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ORIGINAL ARTICLE

Short-term external counterpulsation augments cerebral blood flow and tissue oxygenation in chronic cerebrovascular occlusive disease

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Background and purpose: External counterpulsation improves cerebral perfusion velocity in acute stroke and may stimulate collateral artery growth. However, whether (non-acute) at-risk patients with high-grade carotid artery disease may benefit from counterpulsation needs to be validated.

Methods: Twenty-eight patients (71 ± 6.5 years, five women) with asymptomatic unilateral chronic severe internal carotid artery stenosis (>70%) or occlusion were randomized to receive 20 min active counterpulsation followed by sham treatment or vice versa. Cerebral blood flow velocity (CBFV) (measured bilaterally by transcranial middle cerebral artery Doppler), tissue oxygenation index (TOI) (measured over the bilateral prefrontal cortex by near-infrared spectroscopy) and cerebral hemodynamic parameters, such as relative pulse slope index (RPSI), were monitored.

Results: Ipsilateral mean CBFV (ΔV_{mean} +3.5 ± 1.2 cm/s) and tissue oxygenation (ΔTOI +2.86 ± 0.8) increased significantly during active counterpulsation compared to baseline, whilst the sham had little effect (ΔV_{mean} +1.13 ± 1.1 cm/s; ΔTOI +1.25 ± 0.65). On contralateral sides, neither counterpulsation nor sham control had any effect on either parameter. During counterpulsation, early dynamic changes in ΔRPSI of the ipsilateral CBFV signal predicted improved tissue oxygenation during counterpulsation (odds ratio 1.179, 95% confidence interval 1.01–1.51), whilst baseline cerebrovascular reactivity to hypercapnia failed to show an association.

Conclusions: In patients with high-grade carotid disease, ipsilateral cerebral oxygenation and blood flow velocity are increased by counterpulsation. This is a necessary condition for the stimulation of regenerative collateral artery growth and thus a therapeutic concept for the prevention of cerebral ischaemia. This study provides a rationale for further clinical investigations on the long-term effects of counterpulsation on cerebral hemodynamics and collateral growth.

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Introduction

Internal carotid artery (ICA) occlusion with poor hemodynamic compensation contributes to cognitive decline and increases the annual risk of stroke by more than 10% [1]. It has been demonstrated that

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collateral vessels can provide a level of protection from ischaemic stroke; however, there is considerable variation in the degree of collateralization between at-risk patients [2]. Therefore, non-invasive therapeutic approaches to augment cerebrovascular collateralization and to improve cerebral hemodynamics would be highly advantageous.

Cerebral collateralization, or collateral growth, is induced by an increase in pulsatile blood flow velocity, which elevates intravascular shear rates [3,4]. This results in activation of the endothelium, monocyte accumulation, smooth muscle cell proliferation, and remodeling to form mature collateral vessels. Therapeutic induction of increased shear stress through the cerebral vasculature could therefore be a promising approach to increasing collateralization.

External counterpulsation is a non-interventional technique by which diastolic blood flow is enhanced by the sequential inflation of pneumatic cuffs around the lower extremities during each cardiac cycle [5]. It has been approved for the treatment of patients with ischaemic heart disease who have refractory angina, where it is thought to work by improving endothelial function and augmenting the recruitment and growth of collateral conductance vessels, resulting in reduced myocardial ischaemia [6,7]. Counterpulsation could thus be a future therapeutic option for adaptive cerebrovascular collateral growth.

Counterpulsation has been previously shown to improve cerebral perfusion and oxygenation. In a small cohort of healthy volunteers, the mean and end-diastolic velocities of blood flow through the middle cerebral arteries (MCA) were significantly increased during the application of external counterpulsation [8]. In a separate study, although the peak diastolic cerebral blood flow velocity (CBFV) increased, the mean value was relatively unaffected [9]. Lin *et al.* also found no increase in blood flow velocity in healthy control subjects during counterpulsation; however, in the ischaemic stroke patients that they evaluated (interval from stroke onset <14 days [10] or <7 days [11]), there were significant increases in mean velocity both ipsilateral and contralateral to the site of the infarct. This difference in response was attributed to the potential effects of cerebral autoregulation, which is compromised after stroke [12].

It is clear that response to counterpulsation differs between healthy patients and those who have recently suffered an ischaemic stroke; however, its effects on patients who display poor hemodynamic compensation due to ICA occlusion but who have not recently suffered a stroke have not been investigated.

The purpose of the present study was to evaluate whether non-acute, at-risk patients with high-grade carotid artery disease may benefit from counterpulsation with moderate treatment pressure. In a prospective randomized pre-test/post-test study, the short-term effects of counterpulsation on CBFV and tissue oxygenation were studied.

Methods

Study population

Patients over 60 years of age with unilateral ICA stenosis (>70%) or occlusion as assessed by ultrasound were enrolled in this prospective experimental study. Patients were excluded if they had signs of neurological dysfunction such as transient ischaemic attack or stroke within the last 6 months prior to screening. Patients underwent brain magnetic resonance imaging prior to counterpulsation therapy in order to exclude a recent silent cerebral infarction. Further exclusion criteria were an insufficient transtemporal window for transcranial Doppler (TCD), atrial flutter or fibrillation, blood pressure (BP) ≥180/100 mmHg, left ventricular ejection fraction <35%, valvular heart disease, prior aorto-femoral or femoro-popliteal bypass surgery, lower limb vein thrombosis, a coagulation disorder, dementia or cognitive impairment and participation in any other clinical trial.

All study procedures were in accordance with the Declaration of Helsinki, and the study was approved by the Albert-Ludwigs University ethics review committee. All subjects gave informed consent prior to enrollment.

Study design

Patients were randomized to dual-course counterpulsation treatment (TS4 System; Vasomedical Inc., New York, NY, USA) of either 20 min active counterpulsation (applied pressure 180 ± 20 mmHg according to the diastolic peak flow augmentation detected in the MCA) followed by 20 min sham counterpulsation (applied pressure 80 mmHg) or vice versa (Fig. 1). Resting phases of 10 min were included before the start of the first counterpulsation/sham cycle (rest 1), between the two counterpulsation/sham cycles (rest 2) and following the second counterpulsation/sham cycle (rest 3).

Measurements

Arterial BP (Finapres 2300; Ohmeda, Finapres, Enschede, The Netherlands), heart rate (HR) and end-tidal pCO_2 ($PetCO_2$) (Normocap, Datex, Duisburg Nordrhein-Westfalen, Germany) were monitored continuously throughout the study procedure. CBFV

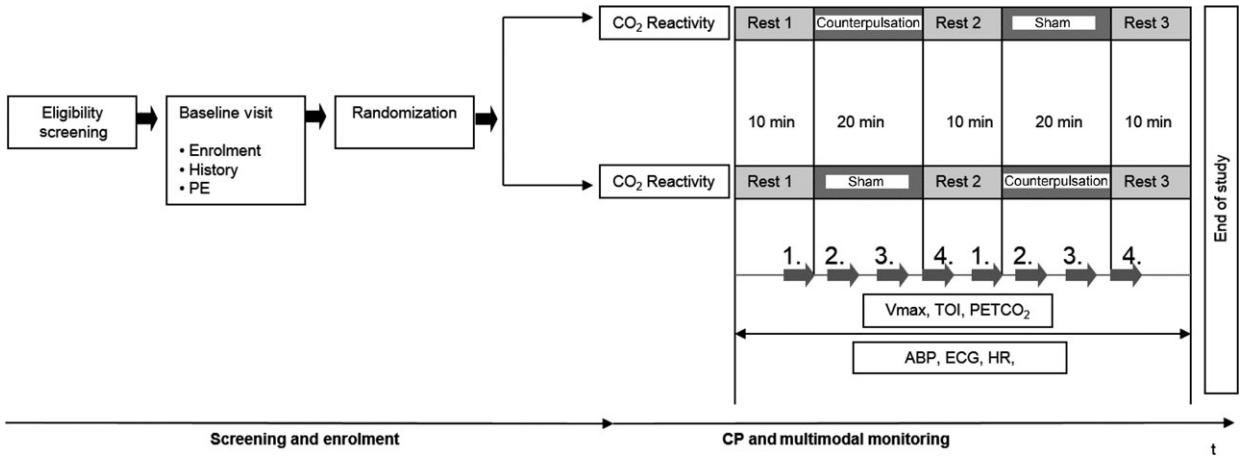

Figure 1 Study design. Patients were randomized 1:1 to counterpulsation followed by sham or vice versa. Hemodynamic parameters were analyzed during the following time intervals: (1) the 2 min prior to the start of the counterpulsation/sham cycle; (2) minutes 3–5 of the counterpulsation/sham cycle; (3) minutes 18–20 of the counterpulsation/sham cycle; and (4) the 2 min immediately after the counterpulsation/sham cycle. ABP, ambulatory blood pressure; CP, counterpulsation; ECG, electrocardiogram; HR, heart rate; PE, physical evaluation; $PETCO_2$, end-tidal pCO_2; TOI, tissue oxygenation index; V_{max}, maximum blood flow velocity.

(Multi-Dop X-4; DWL, GmbH/DWL, Singen, Germany) was continuously measured via TCD in both MCAs through the transtemporal window using probes fixed to a headband. Prior to the counterpulsation part of the study, cerebrovascular CO_2 reactivity was determined as described previously via inhalation of 7% CO_2-enriched air for 2 min [13]. Bilateral CO_2 reactivity was calculated as the maximum percentage increase in flow velocity from MCA baseline values per millimeter mercury change in $PetCO_2$. Impaired reactivity was defined as a value below 1.5% CBFV increase per millimeter mercury change in $PetCO_2$ [13].

Near-infrared spectroscopy monitoring (NIRO-300; Hamamatsu) of the bilateral prefrontal cortex was applied to obtain the tissue oxygenation index (TOI). TOI was calculated using a spatially resolved spectroscopy algorithm and defined as the ratio of oxygenated to total tissue hemoglobin, reflecting cerebral oxygenation with high sensitivity and specificity and allowing clinically relevant calculations of cerebral hemodynamic and oxygenation changes.

Multimodal monitoring data were recorded at a sampling rate of 100 Hz (TurboLab V4.3; Bresser Electronic) and were analyzed with the ICM+ software package (Cambridge Enterprise).

Data analysis

Hemodynamic parameters were analyzed for the following time intervals (Fig. 1): (1) the 2 min prior to the start of the counterpulsation/sham cycle; (2) minutes 3–5 of the counterpulsation/sham cycle; (3) minutes 18–20 of the counterpulsation/sham cycle; and (4) the 2 min immediately after the counterpulsation/sham cycle. Values referred to as 'ipsilateral' were recorded for the cerebral hemisphere affected by the unilateral ICA stenosis/occlusion. Hemodynamic changes were calculated as mean values from the measurements taken at minutes 3–5 and 18–20 for both counterpulsation and sham treatment cycles and compared with baseline. The two time periods were combined as no difference was observed in hemodynamic response during the period of counterpulsation.

The relative pulse slope index (RPSI) was calculated as the ratio between the maximum blood flow acceleration rate (ACC_{max}) and the mean blood flow velocity (V_{mean}) averaged over the heart cycle from intravascular flow velocity profiles obtained by TCD (Fig. S1) [4]. Given the linear relationship between mean shear rate (MSR) and vessel diameter, RPSI is equal to the maximum ΔMSR divided by time-averaged MSR [4].

Statistical analysis

Intra-individual differences between time points and inter-individual differences in response measures were assessed. Values were tested for mean differences by paired or unpaired t tests as appropriate. In addition to absolute values recorded during the counterpulsation/sham cycle, changes in parameters were computed as the difference between those measured at rest and the average of those measured during the counterpulsation/sham cycle. These delta values were tested against the null hypothesis of no change ($\Delta = 0$) using a one-sided t test. To predict sufficient response to treatment as a binary trait, logistic regression was

employed with baseline parameters as independent predictors. These included ΔRPSI, ACC_{max}, CO_2 reactivity (impaired versus preserved), V_{mean}, HR, BP and demographic characteristics. Treatment response was defined as an increase in TOI greater than the median value for the total population. All analyses were carried out using the R program [14]. Data are presented as box and whisker plots showing median values and interquartile ranges, as well as mean values with standard deviations and individual patient values. A P value of <0.05 was considered statistically significant.

Results

Patients

Two patients were excluded from the analysis due to TCD recording artifacts (n = 1) or bilateral ICA stenosis >70% (n = 1), respectively, leaving 28 patients for the final analysis. The mean age of the population was 71 years and 23 (82.1%) were male (Table 1). With regard to the cerebrovascular disease history, more than half of the enrolled patients had a complete ICA occlusion (n = 18), whilst the remaining 10 subjects had an ICA stenosis of >70%. Furthermore, 16 patients had experienced a transient ischaemic attack and nine patients a stroke more than 6 months prior to enrollment.

Hemodynamic parameters

During the counterpulsation cycle the mean arterial BP increased by 25.9 ± 2.7 mmHg compared to baseline. BP also increased during the sham treatment but to a much lesser extent (9.2 ± 2.1 mmHg). The mean HR at baseline was 64 ± 1.8 bpm, rising to 73 ± 2.2 bpm during counterpulsation and 66 ± 1.7 bpm during sham treatment. Measurements taken after the counterpulsation gave a mean value of 66 ± 6.2 bpm, whilst those after sham treatment gave 65 ± 1.6 bpm.

Table 1 Patient characteristics

	Mean ± SD or n (%) (N = 28)
Age (years)	71 ± 6.3
Male	23 (82.1)
BMI (kg/m^2)	26.4 ± 3.8
Cardiovascular risk factors	
Hypertension	24 (85.7)
Dyslipidemia	13 (46.4)
Diabetes mellitus	7 (25.0)
Current smoking	20 (71.4)
Ischaemic heart disease	14 (50.0)
Peripheral arterial occlusive disease	11 (39.3)
Chronic kidney disease ≥ stage 2	1 (3.6)
Cerebrovascular disease history	
ICA stenosis (<70%)	10 (35.7)
ICA occlusion	18 (64.3)
TIA/amaurosis fugax, n (%)	16 (57.1)
Prior stroke (>6 months before inclusion)	9 (32.1)
Percutaneous carotid intervention (contralateral)	2 (7.1)

BMI, body mass index; ICA, internal carotid artery; TIA, transient ischaemic attack.

During counterpulsation, the mean blood flow velocity in the ipsilateral MCA increased significantly from baseline (ΔV_{mean} 3.5 ± 1.2 cm/s, $P < 0.01$; Fig. 2a). This increase was greater than that seen during the sham treatment (ΔV_{mean} 1.13 ± 1.1 cm/s). On the contralateral side there was little change in velocity compared to baseline during either counterpulsation (ΔV_{mean} 1.6 ± 1.5) or sham (ΔV_{mean} −0.033 ± 1.72), with no significant difference found between the two (Fig. 2b).

Counterpulsation significantly increased the TOI of the ipsilateral hemisphere compared to baseline (ΔTOI 2.86 ± 0.8 $P < 0.01$), whilst the sham treatment resulted in only a slight change (ΔTOI 1.25 ± 0.65; P = 0.07; P value for counterpulsation versus sham = 0.01; Fig. 2c). Contralaterally, neither counterpulsation (ΔTOI 0.63 ± 0.72) nor sham (ΔTOI −0.58 ± 0.6) significantly affected cerebral oxygenation indices (Fig. 2d).

No significant changes in $PetCO_2$ were recorded during either counterpulsation or sham for either the ipsilateral (Fig. 2e) or contralateral (Fig. 2f) side.

Predictors of response

Amongst the hemodynamic factors that were evaluated in the logistic regression, the change in RPSI during counterpulsation therapy compared to baseline (ΔRPSI) was identified as predictive of a positive response to the treatment [odds ratio (OR) 1.179; 95% confidence interval (CI) 1.512–1.006; Fig. 3]. ACC_{max} was negatively associated with treatment response (OR 0.440; 95% CI 0.966–0.134). Baseline cerebrovascular reactivity to CO_2 was not found to be predictive, with patients displaying impaired CO_2 reactivity not showing a more pronounced response than patients displaying preserved CO_2 reactivity. Similarly, demographic baseline data as well as changes in several other parameters, including BP, V_{mean} and HR, were not predictive of a distinct increase in oxygenation.

Discussion

This study shows that short-term counterpulsation treatment can cause immediate increases in cerebral oxygenation and intravascular flow velocity – the

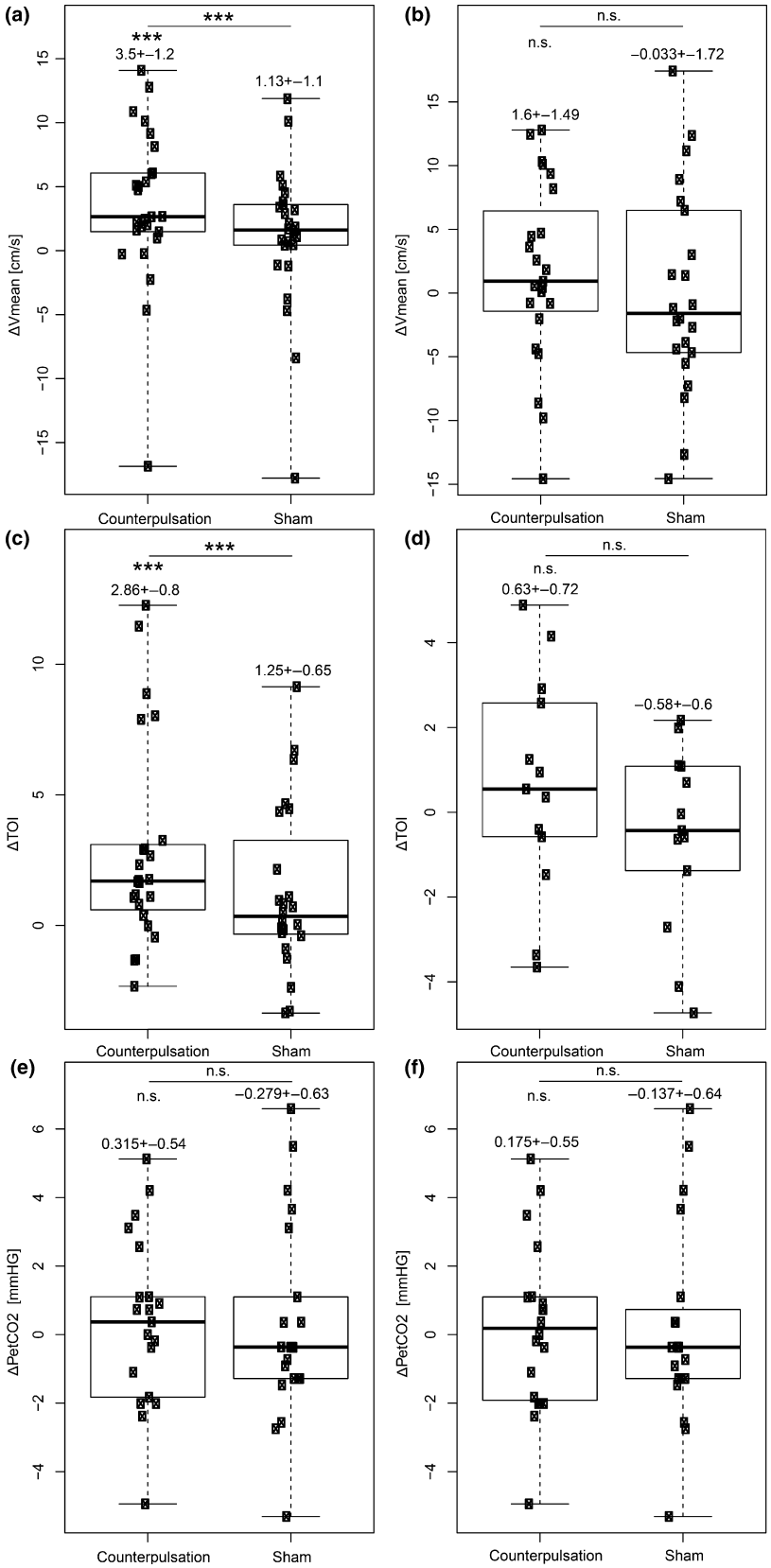

Figure 2 Changes in mean blood flow velocity, tissue oxygenation and CO_2 reactivity during counterpulsation and sham treatment. Changes in mean flow velocity (ΔV_{mean}) from baseline on the (a) ipsilateral and (b) contralateral sides; changes in tissue oxygenation index (ΔTOI) from baseline on the (c) ipsilateral and (d) contralateral sides; changes in cerebrovascular reactivity ($\Delta PetCO_2$) from baseline on the (e) ipsilateral and (f) contralateral sides. Individual patient values are given along with median and interquartile ranges (boxes). Numerical values are means with standard deviations. ***$P < 0.05$; n.s., not significant.

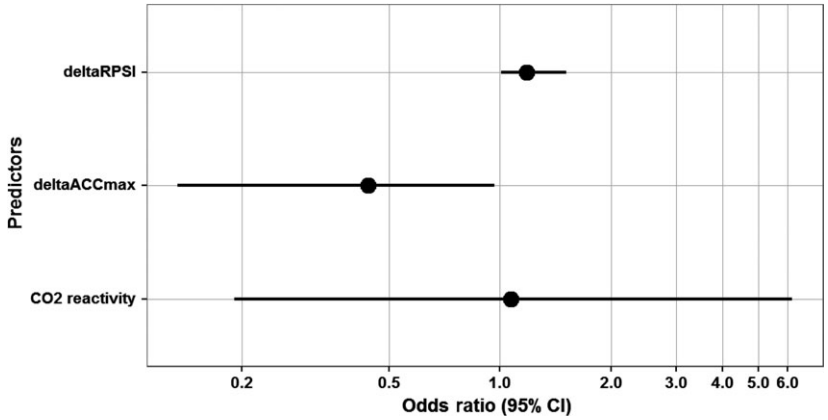

Figure 3 Odds ratios for potential predictors of TOI changes during counterpulsation.

latter being the pivotal mechanism by which cerebral arteriogenesis is triggered. Furthermore, a key TCD parameter was identified that can be measured non-invasively at the initiation of counterpulsation to predict a subsequent response of improved oxygenation.

Previous studies have identified significant differences in the response of healthy and infarcted cerebral vasculature to the application of counterpulsation. In healthy adults, where cerebral autoregulation is intact, counterpulsation was shown not to affect mean blood flow velocity [9], whilst in subacute stroke patients other studies have shown notable increases [10]. In the latter situation, however, cerebral autoregulation is probably impaired [12], with increases in perfusion pressure not counter-regulated by the cerebral circulation.

In our study, counterpulsation enhanced both CBFV and tissue oxygenation in non-acute, at-risk patients with high-grade carotid artery disease. In such patients, the extent to which the autoregulatory mechanisms of the cerebral vasculature remain intact is not known. Interestingly, CO_2 reactivity, as an indicator of autoregulatory function, was not found to be predictive of response to counterpulsation.

Counterpulsation resembles physical exercise with regard to its effects on mean arterial pressure, endothelial function and increased pulsatile flow [9]. In the cardiac vascular bed, counterpulsation is thought to induce the shear-stress-mediated recruitment and growth of collateral arterial pathways (arteriogenesis), enabling enhanced perfusion of tissue downstream of stenosed or occluded vessels [6]. In patients with coronary artery disease, significant increases in coronary collateral flow index have been demonstrated after a program of external counterpulsation, whilst no change was evident for the control patients [7].

Experimental animal models have validated therapeutically induced arteriogenesis in the brain, mainly in the circle of Willis, as a novel approach for the prevention of cerebral ischaemia with arterial stenosis [15]. Counterpulsation, by increasing pulsatile blood flow velocity, as has been shown in our study population, can provide the biomechanical stimulus that is critical for collateral recruitment and growth in the brain [3,4]. It is thus hypothesized that patients with chronic occlusion or stenosis of brain-supplying arteries might benefit from repetitive counterpulsation via induction of microvascular or (previously hypoplastic) macrovascular collateral growth. Further study into the effects of a program of counterpulsation treatment on the cerebral vasculature should elucidate the relationship between enhanced CBFV and the development of collaterals in the brains of such patients.

With the aim of identifying measurable parameters that could be used to predict whether or not a patient is likely to respond to counterpulsation therapy, logistic regression was performed using a cut-off of an increase in TOI greater than the median for the population as a positive outcome. Whilst none of the baseline patient characteristics that were evaluated was found to hold any predictive value, the hemodynamic parameters ACC_{max} and RPSI were both found to be associated with response. In particular, a greater change in RPSI on initiation of the counterpulsation technique was found to indicate a greater likelihood of augmentation of cerebral tissue oxygenation. A clinical follow-up study is proposed to evaluate the suitability of these easily assessed velocity-based parameters to rapidly identify positive counterpulsation responders and thereby enhance practical implementation of the technique in trials and, potentially, in clinical practice.

There were a number of limitations to this study. First, only a small number of participants were recruited. In order to fully elucidate the potential of the techniques, data are needed for a higher number of clinically stable and asymptomatic patients, with mostly ipsilateral impaired autoregulatory reserve.

Secondly, the majority of the study population was male; therefore, it will be important to recruit a more gender-balanced cohort for future investigations. Furthermore, prospective long-term and multicenter studies are needed in order to analyze whether counterpulsation has a sustained effect on CBFV and TOI. Finally, functional analyses after treatment with counterpulsation are required to assess any improvement in cognitive function and compensatory vascular remodeling processes. Here, counterpulsation might in particular affect adaptive arteriogenesis of the leptomeningeal collaterals and the circle of Willis.

In conclusion, this study shows that in patients with chronic high-grade stenosis or occlusion of the ICA, ipsilateral cerebral hemodynamics and oxygenation can be improved during short-term counterpulsation therapy. Future studies in chronic carotid artery occlusion should evaluate whether repetitive counterpulsation can lead to persistent elevation in cerebral oxygenation and whether it can improve cerebral collateral flow.

Disclosure of conflict of interest

The authors declare no financial or other conflicts of interest.

Clinical trial registration

http://www.isrctn.com: ISRCTN77215948.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. The relative pulse slope index (RPSI) and maximum blood flow acceleration (ACC_{max}).

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