Cerebrovascular Dynamics During Continuous Motor Task

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Summary

We investigated the cerebral autoregulation (CA) dynamics parameter phase and gain change when exposed to a longlasting motor task. 25 healthy subjects (mean age ± SE, 38±2.6 years, 13 females) underwent simultaneous recordings of spontaneous fluctuations in blood pressure (BP), cerebral blood flow velocity (CBFV), and end-tidal CO_2 ($ETCO_2$) over 5 min of rest followed by 5 min of left elbow flexion at a frequency of 1 Hz. Tansfer function gain and phase between BP and CBFV were assessed in the frequency ranges of very low frequencies (VLF, 0.02-0.07 Hz), low frequencies (LF, 0.07-0.15), and high frequencies (HF, >0.15). CBFV increased on both sides rapidly to maintain an elevated steady state until movement stopped. Cerebrovascular resistance fell on the right side (rest 1.35±0.06, movement 1.28±0.06, $p<0.01$), LF gain decreased from baseline (right side 0.97±0.07 %/mm Hg, left 1.01±0.09) to movement epoch (right 0.73±0.08, left 0.76±0.06, $p\leq0.01$). VLF phase decreased from baseline (right 1.03±0.05 radians, left 1.10±0.06) to the movement epoch (right 0.81±0.07, left 0.82±0.10, $p\leq0.05$). CA regulates continuous motor efforts by changes in resistance, gain and phase.

Key words

Cerebrovascular dynamics • Motor task • Transcranial Doppler sonography • Transfer function • Physiology

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Introduction

Cerebral autoregulation (CA) is the ability of the brain vasculature to maintain cerebral blood flow constant over a wide blood pressure (BP) range (Kontos *et al.* 1978, Harper *et al.* 1984). When performing cognitive, motor or other tasks the blood supply to the activated brain areas is then further modulated regionally via vasoconstriction and dilation which are based on the metabolic demands. CA is assessable by:

a) static methods which are characterized by measuring cerebral blood flow or its velocity [CBF(V)] under stable conditions before and after a vasodilatory/vasoconstrictory stimulus (Leenders *et al.* 1999, Paulson *et al.* 2010, Powers 1991), and

b) by dynamic methods which analyze the interaction between CBF(V) and BP at spontaneous or induced slow oscillations present in CBF(V) and BP (Claassen *et al.* 2016, Meel-van den Abeelen *et al.* 2014, Müller and Österreich 2014, Zhang *et al.* 1998). When CA fails an additional metabolic mechanism helps to keep oxygen concentration in the needed range by increasing the oxygen extraction rate as increasing the amount of the oxygen concentration released from hemoglobin (Leenders *et al.* 1999). In pathological conditions such as acute stroke the coordinated overlapping of these mechanisms seems to be disturbed (Caldas *et al.* 2018, Maggio *et al.* 2013, Reinhard *et al.* 2012, Rivera-Lara *et al.* 2017) which might be relevant for an early start of rehabilitation (Coleman *et al.* 2017, Li *et al.* 2018, Chi *et al.* 2018).

In recent years the dynamics of the cerebrovascular system was studied by means of mathematical models which usually describe the BP – CBFV system over a wide range of BP and CBFV changes with CBF regulation occurring mostly between CBFV changes of 5 to 50 seconds (Claassen *et al.* 2016, Mitsis *et al.* 2006, Müller and Österreich 2014, Serrador *et al.* 2005, Zhang *et al.* 1998.). To characterize the system better its response to physiological stimuli like hand gripping, arm or leg movements, or visual tasks

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(Caldas *et al.* 2018, Giller *et al.* 2000, Maggio *et al.* 2013, Panerai *et al.* 2012a, Salinet *et al.* 2013) is analyzed. The duration of the used stimuli is usually short (e.g. a minute or less) and repeated several times to allow for an analysis after averaging over all runs, a setting usually addressing neurovasal coupling (NVC). The characteristic NVC response is a rapid, often bilateral CBF(V) increase which continues as long as the stimulus is present. As far as it is deducible from such short interventions, CA in terms of the transfer function (TF) estimates phase and gain is unchanged compared to the baseline prior to the stimulus. Whether these findings are transferrable to continuous tasks is assumed, but not established. The aim of our study was to prove this assumption using as stimulus elbow flexion and extension (at a frequency of 1 Hz) as this task has been shown to provide a feasible CBFV increase (Llwyd *et al.* 2017, Panerai *et al.* 2012a) that enables to study autoregulatory mechanisms.

Methods

The study was approved by the ethics committee of Northwest- and Central Switzerland and followed the Declaration of Helsinki as well as good clinical practice standards. Written informed consent was obtained from all subjects [n=25, women 13, mean age ± standard error of means (SE) 38±2.6 years (range 24-62 years)].

Experimental setting: all investigations followed the recommendation of Claassen *et al.* (2016), were performed in the late morning with the subject in a supine position with the head elevated approximately 30 ° in a room with dimed light. Last coffee or tea uptakes were taken a minimum of 4 hours before the investigations. The subjects were dominantly right-handed (20 of 25), all were non-smokers, healthy and without cerebrovascular risk factors. Participants were carefully instructed to flex and extend the elbow over the full movement range (= one movement cycle) at a pace of 1 Hz which was signaled by a computerized metronome's beep. Before mounting the probes several elbow movement cycles were tried at the metronome's pacing. We assessed the cerebral blood flow velocity (CBFV) in both middle cerebral arteries (MCA) using transcranial Doppler sonography (TCD) by placing the 2-MHz probes of the TCD device (MultidopX, DWL, Compumedics, Sipplingen, Germany) at the temporal skull and fixed them with a head holder provided by the manufacturer. The MCAs were identified as CBFV directed towards the probe/skull in a depth of 50-55 mm. End-tidal CO_2 ($ETCO_2$) was measured via a small nostril tube with the capnography embedded in the TCD device. BP was estimated by finger plethysmography (Finometer Pro, Finapres Medical Systems, Amsterdam, The Netherlands) placed at the fingertip of the right index finger, special attention was paid to its calibration to the brachial artery pressure. The BP signal was imported into the TCD device, and all parameters were recorded simultaneously. After all probes were placed and the subject familiar with the surroundings and the experimental setting, we started with a baseline recording of 5 min, thereafter the elbow movement paradigm was performed over 5 min.

Data preparation: BP, CBFV, and $ETCO_2$ data were collected at 100 Hz. The data were analyzed using Matlab (2015b, Math Works Inc., Natick, MA, USA). The data were visually inspected for artefacts, and only artefact-free data periods of 5 min were used. Each raw data time series was averaged over 1 second interval. The coherence and the TF estimates of phase and gain between the BP and the CBFV time series were extracted from their respective power auto-spectra or cross-spectra using Welch's averaged periodogram method, with a Hann window length of 100 s, window overlap of 50 %, and a total data length of 300 seconds. In each subject, the coherence, the phase (in radian), and the gain (in cm/s/mmHg and in %/mmHg) were calculated over a frequency range of 0.02-0.40 Hz in the epochs of baseline and motor task. Based on recent recommendations (Claassen *et al.* 2016) only those phase and gain values were considered for further use when coherence was >0.44. The results of phase, gain and coherence are reported as their respective average in the very low frequency range (VLF, 0.02-0.07 Hz), low frequency range (LF, 0.07-0.15 Hz), and high frequency range (HF, 0.15-0.4 Hz). Over each epoch we also calculated the cerebrovascular resistance as mean BP/ mean CBFV, and heart rate which was derived from the BP signal.

Statistical analysis

Data analysis was performed with the Matlab Statistical Toolbox. Using a Kolmogorov-Smirnov test, all data showed a normal distribution, and the data are reported as mean ± SE (standard error of the mean). To compare means between the two epochs (baseline and motor task) we used one-way ANOVA including a correction for multiple comparisons when indicated. $P \leq 0.05$ was considered statistically significant.

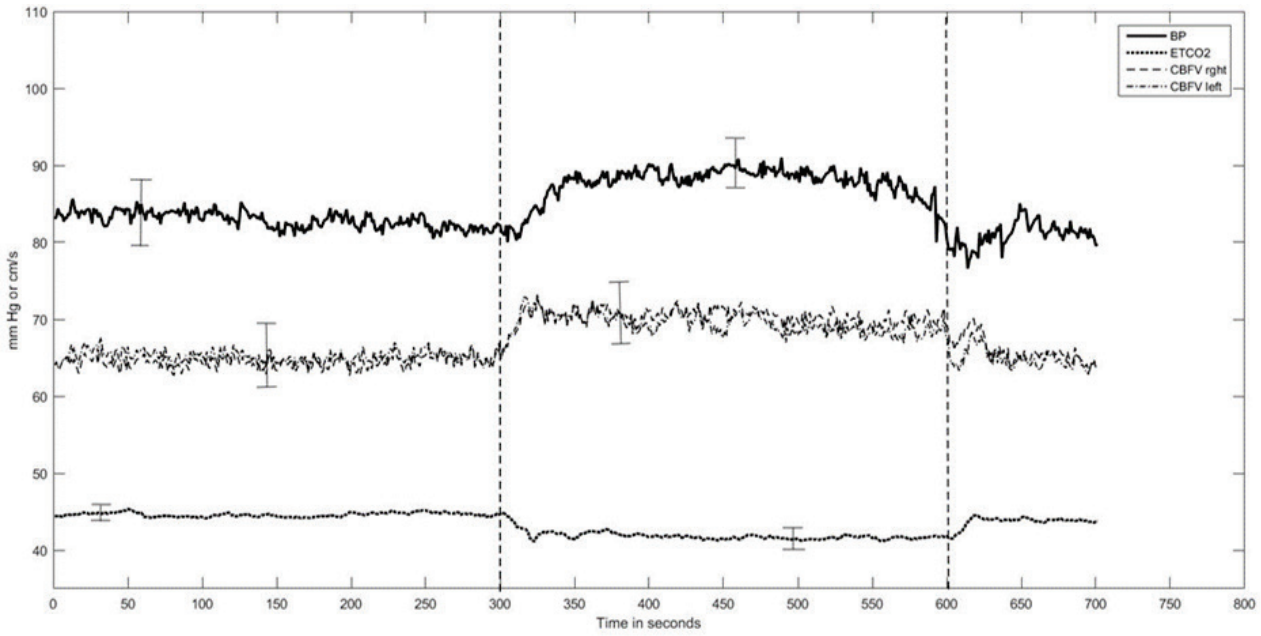

Fig. 1. Time course (group averaged) of blood pressure (BP), end-tidal carbon dioxide ($ETCO_2$), and cerebral blood flow velocity (CBFV) in both middle cerebral arteries (MCA). For simplicity, bars indicate the maximum standard error of mean (SE) achieved in the whole epoch (baseline or elbow movement); the SE bar for CBFV represents the SE in both MCAs. The movement epoch is indicated by the dashed perpendicular lines.

Table 1. Hemodynamic baseline variables and results of transfer function estimates at baseline and at elbow movement over 5 minutes at a frequency of 1 Hz.

	Baseline		**Elbow movement**	
Mean Blood Pressure (mm Hg)	83±2.6		87±3.4†	
Mean ETCO2 (mm Hg)	44.6±0.60		41.7±0.68†	
Mean Heart rate (beats/minute)	65±1.8		74±2.2†	
Mean CBFV right (cm/s)	65±2.4		69±2.4†	
Mean CBFV left (cm/s)	64±2.2		70±2.6†	
Mean CVR right (mm Hg/cm/s)	1.35±0.06		1.28±0.06†	
Mean CVR left (mm Hg/cm/s)	1.32±0.06		1.31±0.06	
Mean Coherence	**Right**	**Left**	**Right**	**Left**
- *Very low frequency*	0.46±0.03	0.48±0.03	0.46±0.03	0.38±0.04
- *Low frequency*	0.77±0.02	0.75±0.02	0.72±0.03	0.67±0.05
- *High frequency*	0.70±0.02	0.68±0.03	0.70±0.03	0.65±0.03
Mean Gain (in cm/s/mmHg)				
- *Very low frequency*	0.24±0.05	0.23±0.3	0.26±0.04	0.19±0.05
- *Low frequency*	0.62±0.05	0.63±0.05	0.54±0.06	0.53±0.06
- *High frequency*	0.70±0.07	0.65±0.07	0.65±0.08	0.59±0.08
Mean Gain (in %cm/s/mmHg)				
- *Very low frequency*	0.37±0.07	0.29±0.05	0.35±0.06	0.26±0.06
- *Low frequency*	0.97±0.07	1.01±0.09	0.73±0.08†	0.76±0.06†
- *High frequency*	1.02±0.10	0.99±0.09	0.93±0.10	0.98±0.10
Mean Phase (radians)				
- *Very low Frequency*	1.03±0.05	1.10±0.06	0.81±0.07†	0.82±0.10*
- *Low frequency*	0.70±0.06	0.67±0.05	0.77±0.05	0.70±0.05
- *High frequency*	0.28±0.10	0.28±0.10	0.37±0.11	0.28±0.11

Values are mean ± SE. $ETCO_2$, end-tidal carbon dioxide, CBFV, cerebral blood flow velocity, CVR, cerebrovascular resistance, ANOVA: *p≤0.05, †p≤0.01

Results

In 24 of the 25 subjects, recordings were possible in both MCAs. In one person only the right MCA was detected. Artefact-free recordings were achieved from all vessels. Figure 1 shows the time course of mean CBFV (right n=25, left n=24), mean $ETCO_2$ (n=25) and mean BP (n=25) over the total experiment. After the baseline epoch CBFV increases rapidly with elbow movement and remained at an elevated steady state over the total time of elbow movement, CBFV increase is slightly higher on the right side (contralateral to the arm movement, Table 1). After starting of arm movement $ETCO_2$ and BP decreased ($ETCO_2$) or increased (BP). We defined the time point at which $ETCO_2$ decreased or BP increased as the time point at which the decreasing or increasing curve was clearly below or above the fluctuation range of the baseline recording curve. $ETCO_2$ dropped 5±0.1 seconds after movement starting from 44.8 to 41.1 mmHg to remain thereafter relatively stable at a mean $ETCO_2$ of 41.7 mm Hg. In contrast to CBFV and $ETCO_2$, BP remained at the baseline level for the first 20±0.3 seconds after starting of the stimulus before rising notably.

Table 1 shows the significant differences between the variables of the baseline and the motor task epochs. BP, CBFV on both sides and heart rate increased while $ETCO_2$ decreased in the motor task epoch. CVR decreased in the right MCA ($p \leq 0.01$) but not in the left MCA. Coherence and gain (in cm/s/mmHg) did not show differences between the two epochs within one side nor between the two sides. Gain in %/mmHg decreased significantly at both sides in the LF range from baseline (right side 0.97±0.07, left 1.01±0.09) to movement epoch (right 0.73±0.08, left 0.76±0.06. $P \leq 0.01$), it remained unchanged in the VLF and HF ranges. Phase (in radian) in the VLF range decreased significantly from baseline (right 1.03±0.05, left 1.10±0.06) to the elbow movement epoch (right 0.81±0.07, left 0.82±0.10. $P \leq 0.05$), it did not change in the LF and HF ranges. Heart rate (in heart beat/s) was 1.11-1.15±0.019 (maximum SE) during the rest period, it was 1.12-1.16±0.022 between starting elbow movement and 12 seconds thereafter (not significant different), it was 1.38±0.011 ($p<0.005$) at 15 seconds after elbow movement start and remained at this level until the end of movement (1.38±0.022, $p<0.005$ compared to baseline).

Discussion

The time course of and the amount of the evoked CBFV achieved by our setting corresponds to other motor tasks evoked flow studies targeting NVC insofar as flow is evoked bilaterally, remains elevated as long as the stimulus is present, and an attenuation does not ensue, a BP increase occurs comparably to those observed in NVC studies (Caldas *et al.* 2018, Giller *et al.* 2000, Llwyd *et al.* 2017, Maggio *et al.* 2013, Nikolic *et al.* 2015). In contrast to these reports on NVC, however, our continuous motor task showed changes in the LF range (% /mmHg) and in the VLF range (phase) which are consistent with a disturbed dynamical CA (dCA, Zhang *et al.*1998, Panerai *et al.* 1999, Panerai *et al.* 2001, Serrador *et al.* 2005). At least in the right MCA, the vessel supplying the cortical areas in which the movement is primarily generated, CVR decreased which can be interpreted as a vasodilation. The CVR decrease seems in agreement with current concepts of neurovasal interaction derived from functional magnetic resonance imaging and from near infrared studies (Huber *et al.* 2017, Petridou *et al.* 2017, Schmid *et al.* 2017): with the beginning of the task a vasodilation occurs which leads to an increase in cerebral blood volume and an increase in the concentration of oxygenated blood which is considered to represent an increase in CBF. When such a vasodilation is induced by CO_2, in dCA the vasodilatory response consists usually of a phase decrease while gain remains not significantly changed (Müller *et al.* 2016, Panerai *et al.* 1999, Zhang *et al.* 1998). Thus, the phase decrease findings in our population could be the result of vasodilation. However, when BP is pharmacologically increased rapidly, dCA's response has been reported to consist of a decrease in both phase and gain accompanied by a CVR increase (Zhang *et al.* 2009). Our findings with phase and gain decreases would then hint more in the direction of a BP related response with CVR decrease indicating some additional regional regulation.

The other variable to influence dCA is $ETCO_2$ change. An $ETCO_2$ decrease as recorded in our subjects leads usually to a phase increase and to a gain decrease (Birch *et al.* 1995, Müller *et al.* 2003). This is contrary to what we have found. An exercise induced lactate acidosis drives a compensatory hyperventilation with the result that dCA's phase and gain were reported unchanged (Ogoh *et al.* 2007). Thus, $ETCO_2$ decrease due to hyperventilation might have nothing to do with the dCA changes.

The BP rise in our subjects could be due to the (most likely exercise induced) heart rate increase or be a result of the brain's metabolic demands. It is beyond our data to clarify whether the dCA changes are primarily

due to the metabolic demands or due to the BP increase. Maybe a study comparable to ours which includes an observation of the metabolic changes in the brain, e.g. by using NIRS devices able of recording cytochrome-oxidase changes (Obrig *et al.* 2000) could be of help for this purpose. Such a study might be relevant especially when patients are included (see next paragraph).

Our phase and gain findings could be considered a disturbed dCA induced by performing repetitive arm movements. This movement induced disturbed CA state will interfere in many stroke patients with a preexisting CA condition which by itself is the combined result of an elevated BP, the effect of cerebral ischemia (Llwyd *et al.* 2018, Reinhard *et al.* 2012) and/or an unstable circulatory response induced by orthostatic stress (Mitis *et al.* 2006, Serrador *et al.* 2005). In clinical practice, in most stroke patient's systolic BP values until 180 mm Hg are tolerated. But high BP handicaps dCA in several conditions: when it is rapidly increased (Zhang *et al.* 2009), when BP is newly diagnosed before treatment is sufficient (Serrador *et al.* 2005, Zhang *et al.* 2007), and in patients with long lasting chronic high BP even when BP is sufficiently treated (Müller *et al.* 2018). Hence, one future question is whether all disturbances will add up, and whether a risk for the patient will result.

Our study has limitations

With TF estimates we used strict linear modeling to assess the relationship between BP and CBFV. This kept nonlinear and nonstationary aspects of the system unconsidered (Castro *et al.* 2017, Giller and Mueller 2003, Placek *et al.* 2017). All nonlinear approaches showed that the coefficient of variance as a sign of the models quality or analog measures become smaller compared to the strict linear models indicating that these models were likely more precise. However, in terms phase, gain or impulse response as measure of comparison such models did not exhibit large differences from linear differential equations models (Kouchakpour *et al.* 2014, Marmarelis *et al.* 2014, Meel-van den Abeelen *et al.* 2014, Panerai 1999a, Smirl *et al.* 2015, Panerai *et al.* 2001). Regarding non-stationarity present in the data, recordings over time periods of several minutes can average out non-stationary effects with the result that time-variant models and time-invariant models produce close results (Kouchakpour *et al.* 2010, Marmarelis *et al.* 2014, Nikolic *et al.* 2015, Placek *et al.* 2017).

We used CBFV instead of CBF. The velocity signal depends strongly on the vessel's diameter and on multiple other influences apart from BP, such as CO_2, autonomic influences, myogenic and cognitive activity (Panerai *et al.* 2012, Panerai *et al.* 2012a, Sohn 1998, Spronck *et al.* 2012). Nevertheless, when a Doppler signal derived index of cerebral blood flow (flow index) was compared to CBFV, this flow index was shown to increase during the hand grip task but the amount of increase was less high compared to the velocity signal (Giller *et al.* 2000).

We suggest that $ETCO_2$ at rest reflects blood partial CO_2 content, a relationship that might be less close and more variable while exercising (Brys *et al.* 2003, JØrgensen *et al.* 1992, Ogoh *et al.* 2007, Robbins *et al.* 1990). This could be relevant to explain the transfer function result differences between the two cycling studies and our investigation because CO_2 reacts slowly and amounts for a considerable fraction of CBFV variations, and hence spectral density, in the LF and VLF range (Kouchakpour *et al.* 2010, Mitsis *et al.* 2006, Panerai *et al.* 2012, Panerai *et al.* 2012a).

Conclusions

Our findings suggest that CA adapt to a continuous motor task by modulating CVR, gain and phase. However, the observed changes could also be considered a CA impairment. BP elevation might be a co-factor to be considered. Whether this is of relevance for motor recovery e.g. after stroke needs further investigation.

Conflict of Interest

There is no conflict of interest.

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