Journal of the Neurological Sciences 365 (2016) 181–187

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

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

Max J. Hilz [a,*], Ruihao Wang [a], Harald Marthol [b], Mao Liu [a], Alexandra Tillmann [a], Stephan Riss [a], Paulina Hauck [a], Katharina M. Hösl [c], Gerald Wasmeier [d], Brigitte Stemper [a,e], Martin Köhrmann [a]

[a] Department of Neurology, University of Erlangen-Nuremberg, Schwabachanlage 6, D-91054 Erlangen, Germany
[b] Department of Psychiatry, Addiction, Psychotherapy and Psychosomatics, Klinikum am Europakanal, Am Europakanal 71, 91056 Erlangen, Germany
[c] Department of Psychiatry and Psychotherapy, Paracelsus Medical University Nuremberg, Prof.-Ernst-Nathan-Strasse 1, 90419 Nuremberg, Germany
[d] Department of Cardiology, Klinik Neustadt a. d. Aisch, Paracelsusstraße 30–36, 91413 Neustadt a. d. Aisch, Germany
[e] Bayer HealthCare, Bayer Pharma AG, Global Development Specialty Medicine, Müllerstr. 178, Building P300, Room 239, 13353 Berlin, Germany

ARTICLE INFO

Article history:
Received 30 October 2015
Received in revised form 24 March 2016
Accepted 7 April 2016
Available online 17 April 2016

Keywords:
Sympathetic nerve activity
Pharmacologic stress
Blood pressure
Cerebral blood flow velocity
Phase angle

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-second 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, BP-LF- and CBFV-LF-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.

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].

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.

* Corresponding author.
E-mail addresses: max.hilz@uk-erlangen.de (M.J. Hilz), ruihao.wang@uk-erlangen.de (R. Wang), haraldmarthol@gmx.net (H. Marthol), mao.liu@uk-erlangen.de (M. Liu), alexatillmann@web.de (A. Tillmann), stephan_riss@yahoo.de (S. Riss), paulina@paulina-hauck.com (P. Hauck), katharina.hoesl@klinikum-nuernberg.de (K.M. Hösl), gerald.wasmeier@kliniken-nea.de (G. Wasmeier), brigitte.stemper@bayer.com (B. Stemper), martin.koehrmann@uk-erlangen.de (M. Köhrmann).

http://dx.doi.org/10.1016/j.jns.2016.04.022
0022-510X/

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 min to ensure cardiovascular stability while monitoring devices were applied [10].

For 5 min 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 (Respitrace Calibrator, Ambulatory Monitoring Inc., Ardsley, NY) [8,10].

From 60-s intervals at rest and during the last 60 s 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 s, 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].