External counterpulsation (ECP) is a noninvasive, beneficial, and well-established treatment for ischemic heart disease with sustained long-term effects. ECP has been investigated for ischemic stroke, and a recent review suggests ECP is associated with a remarkable increase in the number of ischemic stroke patients with neurological improvement. In the ECP system, there are 3 pairs of pneumonic cuffs applied to the calves, lower thighs, and upper thighs. The ECG triggers cuff inflation sequentially from distal to proximal during diastole and releases cuff pressure before the start of systole. The standard duration of external counterpulsation is generally several weeks (5 daily 1-hour sessions each week for 7 weeks, for a total of 35 sessions), based on empirical data from studies in China. ECP has been demonstrated to improve the perfusion of vital organs through diastolic augmentation. Myocardial perfusion and coronary collateral flow in patients with coronary artery disease significantly increased after ECP, which may contribute to clinical benefits of ECP. Hypertension is a well-known risk factor for first or recurrent stroke, but the blood pressure management in acute stroke is controversial in recent years. For decades, induced hypertension has been investigated to improve reperfusion of ischemic brain via blood pressure augmentation. Most clinical studies of induced hypertension used pharmacological agents to elevate blood pressure and suggested that drug-induced hypertension in acute stroke is relatively safe and effective to improve neurological function, particularly for patients with multiple cerebral artery stenosis. In patients with acute ischemic stroke, induced hypertension enhanced cerebral perfusion and increased cerebral blood flow velocity.

Our previous study showed that ECP may help the recovery of ischemic stroke patients with cerebral large artery occlusive disease and moderate neurological deficit. The effects of ECP on ischemic stroke are largely unknown. The
responses of blood pressure and cerebral circulation in stroke patients during ECP are rarely described. We aimed to explore cerebral hemodynamic effects of ECP on patients with recent ischemic stroke. We hypothesized that ECP may augment cerebral blood flow of stroke patients through elevation of blood pressure.

Subjects and Methods

Subjects

We enrolled ischemic stroke patients with large artery occlusive disease to ECP treatment. They were hospitalized in Acute Stroke Unit, Prince of Wales Hospital, during September 2009 to December 2010, because of ischemic stroke that was diagnosed according to the definition of World Health Organization. All patients had corresponding acute or subacute infarct for the index stroke from computerized tomography or magnetic resonance imaging. The interval from stroke onset to recruitment was not >14 days. They were verified with cerebral large artery occlusive disease (moderate artery stenosis or >50% diameter reduction) by transcranial Doppler (TCD), magnetic resonance angiography, or computed tomography angiography. Among patients who agreed to ECP as an adjunctive treatment of conventional medical therapy, those patients with good temporal window for TCD monitoring were consecutively recruited into this study. Patients with cardioembolic stroke and history of intracranial hemorrhage were excluded. Patients with stroke onset−relevant pontine and medullary or cerebellar infarcts were excluded as well, because our data analysis was based on the cerebral infarct side. Exclusion criteria also contained contraindications for ECP, such as sustained severe hypertension (systolic ≥180 mm Hg and/or diastolic ≥100 mm Hg), aortic aneurysm, carotid dissection, and severe peripheral artery disease, severe systemic diseases, and malignancy. Those recruited ischemic stroke patients with cerebral intracranial large artery stenosis were not administered any antihypertensive agents after hospitalization. In addition, we recruited healthy elderly individuals without cerebrovascular events and risk factors as controls. This study was approved by the local medical ethics committee (Joint CUHK–NTEC Clinical Research Ethics Committee). All subjects gave informed consent. Clinical data of all subjects were documented for analysis.

ECP TCD Monitoring

ECP was performed using Enhanced External Counterpulsation system, model number MC2 (Vamed Medical Instrument Company, Foshan, China). The treatment pressure of ECP was 150 mmHg. TCD monitoring was performed at the first session of ECP treatment using ST3 TCD system (Spencer Technologies, Seattle, WA). The subjects lay on the ECP treatment bed and their legs were wrapped with 3 pairs of air cuffs. Two 2-MHz probes were mounted on a head frame, which was fitted individually and worn on the head of subjects. M1 segments of bilateral middle cerebral arteries (MCA) were sonicated at the depth of highest mean flow velocity between 50 and 60 mm. The standard duration of ECP therapy is 35 hours (7 weeks), and we mainly focused on the investigation of hemodynamic changes during ECP in this study. The cerebrovascular reactivity responding to ECP intervention stabilized within 1 minute. Therefore, in a practical way, we performed open-label ECP treatment for 3 minutes and monitored real-time changes of cerebral blood flow. We recorded blood flow velocity of MCA before and during ECP, respectively, for 3 minutes. Immediately after ECP treatment stopped, we recorded another 3 minutes of MCA blood flow changes after ECP measurements. Continuous beat-to-beat blood pressure data were recorded using Task Force Monitor system (CNSystems Medizintechnik AG, Graz, Austria) during the period of TCD monitoring. Blood pressure was measured through finger cuffs on the index fingers and the middle fingers of left hands, and appropriate cuff size (small, medium, or large) was chosen depending on the size of hand. Blood pressure was measured in the supine position.

Results

Forty-six ischemic stroke patients with cerebral large artery atherosclerotic occlusive disease and good temporal window agreed to receive ECP TCD monitoring. Fourteen patients were excluded because of pontine infarct. Finally, there were 32 recent ischemic stroke patients and 20 elderly healthy controls in this study. The healthy controls (age, mean±standard deviation: 60.30±6.57 years) were younger than stroke patients and had more female subjects (50% female). The age of stroke patients was 6±8 years, and mean interval of stroke onset was 6.18±1.8 days. Patients with single cerebral artery stenosis (59.4%), intracranial internal carotid artery in 7 patients, and 15 patients had multiple artery stenosis (at least 2 cerebral arteries involved).

Data Analysis

Mean flow velocity of MCA was automatically recorded by TCD system, which was the mean value of area under the envelope curve in a cardiac cycle. TCD data of stroke patients were analyzed based on ipsilateral to the infarct side or the contralateral side. TCD data of controls were analyzed based on the left or right cerebral side. Cerebral augmentation index was used to evaluate the augmentation effect of ECP, which was calculated by the increase in percentage of mean flow velocity during ECP compared with baseline. Continuous data were presented as mean and standard deviation if normally distributed. Category data were presented as number and percentage. Significance level was inferred at P<0.05.

Table 1. Characteristics of Stroke Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68.84±10.82</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>31 (96.9)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>25 (78.1)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>15 (46.9)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>19 (59.4)</td>
</tr>
<tr>
<td>History of IH, n (%)</td>
<td>4 (12.5)</td>
</tr>
<tr>
<td>Previous CVA history, n (%)</td>
<td>10 (31.2)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>12 (37.5)</td>
</tr>
<tr>
<td>Alcoholism, n (%)</td>
<td>6 (18.8)</td>
</tr>
<tr>
<td>Interval of stroke onset to examination, d</td>
<td>6.18±5.41</td>
</tr>
<tr>
<td>NIHSS score on admission</td>
<td>4 (0−17)</td>
</tr>
<tr>
<td>Left side infarct, n (%)</td>
<td>16 (50)</td>
</tr>
<tr>
<td>Right side infarct, n (%)</td>
<td>16 (50)</td>
</tr>
</tbody>
</table>

CVA indicates cerebrovascular accident; IH, ischemic heart disease; NIHSS, National Institutes of Health Stroke Scale.

Table 2. Blood Pressures of Stroke Subjects at Baseline and External Counterpulsation

<table>
<thead>
<tr>
<th>Mean Blood Pressure</th>
<th>Stroke Patients</th>
<th>Control</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (mm Hg)</td>
<td>94.65±14.37</td>
<td>89.17±9.58</td>
<td>0.168</td>
</tr>
<tr>
<td>ECP (mm Hg)</td>
<td>105.77±12.64</td>
<td>97.49±10.09</td>
<td>0.065</td>
</tr>
<tr>
<td>P Value (baseline vs ECP)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>BP increase during ECP from baseline (%)</td>
<td>12.84±11.06</td>
<td>9.49±4.74</td>
<td>0.639</td>
</tr>
<tr>
<td>After ECP (mmHg)</td>
<td>98.16±11.67</td>
<td>98.37±12.60</td>
<td>0.863</td>
</tr>
<tr>
<td>P Value (baseline vs after ECP)</td>
<td>0.083</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>BP increase after ECP from baseline (%)</td>
<td>4.76±10.77</td>
<td>10.43±3.35</td>
<td>0.079</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; ECP, external counterpulsation.

*Mann−Whitney was used to compare difference between stroke and control group. Paired t test was used to compare BP changes induced by ECP.
to examination was 6.18 days (Table 1). Stroke patients had moderate neurological deficits with median admission National Institutes of Health Stroke Scale score of 4. Half of 32 patients had left-side acute or subacute cerebral infarct and the other half had right cerebral infarct. All patients had at least 1 intracranial large artery stenosis (>50%) according to neuroimaging results. For the location of artery stenosis with highest diameter reduction, MCA was involved in 19 patients (59.4%), intracranial internal carotid artery in 7 patients, and anterior cerebral artery in 2 patients. The remaining 4 patients had narrowest artery lesion located in posterior cerebral artery, and those acute or subacute infarcts were located in thalamus. Seventeen patients (53.1%) had single cerebral artery stenosis and 15 patients had multiple artery stenosis (at least 2 cerebral arteries involved).

Mean blood pressure significantly increased during ECP both in stroke and control groups compared with baseline (Table 2). After ECP, blood pressure of stroke patients did not differ from baseline, but blood pressure of controls remained higher than baseline. Relative changes of blood pressure induced by ECP were comparable in stroke and control groups. ECP induced diastolic augmentation of MCA blood flow at the time of cuff inflation (Figure 1). MCA mean flow velocities of stroke patients markedly increased under ECP on both infarct ipsilateral and contralateral sides compared with baseline (P<0.001; Table 3). However, mean flow velocities of controls were not changed by ECP. Cerebral augmentation index of stroke patients was 9.64% on the ipsilateral side and 9% on the contralateral side. There was no significant difference of cerebral augmentation index between infarct ipsilateral side and contralateral side. After ECP, MCA flow velocities of stroke patients and controls all returned to baseline level. For stroke patients, similar changes of mean flow velocity on both cerebral sides accompanied changes of mean blood pressure (Figure 2).

Discussion

ECP increases mean blood pressure and MCA mean flow velocities on both cerebral sides of ischemic stroke patients. However, it does not change blood flow velocity of elderly controls, although blood pressure is elevated. Based on the assumption that the diameter of insonated cerebral artery and artery perfusion territory remain constant during TCD monitoring, ECP augments cerebral blood flow of ischemic stroke patients, but it does not change flow of elderly healthy subjects. It is consistent with previous findings that ECP does not increase cerebral blood flow in the healthy brain. Cerebral autoregulation ensures the constancy of cerebral blood flow under fluctuant cerebral perfusion pressure. Autoregulation mechanism is impaired after stroke, and it is hypothesized to be caused by damage of cerebral arterioles and capillaries during ischemia or other chronic illness, such as malignant hypertension. During ECP, cerebral blood flow of stroke patients increases after elevated blood pressure. ECP augments cerebral blood flow of ischemic stroke patients, possibly via impaired cerebral autoregulation. ECP could be used as a new method in treatment of ischemic stroke. ECP operates through external pressure applied on pneumatic cuffs on lower extremities with advantages of easy manipulation, adjustable pressure, and good tolerance. Usually, ECP treatment takes 35 hours (daily 1 hourly session) and lasts for 7 weeks. The commonest adverse effects of ECP are leg and lower back pain, hematuria, and skin abrasion. The Multicenter Study of Enhanced External Counterpulsation (MUST-EECP) trial reported most patients tolerated ECP treatment well and were free of limiting side effects. The potential risks of increasing blood pressure during acute stroke may contain intracerebral hemorrhage and aggravation of edema. Sustained severe hypertension in our exclusion criteria and real-time blood pressure monitoring during ECP are helpful to reduce risks of these hypertension-related events.
There is no difference in increase of mean MCA flow velocity between the infarct ipsilateral and contralateral sides when compared with each other. It may correlate with the globally impaired cerebral autoregulation after ischemic stroke in both infarction-affected and nonaffected contralateral hemispheres. Results of bilateral cerebral blood flow augmentation of ECP in ischemic stroke patients suggest that benefits of ECP may be attributable to global improvement of cerebral perfusion. Moreover, the presence and extent of collateral circulation affect the reperfusion of ischemia and are associated with clinical prognosis after acute ischemic stroke. The enhanced cerebral perfusion by ECP, on the infarct side and on the contralateral side, may improve the collateral blood supply of ischemic territories as well.

There are several limitations in this study. First, the sample sizes are relatively small. Second, age and gender differences of controls compared with stroke patients may partially influence their distinct hemodynamic responses to ECP, although we believe that these differences are not the major reason. Third, the delay of initiation of ECP from stroke onset in patients is majorly limited by the time when patients arrived in hospital after stroke events. According to our previous findings, ECP is beneficial to improve functional outcome of ischemic stroke patients with cerebral large occlusive disease, and in those patients the median time from stroke onset to ECP was up to 14 days. The evidence of increased blood pressure during ECP will be stronger if an aortic root arterial pressure line or a peripheral arterial pressure line is used. Blood pressure of the control group remains higher than baseline, which may be attributable to weak power of the small sample size. Cerebral blood flow velocities during ECP are monitored for only 3 minutes instead of 35 hours of daily 1-hour ECP treatment sessions, and these 3 minutes are considered to correlate with and represent the exact condition of ECP treatment. Factors like concurrent left ventricular dysfunction, hydration status, medications use, and subject core temperature may influence intracranial hemodynamics and need to be given attention in further studies. This study mainly investigates hemodynamic effects of ECP on blood pressure and cerebral blood flow, and the functional outcome results of ECP-treated patients are not included. However, there is an ongoing randomized controlled trial with conventional medical treatment of stroke patients used as controls to investigate the effects of ECP on ischemic stroke patients in our center. The functional outcome results from that study will be more convincing.

Conclusions
ECP increases blood pressure and cerebral blood flow of ischemic stroke patients. The extent of cerebral blood flow augmentation during ECP appears to be the same on the infarct side when compared with the contralateral side, which possibly results from globally impaired cerebral autoregulation. ECP provides a new method of induced hypertension to improve cerebral perfusion and collateral blood supply in ischemic stroke.

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Disclosures
None.
References


External Counterpulsation Augments Blood Pressure and Cerebral Flow Velocities in Ischemic Stroke Patients With Cerebral Intracranial Large Artery Occlusive Disease
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