Article

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Functional electrical stimulation improves brain perfusion in cranial trauma patients

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ABSTRACT

Objective: Demonstrate brain perfusion changes due to neuronal activation after functional electrical stimulation (FES). **Method:** It was studied 14 patients with hemiplegia who were submitted to a program with FES during fourteen weeks. Brain perfusion SPECT was performed before and after FES therapy. These patients were further separated into 2 groups according to the hemiplegia cause: cranial trauma and major vascular insults. All SPECT images were analyzed using SPM. **Results:** There was a significant statistical difference between the two groups related to patient's ages and extent of hypoperfusion in the SPECT. Patients with cranial trauma had a reduction in the hypoperfused area and patients with major vascular insult had an increase in the hypoperfused area after FES therapy. **Conclusion:** FES therapy can result in brain perfusion improvement in patients with brain lesions due to cranial trauma but probably not in patients with major vascular insults with large infarct area.

Key words: SPECT, electrical stimulation, cranial trauma.

A terapia com estímulo elétrico funcional pode melhorar a perfusão cerebral no SPECT em pacientes com trauma craniano

RESUMO

Objetivo: Demonstrar mudanças na perfusão cerebral devido à ativação neuronal depois de estimulação elétrica funcional (EEF). **Método:** Foram estudados 14 pacientes com hemiplegia submetidos a quatorze semanas de um programa com EEF. O SPECT de perfusão cerebral foi realizado antes e depois da terapia com EEF. Estes pacientes foram separados em 2 grupos com relação à causa da hemiplegia: trauma craniano e acidente vascular cerebral (AVC). As imagens de SPECT foram analisadas usando SPM. **Resultados:** Houve diferença estatisticamente significativa entre os dois grupos relacionada a idade dos pacientes e extensão da hipoperfusão. Os pacientes com trauma craniano tiveram redução na área de hipoperfusão e pacientes com AVC tiveram aumento na área de hipoperfusão após terapia com EEF. **Conclusão:** A terapia com EEF pode levar a melhora na perfusão cerebral em pacientes com lesões cerebrais secundárias a trauma craniano; entretanto, provavelmente não em pacientes com extensas áreas de infarto secundárias a AVC.

Palavras-chave: SPECT, estímulo elétrico, trauma craniano.

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Rehabilitation of hemiplegic patients is in constant progression since the central nervous system of these patients with major lesions undergoes a func-

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tional reorganization through many different plastic mechanisms, such as axonal growth, hypersensitivities and re-activation of latent synapses. These mechanisms are not well understood, however, the major theory is that training, motivation and attention dedicated to the action help in the re-organization process.

Hemiplegic patients have spasticity and abnormal reflexes which impair normal motor activities. Neurorehabilitation has helped to improve wrist contraction[1], reduce superior limb spasticity[2], recover muscular force[3] and stabilize the hand[4].

The evolution of neurorehabilitation in the area of bioengineering has been tremendous with the use of various stimulating apparatus. The improvement of motor function promotes better performance of daily activities, since selective movements improve while spasticity and synergisms decrease[5].

The electrical neuromuscular stimulation which has been used for rehabilitation in patients with brain lesions provides excellent clinical results. However, the effects of this stimulation in metabolism and perfusion of the central nervous system are still not well understood. There are many studies evaluating brain activation after stroke in patients submitted to a rehabilitation training. To our knowledge there is only one study with brain SPECT in this setting[6].

SPM is an automatic statistical analysis tool for neuroimaging. It has been used in brain SPECT in some pathologies and our group has already applied this tool in epilepsy[7,8].

The purpose of this study was to demonstrate brain perfusion changes due to neuronal activation after functional electrical stimulation in patients with brain stroke and traumatic lesions.

METHOD

Patients and control group

Patients with chronic major stroke and traumatic central nervous system lesions were studied. Exclusion criteria consisted of patients below 13 years and above 60 years of age, patients with other neurological disorders, lesions that occurred prior to 40 months, patients with other co-morbidities (especially cardiac or with severe aphasia) and patients with acute stroke. Inclusion criteria consisted of patients with chronic major stroke or traumatic central nervous system lesions, documented by computed tomography, with upper extremity hemiparesis that occurred between 6 and 40 months.

Fourteen patients were selected (12 men; ages between 13 and 60 years; mean age 37.2 years). The patients were divided into two groups. Group A consisted of patients with traumatic lesions (7 patients) and group B were composed of patients with chronic major strokes (7 patients). All brain lesions occurred between 6 and 40 months (mean 18 months) prior to the study (Table 1).

All patients were submitted to electrical stimulation sessions. The electrical stimulation program was composed of 30-minute sessions, 3 sessions per week during fourteen weeks. The electrodes were placed on the affected forearm.

Patients were submitted to a neurofunctional clinical evaluation, which consisted of conventional neurological tests and functional activity tests, based on the Fugl-Meyer scales[9] and Barthel scales[10]. These evaluations were applied before and after the electrical stimulation sessions. The results of neurofunctional evaluation were described as a percentage of motor recuperation (clinical improve) between the evaluations before and after the electrical stimulation.

The control group consisted of 17 healthy volunteers with ages between 12 and 53 years, mean 34.9 years, 12 women and 5 men.

Brain perfusion SPECT imaging acquisition

Brain perfusion SPECT was performed in all patients at three time points: before the beginning of the electrical stimulation program (baseline SPECT), after seven days of the beginning of electrical stimulation program (SPECT 1) and at the end of electrical stimulation program (SPECT 2).

All patients had a permanent intravenous access through a *butterfly* connected to a catheter with saline solution and received an intravenous injection of 1110 MBq (30 mCi) of ^{99m}Tc-ECD.

The control group and in the baseline SPECT group remained resting in a dark, quiet room for 15 minutes prior to injection and remained resting for another 10 minutes prior to image acquisition.

The SPECT 1 and SPECT 2 groups were submitted to electrical stimulation for 15 minutes prior to the radio-

Table 1. Patient data.

	Group A (n=7)	Traumatic lesions	Group B (n=7)	Chronic major strokes
	Mean	SD	Mean	SD
Age	23.9	10.1	50.6	15.9
Lesion time (months)	17.9	11	18.7	10.3

SD: standard deviation.

tracer injection and electrical stimulation continued for 15 minutes afterwards. Images were acquired.

All SPECT images were performed in a computed scintillation camera with a *fan-beam* collimator. Sixty images were acquired in a 64×64 matrix, every 6 degrees, in a total of 360 degrees. Raw data were reconstructed by filtered back projection and attenuation correction was performed using Chang's method with a 0.115 attenuation coefficient. Images were displayed in the transaxial, coronal and sagital planes for interpretation.

SPECT SPM analysis

The reconstructed brain SPECT images were converted into Analyze format using MRIcro software (www.mricro.com). Voxel-based analysis was performed using SPM2 (Wellcome Department of Cognitive Neurology, www.fil.ion.ucl.ac.uk). To allow group comparison, the size and shape of each individual's scans were normalized to stereotaxic space (warping each image to match the default SPECT template that is distributed with SPM2). This process involves a 12 parameter linear transformation. The normalized images were smoothed by convolution with an Isotropic Gaussian Kernel (FWHM) of 10 mm. The ^{99m}Tc-ECD distribution was standardized to the mean global uptake using a proportional scale.

Statistical analysis

Using the SPM software, the brain SPECT of each patient was compared to the brain SPECT of the control group. These comparisons were performed using a non-paired two-sample T-test with a threshold of $P<0.001$. For each comparison the parameters below were analyzed in the baseline SPECT, SPECT 1 and SPECT 2 images:

[1] The extent of the hypoperfusion: described as the number of hypoperfusion voxels in whole brain - the higher the number of voxels, larger the area of hypoperfusion;

[2] The extent of the hyperperfusion: described as the number of hyperperfusion voxels in whole brain - the higher the number of voxels, larger the area of hyperfusion.

Then, patients were grouped according to the cause of the brain injury: patients with traumatic lesions and patients with chronic major strokes. The Wilcoxon test was applied to compare differences between the two groups related to age, time of lesion, clinical improvement after electric stimulation, hypo and hyperperfused regions for all SPECTs (baseline, SPECT 1 and SPECT 2).

Ethical statment

This study complies with the current laws of Brazil and had the previous approval of the Ethics Committee of the School of Medical Sciences, Campinas State University (UNICAMP), Campinas, Brazil. The SPECTs studies were performed with the understanding and written consent of all the participants.

RESULTS

The statistical analysis comparing the 2 groups (traumatic lesions and chronic major strokes) showed a significant statistical difference between the two groups related to patient age ($P=0.0168$) and hypoperfusion in whole brain ($P=0.0058$) when comparing baseline SPECT and SPECT 2. Patients with stroke were older (mean 50.6 years) than patients with cranial trauma (mean 50.6 years) than patients with cranial trauma (mean 23.9 years). Besides, patients with cranial trauma had a brain perfusion improvement (Fig 1), represented by a decrease in the extent of hypoperfusion and patients with major vascular insult had a brain perfusion worsening (Fig 2), represented by an increase in the extent of hypoperfusion (Table 2).

Interestingly, there was just one patient in the group of cranial trauma which had a brain perfusion worsening with increase in the extent of hypoperfusion. This patient was the oldest of the group with 45 years old.

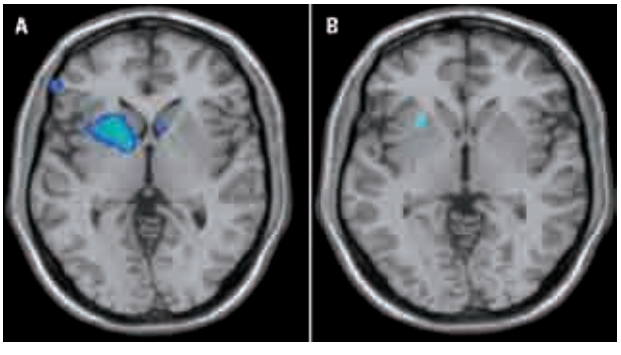

Fig 1. Brain SPECT SPM results a patient with cranial trauma before functional electrical stimulation [A] with 3120 voxels and [B] after electrical stimulation with 88 voxels. Note the great reduction in brain hypoperfusion area.

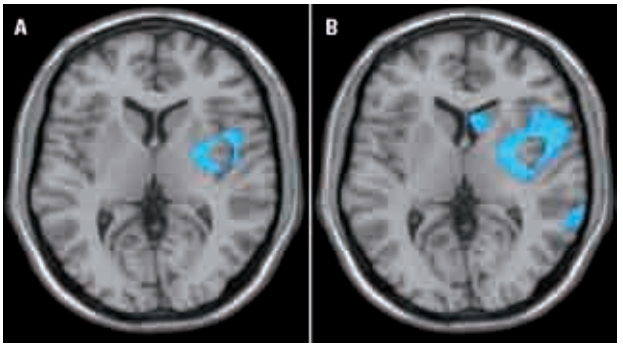

Fig 2. Brain SPECT SPM results in a patient with stroke before functional electrical stimulation [A] with 2294 voxels and after stimulation [B] with 8812 volts. Note the increase in extension of brain hypoperfusion.

Table 2. Results from comparisons between Group A (traumatic lesions) and Group B (chronic major strokes) (Wilcoxon test).

Variables	Lesion type groups		Wilcoxon Test P value
	Cranial trauma group (mean)	Brain stroke group (mean)	
Age (years)	23.7	50.6	0.0168
Time of lesion (months)	17.9	18.7	0.7483
Clinical improvement (%)	58.9	24.4	0.0828
Hypoperfusion in whole brain (voxels)			
(SPECT 2 vs baseline SPECT)	889	–17.124*	0.0058
Hyperperfusion in whole brain (voxels)			
(SPECT 2 vs baseline SPECT)	–3.690**	–3.145**	0.2197

*The negative value means increase of the hypoperfusion areas; **The negative value means decrease of hyperperfusion areas.

There was no statistically significant difference between the groups regarding to hyperperfusion voxels in whole brain.

The cranial trauma patient group had a higher mean clinical improvement (mean 58.9%) than the stroke group (mean 24.4%) (Table 2). However, this difference was not statistically different.

Besides, there was no significant statistical difference between the groups related to the time of lesion.

DISCUSSION

Neuronal plasticity has been previously studied with functional neuroimaging in the evaluation of patients with hemiplegia[11-13]. Neuronal damage due to stroke requires the brain to create alternative functional ensembles with the neurons that remain viable after the stroke. This has been postulated to occur via the unmasking of latent synaptic connections because of the down-regulation of inhibitory mechanisms and synaptogenesis[14].

A recent meta-analysis[15] evaluated cerebral changes in patients with brain stroke leading to upper extremity hemiparesis (patient age between 47.7 and 65.7 years) and treated with rehabilitation training. This meta-analysis included basically studies with transcranial magnetic stimulation (TMS) and functional magnetic resonance (fMRI). Just one study performed F-FDG positron emission tomography (PET) and one performed single photon emission computed tomography (SPECT). This meta-analysis concluded that target therapy improves motor functions in the damaged cortex and that this improvement is due to neural plasticity detected by the physiological measurements.

To our knowledge, there is just one study with brain SPECT in such patients[6]. Kononen et al.[6] evaluated 12 chronic stroke patients with constraint-induced movement therapy (CIMT) using brain SPECT before and after two weeks of CIMT. Increased perfusion was found in motor control related areas. The authors concluded that CIMT appears to change local cerebral perfusion in areas known to participate in movement planning and execution. These changes might be a sign of an active reorganization processes after CIMT in the chronic state of stroke.

One parameter which seems to be important is the time after the stroke. Some papers have suggested that early after the event there is an initial increase of task-related brain activation followed by an overall reduction afterwards[16,17]. Marshall et al.[16] studied patients with corticospinal tract infarction with fMRI 1 to 7 days and 3 to 6 months after the stroke. Calautti et al.[17] used PET H_2O^{15} which also shows brain perfusion in a striatocapsular stroke 7 and 30 days after stroke. These two studies did not perform a basal study without stimulation and their patients did not have a cortical infarct. Both studies found activation task-related in some areas in acute period and a less activation task-related in chronic period. In the present study, the mean time after the event was 18.7 months and the minimum time was 10 months. Patients with acute stroke were excluded from the analysis because during the acute phase of a major stroke, spontaneous neurological perfusion improvement may occur despite rehabilitation training.

It is important to remember the metabolic brain characteristics and neural plasticity in children and adolescents. Some studies suggest a higher brain functional reorganization in children that have had unilateral brain lesions at an early age when compared to those that have had brain lesion later on life[18]. Glucose brain metabolism increases from birth up to 4 years of age, reaches a plateau by the age of 10 and afterwards the glucose metabolism gradually decreases to levels similar to adults between the ages of 16 and 18 years. Glucose metabolism may represent synapses and the increase in glucose metabolism that occurs may represent a period of synaptic

proliferation, while the plateau may represent a great number of synapses and their connections[19].

The main finding of our study is that the two groups had a different perfusion pattern which was statistically significant: patients with cranial trauma had a brain perfusion improvement and patients with major vascular insult had a brain perfusion worsening after FES. To our knowledge, there is no study with cranial trauma patients and task training imaging. In the present study, patients with cranial trauma had a mean age of 23.9 years and the youngest patient was 13 years old. Since the brain metabolism is increased in adolescents, probably these younger patients could recover brain perfusion defects easier.

Until our knowledge, none study found a perfusion worsening. One explanation of this finding is the infarct extension since our brain stroke patients had a large cortical infarct area. Possibly there is a worse vascular supply or worse vascular reserve in large chronic major strokes group and these patients could have an area with less vascularization around the lesion comparing with the cranial trauma group.

Moreover, the cranial trauma patient group had a higher mean clinical improvement than the stroke group, although this difference was not statistically different. Probably, the sample groups were too small to detect a significant difference. More studies with more patients are necessary to confirm these findings.

In conclusion, FES can result in brain perfusion improvement in patients with brain lesions due to cranial trauma but probably not in patients with major vascular insults with large infarct area. Possible reasons could be related to better vascular supply and younger age of patients with cranial trauma patients when compared to major vascular insult group with large cortical infarct. Younger patients with cranial trauma seem to have a higher chance to show brain perfusion improvement and probably also better clinical results. On the other hand, patients with large cortical infarct seem to have a worse vascular supply or worse vascular reserve leading even to a worse vascularization after FES.

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