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Title Page

Reliability of dynamic cerebral autoregulation measurement using spontaneous fluctuations in blood pressure

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Keywords: cerebral autoregulation, transcranial Doppler ultrasound, reproducibility of results, blood pressure, cerebral haemodynamics

Abbreviations: Δ ARI, change in ARI; ANOVA, analysis of variance; ARI, autoregulatory index; BP, blood pressure; BMS, between-subject mean sum of squares; CBFV, cerebral blood flow velocity; CrCP, critical closing pressure; DBP, diastolic blood pressure; dCA, dynamic cerebral autoregulation; HR, heart rate; ICC, intraclass correlation coefficient; L, left; MCA, middle cerebral artery; R, right; RAP, resistance area product; SBP, systolic blood pressure; SEM, standard error of measurement; TCD, transcranial Doppler; WMS, within-subject mean sum of squares;

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Abstract

Spontaneous fluctuations in blood pressure (BP) and subsequent change in cerebral blood flow velocity (CBFV) in the middle cerebral artery (MCA) can be used to assess dynamic cerebral autoregulation using transfer function analysis. However the reliability of this technique has not been assessed, in particular the contribution of intra-subject variability relative to inter-subject variability.

Three bilateral CBFV, BP and R-R interval recordings were performed in ten healthy volunteers on four separate occasions over a 2-week period. Data were analysed to provide autoregulatory index (ARI), CBFV, resistance-area product (RAP), and critical closing pressure (CrCP). We also measured systolic and diastolic BP, and resting heart rate (HR). We calculated the standard error of measurement (SEM) and the intraclass correlation coefficient (ICC) and their 95% confidence limits for each parameter to assess their absolute (intra-subject) and relative (inter-subject) reliability. The coefficient of variation of SEM ranged from 1.7 % (CBFV) to 100.0 % (RAP) whilst the ICC was <0.5 for ARI, rising to >0.8 for CBFV and diastolic BP. This demonstrates excellent absolute and relative reliability of CBFV, while ARI is of comparable reliability to the measurement of HR. Using these results it is possible to determine the sample size required to demonstrate a change in ARI, with a sample of 45 subjects in each group required to show a change in ARI of 1, while to detect a change in ARI >2 would require only 11 subjects per group. These results could be valuable to the future planning of cerebral autoregulation studies, but more work is needed to understand the determinants of intra-subject variability in autoregulatory parameters.

Introduction

Cerebral autoregulation is the mechanism(s) by which constant cerebral blood flow can be maintained despite changes in cerebral perfusion pressure. It is usually described as being static, reflecting the integrity of autoregulatory mechanisms over time, or dynamic, occurring in response to sudden fluctuations in perfusion pressure [1].

Cerebral blood flow (CBF) is difficult to measure directly, and the advent of cerebral blood flow velocity (CBFV) measurement using transcranial Doppler ultrasound (TCD) offers an acceptable alternative [2].

Historically dynamic cerebral autoregulation (dCA) has been measured using induced changes in arterial BP (and hence cerebral perfusion pressure) while measuring the rate of return to baseline of CBF or CBFV. Methods used to induce change in BP include bilateral thigh cuff inflation to suprasystolic BP and their simultaneous release, lower body negative pressure, postural change, Valsalva manoeuvre and cold pressor stimulus. Each of these induces a step change in BP which can be related to changes in CBFV in either the time or the frequency domain, from which an estimate of autoregulatory index (ARI) can be derived [3]. However there are groups of patients in whom a sudden induced fall in BP may be undesirable, including those with heart failure, autonomic failure, and significant carotid stenosis. Several authors have used spontaneous fluctuations in arterial BP to assess dCA in neonates, head injured patients, significant carotid stenosis and following acute ischaemic stroke, using both the time and frequency domain, and this method is now generally accepted as a practical alternative to induced step changes of BP for measurement of cerebral autoregulation [4-6].

Tiecks et al.[3] describe a set of equations for CBFV response to sudden fall in BP from which an ARI can be calculated, from 0 (representing absence of autoregulation, i.e. cerebral blood flow dependent on cerebral perfusion pressure, a 'pressure-passive relationship') to 9 (best autoregulation). Panerai et al found good correlation between ARI derived from induced BP fall with thigh cuffs and spontaneous fluctuations in arterial BP, and thus it is possible to estimate the ARI derived from spontaneous fluctuations in BP at rest and compare the measured CBFV curves against those derived from Tiecks' model, with the 'best fit' being chosen from 0-9 [5].

TCD has been used to measure CBFV and dCA in a number of applications, including demonstrating the effect of hypertension on cerebral autoregulation [7;8], the effect of stroke on cerebral autoregulation [9], and the effect of antihypertensive treatment on cerebral autoregulation [10] or cerebral blood flow velocity [11;12] following stroke. However despite the many recent advances in measurement of CBFV and cerebral autoregulation using TCD, there is little published work regarding its reproducibility in the same subject over time (i.e. the intra-subject variability). Mahony et al.[13] measured dCA using the thigh cuff method up to six times in each subject to establish the variability of the test and any accommodation that may occur. Using analysis of variance (ANOVA) they found no significant difference between measures and there was no evidence of physiological accommodation with repeated testing. The investigators concluded that three sequential thigh cuff releases are sufficient to determine dCA. These were recordings performed on a single visit however, and do not give us an indication of the variability within the same subject over time. Birch et al.[14] studied the reproducibility of dCA using two strengths of lower body negative pressure in five healthy subjects on eight separate occasions (with two recordings at each visit). Their results were reported in terms of phase, and they reported a consistently positive phase on repeated testing, with less variability when the stronger

vacuum was used. Unfortunately subject discomfort and concerns regarding safety may limit the wider applicability of this technique, particularly in studies involving acutely unwell patients. Smielewski et al.[15] assessed the repeatability of dCA measured using transient ipsilateral carotid artery compression on a single occasion in 11 healthy volunteers, and concluded that for arterial compression ≥ 5 seconds the index of autoregulation was reproducible, and showed similar variation in response to changes in CO₂ as the more established thigh cuff method. However there are methodological concerns in that the stimulus to autoregulation is not quantifiable, as well as safety concerns regarding the use of this technique in patients with carotid artery disease.

It is unclear to what extent dCA derived from spontaneous fluctuations in BP may vary during a single recording period or between recordings in the same subject. This information is essential to interpret the results of clinical studies since any change occurring as a result of a disease or a treatment must be greater than the intrinsic variability of the test.

We therefore undertook a study to assess the extent of variability in dCA measured using TCD and spontaneous BP fluctuations both in the same subject during one session and also across serial visits. Due to the contribution of other cerebrovascular parameters like critical closing pressure (CrCP) and resistance area product (RAP) to our understanding of autoregulatory function [16] the reproducibility of these parameters was also examined. This will provide us with vital information which will be of considerable value when planning future clinical studies of cerebral autoregulation. To our knowledge this is the first study looking at the intrasubject variability in dCA measured from spontaneous fluctuations in BP both within one visit and also across serial visits.

Methods

Data Collection

The research was carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association, and was approved by the local research ethics committee. Ten healthy volunteers were recruited from departmental staff. All participants were free from cardiovascular disease and hypertension, none were taking any medications, and all gave informed consent. Each subject underwent four periods of measurement with 3-5 days between each recording, and recordings were made at the same time of day for each subject. Subjects were asked to behave in a similar fashion prior to each visit, and specifically were asked to avoid caffeine, meals and strenuous exertion for at least 4 hours prior to each recording. At each visit three recordings were made, each of five minutes. Heart rate (R-R interval) was measured by 3-lead ECG, BP was measured using a servo-controlled plethysmograph (Finapres), and bilateral MCA insonation was performed using two 2MHz probes secured in place at the temporal bone window with a specially designed head frame. These signals were simultaneously recorded onto a dedicated computer for subsequent off-line analysis. Recordings were performed in a quiet research room with a constant temperature (24°C), and subjects were asked to maintain a constant respiratory rate during recordings (10-12/min). Ten minutes equilibration time was allowed prior to the first recording. Between recordings the Finapres servo-adjust was switched on until there was adequate signal stability (<5% variation), this was switched off during recordings. The MCA were identified according to their signal depth, velocity, and wave characteristics as described by Aaslid et al [2]. Depth, velocity, power, and location of temporal window were noted for each subject and the same window, depth

and power were used at subsequent visits in order to ensure insonation of the same MCA segment at each recording, thus minimising a potential source of variability. All recordings were undertaken by the same two researchers (FB and EA). At the end of each visit, once subjects had been resting supine for >30 minutes, brachial BP and heart rate were measured three times over 5 minutes using a validated machine (AND UA767) and appropriately sized brachial cuff, and the average of the three measures was recorded. The variability of systolic and diastolic BP (SBP, DBP) and HR are presented for comparison with autoregulatory parameters. Handedness was determined using the Edinburgh inventory.

Data Analysis

Data were visually inspected, spikes were removed by linear interpolation, and the BP was calibrated. Fast Fourier transform was used to convert the Doppler signals into maximum frequency velocity envelopes with a 5ms window resolution. The ABP and ECG signals were sampled at 200 samples per second. Signals were low-pass filtered with a zero-phase eighth-order Butterworth filter with a cut-off frequency of 20Hz. Each cardiac signal was marked from the ECG to determine the R-R interval and an estimate of mean CBFV, CrCP and RAP were calculated for each cardiac cycle. Using spline interpolation and resampling the data at 5Hz a uniform time base for all the data was achieved.

The ARI was estimated using the 10 template CBFV response curves to a step change in mean BP proposed by Tiecks et al. [3]. For each segment of data, the real CBFV response to a hypothetical step change in mean BP was derived by transfer function analysis as shown previously [5;6;17]. The Tiecks template curve that provided the best fit to the real CBFV step response was selected by least squares and provided a corresponding value of ARI. We present the ARI for R and L, as well as the absolute difference between the two sides ARI R-L. In some instances ARI R was greater than L, in others L was greater than R, and ARI R-L was normally distributed in the range -1 to 1.5. Only the magnitude of the difference R-L was considered (irrespective of which was greater), i.e. all values are expressed as positive numbers.

In addition we considered the values of CrCP and RAP. CrCP is defined as the arterial pressure below which small vessels collapse and forward blood flow becomes zero, which in the cerebral circulation is equivalent to the sum of intracranial pressure and the contributions of vascular smooth muscle tone [17]. There has been interest in the use of CrCP as a measure of cerebrovascular tone and as a component of cerebral autoregulation [1;16-18]. In the present study CrCP was estimated from the first harmonic for arterial BP and CBFV [17]. RAP is an index of cerebrovascular resistance, which is equal to the product of total cerebrovascular resistance and cross-sectional area of the vessel [19], and was determined as the inverse of the linear regression slope between instantaneous CBFV and ABP relationship for each cardiac cycle [16;17;19].

A maximum of three same-day values were obtained for each subject for each parameter at each of four visits, assuming no data were rejected due to poor quality. Results are reported separately for R and L. Parameters with beat-to-beat values (CBFV, CrCP, RAP, SBP, DBP, and HR) were averaged for the entire 5 min. recording.

Statistics

Each parameter (ARI, CBFV, CrCP, RAP, SBP, DBP and HR) was examined for normality, those which were non-normally distributed (i.e. non-homoscedastic variables) were first log-transformed using the natural logarithm prior to statistical analysis. Using the method described by Pinna et al. [20] repeated measures analysis

of variance (ANOVA) was used to estimate the standard error of measurement (SEM):

$$\text{SEM} = \sqrt{\text{WMS}} \quad (1)$$

(WMS = within-subject sum of mean squares). We report SEM as an index of absolute reliability [20]. The intra-class correlation coefficient (ICC) was then calculated from the ANOVA table using the formula described by Shrout and Fleiss[21]

$$\text{ICC} = [\text{BMS} - \text{RMS}] / [\text{BMS} + (\kappa - 1)\text{RMS}] \quad (2)$$

(BMS = between-subject mean sum of squares, RMS = residual error mean sum of squares, κ =no. of repeated observations), and 95% confidence intervals were calculated. Confidence intervals of parameters which were log-transformed were back transformed using the anti-logarithm. The 95% confidence intervals for homoscedastic variables represent the range within which the difference between subsequent measurements would be expected to lie solely as a result of intrasubject variability, while for the non-homoscedastic variables the confidence intervals represent the expected ratio of subsequent measurements to the first measurement. The coefficient of variation was also calculated as $\text{SEM} \div \text{overall mean}$ for each parameter (expressed as %). We report ICC as an index of relative reliability. The interpretation using the above statistical methods is as follows: high values of SEM represent low absolute reliability, indicating large random variation within an individual. On the other hand, ICC is a measure of relative reliability as it expresses the amount of intrasubject variability in relation to corresponding values of intersubject variability, thus reflecting the ability of a measurement or parameter to discriminate between different individuals. $\text{ICC} \geq 0.8$ is considered to indicate good to excellent reliability [20].

Results

Ten volunteers, five male and five female, were recruited with a mean age of 37.5 years (range 21 – 56). Each had three recordings at each of four visits giving a total of 120 recordings for each side. Thirteen recordings (7 R and 6 L) were rejected due to artefact or poor data quality; these were distributed at random across the group. Demographics for the subjects are presented in Table 1. All subjects who took part were R-handed.

Table 2 presents the mean \pm SD of haemodynamic parameters for each visit, as well as the overall mean \pm SD for the 4 visits. Repeated-measures ANOVA did not show any significant differences in mean values of the parameters in Table 2 between different visit days. CBFV and RAP were found to be non-homoscedastic and required log-transformation prior to statistical analysis. CrCP was found to be non-normally distributed even after log-transform, and was therefore not analysed further. The absolute (SEM) and relative (ICC) reliability for haemodynamic and autoregulatory parameters are presented in Table 3. The implications of the SEM and its 95% confidence limits (Table 3) for the reproducibility of the ARI and other parameters are discussed below. The coefficient of variation (CV) of SEM, also shown in Table 3, is more appropriate to make comparisons of reproducibility between different parameters. Surprisingly, CBFV showed the lowest CV, followed by SBP and DBP. On the other extreme, RAP and the ARI R-L difference showed very high CV (Table 3). For the ARI R-L difference, this was expected due to the relatively low mean values of the difference (Table 2). The CV for the ARI was an order of magnitude greater than that of CBFV, but, on the other hand, not too dissimilar than what was observed for heart rate (Table 3).

The highest ICC values were also obtained for CBFV, followed by diastolic BP. The lowest values resulted for ARI. However, for reasons that are discussed below, the corresponding 95% confidence intervals (Table 3) were fairly broad, suggesting that these estimates were not entirely robust. Similarly to the CV, the ARI ICC and its 95% CI was comparable to the corresponding figures for HR. Of interest is the much higher values of ICC obtained for RAP (Table 3).

The low SEM and high ICC observed for CBFV can be explained by the individual values given in Figure 1. The reduced CV followed from the highly stable intra-subject values recorded for the 4 visits. In addition, the ability to discriminate between different subjects (e.g. subjects #2 and #4), led to the high values of ICC estimated for CBFV. A slightly different picture emerged for the ARI (Figure 2). Although several subjects showed very stable values for all 4 visits, 4 subjects (R-MCA) and 5 subjects (L-MCA) had greater inter-visit variability. The lack of stability of the ARI for these subjects contributed to the relatively high SEM and CV in Table 3. The fact that the ARI values for these subjects also ‘crisscrossed’ the values of the more stable subjects (Figure 2) also reduced the ability of the ARI to discriminate between subjects thus leading to the relatively low values of ICC given in Table 3.

Discussion

Despite the increasing use of TCD for the assessment of cerebral autoregulation using spontaneous fluctuations in BP there have been no previous studies looking at the intrinsic variability of this measurement. This is clearly of importance in order to accurately interpret apparent differences noted in dCA in different clinical situations and further study into its reliability has been advocated [6].

In the present study we made repeated measurements on ten healthy volunteers under identical circumstances using strict data collection and analysis protocols in order to assess variability within one visit and across serial visits.

Despite potential limitations with probe positioning (discussed below), CBFV turned out to be the most reliable of all parameters studied showing superior absolute (i.e. SEM) and relative (i.e. ICC) reliabilities than more established haemodynamic measurements such as SBP, DBP and HR. The relatively lower reliability observed for the ARI and RAP were to be expected due to the mathematical estimation processes involved in their calculation [3;5;18]. The same may apply to CrCP, but we have not assessed its reliability due to the lack of normality. Despite its high CV and SEM, the ICC for RAP was higher than for the ARI, which should encourage further work to confirm its sensitivity to changes in dCA as suggested by preliminary studies [4;16].

The observation that the numerical values of CV and ICC for the ARI are similar to those of HR (Table 3) provide a ‘feeling’ for the physiological variability of ARI, but entirely different considerations apply to its reliability in clinical applications. The low ICC values for ARI (Table 3) suggest that this parameter cannot discriminate well between relatively young healthy subjects, but it does not mean that the ARI will not show good sensitivity and specificity to discriminate against individuals with impaired autoregulation e.g. $ARI < 4.0$ (Fig. 2). Nevertheless, the longitudinal variability observed in approximately half of the subjects (Fig. 2) should caution against relying on single punctual measurements of ARI. In contrast to other studies of reliability of clinical parameters we have performed measurements during four serial visits, rather than the usual test-retest approach [21]. Since the number of tests multiplies the residual mean error (RMS) in the denominator of equation (2), this means that our particular design represented a much harsher situation to estimate the

ICC for parameters that had RMS of the order of 20% of the BMS as was the case with the ARI.

The second important consideration follows from the 95% limits of agreement obtained for the ARI (Table 3) since there appears to be no consensus regarding what is considered a significant change (increase or decrease) in ARI value. Previous work on ARI in patients at risk of impaired cerebral autoregulation has concentrated on identification of a statistically significant difference between ARI in patient and control groups, without pre-specifying an 'acceptable' ARI value or the magnitude of any predicted change. Tiecks et al [3] demonstrated in ten healthy anaesthetised patients a fall in ARI from 4.8 ± 1.0 to 2.3 ± 1.3 ($p < 0.01$) using isoflurane, i.e. an observed difference in ARI of 2.5. It can be seen from the confidence limits of the SEM that a difference > 2.048 is unlikely to be explained by intrasubject variability, and thus it is likely that this difference does at least in part reflect a real difference in ARI. Notwithstanding studies that reported large differences in ARI [9;22], many others obtained differences that fall within the 95% confidence interval for SEM and hence could be reflecting purely random variation rather than a true difference. One recent example was the assertion that ARI is reduced in the morning as compared to values taken the previous evening [23].

The relatively small sample size of our study ($n=10$) limits the precision of the estimates presented in Table 3. In particular, the 95% confidence limits of the ICC tend to be fairly wide for low estimated values of ICC, as in the case of ARI. Applying the values presented by Walter et al [24] more than 180 subjects would be needed to guarantee that the ICC is greater than 0.3 for these parameters, with 80% power at $\alpha = 0.05$. For other parameters showing relatively high values of ICC, such as CBFV, the sample size of $n=10$ already guarantees that the estimated ICC in Table 3 is greater than 0.7 [24]. Although much larger sample sizes are required to improve estimates of 95% confidence limits for parameters with estimated ICC < 0.5 , smaller sample sizes can be predicted for clinical studies aimed at detecting changes in ARI. Based on the ANOVA's mean within-subjects sum of squares of 2.823 (ARI R) (data not shown), the sample size for each group would be $44.6 / (\Delta \text{ARI})^2$ for detecting a difference of ΔARI between the two groups with 80% power at $\alpha = 0.05$ [25]. Therefore, for $\Delta \text{ARI} = 1.0$, 45 subjects would be needed in each group, whilst only 11 subjects would be required to detect a change of 2.0 units in ARI. These estimates correlate well with the clinical studies mentioned above, where differences in $\Delta \text{ARI} > 2.0$ were observed with sample sizes that were not adequate to detect smaller differences. We propose that the above formula for calculating sample sizes may be useful to other investigators designing cerebral autoregulation studies based on the ARI estimated from spontaneous fluctuations in ABP.

It remains unclear to what extent there is an inter-hemispheric relationship in changes in ARI. This is of particular relevance in the study of acute stroke, where comparison may be made between 'affected' and 'unaffected' hemisphere. We demonstrated over serial recordings that there was little mean change in ARI R-L, and that an absolute difference > 1.13 would have to exist between hemispheres to be considered 'real'.

Limitations of Current Study

There are a few limitations to our study. We do not have data on end-tidal CO_2 for our subjects, which may have been helpful to examine CBFV and ARI more closely. However subjects maintained a constant respiratory rate and significant fluctuations in CO_2 would not have been expected. In support of this, CBFV which is highly sensitive to changes in CO_2 demonstrated very little variability.

The CBFV measured using TCD can only be expected to represent CBF if the diameter of the insonated vessel (in this case the MCA) remains constant. Giller [26] examined MCA diameter in patients undergoing craniotomy and demonstrated little variation (<4%) in the diameter of the proximal MCA despite considerable fluctuation in mean arterial pressure and CO₂. In addition depth, power, and location of temporal window were the same at each visit and probes were secured using an adjustable head frame to try and ensure uniformity of signals and avoid insonation of smaller vessels which have shown considerably greater variation in diameter (up to 21%). Although transducer repositioning could contribute to longitudinal variability, the excellent absolute and relative reliabilities observed for CBFV suggested that this was not the case.

A further limitation of this study was the age of the subjects (mean 37.5 years), which limits the extrapolation of our results to other groups such as neonates and the elderly, both of whom may for various reasons demonstrate wider variability than shown here.

Conclusions

This study is the first to look at reliability of ARI derived from spontaneous fluctuations of BP. This method clearly has advantages for the study of acutely ill patients where it may be undesirable or impossible to perform haemodynamic manoeuvres such as thigh cuffs, lower body negative pressure or carotid artery compression. We have shown that mean CBFV is highly reproducible and that serial ARI measurements are of acceptable reliability for clinical study if handled properly. These results help to answer questions regarding the reproducibility of assessment of cerebral autoregulation using spontaneous fluctuations of BP, and in addition they help to address the issue of sample size calculation for future clinical studies using this method.

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Tables

Table 1

Subject Characteristics (overall)

Age (years)	Gender	BMI	SBP (mmHg)	DBP (mmHg)	HR (bpm)
37.5 ± 9.2	5 Male : 5 Female	22.9 ± 3.0	117 ± 8	69 ± 9	64 ± 10

All results presented as mean ± SD

Table 2

Haemodynamic Parameters by Visit

	Visit 1	Visit 2	Visit 3	Visit 4	Overall
ARI Right	5.8 ± 1.1	5.9 ± 0.8	5.8 ± 1.3	6.3 ± 0.9	6 ± 1.2
ARI Left	5.7 ± 1.1	5.6 ± 1.1	5.8 ± 1.0	6.2 ± 0.9	5.9 ± 1.2
ARI R-L	0.4 ± 0.4	0.6 ± 0.5	0.3 ± 0.4	0.3 ± 0.5	0.4 ± 0.4
CBFV R (cm/s)	69.6 ± 25.4	65.9 ± 19.7	70.6 ± 29.1	67.3 ± 22.8	68.3 ± 23.6
CBFV L (cm/s)	66.1 ± 10.5	61.3 ± 15.0	63.2 ± 14.3	63.9 ± 12.7	63.6 ± 12.8
RAP Right (mmHg.s/cm)	1.2 ± 0.4	1.3 ± 0.5	1.2 ± 0.6	1.2 ± 0.4	1.2 ± 0.5
RAP Left (mmHg.s/cm)	1.1 ± 0.3	1.4 ± 0.6	1.3 ± 0.5	1.3 ± 0.4	1.3 ± 0.5
CrCP Right (mmHg)	7.8 ± 6.0	11.7 ± 8.6	10.7 ± 11.4	10.6 ± 8.9	10.2 ± 8.7
CrCP Left (mmHg)	9.4 ± 6.4	10.5 ± 8.2	11.1 ± 10.1	12.2 ± 9.3	10.8 ± 8.4
Systolic BP (mmHg)	119 ± 9	115 ± 9	117 ± 5	117 ± 9	117 ± 8
Diastolic BP (mmHg)	71 ± 9	69 ± 9	68 ± 9	67 ± 9	69 ± 9
HR (bpm)	64 ± 7	65 ± 14	61 ± 7	63 ± 9	64 ± 10

All results presented as mean ± SD

Table 3
SEM and ICC for Haemodynamic and Autoregulatory Indices

	SEM	95% CI	Coefficient of Variation (%)	ICC	95% CI
ARI R	0.739	-2.048, 2.048	12.3	0.51	0.19, 0.81
ARI L	0.784	-2.172, 2.172	13.3	0.43	0.12, 0.77
ARI R-L	0.410	-1.130, 1.130	102.5	n/a	n/a
CBFV R (cm/s)	1.092	0.783, 1.278	1.7	0.91	0.79, 0.97
CBFV L (cm/s)	1.086	0.796, 1.256	1.7	0.86	0.68, 0.96
RAP R (mmHg.s/cm)	1.201	0.602, 1.661	100.0	0.75	0.50, 0.92
RAP L (mmHg.s/cm)	1.198	0.605, 1.652	92.0	0.70	0.42, 0.90
SBP (mmHg)	4.311	-11.950, 11.950	3.7	0.68	0.39, 0.89
DBP (mmHg)	3.550	-9.854, 9.854	5.1	0.82	0.62, 0.95
HR (bpm)	6.123	-16.971, 16.971	9.6	0.56	0.25, 0.84

Figure Legends

Figure 1 - Mean CBFV for each subject for each visit. a) right MCA, b) left MCA

Figure 2 - Mean ARI for each subject for each visit. a) right MCA, b) left MCA.

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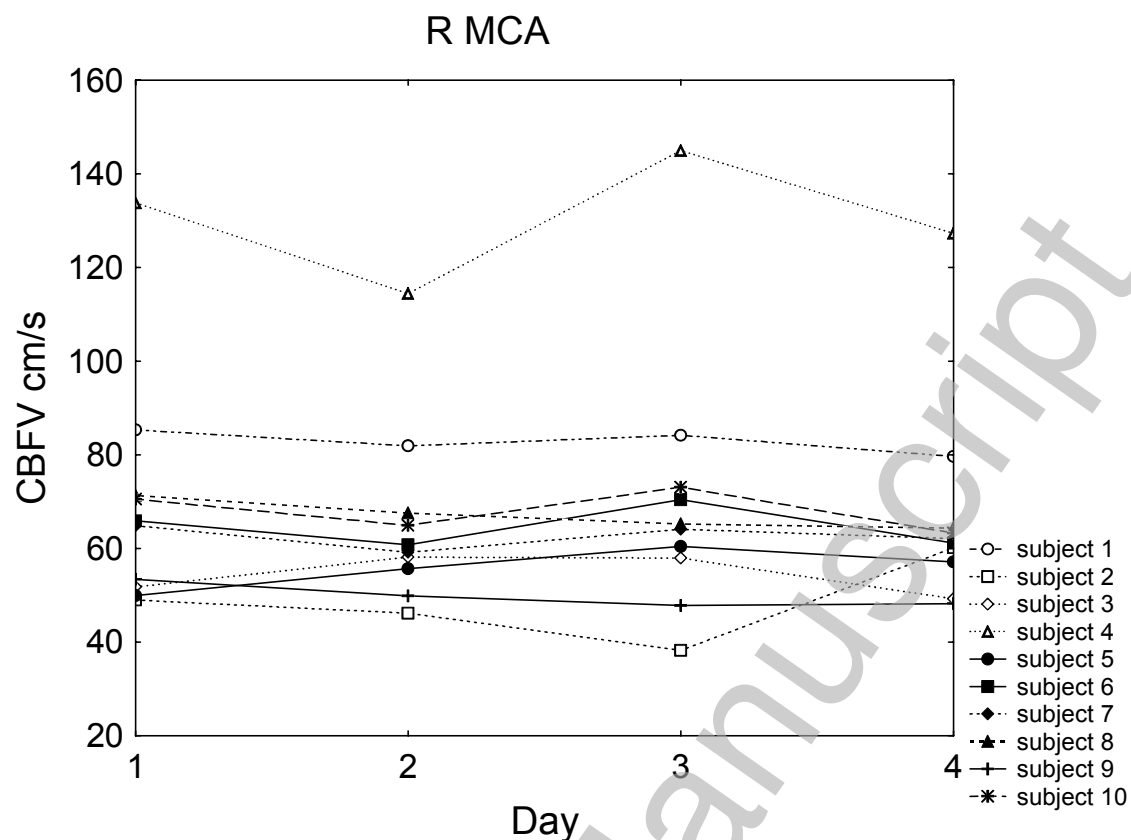


Figure 1a

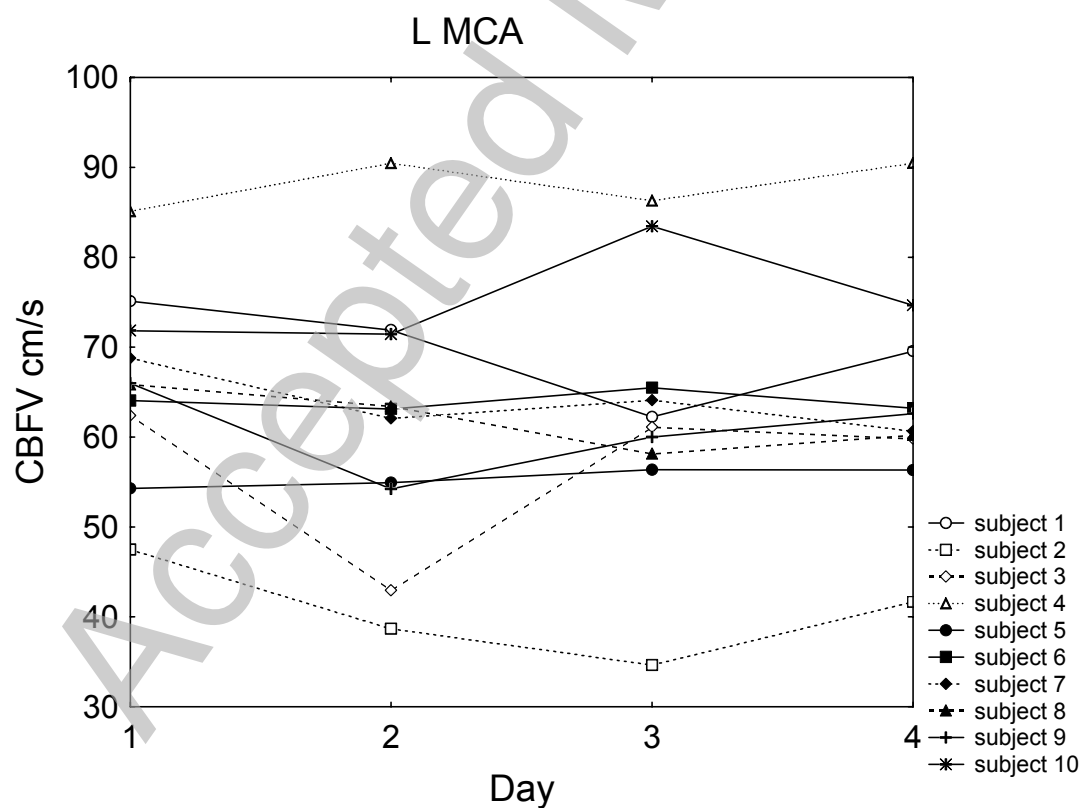


Figure 1b

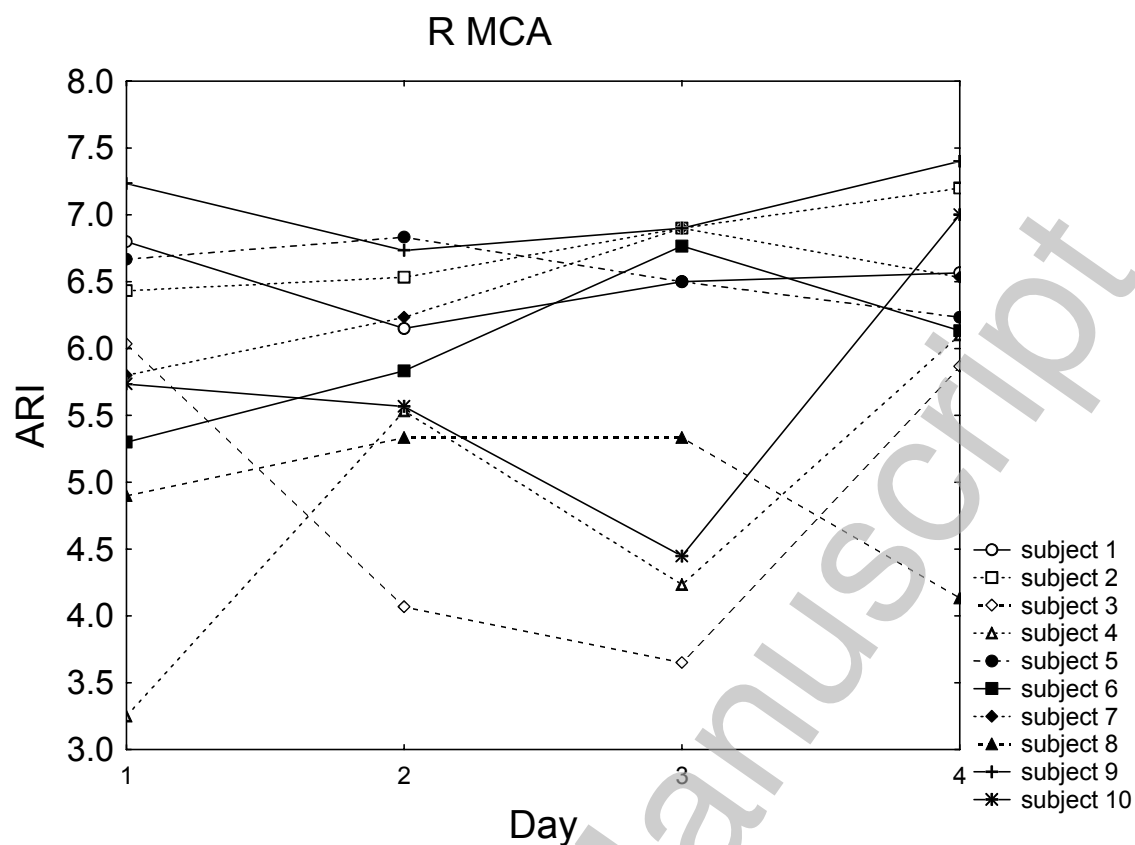


Figure 2a

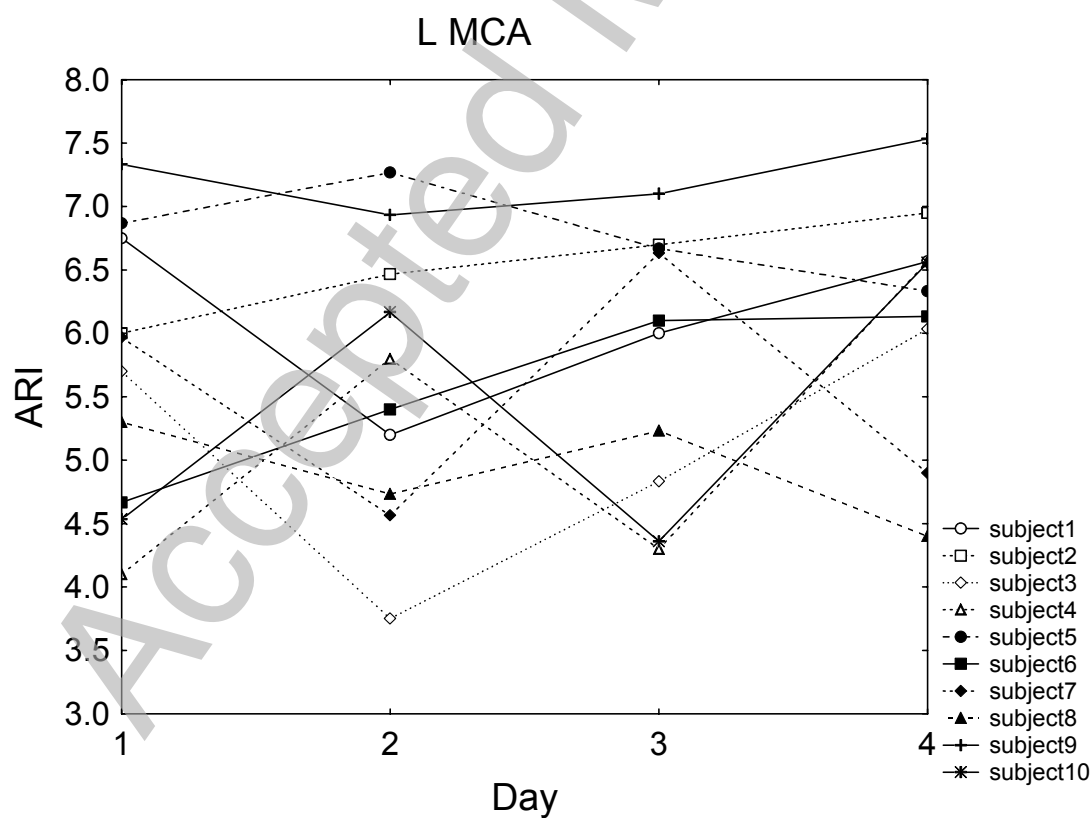


Figure 2b