ACCELERATED REPERFUSION OF POORLY PERFUSED RETINAL AREAS IN CENTRAL RETINAL ARTERY OCCLUSION AND BRANCH RETINAL ARTERY OCCLUSION AFTER A SHORT TREATMENT WITH ENHANCED EXTERNAL COUNTERPULSATION

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Background: To date, no satisfactory therapy has become available for patients with acute central retinal artery occlusion (CRAO) or branch retinal artery occlusion (BRAO). Enhanced external counterpulsation (EECP) is a new noninvasive procedure that increases perfusion of inner organs. In the current study, the authors measured the impact of EECP on reperfusion in ischemic retinal tissue.

Methods: In a prospective, randomized study, 20 patients with CRAO or BRAO were included. Ten patients were given hemodilution therapy and 2 hours of EECP, and 10 patients were given regular hemodilution therapy only. Quantification of changes in retinal perfusion was carried out by means of scanning laser Doppler flowmetry (in arbitrary units).

Results: Enhanced external counterpulsation caused no observable adverse events. A significant increase in perfusion occurred immediately after EECP in the ischemic retinal areas (57 ± 19 arbitrary units versus 99 ± 14 arbitrary units). In contrast, no change was measured in the group not treated with EECP (83 ± 19 arbitrary units versus 89 ± 44 arbitrary units). Forty-eight hours later, a significant increase in perfusion could be shown in the ischemic retina of both groups, and no significant difference of perfusion was found between the two groups any longer.

Conclusion: The current study suggests that EECP could be a clinically useful and safe procedure in patients with CRAO or BRAO to accelerate recovery of perfusion in ischemic retinal areas.

RETINA 24:541–547, 2004

Although the first description of the occlusion of the central retinal artery is more than 140 years old,[1] to date no efficient and generally accepted therapy has become available. Noninvasive therapies, such as aspirin, acetazolamide, oral pentoxifylline, hemodilution and ocular massage, do not influence significantly the natural course of the disease.[2] Conversely, systemic fibrinolytic therapy may be effective but is given at the risk of life-threatening complications in what is a non-life-threatening disease.[3]

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Table 1. Reasons for Exclusion of 15 Patients

Reason for Exclusion	No. of Patients
EECP contraindications	6
Severe peripheral artery disease	2
Atrial fibrillation	2
Aortic regurgitation	1
Anticoagulation with phenprocoumone	1
Ophthalmologic reasons	7
Cataract and no possibility of SLDF	6
Additional central vein thrombosis	1
Legal reasons	2
Alzheimer dementia	1
Refusal of participation	1

EECP, enhanced external counterpulsation; SLDF, scanning laser Doppler flowmetry.

Enhanced external counterpulsation (EECP) is a noninvasive procedure that has been shown to generate improved blood flow to the myocardium. EECP functions by applying pressure to the vascular bed of the lower extremities during diastole by means of three air-filled cuffs. The generated retrograde diastolic pulse wave augments diastolic and mean arterial pressure and coronary, cerebral, and ocular perfusion during diastole.[4–7] Currently, EECP is used as an adjunctive therapeutic option for patients with coronary artery disease.[8] The procedure has been shown to reduce myocardial ischemia.[8,9] Against this background, we asked whether EECP could be used to reduce reperfusion time in poorly perfused retinal areas after a central retinal artery occlusion (CRAO) or branch retinal artery occlusion (BRAO).

Ten patients with a CRAO or BRAO were given hemodilution therapy and 2 hours of EECP, and changes in retinal blood flow were compared with a similar group of 10 patients given regular hemodilution therapy only. Quantification of changes in retinal perfusion was carried out by means of scanning laser Doppler flowmetry.[10] Additionally, in this study, we wanted to evaluate the safety of the procedure in patients with CRAO or BRAO (e.g., the risk of retinal bleedings caused by a higher perfusion pressure).

Patients and Methods

Patients

During a period of 22 months, all patients admitted with acute retinal ischemia in whom a CRAO or BRAO with clinical manifestations had occurred during the past 5 days were screened and asked to participate in this prospective, nonmasked, controlled study. Fifteen of the 35 patients who met these criteria were excluded for reasons listed in Table 1. The remaining 20 patients were randomized into an EECP group and a control group receiving baseline therapy alone. Ten patients were treated for 2 hours with EECP, whereas the other 10 patients not given EECP constituted the control group. Table 2 lists the age, gender, and characteristics of retinal occlusion in both groups. There was no statistically significant difference between the groups. None of the included patients had an additional cilioretinal artery that could influence the changes of retinal perfusion.

Electrocardiography, measurement of blood pressure, echocardiographic examination, and Duplex scanning of the carotid arteries were performed before EECP to exclude precautions against this procedure, such as atrial fibrillation, uncontrolled hypertension, aortic regurgitation, or carotid dissection. Furthermore, all patients underwent physical examination before and after EECP regarding skin abrasions, hematomas, or other side effects. All study participants were asked for any complaints after EECP. Funduscopy was performed after EECP to exclude any bleeding into the ischemic retinal tissue during increased perfusion pressure.

The Ethics Committee of the Faculty of Medicine, Friedrich-Alexander-University, Erlangen-Nuremberg approved the study protocol. Informed consent was obtained from all study participants according to the Declaration of Helsinki.

Methods

The diagnosis of CRAO or BRAO was established by the clinical symptoms and corresponding findings

Table 2. Characteristics of the EECP-Treated Group and Control Group

Characteristics	Treated group	Control group
Age (years)	64.5 ± 5.2	65.3 ± 13.4
Gender (M/F)	7/3	7/3
No. of CRAO/BRAO	6/4	9/1
Baseline hemodilution therapy	6 HAES/4 electrolyte solution	5 HAES/5 electrolyte solution
Age of CRAO or BRAO at beginning of study (days)	2.7 ± 1.3	2.4 ± 1.6

EECP, enhanced external counterpulsation; CRAO, central retinal artery occlusion; BRAO, branch retinal artery occlusion; HAES, hydroxyethyl starch.

in the retinal circulation. All patients received 4 days of hemodilution therapy with hydroxyethyl starch solution (500 mL) or, in patients with severe hypertension or compromised cardiac function, with electrolyte solution (500 mL). This baseline therapy was interrupted 30 minutes before baseline measurement of retinal perfusion by scanning laser Doppler flowmetry (SLDF).

After the initial measurement, the 10 patients randomized to EECP underwent 2 hours of this procedure. The SLDF measurement was repeated 30 minutes after completing the EECP session. The 10 patients randomized to the control group walked the same distance as the treated group to the EECP room but were not given EECP therapy. The SLDF measurements were made at the same times as in the EECP-treated group. The results of the control group were used to document the course of the disease during baseline therapy, and control group aggregate measurements were used to benchmark the effects of the initial hemodilution therapy. After the second SLDF measurement, hemodilution therapy was resumed in both groups. Forty-eight hours later, a third SLDF measurement was carried out to assess possible persistent effects.

Scanning laser Doppler flowmetry provides a high-definition tomographic image of perfused retinal vessels with simultaneous evaluation of blood flow using an optical Doppler effect. The Heidelberg Retina Flowmeter was used for the SLDF operating with a wavelength of 670 nm and a power of 100 μW. Quantification of capillary retinal blood flow was stated in arbitrary units (AUs) describing the product of mean flow velocity and mean amount of moved blood cells in a standardized retinal volume. In all patients, capillary blood flow was measured by SLDF in an area of 2.7×0.7 mm in all four retinal quadrants outside the rim area (nasal superior, nasal inferior, temporal superior, and temporal inferior). Retinal arteries were used as the anatomic landmarks for a clear definition of the measured areas in the two follow-up investigations.

Based on the SLDF measurements, retinal areas were classified into three groups according to their initial perfusion. Regions with perfusion of fewer than 100 AUs were defined as severely disturbed perfusion. Perfusion of 100 to 200 AUs was defined as moderately reduced perfusion. Areas with a blood flow of more than 200 AUs were considered normal.

Visual acuity was assessed after admission into the hospital before the study. A second measurement of visual acuity was carried out before the third SLDF measurement. The following visual acuity gradations were used: amaurosis, hand motions, finger counting, 20/400, 20/320, 20/250, 20/200, 20/160, 20/120, 20/100, 20/80, 20/63, 20/50, 20/40, 20/32, 20/25, and 20/20 (EN ISO 8,596). A significant improvement in visual acuity was defined as a sustained improvement of three or more visual acuity gradations.[11,12]

Enhanced external counterpulsation (Vasomedical, Inc., Westbury, NY) operates by applying electrocardiogram-timed cuff pressure of 250 mmHg to the vascular bed of the calves, thighs, and buttocks sequentially, by means of 3 pairs of inflatable cuffs, during the diastolic period to increase perfusion pressure. Before systole, the cuffs are released simultaneously to reduce left ventricular afterload. Finger plethysmography is used to record the response of blood pressure to EECP and to gauge the augmentation of blood pressure during diastole, which is optimized by adjusting the time delay between the R-wave of the electrocardiogram and the onset of counterpulsation pressure.[13]

Statistical Methods

The two-sided Friedman test was used to analyze differences between averaged values taken at baseline, immediately after 2 hours of EECP respectively 2 hours of no therapy, and after 2 days. The two-sided Mann–Whitney *U*-test was applied to compare data from the EECP-treated patients to those of the controls during the three phases of measurement. The level of significance was set at $P < 0.05$.

Results

Enhanced external counterpulsation was well tolerated by all treated patients. No adverse events occurred; of particular importance, no retinal bleeding was observed.

Perfusion Data

The results of SLDF measurements in the three different regions in both groups are summarized in Table 3. Table 4 gives a comparison of relative changes in blood flow.

No changes in blood flow could be observed in the areas with normal perfusion in the treated group or in the control group. However, significantly different changes in perfusion occurred in both groups in the regions with severely reduced perfusion. In the EECP-treated group, significant changes in perfusion were found in the area with severe ischemia immediately after EECP (57.3 ± 18.9 AUs vs. 98.9 ± 14.2 AUs; $P < 0.001$) and 2 days later (57.3 ± 18.9 AUs vs. 154.3 ± 62.7 AUs; $P < 0.001$). In the control group, reperfusion of severe ischemic tissue could also be

Table 3. Scanning Laser Doppler Flowmetry Measurement Before Study and 3 and 48 Hours Later in EECP-Treated Patients With Retinal Ischemia in Comparison With a Control Group

Group	Retinal Area (Baseline Perfusion)	Before Study	3 Hours of Follow-up	48 Hours Follow-up
EECP-treated group	<100 AUs	57.3 ± 18.9	98.9 ± 14.2*	154.3 ± 62.7*
	100–200 AUs	153.2 ± 26.2	190.2 ± 54.3*	236.5 ± 102.3*
	>200 AUs	329.2 ± 69.2	309.3 ± 75.0	342.1 ± 104.2
Control group	<100 AUs	83.3 ± 18.8	89.1 ± 44.5	250.6 ± 149.7*
	100–200 AUs	146.4 ± 16.1	151.3 ± 45.5	257.5 ± 119.7*
	>200 AUs	249.4 ± 24.2	198.8 ± 45.0	260.4 ± 51.1

* Difference from baseline, $P < 0.05$.
EECP, enhanced external counterpulsation; AUs, arbitrary units.

observed 2 days after the baseline measurement. However, no increase was found 3 hours after the initial measurement in the non-EECP-treated group (83.3 ± 18.8 AUs vs. 89.1 ± 44.5 AUs; not significant). The change in blood flow was significantly different between both groups immediately after EECP and 3 hours of no EECP treatment (94% vs. 5%; $P < 0.05$) (Figure 1). Figure 2 shows an example of the rapid opening of retinal arterioles after EECP.

A significant change in perfusion also could be observed in the retinal areas with moderately reduced perfusion after EECP (153.2 ± 26.2 AUs vs. 190.2 ± 54.3 AUs; $P < 0.05$). Also, in these retinal areas, perfusion increased further during the next 48 hours. In the control group, there was no change initially after the EECP waiting period (146.4 ± 16.1 AUs vs. 151.3 ± 45.5 AUs; not significant). As with the EECP group, there was also an increase 2 days later.

Impact of the Age of the Central or Branch Retinal Artery Occlusion and the Number of Branch Retinal Artery Occlusions

No significant correlation was found when comparing the degree of reperfusion with the age of the CRAO or BRAO before EECP. However, there was also no correlation between the degree of spontaneous reperfusion and the age of the artery occlusion at the beginning of the study in the control group.

Both groups had a similar age of the CRAO or BRAO and a similar age of the patients. However, there was a difference in the distribution of CRAO versus BRAO (Table 2). Therefore, SLDF results of all patients with CRAO were analyzed again after exclusion of patients with BRAO. After EECP, perfusion increased by 105% ± 93% ($P < 0.05$) in the regions with severely reduced perfusion and by 20% ± 22% (not significant) in the areas with moderately reduced perfusion. In contrast, spontaneous perfusion increased by 15% ± 37% (not significant) in the regions with severely reduced perfusion and by 4% ± 32% (not significant) in the areas with moderately impaired perfusion. Thus, the effect of EECP was similar in patients with CRAO or BRAO.

Visual Outcome

Visual acuity was compared after admission and before the final SLDF measurement. On average, visual acuity increased by 0.8 ± 1.7 gradations in the EECP-group and by 0.7 ± 1.7 gradations in the control group. A significant increase in visual acuity by five gradations occurred in one patient in each group.

Table 4. Relative Changes in Perfusion Caused by Additional EECP Compared With the Control Group

Group	Retinal Area (Baseline Perfusion)	Before Study vs. 3 Hours of Follow-up (%)	Before Study vs. 48 Hours of Follow-up
EECP-treated group	<100 AUs	+94 ± 81*	+167 ± 49*
	100–200 AUs	+22 ± 23*	+52 ± 50*
	>200 AUs	−1 ± 35	+9 ± 37
Control group	<100 AUs	+4 ± 43	+212 ± 177*
	100–200 AUs	+3 ± 30	+79 ± 86*
	>200 AUs	−20 ± 19	+6 ± 27

* Difference from baseline, $P < 0.05$.
EECP, enhanced external counterpulsation; AUs, arbitrary units.

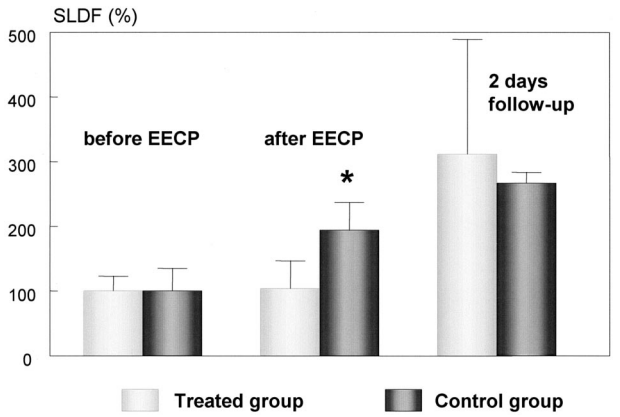

Fig. 1. Relative changes in retinal capillary blood flow in poorly perfused areas, measured by scanning laser Doppler flowmetry, in patients treated with enhanced external counterpulsation and hemodilution or with hemodilution therapy alone (*$P < 0.001$).

Table 5 shows the changes in visual acuity in the EECP-treated group and in the control group.

Discussion

For more than 30 years, intraaortic balloon counterpulsation devices have been used to reduce myocardial ischemia by augmenting diastolic blood flow. Additionally, in the last decade, pilot studies using intraaortic balloon counterpulsation have shown an increased perfusion in cerebral ischemic areas caused by subarachnoidal hemorrhage.[14,15] EECP offers a noninvasive means of bringing about similar hemodynamic modification with the potential for a broader range of applications,[16] especially in the treatment of diseases that do not justify the use of invasive approaches. In our own study, a 12% increase in mean blood flow velocity could be measured during EECP in the ophthalmic artery in patients with atherosclerosis.[6]

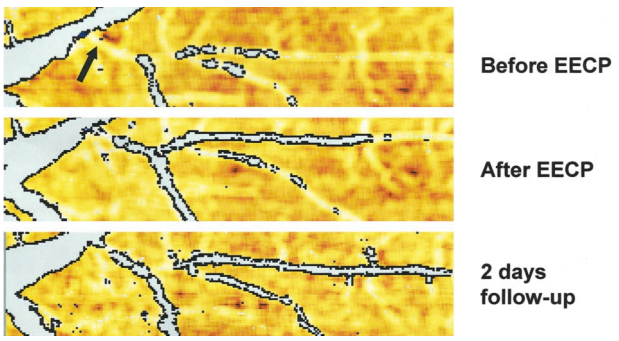

Fig. 2. Example of blood flow in retinal arterioles, recorded by scanning laser Doppler flowmetry, before enhanced external counterpulsation (**A**), after enhanced external counterpulsation (**B**), and after 2 days of follow-up (**C**), showing an arterial reopening. Arrows indicate initial occlusion.

Enhanced external counterpulsation could offer a nearly risk-free means to accelerate reperfusion in acute retinal ischemia. In the current study, a significant difference in reperfusion could be shown between the EECP-treated group and the natural course of the disease assisted by hemodilution (Figure 1). No ocular or general adverse effects were observed during or after EECP. Generally, adverse effects attributed to EECP are minor skin abrasions or bruising of the cuff-wrapped areas, as described in the literature.[8] In our own studies, we have treated a total of 176 patients and volunteers for clinical therapy or hemodynamic studies for an overall of 1,232 hours and observed only smaller side effects, such as skin abrasion (2 patients), hematoma of the legs (2 patients), severe pain in the legs (2 patients), and reproducible premature atrial beats during EECP (1 patient).[17]

The mechanisms leading to better reperfusion of ischemic tissue by EECP are speculative. Numerous studies have shown augmentation of coronary collateral flow after counterpulsation procedures.[18,19] It has also been shown that most eyes with CRAO or BRAO have some residual retinal circulation.[20] Therefore, it could be speculated that the retinal collateral flow is also increased by augmented perfusion pressure during EECP between various anastomoses (e.g., between the retinal artery and pial arterial branches). However, the degree of collateralization is variable in the retinal circulation.[21]

Furthermore, the increased perfusion pressure may mobilize the occluding embolus similar to eye bulb massage. In one patient with BRAO, mobilization and shrinking diameter of an embolus could be observed after EECP. The doubling of pulse waves and resulting increase in vascular wall shear stress seen with EECP may result in the release of vasodilating and antithrombotic factors from the endothelium and from platelets and contribute to reopening of the occluded arteries. It is known, for example, that counterpulsation yields an increase in vasodilating factors, such as nitric oxide or prostacyclin, and down-regulates vasoconstrictive substances, such as endothelin, thromboxane, and angiotensinogen.[22–24] It has also been shown that intraaortic balloon counterpulsation enhances coronary thrombolysis.[25,26] A similar effect could take place in the retinal circulation during external counterpulsation. Additionally, an increase of blood flow in the poorly autoregulated choroid vessels may enhance perfusion in the outer layers of the retina.

Perfusion in the nonischemic retinal segments was not affected by the counterpulsation procedure. A similar result was found by Masuda et al,[27] in a group of patients with angina pectoris and myocardial ischemia. Using positron emission tomography, they showed

Table 5. Visual Acuity in EECP-Treated Patients and Controls Before Study and After 2 Days of Follow-up

Group	Patient	Visual Acuity		
		At Baseline	After 2 Days	Change in Visual Gradations
EECP-treated group	1	Counting fingers	Counting fingers	0
	2	Counting fingers	20/400	1
	3	Amaurosis	Hand motions	1
	4	Counting fingers	Amaurosis	−2
	5	Hand motions	Counting fingers	1
	6	Hand motions	20/200	5
	7	Hand motions	Counting fingers	1
	8	Hand motions	Counting fingers	1
	9	20/40	20/40	0
	10	20/32	20/32	0
	Median			0.8 ± 1.7
Control group	1	20/32	20/25	1
	2	Hand motions	Counting fingers	1
	3	Hand motions	Hand motions	0
	4	Counting fingers	Counting fingers	0
	5	20/250	20/400	−2
	6	Amaurosis	Amaurosis	0
	7	Counting fingers	20/400	1
	8	Hand motions	20/200	5
	9	Hand motions	Hand motions	0
	10	Hand motions	Counting fingers	1
	Median			0.7 ± 1.7

a significant improvement in myocardial perfusion in regions with poor baseline perfusion supplied by a stenotic artery and no change in well-perfused myocardium after a therapeutic course of EECP.

Limitations

The current study was designed to investigate the feasibility of EECP as a means to improve the treatment of acute retinal ischemia. It is therefore adequate neither in size nor in length of follow-up to serve other than as a pilot for more extensive investigations. No conclusions can be drawn as to the long-term clinical effects in these patients. Similarly, although EECP appears to be safe and easy to apply in these patients, too few patients have been included to draw firm conclusions as to safety.

The decision to apply EECP for only 2 hours was arbitrary. When used to treat heart disease, EECP is given in courses of 1 or 2 hours daily for periods of 4 to 7 weeks. As shown in cardiac patients, a longer course of treatment may also produce more profound improvement in patients with acute retinal ischemia.

A period of 4 hours after retinal arterial occlusion is the most that can be tolerated before permanent damage occurs. This reality is the rationale for aggressive thrombolytic therapies to restore visual function.[28] In the current study, the mean age of occlusion was 2.5 days. Thus, as to be expected, visual acuity was not affected by EECP.

Conclusions

The current study suggests EECP to be a feasible procedure to accelerate recovery of perfusion in ischemic retinal areas in patients with CRAO or BRAO. That no retinal bleeding caused by the procedure was observed suggests that EECP is safe in these patients. The measured hemodynamic improvements shown in this study call for wider investigation. A new study is ongoing to determine whether rapid retinal reperfusion engendered by EECP is associated with improvement of the visual field in patients suffering from CRAO or BRAO of less than 12 hours' duration. Finally, the current study shows the general impact of augmented retinal perfusion pressure on the recovery of retinal perfusion.

Key words: enhanced external counterpulsation, central retinal artery occlusion, reperfusion

Acknowledgment

The authors thank Anthony E. Peacock for his expert editorial assistance.

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