

J.D. Lee  
J.S. Chon  
H.K. Jeong  
H.J. Kim  
M. Yun  
D.Y. Kim  
D.I. Kim  
C.I. Park  
H.S. Yoo

## The cerebrovascular response to traditional acupuncture after stroke

Received: 29 May 2003  
Accepted: 30 June 2003  
Published online: 27 August 2003  
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J.D. Lee (✉) · H.J. Kim · M. Yun  
D.I. Kim · H.S. Yoo  
Division of Nuclear Medicine, Department  
of Diagnostic Radiology, Yonsei University  
College of Medicine, 134 Shinchon-dong,  
Seodaemun-gu, 120-752 Seoul,  
South Korea  
E-mail: jdlee@yumc.yonsei.ac.kr  
Tel.: 82-2-3615836  
Fax: +82-2-3933035

J.S. Chon · D.Y. Kim · C.I. Park  
Department of Rehabilitation Medicine,  
Yonsei University College of Medicine,  
134 Shinchon-dong, Seodaemun-gu,  
120-752 120-752, South Korea

H.K. Jeong  
Research Institute of Radiological Science,  
Yonsei University College of Medicine,  
134 Shinchon-dong, Seodaemun-gu,  
120-752 Seoul, South Korea

**Abstract** Acupuncture is useful in treating the nausea and vomiting related to chemotherapy, adult postoperative surgery pain and postoperative dental pain. We obtained single-photon emission computed tomography (SPECT) brain perfusion images of six patients with middle cerebral artery occlusion obtained before and after acupuncture and compared the changes in regional cerebral blood flow (rCBF) to those in normal control. Images were obtained before and after acupuncture at six traditional acupoints (LI 4, 10, 11, 15 and 16 and TE5) in the affected arm. The baseline image was subtracted from the postacupuncture image, to produce a subtraction image displaying only voxels with values  $>2$  SD from the mean and those voxels were coregistered to the baseline SPECT or T2-weighted MRI. Similar images were obtained before and after

acupuncture of eight normal volunteers. Statistical parametric mapping with a threshold of  $P = 0.001$  and a corrected  $P$  of 0.05 was performed for group comparison between postacupuncture and baseline SPECT. Focally increased CBF was seen in all patients especially in the hypoperfused zone surrounding the ischaemic lesion, the ipsilateral or contralateral sensorimotor area, or both. Normal subjects showed increased rCBF mainly in the parahippocampal gyrus, premotor area, frontal and temporal areas bilaterally and ipsilateral globus pallidus. Acupuncture stimulation after stroke patients appears to activate perilesional or use-dependent reorganised sites and might be a way of looking at brain reorganisation.

**Keywords** Acupuncture · Stroke · Cerebral blood flow · Brain reorganisation

### Introduction

Acupuncture is a part of traditional oriental medicine and has been used in Asia for thousands of years to treat clinical disorders. Recently, the NIH Consensus Development Panel on Acupuncture provided information that it is useful for treating nausea and vomiting related to chemotherapy, adult postoperative surgery pain and postoperative dental pain [1]. Functional MRI (fMRI) and positron-emission tomography (PET) have demonstrated brain responses to acupuncture. Stimulation of LI 4 or ST 36 acupoints, the two

most widely used for analgesia, was found to produce deactivation of the limbic system [2, 3] whereas bilateral stimulation of ST 36 and Lu 5 resulted in the activation of the left anterior cingulate gyrus, both insulae and cerebellum [4]. These findings support the fact that the effect of acupuncture in pain control is by means of modulating the antinociceptive pathways in the brain.

Recently, Cho et al. [5] demonstrated a specific acupoint (VA 1) related to the vision-related occipital cortex using fMRI, providing evidence supporting the hypothesis that acupoints are related to specific internal

organs. One can extrapolate this to suggest that disease can be treated by stimulating appropriate points.

Acupuncture is empirically used in Asia for stroke management. Randomised clinical studies of electrical or traditional acupuncture have demonstrated neurological and functional effects, with improvement in power, reduced spasticity and improvement of post-stroke depression [6, 7, 8, 9], but there have also been contradictory reports of no beneficial effects on functional outcome or life satisfaction [10, 11]. The effectiveness of acupuncture therapy in stroke therefore remains to be proved.

We studied acupuncture-induced changes in regional cerebral blood flow (rCBF) after stroke, using single-photon emission computed tomography (SPECT) perfusion imaging with subtraction and MRI coregistration and compared the changes to those in normal controls.

## Materials and methods

We studied six patients, four men, two women, aged 40–69 years, mean 58 years, with hemiplegia due to a major stroke, with total occlusion of the middle cerebral artery (MCA) on the right in three and on the left in the other three. The diagnosis was made by MRI, including T1-, T2- and diffusion weighted (DWI) images and MR angiography. We also examined eight volunteers, five men and three women, 24–62 years of age, with no neurological or psychiatric disease. This study was approved from the Ethics Committee in our institute, and informed consent was obtained from the normal volunteers and assent from the patients' next of kin.

The patients were treated initially with intravenous heparin followed by oral antithrombotic agents such as aspirin or ticlopidine hydrochloride. Baseline SPECT was obtained 2–4 weeks after symptom onset, and postacupuncture SPECT on average 6 days (2–10 days) thereafter. In the normal group, the interval was 2 days. No specific treatment other than physical and occupational therapy was given to the patients between baseline and postacupuncture SPECT studies.

Acupuncture was performed by inserting traditional needles at six acupoints (LI 4, 10, 11, 15 and 16, and TE 5), the points prescribed for relief of spasticity of the affected limb, on the weak arm of the patients and at the same points on the left arm of the volunteers. The needles were intermittently manipulated, and kept in place for 20 min until the characteristic acupuncture responses (heaviness, numbness and feeling of the presence of the needle) were achieved. The radiotracer for SPECT, 740 MBq Tc-99m-ethyl cysteinate dimer (ECD), was injected intravenously thereafter and the needles were removed 5 min later. Acupuncture-induced change in rCBF was studied by image analysis techniques including subtraction with MRI coregistration and statistical parametric mapping (SPM).

SPECT was performed using a dedicated annular crystal gamma camera with low energy, high-resolution parallel-hole collimators. We used a 128×128 matrix with 3 degree angular increment for 20 min to obtain axial images, using the filtered backprojection method and a Butterworth filter (cut-off frequency 1.1 cycle/cm, order no. 10). Attenuation correction was performed by Chang's method, and coronal and sagittal images were reconstructed.

Data from baseline and postacupuncture SPECT of each subject were transferred to a workstation equipped with Solaris version 2.7. The image volumes were transformed to an Analyze file format with an unsigned 8-bit depth. Subtraction was then performed using Analyze AVW 3.0. The average voxel values of baseline and postacupuncture image volumes were normalised to a

voxel value of 100. The transformed, normalised baseline image was subtracted from the normalised postacupuncture image in each subject and the SD of the distribution of the subtraction voxel values was calculated. The subtraction image was the set to display only voxels with values  $>2$  SD from the SD, as described by O'Brien et al. [12], and those voxels were coregistered to the baseline SPECT or to T2-weighted MRI.

SPM analysis was performed in the normal subjects for group comparison between baseline and postacupuncture, using a personal computer operating SPM 99 software (Wellcome Department of Cognitive Neurology, London, U.K.). The reconstructed data, corrected for count rate, attenuation, and scatter were transformed into Analyze header format: 128 pixel matrix, 35 slices, 1.95 mm pixel width and height, 4.25 mm slice thickness, and two bytes of signed integer of pixel values. The postacupuncture and baseline images were separately coregistered to remove variations due to different size and shape of individual brains, using 12-parameter affine transform. The data were then normalised to an MNI (Montreal Neurological Institute, McGill University, CANADA) PET template transforming original images to 79×95 pixel matrix, 68 slices, and 2 mm cubic voxels. Each image was smoothed with a 10 mm isotropic Gaussian kernel prior to statistical analysis. To investigate quantitative rCBF changes, we carried out possible combinations of group comparison. The resulting SPM{t} maps were transformed to the unit normal distribution of SPM{z}. The Z scores were computed and converted into statistical parametric maps by the software. The statistics were displayed as results and rendered on the reference three-dimensional PET images at the threshold of  $P = 0.001$  with a corrected  $P$  of 0.05. In patient group, SPM analysis failed to demonstrate systematic findings due to low statistical power since the lesion sites and activation pattern differed from patient to patient.

## Results

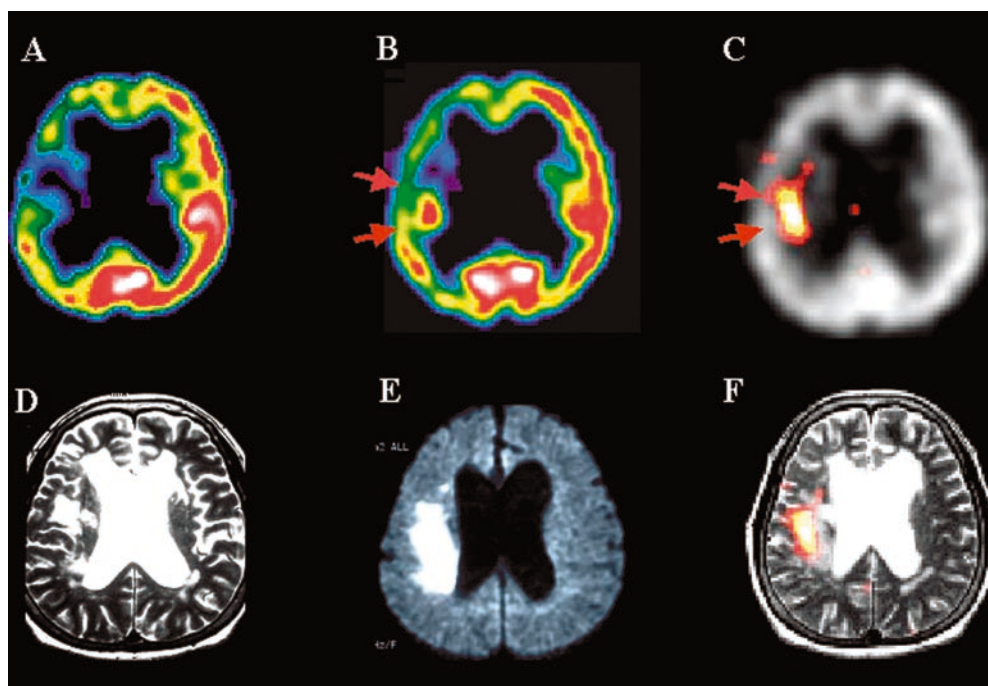
In all patients, postacupuncture images showed multiple activation sites in the periphery of the ischaemic area (Fig. 1) or in the hypoperfused zone in the affected vascular territory (Fig. 2), including the ipsilateral parietal lobe (in five), sensorimotor cortex (four), basal ganglia (four), premotor or prefrontal cortex (two) and thalamus (one). Activation of the contralateral hemisphere (Fig. 3) including basal ganglia (in four), sensorimotor cortex (four), parietal lobe (two) and thalamus (two) or pons (in one) was also seen. There was also bilateral activation of the parahippocampal gyrus (in four), ipsilateral anterior cingulate gyrus (three) and insula (one).

In contrast, the normal volunteers demonstrated clusters of increased rCBF in both hemispheres including parahippocampal gyri, frontal and temporal areas and ipsilateral globus pallidus (Fig. 4).

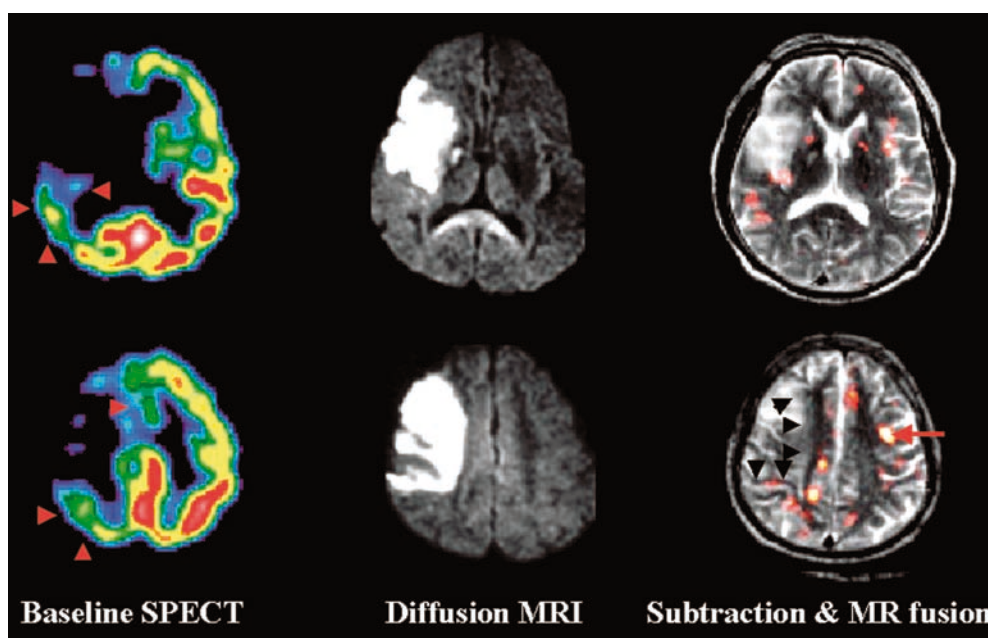
## Discussion

Experimental and clinical evidence suggests that acupuncture produces rhythmic discharge in nerve fibres and causes release of endogenous opioids and various neuropeptides [13, 14]. However, the anatomy and physiology of the acupuncture points and the

**Fig. 1A–F** Increased regional cerebral blood flow (rCBF) in the ischaemic zone after acupuncture. **A** Baseline perfusion single-photon emission computed tomography (SPECT) obtained 3 weeks after symptom onset in a patient with right middle cerebral artery (MCA) occlusion shows perfusion defect in right frontal lobe with surrounding hypoperfusion. **B** SPECT 8 days later shows acupuncture-induced increased rCBF in the hypoperfused zone (arrows). **C** Subtraction of the baseline and postacupuncture image shows this more clearly (arrows). **D**, **E** T2- and diffusion weighted MRI (DWI): the area giving normal signal in **D** high signal intensity in **E** is taken to represent cytotoxic oedema within the viable ischaemic zone. **F** Superimposition of **C** and **D**: acupuncture-induced increase in rCBF occurred in the peri-infarct ischaemic zone



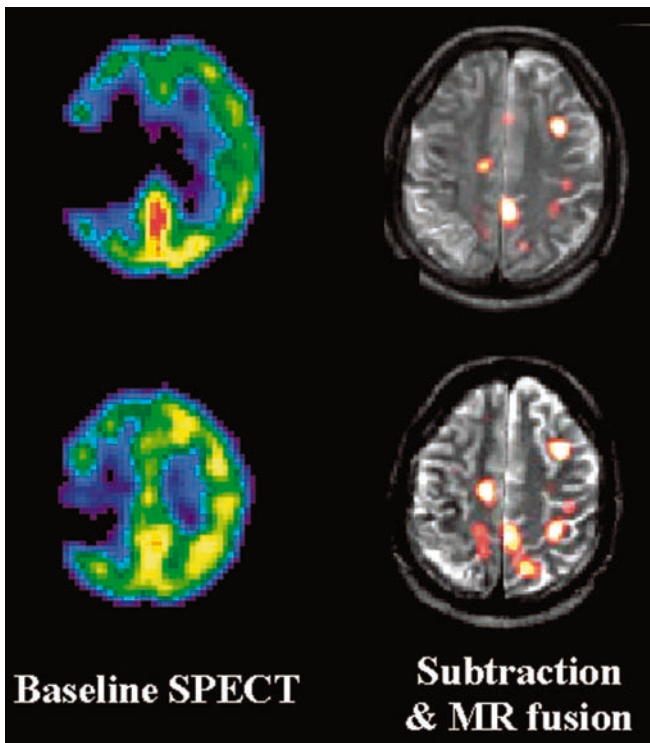
**Fig. 2** Activation of the hyperperfused zone in a patient with right MCA occlusion. *Left* SPECT 5 weeks after symptom onset shows a large perfusion defect and surrounding hypoperfusion (red arrowheads) in the MCA territory. *Centre* DWI shows high signal in the area of perfusion defect. *Right* Postacupuncture SPECT, 2 days after the baseline SPECT, subtracted and coregistered to T2-weighted MRI, demonstrates activation along the periphery of the ischaemic area (black arrowheads) and in the hyperperfused zone, including the basal ganglia and precuneus. There is also activation of the contralateral basal ganglia, premotor cortex (long arrow), insula and anterior cingulate gyrus



effectiveness of acupuncture in stroke are controversial. We showed increased perfusion in all patients, especially within the peri-infarct ischaemic and low perfusion zones in the affected vascular territories, and the ipsi- or contralateral sensorimotor cortex.

Normal volunteers demonstrated multiple sites of increased rCBF in either hemisphere. This pattern appears to be similar to that in a previous study

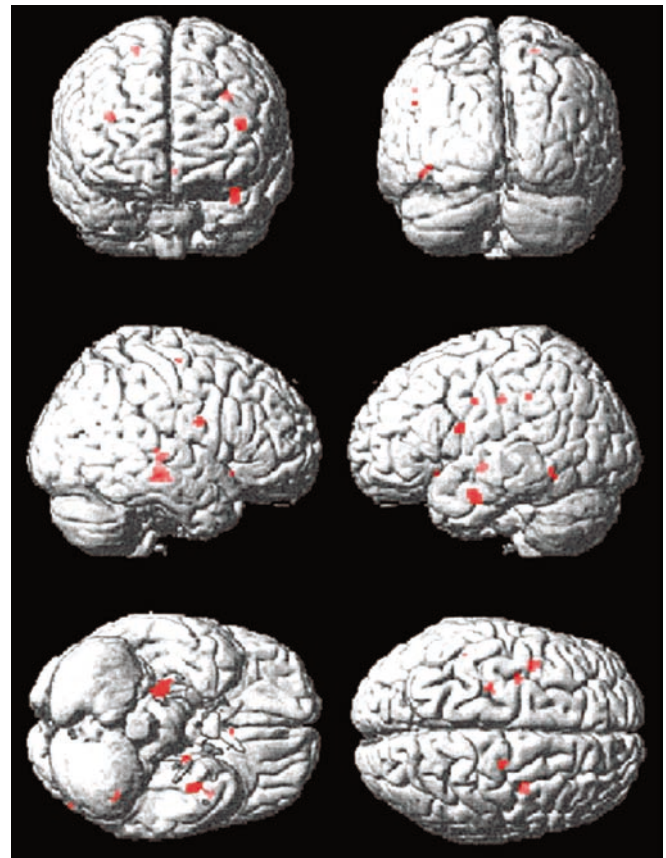
obtained by noxious intramuscular electrical stimulation of the brachioradialis muscle: increased rCBF in the contralateral secondary somatosensory cortex, anterior cingulate cortex, Brodman's area 40, ipsilateral cerebellum and subsignificant activation in contralateral primary motor and sensory cortex, anterior insular cortex, thalamus and lentiform nucleus [15].



**Fig. 3** Activation of the contralateral hemisphere. *Left* Baseline SPECT of a patient with a right MCA occlusion, 4 weeks after symptom onset, shows a large right hemisphere perfusion defect, including the frontoparietal convexity. *Right* Postacupuncture SPECT 4 days later, coregistered as in Fig. 2, demonstrates activation in the contralateral sensory, motor, parietal and prefrontal areas as well as the ipsilateral motor cortex

We found cerebrovascular responses to acupuncture after stroke to be different from those in normal individuals. Activation within the hypoperfused zone appears to be quite similar to that produced by perilesional neuronal plasticity after rehabilitation training or passive movement of the affected limb [16].

In terms of perilesional and use-dependent reorganisation in patients with stroke, morphological studies in the rat indicate that cortical lesions can induce an increase in dendritic branching in the contralateral hemisphere, within at most 2–3 weeks of the insult [17] and a significant increase in dendritic volume in the cortical layer of the contralateral motor cortex 18 days after, and in the number of synapses per neurons 30 days after the insult [18]. These adaptive changes of the cerebral networks to brain damage could provide a basis for functional recovery [19]. Neuroimaging and brain mapping studies enable study of neuronal plasticity; activation of the periphery of the lesion may reflect perilesional plasticity, and activation of the ipsilateral or contralateral sensorimotor cortex and premotor cortex after repetitive finger movement or elbow flexion of the affected limb, use-dependent plasticity [20, 21, 22].



**Fig. 4** Statistical parametric mapping of normal volunteers using SPM 99 software at a threshold of  $P = 0.001$  with a corrected  $P$  of 0.05 shows multiple sites of increased rCBF in both hemispheres including frontal and temporal lobes, parahippocampal gyri and ipsilateral globus pallidus

Higher rCBF within the peri-infarct ischaemic area or hypoperfused zone in our patients may suggest that acupuncture could activate viable tissue, in particular, reorganised neurones. Activation of the contralateral hemisphere may represent activation of the use-dependent reorganisation sites, a response to the painful stimulation, or both.

The mechanism by which acupuncture activates blood flow is unknown. It is also uncertain whether the activated areas represent adapted pain-modulating sites. Increased perfusion after thrombolytic therapy or spontaneous recanalisation of the occluded vessel could be one mechanism, since there was a 2–10 day interval between baseline and postacupuncture SPECT, and acupuncture was undertaken in the subacute stage. However, brain uptake of Tc-99m-ECD does not reflect rCBF within a luxury-perfusion zone but rather, we believe, viability and preservation of metabolic activity of the neurones [23].

We concluded that acupuncture stimulation appears to be an way of assessing brain reorganisation.

However, extensive biological and randomised clinical studies are required to investigate the mechanisms of increased blood flow and to whether acupuncture plays a role in brain remodelling.

**Acknowledgements** This study was supported by the Brain Korea 21 Project for Medical Science.

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