Can we use short recordings for assessment of dynamic cerebral autoregulation? A sensitivity analysis study in acute ischaemic stroke and healthy subjects

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Abstract

Objective: It is unclear whether the duration of recordings influences estimates of dynamic cerebral autoregulation (dCA). Therefore, we performed a retrospective study of the effects of reducing recording durations on dCA estimates; with the potential to inform recording duration for reliable estimates in challenging clinical populations.

Approach: Seventy-eight healthy control subjects and 79 acute ischaemic stroke (AIS) patients were included. Cerebral blood flow velocity was recorded with transcranial Doppler and continuous blood pressure with the Finapres device. The autoregulation index (ARI), derived with transfer function analysis, was calculated for recording durations at one-minute intervals between 1 and 5 minutes using the same starting point of each recording.

Main results: Though recording duration did not affect the overall ARI value, when compared to control subjects, AIS patients had significantly lower ARI values for durations between 3 and 5 ($p<0.0001$), but not 1 and 2 minutes. The intraclass correlation coefficient of all participants, for reproducibility of the five recording durations, was 0.69. AIS patients classified as having impaired cerebral autoregulation (CA; ARI≤4) at 5 min, had a 7.1% rate of false negatives for both 4 and 3 min recordings, reaching 42.9% for 1 min recording. The percentage of false-positives also increased with reduced recording durations (from 0% at 5 to 16.2% at 1 minute).

Significance: Reducing recording durations from 5 to 3 min can still provide reliable estimates of ARI, and may facilitate CA studies in potentially medically unstable AIS patients, as well as in other patient groups.

1. Introduction

Cerebral autoregulation (CA) is a complex mechanism that tends to maintain constant cerebral blood flow (CBF) despite changes in cerebral perfusion pressure (CPP) in the range of 60 to 150 mmHg (Lassen, 1959). CA has been conceptualised as either a *static* or a *dynamic* process (Aaslid et al 1989; Tiecks et al 1995; Panerai 1998). Dynamic CA (dCA) represents the CBF transient response, over a few seconds, to sudden changes in blood pressure (BP) (Aaslid *et al.*, 1989), while static CA (sCA) represents the steady state behaviour of the BP-CBF relationship over several minutes (Panerai, 1998; Tiecks *et al.*, 1995).

One of the main advantages of dCA, when compared to sCA, is the ability to perform physiological and clinical assessments of cerebral haemodynamics parameters, using non-invasive measurements at rest, based on spontaneous fluctuations in BP and CBF, usually estimated as CBF velocity (CBFV) with transcranial Doppler (TCD) ultrasound (Panerai, 2008). As a broader marker of cerebrovascular health, dCA has been shown to be affected by a range of different pathologies including stroke, traumatic brain injury, neonatal prematurity and intracranial hypertension (Aries *et al.*, 2010; Czosnyka *et al.*, 2008; Panerai *et al.*, 2002; Panerai *et al.*, 2016b).

In a recent White Paper (Claassen *et al.*, 2016), the Cerebral Autoregulation Network (CARnet) has proposed the standardisation of TFA settings and parameters, aiming to achieve greater homogeneity and reliability in TFA applications to dCA assessment. One main recommendation was for recordings at rest to be of a minimum duration of 5 min (Claassen *et al.*, 2016). Unfortunately, in clinical studies, good quality recordings of 5 min are not always possible due to patient movement, environmental noise or patient discomfort. Abiding to the CARNet's recommendations in these cases inevitably jeopardises individualised care, due to the need to reject recordings shorter than 5 min. Although the literature reports a wide range of recording durations, from as long as 20 min (Tang *et al.*, 2008; Mahdi *et al.*, 2017; Chi *et al.*, 2017), down to 1 min (Nakagawa *et al.*, 2009; Carey *et al.*, 2001; Carey *et al.*, 2003; Panerai *et al.*, 2001; Puppo *et al.*, 2008), there is a lack of systematic studies describing the influence of recording duration on the TFA outcome parameters of interest. To address this limitation, we have retrospectively studied the influence of recording duration from both healthy subjects and acute ischaemic stroke (AIS) patients, including all subtypes were recorded. By reducing recording duration from the standard 5 min, to durations of 4, 3, 2, and 1 min, we tested the hypothesis that one of the main parameters derived from TFA, namely the ARI index, is not affected by shorter recordings, in either population.

2. Methods

2.1. Subjects and measurements

Data used for this study were extracted from the Leicester Cerebral Haemodynamics Database (Patel *et al.*, 2016), which comprises a large number of recordings performed in both healthy subjects and AIS patients (Llwyd *et al.*, 2018). All studies that contributed to the database had local research Ethics Committee approval (Haunton, 2014; Katsogridakis *et al.*, 2011; Lam *et al.*, 2019; Llwyd *et al.*, 2017; Nogueira *et al.*, 2013; Salinet *et al.*, 2014) and all subjects provided written informed consent. These studies had high homogeneity in protocols for inclusion and exclusion criteria, as well as measurement procedures (Brodie *et al.*, 2009; Saeed *et al.*, 2013; Atkins *et al.*, 2010). In brief, healthy controls did not have a history or symptoms of any neurological, cardiovascular or respiratory disease. AIS patients, diagnosis confirmed by neuroimaging, were admitted to the University Hospitals of Leicester NHS Trust within 48h of mild- (defined as National Institute of Health Stroke Scale [NIHSS] <8) –to-moderate stroke (NIHSS 8-15) (Wahlgren *et al.*, 2007)). Exclusion criteria included any medical history or current evidence of myocardial infarction, renal failure, respiratory disease, or atrial fibrillation. All healthy participants were asked to avoid alcohol, caffeine, and nicotine for at least 4 h before attending the University of Leicester's Cerebral Haemodynamics in Ageing and Stroke Medicine (CHiASM) laboratory which is of controlled temperature (20-24 °C) and free from visual and auditory distraction. Bilateral insonation of the middle cerebral arteries (MCAs) was performed using TCD with 2MHz TCD probes (Viasys Companion III; Viasys Healthcare), which were secured in place using a head-frame in the position of maximum comfort for study participants. The MCAs were accurately identified, with maximal reflected signal power at depths of 45-55 mm. Beat-to beat BP was continuously recorded using the Finometer® device (FMS, Finapres Measurement Systems, Arnhem, Netherlands), which was attached to the middle finger of the non-dominant hand in healthy subjects and the non-hemiparetic hand in AIS patients. The servo-correcting mechanism of the Finometer® was switched on for calibration and off prior to measurements. Heart rate (HR) was recorded using a 3-lead electrocardiogram (ECG) and end-tidal CO_2 ($EtCO_2$) was measured with nasal cannula (Salter Labs) via a capnograph (Capnocheck Plus). Brachial BP was measured with a sphygmomanometer (OMRON Model 705IT), and used to calibrate the Finometer® recordings. A baseline recording with subjects lying supine at rest was performed with a minimum of 5 min duration.

2.2. Data analysis

All signals were simultaneously recorded on the PHYSIDAS data acquisition system (Department of Medical Physics, University Hospitals of Leicester) at a sampling rate of 500Hz. BP was calibrated at the beginning of each recording. All recordings with at least 5min duration were visually inspected and narrow artefacts (<100 ms) were removed by linear interpolation. Smaller artefacts in the CBFV signals

were removed with a median filter. All signals were then low-pass filtered with a zero-phase eight-order Butterworth filter with cut-off frequency of 20Hz. The R wave of the ECG was automatically detected. The beat-to-beat HR sequence was visually inspected and manually corrected in case of missed marks or presence of spikes. The mean values of BP, CBFV, HR and $EtCO_2$ were calculated for each cardiac cycle. The end-tidal value of each breath was detected in the capnographic signal, linearly interpolated, and resampled with each cardiac cycle. Beat-to-beat parameters were spline interpolated and re-sampled at 5Hz to generate signals with a uniform time-base.

Transfer function analysis of the linear relationship between BP and CBFV was estimated using Welch's method. For a five-minute recording, segments with duration of 102.4s (512 samples) were multiplied by a cosine window and the auto- and cross-spectrum were calculated with the FFT algorithm, using 50% superposition as recommended by CARNet's White Paper (Claassen *et al.*, 2016). After obtaining the amplitude and phase frequency responses, the inverse FFT was used to obtain the impulse response that was integrated to produce the CBFV step response to a sudden change in BP (Panerai, 2008). ARI was extracted by comparison of the CBFV step response to the template curves proposed by Tiecks *et al.* (1995); (Panerai *et al.*, 1998). ARI estimates were not accepted if the average coherence function in the frequency interval 0.15-0.25 Hz was lower than the 95% confidence limit, or the normalised mean square error (NMSE) was below the critical limit of NMSE=0.3 for fitting the step response to Tieck's model (Panerai *et al.*, 2016a). All healthy controls selected from the database had ARI $\geq$ 5 taking into account that normal average ARI = 5 (Tiecks *et al.*, 1995; Deegan *et al.*, 2010; Subudhi *et al.*, 2015). In patients, values of ARI$\leq$4 were adopted as the criterion for impaired dCA (Patel *et al.*, 2016; Caldas *et al.*, 2017; Caldas *et al.*, 2019).

Dynamic CA was modelled using transfer function analysis (TFA), adopting spontaneous fluctuations in BP as *input* and corresponding fluctuations in CBFV as *output*, has become the most common approach to assess dCA at rest, in both physiological and clinical studies (Claassen *et al.*, 2016; Zhang *et al.*, 1998; Giller, 1990). In the frequency domain, the main parameters derived with TFA are the coherence, gain (or amplitude) and phase frequency responses. The coherence function, varying between zero and 1, represents the fraction of output power that can be linearly explained by the input power (or variance) at each frequency (Bendat and Piersol, 2011). Estimates of gain and phase can be accepted as reliable markers of dCA only at frequencies where coherence is above its 95% confidence limit (Claassen *et al.*, 2016). Non-significant values of coherence can result from a low signal-to-noise-ratio, a non-linear relationship between BP and CBFV, or when multiple variables are influencing CBFV. Moreover, using the inverse Fourier transform of the gain and phase, it is possible to estimate the CBFV step response to BP changes in the time domain (Panerai *et al.*, 1998; Claassen *et al.*, 2016). This function can be compared to the 10 template curves proposed by Tiecks et al (1995) to provide an estimate of the autoregulation index (ARI), which varies between zero (absence of CA) to 9 (best observed CA). A threshold value of ARI $\leq$4 was adopted by previous studies to classify dCA as impaired, when using 5 min recording durations (Patel *et al.*, 2016; Caldas *et al.*, 2017).

2.3. Durations and segments analysis

To assess the influence of shorter recording durations in the first five to one minutes of recordings on ARI estimates, the following combinations of number of segments and window durations were adopted as the reference condition: 4 min (4x512 samples); 3 min (3x512 samples); 2 min (4x256 samples); and 1 min (4x 128 samples), with 50% superposition in all cases. The influence of reducing window duration was assessed separately for the 3 min and 2 min using 256 samples and 128 samples respectively, as described below.

2.4. Statistical analysis

All data were tested for normality with the Shapiro-Wilk test. For simplicity, only the right hemisphere data was considered in healthy controls and only the affected hemisphere in AIS patients. For non-Gaussian parameters, the Friedman test was used to assess the effect of shortening recording duration in each population. Reliability of successive reductions in recording duration was expressed by the intraclass correlation coefficient (ICC) calculated using the (1, 1) model (Shrout and Fleiss, 1979; Weir, 2005). Agreement between parameter values from recordings with different durations was assessed with the bias and limits of agreement and represented with Bland-Altman plots (Bland and Altman, 1986). Inter-group comparisons were assessed with the Mann–Whitney U test. The interaction between the effects of disease and recording duration was assessed with a 2-way ANOVA. A value of $p < 0.05$ was adopted to indicate statistical significance. Statistical analyses were performed with GraphPad Prism 7 and SPSS Statistics 25.

3. Results

Seventy-eight healthy controls and 79, mainly mild severity (n=67) and moderate stroke (n=12), AIS patients were initially included, with demographic and physiological characteristics given in Table 1. CBFVs were significantly higher in healthy controls compared to AIS patients at right and affected sides (p=0.0002) and left and unaffected sides (p<0.0001) respectively, whereas BP and HR were of lower values (p<0.0001). EtCO$_2$ was significantly lower in AIS patients (p<0.0001).

3.1. Effect of shortening recording duration on population values

Following application of the ARI acceptance criteria (see Methods), complete data for the five different recording durations were available for 67 control subjects and 75 AIS patients. Shorter recording duration did not have a significant effect on ARI for both AIS (p=0.13) and control group (p=0.068), though significant differences in ARI between populations were only maintained with recording durations down to 3 min (Figure. 1). For the combined study population, a 2-way ANOVA confirmed a strong effect of disease (p<0.0001), but did not show an effect of recording duration on the ARI (p=0.56), or an interaction between these factors.

3.2. Intra-subject reproducibility with shorter recording durations

ICC was used to assess the intra-subject consistency of ARI values for the five distinct recording durations. For the 142 subjects with complete values of ARI for the five durations, ICC was 0.69 (95% confidence intervals [CI] 0.62-0.75).

Dynamic CA was impaired (ARI ≤4) in 14 AIS patients over a 5 min recording duration. An ARI >4 with shorter recording durations would represent a false-negative result; rates of 7.1, 7.1, 35.7 and 42.9% being observed for recording durations of 4, 3, 2, and 1 min, respectively (Figure 2a). Similarly, AIS patients with ARI >4 over 5 min (n=65) could be regarded as 'false-positives' if ARI values were ≤ 4 on shorter recordings. Again, the number of false-positive results increased from 3.1, 10.8, 12.3 and 15.4% with a change in recording duration of 4, 3, 2 and 1 min, respectively (Figure. 2b). Though no controls had an ARI ≤ 4 for recording durations ≥4 min, this increased to 2.7%, 6.9% and 16.2% for durations of 3, 2 and 1 min, respectively (Figure. 2c).

3.3. Analysis of agreement

A Bland-Altman plot was used for assessing measurements between 5 min (reference duration) and shorter recording durations (Figure. 3). Table 3 presents the bias and limits of agreement (±1.96.SD) for each recording duration, showing significant differences in bias for controls, but not patients. Differences in ARI between 5 and 1 min showed a significant negative trend (R^2=0.53) with average ARI in controls (Figure. 3a), but not in AIS (Figure. 3b).

3.4. Parameter sensitivity with alternative window durations in Welch's method

Changing the window number of samples in Welch's method to 256 and 128 samples for recording durations of 3 and 2 min, respectively, did not significantly change the overall results. However, the number of control subjects with rejected ARI values was reduced (10 vs. 4).

4. Discussion

4.1. Main findings

Though the influence of recording duration on dCA estimates has been previously reported (Deegan *et al.*, 2011; Mahdi *et al.*, 2017; Chi *et al.*, 2018), to our knowledge, this is the first study to show the effects of shortening recording duration on ARI estimates in both healthy controls and a disease population. Overall, our results show that the ARI did not change within each group when recording durations were gradually reduced from 5 to 1 min, and that the ICC remained high when taking into account other studies of the reproducibility of dCA metrics (Brodie *et al.*, 2009; Sanders *et al.*, 2018;

Tzeng *et al.*, 2012). Nevertheless, a number of other factors need to be considered when reducing recording duration in clinical studies, particularly for between-population comparisons.

4.2. Methodological aspects

In healthy physiological studies, continuous recordings of CBFV, BP and $EtCO_2$ for 5 min or more (Tang *et al.*, 2008; Mahdi *et al.*, 2017; Chi *et al.*, 2017) are relatively straightforward. At the stage of data editing though, large artefacts or signal loss can eventually be identified, resulting in less than the minimum 5 min of signal duration, as recommended by CARNet's White Paper (Claassen *et al.*, 2016) for TFA based studies of dCA. In clinical studies, signal loss and artefacts, compounded by patient discomfort and movement, are a much greater problem, with recordings that maintain good signal quality for $\geq$5 min being more challenging to obtain. The literature highlights a number of different approaches to simulate the effects of recording duration and signal loss. Deegan *et al.* (2011) compared the effect of reducing time series duration from 5 to 1 min on TFA estimates in the 0.03-0.5Hz frequency range. Meel-van den Abeelen *et al.* (2016) illustrated the influence of randomly placed artefacts (loss of signal, motion artefacts and baseline drifts) in CBFV and BP signals on TFA estimates of gain, phase and coherence in selected frequency bands. However, whilst these studies provided alternatives to reducing recording durations and effect of artefacts on TFA outcomes in healthy subjects, effects on patient data, and on the sensitivity of detecting pathological deterioration of dCA, were not established. Mahdi *et al.* (2017) shortened recordings from 16 min to 1 min, studying the stability of three parameters (ARI, Mx and TFA phase), and concluded that the minimum recording duration in healthy subjects should not be <3 min. Chi *et al.* (2018) compared dCA indices (Mx and TFA) of AIS patients and controls between 5 and 10 minute signal lengths, but did not report any significant differences between dCA indices derived with these two different durations. In our study, we used the first 1, 2, 3, or 4 min of a good quality 5 min recording to simulate the effects of signal loss. This design has the advantage of minimising the influence of nonstationarity of dCA (Panerai, 2014), which could result from comparing shorter segments from different sections of the original 5 min recording. Inevitably, with shorter durations, it was not possible to maintain the recommended duration of 102.4 s (N_w=512 samples in our case) for segmented data with Welch's method (Claassen *et al.*, 2016). Our choice of combining the number of windows (hence influencing number of degrees of freedom) with reductions in N_w (hence affecting frequency resolution) aimed to make use of as many segments of N_w=512 as possible, but that could not be maintained satisfactorily for 3 min or less and for this reason alternatives were considered, without showing a dominant influence on results. Although reducing N_w can influence estimates of average gain and phase on specific frequency bands (Zhang *et al.*, 1998), it is important to note that this does not apply to ARI, which tends to remain relatively constant when changing N_w (Panerai *et al.*, 2016a).

On theoretical grounds, reducing the length of data in TFA increases the bias and variance of estimated parameters, like the gain and phase, independently of the physical or biological origin of the data (Bendat and Piersol, 2011). For signals reflecting cerebrovascular control though, this effect can be exacerbated by the contribution of non-stationarity or co-variates, such as arterial CO_2, sensorimotor, or cognitive neural stimulation (Panerai, 2014). Although the partial, theoretical effect of reducing data length could be estimated for different parameters, assuming the data were generated by a stationary process (Bendat and Piersol, 2011), the integrated approach we adopted, as reflected by Figure 1, is preferable as it provides the overall effects of reducing recording duration, that includes any potential contributions of nonstationarity or other physiological co-variates.

In ideal conditions, the dependence of sensitivity and specificity of different dCA metrics on recording duration would be of considerable interest to establish minimum acceptable durations in clinical studies. Unfortunately, in the absence of a standard reference for dCA, it was not possible to construct ROC curves in our study, as not all AIS patients can be assumed to have impaired dCA. This is different from other studies, such as Katsogridakis *et al.* (2013), where hypercapnia was used as a surrogate of impaired dCA, and hence assumed to affect all subjects in the group. Nevertheless, using an empirical criterion (ARI ≤4), we have shown that reducing recording duration to 3 min had a relatively small effect on false-positive and false-negative rates, whilst this effect was considerably more deleterious for durations of ≤2 min. Future studies will need to re-assess these findings, if different criteria are used to classify patients with impaired dCA.

4.3. Clinical implications

The influence of reducing recording duration in AIS patients, below the 5 min recommended by the White paper (Claassen *et al.*, 2016), has not been reported previously. Although Mahdi et al (2017) studied only healthy subjects, and used a different metric to assess the influence of shorter recordings, their conclusions were similar to ours: recordings with less than 3 min duration should not be used in applications of TFA for dCA assessment.

Our conclusions followed from the permanence of significant differences in ARI values between AIS and controls (Figure. 1, Table 2), as well as the sharp rise in false-positive and false-negative rates for recordings shorter than 3 min (Figure. 2).

The conclusion that recordings with 3 min duration might be acceptable for clinical studies of dCA, does not imply that this duration should be standard in data collection protocols. On the contrary, whenever technically possible, and subject to patients' comfort and consent, measurements longer than 5 min should be targeted to allow for the possibility of selecting segments with optimal data quality for TFA. We emphasize that reduced duration, down to a minimum of 3 min should always be regarded as

the exception, not the rule. Moreover, it is important to keep in mind that recordings with 3 min duration incur a false-positive rate of 10.8% in comparison with results obtained with the 5 min standard.

4.4. Limitations of the study

There are several limitations in our study. CBFV can only reflect changes in absolute CBF as long as the diameter of MCA remains constant. This is likely to be the case with subjects at rest and in normocapnia (Table 1). Even though all data were recorded with a similar protocol, and in the same research laboratory, this is a retrospective observational study with data collected by different TCD operators and this might have contributed to a wider distribution of values of CBFV and other parameters. However, the main parameter in this study, namely ARI, is independent of the absolute amplitudes of BP and CBFV, being only dependent on the temporal pattern of the CBFV step response. Although this study did not explicitly present TFA results for coherence, phase and gain, coherence was implicitly incorporated in the acceptance criteria for ARI (Panerai *et al.*, 2016a). Moreover, all the frequency components of gain and phase were used with the inverse FFT to obtain the CBFV step response, from where ARI values were derived.

The reliability of TFA estimates of CA parameters is likely to depend on BP variability and this will tend to be reduced with shorter recording durations (Claassen *et al.*, 2016; Katsogridakis *et al.*, 2013). However, we have not analysed the role of this co-factor in our study, to be consistent with the 'no-choice' aspect of simulating the use of whatever data are available, instead of the alternative of being able to choose segments with the largest BP variability. By using the reduced duration segments always at the beginning of the longer 5 min recording, one would expect that the influence of BP variability would be randomly distributed across subjects and patients, and hence not have affected the main results significantly. Nevertheless, this is a relevant aspect of TFA analysis that deserves further investigation.

Five patients had posterior circulation strokes (POCS), and were not expected to show alterations in dCA based on MCA measurements, since the posterior circulation is supplied by the vertebrobasilar system. Nevertheless, it has been shown that lesions of the posterior circulation can have a diffuse effect on both hemispheres, and for this reason patients with POCS can still show alterations when assessed in the MCA (Guo *et al.*, 2015). Moreover, when analysed separately, these patients did not show any distinct behaviour from those with partial anterior strokes.

Finally, it is important to emphasize that the results of this study are limited to the use of TFA within the set of parameters described above and cannot be extended to other approaches for modelling the BP-CBFV dynamic relationship such as time-domain techniques (Czosnyka *et al.*, 2008; Mahdi *et al.*, 2017; Nogueira *et al.*, 2013; Panerai *et al.*, 2001; Panerai *et al.*, 2016b; Sanders *et al.*, 2018; Tzeng *et al.*, 2012) or closed-loop models as proposed by Marmarelis *et al.* (2013).

5. Conclusions

The possibility of using reduced recording durations, down to a minimum of 3 min, when good quality measurements of the recommended minimum 5 min duration are not possible, may substantially impact on the translation of methods of dCA assessment into clinical practice and, in turn, improve the individualised care of stroke patients. Further work is needed to investigate the applicability of these findings to other disease populations.

Table 1. Demographic and baseline physiological parameters.

	Healthy controls	Stroke patients	P-value
Number (n)	78	79	
Mean Age (SD), years	52.0 (16.3)	67.5 (12.2)	<0.0001
Gender: male (%)	41 (52.6%)	55 (69.6%)	0.0338
CBFV (cm/s), R and AH	52.7 (13.8)	44.9 (15.7)	0.0002
CBFV (cm/s), L and UH	52.2 (17.1)	42.3 (18.9)	<0.0001
MAP (mmHg)	87.8 (14.2)	100.7 (15.0)	<0.0001
HR (bpm)	64.0 (10.3)	71.3 (12.1)	<0.0001
EtCO$_2$ (mmHg)	38.8 (4.0)	27.8 (12.8)	<0.0001
Affected hemisphere (R/L)	-	33/46	-
Mean NIHSS score (SD)	-	4.4 (3.8)	-
Stroke subtype (%)			
TACS	-	8 (10.1%)	-
POCS	-	5 (6.3%)	-
PACS	-	37 (46.8%)	-
LACS	-	29 (36.7%)	-

n, number of participants; R, right; L, left; AH, affected hemisphere; UH, unaffected hemisphere; NIHSS, National Institute of Health Stroke Scale (on the day of dCA assessment); CBFV, cerebral blood flow velocity; MAP, mean arterial blood pressure; HR, heart rate; EtCO$_2$, end-tidal carbon dioxide; TACS, Total Anterior Circulation Stroke; POCS, Posterior Circulation Stroke; PACS, Partial Anterior Circulation Stroke; LACS, Lacunar Stroke; bpm, beats per minute.

Table 2. The mean values (SD) of TFA parameters and comparison of dCA assessment for each recording duration.

ARI	5 min	4min	3min	2min	1min
Healthy controls	**6.7 (0.8) (n=78)**	**6.6 (0.9) (n=77)**	**6.4 (1.1) (n=73)**	6.3 (1.5) (n=73)	6.0 (1.9) (n=74)
AIS patients	**5.6 (1.8)* (n=79)**	**5.6 (1.9)* (n=79)**	**5.6 (1.9)* (n=79)**	5.6 (2.1) (n=78)	5.4 (2.2) (n=76)

ARI, cerebral autoregulation index. (n): number of accepted values of ARI for each recording duration. * p<0.05 compared to controls.

Table 3. Bland-Altman analysis of agreement for autoregulation index for shorter recording durations in comparison with a 5-min recording reference.

ARI	5 min vs 4 min	5 min vs 3 min	5 min vs 2 min	5 min vs 1 min
Healthy controls	**0.112 (0.4 [-0.6-0.8])*** **(n=77)**	**0.235 (0.6 [-1.0-1.5])*** **(n=73)**	**0.327 (1.3 [-2.1-2.8])*** **(n=73)**	**0.768 (1.8 [-2.8-4.3])*** **(n=74)**
AIS patients	-0.065 (0.7 [-1.4-1.2]) (n=79)	-0.009 (1.3 [-2.5-2.5]) (n=79)	-0.105 (1.6 [-3.2-3.0]) (n=78)	0.163 (1.7 [-3.2-3.6]) (n=76)

Values are the bias (SD and [Limits of Agreement]). ARI, cerebral autoregulation index. (n): number of accepted values of ARI for each duration. * p<0.05 for differences in bias compared to the first 5 min.

Figure legends

Figure 1. Population mean ARI and SEM (error bars) of the autoregulation index (ARI) for different recording durations. Healthy controls (dark grey) and stroke patients (light grey). *p<0.05 for difference between strokes and healthy controls.

Figure 2. Percentage of AIS patients classified as (a) false-negatives when ARI >4 for reduced recording durations, based on the original classification of impaired dynamic CA (ARI≤4) in the 5 min recording and (b) false-positives with ARI ≤4 that had ARI >4 in 5 min recording. (c) Percentage of healthy controls with ARI ≤4 in shorter recording durations. AIS: acute ischaemic stroke, HC: healthy control.

Figure 3. Bland-Altman plots of ARI estimates with linear regression for (a) control subjects and (b) AIS patients, comparing durations of 1 min with the 5 min reference. The lower and upper limits of agreements are the dash lines and the bias (mean difference) is the dotted line.
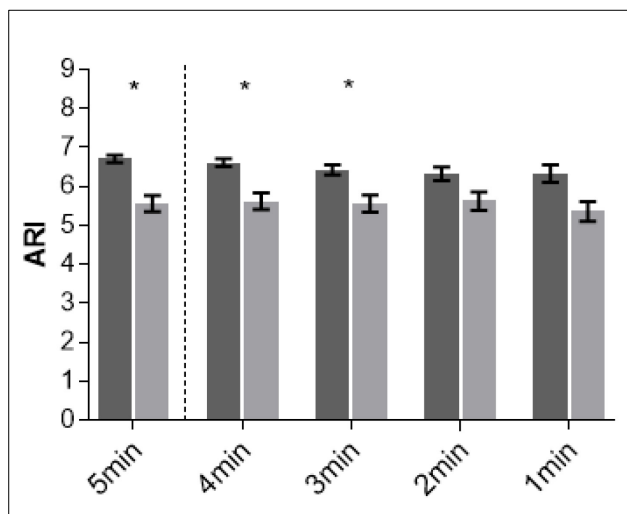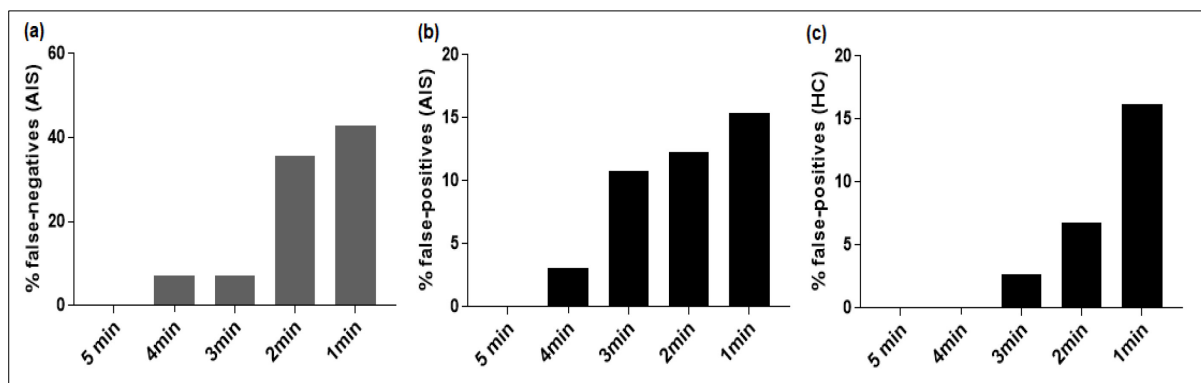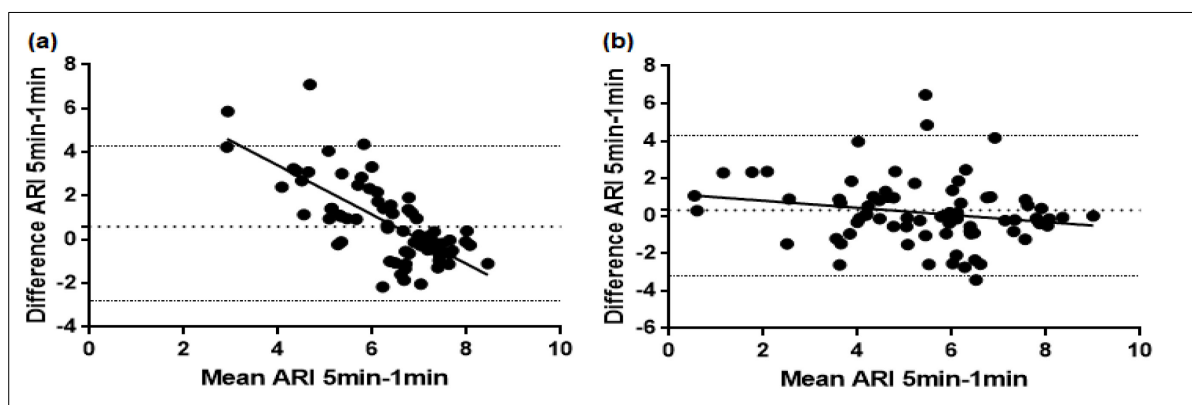
Figure 1.

Figure 2.

Figure 3.

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