LETTER

External counterpulsation enhances neuroplasticity to promote stroke recovery

INTRODUCTION

Improving tissue perfusion in peri-infarct cortex could enhance neuroplasticity and improve functional recovery after stroke.[1] Treatments that enhance corticomotor function may benefit motor recovery. However, the effects of cerebral blood flow augmentation on corticomotor excitability have not been explored in humans.

External counterpulsation (ECP) is a non-invasive method to improve perfusion of vital organs.[2] It operates by applying ECG-triggered pressure to the lower extremities during diastole by means of air-filled cuffs. The diastolic augmentation of blood flow and the reduction of systolic afterload increases blood flow to the heart, brain and kidneys. In patients who had ischaemic stroke, ECP enhances cerebral blood flow velocities and can be associated with improvement in the neurological outcome.[3] ECP may improve cerebral perfusion and collateral blood supply in ischaemic stroke by augmenting blood pressure and cerebral blood flow velocity.[4] The effects of ECP on corticomotor excitability are unknown. We aimed to explore the effects of ECP on corticomotor excitability and upper limb motor recovery. We hypothesised that enhancing cerebral blood flow with ECP will facilitate ipsilesional corticomotor excitability and improve upper limb performance at the subacute stage of recovery after ischaemic stroke.

SUBJECTS AND METHODS

First-ever ischaemic stroke patients with upper limb impairment with onset between 4 days and 21 days were enrolled. Exclusion criteria were cardioembolic stroke, sustained hypertension (systolic >180 mm Hg or diastolic >100 mm Hg), bleeding diathesis, vascular malformation, epilepsy, pregnancy, metal or electronic implants, severe head injury, severe systemic diseases and malignancy. Patients were randomised (1:1) to either real or sham ECP. ECP was performed using an ECP system (MC2, Vamed Medical Instrument Company, Foshan, China). Both groups completed 10 sessions of ECP for 1 hour per day, delivered over 2 weeks. ECP was delivered at a standard pressure of 150 mm Hg for the real ECP group and 75 mm Hg for the sham ECP group. After ECP, all patients received 2 hours once-daily of routine rehabilitation treatments, consisting of standard physical and occupational training. All participants gave written informed consent. Clinical trial registration: ChiCTR-TRC-12002531.

Motor impairment was measured bilaterally with a hand grip (HG) dynamometer (Jamar Hand Dynamometer, Sammons Preston, USA) and a pinch grip (PG) dynamometer (Squeeze Dynamometer, Baseline, USA). Motor function was measured bilaterally using the Purdue Pegboard Task (PPT). Assessments took place at baseline, 1 day (post 1) and 30 days (post 30) after the completion of the 10 ECP sessions and were carried out by assessors blinded to group allocation.

Corticomotor excitability was assessed with single-pulse transcranial magnetic stimulation (TMS) of the primary motor cortex (M1) delivered through a figure-of-eight coil using a Magstim Super Rapid magnetic stimulator (Magstim Company, UK). The coil was positioned tangentially to the scalp and oriented to induce posterior to anterior current flow in the underlying tissue, at a 45° angle from the midsagittal line. The optimal scalp location was determined as the site where TMS evoked motor evoked potentials (MEPs) with the greatest amplitude. Rest motor threshold (RMT) was defined as the lowest percentage of maximum stimulator output that produced MEPs with a peak-to-peak amplitude >0.05 mV at rest in at least four of eight consecutive trials. Twenty MEPs at 130% RMT were retained and averaged for each patient at each time point (baseline, post 1 and post 30).

Clinical measures of the paretic hand were normalised to the non-paretic hand, and neurophysiological measures of the ipsilesional M1 were normalised to the contralesional M1. Repeated measures analysis of variance was used for normalised HG, PG, PPT, RMT and MEP amplitude, with factors time (baseline, post 1 and post 30) and group (real and sham). Two-tailed paired-sample t-tests were used for post hoc analyses, corrected for multiple comparisons. Statistical significance was set at $\alpha=0.05$.

Table 1 Baseline demographic and clinical characteristics

	Real ECP group (n=15)	Sham ECP group (n=15)	P values
Age, years, median (range)	61 (47–80)	65 (41–80)	0.287
Gender, male, n (%)	11 (70)	11 (70)	1.000
Interval of stroke onset to examination, days median (range)	6 (4–12)	6 (4–8)	0.916
Side of cerebral infarction, left/right	10/5	4/11	0.028
Lesion location, cortical/subcortical	1/14	0/15	0.309
NIHSS score, median (range)	6 (2–7)	4 (1–8)	0.250
Hand grip, kg, mean±SD			
Paretic	13.5±9.9	14.6±8.0	0.736
Non-paretic	26.3±8.9	23.2±8.5	0.339
Paretic/non-paretic	0.51±0.26	0.61±0.20	0.247
Pinch grip, psi, mean±SD			
Paretic	2.2±2.1	2.6±1.8	0.619
Non-paretic	4.5±2.0	4.6±1.8	0.953
Paretic/non-paretic	0.49±0.31	0.53±0.23	0.725
Purdue Pegboard Task, mean±SD			
Paretic	4.8±3.7	6.1±2.9	0.306
Non-paretic	11.1±1.9	11.0±2.1	0.929
Paretic/non-paretic	0.43±0.32	0.56±0.26	0.248
RMT, mean±SD			
Ipsilesional	72.2±11.5	66.3±11.1	0.166
Contralesional	59.1±7.6	58.2±8.6	0.154
Ipsilesional/contralesional	1.23±0.16	1.14±0.08	0.066
MEP amplitude, mV, mean±SD			
Ipsilesional	0.23±0.21	0.46±0.49	0.108
Contralesional	1.01±1.02	0.94±0.67	0.822
Ipsilesional/contralesional	0.34±0.29	0.53±0.37	0.142

ECP, external counterpulsation; NIHSS, National Institutes of Health Stroke Scale; RMT, resting motor threshold; MEP, motor evoked potential amplitude. P value superscripts indicate statistical test: T, two-tailed independent samples t-test; C, Pearson χ^2 test; M, independent samples Mann-Whitney U test.

RESULTS

We recruited 30 patients who had first-ever ischaemic stroke and upper limb weakness (22 male, median 62 years, range 41–80 years; 15 patients randomised to real ECP and 15 to sham ECP). Baseline participant characteristics are presented in table 1. The median interval of stroke onset to baseline assessment was 6 days. All patients had moderate neurological deficits with median admission National Institutes of Health Stroke Scale (NIHSS) score of 5. There were no significant differences in age, gender, NIHSS score or clinical and neurophysiological measures between the two groups with the exception of cerebral infarction side ($p<0.05$). Although there is a low risk of seizure and mild headache during TMS, the risk of adverse effects of TMS was minimised through stringent screening by a neurologist prior to participation. Patients may experience skin abrasion due to ECP therapy, and this was avoided by providing adequate skin cushioning. All participants completed all planned ECP sessions and assessments, with no adverse effects.

Normalised paretic HG strength increased more with real ECP than sham (figure 1A). There was an effect of time ($F_{2,56}=14.9$, $p<0.001$) and a group*-time interaction ($F_{2,56}=3.2$, $p=0.046$). Normalised paretic PG strength increased over time ($F_{2,54}=26.2$, $p<0.001$) with no effect of group ($p>0.7$). Normalised paretic Purdue Pegboard score increased over time ($F_{2,56}=29.4$, $p<0.001$) with no effect of group ($p>0.3$). Normalised ipsilesional M1 excitability increased more with real ECP than sham. For RMT, there was an effect of time ($F_{2,56}=24.2$, $p<0.001$) and a group*time interaction ($F_{2,56}=10.4$, $p<0.001$, figure 1B). For MEP amplitude, there was an effect of time ($F_{2,56}=11.6$, $p<0.002$) and a group*time interaction ($F_{2,56}=8.0$, $p=0.001$, figure 1C).

DISCUSSION

The main finding is that 10 daily sessions of ECP can enhance ipsilesional corticomotor excitability and reduce motor impairment of the paretic hand. This study is the first to explore the underlying neurophysiological mechanism of the effects of ECP on upper limb recovery in patients who had subacute stroke.

A number of potential mechanisms may contribute to recovery after stroke. At a cellular level, altered synaptic transmission, collateral and synaptic sprouting, remyelination and other forms of neuronal rearrangement might occur at cortical and subcortical levels.[5] Plasticity in the motor

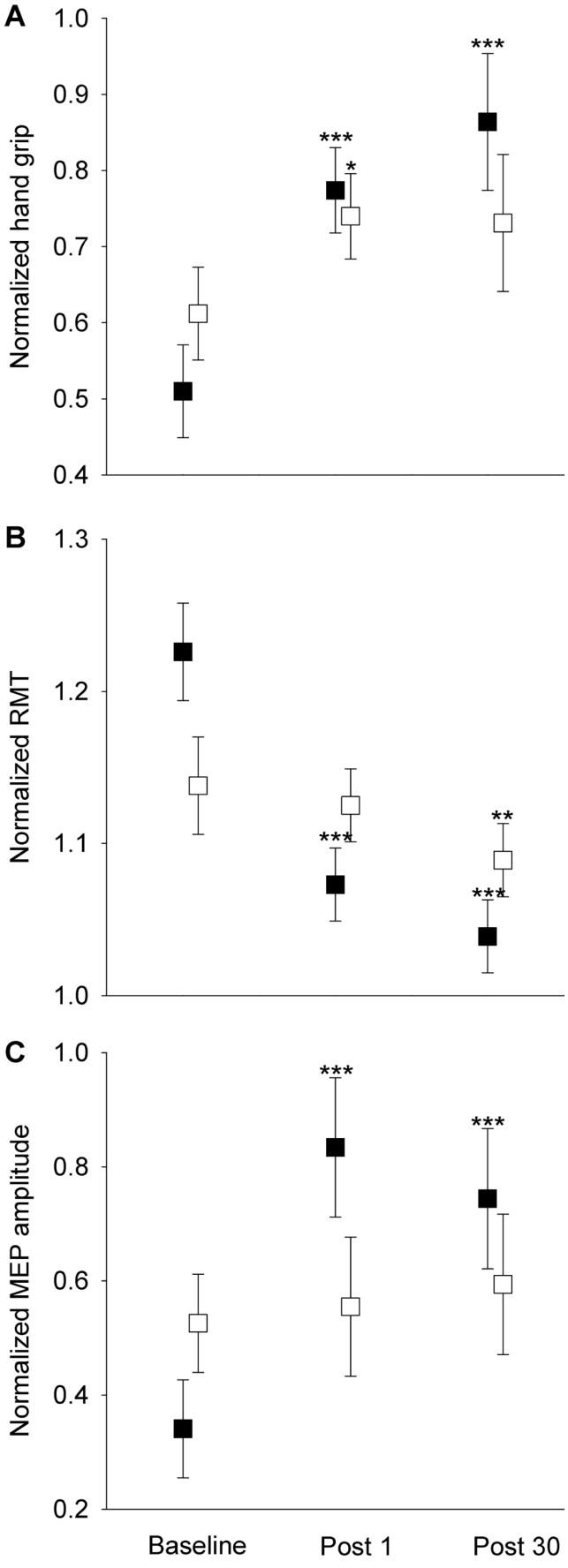

Figure 1 (A) Normalised paretic hand grip strength. (B). Normalised RMT. (C). Normalised MEP amplitude. Filled=real ECP; open=sham ECP. Compared with baseline *p<0.05, **p<0.01, ***p<0.001. ECP, external counterpulsation; MEP, motor evoked potential; RMT, rest motor threshold.

system may occur within the primary motor cortex, and also in other cortical motor areas with a direct corticospinal projection, including the supplementary motor area, premotor areas and cingulate motor areas.[6] ECP increases mean blood pressure and middle cerebral artery mean flow velocities bilaterally in patients who had ischaemic stroke.[4] This augments global cerebral blood perfusion and possibly facilitates neuronal and glial cell metabolism throughout the brain. These effects may benefit plasticity in the corticomotor system and assist motor recovery in patients who had stroke.

In the present study, normalised paretic HG strength increased to a greater extent after real ECP than after sham. It is unclear why the recovery of HG, but not PG, was enhanced by ECP. The PG measures may have been less sensitive to the effects of ECP, due to relatively high interindividual variability. There was no effect of ECP on paretic hand function, measured with the PPT. Ipsilesional RMT decreased, and ipsilesional MEP amplitude increased, to a greater extent after real ECP. Together, these results indicate that ECP can promote an increase in ipsilesional M1 excitability and a decrease in upper limb motor impairment. By enhancing perfusion, ECP might facilitate restoration of transmission in descending corticomotor axons, resulting in a larger proportion of the neuronal population being activated by both TMS and sustained voluntary effort. In contrast, ECP had no effects on a task requiring coordination and fine motor control to complete a task. These findings hint at dissociation between the effects of ECP on motor impairment and function, which could be explored in future studies.

Jing Yi Liu,[1] Li Xiong,[1] Cathy M Stinear,[2] Howan Leung,[1] Thomas W Leung,[1] Ka Sing Lawrence Wong[1]

[1]Division of Neurology, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Shatin, Hong Kong
[2]Clinical Neuroscience Laboratory, Department of Medicine, University of Auckland, Auckland, New Zealand

Correspondence to Dr Cathy M Stinear, Clinical Neuroscience Laboratory, Department of Medicine, University of Auckland, Auckland, New Zealand; c.stinear@auckland.ac.nz

Acknowledgements We would like to acknowledge Dr Shawn Lee for formatting the references.

Contributors JYL performed ECP treatment and TMS measurement for all participants. LX analysed the data and wrote the manuscript. CMS helped design the project and revise the manuscript. HL and TWL helped recruit participants. KSLW conceived and designed the project.

Funding This study was supported in part by the Lui Chi Woo Institute of Innovative Medicine, SH Ho Center for Cardiovascular Disease & Stroke.

Competing interests None declared.

Patient consent Obtained.

Ethics approval This study was approved by the local medical ethics committee (Joint CUHK-NTEC Clinical Research Ethics Committee).

Provenance and peer review Not commissioned; externally peer reviewed.

JYL and LX contributed equally.

To cite Liu JY, Xiong L, Stinear CM, *et al*. *J Neurol Neurosurg Psychiatry* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jnnp-2018-318185

Received 8 February 2018
Revised 17 April 2018
Accepted 30 April 2018

J Neurol Neurosurg Psychiatry 2018;**0**:1–3. doi:10.1136/jnnp-2018-318185

REFERENCES

1 Hamadate N, Yamaguchi T, Sugawara A, *et al*. Regulation of cerebral blood flow in the hippocampus by neuronal activation through the perforant path: relationship between hippocampal blood flow and neuronal plasticity. *Brain Res* 2011;1415:1–7.
2 Han JH, Wong KS. Is counterpulsation a potential therapy for ischemic stroke? *Cerebrovasc Dis* 2008;26:97–105.
3 Han JH, Leung TW, Lam WW, *et al*. Preliminary findings of external counterpulsation for ischemic stroke patient with large artery occlusive disease. *Stroke* 2008;39:1340–3.
4 Lin W, Xiong L, Han J, *et al*. External counterpulsation augments blood pressure and cerebral flow velocities in ischemic stroke patients with cerebral intracranial large artery occlusive disease. *Stroke* 2012;43:3007–11.
5 Nudo RJ. Recovery after damage to motor cortical areas. *Curr Opin Neurobiol* 1999;9:740–7.
6 Rizzolatti G, Luppino G, Matelli M. The organization of the cortical motor system: new concepts. *Electroencephalogr Clin Neurophysiol* 1998;106:283–96.