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Tracking time-varying cerebral autoregulation in response to changes in respiratory PaCO₂

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Abstract
Cerebral autoregulation has been studied by linear filter systems, with arterial blood pressure (ABP) as the input and cerebral blood flow velocity (CBFV—from transcranial Doppler Ultrasound) as the output. The current work extends this by using adaptive filters to investigate the dynamics of time-varying cerebral autoregulation during step-wise changes in arterial PaCO₂. Cerebral autoregulation was transiently impaired in 11 normal adult volunteers, by switching inspiratory air to a CO₂/air mixture (5% CO₂, 30% O₂ and 65% N₂) for approximately 2 min and then back to the ambient air, causing step-wise changes in end-tidal CO₂ (EtCO₂). Simultaneously, ABP and CBFV were recorded continuously. Simulated data corresponding to the same protocol were also generated using an established physiological model, in order to refine the signal analysis methods. Autoregulation was quantified by the time-varying phase lead, estimated from the adaptive filter model. The adaptive filter was able to follow rapid changes in autoregulation, as was confirmed in the simulated data. In the recorded signals, there was a slow decrease in autoregulatory function following the step-wise increase in PaCO₂ (but this did not reach a steady state within approximately 2 min of recording), with a more rapid change in autoregulation on return to normocapnia. Adaptive filter modelling was thus able to demonstrate time-varying autoregulation. It was further noted that impairment and recovery of autoregulation during transient increases in EtCO₂ occur in an asymmetric manner, which should be taken into account when designing experimental protocols for the study of autoregulation.

Keywords: cerebral autoregulation, partial arterial CO₂, time-varying system identification, adaptive filter
Abbreviations

ABP arterial blood pressure;
CBFV cerebral blood flow velocity;
PaCO2 partial arterial pressure of CO2;
EtCO2 end-tidal CO2;
TCD transcranial Doppler;
AV autoregulation variable;
RLS recursive least squares;
RMSE root mean square error;
λ forgetting factor.

1. Introduction

Cerebral autoregulation is a protective control mechanism that maintains relatively constant cerebral blood flow (CBF) despite changes of arterial blood pressure (ABP). Impaired autoregulation is associated with a number of pathophysiological conditions in cerebral vascular diseases including hypertension, stroke, head injury, complications of prematurity in neonates as well as intracranial tumours (Barry 1985, Jorch and Jorch 1987, Aaslid et al. 1989, Paulson et al. 1990, Prashant et al. 2000, Czosnyka et al. 2001). Assessing and monitoring cerebral autoregulation is of great clinical interest for understanding the pathological processes, directing the clinical management of the vulnerable patients and also predicting the outcomes.

Early work on studying cerebral autoregulation focused on the ‘static’ (steady state) response of cerebral blood flow, following prolonged changes in ABP provoked by pharmaceutical interventions (Paulson et al. 1990, Strebel et al. 1995). With the advent of transcranial Doppler, an instrument that allows the non-invasive measurement of CBF velocity (CBFV) with high time resolution, many studies of the ‘dynamic’ properties of cerebral autoregulation were carried out using a range of time- and frequency-domain signal processing techniques (Giller 1990, Birch et al. 1995, Tiecks et al. 1995, Czosnyka et al. 1997, Panerai et al. 1998, Zhang et al. 1998, Simpson et al. 2000, Mitsis et al. 2004, Liu et al. 2005, Payne and Tarassenko 2006, Panerai et al. 2008). These studies focused on the dynamics of CBFV following either spontaneous or induced rapid variation of ABP. By considering ABP as input and CBFV as output of a control system, the ABP–CBFV relationship can be described by mathematical (linear filter) models, and autoregulation thus be assessed from the model coefficients, or the response of the model to standardized input signals (e.g. step-wise or sinusoidal changes in ABP). However, considerable fluctuations in the assessment of autoregulation over quite short periods of time have been reported with these methods when applied to signals containing only spontaneous variations in ABP and CBFV (Mahony et al. 2000, Simpson et al. 2001, Birch et al. 2002, Panerai et al. 2003b, Panerai et al. 2008, Panerai 2009), and it is still unclear if these are genuine changes in autoregulatory performance, or the result of time-varying errors in the estimates resulting from an inappropriate choice of model or noise in the signals—or a combination of these. Better understanding of short-term variations in autoregulation is clearly required. The current study aims to contribute to this by monitoring changes in autoregulation, estimated using adaptive filter methods, as subjects inspire air with raised levels of CO2.

Increasing arterial CO2 level causes cerebral vasodilation, and disturbs cerebral autoregulation. By switching inspiratory air to a CO2/air mixture, hypercapnia can be induced, and this has been exploited in a number of studies to temporarily impair autoregulation, for the purpose of assessing techniques for measuring autoregulation (Ringelstein et al. 1988, Giller et al. 1993, Strebel et al. 1995, Poulin et al. 1996, Panerai et al. 1999, 2000, Simpson et al. 2000,
However it remains unclear how fast autoregulation changes as a result of the transients in partial pressure of CO2 in the blood (PaCO2), as none of the previous studies have investigated the dynamics of cerebral autoregulation during these protocols. The results have potentially important implications for experimental design in terms of the time required for autoregulation to become impaired following hypercapnia, and the recovery on return to normocapnia.

In order to track the time-varying characteristics of autoregulation, an adaptive filter was chosen to identify the ABP–CBFV relationship while manipulating step-wise changes in PaCO2, using data acquired in a previous study in normal subjects (Panerai et al 1999, 2000). Computer-generated data obtained from a mathematical model of cerebral haemodynamics simulating an equivalent experimental protocol (Ursino and Lodi 1998) was used to test the adaptive filter method, in conditions where the true status of autoregulation was known. Previous studies of the dynamics of cerebral autoregulation have used blockwise techniques (overlapped windows) rather than adaptive filters (Panerai et al 2003b, Liu et al 2005, Czosnyka et al 2008, Panerai et al 2008). An adaptive filter has been used in the study of renal autoregulation in rats while forcing broadband spontaneous variations in blood pressure (Zou and Chon 2004, Chon et al 2008). However, no changes in autoregulation were provoked in this work, and it is thus unclear if the variation observed genuinely reflects changes in blood flow control over the time of recording (256 s). Hu et al (2006) introduced a statistical measure that may detect the improvement of cerebral autoregulation when hypocapnia was provoked by hyperventilation (Hu et al 2006). However, the time scale in their work is relatively large. In this work, we focus on short-term continuous assessment of dynamic cerebral autoregulation.

The objectives of this paper are thus to describe and validate an adaptive filtering method for the continuous assessment of cerebral autoregulation. Secondly, for the first time we describe the evolution of autoregulation during the onset of hypercapnia when breathing 5% CO2, and on the return to normocapnia. The methods described here will also allow, in follow-on studies, to gain a better understanding of the short-term fluctuations in autoregulation that have previously been observed, and which may be confounding the assessment of autoregulation in vulnerable patients.

In the next section details of data acquisition and simulation will be provided. The adaptive filter will then be described. In the following section the results from the simulated data are used to test the method and optimize the filter coefficients in terms of the performance of tracking dynamic autoregulatory changes. The adaptive filter was then applied to the recorded data to show the dynamics of autoregulation during changes in PaCO2. This is followed by discussion of the results and their implications for future work.

2. Methods

2.1. Data collection and signal pre-processing

The recorded data were obtained from 11 healthy volunteers between the ages of 23 and 51. Data acquisition has been described in previous work (Panerai et al 1999, 2000). Step-wise changes of PaCO2 were manipulated by switching ambient air (first stage) to a mixed air (second stage) with 5% CO2, 30% O2 and 65% N2 through a face mask worn by the subjects resting in the supine position. The condition of hypercapnia induced by inhaling air mixture lasted approximately 2 min before allowing the subjects to again breathe ambient air (third stage). Continuous CBFV, ABP and end-tidal CO2 (EtCO2) were recorded simultaneously.
and non-invasively by a Scimed QVL-120 transcranial Doppler system (TCD), a finger cuff device to monitor blood pressure (Ohmeda 2300 Finapres) and a capnograph (Hewlett Packard 47210A), respectively. Following visual inspection, evident artefactual spikes in the CBFV signals were manually marked and removed by linear interpolation. All signals were low-pass filtered with a fourth-order Butterworth digital filter with a cut-off frequency of 20 Hz, applied in the forward and reverse directions to compensate for phase shifts. The cardiac cycles of the signals were marked on the ABP signal and mean values of CBFV and ABP were calculated for each heart beat. Then a beat-to-beat time series of mean CBFV and mean ABP were obtained by resampling CBFV and ABP (using spline interpolation) at a uniform sampling rate of 5 Hz. This was then decimated (following appropriate anti-alias filtering) to a 1 Hz sampling rate. The EtCO2 signal was linearly interpolated between successive end-tidal values and was also resampled (following the same procedure as for CBFV and ABP) at 1 Hz. Both CBFV and ABP were normalized by their mean values and the EtCO2 was given in percentage of volume.

A similar experimental protocol was simulated using Ursino’s model of cerebral haemodynamics (Ursino and Lodi 1998) and previously implemented in our research group (Liu and Allen 2002). It should be emphasized that here the model is used purely to simulate well-controlled signals, but not to calculate autoregulatory parameters. The transition from normocapnia to hypercapnia was simulated by changing arterial CO2 level (PaCO2) from 40 mmHg (note that PaCO2 is defined in mmHg in Ursino’s model) to 50 mmHg in a step-wise manner and then back to 40 mmHg for the third stage. Within Ursino’s model, the changes in PaCO2 trigger an alternation of an autoregulation variable (AV) which is an activation factor representing the degree of smooth muscle contraction/dilation (Ursino and Lodi 1998).

Figure 1 shows the step-wise change in PaCO2 driving the model. The ABP input was taken from the recordings in the normal subjects, in order to emulate real data. The model output gives CBFV (showing an increase during hypercapnia), as well as the autoregulation parameter AV (decreasing during hypercapnia). From the input (ABP) and output (CBFV) signals of the model, autoregulation is estimated using an adaptive RLS (recursive least squares) filter (see figure 2). Time-varying autoregulation is then estimated using the phase lead at 1/12 Hz as a parameter, in accordance with previous work (Liu et al 2005). For these simulations, the phase can also be estimated directly from the AV parameter of the model (see figure 1): this is achieved by determining the relationship between AV and phase ($\phi = f(AV)$) through a further series of simulations with differing levels of time-invariant CO2 (e.g. six levels in figure 3). Further details on the signal processing methods used on both the simulated and recorded signals are provided below.

2.2. Data analysis

After obtaining the simulated CBFV signals from the physiological model, a RLS adaptive filter (Haykin 1996) featuring a rapid convergence rate and low misadjustment was utilized in order to estimate the time-varying autoregulation characteristics, as shown in figure 1 for the simulated data. The RLS filter satisfies the need for fast tracking in the system, by recursively minimizing the squared error between the estimated output and the desired CBFV. Figure 2 shows the structure of the adaptive filter, where the recorded ABP is the input signal ($x(n)$) and CBFV from either volunteer subjects or the physiological model are the desired output ($d(n)$); the output of the filter is the estimated CBFV. The goal of the adaptive filter is to minimize the error ($\xi(n)$) between the filter output and the desired signal, by adjusting the filter parameters with each new sample, in a recursive manner (determined by the adaptive weight control mechanism). The main steps of the RLS adaptive filter algorithm are given in
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Figure 1. A flow chart showing the evaluation of the RLS filter in tracking the time-varying dynamics of cerebral autoregulation in the simulation study. The recorded ABP from one volunteer and an ideal step-wise change in PaCO2 were the inputs to Ursino’s model to produce the simulated CBFV and autoregulation variable (AV). From the latter, the time-varying autoregulation was calculated using a conversion function, \( \phi = f(AV) \). Considering the recorded ABP as the input signal and simulated CBFV as the output signal, autoregulation was also estimated using an adaptive filter, and hence the phase difference was calculated. The performance of the RLS filter in tracking the time-varying autoregulation was evaluated by comparing these two traces of phase.

Figure 2. The principle underlying the RLS adaptive filter, where the recorded ABP is the input signal \( x(n) \) and CBFV is the desired output \( d(n) \); the output of the filter is the estimated CBFV. By minimizing the error \( \xi(n) \) between the filter output and the desired signal, optimized filter parameters can be obtained in a recursive manner.

appendix A.1. The transverse (finite impulse response (FIR)) filter \( w(n) \) thus represents the estimated time-varying system characteristics and from this the time-varying autoregulation characteristics are subsequently estimated.

In the current application, the length of the weight vector was chosen to be six samples, corresponding to an impulse response of 6 s duration. This was chosen based on previous
linear modelling of blood flow control (Panerai et al 2003b, Liu et al 2005), in which the most important components of the response were seen to occur within this interval. The RLS algorithm requires a forgetting factor ($\lambda$—see appendix A.1), which determines how fast the filter adapts: a low $\lambda$ allows rapid adaptation (speed of convergence) of the weight vector (impulse response) whilst a high $\lambda$ gives smooth changes (less variability) of the filter coefficients. We thus designed an objective test based on simulated data to determine the most suitable forgetting factor, as a result of which a value of $\lambda = 0.98$ was chosen (see appendix A.2 for details).

The RLS algorithm recalculates the impulse responses sample by sample. From these, autoregulation can be assessed using a number of techniques, including the phase lead between ABP and CBFV. Phase lead is one of the established parameters for indicating the status of cerebral autoregulation and has been used by a number of authors in the study of the CBFV–ABP relationship (Diehl et al 1995, Birch et al 2002, Liu et al 2003, Novak et al 2004, Latka et al 2005, Liu et al 2005, Payne et al 2009). A large phase lead between CBFV and ABP indicates normal cerebral autoregulation whilst the phase difference decreases with an impaired blood flow control mechanism. In this study, the impulse responses calculated from the RLS filter were transformed into frequency responses from which the phase angle (phase lead) was then estimated at the $1/12$ Hz (Birch et al 2002).

To determine if the phase lead estimated from the RLS algorithm matches the time-varying dynamics of cerebral autoregulation predicted by Ursino’s model, the ‘reference’ (‘true’) value of this phase lead was required. However, this is not provided directly from Ursino’s model, in which the parameter $A V$ (defined in Ursino and Lodi 1998 according to details of the model) controls smooth muscle contraction/dilation. Hence the method outlined in figures 3 and 4 was designed to convert the variable $A V$ into ‘reference’ phase lead.

The values of $A V$ and simulated CBFV were obtained by driving Ursino’s model with the recorded ABP (400 s duration) and six constant values of PaCO$_2$, ranging from 35 to 50 mmHg, covering the range of interest in intervals of 3 mmHg. Phase lead between CBFV and ABP was then calculated using a Wiener filter for each pair of simulated CBFV and
recorded ABP signals, resulting in a value of phase lead at each of the six different levels of constant PaCO2. As shown for the example in figure 3, the six points are almost on a straight line. A separate simulation (and thus $\varphi = f(AV)$) was used for each subject.

Hence, $\varphi = f(AV) \approx a \cdot AV + b$, where $a$ and $b$ were computed by linear regression, for each subject. There were only minor differences in the results for each subject, resulting from their differing ABP signals.

Gradients of the transient change of the phase lead were calculated to show how quickly cerebral autoregulation changes following step-wise changes in PaCO2. Based on the phase lead calculated from Ursino’s model, two periods of the transient lasting 40 s starting from the point at which phase lead decreases (EtCO2 step-up) and increases (EtCO2 step-down), respectively, were considered. The gradients were computed from a linear regression line between the start and end of the transient period (identified by visual inspection of CBFV), and quantify the rate of change of autoregulation.

In order to determine if the phase lead estimated from the RLS filter can follow the dynamic changes induced by a step-change in EtCO2, the ‘reference value’ and estimated phases were compared. The time delay between these two sets of phase leads was estimated using cross-correlation, in order to quantify the speed of response.

After testing the suitability of the RLS filter in tracking the time-varying cerebral autoregulation on simulated data, this filter was then applied on the recorded ABP and CBFV to show the time-varying characteristics of cerebral autoregulation during step-wise changes in PaCO2.

3. Results

Figures 5 and 6, and table 1 show the results from the simulation scheme outlined in figure 1. The ideal step-wise change (figure 5(A)) in PaCO2 was used together with ABP
Figure 5. (A) The ideal step-wise change (40 mmHg to 50 mmHg) in PaCO₂ as one of the inputs to Ursino’s model to produce the simulated CBFV. (B) Mean recorded ABP. (C) Mean simulated CBFV generated from Ursino’s model using ABP recordings from 8 subjects and the ideal step-wise change in PaCO₂ as the inputs. (D) The solid line is the mean phase lead and the dashed dot line is the standard deviation. Evident asymmetric changes of the simulated CBFV at the PaCO₂ step-up and step-down are observed, which is in accordance with previous reports (Poulin et al 1996, Garnham et al 1999). Interestingly, we note that a similar asymmetric pattern is obtained also in the phase lead when tracking the dynamics of cerebral autoregulation.

Table 1. Mean ± std of the gradients of the transient changes of the phase lead. The values in the second column were gradients calculated from the phase lead estimated by the RLS filter and the ones in the third column were obtained from the models’ AV.

<table>
<thead>
<tr>
<th>Phase lead</th>
<th>RLS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gradient at PaCO₂ step-up (degree s⁻¹)</td>
<td>−0.33 ± 0.13</td>
<td>−0.35 ± 0.13</td>
</tr>
<tr>
<td>Gradient at PaCO₂ step-down (degree s⁻¹)</td>
<td>0.55 ± 0.29</td>
<td>0.57 ± 0.18</td>
</tr>
</tbody>
</table>

recordings from the 11 subjects (figure 5(B)) as the inputs to Ursino’s model to generate the simulated CBFV. In three recordings, the model did not provide physiologically meaningful simulations of CBFV, and were therefore discarded for this stage of the analysis. Mean simulated CBFV from the remaining eight simulated recordings is plotted in figure 5(B) showing evident asymmetry at the PaCO₂ step-on and step-down, which is in accordance with the previous reports (Poulin et al 1996, Garnham et al 1999) where similar asymmetric changes of CBFV were observed. The similarity between the increase in CBFV reported in the literature and the simulated data supports the validity of Ursino’s model in simulating CBFV during step-wise changes in PaCO₂. The mean time-varying phase lead at 1/12 Hz is given in figure 5(D). The asymmetric pattern in both CBFV and phase lead should be noted. Further analysis of the continuous phase lead, as estimated by the RLS filter is given in figure 6 and table 1.

Figure 6 shows the results of using the RLS filter to track the time-varying cerebral autoregulation in simulated signals. The ‘reference’ (from the model’s AV) and estimated
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From the RLS filter values were compared on simulated data based on eight recordings. Figures 6(A) and (B) illustrate the typical examples from two individual simulations of the phase lead as well as the mean values (figure 6(C)) from the eight cases. Using cross-correlation analysis, the mean ± standard deviation (std) of the time delay between the ‘reference’ phase lead and the RLS phase lead was estimated at 2.5 ± 2.2 s for the simulated recordings. The delay is more evident at PaCO$_2$ step-up than at step-down (see figure 6(C)).

In table 1, the gradients of the transient changes of the phase lead calculated from the adaptive filter are not significantly different from the ones obtained from the AV generated using Ursino’s model ($p > 0.1$ for both PaCO$_2$ step-up and step-down, t-test). Together, these results confirm that the RLS filter is capable in catching dynamics of time-varying cerebral autoregulation induced by the step changes of PaCO$_2$. Furthermore, the gradient of the transient change of phase lead at PaCO$_2$ step-up is significantly lower (in absolute value) than that at PaCO$_2$ step-down ($p < 0.01$, t-test).

The results above indicate that the RLS adaptive filter can track rapid changes of autoregulation with short delay at PaCO$_2$.

We then applied the adaptive filter to the recorded data. The mean EtCO$_2$, CBFV and phase lead from the 11 subjects are plotted in figure 7, showing the responses of CBFV and phase lead to the changes in PaCO$_2$.
CBFV increases at the onset of hypercapnia, and drops back to the baseline level following the \( \text{EtCO}_2 \) step-down. The strong asymmetry in the response to \( \text{EtCO}_2 \) step-up and \( \text{EtCO}_2 \) step-down is evident, and is in accordance with previous reports (Poulin et al. 1996, Garnham et al. 1999). As expected, phase lead drops with hypercapnia as autoregulation is impaired, and recovers on return to normocapnia. The dynamics of this change have however not previously been reported. These indicate that autoregulation deteriorates rather more slowly during the onset of hypercapnia, than is its recovery on return to normocapnia. The estimated gradients (table 2) underline this, and differences are statistically significant \((p < 0.03 \, \text{t-test})\).

The autoregulatory response (see figures 7(B) and (C)) appears to be delayed when comparing with that of CBFV. Using cross-correlation analysis, the mean ± std of the time delay between the \( \text{EtCO}_2 \) and CBFV is 4.9 ± 4.8 s and the time delay between the \( \text{EtCO}_2 \) and phase lead is 31.2 ± 9.8 s.

The phase lead for each recording (thin lines) and their mean values (bold line) are shown in figure 8 and display wide inter-individual variation—as has often been observed (Birch et al. 2002, Panerai et al. 2003a, 2003b, Simpson et al. 2004) in estimates of autoregulation from spontaneously varying data. In previous work we noted that estimates of autoregulation are often poor, when there is low spontaneous variability in ABP (Liu et al. 2005). We therefore plotted the results separately for the recordings with low (figure 8(B)—seven cases) and high variability (figure 8(C) four cases) in ABP; a standard deviation in ABP of \( \sigma_{\text{ABP}} > 3.5\% \) was

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**Table 2.** Comparison between of the gradients of the transient changes of phase lead estimated from all subjects and subjects with high spontaneous fluctuation of ABP.

<table>
<thead>
<tr>
<th>Phase lead</th>
<th>All subjects</th>
<th>Subjects with high ( \sigma_{\text{ABP}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gradient at ( \text{PaCO}_2 ) step-up (degree s(^{-1}))</td>
<td>(-0.30 \pm 0.26)</td>
<td>(-0.37 \pm 0.32)</td>
</tr>
<tr>
<td>Gradient at ( \text{PaCO}_2 ) step-down (degree s(^{-1}))</td>
<td>(0.54 \pm 0.37)</td>
<td>(0.48 \pm 0.26)</td>
</tr>
</tbody>
</table>
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Figure 8. Phase lead estimated from the recorded ABP and CBFV using the RLS algorithm. Each thin solid line represents the phase lead calculated from one subject. The mean of the phase lead is shown by the thick solid line. (A) Phase lead estimated from all subjects. (B) Phase lead estimated from the subjects with low spontaneous variability in ABP. (C) Phase lead estimated from the subjects with high spontaneous variability in ABP (σ_{ABP} > 3.5%). (D) The mean phase lead estimated from the subjects with high spontaneous variability in ABP and the mean EtCO₂ (dashed line). This figure shows that large fluctuations of the phase lead can be avoided by selecting signals with high spontaneous variability in ABP.

4. Discussions

4.1. Major findings

Tracking of the time-varying dynamics of cerebral autoregulation has been carried out in this study. This task was achieved by using an adaptive filter to identify the ABP–CBFV relationship during step-wise changes in EtCO₂. An autoregulation parameter (phase lead) was calculated from the coefficients of the adaptive filter, showing that cerebral autoregulation...
responses to the EtCO\textsubscript{2} step-up are significantly slower than those to the EtCO\textsubscript{2} step-down. The responses are also delayed with respect to CBFV. More detailed discussion is given below.

4.2. Test of the RLS adaptive filter using Ursino’s model

The purpose of using a physiological model in the first part of this work was to test the capability of the RLS algorithm in tracking the time-varying cerebral autoregulation during step-wise changes of PaCO\textsubscript{2}. In this particular case, Ursino’s model was chosen, as it is a well-established model for simulating cerebral blood-flow control. Figure 5 shows that the phase lead from the RLS filter can follow the dynamics of ‘true’ phase lead (as found from the model parameter $A_V$), implying that the convergence of the adaptive filter is fast enough to track the changes of cerebral autoregulation without great delay. This result supports the use of the RLS filter to further investigate the time-varying dynamics of autoregulation from the data recorded in humans.

4.3. The dynamics of time-varying cerebral autoregulation

The method was thus applied to detect the dynamic characteristics of time-varying cerebral autoregulation during step-wise changes of EtCO\textsubscript{2} in a group of 11 healthy adult volunteers. Similar protocols of step changes in EtCO\textsubscript{2} were applied in several previous studies (Poulin et al 1996, Garnham et al 1999, Simpson et al 2000) to investigate the dynamics of CBFV. They all found that the dynamics of CBFV changes differ between CO\textsubscript{2} step-up and step-down. Specifically, a slow response of CBFV was observed at the onset of hypercapnia, whereas CBFV decreases more rapidly at the end of the stimulus (Poulin et al 1996, Garnham et al 1999, Simpson et al 2000). However, none of these studies has reported the dynamics of cerebral autoregulation. Using an adaptive filter and selecting recordings with high spontaneous fluctuation of ABP, figures 7 and 8 show that phase lead decreases slowly and with some delay after the EtCO\textsubscript{2} step-up transient and increases more steeply after the EtCO\textsubscript{2} step-down. The asymmetric changes of the phase lead can be explained by the asymmetric dynamics of CBFV in response to the step-wise changes in EtCO\textsubscript{2}. It is well established that CO\textsubscript{2} is a very strong vasodilation stimulus that may increase cerebral flow markedly. Due to relatively long CO\textsubscript{2} wash-in and short wash-out time from the lung to the arteries, CBFV changes asymmetrically at the onset and offset of hypercapnia (Poulin et al 1996, Garnham et al 1999). During hypercapnia, cerebral autoregulation can be impaired, and it has been suggested (Panerai et al 1999) that since the resistance vessels are dilated, they may have limited further dilatory capacity to regulate blood flow. We therefore expected the dynamics of cerebral autoregulation to roughly follow the changes of CBFV. The results in figures 7 and 8 confirm our expectations, partly. The phase lead follows the changes of CBFV, but responses were consistently slower and steady-state autoregulation may not be achieved during the 2 min of hypercapnia used. Using correlation function analysis, the delays between phase lead and EtCO\textsubscript{2} were found to be $31.2 \pm 9.8$ s. We do not believe that these delays are introduced from the RLS filter, since there is no significant delay observed when applying this filter the simulated data and the delays at EtCO\textsubscript{2} step-up and step-down are different. It appears that autoregulation does not degrade immediately when arteriolar dilation causes CBFV to increase, and thus the simple idea that arteriolar dilatation leads to impaired autoregulation is questionable. This exciting observation clearly deserves further investigation. The relatively slow response may also have had important consequences for the future design of experiments using hypercapnia, suggesting that high CO\textsubscript{2} values need to be inspired for more than 2 mins, in order to fully achieve impaired autoregulation.
4.4. Model consideration

Previously, linear models were widely used to study dynamic cerebral autoregulation (Giller 1990, Panerai et al 1998, Zhang et al 1998, Simpson et al 2000, Liu et al 2001, Liu et al 2005, Edwards et al 2004). Time and frequency domain analysis was applied using the coefficients extracted from these models. A simple model consisting of a single pure delay, gain terms, time constants and offsets was introduced by Poulin et al (1996) to study the behaviour of CBFV after step changes in EtCO2. Simpson et al (2000) employed a finite-impulse-response (FIR) model on normal and pathological subjects to show the different dynamics of CBFV in response to step changes in EtCO2. However, these methods cannot track the dynamics of cerebral autoregulation, since a blockwise time-invariant system was assumed for the cerebral blood flow control mechanism. More recently, Panerai et al (2003b) used an ARMA model to continuously assess cerebral autoregulation by estimating the model coefficients from a sliding window. In these studies of the dynamics of autoregulation it is difficult to distinguish between genuine changes and estimation errors expected in such random signals which relatively low signal-to-noise ratios. In the current work we induced changes in autoregulation (through hypercapnia) and using RLS filters were thus able to observe ‘real’ dynamics of autoregulation. Based on our previous work (Liu et al 2005), we also improved the quality of the results by selecting recordings with high spontaneous fluctuation of ABP (see figure 8).

4.5. Limitation

Although phase lead has been established as one of more robust autoregulation indicators estimated from the ABP–CBFV relationship, the experiments that showed the validity of using this autoregulatory parameter were conducted assuming autoregulation to be time invariant (Birch et al 1995, Diehl et al 1995, Liu and Allen 2002). In the current work, autoregulation is assumed to be a time-varying system, and the validity of using phase lead to represent autoregulation over short periods might be questioned. The simulation results however provide some confidence that the approach is appropriate.

There are large variations in estimates of phase lead between individuals and along time (even during baseline EtCO2). As already observed in previous work (Liu et al 2005), the latter are particularly strong in subjects with low ABP fluctuations. This, together with the relatively small sample analysed, limits possible inferences. In future studies, a larger sample should be analysed. The relatively short period of hypercapnia did not appear to allow the steady state in autoregulatory impairment to be achieved. Repeated recordings of step-wise changes in EtCO2, and longer periods of baseline and hypercapnia should allow more robust results.

5. Conclusion

The major findings of this study are as follows: (1) the RLS algorithm is suitable for tracking the time-varying characteristics of cerebral autoregulation within a relatively short time period; (2) the asymmetric dynamics of cerebral autoregulation following step changes in EtCO2 is similar to that of CBFV, with a slower responses to EtCO2 step-up than step-down; however, autoregulation responses are slower than those of CBFV; (3) by selecting signals with high spontaneous variation of ABP, the random variability on the time-varying trace of cerebral autoregulation can be reduced.
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Appendix A.

A.1. RLS algorithm

The main steps of the RLS adaptive filter algorithm follows Haykin (1996).

Note in the following mathematical expressions, $k(n)$ (called Kalman gain vector) and $P(n)$ are introduced only for convenience of computation. $P(n) = \Phi^{-1}$ is the inverse autocorrelation matrix of the input signal.

• Step 1: Calculate the Kalman gain vector $k(n)$ at sample $n$:

$$k(n) = \frac{\lambda^{-1}P(n-1)x(n)}{1 + \lambda^{-1}x(n)^tP(n-1)x(n)}, \quad (0 < \lambda \leq 1) \quad (A.1)$$

• Step 2: Compute the a priori error\(^5\) $\xi(n)$ using

$$\xi(n) = d(n) - w(n-1)^t x(n), \quad (A.2)$$

• Step 3: Update the weight vector $w(n)$ as

$$w(n) = w(n-1) + \xi(n)k(n), \quad (A.3)$$

• Step 4: Update $P(n)$ as

$$P(n) = \lambda^{-1}P(n-1) - \lambda^{-1}k(n)x(n)^tP(n-1), \quad (A.4)$$

• Step 5: Calculate filtered output $y(n)$ and updated error $e(n)$ using

$$y(n) = w^t x(n), \quad e(n) = d(n) - y(n) \quad (A.5)$$

where \(x(n)\), \(d(n)\) and $\lambda$ are the reference signal (ABP in this case), desired signal (in this case CBFV) and the forgetting factor controlling the speed of adaptation, respectively. The variables in bold and lower case letters are vectors with the same vector length.

The algorithm was initialized ($n = 0$), with $P(0) = (\delta \mathbf{I})^{-1}$ ($\delta$ = small positive constant) where $\mathbf{I}$ is an identity matrix to assure the nonsingularity of the correlation matrix $\Phi_{xx}^{-1}$. A large error might appear at the start of the RLS algorithm if an inappropriate initial assumption for $\delta$ is made. In this study, $\delta = 0.1$ was chosen, since a relatively low error estimated at the beginning of the adaptation was observed from the data set at this value of $\delta$.

\(^5\) The a priori error is the error between the desired response $d(n)$ and the least-squares estimate of the output signal using the weight vector with the previous sample ($n'1$).
Tracking time-varying cerebral autoregulation in response to changes in respiratory PaCO₂

Figure A1. Mean root mean square error (RMSE) calculated from the phase lead from the RLS filter and the ‘reference’ phase lead from Ursino’s model. As the forgetting factor increases, the RMSE reaches a minimum at approximately $\lambda = 0.98$.

A.2. Choosing the forgetting factor, $\lambda$

The following describes a simulation test in order to objectively choose an appropriate forgetting factor, $\lambda$, for the RLS filter. The adaptive filter was applied and phase lead was estimated, using a set of different values of $\lambda$, and the estimated phase lead was then compared to the ‘reference’ phase lead calculated from the Ursino’s model (running in steady state at different levels of CO₂)—as described in section 2. The range of the forgetting factors investigated varied from 0.96 (below which very widely fluctuating phase values were sometimes observed) to 0.998 (above which the RLS filter is almost equivalent to a Wiener filter applied to whole recording) with a 0.002 step interval. Then the resultant phase lead estimated from the adaptive filter was compared with the ‘reference’ phase lead obtained from Ursino’s model. This was repeated for the 11 recorded ABPs, together with the idealized step-wise change in PaCO₂ as inputs to the Ursino’s model. The root mean square error (RMSE) between the two phase leads (calculated from 66 sets of recordings—11 subjects multiplied by six CO₂ levels ranging from 35 to 50 mmHg covering the range of interest in intervals of 3 mmHg) were calculated to show the variability of the estimates from the adaptive filter. Figure A1 illustrates the result of this simulation test. The RMSE drops slowly to a minimum at approximately 0.98 and increases rapidly thereafter. The initial decrease of the RMSE is due to the large variability of the adaptive filter coefficients (misadjustment), though the speed of convergence is fast (small forgetting factor). When the forgetting factor becomes higher, the variability of the estimates is reduced, but the speed of convergence becomes slower. Thus $\lambda = 0.98$ may be considered optimal, and was used in the remainder of this work.

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