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Oscillatory cerebral hemodynamics—the macro- vs. microvascular level

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Abstract

The phase shift between oscillations of blood pressure (BP) and Doppler middle cerebral artery flow velocity (MCAFV) reflects continuous cerebral autoregulatory action. It is not known whether a similar phase shift exists for cortical hemodynamics ('microvascular level') assessed by near infrared spectroscopy (NIRS) and what the effects are of pathological conditions. This study investigates the phase relations between oscillations of BP, MCAFV and NIRS parameters in 38 healthy older adults and 28 patients with unilateral severe obstructive carotid disease. BP was recorded noninvasively by finger plethysmography. Stable 0.1 Hz oscillations of all hemodynamic parameters were induced by regular breathing at a rate of 6/min. Basic results were that: (1) BP-induced cortical microvascular oscillations (NIRS) follow those of macrovascular oscillations (MCAFV) with a phase of 80–90° (corresponding to 2–2.5 s at 0.1 Hz), most likely reflecting a transit time phenomenon; (2) oxy- and deoxyhemoglobin thereby oscillate in counterphase; (3) hemodynamic compromise in carotid obstruction leads to (a) delayed NIRS oscillations in comparison to BP which are highly correlated to a shorter phase lead of MCAFV against BP and (b) a decoupling of the oxy-/deoxyhemoglobin counterphase to 240°. Cortical hemodynamic responses to BP oscillations follow specific phase relationships due to cerebral autoregulatory action and circulatory transit times. With hemodynamic impairment, as in unilateral carotid obstruction, these phases are significantly changed reflecting disturbed autoregulation.

Keywords: Cerebral autoregulation; Cerebral blood flow; Oscillations; Spectroscopy; near infrared; Ultrasonography; Doppler, transcranial; Carotid artery stenosis

1. Introduction

Cerebral autoregulation is an intrinsic protective mechanism of the cerebral vasculature, which aims to maintain the cerebral blood flow stable during changes of blood pressure. Already at rest, however, cerebral perfusion is not a constant, waveless phenomenon. It rather permanently oscillates at different frequencies. Thereby, spontaneous low frequency oscillations around 0.1 Hz of cerebral blood flow velocity (CBFV) mirror the M-waves of arterial blood pressure (ABP) which may represent feedback oscillations of the baroreflex loop. Experimentally, strong low frequency oscillations can also be induced by slow regular breathing at 6/min (=0.1 Hz) [1].

Previous investigations have shown that such spontaneous or respiratory-induced low frequency oscillations of CBFV in the large basal arteries do not occur simultaneous to those of ABP but in a phase shift with CBFV oscillations leading those of ABP [2]. This "phase shift" is regarded to be due to the fast and steady effort of the cerebral autoregulatory system to counterregulate the repetitive falls and rises of cerebral blood flow during oscillating ABP [3]. The phase shift is reduced in various acute and chronic cerebrovascular diseases [1,4–8]. It has, however, not been comprehensively investigated so far, whether such a phase shift can also be observed for oscillations of cortical hemodynamics ('microvascular level') and whether this is then also altered in pathophysiological conditions.

Cortical hemodynamics can be assessed noninvasively at a high time resolution by near infrared spectroscopy (NIRS), which measures changes of oxygenated and deoxygenated

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hemoglobin ([oxyHb], [deoxyHb]) and thus reflects changes in local blood flow and volume [9]. NIRS has shown spontaneous very low and low frequency oscillations in the human cortex and a possible role of these NIRS oscillations for autoregulation testing has been proposed [9,10].

This study investigates the phase relationship between respiratory-induced slow blood pressure oscillations, NIRS signal oscillations and CBFV oscillations in the middle cerebral artery in healthy adults and patients with unilateral severe obstructive carotid disease.

2. Methods

2.1. Subjects

33 patients with critical unilateral stenosis or occlusion of the internal carotid artery (ICA) were studied within a prospective study approved by the local Ethics Committee. Stenoses were graded using Doppler velocities in combination with B-mode imaging according to standard criteria [11]. They showed a mean degree of 95% (range 80–100%). Only 4 patients had suffered from clinical symptoms in the period of 24 months prior to the measurement (=symptomatic stenosis). As a control group, 38 older volunteers without any history of cerebrovascular disease were studied. Carotid obstruction was ruled out by duplex sonography in each control subject. All patients and controls underwent a careful history and review of medical records regarding vascular risk factors (previously-diagnosed hypertension, diabetes, hypercholesterolemia, current smoking). Neuroimaging prior to study inclusion was not routinely performed. Table 1 summarizes baseline characteristics of eligible patients and controls.

Table 1
Baseline characteristics of eligible patients and controls

	Patients (n=28)	Controls (n=38)	Significant p-values
Age (years)	67±8	64±8	ns
Sex (male/female; n)	26/2	25/13	p=0.008
Mean ABP (mm Hg)	74.7± 12.6	76.4± 15.2	ns
Heart rate (beats/min)	66±9	65±9	ns
P_{ETCO_2} (mm Hg)	37.6±6.1	37.0±5.8	ns
Mean CBFV ipsilateral/right (cm/s)	38.6± 11.9	51.6± 13.8	Patients ipsilateral vs. controls: $p<0.001$
Mean CBFV contralateral/left (cm/s)	44.5± 12.9	51.9± 12.6	Patients contralateral vs. controls: ns; patients contra- vs. ipsilateral: p=0.019
Hypertension	23	16	$p<0.001$
Diabetes	6	7	ns
Hyperlipidemia	21	14	ns

Values are reported as mean±one standard deviation. ns=not significant. Only patients entering the final data analysis are considered. Mean ABP (continuously measured by finger plethysmography), cerebral blood flow velocity (CBFV), heart rate and end tidal P_{CO_2} were averaged over 1 min at rest.

2.2. Data acquisition

Continuous non-invasive arterial blood pressure (ABP) recording was achieved via a servo-controlled finger plethysmograph (Finapres© 2300, USA) with the subject's right hand positioned at heart level. End-tidal CO_2 partial pressure (P_{ETCO_2}) was measured in kPa with an infrared capnometer (Normocap©, Datex, Finland) during nasal expiration. Cerebral blood flow velocity (CBFV) was measured in both middle cerebral arteries (MCA) by transcranial Doppler sonography (TCD) through the temporal bone window with 2 MHz transducers attached to a headband (DWL-Multidop-X©, Sipplingen, Germany). NIRS measurements were performed using a modern spectrometer with a sampling rate of 6 Hz (NIRO-300©, Hamamatsu Photonics, Japan; four wavelengths 775, 810, 850, and 910 nm). The basic principle of this method is that near infrared light penetrates the skull and brain and is absorbed by the chromophores oxyhemoglobin ([oxyHb]), deoxyhemoglobin ([deoxyHb]) and cytochrome-c oxidase at different near infrared wavelengths. Assuming constant scattering, the changes in the different absorption spectra of these chromophores can be converted into changes in their concentrations using the modified Lambert–Beer Law [12]. These changes can be quantified if the optical pathlength of the reflected light, which is considerably greater than the pure interoptode distance, is known. Since the employed spectrometer does not measure this parameter, we used the established differential pathlength factor of 5.93 to estimate changes in μmol/l [13]. The NIRS probes were protected from ambient light by a plastic mold and placed on the frontotemporal skull: the transmitting probe 2 cm beside the midline and 3 to 4 cm above the supraorbital ridge, the receiving probe laterally at a distance of 5 cm. The interoptode area thus covered the frontotemporal cortex usually supplied by the MCA. Raw data were digitally converted and recorded with a measurement rate of 100 Hz and further analyses were performed with custom-written software developed in-house and a data analysis program (Glance©, seleon, Germany). From the values of [oxyHb] and [deoxyHb] we also calculated their sum ([sumHb]) and difference ([diffHb]=[oxyHb]−[deoxyHb]).

2.3. Measurement protocol

Subjects were placed in a supine position with 50° inclination of the upper body. Regular breathing at a rate of 6/min (i.e., 0.1 Hz) was performed over 180 s. Fig. 1 shows an illustrative recording. Patients were carefully instructed to breathe with *low* tidal volumes in order to avoid hypocapnia.

2.4. Data analysis

Transfer function analysis was used to determine the phase shift between various parameters [14,15]. Briefly,

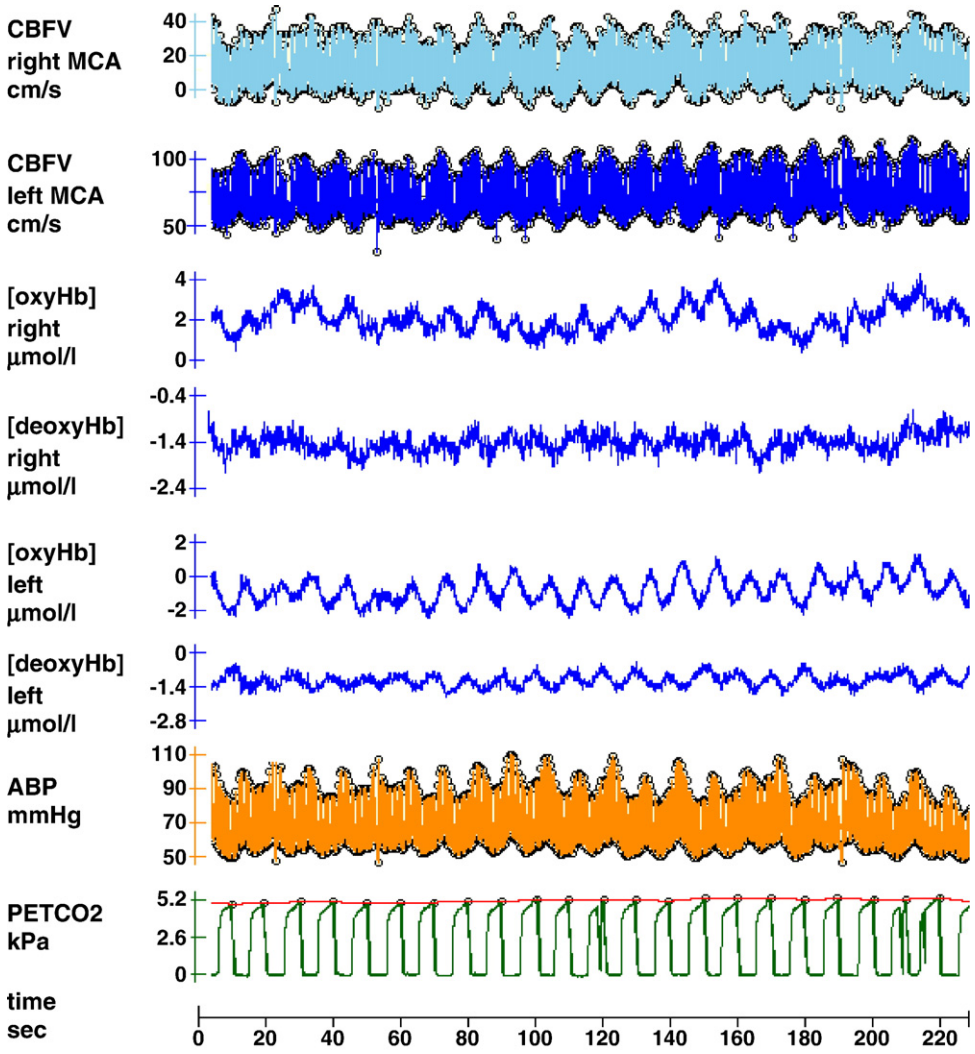

Fig. 1. Illustrative recording. 59-year-old patient with occlusion of the right internal carotid artery. The regular breathing at 6/min leads to oscillations at 0.1 Hz in ABP, CBFV and NIRS parameters.

power spectra and respective cross spectra were estimated by transforming the time series of ABP, NIRS signals and CBFV with discrete Fourier transformation to the frequency domain. Smoothing the respective periodograms resulted in the power spectra and cross spectra (CS) estimates. With the smoothing used (triangular window of half-width 8 frequency bins), the coherence (normalized modulus of CS) is significant at the 95% level if it exceeds 0.49. The phase is the angle between the real and the imaginary part of the cross spectrum. It represents a measure (in frequency space) for the temporal lag between the input and the output signal.

The final data analysis comprised 28 patients and 38 controls. Simultaneous bilateral recordings of TCD and NIRS signals without artefacts were not achieved in 5 patients. NIRS measurements in controls were performed on the right side only in 6 subjects, TCD showed artefacts in 3 patients. Bilateral recordings without artefacts in controls were achieved in 34 patients (TCD) and 31 subjects (NIRS). The remaining recordings were analyzable on one side. In case of bilateral recordings values were averaged for principal analyses.

2.5. Statistical analysis

Calculation of intra- and interindividual differences and correlations was performed using non-parametric tests (Wilcoxon, Spearman's rank coefficient) and Fisher's exact test. We report nominal p-values not adjusted for multiple comparisons. A p-value of less than 0.05 was considered statistically significant. Data are reported as mean ± S.D. After pooling all eligible sides of patients and controls (max. $n = 132$, depending on phase relations used), multivariate analysis of variance (ANOVA) was used to assess the influence of various vascular risk factors on different phase relations controlled for the presence of carotid stenosis. Equality of variance between groups was verified by the Levene test.

3. Results

3.1. Phase relations in controls

Oscillations in CBFV are ahead of those in ABP by approx. −40° to −80° (Table 2, Fig. 2). Note that, for convenience, the $\text{phase}_{\text{ABP–CBFV}}$ is often given as a positive number in the literature, but in relation to ABP its leftward shift is mathematically negative. NIRS oscillations occurred shortly *after* those of ABP (≈+20°, rightward shift). CBFV lead the NIRS oscillations by approx. 80–90° (≈2.5 s at 0.1 Hz). The $\text{phase}_{\text{ABP–CBFV}}$ correlated strongly with the $\text{phase}_{\text{ABP–[diffHb]}}$ ($r=0.74$, $p<0.001$), $\text{phase}_{\text{ABP–[doxyHb]}}$ ($r=0.72$; $p<0.001$) and $\text{phase}_{\text{ABP–[oxyHb]}}$ ($r=0.60$; $p<0.001$). A shorter phase lead of CBFV to ABP thus results in a longer absolute phase between ABP and respective NIRS parameters, keeping the absolute phase between CBFV and NIRS parameters rather constant. Oscillations of [oxyHb] and [deoxyHb] had a mean phase of approx. 180–190°, indicating a counterphase relationship.

3.2. Phase relations in patients

On affected sides, the $\text{phase}_{\text{ABP–CBFV}}$ was significantly reduced and the $\text{phase}_{\text{ABP–[diffHb]}}$ and $\text{phase}_{\text{ABP–[deoxyHb]}}$ were significantly prolonged (Table 2, Fig. 3). The latter two correlated also significantly with the $\text{phase}_{\text{ABP–CBFV}}$ ($r=0.68$ and $r=0.83$; $p<0.001$), which means again that the less negative the $\text{phase}_{\text{ABP–CBFV}}$ is, the more positive is the phase between ABP and the respective NIRS parameters. Significant correlations were also observed between absolute *side-to-side differences* of $\text{phase}_{\text{ABP–CBFV}}$ and $\text{phase}_{\text{ABP–[diffHb]}}$ ($r=0.61$; $p=0.001$), $\text{phase}_{\text{ABP–[sumHb]}}$ ($r=0.65$; $p=0.001$), $\text{phase}_{\text{ABP–[deoxyHb]}}$ ($r=0.69$; $p<0.001$) and $\text{phase}_{\text{ABP–[oxyHb]}}$ ($r=0.63$; $p<0.001$), respectively. The absolute $\text{phase}_{\text{CBFV–[diffHb]/[oxyHb]}}$ was significantly *shorter* on affected sides, whereas the $\text{phase}_{\text{CBFV–[deoxyHb]}}$ was *longer*. The $\text{phase}_{\text{[oxyHb]–[deoxyHb]}}$ was significantly prolonged on affected sides and also correlated with the $\text{phase}_{\text{ABP–CBFV}}$ ($r=0.59$, $p<0.001$).

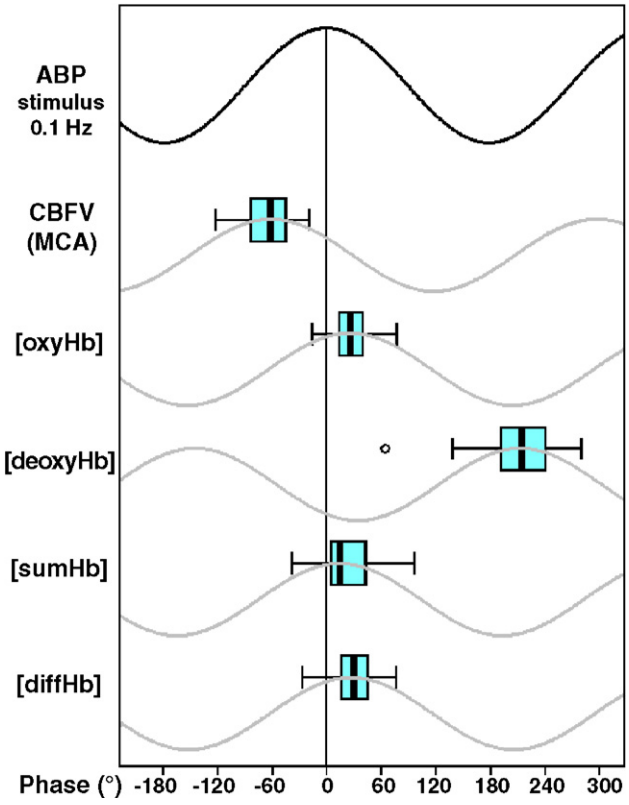

Fig. 2. Physiological phase relationship between oscillations in ABP and different cerebral hemodynamic parameters. Schematic illustration of oscillations. Data are shown as box-and-whiskers plots (median, boxes denote interquartile range, whiskers contain values extending no greater than 1.5 boxlengths from the upper and lower edge of the box, outliers [o] exceed this range). For *p*-values please see Table 2. At 0.1 Hz, a phase shift of 90° corresponds to 2.5 s in the time domain.

3.3. Influence of vascular risk factors

All available sides of patients and controls (max. $n=132$) were pooled. Analyzed phase lags were ABP–CBFV, ABP–[diffHb], CBFV–[diffHb], and [oxyHb]–[deoxyHb]. The presence of stenosis was a significant covariate for all

Table 2
Phase shift between ABP and NIRS oscillations in controls and patients with severe carotid obstruction

Phase shift at 0.1 Hz (°)	Controls (total $n=38$)		Carotid stenosis (total $n=28$)			*p*-values (H=healthy controls, I=stenosis ipsilateral, C=contralateral)
	Significant coherence		Significant coherence	Ipsilateral	Contralateral	
ABP–[oxyHb]	$n=38$	23.5±23.9	$n=27$	28.9±23.4	13.2±29.5	I vs. C: $p=0.25$, I vs. H: ns
ABP–[deoxyHb]	$n=38$	209.3±41.1	$n=22$	261.0±49.5	205.0±52.1	I vs. C: $p<0.001$, I vs. H: $p<0.001$
ABP–[sumHb]	$n=37$	22.6±30.5	$n=24$	19.6±21.6	10.5±30.3	ns
ABP–[diffHB]	$n=38$	25.9±22.4	$n=28$	43.1±35.8	17.2±30.0	I vs. C: $p=0.004$, I vs. H: $p=0.038$
ABP–CBFV	$n=38$	−64.6±26.1	$n=28$	−34.2±29.4	−66.8±29.4	I vs. C: $p<0.001$, I vs. H: $p=0.002$
CBFV–[oxyHb]	$n=38$	84.6±23.3	$n=26$	65.3±22.4	83.8±19.9	I vs. C: $p<0.001$, I vs. H: $p=0.003$
CBFV–[deoxyHb]	$n=37$	273.1±32.9	$n=24$	292.9±35.9	275.7±31.2	I vs. C: $p=0.001$, I vs. H: $p=0.034$
CBFV–[diffHb]	$n=38$	88.9±16.8	$n=28$	65.3±38.1	84.7±18.1	I vs. C: $p=0.002$, I vs. H: $p=0.001$
[oxyHb]–[deoxyHb]	$n=34$	191.5±44.0	$n=21$	239.5±45.8	199.9±50.4	I vs. C: $p<0.001$, I vs. H: $p<0.001$

Values are reported as mean±one standard deviation. ns=not significant. Due to a lack of significant coherence between the analyzed spectra at 0.1 Hz in individual patients and phase relations, the number of analyzed subjects varies. Patients were already excluded from the analysis if one side failed to show significant coherence, explaining the lower rate of analyzed data sets in comparison to controls.

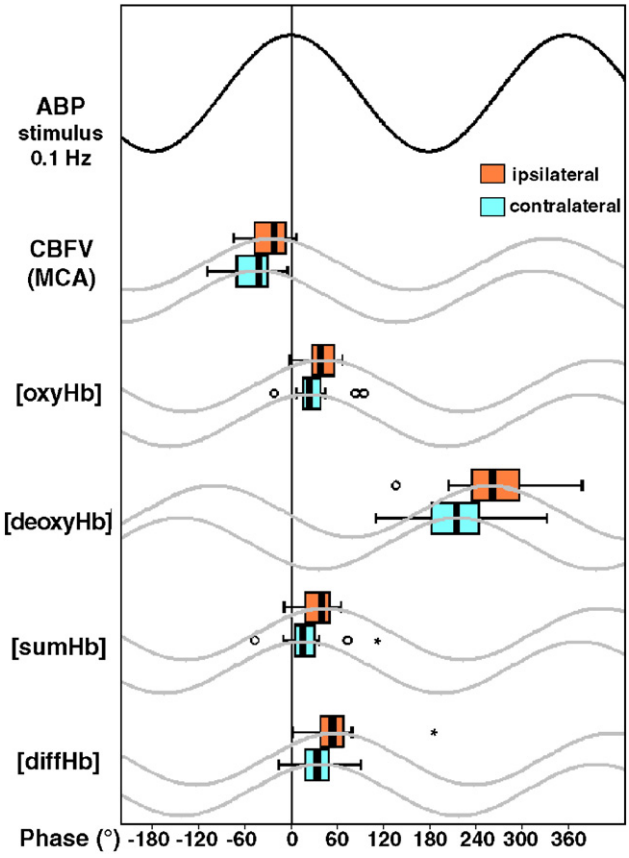

Fig. 3. Phase relationship between oscillations in ABP and different cerebral hemodynamic parameters in unilateral carotid obstruction. Ipsilateral=side of stenosis. Note the different scale compared with Fig. 2. Boxplots as described for Fig. 2. * denote extreme outliers (>3 boxlengths from left/right box edge). For *p*-values please see Table 2.

examined phases ($p=0.001$ or $p<0.001$). Only for phase $_{[oxyHb]-[deoxyHb]}$ a significant independent effect of hypertension ($p=0.035$) and diabetes ($p=0.006$) was observed with higher mean values of phase$_{[oxyHb]-[deoxyHb]}$ in these conditions.

4. Discussion

This study showed that: (1) physiologically, blood pressure-induced cortical microvascular oscillations assessed by NIRS follow those of macrovascular oscillations with a phase difference of 80–90° (mean); (2) oxy- and deoxyhemoglobin thereby oscillate in a counterphase; (3) hemodynamic compromise in carotid obstruction leads to delayed microvascular oscillations in comparison to ABP due to disturbed autoregulation and an abrogation of the oxy-/deoxyhemoglobin counterphase.

4.1. The blood pressure stimulus

To study the response of micro- and macrovascular hemodynamics to blood pressure oscillations a univocal stimulus is needed. We thus did not analyze spontaneous oscillations but used regular breathing of 6/min which leads to 0.1 Hz blood pressure oscillations of high power and interindividual stability [1,14] These oscillations are predominantly mechanically generated by respiratory-induced changes of pleural pressure and ventricular loading [16]. A univocal ABP stimulus is also advantageous because of the noise frequently observed in the NIRS signals reducing the coherence necessary for the applied cross-spectral methods. A limitation of the applied noninvasive finger plethysmography for measuring the ABP oscillations is that we do not know the actual shape and magnitude of perfusion pressure at the circle of Willis particularly in carotid stenosis. The phase shift approach, however, does not record amplitude changes. It solely reflects the temporal difference of cerebral hemodynamics to slow oscillations of ABP in the order of 1–3 s. This difference is reduced in carotid stenosis by 1–2 s, as discussed below. Though invasive experimental data are lacking, it is very unlikely from a hemodynamic point of view that such a large difference is due to delayed oscillations of poststenotic cerebral perfusion pressure.

4.2. Limitations of the NIRS method

When assessing cerebral hemodynamics by NIRS the potential contamination of the signal with extracranial tissue perfusion should be considered. ABP-related oscillations in skin perfusion might thus have been superimposed on those of intracranial tissue in the present study. Skin perfusion has been described to account for up to 16% of the NIRS signal and being dependent on the interoptode distance [17,18]. We used a wide distance of 50 mm and detected highly significant side-to-side differences of NIRS parameters in unilateral obstruction of the *internal* carotid artery and strong correlations to MCA flow velocity phases. We thus assume that a major contribution of the assessed NIRS signals is indeed due to cerebral hemodynamic changes and that the presented phase relations are not unduly influenced by skin flow contributions. Future studies might also use spatial resolved spectroscopy to get an optimal confinement to intracranial tissue.

Changes in [oxyHb], [deoxyHb] and particularly [diffHb] reflect predominantly changes of regional cerebral blood *flow* in the sampled tissue volume, while changes in total hemoglobin represent changes in local blood *volume* [19,20]. Furthermore, the NIRS parameters mirror the interaction between cerebral blood flow, cerebral blood volume and metabolic demands. However, a significant interference of these demands with the presently observed dynamic NIRS signal changes during the repetitive falls and rises of oscillating ABP seems unlikely due to their short time scale.

4.3. Physiological phase relations

Respiratory-induced oscillations of NIRS signals have been previously investigated with simultaneous ABP but not CBFV measurements in six healthy adults [21]. Though phase shifts were not reported, the illustrations resemble the

phase relation between ABP and NIRS parameters observed in our study. Looking at these NIRS oscillations, it seems at first sight that they follow passively those of ABP without any homeostatic autoregulatory interference. However, the present simultaneous analysis of CBFV oscillations in the MCA revealed that the NIRS parameters are closely related to the phase$_{ABP–CBFV}$ and not directly to ABP itself. The mechanism can be interpreted as follows: (1) oscillations in CBFV *precede* those in ABP most probably by fast changes of arteriolar resistance in reaction to the continuous 5 s rises and falls of ABP at 0.1 Hz. This rapid counteraction thus leads to compensatory CBFV changes *ahead* of those in ABP and a CBFV signal oscillation leading that of ABP by approx. 60° [3]. (2) Microvascular NIRS oscillations *follow* those of CBFV with a comparatively fixed phase of ≈80–90° (corresponding to a time delay of ≈2.2–2.5 s). This results in the paradoxical constellation that in the case of a normal autoregulatory CBFV phase lead against ABP the *NIRS* oscillations peak shortly *after* those of ABP but are actually also due to *dynamic* autoregulatory action occurring more than 2 s earlier. It should well be noted that due to the continuously alternating brief falls and rises of ABP during regular breathing the eventual *static* result of autoregulatory action, i.e., homeostasis of cerebral blood flow, is not achieved. We can rather observe the steady effort of the autoregulatory system to counterregulate.

The oscillations of [oxyHb] and [deoxyHb] showed a counterphase relationship. This inverse coupling pattern can also be seen in forehead NIRS recordings during deep breathing in the study of Elwell et al. [21] and at least temporarily during resting spontaneous oscillations in this region [22]. Its physiological interpretation may be that ABP oscillations lead to increasing cerebral blood flow and volume (as indicated by [diffHb], [oxyHb] and [sumHb] increase) which in turn leads to increased washout of [deoxyHb] and thus decreases its concentration.

4.4. Pathophysiological phase relations

Patients with one-sided severe carotid obstruction were analyzed because they represent a model for unilaterally reduced cerebral perfusion pressure, arteriolo-capillary dilation and thus potentially impaired cerebral autoregulation. The extent of hemodynamic impairment in these patients, however, is still heterogeneous because of presumable differences in collateral flow compensation [23]. Confirming previous studies, we found a diminished phase lead of CBFV vs. ABP oscillations indicating partial loss of dynamic autoregulatory ability [24,25]. In line with the reduction of the phase$_{ABP–CBFV}$, the phase between ABP and NIRS parameters increased significantly, thereby also reflecting the autoregulatory disturbance.

The physiological coupling of blood pressure related [oxyHb] and [deoxyHb] oscillations was disturbed on affected sides with a longer latency (phase) to decreases in [deoxyHb]. Without functional activation a metabolic cause seems unlikely and there are no previous investigations regarding this phenomenon. Since decreases in [deoxyHb] may be interpreted as due to increased washout by augmented inflow one may assume an additional delay at the arteriolo-capillary level probably due to local vasodilation with increased blood volume and slow local blood flow.

In addition, multivariate analysis showed that vascular risk factors diabetes and hypertension are independently associated with a higher phase lag between oscillations of oxy- and deoxyhemoglobin. This might be attributed to additional cerebral small vessel disease, which reduces microvascular reagibility [10,26]. As a clear limitation, however, we did not control for the actual presence of cerebral small vessel disease by neuroimaging and further research on this association is needed.

4.5. Implications for magnetic resonance imaging (MRI) studies

NIRS and the blood oxygen level dependent (BOLD)-MRI signal both reflect changes in [deoxyHb]. Future studies may examine whether a specific side-to-side phase desynchronization of BOLD signal oscillations induced by regular breathing can be mapped in patients with unilateral severe carotid obstruction to identify distinct areas of hemodynamic compromise and relate them to functional activity.

5. Conclusions

Cortical microvascular hemodynamic responses to blood pressure oscillations follow specific phase relationships due to cerebral autoregulatory action and circulatory transit times. In case of impaired hemodynamics, as in unilateral carotid obstruction, these phases are significantly changed reflecting disturbed autoregulation.

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