Preliminary Findings of External Counterpulsation for Ischemic Stroke Patient With Large Artery Occlusive Disease

Jing Hao Han, MD; Thomas W. Leung, MD; Wynnie W. Lam, MD; Yannie O. Soo, MD; Anne W. Alexandrov, PhD; Vincent Mok, MD; Yee-Fong V. Leung, PhD; Raymond Lo, MD; Ka Sing Wong, MD

Background and Purpose—We aimed to investigate the feasibility and therapeutic effect of external counterpulsation (ECP) in ischemic stroke.

Methods—The trial was a randomized, crossover, assessment-blinded, proof-of-concept trial. ECP treatment consisted of 35 daily 1-hour sessions. Patients were randomized to either early (ECP weeks 1 to 7 and no ECP weeks 8 to 14) or late group (no ECP weeks 1 to 7 and ECP weeks 8 to 14). Primary outcomes were an overall change in National Institutes of Health Stroke Scale (NIHSS) and cerebral blood flow estimated by color velocity imaging quantification. Secondary outcomes were change in NIHSS, color velocity imaging quantification, favorable functional outcome (modified Rankin scale, 0 to 2), and stroke recurrence at weeks 7 and 14, respectively.

Results—Fifty patients were recruited. At week 7, there was a significant change in NIHSS (early 3.5 vs late 1.9; \(P=0.042\)). After adjusting for treatment sequence, ECP was associated with a favorable trend of change in NIHSS of 2.1 vs 1.3 for non-ECP (\(P=0.061\)). Changes of color velocity imaging quantification were not significant but tended to increase with ECP. At week 14, a favorable functional outcome was found in 100% of early group patients compared to 76% in the late group (\(P=0.022\)).

Conclusion—ECP is feasible for ischemic stroke patients with larger artery disease. (Stroke. 2008;39:1340-1343.)

Key Words: cerebral blood flow ■ counterpulsation ■ stroke

Ischemic stroke occurs when there is an interruption of blood flow to the brain. External counterpulsation (ECP) is a noninvasive method to improve perfusion of vital organs. It operates by applying ECG-triggered diastolic pressure of \(\approx 250\) mm Hg to the lower extremities by means of air-filled cuffs. The diastolic augmentation of the blood flow and the simultaneously decreasing systolic afterload therefore increases blood flow to the heart, brain, and kidneys.1

Currently, ECP is an adjunctive treatment for chronic angina.2 An increase of blood flow in the carotid arteries was noted during ECP.2,3 Because ECP may improve cerebral blood flow, we aimed to explore the therapeutic effect of ECP in recent stroke patients with large artery occlusive disease.

Patients and Methods

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

Inclusion criteria were: age 18 years or older; diagnosis of ischemic stroke within 3 months of randomization; large artery occlusive disease; and normal platelet count and coagulation profile. Patients with atrial fibrillation, significant valvular heart disease or aortic dissection, blood pressure persistently \(>180/100\) mm Hg, severe symptomatic peripheral vascular disease, deep vein thrombosis, bleeding diathesis, history of intracranial hemorrhage, brain tumor or vascular malformation, diabetic retinopathy, and active malignancy were excluded.

Patients were examined by transcranial Doppler and duplex ultrasound. Diagnosis of intracranial or extracranial large artery stenosis was made by standardized protocols.4,5

Study Design

We performed a randomized, crossover, outcome assessment-blinded clinical trial. Patients were randomized to either the early or the late ECP group. A random sequence was generated by computer and randomization was performed using sealed, numbered, opaque envelopes. The early group received 35 daily 1-hour sessions during weeks 1 to 7 after the randomization and then received no ECP during weeks 8 to 14. The late group received no ECP during weeks 1 to 7 and received ECP during weeks 8 to 14 after the randomization.
tion. All patients received 80 to 160 mg aspirin; for those with hypertension, antihypertensive medications were administered for secondary stroke prevention. ECP was provided using the Vamed Medical Instrument Company device, model number MC2 (Guangdong, China), with cuff inflation pressure of 250 mm Hg.

**Outcomes**

The primary outcomes were an overall improvement in National Institutes of Health Stroke Scale (NIHSS) and color velocity imaging quantification (CVIQ) regardless of the treatment sequence. The same experienced technician measured total extracranial blood flow volume by CVIQ using validated method.6

Secondary outcomes included change in NIHSS and CVIQ, proportion of patients with modified Rankin score 0 to 2, and stroke recurrence at end of weeks 7 and 14, respectively. Recurrent ischemic stroke within the study period was considered as a safety end-point and was defined as sudden onset of a new focal neurological deficit with no apparent cause other than that of vascular origin.
Table 1. Baseline Demographic Characteristics of Participants

<table>
<thead>
<tr>
<th>Measure</th>
<th>ECP Early (n=25)</th>
<th>ECP Late (n=25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>16/9</td>
<td>16/9</td>
<td>0.616</td>
</tr>
<tr>
<td>Age (mean±SD, yr)</td>
<td>66.4±9.7</td>
<td>68.6±7.5</td>
<td>0.374</td>
</tr>
<tr>
<td>Median time after symptom onset, d</td>
<td>14</td>
<td>13</td>
<td>0.653</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>18 (72)</td>
<td>21 (84)</td>
<td>0.306</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>13 (52)</td>
<td>12 (48)</td>
<td>0.777</td>
</tr>
<tr>
<td>Ischemic heart disease (%)</td>
<td>3 (12)</td>
<td>4 (16)</td>
<td>0.684</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>9 (36)</td>
<td>10 (40)</td>
<td>0.771</td>
</tr>
<tr>
<td>Hyterlipd (%)</td>
<td>9 (36)</td>
<td>15 (60)</td>
<td>0.089</td>
</tr>
<tr>
<td>Previous stroke (%)</td>
<td>5 (20)</td>
<td>6 (24)</td>
<td>0.733</td>
</tr>
<tr>
<td>NIHSS (mean±SD, median)</td>
<td>5.5±4.8 (3.0)</td>
<td>4.3±4.3 (3.0)</td>
<td>0.266*</td>
</tr>
<tr>
<td>CVIQ (mean±SD, mL/min)</td>
<td>675.2±138.2</td>
<td>652.0±134.7</td>
<td>0.550</td>
</tr>
</tbody>
</table>

* Mann–Whitney U test.
† Fisher exact test.

occurring in a territory separated from the index stroke. Each recurrent stroke was assessed by a physician unaware of the patients’ treatment allocation.

NIHSS, CVIQ, and modified Rankin score (mRS) were assessed at baseline and at weeks 7 and 14. Prestroke modified Rankin score was estimated according to the history provided by the patients or their relatives.

Statistical Analysis
An overall change in NIHSS and CVIQ for ECP and non-ECP treatment was calculated by general linear model corrected for treatment sequence. Intention-to-treat analysis was performed in all randomized patients. The modified Rankin score and NIHSS assessment were complete in all patients. Among 3 patients with recurrent stroke whose condition did not allow performing reliable CIVQ measurement, the last observation was carried forward.

Results
The study flow diagram is shown in Figure. Fifty patients were recruited. Demographic and baseline data are shown in Table 1. No imbalance was found between the 2 groups. Patients had more intracranial artery atherosclerosis than extracranial artery disease (number of intracranial occlusive artery: early 31 vs late 30; extracranial artery: early 7 vs late 6).

Primary Outcome
A reduction of 2.1 (95% CI, 1.5 to 2.7) points in the NIHSS was found after a 7-week course of ECP, compared to a reduction of 1.3 points (95% CI, 0.6 to 1.9) for no ECP (P=0.061). There was a mean increase in CVIQ to 27.3 mL/min (95% CI, −10.4 to 65.1) for ECP therapy, compared to 21.0 (95% CI, −15.1 to 57.2) for non-ECP (P=0.809).

Secondary Outcome
Changes in NIHSS, CVIQ and proportion of patients with modified Rankin score ≤2 at weeks 7 and 14 are shown in Table 2. One patient in the early group experienced recurrent stroke, whereas 4 patients in the late group had a recurrent stroke (4% vs 16%; P=0.349).

Safety
Two patients had minor skin abrasions. Two patients reported low back pain and 1 withdrew. Another patient in the early group had deep vein thrombosis in the lower limb and stopped ECP and underwent medical therapy without further incident. One patient in the early group presented with ocular bruit and diplopia and had carotid-cavernous sinus fistula diagnosed. ECP was stopped and the fistula was closed by endovascular embolization.

Discussion
This is the first report to our knowledge of the use of ECP for ischemic stroke in the English literature, as our search on Medline does not show any similar finding. Intention-to-treat found ECP therapy was associated with better clinical outcomes. There may be some underestimate of the therapeutic effect because some patients did not complete a whole course of treatment. Although not all outcome measures are significant, at least the trends are directing to a positive effect of ECP. The sample size is too small to confirm any definite clinical benefit, but our study has proven the benefit of ECP for a better neurological and functional recovery for ischemic stroke patients.

The reference value of CVIQ in our laboratory for normal healthy subjects aged 50 or older was 781.0 (95% CI, 726.5 to 835.5). The finding that stroke patients had a much lower blood flow volume than controls suggests ECP may be a good strategy to improve outcomes of stroke. Arterial stenosis causes hypoperfusion of the focal brain; in addition, the narrowing of arterial lumen stimulates the formation of thrombi, which further reduces cerebral blood flow. However, decreased perfusion reduces the washout of microemboli that have entered the hypoperfused regions, which leads to further ischemic damage of the brain. Therefore, it is reasonable that ECP-induced brain perfusion augmentation may subsequently result in a favorable outcome.
The presence and adequacy of collateral circulation is a key prognostic factor after ischemic stroke. Studies have shown that ECP may increase collateral perfusion either by releasing vasodilating factors, such as nitric oxide, or by factors related to angiogenesis, such as vascular endothelial growth factors. However, such evidence in stroke patients is not currently available. Further investigations may shed light on possible mechanisms responsible for the clinical benefit of ECP.

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**Disclosure**
None.

**References**
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