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Clinical Study

Increasing pressure of external counterpulsation augments blood pressure but not cerebral blood flow velocity in ischemic stroke

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ABSTRACT

External counterpulsation (ECP) is a noninvasive method used to augment cerebral perfusion but the optimal use of ECP in ischemic stroke has not been well documented. We aimed to investigate the effects of ECP treatment pressure on cerebral blood flow and blood pressure (BP). We recruited 38 ischemic stroke patients with large artery occlusive disease and 20 elderly controls. We commenced ECP treatment pressure at 150 mmHg and gradually increased to 187.5, 225 and 262.5 mmHg. Mean cerebral blood flow velocities (CBFV) of bilateral middle cerebral arteries and continuous beat-to-beat BP were recorded before ECP and during each pressure increment for 3 minutes. Patient CBFV data was analyzed based on whether it was ipsilateral or contralateral to the infarct. Mean BP significantly increased from baseline in both stroke and control groups after ECP commenced. BP increased in both groups following raised ECP pressure and reached maximum at 262.5 mmHg (patients 16.9% increase *versus* controls 16.52%). The ipsilateral CBFV of patients increased 5.15%, 4.35%, 4.55% and 3.52% from baseline under the four pressures, respectively. All were significantly higher than baseline but did not differ among different ECP pressures; contralateral CBFV changed likewise. Control CBFV did not increase under variable pressures of ECP. ECP did increase CBFV of our patients to a roughly equal degree regardless of ECP pressure. Among the four ECP pressures tested, we recommend 150 mmHg as the optimal treatment pressure for ischemic stroke due to higher risks of hypertension-related complications with higher pressures.

1. Introduction

External counterpulsation (ECP) is a noninvasive, highly beneficial and long-term effective treatment for ischemic heart disease [1,2]. Recently ECP has been investigated for ischemic stroke. Three pairs of pneumonic cuffs are applied to the calves, lower thighs, and upper thighs (buttocks) in the enhanced ECP system. The electrocardiogram triggers cuff inflation sequentially from distal to proximal during diastole and releases cuff pressure before the start of systole. Diastolic pressure on the lower extremities improves venous return and cardiac output, while deflation before systole leads to increased systolic unloading. ECP has been demonstrated to improve the perfusion of vital organs through diastolic augmentation, including the brain, liver and kidneys [3].

The improvement of myocardial perfusion and promotion of coronary collaterals has been suggested to contribute to the clinical benefits of ECP in ischemic heart disease [4,5]. In cardiology, different treatment pressures of ECP have distinct effects on hemodynamic parameters in coronary artery disease and the effectiveness ratio is applied to determine the optimal pressure. The effectiveness ratio is calculated by the relative magnitude of diastolic augmentation and systolic unloading, assessed by finger plethysmography [6]. When the effectiveness ratio is manipulated into the range between 1.5 and 2.0 through adjustments of cuff pressure (commonly 250–300 mmHg), aortic flow is maximized [6]. Patients with a higher ratio (>1.5) during ECP have a greater reduction of angina class at 6 month follow-up [7].

ECP is a novel treatment concept for ischemic stroke. Our previous study demonstrated that ECP treatment was significantly associated with favorable clinical improvement of ischemic stroke patients with cerebral large artery occlusive disease [8]. ECP provides a new method of induced hypertension to improve cerebral perfusion and collateral blood supply in ischemic stroke by augmentation of blood pressure (BP) and cerebral blood flow velocity (CBFV) [9]. However, the effects of different cuff pressures on cerebral augmentation remain unclear. In this study we aimed to find the optimal pressure of ECP treatment in relation to the cerebral blood flow of patients with recent ischemic stroke. We

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hypothesized that CBFV of stroke patients may increase as ECP treatment pressure raises.

2. Methods

2.1. Subjects

We recruited ischemic stroke patients with cerebral large artery occlusive disease who were hospitalized in the Acute Stroke Unit, Prince of Wales Hospital in Hong Kong from November 2007 to April 2010. Ischemic stroke was diagnosed according to the World Health Organization definition [10], and the ischemia was confirmed by either CT scan or MRI. Patients were verified with large artery occlusive disease (hemodynamically significant moderate stenosis or >50% diameter reduction) by transcranial Doppler (TCD), magnetic resonance angiography, CT angiography or carotid duplex ultrasound. Patients with good acoustic windows admitted within 7 days of stroke onset were consecutively recruited. Patients with evidence of cardioembolic stroke including atrial fibrillation and rheumatic heart disease; evidence of hemorrhage on brain CT; evidence of arteriovenous malformation, arteriovenous fistula, artery dissection or aneurysm; history of intracerebral hemorrhage, brain tumor or malignancy; sustained hypertension (systolic >180 mmHg or diastolic >100 mmHg); severe symptomatic peripheral vascular disease; evidence of co-existing systemic diseases such as renal failure (creatinine >300 umol/L, if known), cirrhosis, thrombocytopenia (platelet count <100,000/mm^3), severe dementia or psychosis; and pregnancy were excluded. Patients were excluded if their large artery stenosis was due to vasculitis. Patients with stroke-onset relevant pontine, medullary or cerebellar infarcts were excluded as well, as our data analysis was based on the cerebral infarct side. Recruited patients did not receive thrombolysis or thrombectomy treatment and were not given any antihypertensive agents after hospitalization. Twenty healthy volunteers aged $\geqslant$45 years without history of cerebrovascular events and risk factors were recruited as controls. Each healthy subject underwent TCD and carotid duplex ultrasound to rule out large artery occlusive disease.

2.2. Ethics

Written informed consent was obtained from all study participants prior to enrollment. This study was approved by the Joint Chinese University of Hong Kong - New Territories, East Cluster, Clinical Research Ethics Committee.

2.3. ECP and TCD monitoring

ECP was performed using the Enhanced External Counterpulsation System MC3 (Vamed Medical Instrument Company, Foshan, China). The subjects lay on the ECP treatment bed and their legs were wrapped with three pairs of air cuffs. TCD monitoring was performed during the first session of ECP treatment using the ST3 Transcranial Doppler system (Spencer Technologies, Seattle, WA, USA). Two 2 MHz probes were fixed on a headframe worn by the subjects. The M1 segments of the bilateral middle cerebral arteries (MCA) were insonated at the depth of highest mean flow velocity, between 50 to 60 mm. Based on our previous study [9], we started ECP treatment pressure at 150 mmHg (150 mmHg = 0.02 MPa), then gradually increased to 187.5 mmHg (0.025 MPa), 225 mmHg (0.03 MPa) and 262.5 mmHg (0.035 MPa). The minimal adjustable unit of ECP cuff pressure for the ECP system MC3 is 0.005 MPa. CBFV at baseline and under different ECP pressures were recorded for 3 minutes. We also recorded another 3 minutes of MCA CBFV immediately after ECP treatment stopped. The rationale for the use of 3 minute intervals has been described in previous studies [9]. During TCD monitoring, beat-to-beat continuous finger BP was recorded using the Task Force Monitor (CNSystems Medizintechnik, Graz, Austria). BP was measured via finger cuffs on the index and middle finger of the left hand with an appropriate cuff size (small, medium or large) for the size of hand.

2.4. Data analysis

The mean CBFV of the MCA was automatically recorded from the TCD waveform as the mean value of the area under the envelope curve in a cardiac cycle. The cerebral augmentation index (CAI) was calculated using the increased percentage of mean CBFV during ECP compared with baseline, which was used to assess the augmentation effect of ECP. For stroke patients, CBFV and CAI data were analyzed based on whether it was ipsilateral or contralateral to the infarct. For healthy controls, mean CBFV as well as CAI on the right and left MCA were averaged. Statistical analysis was performed using the Statistical Package for the Social Sciences version 16.0 (SPSS, Chicago, IL, USA). Continuous data were expressed as mean and standard deviation if normally distributed, while categorical data were expressed as frequency and percentage. Paired-samples *t*-test was used to compare data under different pressures of ECP treatment and baseline. Repeated measures analysis was used to detect any significant differences for the four pressures of ECP. Statistical significance level was set at $p < 0.05$.

3. Results

There were 38 ischemic stroke patients with cerebral large artery stenosis and an adequate temporal window, as well as 20 elderly healthy controls, included in this study. The mean age of healthy controls was 60.30 years (standard deviation 6.57) and 50% of them were female. The mean age of the stroke patients was 68.21 years and the median admission National Institutes of Health Stroke Scale score for patients was 5.50 (Table 1). For stroke patients, the mean interval from stroke onset to ECP-TCD monitoring was 5.24 days. Of the 38 patients, 21 (55.3%) had left side acute or subacute infarct and 34 (89.5%) had infarcts located in the MCA and anterior cerebral artery territories. All patients had anterior circulation artery occlusive disease, and posterior circulation artery occlusive disease was also seen in 36.8% of patients. Twenty-six patients (68.4%) had multiple large artery stenosis. The majority of stroke relevant cerebral large artery lesions (76.3%) were located in the MCA (right MCA 44.7%, left MCA 31.6%). Twelve patients (31.6%) had verified stroke-relevant cerebral large artery occlusion, and 23.7% of relevant lesions were severe stenosis (75–99% diameter reduction). The rest of the stroke relevant lesions (44.7%) were moderate stenosis (50–75% diameter reduction).

Table 1
Clinical characteristics of stroke patients

	Patients, n = 38
Age in years, mean ± SD	68.21 ± 10.10
Sex, male	34, 89.5%
Hypertension	32, 84.2%
Diabetes mellitus	18, 47.4%
Chronic heart disease	4, 10.5%
Dyslipidemia	16, 42.1%
Previous CVA history	13, 34.2%
Smoking	15, 39.5%
Alcoholism	6, 15.8%
Stroke onset to exam time in days, mean ± SD	5.24 ± 2.28
NIHSS score on admission, mean (range)	5.50 (2–24)
Intracranial large artery stenosis	35, 92.1%
Extracranial large artery stenosis	11, 28.9%
Both intra- and extracranial large artery stenosis	8, 21.1%

Data are presented as n, % unless otherwise stated.
CVA = cerebrovascular accident, NIHSS = National Institutes of Health Stroke Scale, SD = standard deviation.