Statistical criteria for estimation of the cerebral autoregulation index (ARI) at rest

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Abstract

The autoregulation index (ARI) can reflect the effectiveness of cerebral blood flow (CBF) control in response to dynamic changes in arterial blood pressure (BP), but objective criteria for its validation have not been proposed. Monte Carlo simulations were performed by generating five minute long random input/output signals that mimic the properties of mean beat-to-beat BP and CBF velocity (CBFV) as usually obtained by non-invasive measurements in the finger (Finometer) and middle cerebral artery (transcranial Doppler ultrasound), respectively. Transfer function analysis (TFA) was used to estimate values of ARI by optimal fitting of template curves to the output (or CBFV) response to a step change in input (or BP). 2-step criteria were adopted to accept estimates of ARI as valid. The 95% confidence limit of the mean coherence function (0.15-0.25 Hz) (γ^2_{crit}) was estimated from 15,000 runs, resulting in γ^2_{crit} = 0.190 when using five segments of data, each with 102.4 s (512 samples) duration (Welch's method). This threshold for acceptance was dependent on the TFA settings and increased when using segments with shorter duration (51.2 s). For signals with mean coherence above the critical value, the 5% confidence limit of the normalised mean square error ($NMSE_{crit}$) for fitting the step response to Tieck's model, was found to be approximately 0.30 and independent of the TFA settings. Application of these criteria to physiological and clinical sets of data showed their ability to identify conditions where ARI estimates should be rejected, for example due to CBFV step responses lacking physiological plausibility. A larger number of recordings were rejected from acute ischaemic stroke patients than for healthy volunteers. More work is needed to validate this procedure with different physiological conditions and/or patient groups. The influence of non-stationarity in BP and CBFV signals should also be investigated.

Keywords

Cerebral blood flow, Monte Carlo simulation, transfer function analysis, coherence function, transcranial Doppler ultrasound

1. Introduction

The cerebral autoregulation index (ARI) was introduced by Rune Aaslid and co-workers (Tiecks *et al.*, 1995) as a metric to assess the effectiveness of cerebral dynamic autoregulation (CA) in physiological and clinical studies. CA is a potent regulatory mechanism that maintains cerebral blood flow (CBF) within narrow limits, despite changes in mean arterial blood pressure (MBP) (Paulson *et al.*, 1990; Panerai, 1998). Originally regarded as a static mechanism (Lassen, 1959), more recent studies of CA have focused on its dynamic properties, as reflected by the transient response of CBF velocity (CBFV), usually measured with transcranial Doppler ultrasound (Panerai, 2009), following sudden changes in MBP (Aaslid *et al.*, 1989). In its original formulation, the ARI was derived by best fitting one of 10 different template curves to the CBFV response following a sudden drop in MBP, induced by the rapid deflation of thigh cuffs (Aaslid *et al.*, 1989; Tiecks *et al.*, 1995). Each template curve results from a combination of parameters derived from a second order differential equation model leading to values of ARI ranging from 0 (absence of CA) to 9 (best observed CA). In parallel with these developments, transfer function analysis (TFA) was proposed to model the dynamic MBP-CBF relationship as a frequency-dependent phenomenon (Giller, 1990; Zhang *et al.*, 1998), based on spontaneous fluctuations in MBP and CBFV at rest. Compared to the use of inflated thigh cuffs, measurements performed at rest present considerable advantages regarding comfort for subjects, stability of physiological conditions, and the ability to perform repeated observations (Panerai, 1998). The attractive possibility of deriving ARI from spontaneous fluctuations at rest was demonstrated in 1998, based on the CBFV response to a step change in MBP calculated with the inverse Fourier transform of transfer function estimates of amplitude and phase frequency responses (Panerai *et al.*, 1998). From there on, several studies have adopted this approach to combine the compactness of the ARI scale with the advantages of recordings at rest (Panerai, 2008). Clinical applications of this approach have shown that compared to healthy subjects, ARI is reduced in patients with carotid artery disease (Panerai *et al.*, 1998), severe head injury (Panerai *et al.*, 2004), ischaemic stroke (Salinet *et al.*, 2014), and preeclampsia (Van Veen *et al.*, 2015). Moreover, in healthy subjects, ARI estimated from spontaneous MBP fluctuations was shown to be reduced by hypercapnia (Katogridakis *et al.*, 2013), pre-syncope (Carey *et al.*, 2001) and hypobaric hypoxia (Subudhi *et al.*, 2010).

Despite its considerable potential, the accuracy of ARI estimates has been of concern. Firstly, as it comprises a ‘closed’ scale (0-9), unreliable estimates, as for example resulting from recordings with low signal-to-noise ratio (SNR), cannot be spotted as outliers. Secondly, a bootstrap approach demonstrated ARI has limited consistency to differentiate between neighbouring values (Simpson *et al.*, 2004). Finally, and consistent with (Simpson *et al.*, 2004), a reproducibility study indicated that at least 44 subjects need to be enrolled in each group to detect a difference in ARI of 1-unit with satisfactory statistical power (Brodie *et al.*, 2009). These limitations of ARI have been mitigated by closer scrutiny of the robustness of TFA estimates, by checking the statistical significance of the coherence function (Gommer *et al.*, 2010), as well as visual inspection of the CBFV step response, to

guarantee its physiological plausibility (Panerai *et al.*, 2004; Van Veen *et al.*, 2015). This approach has led to satisfactory results, but its subjectivity can lead to bias and inconsistencies amongst operators. A previous attempt to address this problem only included neonatal data and did not consider ARI estimation (Ramos *et al.*, 2006). As an attempt to overcome the limitations outlined above, we have performed Monte Carlo simulations to establish robust confidence limits for the coherence function derived by TFA and also for ARI, based on the quality of fitting of the model of Tiecks *et al* (Tiecks *et al.*, 1995). The applicability of these new statistical criteria to real data was tested on a set of recordings from healthy subjects as well as in ischaemic stroke patients.

2. Methods

Surrogate data

Random time-series of input and output signals were generated with 300 s duration that mirrored the properties of MBP and CBFV signals, often recorded for periods of five minutes at rest. For each run, two separate series of gaussian noise with 10% coefficient of variation were generated for input and output, and low-pass filtered with a zero-phase 8^{th} order Butterworth filter with cut-off frequency of 0.25 Hz. To follow the standard procedure for interpolation and resampling of cardiovascular recordings, a separate random series was generated to play the role of pulse-interval. Using this sequence with both the input and output random signals, interpolation was performed with a third order polynomial followed by resampling at 5Hz to generate signals with a uniform time base (Katogridakis *et al.*, 2013). The TFA and statistical procedures performed on these signals are described later.

Physiological data

Adult subjects without any symptoms or history of neurological or cardiovascular disease were recruited from departmental staff and patient relatives. The study received ethical approval (Northampton REC, ref 11/EM/0369) and all participants gave written informed consent. Participants did not have a heavy meal or caffeinated products for at least two hours before attending a temperature controlled (20-23 °C) laboratory that was free of distraction. They rested supine for at least 20 minutes before any measurements were performed. Continuous non-invasive arterial blood pressure (BP) was recorded with arterial volume clamping of the digital artery (Finometer, Finapres Systems, Amsterdam, The Netherlands); bi-lateral CBFV in the middle cerebral artery (MCA) was measured with transcranial Doppler ultrasound (Viasys Companion III, Viasys Health Care, San Diego CA, USA) at depths of insonation in the range 50-60 mm using a head-frame to fix 2 MHz probes over the temporal windows. A 3-lead ECG was continuously recorded using the add-on feature

of the Finometer. End-tidal CO_2 was measured with an infra-red capnograph (Capnocheck Plus) using nasal prongs.

At the beginning of each recording, lasting a minimum of five minutes, the servo calibration of the Finometer was switched off; systolic and diastolic BP values obtained by brachial sphygmomanometry (OMRON 705IT) were used to calibrate the continuous BP signal offline. All signals were simultaneously recorded and transferred to a computer at a rate of 500 samples/s for each channel.

Clinical data

Data representative of the more challenging conditions prevailing during recordings in critically ill patients were obtained from a previous study (Salinet *et al.*, 2014). Patients with a first episode of ischaemic stroke were studied in the first 72 hours of symptom onset. Exclusion criteria were a history of neurological disease, atrial fibrillation or severe cognitive impairment. The study received ethical committee approval (Nottingham REC, ref. 11/EM/0016) and all subjects gave informed consent. For the purposes of the present study, measurements were performed in the same laboratory as for the physiological data described previously, using the same equipment and procedure to record a five-minute set of baseline data. In a sub-group of patients recruited at the beginning of the study, BP recordings were performed with the Finapres device (Ohmeda 2300, Louisville CO, USA).

Data analysis

TFA was performed for each pair of surrogate signals using the classical FFT approach combined with Welch's method (Welch, 1967). Choice of parameter settings followed the recommendations of the International Cerebral Autoregulation Research Network (CARNet) (Claassen *et al.*, 2015). A five-minute baseline recording allowed the use of five 102.4 s (512 samples) segments of data, with 50% superposition. The mean value of each segment was removed and a cosine window was applied to reduce spectral leakage. Additional spectral smoothing was obtained with a 3-point moving average triangular filter applied to both input and output amplitude spectra. In the frequency domain, only the squared coherence function was considered further with calculation of its mean value in the frequency range 0.15-0.25 Hz (γ^2_m, see Discussion). The CBFV response to a step change in MBP was estimated from the inverse FFT of the transfer function as described previously (Panerai *et al.*, 1998; Panerai *et al.*, 2004). The step response template curves proposed by Tiecks *et al* (Tiecks *et al.*, 1995) were fitted to the CBFV step response for the duration of 8 s after its beginning. The template curve corresponding to the minimum mean square error (MSE) determined the corresponding value of ARI. Parabolic interpolation using neighbouring values of the optimal ARI was employed to obtain estimates with two decimal places. The MSE was normalised (NMSE) by the amplitude of the CBFV step response and used to estimate its 95% confidence limits as described later. In addition to the standard setting of five segments of data with N_L=512 samples, simulations were also performed with

N_L=256 samples and with the number of segments (N_{SEGM}) ranging from 3 to 8. In this case, longer sequences of random data were generated as needed.

Both physiological and clinical data were edited as described previously (Katogridakis *et al.*, 2013; Salinet *et al.*, 2014). In short, the continuous, raw measurements of BP and CBFV were visually inspected and any spikes or artefacts with duration < 100 ms were linearly interpolated. The CBFV signal was low-pass filtered with a median filter and all signals were low-pass filtered with an 8^{th} order, zero-phase Butterworth filter with cufoff frequency of 20 Hz. Using the ECG to mark the occurrence of each cardiac cycle, mean values of BP and CBFV were obtained for each heartbeat. The pulse interval sequence was then used to obtain a 5 Hz uniform time base for MBP and mean CBFV as described above. TFA of the measured signals followed the same procedure described above for surrogate data with each subject thus providing estimates of mean squared coherence (γ^2_m), ARI and NMSE for fitting the Tiecks *et al* model (Tiecks *et al.*, 1995).

Statistical procedure

Fifteen thousand runs were performed with surrogate data to generate corresponding pairs of γ^2_m and NMSE values. The 95% upper confidence limit of γ^2_m was estimated by linear interpolation of the histogram with bin width equal to 0.02; referred to as γ^2_{crit}. Using a similar procedure, the 5% lower confidence limit of NMSE ($NMSE_{crit}$) was determined by the distribution of values after the condition $\gamma^2_m > \gamma^2_{crit}$ was met. This process was repeated for combinations of N_L (256 or 512) and N_{SEGM} (3 to 8).

For each physiological or clinical recording, values of γ^2_m and NMSE were compared to γ^2_{crit} and $NMSE_{crit}$ for the standard condition (N_L=512 samples, N_{SEGM}=5). Corresponding estimates of ARI were considered acceptable if $\gamma^2_m > \gamma^2_{crit}$ and NMSE<$NMSE_{crit}$. The distribution of ARI for recordings found to be acceptable was described by its mean (SD), and differences between estimates for the right and left MCA were assessed with the paired Student's t-test. Values of $p<0.05$ were considered significant.

CBFV step responses were visually inspected by one of the authors (RBP) and classified as either 'physiological' or not (Ramos *et al.*, 2006). Responses were classified as 'non-physiological' if the initial upstroke was negative or missing (slow continuous rise), or the recovery phase led to negative values with absolute values greater than half the amplitude of the initial upstroke.

3. Results

Surrogate data

Values of γ^2_{crit} are given in Table 1 for different combinations of N_{SEGM} and N_L. As expected, these values tend to decrease with increasing number of degrees of freedom. For the standard setting (N_{SEGM}=5, N_L=512), the distribution of NMSE is given in Fig. 1. Differently from γ^2_{crit} , $NMSE_{crit}$ showed random fluctuations after each 15,000 runs but did not change significantly with either N_{SEGM} or N_L. For different combinations (n=24), including changes in the random number generator seed value, the mean (SD) of $NMSE_{crit}$ was 0.308 (0.026). For simplicity, $NMSE_{crit}$=0.30 was adopted for the standard setting. Visual inspection of 145 output step responses with $\gamma^2_m > 0.190$ (standard setting) showed that all cases with NMSE < 0.3 were classified as 'physiological'. On the other hand, for NMSE > 0.3, the number of 'non-physiological' responses tended to increase with NMSE. For NMSE in the interval [0.3,0.6], 41.7% were 'non-physiological', but this rate reached 90.9% for NMSE >1.2. Fig. 2 illustrates the deterioration of the output step response with increasing values of NMSE. According to the NMSE<0.30 criterion, the response in Fig. 2(a) would be accepted, but the other three examples would be automatically rejected.

Table 1 – Values of the 95% upper confidence limit for mean squared coherence in the frequency range 0.15-0.25 Hz (γ^2_{crit}) for surrogate data estimated from 15,000 runs with different values of N_{SEGM} and N_L. The shaded cell indicates the standard condition recommended for dynamic cerebral autoregulation studies (Claassen *et al.*, 2015).

N_{SEGM}	N_L=256	N_L=512
3	0.358	0.292
4	0.300	0.228
5	0.242	0.190
6	0.207	0.164
7	0.176	0.142
8	0.152	0.127

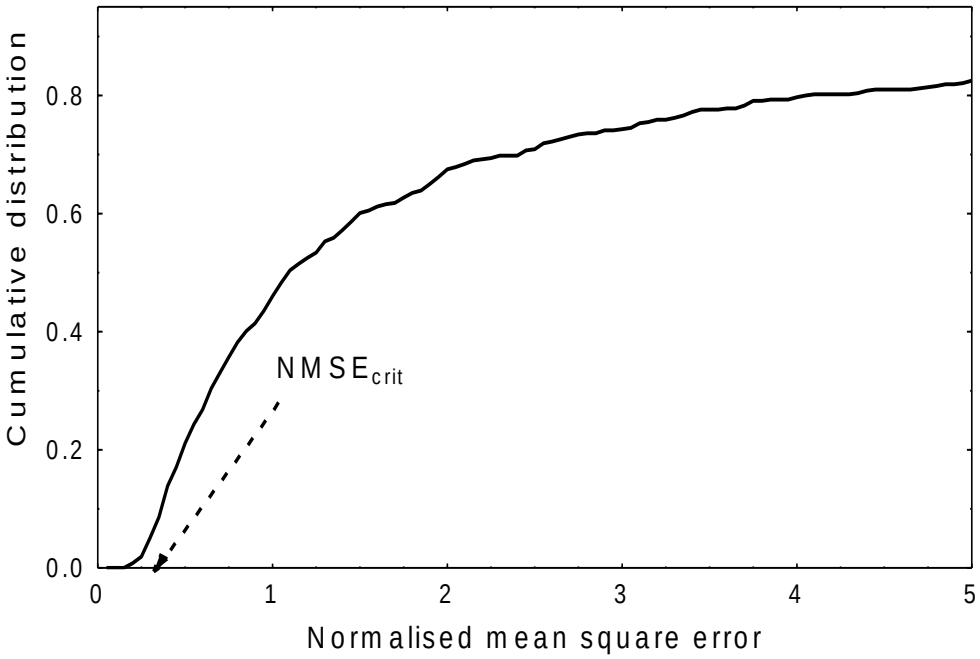

Figure 1 – Cumulative distribution of the normalised mean square error (NMSE) for recordings with mean squared coherence (range 0.15-0.25 Hz) greater than the 95% upper confidence limit (γ^2_{crit} = 0.190 for N_{SEGM}=5, N_L=512 samples). The arrow indicates the position of the 5% lower confidence limit for NMSE ($NMSE_{crit}$ = 0.30).

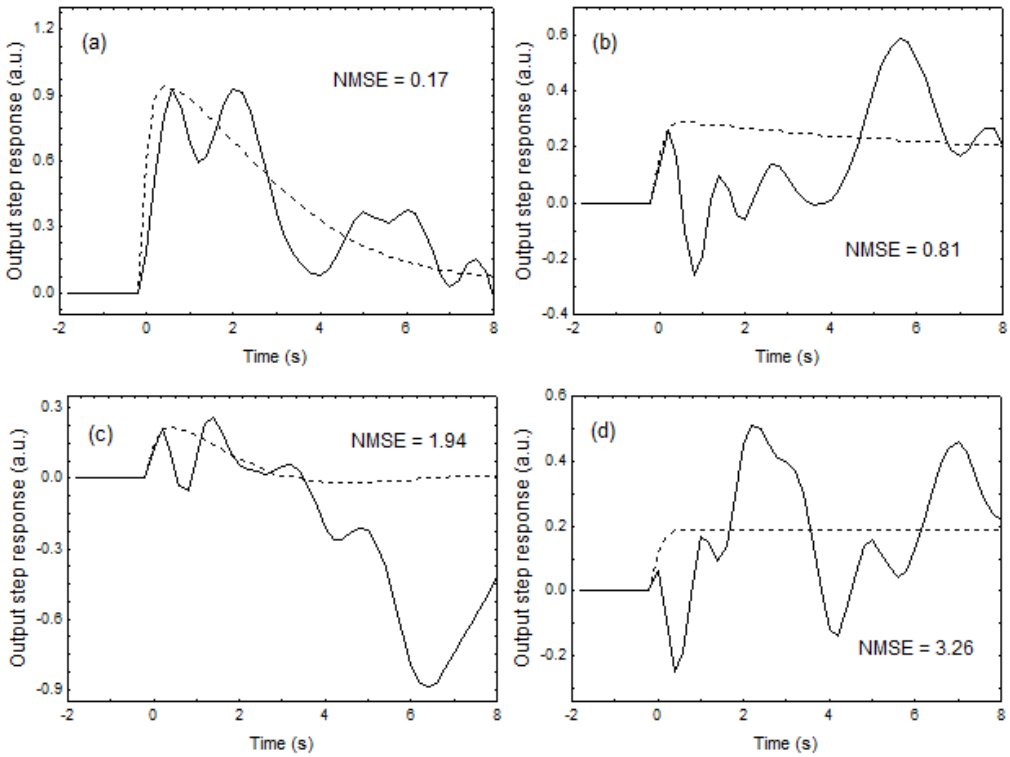

Figure 2 – Representative output step responses (continuous line) obtained from surrogate random data for increasing values of the normalised mean square error (NMSE) and best fit Tiecks model (dashed line). According to the NMSE<0.30 criterion, the step response in (a) would be accepted, but the ones in (b-d) would be rejected. In all cases the mean coherence criterion ($\gamma^2_m > \gamma^2_{crit}$) was satisfied.

Physiological data

Good quality recordings were obtained in 59 subjects (33 males) with mean (SD) age of 62.6 (10.6) years. For this group, systolic/diastolic BP was 127.7 (19.6)/72.2 (9.9) mmHg; CBFV 51.7 (13.1) and 51.0 (12.2) cm/s for the right and left MCAs, respectively. For N_{SEGM}=5 and N_L=512, all recordings had $\gamma^2_m > 0.190$ for both hemispheres. However, for the right MCA, three recordings had NMSE>0.3 whilst for the left MCA there were four such recordings. As a result, there were 54 complete pairs of ARI values corresponding to 5.09 (1.67) and 5.34 (1.53) for the right and left MCAs, respectively. The paired t-test confirmed a non-significant difference between hemispheres. Fig. 3 provides examples of CBFV step responses from the left MCA in four different healthy subjects.

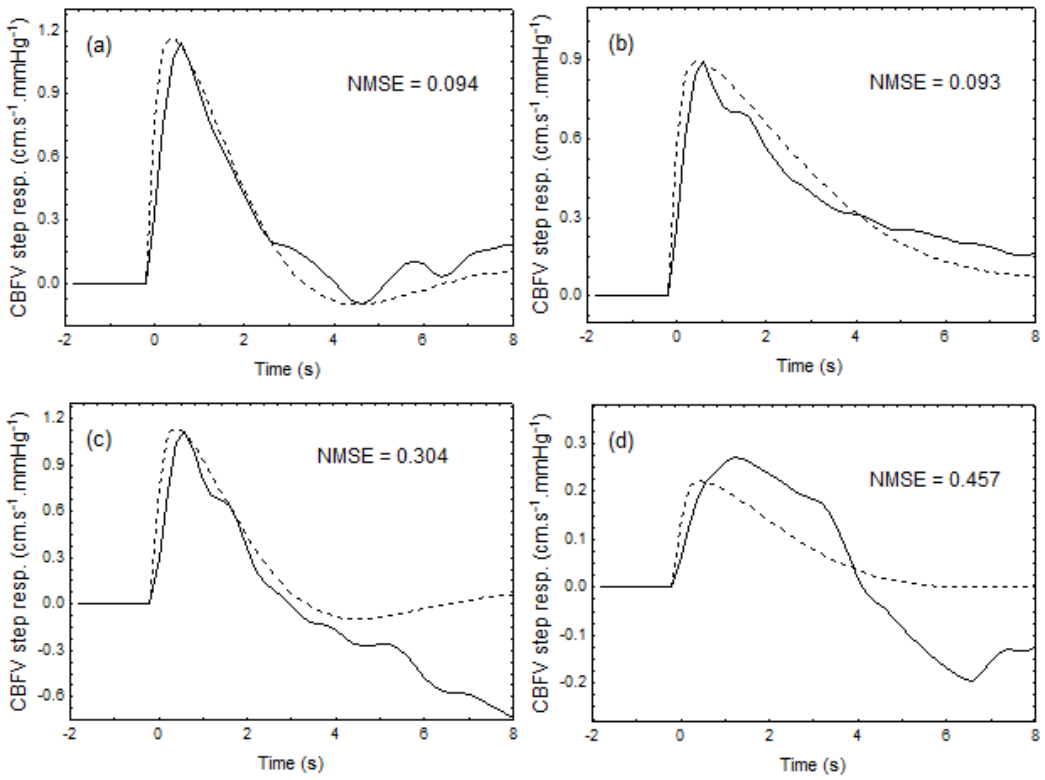

Figure 3 – Representative CBFV step responses (continuous line) in physiological recordings and best fit Tiecks model response (dashed line). The two top cases (a & b) satisfy the normalised mean square error criterion (NMSE<0.30) and would be accepted in further analyses. (c) Example of a borderline response with NMSE ≅ 0.3. The response in (d) has NMSE>0.30 and hence would be rejected. For the accepted responses the corresponding values of ARI are 7 (a) and 5 (b), respectively.

Clinical data

Twenty-six (14 male) recordings of acceptable quality were obtained in acute ischaemic stroke patients with mean (SD) age 63.4 (11.7) years. Systolic/diastolic BP were 146.7 (28.4)/63.9 (13.2) mmHg; CBFV was 40.9 (14.7) and 43.9 (20.7) cm/s for the right and left MCAs, respectively. For the right MCA, all recordings had $\gamma^2_m > 0.190$, but for the left side two subjects did not reach the critical value of mean coherence. With the NMSE criterion, five recordings from the right MCA and another six from the left MCA were rejected for being above the $NMSE_{crit}$ threshold. The resulting values of ARI were 5.40 (2.12) and 5.24 (1.97), for the right and left MCAs, respectively. Comparing the two sides in this group of subjects was not deemed appropriate as discussed below. Fig. 4 provides examples of CBFV step responses from the left MCA in four different stroke patients.

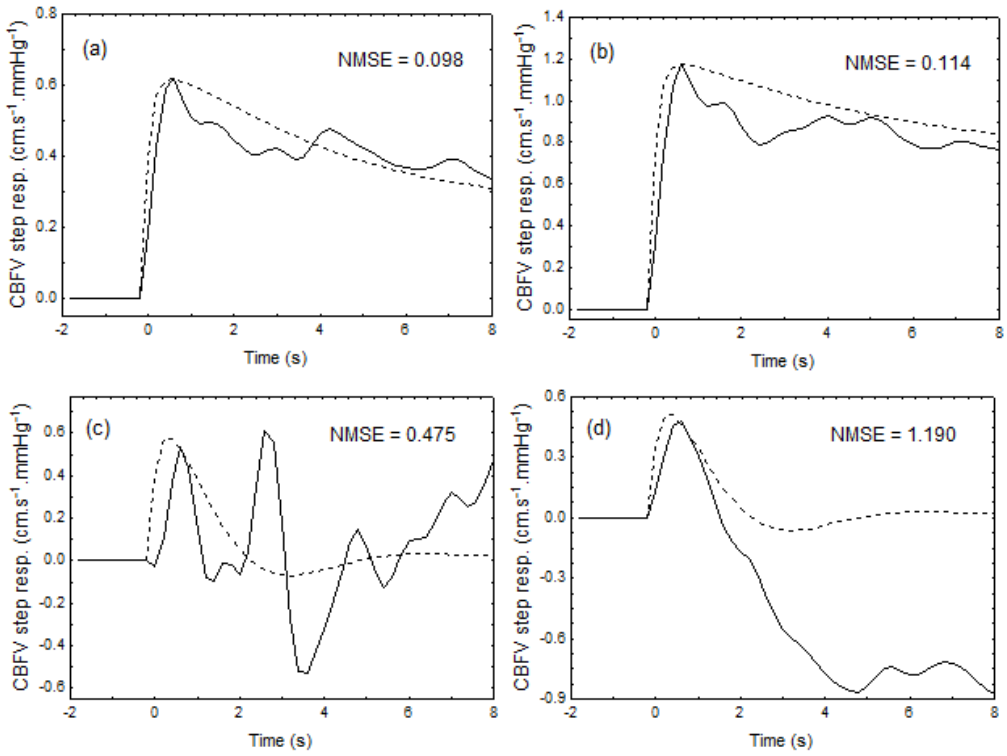

Figure 4 – Representative CBFV step responses (continuous line) in clinical recordings and best fit Tiecks model (dashed line). The two top cases (a & b) satisfy the normalised mean square error criterion (NMSE<0.30) and would be accepted in further analyses. The responses in (c & d) have NMSE>0.30 and hence would be rejected. For the accepted responses, the corresponding values of ARI are 2.9 (a) and 2.4 (b), respectively.

Treating each hemisphere as an independent estimate of ARI led to a total of 5.93 % (7/118) of values rejected in healthy subjects and 25% (13/52) in the patient group (Fig. 5), indicating a highly significant difference (p=0.0004) in the rate of rejection according to the joint criteria.

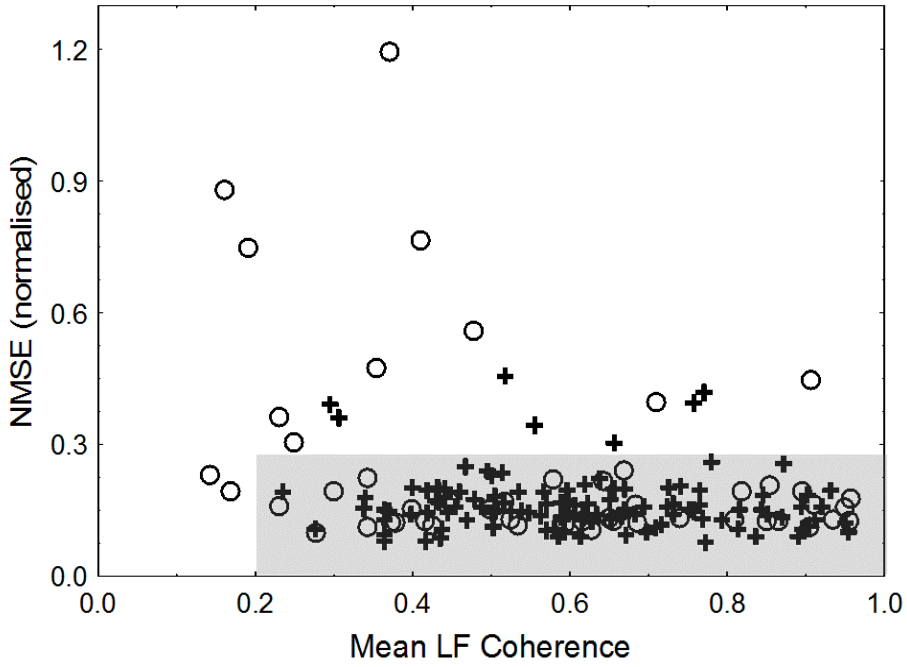

Figure 5 – Combined distribution of NMSE versus mean squared coherence (range 0.15-0.25 Hz) for physiological (circles) and clinical data (crosses). Both hemispheres are included for all subjects. The region of acceptance is indicated by the shaded area.

4. Discussion

Surrogate data

The main contribution of this study is the proposal of a statistically robust procedure for acceptance of estimates of ARI derived by TFA of spontaneous fluctuations of MBP and CBF. At each harmonic, the squared coherence function represents the fraction of output power that can be linearly explained by the input power. Values of coherence will approximate 1.0 for linear univariate systems if measurements have high SNR. On the other hand, in the presence of strong non-linearities, multiple inputs, or poor SNR, the coherence will approach zero. Based on these properties, the 95% upper confidence limit of $\gamma^2(f)$ has been proposed as a suitable threshold to accept TFA estimates of gain and phase frequency responses (Benignus, 1969; Gommer *et al.*, 2010; Claassen *et al.*, 2015). In most previous studies though, this approach has been limited to single harmonics with the objective of accepting or rejecting values of gain and/or phase. A different situation however, occurs with estimates of ARI. Since the inverse FFT of the TFA includes all harmonics, it is not possible to delete individual harmonics from the analysis. Moreover, mean values of coherence cannot be used over the entire spectrum due to the well-known non-linearity of dynamic CA in the frequency range where cerebral autoregulation is active, that is usually accepted as limited to frequencies below 0.10-0.15 Hz (Panerai *et al.*, 2006). For this reason, we adopted the 0.15-0.25 Hz range to obtain mean values of

coherence to determine the statistical significance of the MBP-CBFV relationship as quantified by TFA. The upper limit of 0.25 Hz is a suitable choice due to the limited bandwidth of MBP and CBFV beat-to-beat signals. The values presented in Table 1 are in very good agreement with previous work, when the increased number of degrees of freedom resulting from the average of several harmonics is taken into account (Claassen *et al.*, 2015). Noteworthy, rigorous application of the γ^2_{crit} criterion will need to take into account the individual values of N_{SEGM} and N_L adopted in each case.

Physiological data

Blind application of the criteria derived from Monte Carlo simulations to a set of data from healthy subjects achieved similar results as our previous procedure involving visual inspection of the complete coherence function and also the temporal pattern of the CBFV step response (Brodie *et al.*, 2009; Katogridakis *et al.*, 2013; Salinet *et al.*, 2014). As expected from high quality recordings obtained under ideal conditions, all subjects had mean coherence values above the 95% confidence limit. Nevertheless, some of the CBFV step responses had temporal patterns that were not physiologically plausible as illustrated in Fig. 3(c) and 3(d). For responses of this nature, the automatic procedure for acceptance or rejection based on objective criteria is an important advantage as it rules out subjective decisions that could lead to biases and erroneous conclusions. The responses illustrated in Fig. 3(c) and 3(d) are good examples of cases where individual investigators may not agree about a decision to accept or reject the corresponding ARI estimates.

Clinical data

The inclusion of data from acute ischaemic stroke patients had the objective of testing the application of the new acceptance criteria of ARI estimates to recordings obtained under more difficult conditions, such as in critically ill patients. The use of this dataset for investigating the effectiveness of dynamic CA in stroke patients was reported elsewhere (Salinet *et al.*, 2014) and is beyond the scope of this study. These data are representative of the difficulties of obtaining stable recordings at rest in subjects who can be confused, agitated and not able to cooperate or understand instructions clearly. As expected, the SNR of these measurements was not as high as those obtained with healthy subjects; as a consequence not all patients had values of mean coherence above the critical threshold. Moreover, the number of CBFV step responses with NMSE above the 5% lower confidence limit ($NMSE_{crit}$=0.30) was also significantly higher compared to physiological recordings. Although some CBFV step responses are strikingly ‘non-physiological’ (Fig. 4(c) and 4(d)), the risk of introducing bias due to subjective decisions is as high as with physiological data. However, the potentially damaging consequences of this are even greater in clinical studies, where smaller sample sizes mean that a few misclassifications can produce misleading results.

Due to lateralization of the ischaemic region, inter-hemispheric comparisons were not deemed appropriate in this case nor was the separation of hemispheres into affected/unaffected, given the main objectives of the present study.

Limitations of the study

Although Monte Carlo simulation is a powerful tool to derive properties of stochastic distributions, restraint is needed so as not to extend conclusions beyond its underlying assumptions. In our case, random surrogate data were generated by processes consistent with those of real measurements of BP and CBFV, but did not include the presence of non-stationarities, for example variable levels of BP power. More work is needed to test the sensitivity of the confidence limits of γ^2_m and NMSE to the presence of non-stationarities in the MBP and CBFV time series. One alternative to Monte Carlo simulations would be the computation of the exact confidence limits of coherence as proposed by Wang and Tang (2004).

Our results are also confined to ARI estimates based on transfer function analysis of spontaneous fluctuations in BP and CBFV. As a consequence, three important restrictions need to be kept in mind. First, different values of γ^2_{crit} might result from different physiological conditions, such as the squat-stand test (Smirl *et al.*, 2015). Secondly, $NMSE_{crit}$ was derived for CBFV step responses obtained from the inverse transform of the transfer function. For step responses estimated by other methods, such as autoregressive-moving average models (Panerai *et al.*, 2003), different NMSE thresholds might apply. Finally, neither criterion (γ^2_{crit} or $NMSE_{crit}$) can be used if values of ARI are to be obtained by direct application of Tiecks *et al* (Tiecks *et al.*, 1995) equations to the MBP and CBFV time series.

The effectiveness of the selection criteria proposed also needs to be tested more widely, including in different patient groups and subjects whose breathing patterns might increase MBP variability and power in the 0.15-0.25 Hz frequency range. The latter is likely to shift the mean coherence distribution upwards and lead to different values of γ^2_{crit} and $NMSE_{crit}$.

5. Conclusions

Objective and robust estimates of ARI, obtained with TFA of spontaneous fluctuations in BP and CBF, require confirmation of the statistical significance of the coherence function, as well as strict control of the quality of fitting of the CBFV step response to the standard template curves that correspond to the different values of this index (Tiecks *et al.*, 1995). To apply the criterion based on the 95% confidence limit for the mean value of coherence in the frequency range 0.15-0.25 Hz, it is necessary to take into consideration the number of data segments used for smoothing (Welch, 1967) and the duration (number of data samples) of each segment. On the other hand, the criterion based on the NMSE for fitting the CBFV step response to Tiecks *et al* (Tiecks *et al.*, 1995) model is

independent of the TFA settings. Further work is needed to assess the generalizability of these criteria to different physiological conditions and patient populations. Objective criteria for acceptance of ARI estimates are of considerable importance to improve observer reliability and to minimize the risk of bias in physiological and clinical studies.

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Data Access statement

Due to Ethical Committee requirements for specific patient consent, preceding recent Research Councils UK directive towards making support data publicly available, it is not possible to make the support data for this study openly accessible.

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