

# Enhanced external counterpulsation does not compromise cerebral autoregulation

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**Objectives** – Enhanced external counterpulsation (EECP) rhythmically augments blood pressure (BP) by diastolic lower-body compression. Recently, we showed decreased mean cerebral blood flow velocity (CBFV<sub>mean</sub>) in young healthy persons during EECP, but unchanged CBFV<sub>mean</sub> in atherosclerotic patients. In this study, we assessed EECP effects on dynamic cerebral autoregulation (CA). **Material & methods** – In 23 healthy persons and 15 atherosclerotic patients we monitored heart rate (HR), mean BP (BP<sub>mean</sub>) and CBFV<sub>mean</sub> before and during 5 min EECP. We analyzed spectral powers of HR, BP<sub>mean</sub> and CBFV<sub>mean</sub> in the low (LF: 0.04–0.15 Hz) and high (HF: 0.15–0.5 Hz) frequency ranges to determine CA from the LF-transfer function gain and phase shift between BP<sub>mean</sub> and CBFV<sub>mean</sub> oscillations. **Results** – EECP increased HR and BP<sub>mean</sub>, while transfer function gain and phase shift remained stable. **Conclusions** – Stable gain and phase values suggest that EECP does not compromise CA and, therefore, does not seem to bear cerebrovascular risks.

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Enhanced external counterpulsation (EECP) is a non-invasive alternative to intra-aortic balloon pump (IABP) counterpulsation for the treatment of patients with coronary artery disease, myocardial infarction, congestive heart failure or cardiogenic shock (1).

For EECP, three sets of inflatable cuffs are wrapped around the lower-body area, including legs, thighs and buttocks (1, 2). At the onset of the diastole, pressure is sequentially applied from the lower legs to the thighs and the buttocks, resulting in aortic counterpulsation and increased venous return (2, 3). With aortic counterpulsation, i.e. the mechanical shift of the intraarterial blood pool retrograde towards the aorta and aortic arch vessels, there is an augmentation of diastolic blood volume and blood pressure (BP). Moreover, diastolic compression of the cuffs results in an increased venous return to the right ventricle and, subsequently, in an increased right ventricular output and left ventricular preload (1–3). In addition, the release of the EECP pressure in the early systole results in diminished left ventricular afterload and therefore in lower left ventricular oxygen demand. The lower oxygen demand, in

turn, might improve left ventricular function, which might contribute to an increased cardiac output (2). In healthy controls and in atherosclerotic patients, aortic counterpulsation as well as increased cardiac output contributes to augmentation of mean arterial pressure (4). Previous studies demonstrated that EECP increases myocardial, hepatic and renal blood flow as well as carotid blood flow velocity (1, 4).

In our previous study (5), we observed an increase in mean BP during EECP in the young healthy study participants and in the older atherosclerotic patients. In response to the BP increase, the young, healthy participants had a slight but significant decrease in mean cerebral blood flow velocity (CBFV) while CBFV remained constant in the atherosclerotic patients. We assume that the decrease in CBFV seen in the young participants is an overshoot response of the intact cerebral autoregulation (CA), while the older atherosclerotic patients probably failed to respond adequately to the BP increase induced by EECP (5).

Normally, cerebral blood flow is maintained constant despite fluctuations in BP such as EECP induced BP fluctuations. Various mechanisms

contribute to CA (6). The myogenic or Bayliss component provides the intrinsic capacity of vascular smooth muscles to contract in response to an increase in systemic arterial pressure (7). The neurogenic mechanisms largely depend on intact sympathetic and to a smaller extent on parasympathetic innervation (7, 8). In addition, various neurohumoral, metabolic and endothelial mechanisms, that are highly dependent on intact endothelial function, contribute to stability and adjustment of CBF (6).

Negative effects of EECF on the dynamic function of CA would be detrimental to the use of the technique, e.g. in coronary artery disease patients, and might even entail a contraindication of the technique in patients with generalized atherosclerosis. So far, the impact of EECF on dynamic CA has not been evaluated in healthy persons or in patients with atherosclerosis.

This study was performed to quantify dynamic CA during EECF in a group of young healthy volunteers and in a group of older atherosclerotic patients, using transfer function phase and gain analysis between BP and CBFV fluctuations during EECF.

## Material and methods

### Subjects

We re-evaluated BP and CBFV signals in 23 young, healthy volunteers (seven female, 16 male, mean age  $27.9 \pm 4.0$  years, range 21–36 years) and 15 older patients with severe atherosclerosis (five female, 10 male, mean age  $64.0 \pm 7.3$  years, range 52–75 years) in whom we had previously assessed the effects of EECF on BP and CBFV (5). In the patients, the diagnosis of atherosclerosis was based on the findings of at least one coronary artery stenosis with need for intervention and the presence of at least two atherosclerosis risk factors. Atherosclerosis risk factors included arterial hypertension, diabetes mellitus, smoking, hypercholesterolemia, advancing age and obesity as defined by a body mass index of at least  $30 \text{ kg/m}^2$  (9).

None of the patients had a history of other clinically significant systemic diseases, particularly no neurologic diseases (5). Before the testing procedure, a Duplex sonographic examination of the extracranial arteries was performed to rule out significant stenoses of the carotid arteries.

The ethics committee of the University of Erlangen-Nuremberg approved the study and written informed consent was obtained according to the declaration of Helsinki.

### Procedures

All testing procedures were performed in the afternoon between 2 PM and 6 PM. Patients and healthy volunteers were tested in a relaxed and comfortable position in a quiet room with stable environmental conditions. All participants were asked not to consume nicotine, caffeine or alcohol 18 h before testing. Before testing, the patients and volunteers rested for at least 30 min to ensure that there was a stable sympathetic and parasympathetic cardiovascular modulation.

We continuously monitored heart rate (HR) using a standard 5-lead electrocardiogram with superficial skin electrodes attached to the area under the right and left clavicles, the right and left iliac crest and the chest. We continuously monitored BP from the left radial artery at the wrist, with the hand at the level of the heart, using non-invasive applanation tonometry. The tonometer consists of an array of 31 equally spaced piezoresistive pressure transducers, an automated positioning system, and signal conditioning and initial calibration by oscillometric cuff measurement of the left brachial artery (Colin Pilot™; Colin Medical Instruments Corp., San Antonio, TX, USA). To rule out possible interferences of mechanical artifacts induced by EECF with the continuous BP measurements of the Colin monitor by applanation tonometry, we positioned the left forearm and hand in a cushioned wrist brace and on a soft pillow dampening any movement artifacts during EECF. Moreover, we assured that continuous BP values were reliable during EECF by repeatedly comparing the continuous BP values to values of conventional oscillometric measurements at the level of the contralateral brachial artery before and during EECF. We recorded peak-systolic, end-diastolic BPs ( $BP_{\text{sys}}$ ,  $BP_{\text{dia}}$ ), the peak BP augmented by EECF during diastole ( $BP_{\text{aug}}$ ), and the mean BP averaged over the entire BP cycle ( $BP_{\text{mean}}$ ). Mean and augmented diastolic cerebral blood flow velocities ( $CBFV_{\text{mean}}$  and  $CBFV_{\text{aug}}$ ) were studied at the proximal segment of the middle cerebral artery (MCA) by means of transcranial Doppler sonography (Multidop XL™; DWL, Sipplingen, Germany). The MCA was insonated through the temporal window approximately 1 cm above the zygomatic arch at a depth of 35–55 mm using pulsed 2 MHz Doppler probes. In order to assure reliable values of CBFV during EECF despite possible movement artifacts, we first optimized the individual TCD signal by selecting an insonation depth between 35 and 55 mm. In the analysis, we then compared the CBFV values of each individual participant before

EECP to his or her CBFV values during EECP, but did not compare CBFV values of one person to those of another person insonated at a different depth. After optimizing the Doppler signal, the probe was attached to the skull at a fixed angle using a headband with an adjustable positioning system.

All parameters were recorded at rest and during EECP for 90 s each. Before EECP, the sampling epoch ended 90 s prior to the onset of EECP to avoid any bias because of preparatory influences. During EECP, the sampling epoch started 3 min after onset of EECP, i.e. after the initial cardiovascular and mental adaptation to the counterpulsation. Respiration was paced at 12 cycles per minute (cpm) (0.2 Hz). To familiarize the study participants with the respiratory frequency prior to the study, they were taught to follow visual and verbal signals to inspire and expire within 5 s, i.e. close to their normal respiratory frequency. The study participants had to follow the 12 cpm respiratory pattern to avoid respiratory interferences with autonomic cerebro- and cardiovascular modulation, but also to assure a higher stability of the biosignals during EECP. To ensure that the breathing rate was constant, we monitored respiratory frequency with a two-belt chest-abdomen inductance plethysmograph (Respirace Calibrator<sup>TM</sup>; Ambulatory Monitoring Inc., Ardsley, NY, USA). During EECP, an electrocardiogram-triggered diastolic pressure of approximately 250 mmHg was rhythmically and successively applied to the vascular bed of the calves, thighs and buttocks by means of three air-filled cuffs (EECP®, Vasomedical Inc., Westbury, NY, USA). Finger-plethysmography was used to record the response of BP to EECP and to optimize the diastolic BP augmentation by adjusting the time delay between the R-wave of the electrocardiogram and the onset of the counterpulsation pressure.

#### Data acquisition and analysis

All biosignals were transferred via analogue output into a custom designed data acquisition and analysis system (HRview<sup>TM</sup>; Boston Medical Technologies, Wakefield, MA, USA). The analogue data were digitized by a 32-channel, 16-bit resolution analogue-digital converter (CIO-DAS64-02/16; ComputerBoards Inc., Mansfield, MA, USA). All data were transferred to a personal computer, sampled at 1 kHz and stored for off-line analysis.

From the 90-s epochs, we calculated mean values and standard deviation of all biosignals (5). In addition, we assessed cerebrovascular resistance (CVR) as the ratio between  $BP_{\text{mean}}$  at the level of

insonation and  $CBFV_{\text{mean}}$  (10). Our measurements were performed in the supine position.  $BP_{\text{mean}}$  at the level of insonation was considered to closely correspond to  $BP_{\text{mean}}$  recorded from the artery at the level of the wrist. Therefore, CVR was calculated by dividing  $BP_{\text{mean}}$  by  $CBFV_{\text{mean}}$ .

#### Spectral analysis

To assess the contribution of the sympathetic and parasympathetic systems to HR, BP and CBFV modulation, we evaluated HR, BP and CBFV variability using spectral analysis (11). For spectral analysis, 90-s recordings of the biosignals before and during EECP were manually cleaned from artifacts by linear interpolation, resampled at 4 Hz, and then taken for spectral processing using the Blackman-Tukey algorithm (12, 13). HR, BP and CBFV values show slow underlying fluctuations that are largely mediated by the undulating activity of the sympathetic and parasympathetic nervous systems (14–16). Sympathetic and parasympathetic influences on HR, BP and CBFV variability were assessed by quantifying the low frequency (LF: 0.04–0.15 Hz) and high frequency (HF: 0.15–0.5 Hz) components of the biosignals. The magnitude of these oscillations was determined as the integral under the power spectral density curves and expressed as LF- and HF-powers of HR ( $\text{bpm}^2$ ), BP ( $\text{mmHg}^2$ ) and CBFV ( $\text{cm}^2/\text{s}^2$ ) (12, 15).

As changes LF- and HF-powers of HR may be due to changes in total power (11), we normalized the LF- and HF-powers to more precisely quantify sympathetic and parasympathetic cardiac modulation (11). For normalization of the powers, we divided the LF- or HF-powers by the sum of LF- and HF-powers and multiplied the resulting value by 100 (17).

The mechanisms of CA can be considered to reflect a high-pass filter that dampens slow fluctuations of BP but allows for passing through of rapid oscillations, such as the pulsatile signals of the BP and CBF waves (18, 19). To assess dynamic autoregulation, we evaluated the transfer of BP fluctuations onto oscillations in CBFV by performing transfer function analysis and calculating the transfer function gain and phase shift between  $BP_{\text{mean}}$  and  $CBFV_{\text{mean}}$  in the LF band, provided there was significant coherence between both signals (19–21).

Within the LF band, the coherence between  $BP_{\text{mean}}$  and  $CBFV_{\text{mean}}$  oscillations might span from 0 (i.e. no association) to 1 (i.e. maximal association) (11). If coherence was 0.5 or higher, the two signals were considered to have a stable phase relation for a given frequency of oscillation

and the signals were considered synchronized with each other and the LF gain and phase shift between CBFV and BP oscillations were calculated.

Cerebral blood flow velocity within the MCA not only depends on CVR of the downstream resistance vessels, but also directly on vascular resistance changes in all other parallel coupled circulatory units. Therefore, measurements of CVR only are not suited to assess dynamic CA. Dynamic CA is only indirectly related to CVR as the dynamic CA is calculated as the transfer function gain between the powers of  $BP_{mean}$  and  $CBFV_{mean}$  in the sympathetically mediated LF band of signal oscillations. To adjust these powers for inter-individual differences resulting from individually varying  $BP_{mean}$  or  $CBFV_{mean}$  values of each study participant, the dynamic CA should be assessed by normalizing the gain of the LF powers of  $BP_{mean}$  and  $CBFV_{mean}$  by the individual BP and CBFV values (10, 18, 22). Consequently, the values of the transfer function gain, i.e. the ratio of the LF powers of  $CBFV_{mean}$  to the LF powers of  $BP_{mean}$  are normalized by the values of  $BP_{mean}$  and  $CBFV_{mean}$ , i.e. multiplied by a value that happens to be identical with the CVR value ( $CVR = BP_{mean} / CBFV_{mean}$ ) and expressed as normalized gain in arbitrary units (a.u.) (18).

Statistical analysis

All values are presented as mean  $\pm$  SD. To identify effects of EECP on cardiovascular regulation and parameters of CA, we used the two-sided Wilcoxon test for further comparison of biosignals before and during EECP in each group. The level of significance was set at  $P < 0.05$ .

Results

Values of HR, BP, CBFV, LF- and HF-powers and gain and phase shift between BP and CBFV oscillations are summarized in Table 1.

Young, healthy persons

In the healthy persons, EECP induced the typical augmented diastolic peak in BP ( $BP_{aug}$ ) and CBFV ( $CBFV_{aug}$ ; Fig. 1). HR and  $BP_{mean}$  were significantly higher during EECP, while  $CBFV_{mean}$  was significantly lower during EECP than at baseline, as previously reported (5). In contrast, CVR values were higher during EECP than at baseline ( $P < 0.01$ ).

Normalized LF- and HF-powers of HR did not change significantly with EECP. In contrast,

**Table 1** Results recorded before and during enhanced external counterpulsation (EECP)

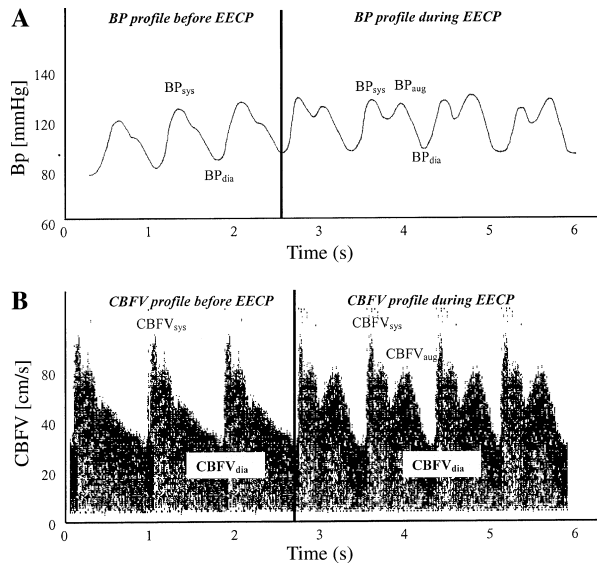
Group	Before EECP	During EECP	Wilcoxon ( <i>P</i> -value)
HR [bpm]			
Patients	69.7 $\pm$ 9.4	73.6 $\pm$ 9.1	<0.01
Controls	72.7 $\pm$ 9.0	75.6 $\pm$ 8.6	<0.05
LF <sub>nu</sub> of HR (%)			
Patients	41.0 $\pm$ 18.3	47.4 $\pm$ 17.0	>0.05
Controls	33.9 $\pm$ 19.9	35.9 $\pm$ 16.0	>0.05
HF <sub>nu</sub> of HR (%)			
Patients	59.0 $\pm$ 18.3	52.6 $\pm$ 17.0	>0.05
Controls	66.1 $\pm$ 19.9	64.1 $\pm$ 16.0	>0.05
$BP_{mean}$ (mmHg)			
Patients	86.4 $\pm$ 20.0	92.4 $\pm$ 24.1	<0.01
Controls	83.4 $\pm$ 10.2	86.2 $\pm$ 9.8	<0.05
LF-power of $BP_{mean}$ (mmHg <sup>2</sup> )			
Patients	3.1 $\pm$ 2.1	1.1 $\pm$ 0.8	<0.05
Controls	2.7 $\pm$ 2.0	1.2 $\pm$ 1.0	<0.01
HF-power of $BP_{mean}$ (mmHg <sup>2</sup> )			
Patients	3.0 $\pm$ 2.4	2.3 $\pm$ 2.3	>0.05
Controls	1.5 $\pm$ 1.3	3.0 $\pm$ 2.5	<0.01
$BP_{aug}$ (mmHg)			
Patients		100.4 $\pm$ 23.9	
Controls		114.7 $\pm$ 13.3	
$CBFV_{mean}$ (cm/s)			
Patients	46.7 $\pm$ 11.5	47.0 $\pm$ 11.8	>0.05
Controls	55.0 $\pm$ 18.5	50.1 $\pm$ 17.0	<0.05
LF-power of $CBFV_{mean}$ (cm <sup>2</sup> /s <sup>2</sup> )			
Patients	2.6 $\pm$ 1.9	2.4 $\pm$ 2.4	>0.05
Controls	2.0 $\pm$ 1.2	2.6 $\pm$ 2.1	>0.05
HF-power of $CBFV_{mean}$ (cm <sup>2</sup> /s <sup>2</sup> )			
Patients	1.9 $\pm$ 1.2	2.7 $\pm$ 2.2	>0.05
Controls	2.0 $\pm$ 2.2	3.0 $\pm$ 2.8	0.01
$CBFV_{aug}$ (cm/s)			
Patients		51.4 $\pm$ 11.9	
Controls		61.0 $\pm$ 15.0	
$CVR = BP_{mean}/CBFV_{mean}$ (mmHg/scm)			
Patients	1.9 $\pm$ 0.7	2.0 $\pm$ 0.8	>0.05
Controls	1.6 $\pm$ 0.5	1.9 $\pm$ 0.5	<0.01
LF gain between BP and CBFV (cm/s/mmHg)			
Patients	0.8 $\pm$ 0.3	1.1 $\pm$ 0.8	>0.05
Controls	0.8 $\pm$ 0.3	1.0 $\pm$ 0.5	>0.05
LF gain <sub>mean</sub> = gain $\times$ $BP_{mean}/CBFV_{mean}$ (a.u.)			
Patients	1.2 $\pm$ 0.3	1.6 $\pm$ 0.7	>0.05
Controls	1.1 $\pm$ 0.4	2.1 $\pm$ 1.6	>0.05
LF phase between BP and CBFV (degrees)			
Patients	52.6 $\pm$ 25.8	53.4 $\pm$ 65.3	>0.05
Controls	44.7 $\pm$ 14.3	53.8 $\pm$ 25.2	>0.05

All data are presented as mean  $\pm$  SD.

*P*-values below 0.05 indicate a significant difference between values recorded before and during EECP.

HR, heart rate;  $BP_{mean}$ , mean blood pressure;  $BP_{aug}$ , augmented diastolic blood pressure;  $CBFV_{mean}$ , mean cerebral blood flow velocity;  $CBFV_{aug}$ , augmented cerebral blood flow velocity; CVR, cerebrovascular resistance; LF, low frequency; HF, high frequency; LF<sub>nu</sub>, normalized LF-power = LF-power/(LF-power + HF-power)  $\times$  100; HF<sub>nu</sub>, normalized HF-power = HF-power/(LF-power + HF-power)  $\times$  100; gain<sub>norm</sub>, normalized gain = gain  $\times$   $BP_{mean}/CBFV_{mean}$ ; a.u., arbitrary units.

LF-power of  $BP_{mean}$  was lower during EECP than at baseline ( $P < 0.01$ ). Mechanically induced HF-powers of  $BP_{mean}$  and of  $CBFV_{mean}$ , however, were significantly higher during EECP than at baseline ( $P < 0.01$ ). Sympathetically mediated LF-power of  $CBFV_{mean}$  remained stable during EECP in the



**Figure 1.** Blood pressure (BP) (A) and cerebral blood flow velocity (CBFV) wave forms (B) before and during EECP. EECP induces a second BP and CBFV peak during diastole ( $BP_{aug}$ ,  $CBFV_{aug}$ ). ( $BP_{sys}$ , peak-systolic blood pressure;  $BP_{dia}$ , end-diastolic blood pressure;  $CBFV_{sys}$ , peak-systolic cerebral blood flow velocity;  $CBFV_{dia}$ , end-diastolic cerebral blood flow velocity).

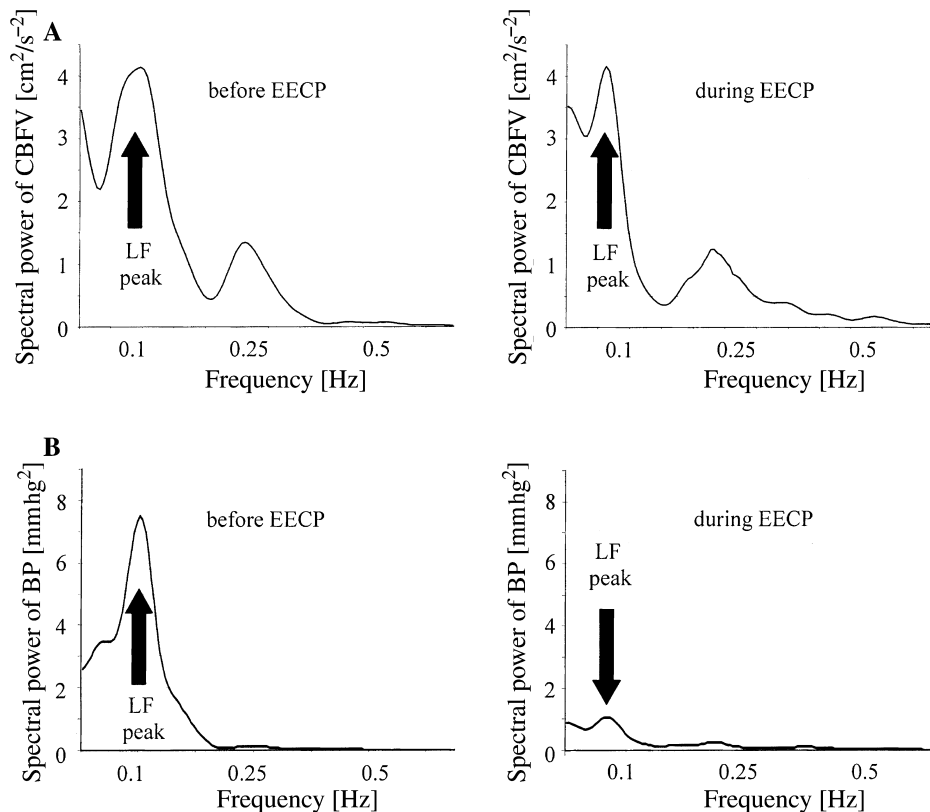
healthy persons. Similarly, the absolute and normalized values of the transfer function gain and phase shift remained unchanged during EECP (Fig. 3).

Atherosclerotic patients

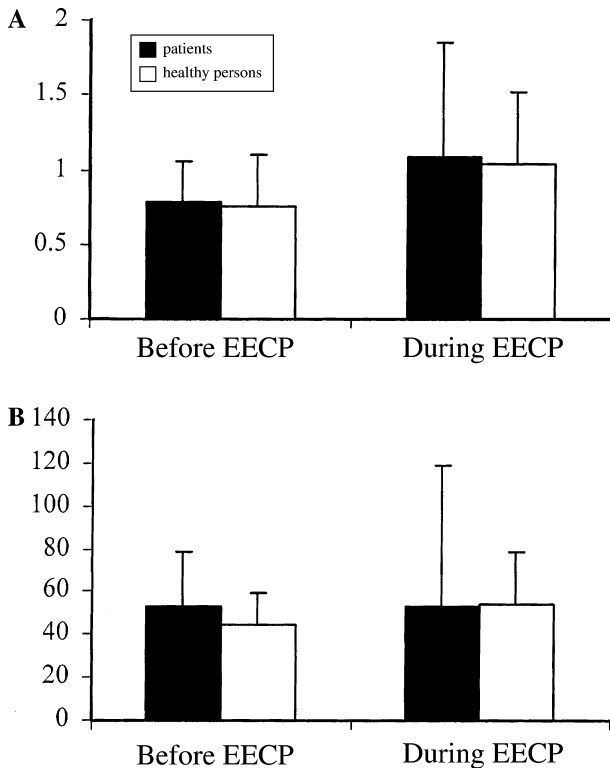
Despite their higher age and their arteriosclerosis, patients showed changes of cardiovascular parameters during EECP that were rather similar to the changes in the healthy persons.

Similar to the younger healthy persons, the patients also had significantly higher HR and  $BP_{mean}$  values during than before EECP. EECP also induced the typical BP augmentation and augmented CBFV during diastole, as previously reported (5) (Fig. 1). In contrast to the younger persons,  $CBFV_{mean}$  did not decrease (5) and CVR did not increase, but remained unchanged during EECP.

The LF-power of  $BP_{mean}$  also was lower during than before EECP ( $P < 0.05$ ), while LF-power of  $CBFV_{mean}$  remained unchanged during EECP (Fig. 2). EECP had no influence on the



**Figure 2.** Spectral analysis of mean cerebral blood flow velocity ( $CBFV_{mean}$ ) (A) and mean blood pressure ( $BP_{mean}$ ) (B) modulation before and during enhanced external counterpulsation (EECP) in a 65-year-old patient with atherosclerosis. LF-power of  $BP_{mean}$  was lower during than before EECP. EECP might stimulate arterial baroreceptors resulting in sympathetic withdrawal. LF-power of  $CBFV_{mean}$  did not change during EECP. Consequently, changes in LF blood pressure fluctuations were not entirely transferred onto the cerebrovascular system, indicating intact dynamic cerebral autoregulation.



**Figure 3.** Transfer function gain (A) and phase shift (B) between mean blood pressure ( $BP_{\text{mean}}$ ) and mean cerebral blood flow velocity ( $CBFV_{\text{mean}}$ ) oscillations in the low frequency band in 15 older patients with atherosclerosis and 23 younger healthy persons before and during enhanced external counterpulsation (EECP). Transfer function gain as well as phase shift remained stable in both groups, indicating that EECP did not influence dynamic cerebral autoregulation.

HF-powers of  $BP_{\text{mean}}$  and  $CBFV_{\text{mean}}$ . As in the young healthy persons, EECP did not change transfer function gain and phase shift in the older patients. Normalized transfer function gain also remained stable (Fig. 3).

### Discussion

Our study showed two major findings regarding the central and peripheral autonomic modulation during EECP in healthy persons and in atherosclerotic patients. EECP did not affect dynamic CA in either group, as revealed by stable values of transfer function gain and phase shift between BP and CBFV oscillations, and EECP had no major influence on the autonomic cardiovascular modulation.

In both our groups, the younger, healthy participants and the older atherosclerotic patients, EECP typically augmented BP and CBFV during diastole and increased mean BP (5). The major difference between both groups was the slight but

significant decrease in mean CBFV (from 55.0 to 50.1 cm/s) and increase of CVR in the younger group and the lack of EECP effect on  $CBFV_{\text{mean}}$  and CVR in the patients. We had expected that CBFV remains stable with adequate CA despite BP changes during EECP.

We assume that the decrease in CBFV seen in the young participants is an overshoot response of the intact CA to the higher frequency of BP increases during EECP with two stimuli in one cardiac cycle and to the increase in mean BP. We speculate that the autoregulatory response of the young participants induced a constriction of cerebral resistance vessels downstream of the insonation site, while the older atherosclerotic patients probably failed to generate a similar vasoconstriction because of a reduction of the vessel elasticity.

Because of reduction of the systolic peak and a second BP increase during EECP, the BP profile is smoothed, which results in more laminar shear stress. It has been suggested that laminar shear stress furthers vasodilatation, e.g. by nitric oxide release. Therefore, the decrease of CBFV in the proximal MCA in the healthy volunteers might not only result from an autoregulatory constriction of downstream cerebral resistance vessels, but there might also be a vasodilatation of the proximal MCA-segment because of shear stress mediated NO release (23–25). Similarly, we assume that CBFV of patients remained unchanged during EECP because atherosclerotic vessel wall alterations and reduced NO release resulted in less constriction of intracerebral resistance vessels and allowed for less NO mediated dilatation of the proximal MCA-segment. Consequently, in the older atherosclerosis patients, the local MCA dilatation might have been less prominent. However, as we did not reveal cerebral small vessel disease by direct measures such as magnetic resonance imaging scans, we were not able to demonstrate that our patients had cerebral atherosclerosis indeed.

In several biosignals, there are slow underlying fluctuations that are largely mediated by the undulating activity of the autonomic nervous system (14–16). Parasympathetic modulation of HR is most pronounced at the frequency of respiration, e.g. at 0.2 Hz with a breathing rate of 12 cpm (12, 14–16). Parasympathetic respiratory influences are considered to account for HR modulation occurring in the so-called high frequency (HF) range between 0.15 and 0.5 Hz (12, 14–16). Therefore, we used HR modulation in the HF range as an index of parasympathetic modulation (12, 14–16).

In contrast, fluctuations in the BP and CBFV signal in the HF range are primarily a mechanical consequence of respiration-induced increases in venous return (12, 14–16). However, parasympathetic influences on HR still occur at frequencies below 0.15 Hz while fluctuations of the BP and CBFV signals in the so-called low frequency (LF) range between 0.04 and 0.15 Hz are considered to be related to sympathetic outflow only (12, 14–16). Therefore, we determined the degree of sympathetic signal modulation from the amount of LF BP and CBFV modulation (12, 14–16).

The patients and the younger volunteers showed a similar adaptation of their sympathetically mediated BP modulation during counterpulsation. In both groups, there was a decrease of the LF-powers of  $BP_{\text{mean}}$  during EECP. The withdrawal of sympathetic BP modulation may be because of baroreceptor stimulation. Normann and Kennedy suggested that the presence of two peak pressures in one cardiac cycle might stimulate the arterial baroreceptors (26). Moreover, increased mean BP during EECP may contribute to an increased baroreceptor activity (11). A reduction of sympathetic activity during EECP should result in a decrease of HR. Yet, we observed an increase of HR in both groups. We assume that the effects of the higher venous return and increased central venous pressure during counterpulsation (3) override any baroreflex mediated HR slowing and induce the HR acceleration. In addition, the reduction in systolic BP during EECP might induce baroreceptor unloading resulting in cardiovagal withdrawal and sympathetic activation, which might add to the HR acceleration.

In contrast to the LF modulation of BP, the LF-power of  $CBFV_{\text{mean}}$  did not change during counterpulsation in either group. This discrepancy between sympathetic modulation of BP and CBFV indicates that changes in LF BP fluctuations were not entirely transferred onto the cerebrovascular system. Dynamic CA largely depends on sympathetically mediated vasoconstriction of cerebral vessels (6, 7, 27). Thus, the finding of preserved sympathetic CBFV modulation in the presence of reduced sympathetic BP modulation indicates that dynamic CA, i.e. the ability of the cerebral resistance vessels to buffer low-frequency BP fluctuations, remained intact in the young healthy participants but also in the older arteriosclerosis patients.

Furthermore, EECP had no influence on the transfer function gain or phase shift between BP and CBFV oscillations. Calculation of transfer function gain and phase shift have been well established for the assessment of dynamic CA

and provides a more accurate analysis of autoregulatory responses to EECP.

The analysis of the transfer function of mean BP ( $BP_{\text{mean}}$ ) oscillations as the input signal of CA and  $CBFV_{\text{mean}}$  oscillations as the output signal can be used to calculate the gain between both parameters. This gain reflects the extent to which there is a transmission of BP fluctuations on CBFV fluctuations or a buffering of such fluctuations by the mechanisms of autoregulation (11, 19). Low transfer function gain indicates adequate buffering of BP fluctuations by cerebral resistance vessels, i.e. intact CA (11, 19).

In addition, the phase relation between oscillations in  $BP_{\text{mean}}$  and  $CBFV_{\text{mean}}$  can be used to determine the quality of CA. Diehl et al. demonstrated that BP oscillations induced by 6 cpm breathing generate similar CBFV oscillations which are not only dampened but also shifted to the left because of the high pass filter characteristics of CA (11, 20). An increase in BP caused by metronomic breathing activates CA. Autoregulation induces a counterregulation of the vascular resistance bed with vasoconstriction. This counterregulation causes CBFV to be maximal before the BP increase has reached its maximum. While BP approaches its maximum, the autoregulatory responses already start to slow CBFV. When BP finally declines, CBFV declines even faster because of the continued response to the preceding BP increase. As BP further declines, autoregulation now opposes slowing of CBFV by dilating the resistance bed. Again, CBFV reaches its minimum before BP is at its lowest value. Consequently, CBFV recovers before the next rise of BP. This relation between BP and CBFV oscillations can be described by calculating the phase shift between the leading CBFV and the lagging BP signal (11, 20). According to Diehl et al., the phase shift between BP and CBFV oscillations induced by metronomic breathing at a rate of 6 cpm is between 30 and 90°. A decrease of the phase angle below such normal values indicates a more passive behavior of the cerebral vessel bed and is an indicator of impaired CA (11, 18, 20).

The stability of both parameters during EECP confirms the assumptions of our previous CBFV analysis (5) that EECP does not compromise CA. Obviously, EECP does not impair the mechanisms protecting the cerebral vascular bed against changes in arterial pressure and maintaining stability of cerebral blood flow by dampening of BP oscillations.

To conclude, this study confirms that EECP does not compromise the dynamic mechanisms of CA. Transfer function gain and phase between BP

and CBFV oscillations remain stable during counterpulsation not only in younger healthy persons, but also in older atherosclerotic patients in whom EECP might provide a treatment alternative for coronary artery disease. For these patients, EECP does not seem to bear a cerebrovascular risk such as inadequate increase of cerebral perfusion with secondary complications such as cerebral hemorrhage (5).

In the current study, we did not attempt to evaluate possible EECP side-effects on cerebral blood flow or autoregulation in any high risk patients during acute emergencies. Consequently, we cannot exclude contra-indications for the emergency treatment, e.g. of patients in cardiogenic shock with low BPs. In fact, there might be inadequate cerebral perfusion and altered CA during EECP if applied in patients during cardiogenic shock and low BP.

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