Acta Neurol Scand 2003: 107: 405–411
Printed in UK. All rights reserved

ACTA NEUROLOGICA
SCANDINAVICA
ISSN 0001-6314

Changes of cerebral blood flow velocities during enhanced external counterpulsation

Werner D, Marthol H, Brown CM, Daniel WG, Hilz MJ. Changes of cerebral blood flow velocities during enhanced external counterpulsation.
Acta Neurol Scand 2003: 107: 405–411. © Blackwell Munksgaard 2003.

Objectives – Intra-aortic counterpulsation is the most frequently used cardiac assist device. However, there are only few studies of the effects of counterpulsation on cerebral blood flow and these report conflicting outcomes. The new enhanced external counterpulsation (EECP) technique reproduces non-invasively the effects of intra-aortic counterpulsation. In this study, we evaluated effects of EECP on blood pressure (BP) and on cerebral flow velocity (CBFV). *Subjects and methods* – Twenty-three healthy controls and 15 atherosclerotic patients each underwent a 5-min session of EECP. Before, during and after EECP we monitored heart rate, beat-to-beat radial artery BP and CBFV. *Results* – EECP induced a second increase in BP and CBFV during diastole with a significant increase of mean BP and a decrease of systolic BP in patients and controls. Mean CBFV increased in both groups during the first 5 s of EECP. After 3 min of EECP, diastolic CBFV was still higher than at baseline, but systolic CBVF was lower than at baseline; mean CBFV was as low as before EECP in the patients and lower than the baseline values in the controls. Three minutes after ending EECP, mean and systolic BP were lower in the patients than the corresponding baseline values. Otherwise, CBFV and BP values did not differ from baseline in patients and controls. *Conclusion* – Cerebral autoregulation ensures the constancy of cerebral blood flow even though EECP creates marked systemic changes. In the patients, the decrease of BP after EECP with maintained CBFV indicates an improved BP–CBFV relation and a more economic autoregulation.

D. Werner[1], H. Marthol[2], C. M. Brown[3], W. G. Daniel[1], M. J. Hilz[2,3]

[1]Department of Cardiology, Friedrich-Alexander-University, Erlangen-Nuremberg, Germany; [2]Department of Neurology, New York University Medical Center, New York, USA; [3]Department of Neurology, Friedrich-Alexander-University, Erlangen-Nuremberg, Germany

Key words: enhanced external counterpulsation; transcranial Doppler sonography; cerebral autoregulation

Dierk Werner, II. Medical Clinic (Cardiology, Angiology), Friedrich-Alexander-University, Ulmenweg 18, 91054 Erlangen, Germany
Tel.: +49 9131 8535301
Fax: +49 9131 8533838
e-mail: dierk.werner@nexgo.de

Accepted for publication October 13, 2002

For more than three decades, intra-aortic counterpulsation (intra-aortic balloon pumping, IABP) has been used to improve coronary perfusion in patients with acute cardiac failure. The effects of IABP are based on the intermittent inflation of a balloon in the descending aorta at the beginning of diastole and deflation at the end of diastole. The hemodynamic effects of IABP are an increase of diastolic blood flow to the organs and a reduction in cardiac afterload. The device is mainly used to support coronary circulation and to improve outcome of patients in cardiogenic shock.

Counterpulsation also has been used for the treatment of cerebrovascular diseases. Animal studies demonstrated a benefit of IABP in ischemic strokes or cerebral vasospasm (1, 2). Several clinical case reports illustrated the potential usefulness of intra-aortic counterpulsation in patients suffering from cerebral vasospasm after subarachnoidal hemorrhage or from post-procedural hypotension following carotid stenting (3–6). Yet, most probably because of the increased risks associated with this invasive method there are only a few published studies. Furthermore, data on the effect of counterpulsation on cerebral perfusion are inconsistent (Table 1). Some studies show an increase of cerebral blood flow of up to 56% (7), while others show a decrease of as much as 12% (8). We assume that the mechanisms of cerebral autoregulation ensure constancy of cerebral blood flow during counterpulsation despite the augmented diastolic pressure.

Enhanced external counterpulsation (EECP) is a new method that can reproduce the diastolic

Table 1 Studies on cerebral blood flow (CBF) during IABP

Authors	Study design	Change of CBF
Gee et al. (8)	Pneumoplethysmographic assessment of ocular blood flow (56 patients)	11.6% decrease ($P < 0.005$)
Tranmer et al. (1)	Measurement of CBF in a canine stroke model with microsphere technique (six dogs)	No significant change (+4.0%)
Applebaum et al. (15)	Duplex scanning of common carotid artery (14 patients)	No significant change (+3.2%)
Nussbaum et al. (2)	Measurement of CBF in a cerebral vasospasm model with microsphere technique (10 dogs)	18.9% increase ($P < 0.0001$)
Wesley and Morgan (22)	Measurement in a canine resuscitation model (seven dogs)	31.3% increase ($P < 0.05$)
Bhayana et al. (7)	Animal model of cardiogenic shock (10 dogs)	56% increase ($P < 0.05$)

augmentation of intra-aortic counterpulsation in a non-invasive manner. According to the study of Taguchi et al. (9), external counterpulsation has rather similar effects on diastolic blood pressure (BP) and systemic vascular resistance as intra-aortic counterpulsation. The authors showed that diastolic BP increased by 36% after 1 h of IABP and by 33% after 1 h of EECP. Systolic systemic vascular resistance decreased by 18% after 1 h of IABP and by 20% after 1 h of EECP. Also, heart rate showed no change during 1 h of both procedures.

EECP produces the retrograde pulse wave via pressure to the lower limbs during diastole. Clinically, EECP is used as a new therapeutic option for patients with angina pectoris (10). There are two studies of blood flow changes in the carotid arteries during EECP suggesting an enhancement of perfusion (11, 12). To date, however, there are no studies evaluating whether cerebral blood flow increases as a consequence of increased carotid artery blood flow or remains constant because of autoregulatory mechanisms.

In the present study, we tested whether EECP induces any change of flow velocities in the middle cerebral artery (MCA) using transcranial Doppler sonography in healthy volunteers. Moreover, we studied whether effects of EECP on cerebral blood flow are different in patients with atherosclerosis from those in young healthy controls.

Subjects and methods

Subjects

Twenty-three healthy volunteers with no history of cardiovascular or neurological disease (mean age: 27.9 ± 4.0 years) and 15 patients (mean age: 64.0 ± 7.3 years) with severe atherosclerosis (inclusion criteria: at least one coronary artery stenosis with need for intervention and at least two atherosclerotic risk factors) participated in the study. Hypertension (five patients), diabetes mellitus (eight patients), smoking (eight patients), overweight (10 patients) and hypercholesterolemia (12 patients) were considered as atherosclerotic risk factors. Informed consent was obtained from all study participants according to the declaration of Helsinki.

Method

EECP operates by applying electrocardiogram-triggered diastolic pressure of approximately 250 mmHg to the vascular bed of the calves, thighs, and buttocks by means of three air-filled cuffs (Vasomedical Inc., Westbury, NY, USA; Fig. 1). Finger-plethysmography is used to record the response of BP to EECP and to optimize the augmentation of BP during diastole by adjusting the time delay between the R-wave of the electrocardiogram and the onset of counterpulsation pressure (13).

We assessed the mean, systolic and augmented diastolic cerebral blood flow velocity (CBFV) of the MCA by means of transcranial Doppler sonography (MultiDop X4™, DWL, Sipplingen, Germany). A 2-MHz pulsed Doppler probe insonated the MCA through the temporal window above the zygometic arch at a depth of 35–55 mm. The probe was held in a stable position by means of an adjustable headband and a positioning system. The cerebrovascular resistance index was calculated under resting conditions.

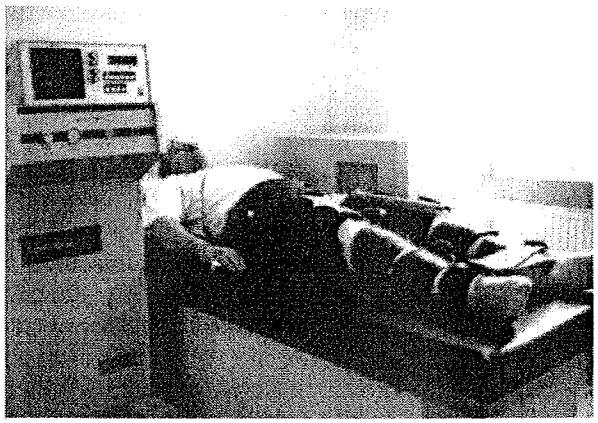

Figure 1. Enhanced external counterpulsation device (Vasomedical Inc., Westbury, NY, USA).

Values were derived from the ratio of the difference between systolic and diastolic blood flow velocities divided by systolic blood flow velocity.

Heart rate and mean, systolic and augmented diastolic beat-to-beat radial artery BP were recorded by means of applanation tonometry (Colin Pilot™, San Antonio, TX, USA). The tonometer consisted of an array of 31 equally spaced piezoresistive pressure transducers, an automated positioning system, and signal conditioning and intermittent calibration by oscillometric cuff measurement of brachial artery BP (14). A wrist support and supporting strap assured positional stability of the tonometer. Mean arterial BP was calculated by measuring the area under each pulse curve. Mean BP was taken as that BP that divided the area under curve in two equal portions above and below this value.

Respiratory frequency and tidal volume were monitored with a two-belt chest–abdomen inductance plethysmograph after calibration (Respitrace Calibrator™, Ambulatory Monitoring, Inc., Ardsley, NY, USA).

After a resting period of at least 30 min, biosignals were averaged for 90 s at baseline in supine position. After onset of EECP, signals were averaged during the first 5 s of counterpulsation to assess the initial hemodynamic response to the stimulation. After 3 min of EECP, we monitored biosignals for another 90 s. Finally, 90 s of biosignals were recorded after EECP had been terminated for 3 min to assess responses after recovery. Study participants were asked to breathe at a paced frequency of 12 cycles per minute during the entire recording.

Statistical method

During the four periods of analysis, we calculated averaged values of mean, systolic and augmented diastolic flow velocities and BP. The two-sided Friedman test was used to analyze differences between averaged values taken at baseline, during the first 5 s of EECP, during 90 s of EECP, 3 min after EECP onset, and during 90 s averaged after 3 min of recovery. The two-sided Mann–Whitney *U*-test was applied to compare data of the atherosclerotic patients to those of the controls during the four recording phases. The level of significance was set at $P < 0.05$.

Results

EECP generated a characteristic second increase in BP and CBFV waves during diastole. Fig. 2 gives an example of the diastolic augmentation of every second pulse wave due to EECP applied after every second heart beat.

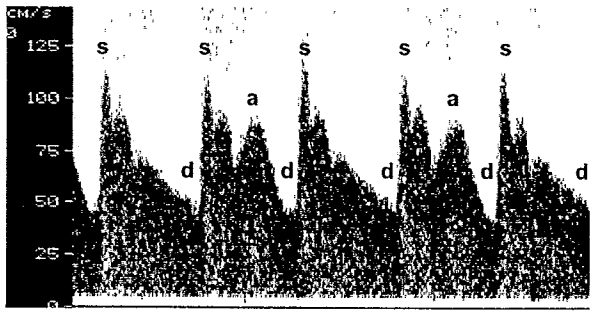

Figure 2. Transcranial Doppler sonography of middle cerebral artery with and without EECP. To demonstrate differences between EECP-augmented pulse waves and baseline pulse wave, counterpulsation is only carried out during every second heart beat (s, systole; d, diastole; a, augmentation by EECP).

At baseline, heart rate, BP and CBFV values did not differ between patients and controls, although mean BP was somewhat higher in the patients than in the controls (86.4 ± 20.0 versus 83.4 ± 10.2 mmHg, ns) while mean CBFV was lower in the patients than in the controls (46.7 ± 11.5 versus 55.0 ± 18.5 cm/s, ns). At baseline, the cerebrovascular resistance index was significantly higher in patients than in controls (0.57 ± 0.09 versus 0.50 ± 0.07, $P < 0.05$).

Healthy controls

During the first 5 s of EECP, mean BP of the controls was significantly higher than at baseline ($P < 0.001$). EECP induced a peak augmented diastolic BP of 114.1 ± 9.7 mmHg (Table 2). In contrast, systolic BP decreased from 125.4 ± 11.8 at baseline to 120.9 ± 13.0 mmHg after EECP onset ($P < 0.001$). After an adaptation of 3 min EECP, mean BP was significantly lower than during the first 5 s of EECP (89.5 ± 8.8 versus 86.2 ± 9.8 mmHg, $P < 0.01$), but still significantly higher than at baseline (83.4 ± 10.2 versus 86.2 ± 9.8 mmHg, $P < 0.05$). In contrast, systolic BP averaged after 3 min of EECP was not only lower than the corresponding values during the first 5 s of EECP, but also significantly lower than at baseline.

After 3 min of recovery, BP values averaged over 90 s did not differ from baseline values, and mean BP was significantly lower than during EECP (81.5 ± 9.2 versus 86.2 ± 9.8 mmHg, $P < 0.01$, Fig. 3).

Mean CBVF increased significantly from 55.0 ± 18.5 cm/s at baseline to 60.0 ± 17.2 cm/s during the initial 5 s of EECP. The peak augmented diastolic CBFV was 67.8 ± 16.0 cm/s. Systolic

Table 2 Heart rate, blood pressure (BP) and cerebral blood flow velocities (CBFV) in the middle cerebral artery before, during and after EECP

Parameter	Group	At rest	Initial EECP	After 3 min of EECP	Three minutes after EECP
Heart rate (bpm)	Controls	72.7 ± 9.0	72.5 ± 10.8	**75.6 ± 8.6**	**67.0 ± 6.6***
	Patients	69.7 ± 9.4	**73.4 ± 9.4**	**73.6 ± 9.1**	69.7 ± 9.9*
Systolic BP (mmHg)	Controls	125.4 ± 11.6	**120.9 ± 13.0**	**116.4 ± 13.5**	122.1 ± 13.2
	Patients	127.9 ± 29.7	126.3 ± 33.1	124.2 ± 35.2	**119.5 ± 33.9**
Peak augmented diastolic BP (mmHg)	Controls		114.1 ± 9.7	114.7 ± 13.3	
	Patients		*102.9 ± 24.1*	*100.4 ± 23.9*	
Enddiastolic BP (mmHg)	Controls	65.1 ± 11.0	67.0 ± 8.3	63.3 ± 11.1	65.0 ± 12.5
	Patients	66.5 ± 16.6	68.1 ± 12.2	67.2 ± 17.5	62.4 ± 20.1
Mean BP (mmHg)	Controls	83.4 ± 10.2	**89.5 ± 8.8**	**86.2 ± 9.8**	81.5 ± 9.2*
	Patients	86.4 ± 20.0	**93.6 ± 22.6**	**92.4 ± 24.1**	**82.2 ± 22.0***
Systolic CBVF (cm/s)	Controls	75.6 ± 22.3	73.7 ± 23.0	**64.9 ± 18.9**	70.6 ± 21.7*
	Patients	73.4 ± 20.5	71.8 ± 21.0	**69.6 ± 21.9**	78.1 ± 29.1*
Peak augmented diastolic CBFV (cm/s)	Controls		67.8 ± 18.0	61.0 ± 15.0	
	Patients		*55.2 ± 15.6*	*51.4 ± 11.9*	
Enddiastolic CBFV (cm/s)	Controls	37.8 ± 12.8	39.6 ± 10.4	33.5 ± 11.8	36.2 ± 11.3
	Patients	30.9 ± 8.5	32.1 ± 8.0	27.0 ± 7.7	31.2 ± 7.9*
Mean CBFV (cm/s)	Controls	55.0 ± 18.5	**60.0 ± 17.2**	**50.1 ± 17.0**	50.4 ± 15.3
	Patients	46.7 ± 11.5	51.5 ± 12.4	47.0 ± 11.8	46.0 ± 11.3

Bold numbers indicate a significant difference from baseline values. Italic numbers indicate a significant difference between patients and controls. Asterisk indicates a significant difference between values averaged after recovery and after 3 min of EECP.

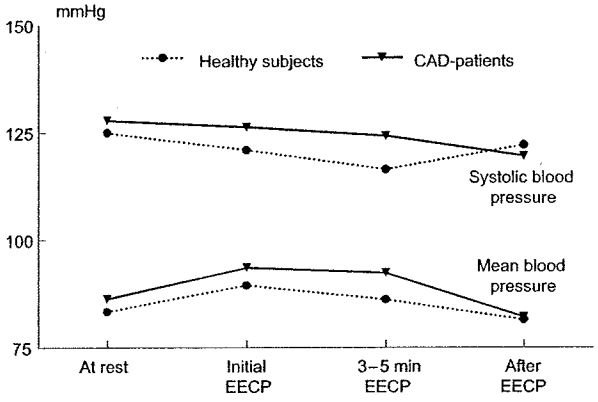

Figure 3. Impact of EECP on blood pressure (in mmHg).

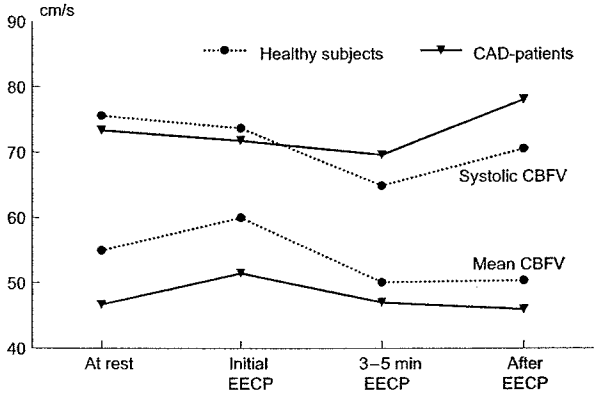

Figure 4. Impact of EECP on blood flow velocities in the middle cerebral artery (in cm/s).

CBFV did not change during the first 5 s of EECP. After an adaptation of 3 min EECP, mean as well as systolic CBFV averaged over 90 s were lower than during the initial 5 s of EECP and also lower than baseline values. Three minutes after the end of EECP, systolic CBFV increased again and was significantly higher than during EECP (70.6 ± 21.7 versus 64.9 ± 18.9 cm/s, $P < 0.001$). Mean and systolic CBFV averaged after recovery did not differ from baseline values (Fig. 4).

Atherosclerotic patients

Mean BP of the patients increased significantly during the first 5 seconds of EECP from 86.4 ± 20.0 to 93.6 ± 22.6 mmHg ($P < 0.01$), while systolic BP did not differ from baseline values. The peak augmented diastolic BP was 102.9 ± 24.1 mmHg. After 3 min of EECP, values averaged for 90 s were higher for mean BP (86.4 ± 20.0 versus 92.4 ± 24.1 mmHg, $P < 0.01$) than at baseline, while systolic BP did not differ significantly from baseline values.

Three minutes after the end of EECP, systolic BP (127.9 ± 29.7 versus 119.5 ± 33.9 mmHg, $P < 0.05$) and mean BP (86.4 ± 20.0 versus 82.3 ± 22.0 mmHg, $P < 0.05$) were significantly lower than at baseline. Mean BP was also lower than the corresponding values during EECP (92.4 ± 24.1 versus 82.2 ± 22.0 mmHg, $P < 0.01$), while systolic BP did not differ from values during EECP (Fig. 3).

Mean CBFV increased from 46.7 ± 11.5 cm/s at baseline to 51.5 ± 12.4 cm/s ($P < 0.01$) during the initial 5 s of EECP. Systolic CBFV did not change during this period. After the adaptation of 3 min

EECP, mean CBFV no longer differed from baseline values (46.7 ± 11.5 versus 47.0 ± 11.8 cm/s, ns) although there was an EECP induced augmentation of diastolic CBFV (51.4 ± 11.9 cm/s); systolic CBFV was significantly lower than at rest (73.4 ± 20.5 versus 69.6 ± 21.9 cm/s, $P < 0.01$).

Three minutes after the end of EECP, mean CBFV did not differ from values during EECP, while systolic CBFV was significantly higher than during EECP (69.6 ± 21.9 versus 78.1 ± 29.1 cm/s, $P < 0.05$, Fig. 4).

Difference in response to EECP between patients and controls

The peak augmented diastolic BP (114.7 ± 13.3 versus 100.4 ± 23.9 mmHg, $P < 0.05$) and the peak augmented diastolic CBFV (61.0 ± 15.0 versus 51.4 ± 11.9 cm/s, $P < 0.05$) were significantly higher in the controls than in the patients. At baseline and during EECP, end-diastolic BP and end-diastolic CBFV values did not differ between both groups.

Discussion

This study shows that EECP induces changes in BP and CBFV in both, healthy controls and atherosclerotic patients. However, there are significant differences between the responses of patients and controls. In patients and the controls, mean BP increases immediately after onset of EECP. After an adaptation period of 3 min, mean BP of the controls normalizes and no longer differs from values at baseline despite counterpulsation. In contrast, mean BP of the atherosclerotic patients is still increased. Only after recovery from the stimulus, mean BP values of the patients return to baseline values as in the controls. In the controls, systolic BP, the main input signal of the baroreflex loop and of cerebral autoregulation decreases immediately after onset of EECP and even falls to values lower than baseline values after adaptation. In the patients, there is no such decrease of systolic BP during EECP. We assume that mean BP remains elevated in the patients even after adaptation and that systolic BP does not show major changes from baseline during EECP because of a higher resistance and rigidity of the atherosclerotic vascular bed. In our study, the increase of the mean BP after adaptation to EECP was 6.9% in the patients. Rosenbaum et al. (15) measured a similar increase of mean BP of 6.8% in a group of 16 atherosclerotic patients treated with IABP.

In the patients, augmentation of BP during diastole was significantly less pronounced than in the volunteers. It is known that the blood volume in the lower extremities is less in elderly patients than in young healthy persons because the mass of leg muscles is significantly lower in older persons than in younger persons (16, 17). Consequently, the vascular bed supplying the muscles is smaller and the volume pumped from the lower extremities to the trunk and head during counterpulsation is significantly smaller in the patients than in the younger controls resulting in a lower augmentation of BP in the patients (18).

EECP induces an immediate significant increase in mean CBFV and lowers systolic CBFV after 3 min of counterpulsation in both, controls and atherosclerotic patients. Transcranial Doppler monitoring of CBFV reveals a second diastolic peak flow in the MCA during EECP (Fig. 2). After the 3 min of adaptation, mean and systolic CBFV are significantly lower than at baseline in the controls. In the patients, only systolic CBFV is lower than at baseline. These data demonstrate that the cerebral autoregulation guarantees the constancy of cerebral perfusion during EECP in healthy controls as well as in patients with atherosclerosis after an adaptation period. The differences in change of mean CBVF could be attributed either to a more pronounced vascular autoregulation in the younger control group or to the reduced elasticity of the cerebral vessels in the older group of atherosclerotic patients. This assumption is supported by our finding of significantly higher values of the cerebrovascular resistance index in the patients than in the healthy controls.

Interestingly, mean CBFV remained constant after recovery despite a significant decrease of mean BP in the atherosclerotic patients. This phenomenon can be explained by a reduction of intracerebral resistance of small vessels downstream to the insonated MCA segment and indicates an improvement of cerebral perfusion after stimulus of EECP with a more economic and physiologic relation between cerebral blood flow and systemic BP.

The mechanisms accounting for this increased CBVF after EECP are not well understood. However, it has been shown in atherosclerotic patients that EECP downregulates vasoconstrictive substances like endothelin 1 or angiotensin II (19, 20). Furthermore, there is evidence that counterpulsation induces an increase of short-acting vasodilatory factors such as nitric oxide (20). We assume that these hormonal effects contribute to the mechanism that increases systolic CBFV after EECP.

Similar to our findings, Applebaum et al. (21) reported an increase of diastolic blood flow

velocity and a decrease of systolic blood flow velocity in the common carotid artery during IABP in a study of 14 patients with coronary artery disease. As in our study, the mean blood flow velocity did not change significantly.

Such preserved regulatory response cannot be found under conditions of disturbed autoregulation, e.g. in cardiogenic shock or ischemic tissue. In two canine studies, IABP was used for therapy of experimental cardiogenic shock. There, Bhayana et al. (7) measured cerebral blood flow in 13 dogs by radioactive microspheres and found an increase of cerebral blood flow by 56%. Wesley et al. (22) used the same radioactive microsphere technique in seven dogs and described an increase of cerebral blood flow by 31%. From these studies, it can be concluded that counterpulsation increases cerebral blood flow under conditions of impaired autoregulation in cardiogenic shock. These results are in agreement with our previous study of the effects of 2 h of EECP in five patients with retinal infarction after occlusion of a branch of the retinal artery. The ischemic and therefore poorly autoregulated retinal area demonstrated a 26% increase in perfusion after 2 h of EECP, whereas perfusion in the non-ischemic retinal area remained unchanged (23).

Limitations

The study was a comparison of circulatory parameters between an older group of atherosclerotic patients and younger healthy controls undergoing EECP. Numerous studies have shown an effect of age on cerebrovascular reactivity to various stimuli (24).

EECP was applied only once, and parameters were only measured during and shortly after (3 min) stopping EECP. This study did not attempt to assess long-term effects of EECP.

We cannot rule out that the atherosclerosis might have altered baroreceptor sensitivity in the patients. Baroreflex sensitivity decreases in patients with long-standing atherosclerosis. Changes of baroreflex sensitivity might also contribute to the different BP and CBFV responses seen in the atherosclerotic patients (25).

Conclusion

Our data demonstrate that intact cerebral autoregulation ensures the constancy of cerebral blood flow during EECP-augmented diastolic blood flow. This autoregulatory process can not only be observed in healthy young volunteers but also in older and atherosclerotic patients. EECP therapy of patients with atherosclerotic diseases does not seem to be associated with a risk of cerebral hyperperfusion.

Immediately after EECP, there is a better coefficient between cerebral blood flow and systemic BP in the atherosclerotic patients. Our results encourage further studies evaluating whether EECP has longer effects on CBFV.

References

1. Tranmer BI, Peniston C, Iacobacci R, Salerno TA, Hudson AR. Intra-aortic balloon counterpulsation: a treatment for ischemic stroke? Neurol Res 1989;**11**:109–13.
2. Nussbaum ES, Heros RC, Solien EE, Madison MT, Sebring LA, Latchaw RE. Intra-aortic balloon counterpulsation augments cerebral blood flow in a canine model of subarachnoid hemorrhage-induced cerebral vasospasm. Neurosurgery 1995;**34**:879–86.
3. Apostolides PJ, Greene KA, Zabramski JM, Fitzgerald JW, Spetzler RF. Intra-aortic balloon pump counterpulsation in the management of concomitant cerebral vasospasm and cardiac failure after subarachnoid hemorrhage: technical case report. Neurosurgery 1996;**38**:1056–60.
4. Nussbaum ES, Sebring LA, Ganz WF, Madison MT. Intra-aortic counterpulsation augments cerebral blood flow in the patient with cerebral vasospasm: a xenon-enhanced computed tomography study. Neurosurgery 1998;**42**:206–14.
5. Montessuit M, Chevalley C, King J, Faidutti B. The use of intraaortic counterpulsation for the treatment of cerebral vasospasm and edema. Surgery 1999;**126**:230–3.
6. Hennen B, Groschel-Guth A, Scheller B, Hammer B, Bohm M. Intra-aortic counterpulsation during carotid stenting. Catheter Cardiovasc Interv 2001;**53**:546–8.
7. Bhayana JN, Scott SM, Sethi GK, Takaro T. Effects of intra-aortic balloon pumping in cardiogenic shock. J Surg Res 1979;**26**:108–13.
8. Gee W, Smith RL, Perline RK, Gallagher HS. Assessment of intra-aortic balloon pumping by ocular pneumoplethysmography. Am Surg 1986;**52**:489–91.
9. Taguchi I, Ogawa K, Oida A, Lang G, Liuzzo J, Cohn PF. Comparison of hemodynamic effects of enhanced external counterpulsation and intra-aortic balloon pumping in patients with acute myocardial infarction. Am J Cardiol 2000;**15**:1139–41.
10. Arora RR, Chou TM, Jain D et al. The multicenter study of enhanced external counterpulsation (MUST-EECP): Effect of EECP on exercise-induced myocardial ischemia and anginal episodes. J Am Coll Cardiol 1999;**33**: 1833–40.
11. Applebaum RM, Kasliwal R, Tunick PA et al. Sequential external counterpulsation increases cerebral and renal blood flow. Am Heart J 1997;**133**:611–15.
12. Werner D, Schneider M, Weise M, Nonnast-Daniel B, Daniel WG. Pneumatic external counterpulsation – a new non-invasive method to improve organ perfusion. Am J Cardiol 1999;**84**:950–2.
13. Suresh K, Simandl S, Lawson WE et al. Maximizing the hemodynamic benefit of enhanced external counterpulsation. Clin Cardiol 1998;**21**:649–53.
14. Kemmotsu O, Ohno M, Takita K et al. Noninvasive, continuous blood pressure measurement by arterial tonometry during anesthesia in children. Anesthesiology 1994;**81**: 1162–8.

15. Rosenbaum AM, Murali S, Uretsky BF. Intra-aortic balloon counterpulsation as a 'bridge' to cardiac transplantation. Chest 1994;**106**:1683–8.
16. Baumgartner RN. Body composition in healthy aging. Ann NY Acad Sci 2000;**904**:437–48.
17. McCully KK, Posner JD. The application of blood flow measurements to the study of aging muscle. J Gerontol A: Biol Sci Med Sci 1995;**50**:130–6.
18. Stys T, Lawson WE, Hui JCK, Abe S, Kaneko N, Sakio H. Acute hemodynamic effects and angina improvement with enhanced external counterpulsation. Angiology 2001; **52**:653–8.
19. Lu L, Zheng ZS, Zhang MQ, Lawson WE, Hui JCK. Beneficial effects of EECP on the renin–angiotensin system in patients with coronary artery disease. Eur Heart J 2001; **22** (Suppl.):538.
20. Wu GF, Zheng QS, Zheng, ZS, Lawson WE Hui JCK. A neurohumoral mechanism for the effectiveness of enhanced external counterpulsation. Circulation 1999;**100** (Suppl. 1): 832.
21. Applebaum RM, Wun HH, Katz ES, Tunick PA, Kronzon I. Effects of intraaortic balloon counterpulsation on carotid artery blood flow. Am Heart J 1998;**135**:850–4.
22. Wesley RC, Morgan DB. Effect of continuous intra-aortic balloon inflation in canine open chest cardiopulmonary resuscitation. Crit Care Med 1990;**18**:360–3.
23. Werner D, Harazny J, Michalk F, Voigt JU, Daniel WG. Externen Gegenpulsationstechnik in der Ophthalmologie. Biomed Tech 2000;**45** (Suppl. 1):423–4.
24. Oblak JP, Zaletel M, Zvan B, Kiauta T, Pogacnik T. The effect of age on cerebrovascular reactivity to cold pressor test and head-up tilt. Acta Neurol Scand 2002;**106**:30–3.
25. Gianaros PJ, Jennings R, Olafsson B et al. Greater intima-media thickness in the carotid bulb is associated with reduced baroreflex sensitivity. Am J Hypertens 2002;**15**: 486–91.