Original Article

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Incomplete recovery of cerebral blood flow dynamics in sufficiently treated high blood pressure

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Objective: Whether cerebrovascular regulation is different in patients with controlled high blood pressure (HBP) with and without small vessel disease (SVD).

Methods: Sixty-seven healthy controls (mean age ± SD, 45 ± 16 years; 30 women, 37 men) and 40 patients (mean age, 64 ± 13 years; 14 women, 26 men) with HBP and different stages of SVD, underwent simultaneous recordings of the spontaneous fluctuations of BP, blood flow velocity (CBFV) in both middle cerebral arteries (MCA), and of end-tidal CO_2 ($ETCO_2$). Coherence and transfer function gain and phase between BP and CBFV were assessed in the frequency ranges of VLF (0.02–0.07 Hz), low frequency (0.07–0.15), and high frequency (>0.15). BP SD indicated BP variability (BPV).

Results: In controls (BP, 86 ± 13 mmHg; $ETCO_2$, 39 ± 4 mmHg; BPV, 15 ± 6 mmHg), gain, phase and coherence were not age-dependent in simple or a multiple regression models. BPV correlated significantly in both MCAs with gain in low frequency and high frequency, and with phase in VLF and high frequency. In patients (BP, 91 ± 16 mmHg, $ETCO_2$, 39 ± 4 mmHg, BPV 18 ± 5 mmHg), only gain showed some differences between different SVD groups. Comparing all patients with 25 controls of similar age and sex, patients exhibited significantly ($P < 0.05$–$P < 0.005$): increased coherence and gain in VLF, decreased phase in VLF and low frequency, correlations between BPV with phase in low frequency (left) and with gain in VLF (left) and in high frequency (left and right).

Conclusion: Phase seems an age independent autoregulatory index. In controlled HBP, CBF regulation is degraded at longlasting CBF changes; BPV effects lose their physiological bilateral distribution.

Keywords: aging, cerebral autoregulation, cerebrovascular disease, hypertension, small vessel disease, transcranial Doppler

Abbreviations: BP, blood pressure; BPV, blood pressure variability; CBF(V), cerebral blood flow (velocity); CVR, cerebrovascular resistance; $ETCO_2$, end-tidal carbon dioxide; MCA, middle cerebral artery; SD, standard deviation; SVD, small vessel disease; Vlf, very low frequency

INTRODUCTION

Cerebral small vessel disease (SVD) is a major cause of stroke, cognitive decline, and dementia [1,2]. The pathogenesis of SVD is still not clear insofar as, for example, high blood pressure (HBP) and diabetes mellitus provide similar clinical pictures and similar imaging results but lack an obvious common formal pathogenesis. Additionally, there are some genetic microangiopathic disorders, which do not have much in common with either HPB or diabetes as an SVD cause. Recent research has tried to close these missing links by analysis of genetic polymorphism [3,4].

Pathophysiological mechanisms of SVD in patients with HBP currently discussed include: a constant elevated level blood pressure and its variability [5,6]; autonomic BP regulation disturbances [7]; an increased pulse pressure amplitude [8]; and/or a suggested ischemic effect on the brain [9–13]. SVD can progress even when HBP is controlled for. In HBP patients with normal BP, one question, therefore, is whether cerebral blood flow (CBF) regulation is really normal as studies investigating the mostly pressure-dependent cerebral autoregulation might suggest, or is it continuously dysfunctional because CO_2 reactivity can be degraded while cerebral autoregulation is normal [14,15]. In recent years, the cerebrovascular system is increasingly considered a dynamical system in which cerebral perfusion is regulated differently at different cycles of CBF velocity (CBFV) changes [16–18]. To describe the dynamics of the relationship between BP and CBFV, phase shift and gain are the most frequently used parameters. At a given cycle of BP and CBFV changes, for example, of 10 s (0.1 Hz), gain describes the power transformation from BP to CBFV, and phase shift indicates how much earlier or later in time the BP cycle will be found in the CBFV. A characteristic normal finding is that BP cycles around 0.1 Hz are delayed between 1.06 and 1.78 s [19]. In patients with recently diagnosed untreated HBP, or in individuals in whom BP was elevated by phenylephrine, phase was shown to be reduced and gain to be increased in the frequency band of

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0.07–0.15 Hz [14,20]. We used this dynamic approach on spontaneous oscillating fluctuations in BP and CBFV in healthy normal individuals and in a cohort of patients with HBP with and without cerebral microangiopathy and address three major questions. First, are phase and gain age-independent? Second, is BPV in addition to $ETCO_2$ a considerable variable when phase and gain are used for analysis of cerebrovascular dynamics? And third, are alterations in the cerebrovascular system behaviour still present in patients with chronic HBP with and without HBP-associated SVD even if BP is controlled for ? We hope that our findings will contribute to insights on mechanisms of how SVD progresses.

MATERIAL AND METHODS

The study was approved by the ethics committee of Northwest and Central Switzerland and followed the Declaration of Helsinki as well as good clinical practice standards. Written informed consent was obtained from patients and healthy controls.

Between August 2015 and October 2017, we investigated:

1. Sixty-seven healthy controls with an age range between 22 and 87 years. Table 1 shows their distribution with respect to age group and sex. Bilateral transcranial Doppler (TCD) recordings were not possible in all controls, so we report left and right middle cerebral arteries (MCA) separately. All of the controls were free of known diseases and were nonsmokers.
2. Forty patients (mean age, 64 ± 13 years; 14 women, 26 men) with a known history of HBP of a minimum of 2 years and a brain MRI within the 3 months prior to the investigation. HBP diagnosis was based on SBP values of at least 140 mmHg or DBP values at least 90 mmHg at the time of diagnosis. The patients were recruited out of our neurovascular facilities in which they were diagnosed as to whether a cerebrovascular disease was present or not. After completion of all clinical and diagnostic procedures [including MRIs (Philips Achiva 3Tesla device or Siemens Magnetom 3T device using DWI Sequences, T2 Sequences, and Flair Sequences)] eligible patients were then asked to participate in the study. At that point in time, their final diagnoses were as follows: minor stroke 18 times; transient ischemic attack 12 times; and asymptomatic 10 times. Patients and their general practitioners were asked to look closely at BP control. After 3 months of BP control, the examinations were done as long as no cerebrovascular event had occurred in the meantime. At the time of the investigation, each patient had a duplex ultrasound examination of the brain supplying extracranial and intracranial arteries (Acuson Antares S2000, Siemens, Germany). The study exclusion criteria were: any at least 50% stenosis or occlusion of the extracranial or intracranial arteries, presence of other (than HBP) vascular risk factors such as smoking, diabetes mellitus, obesity (BMI >30 kg/m^2), presence of cardiac arrhythmias (atrial fibrillation) or a clinically manifest heart failure. Only treated dyslipidaemia was allowed as an additional risk factor. All MRIs were examined by the same neuroradiologist (A.v.H.) who graded a present SVD according to Fazekas *et al.* [21]. Those MRIs without any SVD were included in the Fazekas grading as Fazekas 0. Thus, all patients were considered to be one group suffering from HBP (with and without imaging signs of SVD).

TABLE 1. Baseline characteristics and transfer function estimates in the healthy population

	All	Group of left MCA	Group of right MCA
N	67	64	62
Women/men	30/37	27/37	29/33
Mean age (years)	45 ± 16	46 ± 16	44 ± 15
Age distribution			
<40	26	24	26
40–59	25	25	24
At least 60	16	15	11
Mean BP (mmHg)	86 ± 13	87 ± 13	86 ± 12
BP variability (mmHg)	15 ± 6	15 ± 6	15 ± 5
$ETCO_2$ (mmHg)	39 ± 4.0	38.5 ± 4.1	39.5 ± 3.9
CBFV (cm/s)	61 ± 14	60 ± 13	61 ± 13
CVR	1.50 ± 0.49	1.52 ± 0.47	1.49 ± 0.52
Coherence			
VLF		0.48 ± 0.13	0.46 ± 0.12
Low frequency		0.74 ± 0.14	0.71 ± 0.15
High frequency		0.65 ± 0.14	0.65 ± 0.14
Gain (cm/s per mmHg)			
VLF		0.23 ± 0.25	0.32 ± 0.34
Low frequency		0.69 ± 0.44	0.68 ± 0.39
High frequency		0.80 ± 0.49	0.85 ± 0.52
Percentage gain (%/mmHg)			
VLF		0.31 ± 0.41	0.34 ± 0.45
Low frequency		1.14 ± 0.67	1.12 ± 0.62
High frequency		1.31 ± 0.69	1.36 ± 0.76
Phase (radians)			
VLF		1.12 ± 0.33	1.12 ± 0.38
Low frequency		0.74 ± 0.19	0.74 ± 0.22
High frequency		0.38 ± 0.35	0.36 ± 0.32

BP, blood pressure; CBFV, cerebral blood flow velocity; CVR, cerebrovascular resistance; $ETCO_2$, end-tidal carbon dioxide; MCA, middle cerebral artery.

All investigations were performed with the participant in a supine position with the head elevated approximately 30°. The investigations were performed in the late morning. Last coffee or tea uptakes were a minimum of 3 h prior. After mounting all probes and adapting the participant to the experimental setting, all parameters were simultaneously recorded over a minimum period of 10 min. To assess CBFV, we used Transcranial Doppler Ultrasound (MultidopX, DWL; Compumedics, Sipplingen, Germany) with a 2-MHz probe to insonate both MCAs through the temporal skull. The probes were fixed using a head holder provided by the manufacturer. The MCAs were identified according to commonly used criteria. BP was measured noninvasively by finger plethysmography (Finometer Pro; Finapres Medical Systems, Amsterdam, The Netherlands) with special attention paid to its calibration to the brachial artery pressure. Apart from the mean BP (averaging of all BP values over the total recording period), we recorded separately in each participant/patient the standard deviation (SD) of the BP over the recording time, which we then used as an indicator of BP variability (BPV). End-tidal pCO_2

($ETCO_2$) concentration was measured via nostril tubes and the capnography embedded in the TCD device. The $ETCO_2$ for each patient is reported as the mean $ETCO_2$ over the total recording period. Cerebrovascular resistance (CVR) was calculated from BP/CBFV.

Data preparation: BP, CBFV, and $ETCO_2$ data were collected at 100 Hz. The data were analysed using Matlab (2015b; Math Works Inc., Natick, Massachusetts, USA). The data were visually inspected for artefacts, and only artefact-free data periods of 5 min were used. Each raw data time series was averaged over 1-s interval. The coherence and the transfer function estimates of phase and gain between the BP and the CBFV time series were extracted from their respective power auto-spectra or cross-spectra using Welch's averaged periodogram method, with a Hanning window length of 100 s, window overlap of 50%, and total Fast Fourier Transformation data length of 300 s. For each participant, the coherence, the phase (in radians), and the gain (in cm/s/mmHg and in percentage CBFV change/mmHg) were calculated over a frequency range of 0.02–0.40 Hz. The results of phase, gain, and coherence are reported as their respective average in the very low frequency range (VLF, 0.02–0.07 Hz), low frequency range (low frequency, 0.07–0.15 Hz), and high frequency range (high frequency, 0.16–0.4 Hz).

Statistics

For all data analysis, the Matlab Statistical Toolbox was used. Using a Kolmogorov–Smirnov test, all data showed a normal distribution, and the data are reported as mean ± SD. For the analysis within each group (control group, respectively, patient group), we used one-way ANOVA to compare the means. For comparing the means between the control and patient groups, a *t*-test was used. In simple linear regression analysis, BVP, age, $ETCO_2$, and CVR were used as independent variables and the transfer function parameters as the dependent ones. As a result, gain was dependent on all four independent variables; we, therefore, used multiple linear regression analysis to estimate the predictive effects of each of the four independent variables. P 0.05 or less was considered statistically significant.

RESULTS

Results are reported in two steps. In the first step, the findings in all controls as one whole group (control group I) are presented. In the second step, we used all controls aged 50 years or older to assemble a control group of similar age and sex distribution (control group II) for comparison with the patient group.

Healthy population

The healthy population (control group I) consists of a total of 67 persons (mean age 45 ± 16 years; women/men 30/37). Fifty-nine participants were insonated bilaterally, eight could only be insonated unilaterally (five left MCAs; three right MCAs), resulting in two slightly different groups (Table 1) with nearly identical baseline characteristics, hemodynamic parameters, and transfer function estimates. Sex-specific differences were found for two parameters only: Women exhibited a higher CBFV in the MCAs than men (men, left 56 ± 13 cm/s, right 59 ± 12; women, left 65 ± 14, right 64 ± 15; $P < 0.01$ for each side); and men showed a higher coherence in the VLF band than women (men, left 0.52 ± 0.11, right 0.49 ± 0.11; women, left 0.42 ± 0.13, right 0.43 ± 0.13; $P < 0.01$ for each side).

In simple linear regression analysis, we found age: it was a significant predictor of increasing BP [left MCA: $F(2,62)$ 12.8, $P < 0.001$, $R^2 = 0.158$, $\beta = 0.33$; right MCA: $F(2,60)$ 7.75, $P < 0.01$, $R^2 = 0.09$, $\beta = 0.027$], increasing CVR (left $F(2,62)$ 58.2, $P < 0.0001$, R^2 0.476, $\beta = 0.01$; right: $F(2,60)$ 46.4, $P < 0.0001$, R^2 0.427, $\beta = 0.022$], increasing BPV [left only, $F(2,62)$ 5.18, $P = 0.02$, R^2 0.06, $\beta = 0.08$], decreasing gain in the low frequency [left: $F(2,62)$ 9.01, $P = 0.003$, R^2 0.113, $\beta = -0.009$; right: $F(2,60)$ 6.99, $P = 0.01$, R^2 0.089, $\beta = -0.008$], decreasing gain in the high frequency range [left: F(2,62) 8.62, $P = 0.004$, R^2 0.108, $\beta = -0.01$; right: F(2,60) 6.96, $P = 0.01$, R^2 0.09, $\beta = -0.010$], and decreasing CBFV [left: $F(2,62)$ 30.5, $P < 0.0001$, R^2 0.319, $\beta = -0.447$; right: $F(269)$ 31.1, $P < 0.0001$, R^2 0.331, $\beta = -0.511$]. All other variables were age-independent.

BPV: increasing BPV (Table 2) predicted on both sides significantly ($P \leq 0.01$–0.0001) increasing coherence in the high frequency range; it was inversely related to gain and percentage gain in the low-frequency and high-frequency range and to phase in the VLF and high-frequency range. All other variables were unrelated to BPV.

$ETCO_2$: it predicted significant gain [left: $F(2,62)$ 9.4, $P = 0.0003$, R^2 0.124, $\beta = -0.03$; right: $F(2,60)$ 15.5, $P = 0.0002$, R^2 0.192, $\beta = -0.053$] and percentage gain [left: $F(2,62)$ 9.4, $P = 0.0003$, R^2 0.118, $\beta = -0.05$; right: $F(2,60)$ 13.3, $P = 0.0005$, R^2 0.168, $\beta = -0.068$] in the high-frequency range. $ETCO_2$ was not predictive for all other transfer function parameters.

CVR: it predicted significantly only gain in the low-frequency range [left: $F(2,62)$ 7.38, $P = 0.008$, R^2 0.09, $\beta = -0.30$; right: $F(2,60)$ 6.02, $P = 0.01$, R^2 0.76, $\beta = -0.228$] and gain in the high-frequency range [left: $F(2,62)$ 6.6, $P = 0.01$, R^2 0.08, $\beta = -0.32$; right: $F(2,60)$ 10.5, $P = 0.001$, R^2 0.135, $\beta = -0.375$]; it was not predictive for $ETCO_2$, BPV, coherence or phase.

Of note, BP did not have a predictive relationship to BPV or to any of the transfer function parameters.

Amid the transfer function estimates only gain in the low-frequency and high-frequency bands were significantly predicted by several variables (age, $ETCO_2$, CVR, BPV) in the simple linear regression models. To estimate their respective influences, we performed a multiple linear regression model with all four variables as independent variables and the gains as the dependent variables (Table 3). Among the four variables, BPV remained the only significant predictor for gain in the low-frequency range on both sides; in the high-frequency range, BPV was the only significant predictor on the left side, but was accompanied by CVR as a significant predictor on the right side.

High blood pressure patients

The patient group consists of 40 patients of which 40 were insonated on the left side and 38 on the right side. Across the group, mean BP was 91 ± 16 mmHg, mean $ETCO_2$ 39 ± 4 mmHg, and mean BPV 18 ± 5 mmHg. For BP treatment, ACE inhibitor (17 times), Ca-antagonists (14×), diuretics

TABLE 2. Simple regression analysis between blood pressure variability as independent variable and the transfer function estimates (as dependent variables) within the control group and within the group of high blood pressure patients

BP variability as predictor of:	Controls left ($N=64$)	Controls right ($N=62$)	Patients left ($N=40$)	Patients right ($N=38$)
Coherence				
VLF	Ns	ns	Ns	ns
Low frequency	Ns	ns	Ns	ns
High frequency	$F(2,62)$ 6.15 $P=0.01$ $R^2=0.071$ $\beta=-0.085$	$F(2,60)$ 11.7 $P=0.001$ $R^2=0.149$ $\beta=0.011$	Ns	ns
Gain (cm/s per mmHg)				
VLF	Ns	ns	$F(2,38)$ 4.89 $P=0.03$ $R^2=0.097$ $\beta=-0.022$	ns
Low frequency	$F(2,62)$ 31.9 $P<0.0001$ $R^2=0.329$ $\beta=-0.052$	$F(2,60)$ 25.0 $P<0.0001$ $R^2=0.283$ $\beta=-0.043$	Ns	ns
High frequency	$F(2,62)$ 37.3 $P<0.0001$ $R^2=0.365$ $\beta=-0.053$	$F(2;60)$ 29.7 $P<0.0001$ $R^2=0.434$ $\beta=-0.096$	$F(2,38)$ 7.31 $P=0.01$ $R^2=0.139$ $\beta=-0.020$	$F(2,36)$ 5.48 $P=0.02$ $R^2=0.108$ $\beta=-0.021$
Percentage gain (%/mmHg)				
VLF	Ns	ns	Ns	ns
Low frequency	$F(2,62)$ 31.4 $P<0.0001$ $R^2=0.326$ $\beta=-0.075$	$F(2,60)$ 32.8 $P<0.0001$ $R^2=0.343$ $\beta=-0.074$	Ns	ns
High frequency	$F(2,62)$ 42.5 $P<0.0001$ $R^2=0.397$ $\beta=-0.081$	$F(2,60)$ 48.9 $P<0.0001$ $R^2=0.440$ $\beta=-0.096$	$F(2,38)$ 6.35 $P=0.01$ $R^2=0.121$ $\beta=-0.03$	$F(2,36)$ 9.08 $P=0.004$ $R^2=0.179$ $\beta=-0.032$
Phase (radians)				
VLF	$F(2,62)$ 5.78 $P=0.02$ $R^2=0.070$ $\beta=-0.021$	$F(2,60)$ 3.9 $P=0.05$ $R^2=0.045$ $\beta=-0.013$	Ns	ns
Low frequency	Ns	ns	$F(2,38)$ 5.03 $P=0.03$ $R^2=0.093$ $\beta=-0.013$	ns
High frequency	$F(2,62)$ 5.78 $P=0.02$ $R^2=0.072$ $\beta\beta=-0.023$	$F(2,60)$ 6.59 $P=0.01$ $R^2=0.084$ $\beta=-0.020$	Ns	ns

F, F-statistics, P, level of significance of the model; R^2, adjusted coefficient of determination; β, beta coefficient; ns, not significant.

(12×), AT-1 inhibitor (9×), and beta-blocker (6×) were used. Glyceryl trinitrate or analogue drugs were not used for BP management in any case. Almost all patients received a statin and acetylsalicylic acid. There were no significant differences between the patients taking one, two, or at least three medication classes regarding mean BP, BPV, $ETCO_2$, and all cerebral hemodynamic and transfer function parameters.

With respect to Fazekas classification, 17 HBP patients were classified as Fazekas 0; Fazekas 1 was present nine times, Fazekas 2 eight times, and Fazeks 3 six times (left MCA); regarding right MCA the distribution was Fazekas 0 seventeen times, Fazekas 1 seven, Fazekas 2 eight, Fazekas 3 seven. To generate similar group sizes, we summarized Fazekas 1–3 to one group [with (visible) microangiopathy]

TABLE 3. Multiple linear regression analysis of those factors influencing LF and HF gain

			Model			
	F statistics	*P*	Adjusted R^2	Significant predictor	*P*	β
Gain LF						
Left MCA	F(5,59) 9.40	<0.0001	0.349	BPV	<0.0001	−0.048
Right MCA	F(5,57) 8.37	<0.0001	0.326	BPV	<0.0001	−0.041
Gain HF						
Left MCA	F(5,59) 11.3	<0.0001	0.395	BPV	<0.0001	−0.048
Right MCA	F(5,57) 13.3	<0.0001	0.446	BPV; CVR	<0.0001; =0.01	−0.050; −0.311

The four variables, $ETCO_2$, age, CVR, blood pressure variability were entered in a multiple linear regression model to further identify the significant predictors of gain. β, beta coefficient; BPV, blood pressure variability; CVR, cerebrovascular resistance; $ETCO_2$, end-tidal carbon dioxide; LF, low-frequency range; HF, high-frequency range; *P*, level of significance.

TABLE 4. Blood pressure, blood pressuere variability and transfer function estimates in the middle cerebral artery of the high blood pressure patients without (Fazekas 0) and with cerebral microangiopathy (Fazekas 1–3)

Fazekas grading scale/variable	0 Left MCA ($N=17$)	1–3 Left MCA ($N=23$)	0 Right MCA ($N=17$)	1–3 Right MCA ($N=21$)
Mean BP (mmHg)	92 ± 13	88 ± 19	92 ± 13	89 ± 19
BP variability (mmHg)	17 ± 4	19 ± 6	18 ± 4	19 ± 4
CBFV (cm/s)	56 ± 10	50 ± 16	56 ± 8	50 ± 16
CVR	1.68 ± 0.42	1.84 ± 058	1.67 ± 0.32	1.88 ± 0.58
Coherence				
VLF	0.52 ± 0.16	0.55 ± 0.15	0.55 ± 0.16	0.54 ± 0.13
Low frequency	0.67 ± 0.15	0.70 ± 0.16	0.68 ± 0.15	0.72 ± 0.16
High frequency	0.69 ± 0.17	0.65 ± 0.15	0.69 ± 0.16	0.67 ± 0.16
Gain (cm/s/mmHg)				
VLF	0.47 ± 0.40*	0.26 ± 0.15*	0.40 ± 0.40	0.27 ± 0.24
Low frequency	0.61 ± 0.23**	0.45 ± 0.15**	0.53 ± 0.18	0.44 ± 0.22
High frequency	0.66 ± 0.28	0.58 ± 0.19	0.63 ± 0.24	0.59 ± 0.30
Percentage gain (%/mmHg)				
VLF	0.82 ± 0.64	0.51 ± 0.34	0.84 ± 0.69	0.51 ± 0.47
Low frequency	1.08 ± 0.34	0.92 ± 0.29	0.92 ± 0.33	0.88 ± 0.25
High frequency	1.16 ± 0.40	1.19 ± 0.35	1.17 ± 0.33	1.19 ± 0.25
Phase (radians)				
VLF	0.84 ± 0.27	0.84 ± 0.40	0.83 ± 0.21	0.71 ± 0.29
Low frequency	0.58 ± 0.23	0.62 ± 0.26	0.71 ± 0.29	0.58 ± 0.28
High frequency	0.28 ± 0.32	0.30 ± 0.18	0.22 ± 0.31	0.30 ± 0.18

BP, blood pressure; CBFV, cerebral blood flow velocity; CVR, cerebrovascular resistance; $ETCO_2$, end-tidal carbon dioxide; MCA, middle cerebral artery; VLF, very low frequency.
*$P=0.04$ (ANOVA).
**$P=0.02$ (ANOVA).

and compared them to the HBP patients without microangiopathy. Comparing their means by one-way ANOVA, only gain in the VLF and low-frequency range on the left side were significantly different between the two groups; gain was lower in the group with microangiopathy compared with the group without (Table 4). As these differences were only small, and all other comparisons did not show significant differences, we summarized all patients to one group for final analysis using control group II to consider the age dependency of gain in the simple linear regression model.

For the left side, control group II consisted of 25 participants (7 women/18 men; patients 14 women/26 men; chi-square $P=0.55$) with a mean age of 64 ± 10 years, for the right side, it consisted of 23 participants (9 women/14 men; patients 13 women/25 men, chi-square $P=0.69$) with a mean age of 62 ± 9 years. Using a *t*-test to analyse significant ($P<0.05-P<0.005$) differences between the controls and the patients, the patients exhibited in the VLF range a higher CVR, a higher coherence, a higher gain and percentage gain and a lower phase, and in the low-frequency range, they exhibited a lower phase (Table 5). BPV influences on the

TABLE 5. Comparison between all high blood-pressure patients and the controls of similar age and sex distribution

MCA/variable	Left controls ($N=25$)	Left patients ($N=40$)	*t* test, $P=$ level of significance	Right controls ($N=23$)	Right patients ($N=38$)	*t*-test, $P=$ level of significance
Mean BP (mmHg)	93 ± 16	90 ± 16	ns	91 ± 15	90 ± 16	ns
BP variability (mmHg)	17 ± 5	18 ± 4	ns	16 ± 4	18 ± 5	ns
$ETCO_2$ (mmHg)	38.5 ± 4.1	39.5 ± 4.0	ns	38.5 ± 4.0	39.5 ± 4.1	ns
CBFV (cm/s)	52 ± 10	53 ± 10	ns	51 ± 10	53 ± 13	ns
CVR	1.52 ± 0.41	1.75 ± 0.49	$P=0.01$	1.49 ± 0.52	1.79 ± 0.49	$P=0.006$
Coherence						
VLF	0.48 ± 0.12	0.54 ± 0.16	ns	0.46 ± 0.12	0.54 ± 0.12	0.02
Low frequency	0.70 ± 0.15	0.69 ± 0.15	ns	0.67 ± 0.17	0.70 ± 0.16	ns
High frequency	0.63 ± 0.14	0.67 ± 0.16	ns	0.63 ± 0.14	0.68 ± 0.16	ns
Gain (cm/s/mmHg)						
VLF	0.18 ± 0.20	0.35 ± 0.30	0.02	0.19 ± 0.22	0.36 ± 0.33	0.03
Low frequency	0.51 ± 0.29	0.52 ± 0.20	ns	0.51 ± 0.30	0.49 ± 0.21	ns
High frequency	0.58 ± 0.40	0.62 ± 0.23	ns	0.61 ± 0.44	0.61 ± 0.28	ns
%Gain (%/mmHg)						
VLF	0.34 ± 0.36	0.64 ± 0.50	0.01	0.31 ± 0.35	0.66 ± 0.57	0.01
Low frequency	0.98 ± 0.45	0.98 ± 0.32	ns	0.99 ± 0.53	0.90 ± 0.29	ns
High frequency	1.15 ± 0.62	1.18 ± 0.37	ns	1.19 ± 0.70	1.18 ± 0.33	ns
Phase (radians)						
VLF	1.07 ± 0.37	0.84 ± 0.35	0.01	1.04 ± 0.42	0.76 ± 0.28	0.003
Low frequency	0.74 ± 0.23	0.60 ± 0.23	0.02	0.74 ± 0.26	0.63 ± 0.27	0.04
High frequency	0.44 ± 0.43	0.29 ± 0.25	ns	0.40 ± 0.36	0.26 ± 0.25	ns

BP, blood pressure; CBFV, cerebral blood flow velocity; CVR, cerebrovascular resistance; $ETCO_2$, end-tidal carbon dioxide; MCA, middle cerebral artery; VLF, very low frequency.

transfer function parameters were analysed again with simple linear regression analysis, which showed a remarkable change compared with the healthy persons (Table 2). BPV kept its bilateral symmetrical predictive effects only on gain and percentage gain in the high-frequency range on both sides; in all other frequency ranges with bilateral symmetry it became asymmetrical, lost its significance, or a new significant relationship became uncovered where no relationship was present in the healthy population.

DISCUSSION

There are four main results of our study.

First is age dependency. Coherence and phase are not age-dependent; especially phase offers the ability to serve as an autoregulatory marker across all ages. Our findings correspond very well with the recent results in two other large cohorts of healthy persons [22,23] in which phase and coherence were found age-independent. That BP, CVR, and CBFV are age-dependent is well established. We found gain in the low-frequency and high-frequency range decreasing with age but age dependency diminished in the multiple linear regression model. Other authors have found gain increasing or decreasing with age [22,23]. According to our analysis, these differing results regarding gain behaviour could be related to factors other than age itself such as BPV [24] or CVR [14]. Thus, age dependency of gain will remain under discussion.

Second, influence of BPV. In the healthy persons, BPV had had a recognizable effect on gain (LH and high-frequency range) and phase (VLF and high-frequency range). The lack of any effect on phase in the low-frequency range could be interpreted as evidence that autoregulation in this frequency range buffers BPV. We found BPV inversely related to gain and phase. To our knowledge, a similar influence of BPV on phase and gain has not yet been reported. Our findings might be relevant, because the induced higher BPV by sit-to-stand-manoeuvres, thigh-cuff tests, passive leg movements, or lower body negative pressure, is used to stimulate the autoregulatory system with the effect that coherence is increased and the consistency/reproducibility of transfer function estimates increases [24–31]. Hence, these manoeuvres expose transfer function analysis to the risk of too low gain and phase values in the VLF and low-frequency ranges. Indeed, in a very recent work, by Mahdi *et al.* [27], nearly all of the dynamic cerebral autoregulation (dynCA) parameters investigated decreased in parts significantly after stand up. Similarly, Barnes *et al.* [28] demonstrated that the autoregulatory index (ARI) they used, was significantly reduced after squat/stand manoeuvres compared with the baseline recordings at standing.

Third, effect of SVD on dynCA. Overall, we did not find impressing differences between the patients with and without microangiopathy. This result corresponds to findings of Birns *et al.* [15] who reported that the autoregulatory index (ARI) they used did not correlate with the amount of white matter lesion volume in patients with SVD. Purkayastha *et al.* [32] demonstrated by MRI diffusion tensor imaging that the loss of white matter integrity in patients with treated HBP without visible white matter lesions was accompanied by a significantly degraded dynCA; they discussed the loss of white matter integrity might be the initial step for white matter lesion appearance and that the degraded dynCA might accelerate this process. Together with our results, it seems reasonable to assume that dynCA is degraded over all stages of microangiopathy. According to our results, CBFV regulation disturbances, which are predominantly detectable in the VLF range CBF cycles of 20–50 s) and to a much lesser degree in the low-frequency range (CBF cycles of 7–14 s). Previous reports on HBP in which dynCA was investigated [14,15,33,34] have found that phase in the low-frequency range were normal, and that the gain was the main regulatory component on HBP. However, a direct comparison to our findings requires caution because the studies were either performed on patients in a sitting or a standing position or the used method to assess autoregulation differed from ours. Our results may, therefore, lead to the suggestion that other mechanisms than sole pressure-dependent ones are additionally involved in the impairment of CBF regulation dynamics.

Fourth is the effect of HBP on the interaction between BPV and transfer function parameters. A further remarkable finding is that the homogenous behaviour between BPV and transfer function parameters becomes unbalanced in the HBP condition and shows side-to-side asymmetries. The reason is not obvious from our data. Group consistency or the medication used [35] may play a role but we doubt that both are enough to explain these results. To some extent, asymmetries can be recorded with Doppler ultrasound methods in healthy persons [36]. CBF asymmetries in healthy persons, however, are a prominent finding in ^{99m}Tc-hexamethyl propyleneamine oxime single-photon emission computed tomography (SPECT) [37,38]. These SPECT asymmetries increase in diffuse brain diseases, such as meningitis [37]. Compared with SPECT, Doppler ultrasound methods might be less sensitive to detect CBF regulation disturbances. However, the SPECT findings could be a bridge to our results in HBP and to the results of others who have found CBFV regulation asymmetries in diffuse traumatic brain injury [36,39] leading to suggestions that side-to-side asymmetries become more obvious in pathological conditions.

Our study has limits. We investigated our participants in a supine position. Therefore, our results may not be comparable with studies with additional orthostatic challenges like sitting, standing, or squatting. We did not use the beat-by-beat technique, but used raw wave form analysis. As part of a recent multicentre study, we could demonstrate our approach in good agreement with other working groups preferring the beat-by-beat technique [17,18]. Due to the small number of patients, we could not analyse our results with respect to medication effects; some of the antihypertensive drugs (ACE inhibitors and AT-II receptor blockers) increase the autoregulatory ability [40,41] and Ca-antagonists may influence the myogenic response [42,43].

In conclusion, when CBFV regulation is assessed in a supine position using transfer function estimates on spontaneous oscillations of BP and CBFV, neither gain nor coherence and phase exhibit an age dependency. BPV effects are homogenous and present in gain (low-frequency and high-frequency ranges) and phase (VLF and high-

frequency ranges), and may be a concurrent variable to CO_2 for modelling CBFV from BP. The cerebrovascular dynamic parameters did not differ between the different small vessel disease groups. Summarizing all HBP patients with controlled HBP, they exhibited a CBF regulation degrading predominantly in CBF cycles with a period length of 20–50 s (VLF range), and an interruption of the normal physiological behaviour between BPV and dynCA.

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Conflicts of interest

There are no conflicts of interest.

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Reviewer's Summary Evaluation

Reviewer 1

Müller *et al*. have shown that blood pressure variability influenced phase and gain in a symmetrical manner using transcranial doppler ultrasound. The strength of this study was that they found that those relationships were not found in the high blood pressure patients. The weakness of this study was a small sample size.