0.67	−0.21	−0.25
8	−0.94*	−0.85	−0.87	−0.85	−0.88*	−0.67	−0.54	−0.30
9	−0.93*	−0.90	−0.84	−0.66	−0.88*	−0.81	−0.56	−0.36
10	−0.94*	−0.90	−0.84	−0.87	−0.90*	−0.67	−0.57	−0.53
11	−0.94*	−0.88	−0.84	−0.85	−0.86*	−0.64	−0.57	−0.51
12	−0.94*	−0.87	−0.86	−0.82	−0.85*	−0.63	−0.64	−0.50
13	−0.93	−0.85	−0.85	−0.82	−0.83*	−0.64	−0.64	−0.50
14	−0.90	−0.83	−0.83	−0.84	−0.80	−0.56	−0.56	−0.63
15	−0.90	−0.83	−0.80	−0.85	−0.79	−0.56	−0.57	−0.62
16	−0.89	−0.80	−0.80	−0.84	−0.79	−0.57	−0.54	−0.63
17	−0.90	−0.90	−0.91	−0.84	−0.73	−0.77	−0.75	−0.56
18	−0.90	−0.90	−0.90	−0.83	−0.73	−0.75	−0.73	−0.49
19	−0.90	−0.90	−0.86	−0.77	−0.73	−0.73	−0.68	−0.49
20	−0.89	−0.89	−0.84	−0.77	−0.72	−0.67	−0.63	−0.47

*If $p < 0.05$ from the resampling test.

having the highest σ_{ABP}, and phase-lead and ARI were used to assess autoregulation. In both cases the right-hand figures clearly show improved correlation from the selected recordings, and the statistical resampling test confirms this. The results for all selections are given in table 2. The first column gives the number of recordings selected, using as criterion that they have the highest σ_{ABP}, or lowest $Pstd_{impulse}$, $Pstd_{step}$ and nRMSE. It may be noted that the correlation coefficients from the recordings with higher σ_{ABP} were found to be higher than those from any of the other three criteria (with the exception of 5 out of a total of 96 comparisons made). There is also statistically significant improvement (from the resample test) in the correlation coefficient when selecting the 5 to 12 recordings with the highest σ_{ABP}. The corresponding p values are shown in figure 5, where $p < 0.05$ for selecting up to 12 recordings, for both ARI and the phase-lead. Equivalent plots but using nRMSE, $Pstd_{impulse}$ or $Pstd_{step}$ to select recordings do not suggest that CoC is improved by the selection (see table 2).

3.3. Results for selecting segments

Since reduced standard deviation of the parameters, and higher $CoC_{pco_2\text{-para}}$ were obtained by selecting recordings with high σ_{ABP}, we extended our study to select segments within each recording to test if higher variability of ABP helps assessment of cerebral autoregulation in shorter data lengths (1 min for each segment). Figure 3 gives an example of the mean step responses (averaged within each subject) obtained from the two subsets of segments at the 1% level for σ_{ABP}. Larger dispersion (figures 3(b) and 5(d)) of the step responses for signals with low σ_{ABP} is observed in this figure, indicating high inter-subject variability. There is also significant correlation between σ_{ABP} (log-transformed) and the variability of autoregulatory

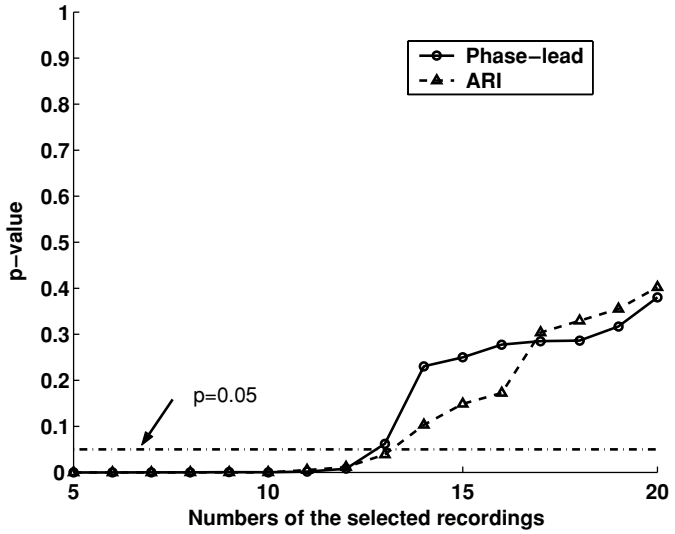

Figure 5. The p value of the significance test to determine whether the parameters phase-lead (solid line and circles) and ARI (dashed line and triangles) from the set of recordings with the highest σ_{ABP}. The horizontal line marks $p = 0.05$.

Table 3. Mean value ± standard deviation of the correlation coefficients in selecting segments, as calculated from the 500 resamples.

Levels of		σ_{ABP}		
σ_{ABP} (%)	Parameters	High	Low	p value
1	Phase-lead	-0.73 ± 0.083	-0.69 ± 0.090	<0.0002
	ARI	-0.43 ± 0.12	-0.41 ± 0.10	<0.0002
1.5	Phase-lead	-0.73 ± 0.083	-0.69 ± 0.092	<0.0002
	ARI	-0.43 ± 0.11	-0.40 ± 0.10	<0.0002
2	Phase-lead	-0.74 ± 0.067	-0.69 ± 0.099	<0.0002
	ARI	-0.44 ± 0.10	-0.42 ± 0.10	<0.0002
2.5	Phase-lead	-0.75 ± 0.063	-0.68 ± 0.088	<0.0002
	ARI	-0.50 ± 0.092	-0.42 ± 0.097	<0.0002
3	Phase-lead	-0.75 ± 0.059	-0.68 ± 0.084	<0.0002
	ARI	-0.47 ± 0.091	-0.42 ± 0.085	<0.0002
3.5	Phase-lead	-0.75 ± 0.060	-0.69 ± 0.10	<0.0002
	ARI	-0.43 ± 0.090	-0.40 ± 0.088	<0.0002
4	Phase-lead	-0.75 ± 0.074	-0.69 ± 0.12	<0.0002
	ARI	-0.44 ± 0.087	-0.42 ± 0.065	<0.0002
4.5	Phase-lead	-0.75 ± 0.060	-0.69 ± 0.10	<0.0002
	ARI	-0.44 ± 0.092	-0.41 ± 0.097	<0.0002
5	Phase-lead	-0.74 ± 0.067	-0.69 ± 0.096	<0.0002
	ARI	-0.44 ± 0.087	-0.41 ± 0.096	<0.0002

parameters obtained from the subsets of segments: $r = -0.41$ and $p = 0.0043$, and $r = -0.33$ and $p = 0.019$ for phase-lead and ARI, respectively.

By random selection of the segments, 500 $\mathrm{CoC}_{\mathrm{pco_2\text{-}para}}$ were computed for each group. The results were compared through the Mann–Whitney U-test (table 3). All the $\mathrm{CoC}_{\mathrm{pco_2\text{-}para}}$ from the segments with high σ_{ABP} are higher than those from low σ_{ABP} ($p < 0.0001$).

Similar to selecting recordings, strong correlations were also observed between the other two criteria and the standard deviation of the parameters ($Pstd_{step}$: $r = 0.68$ and $p < 0.0001$, and $r = 0.52$ and $p = 0.0003$ for the correlations of phase-lead and ARI, respectively; nRMSE: $r = 0.38$ and $p = 0.0078$, and $r = 0.25$ and $p > 0.05$ for the correlations of phase-lead and ARI, respectively). As in the selection of whole recordings, $Pstd_{step}$ gives the highest correlation. However, when using Pstd and nRMSE as criteria for selecting data segments, $CoC_{pco_2\text{-para}}$ was not increased significantly ($p > 0.05$, Mann–Whitney U-test), indicating that the use of Pstd and nRMSE does not help improve the sensitivity of detecting the autoregulatory changes.

4. Discussion

4.1. Reducing the variability of the autoregulatory parameters by selecting data

In previous work, changes in autoregulation have been induced by hypercapnia (e.g. Simpson *et al* 2000, 2001, Liu and Allen 2002). However, measures of autoregulation used do not always indicate impairment of autoregulation in each individual subject, though statistically significant changes in the average values obtained from groups of subjects are consistently evident in many studies. It is likely that this poor sensitivity is at least partly due to the large inter- and intra-subject variability of autoregulatory parameter estimates, which has also been noted repeatedly (Birch *et al* 1995, Simpson *et al* 2001, Panerai *et al* 2003a, 2003b). The sources of the variability have been summarized by Birch *et al* (1995) and Panerai *et al* (2003b). Physiological variations and methodological issues, compounded when analyzing signals that may not be eliciting strong autoregulatory responses, probably contribute to the strong variations in results observed. It is this latter aspect that the current work focuses on.

By increasing the power of the induced changes of ABP and introducing new autoregulatory indices, efforts have been made to achieve more reliable assessment of autoregulation with less variability (Birch *et al* 1995, Panerai *et al* 2003a). In a recent study, using Tiecks' model, (ARI) and a bootstrap method to assess the statistics of ARI estimates, Simpson *et al* (2004) showed that in some recordings, the ARI estimates appear very robust, but in others there is considerable spread, and sampling distribution of ARI estimates may even be bimodal, suggesting that two very different values of ARI may be appropriate for different parts of a recording. Importantly for the current investigation, the authors found an inverse relationship between the standard deviation of the ARI and the variability of ABP (Simpson *et al* 2004), suggesting that high variability of ABP might assist in achieving a robust assessment of ARI.

In the current work we therefore tested if, when analyzing signals during only spontaneous fluctuations in ABP and CBFV, some recordings or segments within recordings should be eliminated from the study of cerebral autoregulation, and investigated different criteria for selecting such data.

The current work on adult data is in agreement with the previous results from neonates, showing correlation between the variability of ABP and the standard deviation of ARI. In addition, we found that the criteria of Pstd and nRMSE are also correlated with the dispersion in the estimates of ARI (table 1). Similar results hold for phase-lead as a parameter to assess autoregulation. These criteria are thus useful both in selecting whole recordings and segments within the recordings. However, reduced dispersion in estimates does not ensure greater sensitivity to changes in autoregulation, and that was then considered by correlating autoregulation measures with arterial pCO_2.

4.2. Correlation between end-tidal pCO_2 and parameters

It is well known that arterial pCO_2 is a very powerful systemic stimulus in cerebral vasodilation (Paulson *et al* 1990, Panerai *et al* 1998). Impaired autoregulation can also be induced by an increase of pCO_2 level. This can be understood by considering the effect of increasing metabolic demand, which leads to increased production of CO_2, triggers cerebral vasodilation, and reduces the brain's ability to further respond to changes in arterial blood pressure (Paulson *et al* 1990). Different autoregulatory parameters have been found to be strongly correlated with pCO_2 levels (Simpson *et al* 2000, Liu and Allen 2002). This has been exploited in many papers (Lodi *et al* 1998, Panerai *et al* 1999a, 1999b, Simpson *et al* 2000, 2001) as a simple means of altering autoregulatory status. In our experiments, the $CoC_{pco_2\text{-para}}$ played an important role in determining the validity of selecting data. The analysis of the dispersion in the estimates suggests that Pstd might be the best criterion for selecting recordings (table 1). However, in comparing the $CoC_{pco_2\text{-para}}$, significantly higher ($p < 0.05$) $CoC_{pco_2\text{-para}}$ was obtained from the recordings with high σ_{ABP} than from the recordings selected by the criteria of $Pstd_{impulse,}$ $Pstd_{step}$ or nRMSE (with very few exceptions, see table 2), or a random selection of the recordings. In the experiment of selecting segments, the parameters estimated from the segments with high σ_{ABP} were also more strongly correlated with the pCO_2 levels than those from the segments with low σ_{ABP}.

4.3. High variability of ABP

According to the results of this study, high σ_{ABP} is helpful in assessing cerebral autoregulation in spontaneously varying data. In a previous study of spontaneous ABP transients, it was found that small mean ABP amplitude of the transients from healthy subjects was associated with weak cerebral autoregulation (Panerai *et al* 2003b). The authors hypothesized that there is possibly a pressure threshold below which the response is not fully developed. The threshold suggested in their work was a pressure difference from the foot to the top of the transient of approximately 5 mmHg. In our approach, we used linear filters to identify cerebral autoregulation from longer segments of data, not just from selected transients. We did not observe statistically significant correlation between σ_{ABP} and the autoregulatory parameters (i.e. no higher autoregulatory parameter values when σ_{ABP} increased), in disagreement with the observations cited above (Panerai *et al* 2003b). This may have arisen from the different techniques: they only selected fragments of the signals, whereas we used longer continuous segments. However, both of the studies suggest that data with only small changes of ABP should be avoided in the analysis of autoregulation.

Birch *et al* (1995), using lower body negative pressure to study autoregulation, also found that large changes of ABP induced by increasing the power of the 'vacuum box' can lead to less variant assessments of cerebral autoregulation. These results again suggest that there may be a minimal value of variability necessary for the robust assessment of autoregulation. However, they only tested two pressure levels and did not systematically compare the effects of applying different strengths of the vacuum in the assessment of autoregulation. In our study, we compared the $CoC_{pco_2\text{-para}}$ at different σ_{ABP} levels to show a threshold level of σ_{ABP} above which significantly better assessment of autoregulation can be achieved (see figure 5).

In order to seek thresholds for selecting recordings and segments, different numbers of recordings and different σ_{ABP} levels were tested in our study. For the selection of recordings, p-value lines below 5% were observed when selecting from 5 to 12 of the 24 recordings. When $\sigma_{ABP} > 3.5\%$, 12 of the 24 recordings were selected, and both parameters ARI and phase-lead achieve significant improvements in $CoC_{pco_2\text{-para}}$ (see figure 5). Therefore, $\sigma_{ABP}>3.5\%$ may

be a suitable threshold level, and recordings with σ_{ABP} below this level should possibly be discarded for assessing autoregulation. For the selection of segments within recordings, eight different levels of the σ_{ABP} were tested, as shown in table 3, but results are all very similar (see table 3). In order to discard as little data as possible, we recommend that the 1% threshold level be chosen for selecting segments.

In the light of system analysis considerations, it is not surprising that greater power in the input signal (ABP) leads to more robust system identification. However, this still required experimental confirmation on data from adult human volunteers, considering that recorded signals may be contaminated by noise and artifact, and that this is a very complex system, for which only a single input (ABP)–single output (CBFV) model was studied. Thus other inputs that are known to be important (spontaneous fluctuations in CO_2, metabolic activity, intracranial pressure) are neglected. The results confirm that high variability of ABP is associated with both reduced dispersion in estimates of ARI and phase-lead, and also increased correlation with CO_2 levels. The alternative criteria considered, Pstd and nRMSE, were found to be less appropriate for identifying the signals most suited for the robust estimation of autoregulation.

4.4. Limitations of the study

In the current work intracranial pressure has not been considered. It has been argued (Lassen *et al* 1959, Paulson *et al* 1990, Czosnyka *et al* 2001) that cerebral perfusion pressure (usually given as the difference between arterial blood pressure and intracranial pressure) should be considered when assessing autoregulation. This is physiologically more appropriate, and avoids the risk of confusing autoregulation (active control of cerebral arterioles) with 'false autoregulation' (intracranial pressure increasing simultaneously with arterial blood pressure, leaving blood flow unchanged, without arteriolar contraction—Enevoldsen and Jensen (1978)), thus failing to detect a potentially important dysfunction. However, intracranial pressure measurement usually requires invasive techniques, which cannot be carried out in normal volunteers (or indeed most patients). In the normal subjects considered in this study, intracranial pressure should be low, and fairly constant, and thus is expected to have a reduced effect in this study that only considers the relative change in blood pressure (ΔABP). In common with most other studies, we have therefore neglected intracranial pressure.

According to our results, larger variability of ABP leads to more reliable assessments of cerebral autoregulation. It is, however, unknown if very large spontaneous changes of blood pressure could worsen the accuracy of the assessment. There might be an upper limit, above which the changes of blood pressure variations are likely to have been caused by some artifact, and these data should be eliminated as well. However, in this work the variability of blood pressure was found to be significantly correlated with the variability of ARI and phase-lead ($r = -0.44$, $p < 0.05$ for both ARI and phase-lead), indicating there is no such upper limit in our data. The removal of large spikes in ABP and CBFV during pre-processing was aimed at removing artifacts that may originally have been there.

All results and conclusions are based on the data from healthy adults. The sample is rather small, but statistically significant results that take the sample size into account were clearly obtained, and observations are consistent with those obtained in previous investigations. A larger study including data from neonates and patients is desirable in order to test if the thresholds found here are also appropriate for clinical settings.

In spite of many techniques for assessing dynamic autoregulation having been described in the literature (Aaslid *et al* 1989, Giller 1990, Birch *et al* 1995, Panerai *et al* 1998, Zhang *et al* 1998, Czosnyka *et al* 2001, Liu and Allen 2002), no method has emerged that has become

an accepted 'gold' standard. Static autoregulation measurements involving the change in CBFV in response to steady-state changes in ABP may be more robust, but are more complex and potentially dangerous to carry out in human subjects (Panerai *et al* 1998). We therefore correlated autoregulation parameters with the CO_2 levels, and induced impaired autoregulation by provoking hypercapnia (Paulson *et al* 1990, Panerai *et al* 1998). Clearly, in future work it would be desirable to test the results against other measurements of autoregulation.

5. Conclusion

In this study of selecting data for the assessment of cerebral autoregulation, lower intra-subject variability and higher CoC between the pCO_2 level and quantitative measures of autoregulation has been achieved when using recordings or segments of recordings with relatively high σ_{ABP}. We therefore conclude that high variability of blood pressure is helpful to develop more reliable response of blood flow. Data with low σ_{ABP} might not contain sufficient information to allow the robust assessment of cerebral autoregulation, and should possibly be discarded in future studies.

Acknowledgments

The authors are very grateful to Dr Yi Liu and Anthony Birch for data collection and signal pre-processing.

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