

Lack of linear correlation between dynamic and steady-state cerebral autoregulation

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Key points

- For correct application and interpretation of cerebral autoregulation (CA) measurements in research and in clinical care, it is essential to understand differences and similarities between dynamic and steady-state CA.
- The present study found no correlation between dynamic and steady-state CA indices in healthy older adults.
- There was variability between individuals in all (steady-state and dynamic) autoregulatory indices, ranging from low (almost absent) to highly efficient CA in this healthy population.
- These findings challenge the assumption that assessment of a single CA parameter or a single set of parameters can be generalized to overall CA functioning. Therefore, depending on specific research purposes, the choice for either steady-state or dynamic measures or both should be weighed carefully.

Abstract The present study aimed to investigate the relationship between dynamic (dCA) and steady-state cerebral autoregulation (sCA). In 28 healthy older adults, sCA was quantified by a linear regression slope of proportionate (%) changes in cerebrovascular resistance (CVR) in response to proportionate (%) changes in mean blood pressure (BP) induced by stepwise sodium nitroprusside (SNP) and phenylephrine (PhE) infusion. Cerebral blood flow (CBF) was measured at the internal carotid artery (ICA) and vertebral artery (VA) and CBF velocity at the middle cerebral artery (MCA). With $CVR = BP/CBF$, Slope-CVR_{ICA}, Slope-CVR_{VA} and Slope-CVR_{iMCA} were derived. dCA was assessed (i) in supine rest, analysed with transfer function analysis (gain and phase) and autoregulatory index (ARI) fit from spontaneous oscillations (ARI_{Baseline}), and (ii) with transient changes in BP using a bolus injection of SNP (ARI_{SNP}) and PhE (ARI_{PhE}). Comparison of sCA and dCA parameters (using Pearson's r for continuous and Spearman's ρ for ordinal parameters) demonstrated a lack of linear correlations between sCA and dCA measures. However, comparisons of parameters within dCA and within sCA were correlated. For sCA slope-CVR_{VA} with Slope-CVR_{iMCA} ($r = 0.45$, $P < 0.03$); for dCA ARI_{SNP} with ARI_{PhE} ($\rho = 0.50$, $P = 0.03$), ARI_{Baseline} ($\rho = 0.57$, $P = 0.03$) and Phase_{LF} ($\rho = 0.48$, $P = 0.03$); and for Gain_{VLf} with Gain_{LF} ($r = 0.51$, $P = 0.01$). By contrast to the commonly held assumption based on an earlier study, there were no linear correlations between sCA and dCA. As an additional observation, there was strong inter-individual variability, both in dCA and sCA, in this healthy group of elderly, in a range from low to high CA efficiency.

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Abbreviations ARI, autoregulatory index; BP, blood pressure; CA, cerebral autoregulation; CBF, cerebral blood flow; CBFV, cerebral blood flow velocity; CVR, cerebrovascular resistance; CVRi, cerebrovascular resistance index; dCA, dynamic cerebral autoregulation; EtCO₂, end-tidal carbon dioxide; ICA, internal carotid artery; LF, low frequency (0.07–0.2 Hz); MAP, mean arterial pressure; MCA, middle cerebral artery; MCBFV, mean cerebral blood flow velocity; NSME, normalized mean SE; PhE, phenylephrine hydrochloride; sCA, steady-state cerebral autoregulation; SNP, sodium nitroprusside; TAMV, time-averaged mean blood flow velocity; TFA, transfer function analysis; VA, vertebral artery; VLF, very low frequency (0.02–0.07 Hz).

Introduction

The brain has an important role in maintaining homeostasis of the human body (Craig, 2002; Ransom, 2005). However, the brain lacks energy reserves and therefore depends on a stable blood flow to maintain its own function (Brown & Ransom, 2007). Consequently, the brain has local mechanisms to maintain adequate perfusion when systemic blood pressure (BP) homeostasis is disrupted. This mechanism is captured in the concept of cerebral autoregulation (CA): the intrinsic ability of the brain to maintain an adequate perfusion during BP changes (Sancho *et al.* 1976; Lipsitz, 1989; Willie *et al.* 2014).

Research into CA has led to two approaches in quantification: dynamic CA (dCA) and steady-state or static CA (sCA) (Aaslid *et al.* 1989; Tiecks *et al.* 1995; Panerai, 2008, 2009; Liu *et al.* 2013; Numan *et al.* 2014). The dynamic models, which require high temporal resolution measurements, investigate the transient relationship between BP and cerebral blood flow (CBF), and thus assess how a transient change in BP would affect CBF (e.g. during orthostatic hypotension) (Aaslid *et al.* 1989; Panerai, 2008, 2009; Tan & Taylor, 2014). By contrast, the static models approach the steady-state outcome of CBF following a persistent change in BP, such as when BP increases over time as a result of hypertension, or when BP is reduced over time, following treatment of hypertension (Lassen, 1959; Panerai, 2009; Numan *et al.* 2014).

Although dCA and sCA both model the functioning of CA, there are theoretical differences between these concepts. Although dCA parameters quantify the gain (damping) and latency (response delay) of the transient changes in BP and CBF, sCA parameters quantify the final equilibrium of BP and CBF (Dawson *et al.* 2003; Steiner *et al.* 2003; Gommer *et al.* 2008; Tan & Taylor, 2014; Willie *et al.* 2014). Despite these conceptual differences, it has been widely assumed that estimates of dCA correlate with estimates of sCA (Mahony *et al.* 2000). To date, little evidence exists concerning the relationship between dCA and sCA. In adults, one study found a robust linear correlation ($r = 0.93$, $P < 0.0001$) between

measures of sCA and dCA, as measured during isoflurane and propofol anaesthesia (Tiecks *et al.* 1995). In that previous study, conducted in a small sample ($n = 10$) of young, otherwise healthy, patients undergoing orthopaedic surgery (mean age 35 years), CA was measured during propofol anaesthesia and during high-dose isoflurane anaesthesia. Because isoflurane is known to impede sCA and dCA by causing cerebral vasodilatation (Summors *et al.* 1999) and propofol has a limited effect on cerebrovasculature (from no effect to a small vasoconstrictive effect) (Kaisti *et al.* 2003), the anaesthesia protocol served to induce variation in CA measures. In a similar study, under a high dose of isoflurane, both dCA and sCA were impaired (Strebel *et al.* 1995). However, at a low dose of isoflurane, only dCA was impaired. It remains unknown whether dCA and sCA are correlated under conditions outside anaesthesia and without pharmacologically impaired CA.

Understanding the relationship between dCA and sCA could yield important clinical applications for patient management. For example, in the treatment of an elderly hypertensive person, it would be of great benefit for an assessment of dCA (which can safely be obtained during 5–10 min of recording in seated or supine position, without the need for any intervention) to reflect the sCA (i.e. how CBF is affected by BP lowering following anti-hypertensive treatment). Accordingly, the assessment of dCA could inform what level of BP reduction would be safe (intensive *vs.* conservative). Similarly, for a patient in an intensive care unit, assessments of dCA could indicate safe BP targets.

The present study aimed to investigate the relationship between dCA and sCA so as to better understand the homeostatic control of brain perfusion under rapid and steady-state changes in BP.

Methods

Subjects and ethical approval

Twenty-eight healthy older adults (67 ± 7 years; 13 women) were recruited from the local community in

Dallas, Texas. Exclusion criteria included tobacco use, neurological disease (e.g. clinical diagnosis of stroke, traumatic brain injury and dementia), carotid and vertebral arterial steno-occlusive disease, major medical and psychiatric disorders (e.g. schizophrenia, psychosis), unstable heart diseases (e.g. myocardial infarction, angina), uncontrolled hypertension, obstructive sleep apnoea, and diabetes mellitus. Participants were asked to abstain from alcohol, caffeinated beverages and high-intensity exercise at least 24 h before the examinations. Participants underwent all examinations consecutively on the same day, starting with two procedures to assess dCA (baseline and bolus injection), followed by the procedure to assess sCA (stepwise drug infusion) (Fig. 1). The study was conducted in accordance with the standards of the *Declaration of Helsinki* for medical research involving human subjects. All participants provided their written informed consent with the study protocol, which was approved by the Institutional Review Boards of the UT Southwestern Medical Centre and Texas Health Presbyterian Hospital of Dallas.

Data collection

Study protocol for sCA. To assess sCA, stepwise changes in BP were induced using i.v. infusions of sodium nitroprusside (SNP) and phenylephrine hydrochloride (PhE) (Liu *et al.* 2013). Measurements started with a 3 min baseline. BP, using finger plethysmography (Ohmeda; Finapres, Enschede, The Netherlands); CBFV

in the middle cerebral artery (DWL Elektronische Systeme, Singen, Germany); three-lead ECG (Solar 8000M; GE Healthcare, Milwaukee, WI, USA); and end-tidal CO₂ (EtCO₂) (Capnogard; Novamatrix, San Diego, CA, USA) were recorded continuously using a data acquisition system (Acqknowledge; BIOPAC Systems, Goleta, CA, USA). After baseline collection, SNP was started with an infusion rate of 0.25 $\mu\text{g kg}^{-1} \text{min}^{-1}$, incrementally increased in steps of 0.25 $\mu\text{g kg}^{-1} \text{min}^{-1}$ until BP dropped 20 mmHg or 25% from baseline, whichever came first. Afterwards, there was a time interval of at least 20 min until haemodynamics restored to baseline. Then PhE started with an infusion rate of 0.5 $\mu\text{g kg}^{-1} \text{min}^{-1}$, incrementally increased in steps of 0.5 $\mu\text{g kg}^{-1} \text{min}^{-1}$ until BP increased 25 mmHg or 30% from baseline, whichever came first. During each step of drug infusion, as soon as BP had stabilized, brachial arterial pressure was measured using a sphygmomanometer (Tango+; Suntech, Morrisville, NC, USA). CBF was calculated using colour-coded duplex ultrasonography (CX-50; Philips Healthcare, Eindhoven, The Netherlands). Time-averaged mean blood flow velocity (TAMV) and the luminal area (over at least five beats) in the internal carotid artery (ICA) (CBF_{ICA}) and vertebral artery (VA) (CBF_{VA}) were recorded three times at each stage and CBF was calculated as $\text{CBF} = \text{TAMV} \times [(\text{mean diameter}/2)^2 \times \pi] \times 60$. Subsequently, flow velocity in the middle cerebral artery (MCA) was calculated by averaging the mean cerebral blood flow velocity (MCFV), as measured with the transcranial Doppler, over 3 min of rest in each condition.

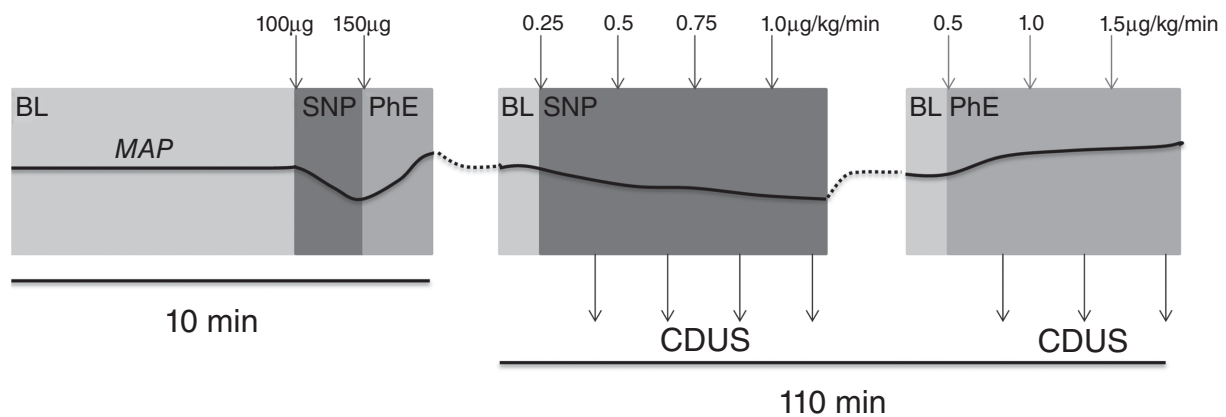


Figure 1. A schematic overview of the procedure for data collection

The measurement procedure started with an 8 min baseline (BL) measurement, followed by an i.v. bolus of 100 μg of SNP and, 1 min later, by 150 μg of PhE. After a resting period without drugs in which haemodynamics restored to baseline, the measurements continued with a second BL. After this BL, SNP was started with an infusion rate of 0.25 $\mu\text{g kg}^{-1} \text{min}^{-1}$, incrementally increased in steps of 0.25 $\mu\text{g kg}^{-1} \text{min}^{-1}$ until BP dropped by 20 mmHg or 25% from baseline, whichever came first. This was followed by an interval of at least 20 min, until haemodynamics restored to baseline. After a third BL, PhE was started with an infusion rate of 0.5 $\mu\text{g kg}^{-1} \text{min}^{-1}$, incrementally increased in steps of 0.5 $\mu\text{g kg}^{-1} \text{min}^{-1}$ until BP increased by 25 mmHg or 30% from baseline, whichever came first. During each step of drug infusion, as soon as BP had stabilized, brachial arterial pressure was measured using a sphygmomanometer (Tango+; Suntech). CBF was measured using colour-coded duplex ultrasonography (CDUS) (CX-50; Philips Healthcare).

Study protocol for dCA. The dCA was assessed by spontaneous oscillations of BP and CBFV, as well as their rapid changes induced by bolus injections of vasoactive drugs. Spontaneous oscillations in BP were assessed during an 8 min baseline measurement in the supine position. Dynamic 'step-like' changes in BP were induced by the Modified-Oxford method, originally designed to assess baroreflex sensitivity (Lipman *et al.* 2003). Participants received a 100 μg of i.v. bolus of SNP to induce a rapid decrease in BP. Exactly 1 min later, a bolus of 150 μg of PhE was injected to induce a rapid increase in BP.

Data analysis

sCA: slope estimation method. The sCA was quantified by a linear regression slope (defined as cerebral autoregulatory slope) of proportionate (%) changes in cerebrovascular resistance (CVR) [$\text{CVR} = \text{mean arterial pressure (MAP)}/\text{CBF}$] or cerebrovascular resistance index (CVRI) ($\text{CVRI} = \text{BP}/\text{CBFV}$) in response to proportionate (%) changes in BP relative to their baseline levels (Liu *et al.* 2013). CVR was calculated both for CBF_{ICA} as for CBF_{VA} ; CVRI was calculated for CBFV_{MCA} .

dCA: transfer function analysis (TFA). Approaches to assess dCA focus on quantifying magnitude and latency from BP to CBFV, assuming a linear relationship. In TFA, this relationship is estimated in the frequency domain (Giller, 1990; Zhang *et al.* 1998). Every signal can be deconstructed in sine waves from the frequency spectrum. With TFA, BP and CBFV are decomposed in sine waves and the difference in magnitude (gain) and latency (phase) for each frequency is calculated. Typically, dCA is active in the range of 0.02–0.20 Hz changes (Claassen *et al.* 2016).

From the 8 min baseline measurement, a 5 min data segment of artefact-free beat-to-beat mean CBFV and mean BP served as input for the TFA, using the CARNet Matlab script with default settings (version 1, 2016; <http://www.car-net.org>) (Claassen *et al.* 2016). In short, these methods encompass the use of 100 s Hanning windows with 50% overlap; spectral smoothing with a triangular moving average window and a coherence threshold of 0.34. Gain, phase and coherence were averaged over the frequency bands: very low frequency (VLF): 0.02–0.07 Hz; low frequency (LF): 0.07–0.2 Hz.

Autoregulatory index (ARI). The ARI model uses a second-order linear differential equation to model the transient response of CBFV to a step-like change in BP (Tiecks *et al.* 1995; Panerai *et al.* 2001). Ten template responses to the presented BP change are constructed using three variables to model gain and latency (damping and time constant) and the best fit is calculated.

With the modified-Oxford method, step-like changes in BP were induced, which can be assessed in the time

domain. For the present, the onset of the change in BP was determined based on visual inspection. The 10 s average before this change was used as the control value for BP (cBP) and CBFV (cCBFV) and the 30 s response was used to model the CBFV response. The model (see Appendix) where the difference between the model and the measured CBFV response had the lowest SEM was regarded as the best fit.

ARI was also determined for the baseline recording (spontaneous oscillations but no induced BP changes). The frequency response from this baseline measurement served as input for an inverse Fourier transform, used to calculate the step-response (Panerai *et al.* 1998; Panerai *et al.* 2016). Subsequently, the best fit between the models and the step-response was calculated using the normalized mean SE (NMSE). To improve the reliability of this method, fits with $\text{NMSE} > 0.15$ were rejected (Panerai *et al.* 2016)

Statistical analysis

All variables were tested for normality using the Shapiro–Wilk test and, in the case of non-normality, a log-transformation was applied. The bivariate correlation among the different sCA and dCA metrics was tested using Pearson's correlation (r , for continuous variables) or Spearman's rank correlation (ρ , for ordinal variables). Based on the tertiles of Slope-CVR_{ICA}, subjects were categorized as low, normal and highly efficient sCA (Liu *et al.* 2016). Sex differences in the CA measures and differences in dCA metrics between the low and highly efficient sCA groups were tested using the non-parametric Mann–Whitney U test. There was no correction for multiple comparisons to prevent filtering out of weak correlations. $P < 0.05$ was considered statistically significant. Data were analysed using SPSS, version 22 (IBM Corp., Armonk, NY, USA).

Results

The baseline characteristics of the participants are provided in Table 1.

sCA

Figure 2 provides an overview of the experiments assessing sCA, including a representative time series of BP and CBFV from one of the participants. An overview of individual sCA estimates is shown in Fig. 3. The average sCA values obtained were within the normal ranges in ICA (1.1 ± 0.4), VA (1.1 ± 0.8) and MCA (1.0 ± 0.2), indicating normal sCA in this healthy population (Table 2). However, there was a high inter-individual variability leading to a wide range of values between low (almost absent) and highly efficient sCA (Fig. 3). Slope-CVR_{ICA} and Slope-CVR_{MCA}

Table 1. Baseline characteristics

Men/women (<i>n</i>)	13/15
Age (years)	67 ± 6
Height (cm)	170 ± 8
Body mass (kg)	78 ± 15
Body mass index (kg m ⁻²)	27 ± 4
Heart rate	60 ± 9
SBP (mmHg)	122 ± 15
DBP (mmHg)	75 ± 9
MAP (mmHg)	90 ± 10
EtCO ₂ (mmHg)	37 ± 4
Flow _{ICA} (cm ³ min ⁻¹)	232 ± 61
Flow _{VA} (cm ³ min ⁻¹)	76 ± 32
Ø _{ICA} (cm)	4.6 ± 0.7
Ø _{VA} (cm)	3.1 ± 0.6
SCBFV (cm s ⁻¹)	82 ± 26
MCBFV (cm s ⁻¹)	53 ± 17
DCBFV (cm s ⁻¹)	32 ± 10

Values are the mean ± SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; Flow_{ICA}, flow right internal carotid artery; Flow_{VA}, flow right vertebral artery; Ø_{ICA}, diameter right internal carotid artery; Ø_{VA}, diameter right vertebral artery; SCBFV, systolic flow velocity in MCA; MCBFV, mean flow velocity in MCA; DCBFV, diastolic flow velocity in MCA.

which both represent the anterior circulation, were correlated ($r = 0.45$, $P = 0.03$), whereas Slope-CVR_{VA} (representing the posterior circulation) did not correlate with sCA estimates from the anterior circulation (Table 3).

dCA

TFA. Figure 4 shows the transfer function estimates of dCA determined from the baseline measurement, presented in frequency plots for gain, phase and coherence. For the benefit of comparison with sCA, these plots of dCA have been divided into groups with highest vs. lowest tertile for sCA based on Slope-CVR_{ICA}. Figure 4 shows that gain is low and phase is high in the low frequencies, with gain increasing and phase decreasing with higher frequencies. This observation is consistent with the expected 'high-pass filter' behaviour observed with TFA in a healthy population (Zhang *et al.* 1998; van Beek *et al.* 2008). With an average Gain_{LF} of 0.80 ± 0.31 and Phase_{LF} of 0.70 ± 0.32 in the LF band (Table 2), the observed values were within the expected range for TFA studies, as established recently (Meel-van den Abeelen *et al.* 2014). The range was wide, however, and would indicate variance from low (almost absent) to highly efficient CA (similar as described above for the observations for sCA). Within these TFA parameters, Gain_{VLF} correlated with Gain_{LF} (for both absolute and normalized gain), although gain estimates did not correlate with phase estimates (Table 3).

ARI. Representative time series from two participants are shown in Fig. 5. Note, a lower absolute MCBFV is common in ageing subjects (Lipsitz *et al.* 2000). The ARI estimate for a decrease in BP (ARI_{SNP}) was on average 4.7 ± 2.3 , whereas ARI for an increase in BP (ARI_{PhE}) was slightly higher 5.6 ± 1.8 ($P = 0.04$) (Table 2). These mean values are within the range observed in earlier studies using ARI in a healthy population but, again (as for sCA and for dCA TFA), the individual subjects showed a wide range from low to normal to highly efficient CA (Fig. 6). The ARI-response estimated from the baseline-measurement (see Methods; ARI_{Baseline}) was 3.4 ± 2.3 ($P = 0.02$) which is below the range for normal CA. ARI_{SNP} correlated both with ARI_{PhE} ($\rho = 0.50$, $P = 0.03$) and ARI_{Baseline} ($\rho = 0.57$, $P = 0.03$), whereas ARI_{PhE} and ARI_{Baseline} did not correlate ($\rho = 0.42$, $P = 0.15$) (Table 3).

Correlation between the dCA methods TFA and ARI.

ARI_{Baseline} and ARI_{SNP} and ARI_{PhE} were compared with the six TFA parameters (gain, gain-norm and phase in the two frequency bands). There were correlations between Phase_{LF} and ARI_{SNP} and ARI_{PhE} ($\rho = 0.48$; $P = 0.03$ and $\rho = 0.67$; $P < 0.01$) but not between ARI and Gain-parameters or Phase_{VLF}.

Correlation between sCA and dCA

In Table 3, correlations between sCA parameters and the TFA parameters are presented. Gain_{VLF} correlated with sCA but this correlation was positive, indicating incongruity and not correspondence: high Gain (indicating poor dCA) correlated with high sCA (indicating efficient sCA). This non-physiological correlation was the strongest for sCA estimates in the posterior circulation (VA; $r = 0.44$; $P = 0.03$) and borderline significant for the anterior circulation (ICA; $r = 0.40$; $P = 0.05$). This can also be observed in Fig. 4, where gain in the VLF-band differs between the low and high sCA groups.

Phase did not correlate with sCA. There was no correlation between the ARI and the sCA parameters, which is in line with the absence of difference between the ARI for the low and high sCA groups (Fig. 6).

Discussion

The present study investigated whether estimates of sCA, obtained in both the anterior and posterior circulation, were related to estimates of dCA, derived from both spontaneous and induced BP changes, in a population of healthy older participants. The two key findings of the present study are: (i) the obtained indices of dCA, as well as sCA, showed a large variation in this group of healthy older subjects who were expected to have normal CA, indicating

a range from low (almost absent) to highly efficient CA, and (ii) although there were correlations between different measures of dCA, as well as between different measures of sCA, there was a lack of correlations between indices of dCA and sCA.

The large variation in the different indices of dCA and sCA (Figs 3, 4 and 6 and Table 2) is not a new finding. In previous research in animals, sCA varied from highly efficient to absent and only after averaging all animals was the classical autoregulatory pattern was observed

(Jones *et al.* 2002). In humans, the high variation in sCA in the population investigated in the present study has recently been reported by Liu *et al.* (2016). The heterogeneity of dCA in subjects has also been acknowledged (Chan *et al.* 2011) and several studies have addressed this variability (Panerai *et al.* 2003; Tzeng *et al.* 2012; Meel-van den Abeelen *et al.* 2014). However, this was from the perspective of reproducibility; the implicit assumption was that the underlying CA mechanisms were relatively stable among individuals, and that variability

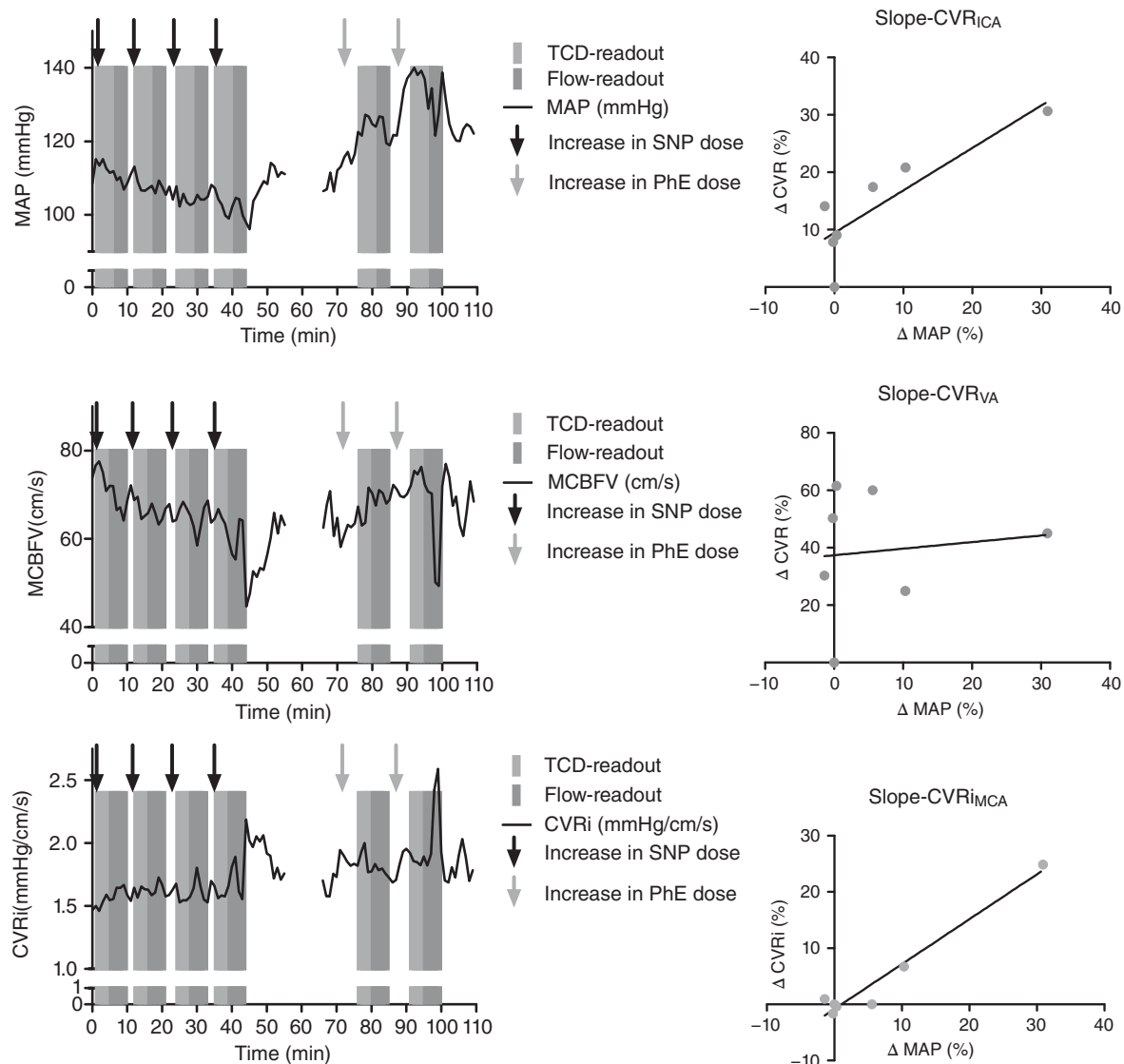


Figure 2. Representative data of CBF and CVRi (MAP/MCBFV) in response to steady-state changes in BP (left) and the method to estimate sCA (right)

A progressive, sustained decrease in BP was induced by continuous infusion of SNP with a stepwise increasing dose (black arrows) over a period of 40 min. After a recovery interval, a progressive, sustained increase in BP was induced by continuous infusion of PhE with a stepwise increasing dose (light grey arrows). The light grey bars indicate the segments used for calculation of MCBFV. The dark grey bars indicate within which time span the MAP and FV in the ICA and VA were measured. From these values, the CVR (MAP/CBF) and CVRi (MAP/MCBFV) were calculated and, using linear regression, the Slope-CVR_{ICA} (0.74), Slope-CVR_{VA} (0.23) and Slope-CVR_{MCA} (0.80) were calculated (see plots on the right).

Table 2. Mean values of the observed sCA and dCA measures

		Whole group, mean ± SD (n)	Female, mean ± SD (n)	Male, mean ± SD (n)		
sCA	Slope-CVR _{ICA} (%/%)	1.10 ± 0.4 (28)	1.07 ± 0.4 (15)	1.14 ± 0.5 (13)		
	Slope-CVR _{VA} (%/%)	1.15 ± 0.8 (28)	1.27 ± 0.8 (15)	1.01 ± 0.8 (13)		
	Slope-CVR _{iMCA} (%/%)	1.04 ± 0.2 (23)	1.01 ± 0.2 (11)	1.06 ± 0.2 (12)		
dCA	ARI	ARI _{SNP}	4.67 ± 2.3 (21)	4.30 ± 1.7 (10)	5.00 ± 2.7 (11)	
		ARI _{PhE}	5.65 ± 1.8 (20)	6.11 ± 1.8 (9)	5.27 ± 1.9 (11)	
		ARI _{Baseline}	3.41 ± 2.3 (17)	3.62 ± 2.3 (8)	3.22 ± 2.4 (9)	
	TFA	VLF	Gain _{VLF} (cm s ⁻¹ mmHg ⁻¹)	0.75 ± 0.29 (24)	0.80 ± 0.28 (11)	0.72 ± 0.30 (13)
			Gain-norm _{VLF} (% mmHg ⁻¹)	1.47 ± 0.56 (24)	1.59 ± 0.48 (11)	1.37 ± 0.61 (13)
			Phase _{VLF} (rad)	0.87 ± 0.40 (24)	1.00 ± 0.48 (11)	0.76 ± 0.30 (13)
		LF	Gain _{LF} (cm s ⁻¹ mmHg ⁻¹)	0.80 ± 0.31 (24)	0.81 ± 0.25 (11)	0.78 ± 0.37 (13)
			Gain-norm _{LF} (% mmHg ⁻¹)	1.49 ± 0.32 (24)	1.59 ± 0.38 (11)	1.41 ± 0.26 (13)
			Phase _{LF} (rad)	0.70 ± 0.32 (24)	0.70 ± 0.35 (11)	0.69 ± 0.31 (13)

Values are the mean ± SD. Gain is presented in absolute and normalized values, in accordance with Claassen *et al.* (2016).

may be driven by methodological issues rather than physiology.

The majority of studies on CA averaged autoregulatory indices to report comparisons between groups; thus, the presence of large individual autoregulatory indices suggesting either highly efficient CA or absence of CA has been neglected. These factors may explain why, thus far, the attention paid to the individual variations in CA has been minimal. Before we discuss the possible underlying mechanisms and consequences of this variation in CA, we first address the question of whether the observed variability could be a result of inaccuracy in measurements. For the sCA measurements, the method used to assess sCA was robust compared to previous studies on sCA because, for each slope-CVR calculation, at least three data-points were used (Fig. 2) (Strebel *et al.*

1995; Tiecks *et al.* 1995; Dawson *et al.* 2000; Dawson *et al.* 2003; Numan *et al.* 2014). Also, CBF measurements were repeated three times to reduce the effects of intrinsic CBF oscillations (e.g. respiratory cycle), as well as to minimize the influence of random noise.

For dCA, the observed inter-individual variability in the estimates of ARI and TFA is in line with the variations observed in previous studies (Brodie *et al.* 2009; Tzeng *et al.* 2012; Panerai *et al.* 2016). Statistical criteria such as the coherence and NMSE threshold were applied to increase the reliability of the measures (Claassen *et al.* 2016; Panerai *et al.* 2016). Indeed, even though the three ARI measures were estimated from different segments of the data, the correlation between these different ARI-measures indicates intraperson reliability. In addition, the slightly higher ARI_{PhE} compared to ARI_{SNP} is consistent with previous suggestions of hysteresis in CA (Aaslid *et al.* 2007; Tzeng *et al.* 2010; Ainslie & Brassard, 2014; Tzeng & Ainslie, 2014). The absence of a relationship between the ARI and TFA measures, with exception of the Phase_{LF}, is in line with the findings of Tzeng *et al.* (2012). Nevertheless, a correlation might have been expected because, for the ARI indices that were derived from a second-order linear model, the information from transfer function gain and phase was combined.

In summary, the high inter-individual variations of CA measures that we observed are in line with previous studies, and the intra-individual correlations found within sCA measures and within dCA measures suggest that these inter-individual variations probably represent ‘true’ physiological variations rather than simply measurement errors.

These inter-individual CA variations can have different origins. It may originate from non-stationary behaviour of CA, which is receiving increased attention in literature (Tan & Taylor, 2014; Willie *et al.* 2014). This

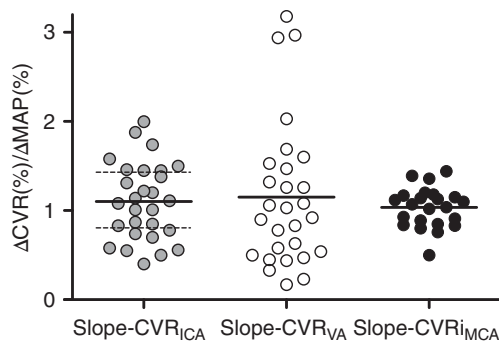


Figure 3. Scatter plot of the individual sCA outcomes, showing the variation of Slope-CVR or Slope-CVRi from the average values of ~1

For each column, each dot represents one subject. The y-axis represents the Slope-CVR, calculated using $\Delta\text{CVR}(\%)/\Delta\text{MAP}(\%)$ for the Slope-CVR_{ICA} and Slope-CVR_{VA} but $\Delta\text{CVRi}(\%)/\Delta\text{MAP}(\%)$ for the Slope-CVR_{iMCA}. The dashed lines represent the tertile boundaries for the ICA at 0.84 and 1.34.

Table 3. Correlation between different sCA and dCA parameters

Variables	sCA					dCA				
	Slope-CVR _{ICA}	Slope-CVR _{VA}	Slope-CVR _{IMCA}	ARI _{SNP}	ARI _{PHE}	ARI _{baseline}	Gain _{VLF}	Gain _{normVLF}	Gain _{normLF}	Phase _{VLF}
sCA										
Slope-CVR _{VA}	p↓ ρ→	0.19	0.45*	0.29)	0.10	0.01	0.40	0.12	0.20	0.03
Slope-CVR _{IMCA}	0.35	p↓ ρ→	0.08	-0.22	0.12	-0.17	0.44*	-0.02	0.23	0.25
dCA										
ARI	0.03	0.73	p↓ ρ→	0.05	-0.12	-0.14	0.30	-0.02	0.04	-0.24
ARI _{SNP}	0.21	0.33	0.84	p↓ ρ→	0.50*	0.57*	-0.34	0.05	-0.01	0.11
ARI _{PHE}	0.67	0.63	0.64	0.03	p↓ ρ→	0.42	-0.11	-0.18	0.06	0.48*
ARI _{baseline}	0.98	0.51	0.60	0.03	0.15	p↓ ρ→	0.03	0.42	0.38	0.67**
TFA										
Gain _{VLF}	0.05	0.03	0.16	0.13	0.66	0.90	p↓ ρ→	0.57**	0.53**	0.12
Gain _{normVLF}	0.59	0.93	0.94	0.84	0.45	0.10	< 0.01	p↓ ρ→	0.09	0.08
Gain _{normLF}	0.10	< 0.01	0.21	0.15	0.67	0.53	< 0.01	0.67	p↓ ρ→	0.19
Phase _{VLF}	0.34	0.28	0.90	0.96	0.80	0.13	< 0.01	< 0.01	p↓ ρ→	0.13
Phase _{LF}	0.26	0.57	0.55	0.63	0.20	0.12	0.67	0.23	0.23	0.26
	0.90	0.25	0.28	0.03	< 0.01	0.52	0.58	0.37	0.53	0.23

Correlation between sCA (slope method) and dCA (ARI and TFA). Values are presented as Pearson's r for normally distributed data or Spearman's ρ for non-normal data (upper-right corner); P values are shown in the left corner. Significant correlations ($P < 0.05$) are indicated in bold; $*P < 0.05$, $**P < 0.01$. Slope-CVR_{VA} was not normally distributed, and so the log-transformed Slope-CVR_{VA} was used in these analyses.

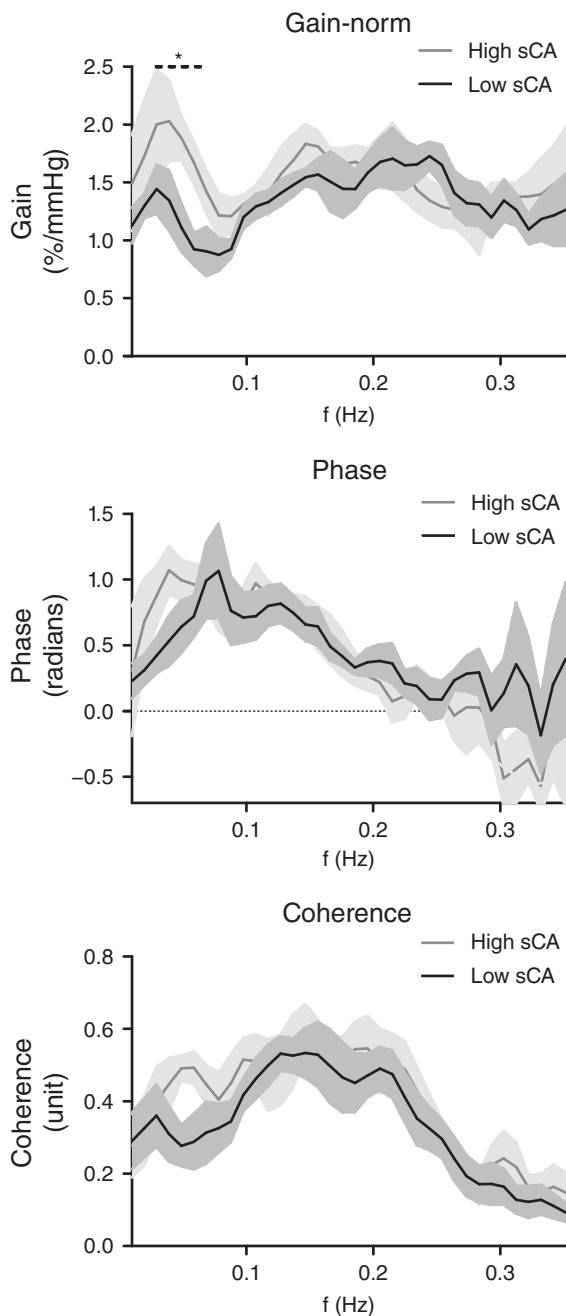


Figure 4. Transfer function analysis frequency plots

Frequency plots showing the mean TFA response with the SEM of gain, phase and coherence for the group divided in the upper tertile for Slope-CVR_{ICA} > 1.34 (High sCA, $n = 8$), as well as the lower tertile (Slope-CVR_{ICA} < 0.84; Low sCA, $n = 8$). The gain plot increases with increasing frequency, and the phase plot shows the characteristic decrease in phase with increasing frequency as expected from the high-pass filter model of dynamic cerebral autoregulation. * $P < 0.05$ between the two groups in that frequency band, using the Mann-Whitney U test.

non-stationary behaviour is caused by processes that may influence both BP and CBF. For dCA, spontaneous oscillations in BP are partly of unknown origin (i.e. because of autonomic neural control, vasoactive peptide activity or cardiac-vascular coupling). Some factors may only affect BP, whereas others only affect CBF (Kuo *et al.* 1998). For example, the role of autonomic neural control in CA is not well understood because, in humans, sympathetic and parasympathetic cerebral blood vessel innervation cannot be studied in isolation (Ainslie & Brassard, 2014). Similarly, BP may not be the only origin of oscillations in CBF, which may be related in part to the spontaneous oscillatory vasomotor or neuronal activity (Schroeter *et al.* 2004). These and other confounding factors (e.g. arterial pCO₂, cerebral vasomotion) may contribute to CA variability.

The inter-individual variation may also indicate strong CA heterogeneity between individuals, with some having a highly efficient CA and others an almost absent CA. Several factors might contribute to this heterogeneity, including sex, age and clinical condition (Krejza *et al.* 1999; Deegan *et al.* 2011). Although the group in the present study is too small to show significant differences in sex, it does appear to contribute to the variability (Table 2). Previous studies have shown that biological variability increases with ageing (Mancia *et al.* 1980; Krejza *et al.* 1999), although, in the present study, it cannot be determined whether the large individual CA variability observed in healthy older adults reflects the effects of age. The clinical correlates of this large heterogeneity in CA are unknown because all participants met criteria for healthy ageing.

The primary aim of the present study was to investigate the relationship between dCA and sCA, by assessing the correlation between multiple indices for both dCA and sCA. A prerequisite for studying correlations is that there is sufficient variability within the population studied, which was the case for CA observed in the present study. Despite this, there were no correlations between sCA and dCA with the exception of Gain_{VLF} with Slope-CVR_{VA}. However, this correlation was discordant, in that low gain (indicating good dCA) correlated with low Slope-CVR_{VA} (indicating poor sCA) and would not remain significant after correction for multiple comparisons. In addition to correlation analysis, we divided participants in two groups, efficient *vs.* poor sCA, and compared dCA indices between the groups. In line with the absence of correlations, there were no differences between the groups (Figs 4 and 6).

The absence of correlation between the sCA and dCA measures is in contrast to the observations reported by Tiecks *et al.* (1995), where the correlation between sCA and dCA was highly significant ($r = 0.93$, $P < 0.0001$). However, the effects of the chosen methodology on the observed correlation may have been underestimated. The variability of sCA and dCA was pharmacologically induced

using isoflurane (which impairs CA measures), possibly inducing a coupling between the two. The present study used the variability present in an ageing population. With multiple dCA measures and with a methodologically improved assessment of sCA (CBF instead of CBFV and using multiple equilibriums instead of only baseline and PhE-induced MAP increase of ~ 20 mmHg), the evidence is pointing towards a lack of correlation between sCA and dCA. This is in line with the observed dissociation between dCA and sCA in specific conditions, such as during anaesthesia (Strebel *et al.* 1995), in sepsis (Berg *et al.* 2012) and in type 2-diabetes patients (Kim *et al.* 2008). Also, in other studies that assessed both sCA and dCA, there was no linear association between the two (Strebel *et al.* 1995; Dawson *et al.* 2000; Dawson *et al.* 2003; Steiner *et al.* 2003).

Theoretically, a direct linear correlation between sCA and dCA variables may not exist. As illustrated by Tzeng & Ainslie (2014), the implicit conceptual paradigm for sCA and dCA consists of both fixed and variable resistance. For sCA, it assesses the steady-state BP–CBF

relationship over time scales from minutes to hours or even days and is quantified generally by static linear regressions. For dCA, the variable resistances or impedances are frequency-dependent, with resistance or impedance changing at different frequency bands (e.g. at the LF band; $f = 0.07\text{--}0.2$ Hz). In other words, dCA describes the dynamic BP–CBF relationship over time scales from seconds to minutes and is assessed by the transfer function gain and phase. In summary, the mechanisms responsible for changes in CVR or impedance over different time scales are probably different, and could explain the lack of linear correlations between sCA and dCA.

Strengths and limitations

One of the limitations is the use of drugs to manipulate BP, which have possible cerebrovascular effects. These effects could be (i) general vasoconstriction leading to reduced CBF with PhE and vasodilatation with increased CBF with SNP or (ii) more proximal effects only on, for example,

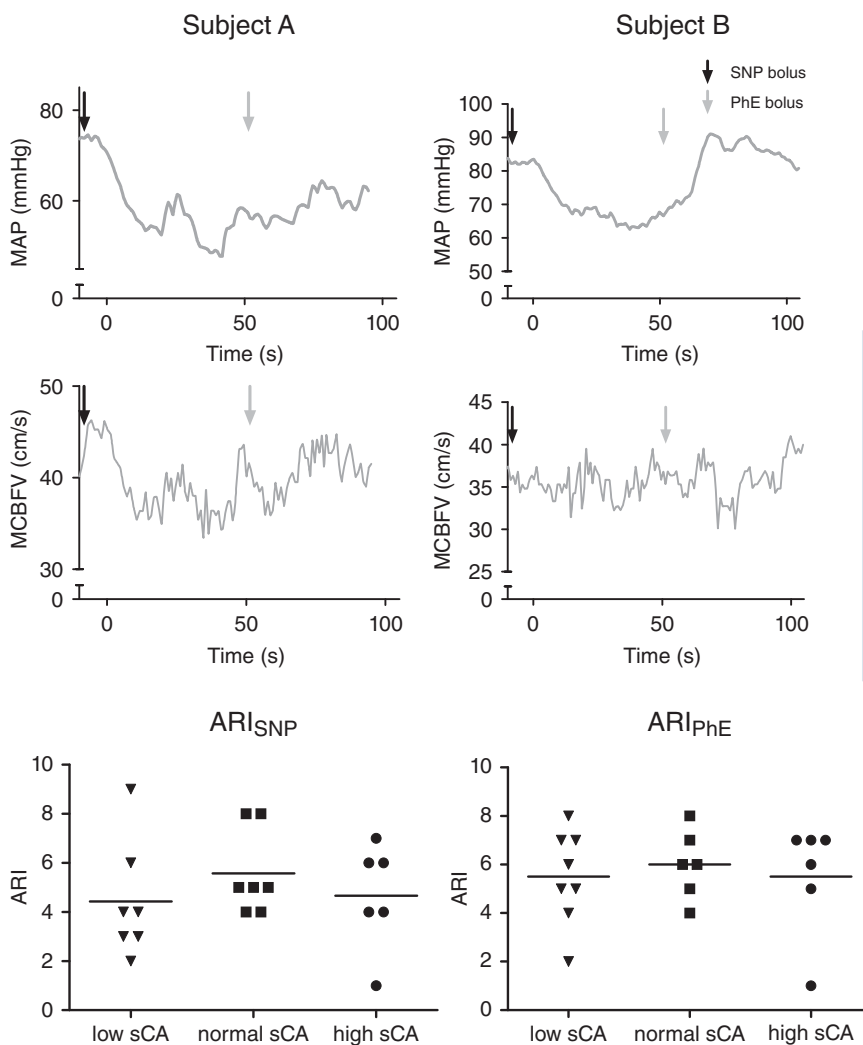


Figure 5. Two individual examples of the response of CBF to rapid, transient changes in blood pressure to estimate dynamic cerebral autoregulation

A decrease in blood pressure was induced by a bolus i.v. infusion of SNP (dark arrow) followed 1 min later by a bolus of PhE (light arrow), inducing an increase in BP. Subject A shows a weak autoregulatory response ($ARI_{SNP} = 1$ and $ARI_{PhE} = 1$); MCBFV appears to passively follow the MAP. Subject B has a good autoregulatory response ($ARI_{SNP} = 5$ and $ARI_{PhE} = 7$); mean flow velocity (mFV) is less influenced by the MAP.

Figure 6. Scatter plot of the individual ARI outcomes, showing the variation of ARI_{SNP} and ARI_{PhE} , categorized on the tertiles of the functioning of the sCA

Each dot represents one subject, showing their ARI after a bolus of SNP and after a bolus of PhE. Subjects were divided in the lower tertile for $Slope-CVR_{ICA} < 0.84$ (low sCA), as well as the upper tertile ($Slope-CVR_{ICA} > 1.34$; high sCA) and middle tertile ($0.84 < Slope-CVR_{ICA} < 1.34$; normal sCA).

the MCA, which would affect CBFV. There is evidence from several studies that PhE and SNP do not affect the cerebral vasculature (Olesen, 1972; Mutch *et al.* 1989; Giller *et al.* 1993; Strebel *et al.* 1995; Tiecks *et al.* 1995), although some studies suggest otherwise (Stewart *et al.* 2013). The correlation between the ARI_{Baseline} and ARI_{SNP} also suggests that any effects, if present, were only modest and cannot explain the lack of correlation or the large variability.

The induced BP changes also led to subtle changes in breathing pattern, which resulted in small elevations and reductions in EtCO_2 (group average ranges from -1.4 mmHg to $+0.7$ mmHg compared to baseline). Because even small changes in EtCO_2 can have strong effects on CBF ($3\text{--}7\%$ CBF/mmHg EtCO_2) (Claassen *et al.* 2007; Willie *et al.* 2012), independent from the effects of BP, this may have contributed to the variability in estimates. Because the sensitivity differs among individuals, we did not apply these group averages to correct the potential effects of EtCO_2 on CBF.

The major strength of the present study is the extensiveness of measurements, indices and analyses. In the present study, different techniques were used for the assessment of CBF(V) and BP. One of the major limitations of CBFV measurements is the uncertainty of a constant diameter of the vessel, in most cases the MCA. Sympathetic activation as a result of exercise can induce a 2% change in the cross-sectional area of the MCA (Verbree *et al.* 2016), which has only a very small effect on CBFV estimates. The effects of sympathetic activation or inactivation associated with changes in BP on the cross-sectional area of the MCA under supine resting conditions is probably minimal because a good correlation between Slope-CBF_{ICA} and the Slope-CBFV_{MCA} was observed in the present study.

In addition, multiple indices were assessed, based on both spontaneous and induced BP oscillations. These linear parameters are most conventional to study, although there is a movement towards more non-linear models (Marmarelis *et al.* 2012; Tan & Taylor, 2014). These non-linear methods may be better able to handle the physiological variability in dCA. However, the correlation between the different linear dCA estimates was reasonable; therefore, application of non-linear dCA methods would probably not alter the main findings of the present study.

Lastly, different statistical approaches with respect to investigating the relationship between sCA and dCA indices were used. A comparison of dCA between groups, based on sCA quality, showed the absence of a linear relationship between sCA and dCA (Figs 4 and 6). In addition, correlation analysis was performed (Table 3). Although correlations are sometimes misused for comparing quantitative methods, correlations can be used to investigate the presence or absence of a relationship between indices (Giavarina, 2015). Indeed,

in the present study, the absence of correlations is in line with the group comparison that we performed.

Implications

The potential benefit of a strong relationship between sCA and dCA would be that it makes the prediction of sCA from dCA measures possible, which could change clinical routine. The results of the present study show that such predictions are presently not possible, mainly for two reasons. First, sCA and dCA are not linearly related to each other, as indicated by the absence of correlation. Second, there is high variation in estimates of CA functioning in healthy older subjects, showing that a finding of almost absent CA can occur in healthy older subjects.

The absence of correlation between different measures, as shown in the present study and also in previous studies (Tzeng *et al.* 2012), indicates that careful consideration of measures is required. Most studies dealing with CA choose one measurement to assess CA. Thus, investigators must be aware that, instead of assessing overall CA, in reality, they assess only one element of CA. Depending on purpose and hypothesis, the choice for steady-state or dynamic measures and for TFA or ARI measures should be weighed carefully.

The high variation in the different CA measures also has considerable consequences for the design of future research. However, the consequences do depend on the underlying cause of the high variability. There are two possible explanations for this.

First, the non-stationarity of the CA is high (i.e. within a subject CA-efficiency may vary over time). This aspect may be highly underestimated. A study investigating the variability of CA within participants on a day-to-day basis would therefore be recommended. If there is indeed a high non-stationary CA, this would advocate averaging CA over several measurements.

Second, CA is stationary, although there is a high inter-subject variability, ranging from poor to good CA even in healthy subjects. This would limit studies that aim to use CA as a biomarker for disease, especially for the elderly. Precisely, in this group, the diseases that may affect CA, such as stroke, diabetes or neurodegenerative disease, have the highest prevalence. However, CA assessment can still be used to investigate differences in physiology between health and disease state, although the groups need to be sufficiently large.

Thus, for estimating effects of prolonged changes in BP, an assessment of dynamics of the CA system is not adequate because these measures are unable to predict more steady-state effects of the systems. This implies that the use of long-term monitoring of CA cannot be replaced by short measurement-procedures; the requirement of the long-term monitoring of cerebral perfusion pressure and CBF remains.

Conclusions

There was a high variation in dCA and sCA parameters, indicating a wide range of CA functioning in this aged population. Although there were moderate to strong correlations within sCA and dCA parameters, there were no linear correlations between sCA and dCA. Indeed, when the groups were ranked based on sCA functioning, this did not translate to differences in dCA functioning. Accordingly, the results of the present study show that the gain and latency of transient responses of CBF to dynamic changes in BP are not related to the steady-state responses of CBF to steady-state changes in BP.

Appendix

The ARI-templates are calculated using a second-order linear differential equation:

$$dP = \frac{MAP - cBP}{cABP - CrCP}$$

$$x_2 = \frac{x_2 + (x_1 - 2D \cdot x_2)}{fs \cdot T}$$

$$x_1 = x_1 + \frac{dP - x_2}{fs \cdot T}$$

$$mV = cMCFV * (1 + dP - K \cdot x_2)$$

where dPn is the normalized change in mean arterial pressure (MAP) relative to the control value (cBP) adjusted for the estimated critical closing pressure (CrCP; equal to 12 mmHg), x_2 and x_1 are state variables (equal to 0 at baseline), mV is modelled mean velocity, $cMCFV$ is baseline MCBFV and fs is the sampling frequency (10 Hz). mV values generated from 10 predefined combinations (Table A1) of the time constant (T), dampening factor (D) and autoregulatory gain (K) were fitted to the actual MCBFV recording within a 30 s window to identify the best-fit model associated with the minimum quadratic error.

Table A1. Parameters for calculation of Autoregulatory indices

ARI	T	D	K
0	2	0	0
1	2	1.60	0.20
2	2	1.50	0.40
3	2	1.15	0.60
4	2	0.90	0.80
5	1.9	0.75	0.90
6	1.6	0.65	0.94
7	1.2	0.55	0.96
8	0.87	0.52	0.97
9	0.65	0.50	0.98

ARI, autoregulatory index; T, time constant; D, dampening factor; K, autoregulatory dynamic gain.

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Additional information

Competing interests

The authors declare that they have no competing interests.

Author contributions

DJ was responsible for the data analysis and interpretation and drafting of the manuscript. TT and JL were responsible for data acquisition, analysis and interpretation. RZ and JC were responsible for the study concept and experimental design, provision of study materials, data analysis and interpretation. All authors edited and revised the manuscript and approved the final submission. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed. All experiments were performed at the Texas Health Presbyterian Hospital of Dallas.

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Translational perspective

Cerebral autoregulation (CA) is the brain's mechanism for maintaining adequate perfusion during changes in blood pressure (BP). CA can be measured in a steady-state condition, such as by measurements of cerebral blood flow (CBF) before and after a persistent (hours, days or weeks) change in BP. The dynamics of CA can also be measured as the perturbation and subsequent recovery of CBF by a transient change in BP (seconds, minutes) (e.g. orthostatic hypotension). The most accepted hypothesis was that the dynamics of CA reflect linearly on the steady-state behaviour of CA and vice versa. The present study challenges this assumption. We were unable to identify any linear relationship between steady-state CA and dynamic CA in a healthy aged population. This implies that a dynamic assessment of CA may not reliably predict the outcome of steady-state CA (e.g. the effect of BP-lowering treatment). Long-term monitoring of CA may not be replaced by short dynamic CA measurements. By contrast, normal steady state CA does not guarantee adequate autoregulation for a faster, transient change in BP. The large variability in all CA measures that we observed may be caused by within-subject variability as a result of the non-stationarity of CA. This would advocate for multiple CA measurements in a single individual before a reliable estimate of CA is possible. Inter-subject variability in CA function may also be an underlying cause, which could reduce the potential of CA as a clinical marker. The physiology behind this variability remains a subject for further study.