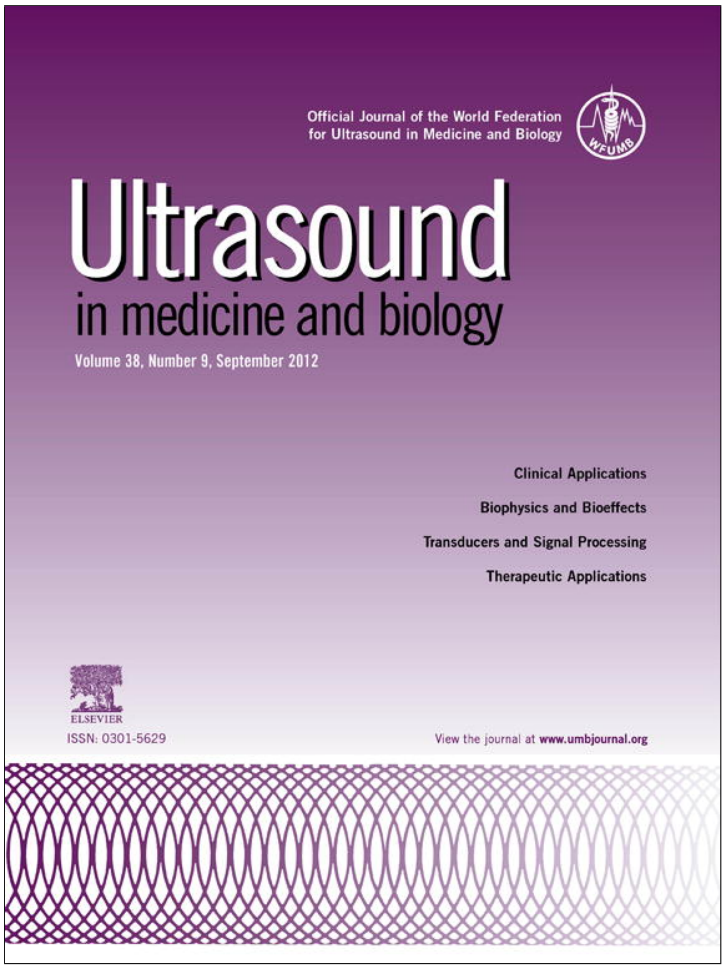

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● *Original Contribution*

GRADING OF DYNAMIC CEREBRAL AUTOREGULATION WITHOUT BLOOD PRESSURE RECORDINGS: A SIMPLE DOPPLER-BASED METHOD

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Abstract—Transcranial Doppler sonography allows for noninvasive assessment of dynamic cerebral autoregulation. A wider clinical use of this approach has been hampered by the need for continuous arterial blood pressure (ABP) measurements. We describe a new method of a pure Doppler signal based estimation of dynamic autoregulation using heart rate (HR) and cerebral blood flow velocity (CBFV) information. The phase between these two signals was assessed from 0.1 Hz oscillations induced by regular breathing. We compared this new approach with the standard method (phase between ABP and CBFV oscillations) in 93 patients with unilateral severe carotid artery obstruction. On a group level, the phase HR-CBFV differed significantly between ipsi- and contralateral sides ($p = 0.024$) and correlated significantly with the standard phase ABP-CBFV ($r = 0.369$, $p < 0.001$). The proposed method can, thus, detect impaired dynamic autoregulation in occlusive carotid artery disease using a single Doppler probe. (E-mail: matthias.reinhard@uniklinik-freiburg.de) © **2012 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Dynamic cerebral autoregulation, Transcranial Doppler sonography, Blood pressure measurement.**

INTRODUCTION

Cerebral autoregulation is an intrinsic and rapid regulatory mechanism of the cerebral vasculature. Its clinical measurement has long been regarded as difficult because of the need for invasive arterial blood pressure (ABP) manipulation and the low temporal resolution of cerebral blood flow measurements. With the advent of transcranial Doppler sonography (TCD), continuous assessment of short-term changes in cerebral hemodynamics became possible (Bellapart and Fraser 2009; Panerai 2009). Together with the use of rapid ABP transients, an entirely noninvasive assessment of dynamic characteristics of cerebral autoregulation has evolved (Aaslid et al. 1989; Sorond et al. 2009). Besides mechanically induced ABP stimuli also repetitive up- and downward stimuli of oscillating ABP are used (Reinhard et al. 2003). Using cross-spectral analysis from orthostatic, spontaneous or respiratory-induced ABP oscillations, a phase shift between ABP oscillations and the steadily regulating cerebral perfusion has been found (Diehl et al. 1995; Kuo et al. 1998; van Beek et al. 2010). This phase shift is variably impaired (*e.g.*, in severe carotid stenosis and occlusion) and predicts the risk of transient ischemic attack (TIA) and stroke in these patients (Hu et al. 1999; Reinhard et al. 2008).

One of the most important obstacles to a broader application of dynamic autoregulation measurements is the need of a continuous assessment of blood pressure to track the stimulus for the rapid dynamic autoregulatory response. Invasive blood pressure recordings are not justified in outpatients. Noninvasive continuous manometers are costly and, thus, not suitable ftor a widespread application of autoregulation testing in the regular clinical ultrasound lab. A simple ultrasound-based autoregulation test without the need of continuous ABP measurement would be a promising approach for a wide-spread applicability of dynamic autoregulation measurements. Furthermore, since many labs only have the possibility of unilateral transcranial Doppler or Duplex studies at a time, an autoregulation test with a single Doppler or Duplex probe is desirable.

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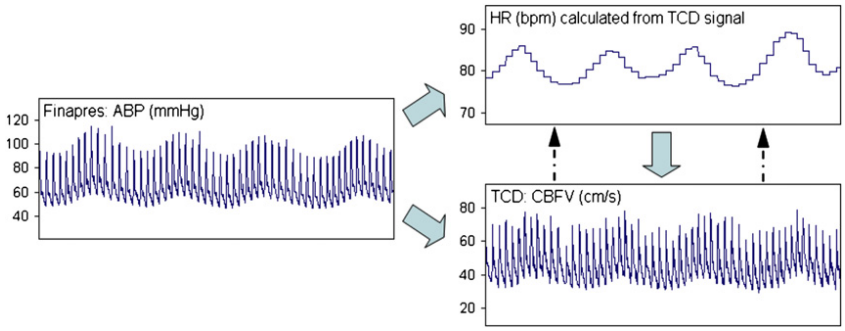

Fig. 1. Hypothesis of a single transcranial Doppler sonography (TCD) probe method for assessment of dynamic autoregulation. Short data segment of 0.1 Hz oscillations of arterial blood pressure (ABP), heart rate (HR) and cerebral blood flow velocity (CBFV) induced by slow regular breathing at a rate of 6 breathes per minute. The usual calculation refers to the phase shift between the ABP signal (left) and CBFV (lower right). ABP oscillations are accompanied by HR oscillations (upper right), which can be calculated from the electrocardiogram signal (RR interval) or the systolic ABP peaks (Finapres signal, left). HR values can, however, also be calculated from the systolic peaks of the Doppler signal (lower right) resulting in the upper right curve in this example. Assuming a fixed phase relation between ABP and HR oscillations, ABP oscillations could be substituted as input signal for calculation of dynamic autoregulation. Because the HR signal can be calculated from the CBFV signal of the Doppler probe, calculation of dynamic autoregulation would ideally become possible by using a single Doppler probe ('single Doppler probe method').

For this purpose, the autoregulation test of phase shift calculation between oscillations of ABP and cerebral blood flow velocity (CBFV) could be modified by replacing ABP by another fix oscillating cardiovascular signal. The heart rate (HR) signal also oscillates in a certain phase relation to ABP during spontaneous or respiratory-induced oscillations in ABP (Keyl et al. 2002).

Although additional interindividual variability might be introduced, HR oscillations could potentially serve as an individual temporal surrogate for the ABP signal, allowing the estimation of absolute phase values for determination of dynamic autoregulation. Even more, HR oscillations can be estimated from the intersystolic interval of the Doppler signal, resulting in a single transcranial Doppler probe as a sufficient tool to gain information on dynamic cerebral autoregulation. This hypothesis is illustrated in Figure 1.

In this study, we investigated the feasibility of a single Doppler probe based determination of dynamic autoregulation using the phase shift between heart rate and CBFV in patients with severe unilateral stenosis or occlusion of the ICA.

PATIENTS AND METHODS

Data sets of 93 patients (mean age 67, range 36–85 years, 11 female) with severe unilateral stenosis (≥80% local degree of stenosis) or occlusion of the internal carotid artery (ICA) were analyzed. Moderate stenosis on contralateral ICA sides was allowed. Recordings were obtained in a previous study on dynamic autoregulation (Reinhard et al. 2008), which had been approved by the local ethics committee. All patients gave informed consent to participate. A complete neurosonological workup, including extracranial and intracranial color-coded and transcranial Doppler sonography, was performed in all patients. Grading of stenosis was performed using Doppler velocities pre-, intra- and poststenotically in combination with B-mode imaging. Baseline characteristics of patients are given in Table 1.

Autoregulation measurements were performed with the patients in a supine position with an inclination of 50° of the upper body in quiet room with ambient temperature kept constant at 21°C. CBFV was measured in both middle cerebral arteries (MCA) by standard transcranial Doppler sonography (button-shaped 2 MHz ultrasound probes fixed to a headband, pulsed wave directional insonation, axial width of the sample volume 6–10 mm, mean I_{SPTA} 597.2 mW/cm^2, MCA insonated in depths ranging between 50 and 60 mm; device type and manufacturer: Multidop X4©, DWL Medizinische Systeme, Singen, Germany). ABP at heart level was recorded *via* a servo-controlled finger plethysmograph (Finapres 2300©; Ohmeda, Englewood, CO, USA) and this device was also used for heart rate assessment using intersytolic ABP intervals. After establishing stable baseline signals and careful instruction of the patient, oscillations in ABP and CBFV were elicited by paced breathing at a rate of 6 breathes per minute (*i.e.*, 5 s periods of in- and expiration) for 180 s. Paced breathing was achieved both by visual feedback of a large clock with a red sweep hand and additionally by verbal instruction of the examiner to breathe in and out. Accuracy of paced breathing was checked during the investigation by thoracic excursions and by capnometry (measurement of end tidal carbon dioxide partial pressure). A block diagram of the set-up is shown in Figure 2.

Table 1. Clinical characteristics

	$n = 93$	
Age, year ±SD	67	±8
Male, *n* (%)	82	(88)
Mean degree of ipsilateral ICA stenosis, % ±SD	90	±11
Mean degree of contraleral ICA stenosis, % ±SD	26	±27
Ipsilateral ischemic symptoms (within last 2 year), *n* (%)	36	(37)
Hypertension, *n* (%)	83	(89)
Diabetes, *n* (%)	22	(24)
Coronary artery disease, *n* (%)	36	(39)
ACE inhibitors, *n* (%)	77	(83)
Beta blocker, *n* (%)	46	(49)
Diuretics, *n* (%)	46	(49)
Calcium antagonists, *n* (%)	29	(31)
ARB, *n* (%)	19	(20)
Other antihypertensive medications, *n* (%)	8	(9)

ARB = angiotensin receptor blocker.

Data analysis

Heart rate (HR) was extracted from the right CBFV signal by evaluating the length of each heart-cycle measured from systole to systole. To this aim, the peaks of the systoles were automatically detected by software written in house. The resulting values were smoothed by convolution with a triangular window of width two heartbeats. To gain a continuous signal of HR, a step function was created by assuming a constant HR for each heart cycle. Unlike during an online measurement, values were sorted to the interval from which they were calculated. The phase shift between oscillations of ABP, HR and CBFV was then determined by transfer function analysis (Timmer et al. 1998). Briefly, power spectra and respective cross spectra were estimated by Fourier transformation of the time series of ABP, CBFV and HR signals to the frequency domain. Smoothing the respective squared Fourier transformations, the so-called periodograms, resulted in an estimator for the power spectra and cross spectra. The phase is the angle between the real and the imaginary part of the cross spectrum. It provides a measure in frequency domain for the temporal lag between the input and the output signal. A phase shift with CBFV oscillations leading those of ABP indicates functioning autoregulation (Kuo et al. 2003). As a new measure of cerebral autoregulation, the phase shift between HR and CBFV oscillations at 0.1 Hz was estimated for the data obtained during paced breathing. Coherence at 0.1 Hz was tested for significance using a 5% significance level, which corresponds to a threshold for coherence of 0.63–0.93 depending on the signal lengths (see below). Phases of non-coherent signals (*i.e.*, where coherence was not significant), were excluded from the evaluation since in this case phase estimation is not possible. The short-term reproducibility of the phases was assessed by cutting the measurement into two non-overlapping segments of 60 s length. Additionally, phase shifts were estimated from segments of 120 s length to investigate the influence of the measurement length on the presented single Doppler probe method.

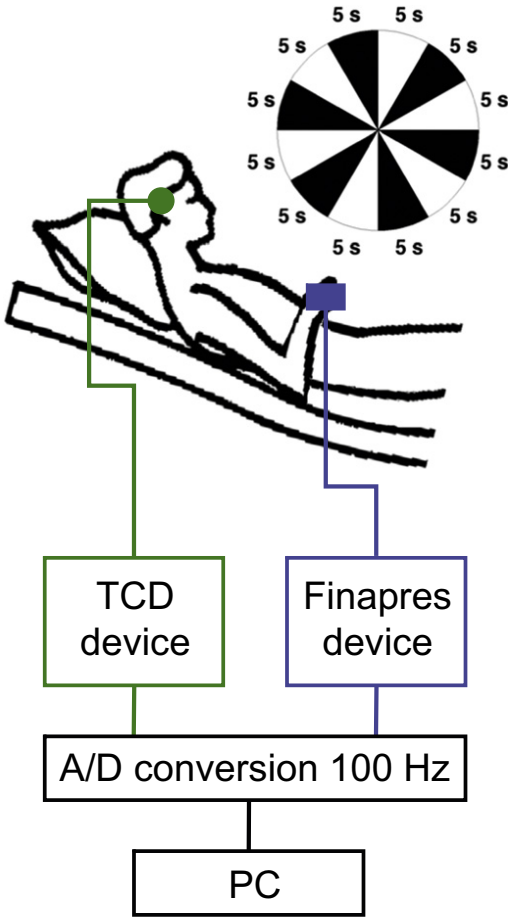

Fig. 2. Block diagram of the measurement setup. Diagram of the measurement set-up. The clock indicates duration of in- and expiration for induced breathing. Transcranial Doppler (TCD) probes are attached to both sides of the head while the patients are in a supine position. Finger plethysmography (Finapres device) measures blood pressure and heart rate at the right index finger at heart level. Signals are converted by an analog to digital (A/D) converter at a sampling rate of 100/s (100 Hz) and stored on a personal computer (PC).

Statistical analysis

Calculation of correlations was performed using Spearman's rank correlation coefficient. For the comparison of phase values, the intraclass correlation coefficient (ICC) was used. Differences between ipsi- and contralateral sides were tested using the Wilcoxon rank sum test. For all statistical analyses a value of $p < 0.05$ was considered statistically significant.

RESULTS

Phase ABP-HR

To test if the heart rate can be used as a reference for phase estimation we first analyzed the phase shift between ABP and HR. Primarily, the HR curve of the

Finapres signal, which is based on intersystolic ABP interval, and the HR curve derived from the Doppler signal, intersystolic CBFV interval, showed a good agreement in all 93 patients. Since no significant difference was found comparing HR estimated from the left or right CBFV measurement, we used the right CBFV signal. Further analyses on phase ABP-HR were based on the Doppler derived HR signal. An estimation of the phase ABP-HR was not possible because of low coherence in $n = 16$ patients. Correlation analysis revealed no significant correlation ($p > 0.05$) of phase ABP-HR with a history of hypertension, diabetes or coronary artery disease, degree of ICA stenosis, previous cerebral ischemic symptoms within the last 2 years, concomitant antihypertensive medication and the age of the patients. The power of the ABP oscillations did not significantly associate with the phase ABP-HR ($p > 0.05$).

The phases ABP-HR extracted from two separate 60 s segments within the recording showed a significant short-term correlation ($r = 0.836$, $p = 1.4 \cdot 10^{-6}$, analysis for $n = 28$ patients with significantly coherent ABP-HR oscillations within both 60 s periods).

Phase HR-CBFV

Of the 186 signals in 93 patients, a significant coherence of ABP and CBFV was observed in $n = 177$ (95%) recordings. A significant coherence of HR and CBFV over 180 s was observed for $n = 150$ recordings (81%). Concerning the 120 s segments, coherence of HR and CBFV was significant for $n = 133$ recordings (72%). For even shorter segments of 60 s, the number of coherent signals was much lower ($n = 88$, *i.e.*, 47% and $n = 76$, *i.e.*, 41% for the two segments, respectively). This additional reduction is caused by the even further restricted amount of data points.

All following calculations of phase HR-CBFV only refer to recordings with significant coherence. The mean and standard deviation of all estimated coherences and phase values and respective group sizes are summarized in Table 2.

The phase ABP-CBFV and phase HR-CBFV significantly correlated to the degree of stenosis ($r = 0.399$, $p = 8.8 \cdot 10^{-7}$, and $r = 0.256$, $p = 0.0021$). Phase values for ipsilateral and contralateral sides were significantly different for both phase ABP-CBFV and phase HR-CBFV (Wilcoxon rank sum test $p = 2.8 \cdot 10^{-4}$ for phase ABP-CBFV and $p = 0.024$ for phase HR-CBFV; Fig. 3). Comparing the phase ABP-CBFV with the phase HR-CBFV, we found a significant correlation (ICC $r = 0.369$, $p = 2.8 \cdot 10^{-6}$; Fig. 4). The phase differences between ipsilateral and contralateral sides obtained for phase HR-CBFV almost perfectly correlated to those obtained by phase ABP-CBFV ($r = 0.994$, $p = 1.02 \cdot 10^{-5}$).

Table 2. Results of coherence and phase shift analysis

	mean	±SD
Phase HR-ABP 180 s ($n = 77$)	−93	±7
Coherence HR-ABP 180 s ($n = 77$)	0.880	±0.010
Phase HR-ABP 60 s first segment ($n = 49$)	−96	±7
Coherence HR-ABP 60 s first segment ($n = 49$)	0.972	±0.002
Phase HR-ABP 60 s second segment ($n = 40$)	−92	±10
Coherence HR-ABP 60 s second segment ($n = 40$)	0.971	±0.003
Phase ABP-CBFV 180 s ipsilateral ($n = 90$)	−38	±3
Coherence ABP-CBFV 180 s ipsilateral ($n = 90$)	0.951	±0.007
Phase ABP-CBFV 180 s contralateral ($n = 87$)	−55	±3
Coherence ABP-CBFV 180 s contralateral ($n = 87$)	0.936	±0.009
Phase HR-CBFV 180 s ipsilateral ($n = 77$)	54	±8
Coherence HR-CBFV 180 s ipsilateral ($n = 77$)	0.873	±0.011
Phase HR-CBFV 180 s contralateral ($n = 73$)	34	±8
Coherence HR-CBFV 180 s contralateral ($n = 73$)	0.864	±0.011
Phase HR-CBFV 120 s ipsilateral ($n = 68$)	55	±8
Coherence HR-CBFV 120 s ipsilateral ($n = 68$)	0.933	±0.005
Phase HR-CBFV 120 s contralateral ($n = 65$)	41	±7
Coherence HR-CBFV 120 s contralateral ($n = 65$)	0.932	±0.006
Phase HR-CBFV 60 s first segment ipsilateral ($n = 49$)	57	±9
Coherence HR-CBFV 60 s first segment ipsilateral (n = 49)	0.966	±0.003
Phase HR-CBFV 60 s first segment contralateral ($n = 39$)	50	±9
Coherence HR-CBFV 60 s first segment contralateral ($n = 39$)	0.970	±0.003
Phase HR-CBFV 60 s second segment ipsilateral ($n = 40$)	58	±10
Coherence HR-CBFV 60 s second segment ipsilateral ($n = 40$)	0.969	±0.003
Phase HR-CBFV 60 s second segment contralateral ($n = 36$)	44	±9
Coherence HR-CBFV 60 s second segment contralateral ($n = 36$)	0.969	±0.003

ABP = arterial blood pressure; CBFV = cerebral blood flow velocity; HR = heart rate.

Using the two 60 s segments of data for each patient for analysis of short-term reproducibility, a smaller n of patients could be analyzed because significant coherence was not reached in these short recordings in a number of patients (Table 2). Overall, a strong correlation between the two measurement periods for phase HR-CBFV was found (ICC $r = 0.942$, $p < 0.0001$). The comparison of different segment lengths showed that the obtained phase shifts for 60 s and 120 s segments correlate almost perfectly with the full 180 s segments (ICC $r = 0.972$, $p < 0.0001$ and $r = 0.993$, $p < 0.0001$, respectively).

DISCUSSION

A broader clinical application of autoregulation testing is only possible if the assessment of autoregulation becomes easier and is not based on costly equipment. We present a method for the estimation of dynamic autoregulation based on the phase shift analysis between the

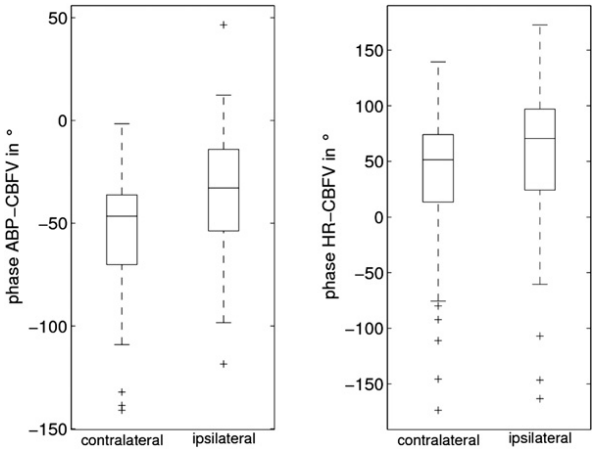

Fig. 3. Boxplots of phase arterial blood pressure (ABP)-cerebral blood flow velocity (CBFV) and phase heart rate (HR)-CBFV. For both methods ipsi- and contralateral sides differ significantly (Wilcoxon rank sum test $p = 7.6 \cdot 10^{-4}$ for phase ABP-CBFV and $p = 0.024$ for phase HR-CBFV, $n = 71$). Only those patients were included that showed significant coherences for both sides and both methods.

heart rate signal calculated from systolic Doppler intervals and the Doppler flow velocity signal itself during regular breathing. This enables estimation of dynamic autoregulation with the use of a single Doppler probe. We have found a significant correlation between this new method and the more established dynamic autoregulation method based on continuous blood pressure measurement as input signal.

As far as we know, there is only one other method allowing estimation of dynamic autoregulation with a single hand-held Doppler probe approach: the transient hyperemic response test (Smielewski et al. 1996). Hereby, the transient hyperemia after a short period of complete common carotid artery compression is regarded as a sign of the autoregulatory dilation having occurred during the compression period. Although this method might be theoretically influenced by the capacity of the circle of Willis, it has shown a good correlation with other autoregulation tests (Smielewski et al. 1996). A disadvantage of this approach is, however, that common carotid artery compression is a semi-invasive maneuver that could rarely lead to ischemic complications, (*e.g.*, by plaque mobilization from the carotids) (Khaffaf et al. 1994). It is, thus, not routinely applicable in older patients with neurovascular diseases.

The noninvasive method presented here makes a basic physiologic assumption. Because it takes the HR signal instead of the fluctuating ABP signal, it assumes that there is a fixed phase relation between HR oscillations and ABP oscillations during regular breathing at 0.1 Hz with HR oscillations leading those of ABP oscillations. This phase relation is primarily caused by the time constant of the baroreflex with both

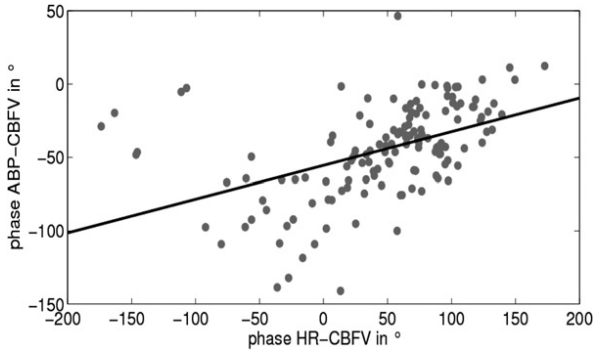

Fig. 4. Scatter plot between phase arterial blood pressure (ABP)-cerebral blood flow velocity (CBFV) and phase heart rate (HR)-CBFV. Significant correlation was found using the intraclass correlation coefficient ($p = 2.8 \cdot 10^{-6}$, $r = 0.369$, $n = 71$). Only those patients were included, that showed significant coherences for both sides and both methods.

vagal and sympathetic control mechanisms being involved (deBoer et al. 1987). It is, thus, per se subject to interindividual variability, although the standard deviation found in the present study was rather low for phase ABP-HR ($-93 \pm 7°$). Still, it introduces an additional confounding factor for estimation of autoregulatory ability. In the case of a rapidly working baroreflex (phase ABR-HR more negative), we would observe a larger "autoregulatory" phase shift by the HR-CBFV analysis. In the case of poor systemic baroreflex action (phase ABP-HR less negative), we observe a lower "autoregulatory" phase shift. The current method, thus, reflects a combination of rapid systemic hemodynamic and cerebral regulatory mechanisms. Theoretically, intercurrent factors like medication or cardiac disease might influence the phase ABP-HR and, thus, the phase HR-CBFV. Still, the phase ABP-HR was found not to be different between healthy young and old persons and patients with coronary artery disease (Halamek et al. 2003). Only the instantaneous short-term variability of the phase ABP-HR was higher in patients with coronary heart disease (Halamek et al. 2003). In terms of comparing phase ABP-HR from two short segments, we found a short-term stability of the phase ABP-HR. The intraindividual stability of the phase ABP-HR or its reproducibility over a longer period is, however, not known. If this stability could be assured, an individual calibration with one ABP-HR phase determination could be performed.

In case the variability of the absolute values of phase HR-CBFV is considered too strong, the presented method still allows for individual analysis of side-to-side differences. The latter is possible even with one Doppler probe by sequential analysis of the phase HR-CBFV of the two MCA sides. Such a procedure is acceptable considering the good short-term reproducibility for phase ABP-HR.

A main limitation of the proposed method is that with the short regular breathing period of 180 s, a reliable

calculation of phase HR-CBFV is not always possible because of nonsignificant coherence in approximately 20% of the patients in the present study. This challenge requires longer recordings. It becomes particularly evident when reducing the analysis time to 60 s (*i.e.*, six oscillatory cycles). In conclusion, the recording time should be at least 120 s, even better at 180 s. A principal limitation of the paced breathing test itself is that approximately 7% of patients are not able to successfully perform the 0.1 Hz breathing over a couple of minutes (*e.g.*, because of lung disease or cognitive deficits) (Reinhard et al. 2008).

Further limitations of the present study are that we were not able to compare the HR signal calculated from the CBFV signal with the gold standard HR signal of an electrocardiogram. However, the HR signal calculated from the Finometer signal adequately reflects that of the ECG (Giardino et al. 2002) and this HR signal was in good accordance with the HR signal calculated from the CBFV signal in the present study. Concerning the estimated phase HR-CBFV we had to deal with a higher number of noncoherent signals compared with the phase ABP-CBFV. Thus, a limitation of the proposed single Doppler probe method is that a higher quality of data acquisition is necessary to analyze the same proportion of patients reliably. Analysis of different measurement lengths indicated that 120 s of oscillating signals were sufficient in 72% of the studied cases. A shorter measurement of 60 s led to an unacceptable decrease of coherent signals below 50%. On the other hand, for longer measurements of 180 s, 81% of the analyzed data sets showed significant coherence.

Finally, further methods apart from transcranial Doppler ultrasound might be used. To further simplify the test, extracranial ultrasound at the submandibular internal carotid artery level could be used. This might, however, further lower the spatial resolution of autoregulatory assessment. Contrarily, the spatial resolution could be improved by using other noninvasive methods with the same HR based approach like blood oxygen level dependent magnetic resonance imaging or multichannel near-infrared spectroscopy.

CONCLUSIONS

The proposed single Doppler probe method can detect impaired autoregulation ipsilateral to severe carotid obstruction within a 2-min period of regular breathing. Since it uses the phase between HR and CBFV, it includes information on dynamic properties of baroreflex function. We found a moderate but still highly significant correlation with the standard autoregulatory phase shift between ABP and CBFV. Future research on this new method should focus on its reproducibility, confounding factors and performance in other clinical situations.

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