Can we assess dynamic cerebral autoregulation in stroke patients with high rates of cardiac ectopicity?

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Abstract

It is unclear whether physiological recordings containing high numbers of ectopic heartbeats can be used to measure the cerebral autoregulation (CA) of blood flow. This study evaluated the utility of such data for assessing dynamic CA capacity.

Physiological recordings of cerebral blood flow velocity, heart rate, end-tidal CO_2 and beat-to-beat blood pressure from acute ischaemic stroke (AIS) patients (n = 46) containing ectopic heartbeats of varying number (0.2 to 25 occurrences per minute) were analysed. Dynamic CA was determined using the autoregulation index (ARI) and the normalised mean square error (NMSE) was used to evaluate the fitting of the step response between BP and CBFV to Tiecks' model. We fitted linear mixed models on the CA variables incorporating ectopic burden, age, sex and hemisphere as predictor variables.

Ectopic activity demonstrated an association with mean coherence (p = 0.006) but not with ARI (p = 0.162), impaired CA based on dichotomised ARI (p = 0.859) or NMSE (p = 0.671).

Dynamic CA could be reliably assessed in AIS patients using physiological recordings with high rates of cardiac ectopic activity. This provides supportive data for future studies evaluating CA capability in AIS patients, with the potential to develop more individualised treatment strategies.

Keywords

Ectopic, Acute Ischaemic Stroke, Cerebral Haemodynamics, Transcranial Doppler Ultrasound

Authors Biography

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Fiona Brodie graduated MBBS from Newcastle University in 2000, and MD (Cardiovascular Sciences) University of Leicester in 2009. She is a geriatrician in Lanarkshire, and an honorary senior lecturer at Glasgow University.

Thompson G. Robinson undertook his medical training in Nottingham, Newcastle-Upon-Tyne and Leicester, and is currently Head of the Department of Cardiovascular Sciences and Professor of Stroke Medicine at the University of Leicester.

Ronney B. Panerai graduated in electronic (BSc 1970) and biomedical engineering (MSc 1973; PhD 1978). He was a Full Professor of Biomedical Engineering at the Federal University of Rio de Janeiro until Dec 1991, before moving to the University of Leicester, where he is now an Emeritus Professor in the Department of Cardiovascular Sciences.

1. Introduction

Cerebral autoregulation (CA) of blood flow has been shown to be impaired following acute ischaemic stroke [1–3]. Patients with stroke often have cardiac comorbidities, which may include ectopic rhythms [4, 5]. Such premature ventricular contractions can produce haemodynamic instability, which if severe, may disrupt normal cerebral perfusion [6, 7]. Due to the unpredictability of both arterial blood pressure (BP) and cerebral haemodynamics caused by ectopic beats, physiological recordings with high rates of ectopicity, typically three to four ectopic beats per minute, are usually rejected during analyses of dynamic CA [8–11]. However, it has not been determined whether there is a threshold whereby dynamic CA cannot be reliably calculated. A higher prevalence of ectopic heartbeats can be expected in stroke populations, where increases in ectopic frequency have been associated with risk of stroke [4]. In addition, hyperacute stroke patients are particularly vulnerable to arrhythmia, with up to 25% experiencing arrhythmic episodes, including atrial or ventricular arrhythmia, within the first 72 hours [5]. This, therefore, represents a sizeable number of individuals where assessment of dynamic CA would not be possible based on current practice. As clinical research and medicine move towards more personalised care, this issue presents a specific methodological concern as a substantial proportion of patients will be excluded from physiological studies.

Transcranial Doppler ultrasound (TCD) offers non-invasive and real-time monitoring of cerebral blood flow velocity (CBFV) and, when assessed with changes in BP, provides an understanding of haemodynamic control in vascular beds [12]. A range of methods and models are available to determine the dynamic relationship between BP and CBFV [12, 13]. Accurate transfer function estimates from BP readings and CBFV have technical limitations if the recordings are not continuous, or if a large amount of non-physiological artefacts are

present [14, 15]. We have previously analysed and reported cerebral haemodynamic data from physiological recordings containing ectopic rates of 8% or less [16]. These data demonstrated that, although the transfer function parameters coherence and gain can be influenced by the spikes in data caused by ectopic beats, they are still reliable in determining CA [16]. However, to date, there have been no studies examining whether higher rates of ectopic beats can influence CA measurements, including in patients with stroke. Using updated criteria for acceptance of dynamic CA estimates using the autoregulation index (ARI) [17], we conducted a preliminary study to evaluate the effect of recordings containing a large number of ectopics on the estimation of dynamic CA.

2. Methods

2.1 Subjects and Measurements

Physiological recordings containing ectopic beats, obtained during acute ischaemic stroke (AIS) studies at the University Hospitals of Leicester NHS Trust from 2007-2017, were identified within the Leicester Cerebral Haemodynamics in Ageing and Stroke Medicine database [18]. All participants had provided informed consent in compliance with local ethics committee approvals. All studies had common inclusion criteria: patients with clinical diagnosis of AIS, aged $\geq$18 years, able to participate in study measurements, and informed consent (or relative assent); and a common exclusion criterion of co-morbidity with life expectancy less than 3 months. Patients were excluded from the database in the presence of: (i) missing key information (age, sex and classification of stroke subtype according to the Oxfordshire Community Stroke Project (OCSP) classification), (ii) poor data quality, (iii) duplication arising from overlapping studies.

All investigators were trained at the same laboratory (Department of Cardiovascular Sciences, University of Leicester, U.K), and acquired physiological data to a standard data collection and analysis protocol. Briefly, beat-to-beat BP was recorded continuously using the Finapres or Finometer devices (FMS, Finapres Measurement Systems, Arnhem, Netherlands). Heart rate (HR) was recorded using a 3-lead electrocardiogram (ECG) and end-tidal CO_2 ($etCO_2$) was measured via nasal prongs (Salter Labs) by an infrared capnograph (Capnocheck Plus). Bilateral insonation of the MCA was performed using TCD (Viasys Companion III; Viasys Healthcare) with a 2 MHz probe, which was secured in place using a head-frame. During the entire procedure, subjects were in a supine position and detailed instructions were given before taking measurements. Following set-up and a

minimum stabilisation period of 15 min, BP measurement was performed by brachial sphygmomanometry before a 5-minute baseline recording. Stroke subtype was defined by the OCSP classification, and stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS) at the time of cerebral haemodynamic assessment.

2.2 Data Analysis

This has previously been described in detail elsewhere [18]. In brief, data were simultaneously recorded onto a data acquisition system (PHYSIDAS, Department of Medical Physics, University Hospitals of Leicester) for subsequent off-line analysis using a sampling rate of 500 samples s^{-1}. BP was calibrated at the start of each recording using systolic and diastolic values from brachial sphygmomanometry and all signals were visually inspected to identify artefacts and noise, with narrow spikes (<100 ms) removed by linear interpolation. CBFV channels were subjected to a median filter and all signals were low-pass filtered with a cut-off frequency of 20 Hz.

The R–R interval was automatically marked from the ECG and continuous HR was plotted against time. Missed marks were re-marked at the time points at which they occurred. This included marking all ectopic heartbeats with an R wave. Each baseline recording was visually inspected by one investigator (OLL) for the total number of ectopic heartbeats and calculated as number of ectopics per minute.

Mean BP and mean CBFV (MCBFV) values were calculated for each cardiac cycle. The end of each expiratory phase was detected in the $etCO_2$ signal, linearly interpolated, and resampled with each cardiac cycle. If the $etCO_2$ recording was not consistent due to periods of breathing through the mouth, the highest $etCO_2$ value was used. Beat-to-beat data were

spline interpolated and resampled at 5 samples per second to produce signals with a uniform time-base.

Transfer function analysis was performed in accordance with standardised guidelines [19] that included using for each recording: 256 seconds of data for analysis with 4 window segments (Welch's method), 512 data points (102 seconds) in length, with a superposition of 50% overlapping data segments. Frequency-dependent estimates of gain and phase were used to reconstruct the CBFV step response to a sudden change in BP. The coherence function was averaged over the 0.15-0.25 Hz frequency interval for assessment of the reliability of the BP-CBFV relationship [17]. ARI, which represents dynamic CA, was extracted by using the least-squares best fit between the CBFV step response and one of the 10 template ARI curves proposed by Tiecks et al [20]. For each recording, data were computed for the affected (AH) and unaffected (UH) hemispheres; excluding 2 subjects that were classified as having posterior circulation syndrome (POCS), where right and left hemispheres were arbitrarily allocated AH and UH, respectively, in subsequent inter-hemispheric analysis. Values of ARI were only accepted into further analyses if they met strict criteria regarding the significance of the coherence between mean arterial BP (MAP) and CBFV and the normalised mean square error (NMSE) of fit to Tiecks' model [17, 20].

2.3 Statistical Analysis

Mean values of each variable were calculated from the entire baseline recording. Tests for normality were performed using the Shapiro-Wilk normality test. For ease of reference, data are presented as median and interquartile range (25th-75th percentile) and mean (SD) unless stated otherwise. Based on previous studies [8, 11], ectopic heartbeat activity was categorised into two levels: low (<4 ectopic beats per min) and high (≥4 ectopic beats per

minute) ectopic activity. The data on autoregulation index (ARI), coherence, and normalised mean square error (NMSE) were modelled using a separate linear mixed model. Impaired CA was defined by an ARI < 4 [18, 21] and we also fitted a generalised linear mixed model with logit link function on the dichotomised ARI value (ARI<4 vs. ARI ≥4), assuming a binomial distribution of the data. For both modelling scenarios, fixed effects included sex (female and male) and hemisphere (unaffected and affected) as categorical variables and age (year) as a continuous variable. We explored the fixed effect of ectopic activity both as a continuous (ectopic heartbeats per minute) as well as categorical (low and high) variable using separate models. Possible two-way interaction terms of these predictor variables were also explored. All models included a random intercept term for each patient. The Akaike's information criterion (AIC) and Bayesian information criterion (BIC) were used to perform the model selection. The models on ARI were only fitted where the acceptance vector was true and the model on NMSE was fitted using the log-transformed NMSE data. All statistical tests were two-sided with the type 1 error rate (p-value) of 0.05 to determine statistical significance and were performed using the R package nlme and lme4 in R software environment (version 3.4).

3. Results

3.1 Study Population

Data were included (Table 1) for 46 AIS patients of mean (SD) age 71 (12) years with good quality baseline recordings that contained a range of cardiac ectopic activity (0.2-25 per min) with a median of 2.7 per minute. Approximately half of the patients (49.3%) exhibited higher ectopic activity. The majority of strokes were minor in severity, with similar proportions of cortical and subcortical origins. Among all patients, 43% received intravenous

thrombolysis. Thirty-four patients had bilateral MCA recordings, five had unilateral AH recording only, and seven had unilateral UH recording.

3.2 Influence of ectopic severity

We modelled the ectopic activity both as a continuous (Table 2) and categorical variable (Figure 1). Both modelling scenarios showed similar results; here we present and discuss the outcomes from the models incorporating categorical ectopic activity. Table 2 presents the outcomes from the linear and generalised linear mixed model for both fixed and random effects terms. The estimates of between patient SD (Table 2) showed reasonably higher estimates suggesting observations on the same patient were highly correlated. Hence it highlights the importance of the inclusion of the random effect term for the patient in the linear and generalised linear mixed effect modelling framework. The estimates of between and within patient variabilities, as obtained in this study, would be useful for designing prospective studies on ectopicity by other researchers in wider populations of patients. We did not find any evidence that the ectopic activity was associated with ARI ($p = 0.162$), impaired CA based on dichotomised ARI ($p = 0.859$) and NMSE ($p = 0.671$). The ectopic activity, however, showed a statistically significant association with mean coherence ($p = 0.006$), indicating improved coherence with greater ectopicity (Fig. 1). The two-way interaction term of sex and affected hemisphere also had a statistically significant effect ($p = 0.009$) on the mean coherence (Table 2).

4. Discussion

We did not find evidence that high rates of cardiac ectopic activity were associated with the TFA of spontaneous fluctuations in BP and CBFV in AIS patients, a key criterion for acceptance of the main parameters often used for assessment of dynamic CA in clinical and physiological studies [19]. Also, the NMSE for estimating the ARI index from the CBFV step response matching to Tiecks' et al [20] standardised response curves, was not affected by increased ectopic rates, enabling appropriate estimates of ARI in these patients [17]. These results suggest that the standard approach of TFA for assessment of dynamic CA could be reliably extended to AIS patients with higher rates of ectopicity, and possibly, rejecting AIS patients with ectopic rates, defined as above 4 occurrences per min, in studies of dynamic CA, might not be justified solely based on this empirical criterion.

This study provides supportive data which allow for further investigations of dynamic CA in the context of higher ectopic rates. In this pilot study, we have implemented a comprehensive statistical modelling strategy which incorporates relevant covariates and their interaction effects, as well as between patient variability. Our findings provide an important platform for future studies to evaluate CA capability in larger cohorts of AIS patients, with the potential to develop more individualised treatment strategies.

The reasons for the prudent rejection of individuals showing a high frequency of ectopics in previous studies of dynamic CA are understandable, given the corresponding alterations to the beat-to-beat values of mean BP and CBFV resulting from disturbances in cardiac rhythm (Figure 2). However, it could be argued that the increased variability of the BP time-series, induced by significant alterations of cardiac rhythm, is actually beneficial to the quality of estimates obtained with TFA [8]. Insufficient BP variability is often quoted as a potential

limitation for reliable use of TFA in dynamic CA studies, although further work is needed to determine more precise thresholds of acceptability [19, 22].

More complex than meeting the technical requirements of TFA though are the changes in physiological conditions that could result from high rates of ectopic heartbeats. When AIS patients show a high frequency of ectopic heartbeats, is this a sign that dynamic CA could be affected by changes in other physiological variables that could be regarded as co-variates of CA parameters? Examples would be pharmacological agents, autonomic nervous system activity, or blood gases. At present, this is unclear given our limited understanding of the determinants of dynamic CA. The demonstration that ARI values tend to remain comparable in the presence of increasing rates of ectopic beats (Figure 1) suggests that the physiological effects of increased irregularity are limited, especially if MAP, as shown in our examples, is maintained within the traditional autoregulatory curve. Further studies on this aspect are needed, where the ideal dataset would contain repeated intra-subject measurements with recordings for both low and high rates of ectopics. Unfortunately, spontaneous occurrences of such recordings are uncommon. Figure 2 shows a rare example where two separate recordings were obtained from the same patient, one containing 18 ectopic beats per min and the second 0.5 ectopic beats per min. There were no differences during time and frequency domain analyses (Figure 2). The second recording, performed later following stroke onset, shows a less erratic haemodynamic response in BP and CBFV (Figs. 2A and 2C), but a similar step response and ARI (Figs. 2E and 2F), and phase and coherence (Figs. 2G and 2H). The reduced number of these recordings in our database (14/46 patients with variable ectopic activity) could constrain estimating between and

within patients' variability reliably, given the reported limitations of the reproducibility of ARI and other TFA parameters [23, 24].

Limitations

Results from TCD studies always need to be scrutinised for any potential changes in MCA diameter that would invalidate the assumption that CBFV normally reflects changes in CBF. Apart from extreme levels of hypercapnia [25, 26], the MCA diameter tends to remain constant and there is no reason to suspect that that would not be the case in this patient cohort [27].

Due to insufficient numbers, the study did not account for the differentiation in patients on medication that regulate arrhythmic disturbances or those receiving different treatments. However, the main objective of this analysis was to determine if ARI measurement was possible in physiological recordings containing a range of ectopics. The study could have been performed in healthy individuals to exclude influences that might arise from unhealthy tissue, however, capturing a similar rate of ectopic occurrence in a healthy population would be challenging and it would not reflect the future clinical intentions and application of these measurements. Despite our encouraging results, it is not possible to generalise our findings to other cardiac rhythm disturbances or conditions, where assessment of dynamic CA is relevant and elevated rates of arrhythmia are also to be expected, such as heart failure [21], carotid artery disease [28], postural tachycardia syndrome [29], and sepsis [30]. The observational design of the study is also a limitation. However, apart from experimental studies in animals, it is difficult to envisage the possibility of a different approach in humans.

Our analysis was also limited to the ARI parameter and further studies are warranted of alternative indices or metrics that have been proposed for dynamic CA assessment, like TFA phase frequency response [19], the rate of regulation [31], or flow-reactivity index [32]. Until such studies are performed, it is not possible to generalise our findings to the entire range of methods and indices that have been proposed for dynamic CA assessment.

5. Conclusion

We did not find evidence that high rates of cardiac ectopicity lead to impairment of the key parameters used for assessing dynamic CA in clinical studies, suggesting that dynamic CA in AIS patients could be reliably assessed in this context. Our results provide an important platform for future studies to evaluate CA capability in much larger cohorts of stroke patients, which will help in developing more individualised treatment strategies.

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Author contributions

Study design: O.LL, V.H., T.G.R., R.B.P; Patient recruitment, data collection and data preparation: O.LL, A.S.M.S., M.Y.L, N.P.S., F.B.; Data analysis: OLL, M.N.; Interpretation of data: O.LL, V.H., M.N., T.G.R., R.B.P; Drafted manuscript: O.LL, V.H., M.N., T.G.R., R.B.P;

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Table 1 - Clinical and physiological characteristics of acute ischaemic stroke patients during first assessment.

	n	
Total	46	
Demographics		
Age, years (mean, SD)	46	71 (12)
Female (%)	16	35
AIS features		
Cortical, Subcortical, POCS (%)	46	46, 48, 7
Thrombolysed (%)	10	43
Ass. NIHSS score (median, IQR)	37	5 (2-8)
Ipsilateral ICA Stenosis >50% (%)	1	3
Contralateral ICA Stenosis >50% (%)	4	13
Physiological		
MCBFV ($cm.s^{-1}$) - AH	39	42 (14)
MCBFV ($cm.s^{-1}$) - UH	41	42 (15)
MAP (mmHg)	46	100 (17)
$etCO_2$ (mmHg)	40	34 (4)
HR (bpm)	46	73 (14)
Ectopic beats per min (median, IQR)[$]	46	2.7 (0.5-9.3)
Ectopic beats categorical (>4 per minute, %)[$]	35	49
ARI - AH	39	5.0 (3.5-5.9)
ARI - UH	41	5.0 (4.2-6.0)

Data are presented as n (% of available data), mean (standard deviation) or median (inter-quartile range, 25th to 75th percentile), as appropriate

n, number of participants; AIS, acute ischaemic stroke; POCS, posterior circulation stroke syndrome; R, right; L, left; Ass., assessment; NIHSS, National Institutes of Health Stroke Scale; IQR, inter-quartile range (25^{th} – 75^{th} percentile); SD, standard deviation; ICA, internal carotid artery; MAP, mean arterial blood pressure; HR, heart rate; $etCO_2$, end tidal CO_2; MCBFV, mean cerebral blood flow velocity; ARI, autoregulation index; AH, affected hemisphere; UH, unaffected hemisphere

$, Summary statistics are based on measurements from both the affected and unaffected hemispheres

Table 2 – Estimates and SE of Coherence, NMSE, ARI and impaired CA[§] (on the logit scale) for different predictors and corresponding *p*-values based on the fitted linear mixed model and generalised linear mixed model.

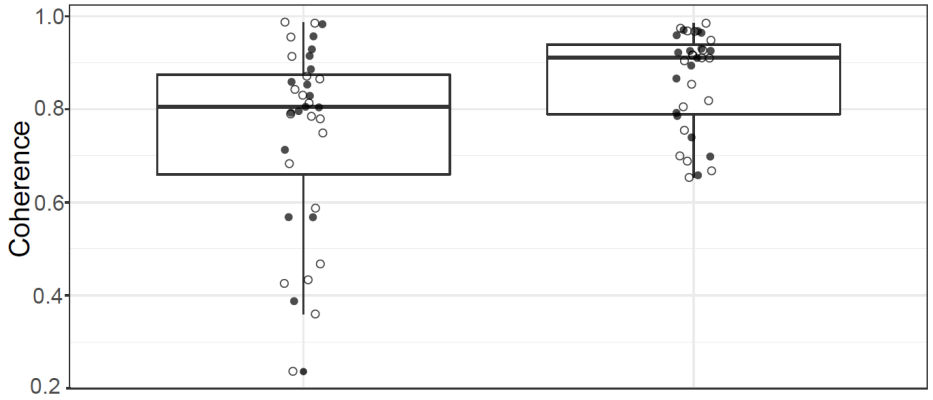
Predictor	**Coherence**		**NMSE**		**ARI**		**Imp. CA**[§]	
Fixed effects	Est. (SE)	*p-value*	Est. (SE)	*p-value*	Est. (SE)	*p-value*	Est. (SE)	*p-value*
Intercept[$]	0.669 (0.054)		-2.101 (0.080)		4.775 (0.447)		-23.957 (7.39)	
Age (year)	0.001 (0.002)	*0.503*	0.004 (0.003)	*0.186*	0.018 (0.018)	*0.321*	-0.117 (0.297)	*0.693*
Sex Male	0.062 (0.057)	*0.283*	0.138 (0.083)	*0.106*	-0.203 (0.462)	*0.664*	-1.614 (5.366)	*0.764*
AH	0.051 (0.019)	*0.012*	-0.025 (0.027)	*0.365*	0.127 (0.139)	*0.370*	13.218 (4.76)	*0.005*
Sex Male: AH	-0.065 (0.023)	*0.009*	-	-	-	-	-	
Ectopic High	0.156 (0.054)	*0.006*	-0.034 (0.079)	*0.671*	0.611 (0.429)	*0.162*	-0.840 (4.720)	*0.859*
Random effects	SD		SD		SD		SD	
Patient	0.174		0.245		1.31		69.17	
Residual	0.040		0.104		0.80		-	

[§] The dichotomised ARI was considered as the impaired cerebral autoregulation (CA) for subjects who recorded ARI <4. The binary ARI <4 data were fitted by a generalised linear mixed model. The table presents the estimates on the logit scale. [$] *Intercept indicates the average value of Coherence (unit), NMSE (unit), ARI and ARI<4 (logit scale) at the reference value of other predictors included in the corresponding model i.e. the unaffected hemisphere, female, age 71 years and low ectopic activity (< 4 per minute).*

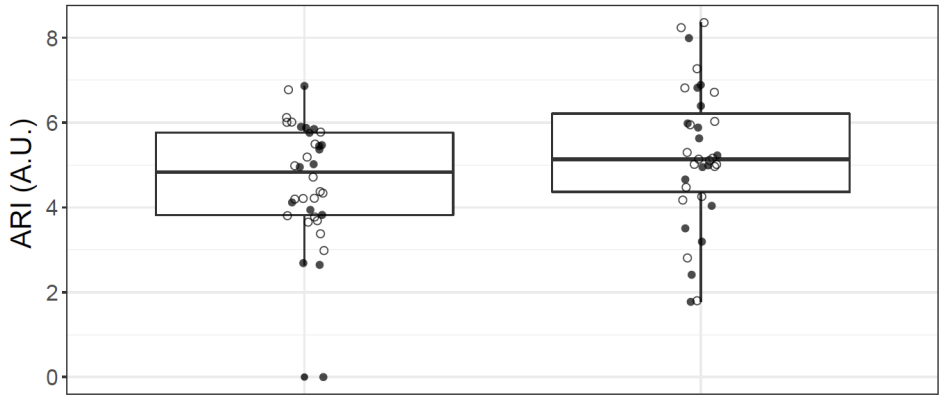
Estimates of fixed effects: For different levels of a categorical variable (hemisphere and sex) indicate the mean difference between the given level of a category and the reference level. Estimates for continuous variables (age) indicate the slope i.e. the rate of change in the outcome variable for one-unit change in the predictor.

Estimates of random effects present the standard deviation (SD).

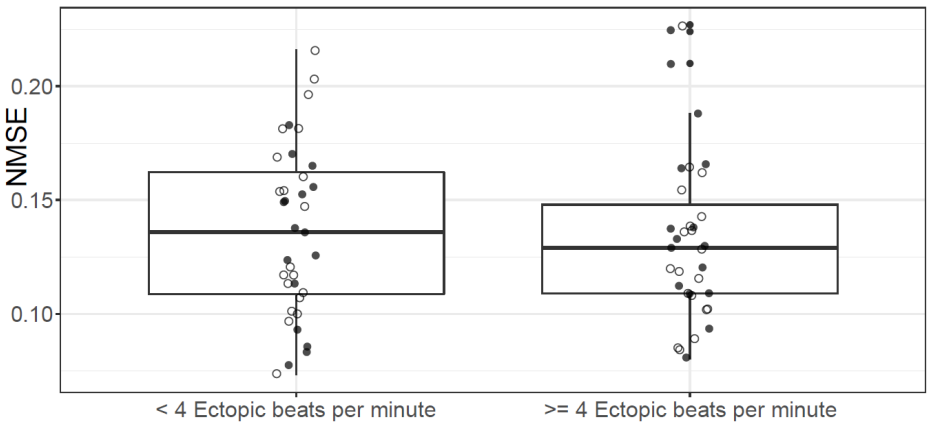
Est, Estimate; SE, standard error of the linear mixed model or generalised linear mixed model; ARI, autoregulation index; Imp., Impaired; AH, affected hemisphere



(a)



(b)



(c)

Figure 1 - Influence of ectopic beats within a recording on (a) coherence (range 0.15-0.25 Hz), (b) ARI and (c) NMSE. Solid black and open white circles denote measurements from UH and AH, respectively.

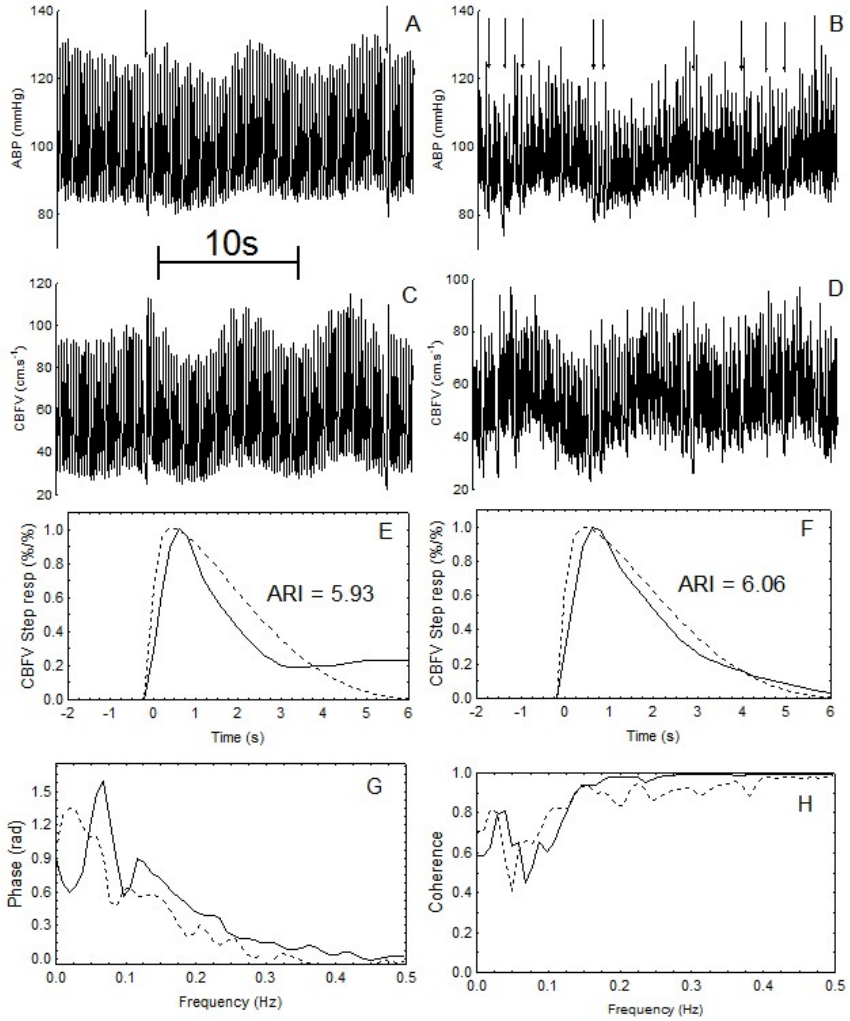


Figure 2 - Comparison of separate day measurements in a 76-year-old, male acute stroke patient, where one recording shows an average rate of 0.5 ectopic beats per min (a, c, e, solid line g and h) and the second 18 ectopic beats per min (b, d, f, dashed line g and h). The positions of ectopic beats are indicated by arrows (a, b). (a, b) Blood pressure; (c, d) Cerebral blood flow velocity; (e, f) CBFV step responses (solid line) and best fit Tiecks' model curves (dashed line); (g) Phase frequency responses (solid line 0.5 ectopic beats per min, dashed line 18 ectopic beats per min); (h) Coherence function responses (solid line 0.5 ectopic beats per min, dashed line 18 ectopic beats per min).