

Partial pharmacologic blockade shows sympathetic connection between blood pressure and cerebral blood flow velocity fluctuations

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Abstract

Cerebral autoregulation (CA) dampens transfer of blood pressure (BP)-fluctuations onto cerebral blood flow velocity (CBFV). Thus, CBFV-oscillations precede BP-oscillations. The phase angle (PA) between sympathetically mediated low-frequency (LF: 0.03-0.15 Hz) BP- and CBFV-oscillations is a measure of CA quality. To evaluate whether PA depends on sympathetic modulation, we assessed PA-changes upon sympathetic stimulation with and without pharmacologic sympathetic blockade.

In 10 healthy, young men, we monitored mean BP and CBFV before and during 120-seconds cold pressor stimulation (CPS) of one foot (0°C ice-water). We calculated mean values, standard deviations and sympathetic LF-powers of all signals, and PAs between LF-BP- and LF-CBFV-oscillations. We repeated measurements after ingestion of the adrenoceptor-blocker carvedilol (25 mg). We compared parameters before and during CPS, without and after carvedilol (analysis of variance, post-hoc t-tests, significance: $p < 0.05$).

Without carvedilol, CPS increased BP, CBFV, LF-BP- and LF-CBFV-powers, and shortened PA. Carvedilol decreased resting BP, CBFV, BP-LF- and CBFV-LF-powers, while PAs remained unchanged. During CPS, BPs, CBFVs, BP-LF- and CBFV-LF-powers were lower, while PAs were longer with than without carvedilol. With carvedilol, CPS no longer shortened resting PA.

Sympathetic activation shortens PA. Partial adrenoceptor blockade abolishes this PA-shortening. Thus, PA-measurements provide a subtle marker of sympathetic influences on CA and might refine CA evaluation.

Key words

sympathetic nerve activity; pharmacologic stress; blood pressure; cerebral blood flow velocity; phase angle

Abbreviations

CA:	cerebral autoregulation
BP:	blood pressure
CBFV:	cerebral blood flow velocity
CPS:	cold pressor stimulation
ETCO ₂ :	end-tidal carbon dioxide levels
HF:	high-frequency
LF:	low-frequency
PA:	phase angle
RRI:	RR-interval
SD:	standard deviation
TCD:	transcranial Doppler sonography

1. Introduction

Cerebral autoregulation (CA) assures constant cerebral blood flow in the face of changing blood pressure (BP) [1, 2], and is altered in neurovascular disorders [3-7]. Under physiologic conditions, various components, such as myogenic, endothelial and neurogenic, primarily sympathetic mechanisms, contribute to dampening the transfer of BP fluctuations onto CBFV [8-10].

While there is controversy regarding the autonomic contribution to static cerebral autoregulation, operating over several minutes [2, 11-14], there is increasing evidence that sympathetic innervation contributes to the dynamic component of cerebral autoregulation, i.e. to the mechanisms maintaining stable cerebral blood flow in response to transient blood pressure changes that occur within several seconds, e.g. upon standing-up [15-19].

To ascertain stable cerebral perfusion, autoregulation buffers the effects of BP changes onto CBFV and keeps CBFV fluctuations significantly smaller than BP fluctuations [1, 20, 21].

The CA dynamics can be compared with a high-pass filter, which dampens slow BP changes more prominently than rapid BP perturbations [10, 16, 20, 22, 23]. Since the buffering effects of CA are frequency-dependent, CA quality can be evaluated by comparing BP and CBFV oscillations in the frequency domain [10, 16, 20, 22, 23].

The high-pass filter characteristics of autoregulation shift CBFV-oscillations to the left of corresponding BP-oscillations [20, 22, 24-26]. Therefore, buffered maxima or minima of CBFV-oscillations occur prior to maxima or minima of corresponding BP-oscillations [1, 20, 22].

The shift between “leading” CBFV-oscillations and “lagging” BP-oscillations [1, 20, 22] can be reliably assessed as phase angle (PA) between sinusoidal, sympathetically mediated BP- and CBFV-oscillations that occur in the so-called low frequency (LF) range from 0.03 to 0.15 Hz [1, 10, 16, 20, 27, 28]. PA between coherent LF-oscillations of BP and CBFV constitutes a valid measurement tool of CA [1, 10, 20, 22, 29-31]. Normally, PA between LF-oscillations of BP and CBFV ranges from -30° to -90° [1, 22, 29, 31, 32]. However, cerebrovascular pathology, for example cerebrovascular stenosis [22] or cerebral angiopathy with progressive intracranial artery

stiffening [30], is associated with compromised CA and causes PA reduction due to impaired dampening of BP fluctuations and a more passively driven change in CBFV that follows changes in BP [22, 31].

However, even in healthy persons, the change in body position from supine to standing decreases the PA between LF-oscillations of BP and CBFV [29]. Cencetti and co-workers therefore assumed that an increase in sympathetic activity as induced e.g. during standing-up can decrease PA [29].

During phenylephrine-induced BP increases, Zhang et al. also found PA decreases associated with increased cerebrovascular resistance [17].

Improved understanding of mechanisms underlying PA-changes promises clinical relevance for a refined assessment of cerebrovascular diseases, particularly diseases with altered sympathetic activity, e.g. subarachnoid hemorrhages [10, 33-37].

Since BP- and CBFV-oscillations in the LF-range are associated with sympathetic activity [10, 20, 38, 39], we hypothesize that changes in the PA between coherent LF-oscillations of BP and CBFV are also related to changes in sympathetic activity.

To evaluate this hypothesis, we tested whether the PA between LF-BP- and LF-CBFV-oscillations decreases with sympathetic stimulation and - if so - whether such PA-decrease attenuates upon partial pharmacologic sympathetic blockade.

2. Material and Methods

2.1. Subjects

Ten healthy men (mean age 25 ± 2 years) participated in the study. No participant had any disease or took medication affecting the cardiovascular or autonomic nervous system. Before testing, participants underwent physical examination (Wasmeier G), duplex sonography of the extracranial carotid and vertebral arteries to rule out vascular pathologies, a 12-lead electrocardiogram and an echocardiogram ruling out cardiac abnormalities. Transcranial Doppler sonography (TCD) at the temporal and suboccipital windows confirmed normal intracranial CBFVs of the vertebral, basilar, middle, posterior, and anterior cerebral arteries [10].

2.2. Procedures

Studies were performed in a quiet room with 24°C ambient temperature and stable humidity. Initially, participants rested in supine position for 45 minutes to ensure cardiovascular stability while monitoring devices were applied [10].

For 5 minutes at rest and during 120-second cold pressor stimulation (CPS, see below), we continuously recorded electrocardiographic RR-intervals (RRI) using a 5-lead ECG. We non-invasively monitored mean arterial BP by radial artery-tonometry with calibration at the brachial artery [8]. End-tidal carbon dioxide levels (ETCO_2) were monitored using infrared spectrometry via nasal cannulae (Colin Pilot, San Antonio, TX). Mean CBFV of the proximal middle cerebral artery (MCA) was assessed by 2 MHz transcranial Doppler sonography (TCD; Multidop XL, DWL, Germany) through the temporal window, approximately 1 cm above the zygomatic arch at a depth of 35 to 55 mm. The Doppler probe was attached to the skull at a fixed angle using a headband with adjustable positioning system. Respiratory frequency was monitored by inductance plethysmography using 2 calibrated belts attached around the thorax and abdomen (Respirace Calibrator, Ambulatory Monitoring Inc., Ardsley, NY) [8, 10].

From 60-second intervals at rest and during the last 60 seconds of the 120-second CPS, we calculated mean values and standard deviation of all bio-signals.

2.3 Data acquisition and analysis

Data were digitized by a custom-made analogue-to-digital converter at a sampling rate of 300 Hz and fed to a Macintosh PowerBook computer (Apple Inc.), manually cleaned from artifacts by linear interpolation and stored for offline analysis [40]. A C-language program identified all electrocardiographic QRS-complexes in each sequence, located the peak of each R-wave and calculated consecutive RRIs. From the continuous waveforms of all parameters, beat-to-beat mean values were calculated and interpolated linearly between adjacent values to construct a corresponding continuous time series [40].

RRI-, BP- and CBFV-values show underlying fluctuations that are largely mediated by undulating activity of the sympathetic and parasympathetic nervous systems [20]. These underlying fluctuations were characterized by autoregressive analysis using a linear detrending option and model order estimation according to Akaike information criteria [41]. The autoregressive algorithm reliably estimates the frequencies and powers of the relevant oscillations within a single segment based on a relatively small amount of data that still assures signal-stationarity [40]. To meet requirements of signal-stationarity, we maintained a 45 min. resting period and performed autoregressive bivariate analysis with an adequate model order of 12 which is suited for analysis of short-term data, e.g. of only 60 seconds, and allows for a better frequency resolution than simpler Fourier-based approaches [42, 43].

Parasympathetic, respiratory influences are considered to account for RRI-modulation in the so-called high-frequency (HF-) range between 0.15 and 0.5 Hz, as parasympathetic modulation of RRIs is most pronounced at the frequency of respiration [20, 38]. Therefore, we used RRI-modulation in the HF-range as index of parasympathetic modulation [20, 38]. In contrast, BP-fluctuations in the HF-range are primarily a mechanical consequence of respiration-induced

increases in venous return and stroke volume [20, 38, 44]. While parasympathetic influences on RRI may still occur at frequencies below 0.15 Hz, BP- and CBFV-fluctuations in the so-called low-frequency (LF-) range between 0.03 and 0.15 Hz are considered to be related to sympathetic outflow only [10, 20, 38]. Therefore, we determined the degree of sympathetic signal-modulation from the amount of LF-BP- and LF-CBFV-modulation [20, 38].

Sympathetic and parasympathetic influences on RRI-, BP- and CBFV-variability were assessed by quantifying the LF- and HF-components of the bio-signals. The magnitude of sympathetic or parasympathetic modulation was determined as integral under the power spectral density curves [8, 20, 38].

Additionally, we calculated the PA between LF-oscillations in BP and CBFV reflecting the integrity of cerebral autoregulation (CA) [10, 30, 40, 43, 45] using the algorithm described by SLJ Marple [45] and applied in many previous studies assessing PA as a parameter of cerebral autoregulation [10, 24, 25, 29, 30, 40, 43, 46].

Dynamics of autoregulation can be compared with a high-pass filter [20, 22]. Rapid BP-perturbations are transferred onto CBFV, whereas slow BP-changes below 0.07 Hz are dampened [10, 16, 22, 23]. As mentioned above, the relation between BP- and CBFV-oscillations can be described by calculating PA between the leading CBFV- and the lagging BP-signal [22].

Coherence between BP- and CBFV-oscillations might span from 0 (no association) to 1 (maximal association) [40]. Two signals were considered to have a stable phase relation for a given frequency of oscillation if coherence was above 0.5 [40].

To calculate PAs at the most coherent frequency-peak within the LF range, we used the following formula [40]: $\theta(f) = \tan^{-1}[\text{Im}\{\Phi_{xy}(f)\} / \text{Re}\{\Phi_{xy}(f)\}]$, where $\theta(f)$ is the phase angle (PA), $\text{Im}\{\Phi_{xy}(f)\}$ and $\text{Re}\{\Phi_{xy}(f)\}$ represent the image and real part of the transfer function respectively [45].

Before and after pharmacological blockade (as described below), we assessed CPS-induced changes in PA between BP-oscillations and CBFV-oscillations in the LF-range, i.e. the frequency range that is considered to reflect oscillations mediated by sympathetic outflow [10, 47].

2.4. Cold pressor stimulation (CPS) without and with partial sympathetic blockade

To assess whether changes in the PA between sympathetically mediated LF-oscillations of BP and CBFV reflect changes in sympathetic influences on cerebral autoregulation, we used CPS as a stimulus that induces sympathetic activation [48, 49]. On two consecutive days, we evaluated CPS-related changes in bio-signals and PA without and with partial sympathetic blockade using the alpha- and beta-adrenoceptor-blocker carvedilol. In one session, we tested CPS effects on RRIs, BPs and CBFVs and on LF- and HF-spectral powers of RRIs, BPs, and CBFVs without sympathetic blockade; in the other session we assessed CPS-effects two hours after participants had orally taken 25 mg carvedilol in order to evaluate whether the alpha- and beta-adrenoceptor-blocker affects the recorded bio-signals and the PA between sympathetically mediated LF-oscillations in BP and CBFV.

After the 45-minute resting-period, participants immersed one foot up to the ankles into ice-water with a temperature of 0-1 °C for 120 seconds. Since changes in carbon dioxide levels alter the diameter of cerebral vessels and thus cerebral blood flow velocity [2], participants were instructed not to hold their breath but to maintain their normal breathing pattern during the entire test.

After the test, participants rated their level of discomfort or pain perception on a scale from 1 to 10 with 1 as the lowest and 10 as the highest level of discomfort or pain [48].

2.5. Statistical analysis

We used the Kolmogorov-Smirnov test to test for normal distribution of data. Normally distributed data are presented as mean \pm standard deviation (SD). Differences in cardiovascular parameters between measurements performed without and with pharmacologic blockade were evaluated by

analysis of variance for repeated measurements (ANOVA, general linear model), with “CPS” (before and during CPS) as first within subject factor and “blockade” (with and without pharmacologic blockade) as second within subject factor. Suitability of the ANOVA model was assessed by Mauchly's Test of Sphericity. In case of violation of the sphericity assumption, the Greenhouse-Geisser-correction was employed. In case of significant ANOVA results, post-hoc single comparisons were performed using t-test for paired groups and normally distributed data or the Wilcoxon-test in case of not normally distributed data. A commercially available statistical program (SPSS™, SPSS Inc., Chicago, Ill, USA) was used for data analysis. Significance was set at $p < 0.05$ [10].

3. Results

Cold stimulation was perceived by all participants. On the 1 to 10 scale of discomfort and pain, participants indicated similar discomfort in the session without and the session with partial sympathetic blockade (7.4 ± 1.3 vs. 6.9 ± 0.7 , $p > 0.05$, Table 1).

3.1. Cardio- and cerebrovascular responses to CPS without carvedilol medication

Without carvedilol, CPS significantly accelerated heart rate, i.e. decreased RRIs (1018.8 ± 164.8 vs. 865.1 ± 162.9 ms), and increased BP (83.7 ± 7.3 vs. 98.3 ± 11.3 mmHg) and CBFV (55.3 ± 20.7 vs. 62.6 ± 22.1 cm s⁻¹; $p < 0.05$). ETCO₂ remained unchanged ($p > 0.05$).

Moreover, CPS significantly increased LF-powers of RRIs (1338.1 ± 1455.5 vs. 2546.1 ± 2700.1 ms²), of BP (4.0 ± 3.6 vs. 7.4 ± 7.9 mmHg²) and of CBFV (5.2 ± 2.6 vs. 11.7 ± 7.1 cm² s⁻²) ($p < 0.05$), but did not change HF-powers of RRIs, BP and CBFV ($p > 0.05$).

During CPS, PA between BP- and CBFV-oscillations in the LF-range was significantly smaller ($-34.3 \pm 18.3^\circ$) than PA at baseline, without stimulation ($-53.0 \pm 20.1^\circ$, $p < 0.05$, Table 1, Fig. 1).

3.2. Effect of carvedilol medication on cardio- and cerebrovascular parameters at baseline

At rest, carvedilol intake resulted in higher RRIs (1018.8 ± 164.8 vs. 1110.9 ± 177.9 ms), i.e. slower heart rates, and lower BPs (83.7 ± 7.3 vs. 77.2 ± 6.7 mmHg) and CBFVs (55.3 ± 20.7 vs. 46.7 ± 21.0 cm s⁻¹) ($p < 0.05$). ETCO₂ at baseline was similar with and without carvedilol ($p > 0.05$).

Carvedilol also lowered resting LF-powers of RRIs (1338.1 ± 1455.5 vs. 489.1 ± 390.5 ms²), of BP (4.0 ± 3.6 vs. 2.3 ± 2.9 mmHg²) and of CBFV (5.2 ± 2.6 vs. 3.3 ± 1.6 cm² s⁻²) ($p < 0.05$), but did not change resting HF-powers of RRIs, BP and CBFV ($p > 0.05$, Table 1).

At rest, the PA between BP- and CBFV-oscillations in the LF-range was similar without ($-53.0 \pm 20.1^\circ$) and with carvedilol ($-62.3 \pm 26.1^\circ$; Table 1), i.e. the carvedilol induced PA-increase was not significant ($p > 0.05$, Fig. 1).

3.3. Effect of carvedilol on cardio- and cerebrovascular parameters during CPS

With partial pharmacologic blockade, CPS still decreased RRIs (1110.9 ± 177.9 vs. 1041.5 ± 185.4 ms), i.e. increased heart rate, and increased BP (77.2 ± 6.7 vs. 88.2 ± 11.1 mmHg) and CBFV (46.7 ± 21.0 vs. 51.8 ± 20.4 cm s⁻¹) from baseline-values ($p < 0.05$, Table 1). ETCO₂ during CPS again was similar with and without carvedilol ($p > 0.05$).

However, during CPS, signal-values were higher with than without carvedilol for RRIs (1041.5 ± 185.4 vs. 865.1 ± 162.9 ms), and lower with than without carvedilol for BP (88.2 ± 11.1 vs. 98.3 ± 11.3 mmHg) and CBFV (51.8 ± 20.4 vs. 62.6 ± 22.1 cm s⁻¹, $p < 0.05$, Table 1).

Carvedilol also affected spectral powers of RRI, BP and CBFV. After carvedilol, CPS still increased LF-powers of RRIs (489.1 ± 390.5 vs. 948.9 ± 1055.9 ms²), BP (2.3 ± 2.9 vs. 3.3 ± 3.2 mmHg²) and CBFV (3.3 ± 1.6 vs. 5.8 ± 3.4 cm² s⁻²) from baseline-values ($p < 0.05$, Table 1). However, during CPS, LF-powers were lower with than without carvedilol for RRI- (948.9 ± 1055.9 vs. 2546.1 ± 2700.1 ms²), BP- (3.3 ± 3.2 vs. 7.4 ± 7.9 mmHg²) and CBFV- (5.8 ± 3.4 vs. 11.7 ± 7.1 cm² s⁻²) oscillations ($p < 0.05$). In contrast, neither carvedilol nor CPS changed HF-powers of RRIs, BP and CBFV ($p > 0.05$, Table 1).

During CPS, carvedilol increased or widened PA between LF-BP- and LF-CBFV-oscillations from $-34.3 \pm 18.3^\circ$ without sympathetic blockade to $-57.0 \pm 23.8^\circ$ with partial sympathetic blockade ($p < 0.05$, Table 1). After blockade, there was no difference between the PA during CPS and the PA at rest ($p > 0.05$, Table 1, Fig. 1).

4. Discussion

Our data add to the increasing evidence that sympathetic innervation contributes to the dynamic component of cerebral autoregulation [15-19] and confirm our previous findings that 0.1 Hz CBFV oscillations are related to sympathetic modulation [10]. The results moreover show that the PA between sympathetically mediated LF-oscillations of BP and CBFV decreases with sympathetic activation, induced by cold pressor stimulation, and that partial sympathetic blockade completely abolishes the CPS-induced decrease in PA.

At first sight, changes in PA, BP and CBFV from baseline values without sympathetic blockade to baseline values with blockade seem to suggest a discrepancy: Partial sympathetic blockade did not significantly change baseline PA values ($-62.3 \pm 26.1^\circ$) from values without blockade ($-53.0 \pm 20.1^\circ$; $p > 0.05$) and thus indicated preserved autoregulation. In contrast, baseline values of BP (83.7 ± 7.3 mmHg) and CBFV (55.3 ± 20.7 cm s⁻¹) decreased significantly upon sympathetic blockade (to 77.2 ± 6.7 mmHg and to 46.7 ± 21.0 cm s⁻¹ respectively). One might assume that the decrease in CBFV results from the BP decrease and thus indicates compromised cerebral autoregulation.

However, several studies show 15% to 20 % changes in CBFV upon BP decreases during orthostasis [21, 25, 50-53] or ganglion blockade [15, 54] or in association with drug-induced BP increases [55], and demonstrate that CBFV changes may be discrepant or even diametrical to BP changes in healthy persons with intact cerebral autoregulation [21, 50, 51, 54].

During increasing orthostatic challenge induced by increasing levels of lower body negative pressure (LBNP) stimulation, Levine and co-workers showed an increase in mean blood pressure (from 82 ± 2 mmHg to 88 ± 3 mmHg, mean \pm SEM) but a decrease in CBFV by up to $15.5 \pm 5\%$ [50].

In 13 healthy persons aged 21 to 38 years, Immink et al. observed a significant increase in mean BP upon standing-up from 80 ± 2 mmHg to 88 ± 3 mmHg (mean \pm SEM, $p < 0.05$) while CBFV decreased significantly from 65.3 ± 3.8 cm s⁻¹ to 54.6 ± 3.3 cm s⁻¹, i.e. by 16.4% [51]. In healthy controls, aged 23 to 51 years, Mahony et al. induced a 26.4 ± 7.1 mmHg step-drop in mean BP by means of the thigh-cuff method, i.e. after release of 2 minute blood flow occlusion to the lower extremities, and

recorded a decrease in CBFV by $15.6 \pm 5.8 \text{ cm s}^{-1}$ that preceded BP decrease by more than 2 seconds [56]. In 11 healthy controls, aged 24.1 ± 0.6 years, Medow et al. induced a 10% increase in mean BP with intravenous phenylephrine infusion, and recorded a significant increase in CBFV by 10.6% ($P < 0.05$) [55]. In 15 healthy persons, aged 30.7 ± 1.7 years (mean \pm SEM), Schondorf et al. recorded a significant increase in diastolic BP by $14.1 \pm 1.7 \text{ mmHg}$ ($p < 0.0001$) and a slight increase in systolic BP by $3.4 \pm 4.1 \text{ mmHg}$ upon head-up tilt, while there was a significant decrease in systolic CBFV by $-20.0 \pm 3.4 \text{ cm s}^{-1}$ ($p = 0.0001$) and in diastolic CBFV by $-8.8 \pm 2.0 \text{ cm s}^{-1}$ ($p = 0.0006$) [21]. In one of our previous studies assessing LBNP effects in healthy persons and type II diabetic patients, we even saw that CBFV decreased in healthy persons from $47.4 \pm 18.8 \text{ cm s}^{-1}$ at baseline to $40.7 \pm 13.3 \text{ cm s}^{-1}$ during -40 mmHg LBNP although mean BP did not drop during -40 mmHg LBNP stimulation ($92.0 \pm 16.9 \text{ mmHg}$) but remained unchanged from baseline BP values ($91.8 \pm 12.7 \text{ mmHg}$) [25]. In a study assessing cardio- and cerebrovascular responses to 180 seconds head-up tilt in patients with Familial Dysautonomia (i.e. Riley Day syndrome) and in healthy controls [53], our healthy participants showed a significant decrease in mean CBFV from $65.4 \pm 8.9 \text{ cm s}^{-1}$ to $58.6 \pm 8.3 \text{ cm s}^{-1}$ while mean BP did not drop but even slightly – though not significantly - increased from $72.3 \pm 7.6 \text{ mmHg}$ to $77.0 \pm 17.2 \text{ mmHg}$.

Thus, the 15.6% decrease in CBFV seen in our study upon partial sympathetic blockade at rest is not necessarily a direct response to the 7.8% decrease in BP but might also reflect a response to the partial sympathetic blockade which seems to cause MCA dilatation - and thus CBFV slowing - at the insonated, proximal artery where the density of alpha-adrenergic sympathetic innervation is higher than at distal, small cerebral arteries [1, 9, 57-60].

The above mentioned variability of BP and CBFV changes upon orthostatic challenge [21, 25, 50, 51, 53, 54], with no change or a decrease in one or both signals, or even diametrical changes, indicates that changes in CBFV within a limit of 15% to 20% are poorly suited to determine the quality of cerebral autoregulation. In contrast, the phase angle between 0.1 Hz sinusoid BP

oscillations and 0.1 Hz sinusoid CBFV oscillations proves to be a better suited parameter to assess the quality of cerebral autoregulation [10, 22, 24, 29, 30, 40, 43].

The 120-second cold pressor stimulation was sufficient to induce sympathetic activation as shown by the increases in heart rate (HR), BP [48, 61] and CBFV [62], and in the powers of sympathetically mediated LF-oscillations of RRI, BP and CBFV [10, 20, 38, 39].

The resulting PA-shortening might be ascribed to various mechanisms. One explanation may be the fact that higher LF-fluctuations of BP and CBFV during CPS are not buffered as early as are less pronounced LF-fluctuations recorded under baseline conditions [1, 9, 20, 22, 29, 31, 62]. Consequently, the PA between the leading LF-fluctuations of CBFV and the lagging LF-fluctuations of BP is smaller during than before CPS [1, 20, 22].

Moreover, the CPS-induced BP increase itself might contribute to the PA shortening. Higher BP or pulse pressure augments the myogenic tone in large cerebral arteries and small cerebral arterioles [63] resulting in increased cerebrovascular resistance and decreased vascular compliance. The BP-induced changes in visco-elastic properties of cerebral arteries may again alter CBFV-oscillations and in turn affect the PA [17]. “Stiffening” of intracerebral vessels caused by BP increases might shorten PA similar to the mechanisms that shorten PA in patients with intracranial arteriosclerotic stenosis [22].

While the carvedilol-induced BP attenuation, i.e. the decrease in the input-signal of cerebral autoregulation, may also result in reduced myogenic autoregulatory responses, with less resistance and increased compliance of cerebral arteries [17], such direct effects of BP changes on PA seem to be minor. During head-up tilt, Cencetti et al. also saw shortening of the PA between LF-oscillations in CBFV and BP [29]. During orthostatic challenge, the authors observed a slight BP decrease but a significant increase in sympathetically mediated LF-BP- and LF-CBFV-oscillations [29]. Therefore, the PA-shortening cannot be ascribed to any BP increase. Instead, Cencetti et al. assume that PA-shortening reflects stiffening of intracerebral vessels induced by increased sympathetic activity [29].

Moreover, changes recorded upon CPS–induced sympathetic activation but concurrent sympathetic blockade do not suggest a major direct contribution of BP to PA-changes. Despite carvedilol application, CPS still significantly increased BP from values prior to CPS. Thus, the 25mg carvedilol only induced a partial sympathetic blockade. Nevertheless, even such partial sympathetic blockade was sufficient to completely abolish PA-shortening during CPS (Table 1).

Consequently, our data not only confirm the conclusion of Cencetti and co-workers that PA-shortening during sympathetic challenge may be ascribed directly to increased sympathetic activation. The completely abolished PA response to even partial sympathetic blockade suggests that even gradual changes in sympathetic activity may alter PA.

While Cencetti et al. presume that PA-shortening upon sympathetic activation is due to “stiffening” of distal cerebral vessels [29], we assume that there are opposing sympathetic effects on proximal, cerebral artery segments and on the distal cerebral arterioles.

Sympathetic innervation is denser and primarily alpha-adrenergic at the proximal cerebral arteries than at the distal, primarily beta2-adrenergic cerebral arterioles [1, 9, 57-60]. Thus, the CPS associated CBFV increase and PA-shortening are likely to result from sympathetically mediated alpha-adrenergic vasoconstriction at the proximal MCA, i.e. at the site of our TCD-insonation, and from beta-adrenergic vasodilatation at distal cerebral resistance vessels [1, 10].

After carvedilol, the absence of CPS-induced PA-shortening very likely also results from diametric carvedilol effects on large, proximal and small, distal cerebral vessels. Carvedilol has a 2- to 3-times higher selectivity for beta- than alpha-receptors [64]. Yet, the higher density of alpha-adrenergic nerve terminals at proximal cerebral arteries and the lower density of predominantly beta-adrenergic nerve terminals at distal cerebral arterioles may outweigh the carvedilol specific differences in alpha- and beta-receptor selectivity [1, 9, 62]. Therefore, not only the CBFV increase and PA-shortening upon sympathetic activation seem to result from combined proximal vasoconstriction and distal vasodilatation of cerebral vessels. After carvedilol, the absent PA-shortening and the attenuated CBFV increase during CPS also seem to result from partial blockade

of proximal vasoconstrictor and distal vasodilator activity. Mitigated proximal vasoconstriction as well as distal vasodilatation after carvedilol both explain the attenuated CBFV increase at the site of TCD-insonation during CPS [64].

5. Conclusions

Our data show that sympathetic stimulation shortens the PA between sympathetically mediated LF-oscillations of CBFV and BP, while partial alpha- and beta-adrenergic blockade that is insufficient to fully block BP-increases during sympathetic stimulation still abolishes PA-shortening.

We therefore conclude that shortening of the PA between LF-oscillations of CBFV and BP during sympathetic stimulation such as CPS may serve as a measure of sympathetic effects on the proximal and distal cerebral arteries.

Assessing the PA between coherent BP- and CBFV-oscillations in the LF-range might be clinically relevant and could provide an early marker of altered cerebrovascular autoregulation [1, 20, 30, 31].

6. Study limitation

One limitation of our study arises from the TCD technology that does not directly assess diameter-changes in the insonated, proximal nor in the distal MCA-segments. Although changes in the proximal MCA diameter seem to contribute less to CBFV changes than do changes in the distal resistance vessels, a CBFV-increase measured at the proximal MCA segment might reflect not only an increased diameter in downstream resistance vessels, but also a decrease in the proximal MCA diameter [1, 10, 65-71].

Moreover, our results only show sympathetic effects on the phase angle between BP- and CBFV-oscillations at frequencies between 0.04 and 0.15 Hz in response to dynamic BP changes occurring within seconds. Yet, the study cannot determine whether sympathetic activity also has a relevant effect on cerebral blood flow adjustment over an extended period of time, i.e. on CA under steady state conditions.

7. Ethical standards

The study has been approved by the ethics committee of the University of Erlangen-Nuremberg and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their written informed consent prior to their inclusion in the study.

8. Conflicts of interest

Max J. Hilz: The author received research support from Genzyme Corp. Cambridge, MA, USA, Bayer HealthCare, Berlin, Germany and Novartis Pharma GmbH, Nuremberg, Germany. The author received speaker and consulting honoraria from Genzyme Corp. Cambridge, MA, USA.

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Figure captions

Fig. 1

Phase angle between sympathetically mediated LF-oscillations of blood pressure (BP) and cerebral blood flow velocity (CBFV) in 10 young, healthy volunteers before and during cold pressor stimulation (CPS) without and after oral intake of 25 mg carvedilol.

Data are expressed in box plots. Without carvedilol, the phase angle was significantly smaller during than before CPS. This significant phase angle decrease upon CPS without carvedilol is indicated by an asterisk (*). The phase angle before CPS was similar with and without carvedilol. However, carvedilol increased (or widened) the phase angle during CPS ($p < 0.05$), and the phase angle during CPS no longer differed from the phase angle before CPS (analysis of variance, post-hoc t-tests).

Table 1

Level of discomfort and cardiovascular parameters in 10 young, healthy volunteers before and during cold pressor stimulation without and after oral intake of 25 mg carvedilol.

<i>Parameter</i>		<i>before cold pressor stimulation</i>	<i>during cold pressor stimulation</i>	<i>t-test or Wilcoxon -test</i>
level of discomfort	without carvedilol		7.4 ± 1.3	
	with carvedilol		6.9 ± 0.7	
RRI	without carvedilol	1018.8 ± 164.8*	865.1 ± 162.9*	p < 0.05
[ms]	with carvedilol	1110.9 ± 177.9*	1041.5 ± 185.4*	p < 0.05
BP	without carvedilol	83.7 ± 7.3*	98.3 ± 11.3*	p < 0.05
[mmHg]	with carvedilol	77.2 ± 6.7*	88.2 ± 11.1*	p < 0.05
CBFV	without carvedilol	55.3 ± 20.7*	62.6 ± 22.1*	p < 0.05
[cm s ⁻¹]	with carvedilol	46.7 ± 21.0*	51.8 ± 20.4*	p < 0.05
ETCO ₂	without carvedilol	35.1 ± 1.0	34.9 ± 1.4	p > 0.05
[mmHg]	with carvedilol	35.2 ± 1.6	34.9 ± 1.7	p > 0.05
LF-powers of RRI	without carvedilol	1338.1 ± 1455.5*	2546.1 ± 2700.1*	p < 0.05
[ms ²]	with carvedilol	489.1 ± 390.5*	948.9 ± 1055.9*	p < 0.05
HF-power of RRI	without carvedilol	1189.5 ± 1650.4	1257.9 ± 2196.1	p > 0.05
[ms ²]	with carvedilol	1287.9 ± 1383.1	1437.7 ± 2154.5	p > 0.05
LF-power of BP	without carvedilol	4.0 ± 3.6*	7.4 ± 7.9*	p < 0.05
[mmHg ²]	with carvedilol	2.3 ± 2.9*	3.3 ± 3.2*	p < 0.05
HF-power of BP	without carvedilol	0.4 ± 0.2	0.7 ± 0.7	p > 0.05
[mmHg ²]	with carvedilol	0.4 ± 0.2	0.6 ± 0.4	p > 0.05
LF-power of CBFV	without carvedilol	5.2 ± 2.6*	11.7 ± 7.1*	p < 0.05
[cm ² s ⁻²]	with carvedilol	3.3 ± 1.6*	5.8 ± 3.4*	p < 0.05
HF-power of CBFV	without carvedilol	1.5 ± 1.2	1.7 ± 1.0	p > 0.05
[cm ² s ⁻²]	with carvedilol	1.2 ± 0.6	1.7 ± 1.8	p > 0.05
Phase shift	without carvedilol	-53.0 ± 20.1*	-34.3 ± 18.3*	p < 0.05
[°]	with carvedilol	-62.3 ± 26.1	-57.0 ± 23.8	p > 0.05

Data are means ± SD. Significant differences in parameters at rest and during cold pressor stimulation are indicated by an asterisk (*). Significant differences in values recorded without partial sympathetic blockade and values recorded 2 hours after oral intake of 25 mg carvedilol are printed in bold. (RRI: RR-interval, BP: blood pressure, CBFV: cerebral blood flow velocity, ETCO₂: end-tidal carbon dioxide level, LF: low-frequency, HF: high-frequency)

Fig. 1

