SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Development and application of devices for improving mobility and measuring the amount of movement in post stroke patients

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The Examination takes place at Department of Neurology, Faculty of Medicine, University of Debrecen, at 11:00 a.m. 2nd of June, 2017.

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The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, at 13:00 p.m. 2nd of June, 2017.

1. INTRODUCTION, AIMS

Cerebrovascular diseases rank third among leading causes of mortality in the developed countries and they are the single most important disease leading to acquired disability. Approximately 40-50 000 stroke events are registered in Hungary annually. Prevalence among the Hungarian population is 180 000 (chronic and acute). Patients require care and lengthy rehabilitation, which is a huge financial burden for the individual, their family and the whole society.

After a stroke:

- The initial phase of the disease is characterized by flaccid muscles on the paretic limb ("Flaccid phase");
- Stages of the disease may overlap, and even in the initial phase of the disease muscle tone may increase within days ;
- High tone of the antigravitation muscles may develop, i.e. the Wernicke-Mann posture with increased flexion tone in the upper limbs, increased extension tone in the lower limbs, extension, lateral rotation and abduction in the hip joint, extension in the knee joint and plantar flexion in the ankle joint;
- Movement disorders are most pronounced and most difficult to restore in the distal parts;
- Due to immobility, procedures responsible for contractures in the muscles already start within the first 24 hours;
- Muscle weakness, as well as the effect of either immobilization and/or increased muscle tone on passive range of motion of the ankle joint can be experienced and measured within a short period of time ;
- Common phenomena are flexible equinus, equinovarus (club foot), and equinovalgus positions of the ankle (weight bearing over the medial border of the foot) are;
- Equinovalgus deformity is caused by spasticity of the gastrocnemius medialis, gastrocnemius lateralis, musculus soleus, and the musculus peroneus brevis, as well as the weakening of the anterior and posterior tibial muscles. The foot rotates laterally, patients walk on the medial border of their feet, foot swings get unstable and gait unsafe;
- Prevention and treatment of spasticity are yet to be solved:
    - Muscle relaxants reduce high muscle tone, however, they weaken the muscles and have a sedative, addictive effect,

- Ankle – foot: the Peroneal Dafo, i.e. j-SpD or Dynamic Ankle Foot Orthosis (DAFO) is a widely and commonly used orthosis in the daily practice**,** which reduces the increased muscular tonus and stabilizes the foot when walking. However**,** if peroneal orthosis is used the amount of movement of muscles needed for dorsiflexion is rather reduced, which often makes patients feel uncomfortable about wearing the orthosis;
- Orthopedic surgery can be considered if the deformities caused by paresis and spasticty become fixed. Surgery includes tenotomy (V or Z-plasty), muscle or tendon transposition, incision or extirpation of the tendon sheath, and partial or total removal of the fascia;
- Ablative neurosurgical procedures are effective, their impact, however, is irreversible,
- In case of thermotherapy, it is difficult to define the optimal duration of treatment, while in case of cryotherapy short treatment period may have a reverse impact;

- A commonly applied therapy is passive movement with the aim of:
  - maintaining and increasing the range of motion of joints surrounded with hypotonic or spastic muscles,
  - reducing increased muscle tone,
  - breaking the pathological stance pattern,
  - supporting return of selective movements,
  - restoring the movement function,
  - sending stimuli towards the cerebral cortex,
  - preventing deep vein thrombosis.

In the majority of stroke care units however:

- no early rehabilitation is done;
- passive movement is mostly done manually by physiotherapists but its effectiveness may be subject to their individual performance;
- the number of physiotherapists available is limited (1-2);
- passive movement is tiresome for the therapist and the intensity of movement may decrease after some repetitions;
- there are few, if any, physiotherapy treatments at weekends;
- human resources are continuously shrinking, therefore it is imperative to develop cost-effective methods that may replace diminishing workforce or assist their activity.

Severity and progress of post stroke motor damage is usually judged by professionals on a subjective basis and/or with semi quantitative methods. An alternative solution for this may be offered by the use of a motion sensor device, which:

- facilitates objective measurement of patients' current condition, and monitoring disease progression;
- facilitates objective measurement of changes in motor function loss in time, and change in motor output;
- makes prognosis more accurate, treatment and rehabilitation of patients more effective;
- facilitates tracking the efficiency of medicinal and non-medicinal therapy;
- senses localization, start time and duration of epileptic seizures with the help of the software;
- due to technical innovations, may apart from reducing the load on human resources, improve acute care, quality of at-home-physiotherapy in the framework of rehabilitation and home care, and allows health care professionals to draw conclusions from data collected in sync with therapy and diagnostics about efficiency of the therapy and changes in the disease in the acute and chronic phases.

Aims:

1. Our objective is to develop an electronically operated device with tailored action radius provoking plantar and dorsiflexion, which is altogether better and more appropriate to treat acute stroke patients than the ones presently available on the market and reported in the literature.

Expectations from the device:

- treatment should be feasible on the patient's bed;
- should the device detect resistance during treatment it should stop automatically thus preventing injuries, like overstretching ligaments or tendons, and injuries of the joint capsule;
- its shape should facilitate treatment of both the left and the right leg;
- physiotherapists and/or care personnel should be able to set treatment parameters;
- it should be cheaper than devices currently available on the market;
- it should be fully sterilizable;

- it should be portable.

2. Testing the ankle motion device on the paretic lower limb focusing on the following considerations:

- How does movement by the device between plantar and dorsiflexion influence the increased soleus muscle tone?;
- How does the treatment affect the motion range of passive plantar and dorsiflexion?;
- Does movement between plantar and dorsiflexion have an impact on equinovalgus position? By way of an explanation, movement not only happens in the ankle joint proper at the ends of the range, joints between the metatarsals also add a few degrees to the entire range of motion.

3. Functional magnetic resonance imaging (fMRI) scans are done to find out which brain regions are activated during manual passive movement of the ankle and continuous passive movement of the ankle with the ankle motion device.

4. Movement artifacts happening while fMRI scans are made and evaluated cause a problem, therefore our objective is to examine potential sources of systematic motion artifacts focusing on the sources of stimuli-associated movements at the level of the individual.

5. If a therapy or a treatment results in the movement of limbs, it is essential to monitor it with objective methods, therefore we invented a motion sensor device, which:

- is suitable for objectively monitoring the improvement of the amount of movement;
- uses a novel assessment to measure the amount of movement;
- is suitable for comparison with the results of conventional clinical performance tests.

6. Results of our new device are validated with instruments approved in the current clinical practice.

2. MATERIALS AND METHODS

2.1. Subjects, inclusion and exclusion criteria

2.1.1. The effect of manual and ankle passive motion device therapy for paretic ankle and foot joints

Sixty-four acute ischemic and hemorrhagic stroke patients with impaired ankle-foot motor function were investigated. Patients were assigned to two groups consecutively: one group (n=49) (mean [standard deviation, SD] age: 62.2 [12.38] years); female to male ratio: 18 to 31) received manual therapy combined with 30 minutes device therapy (M+D) for one week,

and the manual group (M) (n=15) (mean [SD] age: 71.3 [10.39] years); female to male ratio: 7 to 8) received only 15 minutes manual therapy for one week by a physiotherapist. We had no influence on the sequence of patients. Manual and device-based therapy were started 24 to 48 hours after stroke onset. No patients received oral or parenteral antispastic therapy (e.g. botulinum toxin).

2.1.2. The effect of manual and ankle passive motion device therapy for brain activity

A third group of ischemic stroke patients (n=12) (mean [SD] time of stroke: 56.08 [133.9] days; mean [SD] age: 65.3 [9.6] years; female to male ratio: 7 to 5) were treated by our device on single occasion and investigated by fMRI (fMRI group) before and immediately after 30 minutes device therapy.

There was no direct relation between the patient group examined by fMRI and the two (M+D and M groups) other patient groups.

The inclusion criteria for the M, M+D, and fMRI groups were ischemic and/or hemorrhagic stroke confirmed via clinical investigations and computed tomography.

Patients suffered from mild, moderate or severe lower limb paresis (item 6 of the National Institutes of Health Stroke Scale ≥ 1 point) due to ischaemic or haemorrhagic stroke.

Patients were excluded from participation if any of the following criteria were met: primary brain tumour, brain metastasis, Parkinson's disease, multiple sclerosis, rheumatoid arthritis, ankylosis of the ankle and foot joints, trauma or surgery of the foot and ankle; and patients with psychosis and delirium symptoms were also excluded. The study was approved by the Regional and Institutional Ethics Committee (DE OEC RKEB/IKEB 3772-2012; DE OEC RKEB/IKEB 3983-2013); written informed consent was obtained from each patient.

2.1.3. Development and testing of the motion sensor device on the paretic upper limb

Seventeen acute stroke patients were investigated during the tests of the motion sensor device. Twelve patients were admitted to the Neurology Clinic of the University of Debrecen, Medical and Health Science Center for acute ischemic and five for hemorrhagic stroke.

We enrolled patients aged 18–85 (average age ± SD 63 ± 10 years; male to female ratio: 6:11) who suffered stroke 7 or less than seven days earlier.

Patients were excluded from investigation for the following reasons: primary brain tumor, brain metastasis, Parkinson's disease, multiple sclerosis, rheumatoid arthritis, ankylosis of the upper

limb's joints, trauma or surgery of the upper limbs; patients with chronic stroke symptoms, severe aphasia, patients with psychosis and delirium symptoms were also excluded.
We investigated 22 control subjects (average age ± SD 64 ± 12 years; male to female ratio:13:9) on the Department of Cardiology at the University of Debrecen.
Patients were excluded from investigation for the following reasons: primary brain tumor, brain metastasis, Parkinson's disease, multiple sclerosis, rheumatoid arthritis, ankylosis of the upper limb's joints, trauma or surgery of the upper limbs; patients with acute or chronic stroke symptoms, severe aphasia, disorientation, and agitation were also excluded.
For the control group we recruited, from the Department of Cardiology at the University of Debrecen, patients of comparable age with no cerebrovascular events and no upper limb injury or use-limiting conditions in the anamnesis. The control group had a daily routine similar to that of stroke patients (doctor's rounds physiotherapy, meal arrangements, etc.).
The study was approved by the Regional and Institutional Ethics Committee (DE OEC RKEB/IKEB: 2975-2009); written informed consent was obtained from each patient.

2.2. Methods

2.2.1. Ankle passive motion device

The device was developed together with László Menyhárt, electrical engineer (Medical Systems Hungary LLC). As part of our cooperation we discussed the objectives, the target groups and their expected symptoms, anatomical structure of the ankle and foot, their function, and work, and what problems we would like to solve with the device (maintain and increase range of motion, decrease equinovalgus, spasticity relief). The prototype has been created with respect to all of the above.
As a result of our developing and testing activity:

- Currently in the prototype phase (MoStim), the passive motion device works by mobilizing the paretic foot in a repeated fashion across the ankle's entire range of motion, from plantar (max. 40 degrees) to dorsiflexion (max. 20 degrees) in one plane; the patient is in supine position during treatment;
- Motion parameters (angle, power, speed) can be individualized to suit the patient's level of tolerance and pain threshold;
- It is safe, does not cause injuries or pain and there is no danger of electrocution;
- Upon sensing resistance it will automatically stop and give a sound signal (due to prevention of muscles, ligaments and tendons injuries);

- Measuring 25 by 52 by 45 cm and weighing only 7 kg, the device is designed for optimum portability and usability at the bedside;
- Actuation is provided by a 24-volt direct current (DC) motor;
- Operating frequency limits include 7 cycles per minute from plantar to dorsiflexion (0 to 60 degrees) at the high, and 4 cycles per minute from plantar to dorsiflexion at the low end;
- Resistance parameters were mostly set between 1 to 7 Nm of maximum resistance torque in dorsiflexion, and 1 to 10 Nm maximum resistance torque in plantar flexion;
- After the treatment duration it will automatically stop and give a sound signal.

2.2.2. Defining the severity of stroke, and taking test parameters of the lower limb, and the ankle-foot

Status of the patients was assessed with the NIHSS scale, with item 6 of the NIHSS scale, and with the modified Rankin scale on the first and last days of treatment, except in case of patients of the fMRI group, where we used the scoring scales on a single occasion.

All patients were assessed using the Modified Ashworth Scale (MAS), National Institute of Health Stroke Scale (NIHSS) and goniometer measurements. Everyday tone of the soleus muscle was assessed with the Modified Ashworth Scale (MAS) before and after treatment. Modified Ashworth Scale (MAS), a quick and easy-to-use tool to evaluate spasticity.

Since the soleus muscle plays an important role in the foot's plantar flexion, and also in maintaining a stable stance, we assessed the level of spasticity in this muscle using the MAS.

Passive range of motion of the ankle joint and extent of equinovalgus deformity were measured with a goniometer designed and manufactured in cooperation with the engineers of National Instruments, (László Ábrahám, András Kiss) Two types of measurements can be performed with the goniometer according to the preset attachment points (ankle plantar and dorsiflexion and equinovalgus deformity).

The goniometer was used for measuring the–range of motion (in degrees) of passive ankle plantar or dorsiflexion, and equinovalgus deformity before and after treatment.

The active range of motion of the ankle joint was not evaluated because mental confusion, difficulty of communication and unstable state (bleeding) present during acute stroke are known to substantially impede or bias the accurate assessment of active range of motion.

2.2.2.1. Statistical analysis of the manual (M) and device (M+D) groups

Within-subject changes were calculated as the difference between pre-session readings at the last available session and baseline readings. Such changes were tested for significance using Student's paired t-tests or Wilcoxon's matched-pairs signed-ranks tests. We considered correlations or effects significant if the p-value was <0.05. The statistical package Stata was used for data analysis (StataCorp. 2009).

2.2.3. Investigation of the fMRI group; image acquisition

Images were acquired at Kenézy Hospital, Debrecen using a 1.5 Tesla Siemens Magnetom Essenza magnetic resonance scanner. A 3D T1-weighted axial magnetization-prepared rapid acquisition with gradient echo (MP-RAGE) structural image was obtained (echo time (TE)=4.73 ms, repetition time (TR)=1540 ms, inversion time (TI)=800 ms, flip angle=15 slices with 0.9×0.9×0.9 mm voxels). Functional images were obtained using a BOLD contrast sensitive gradient-echo echo-planar sequence (TE=42 ms, flip angle=90, in-plane resolution=3×3 mm; volume TR=4000 ms). Whole-brain coverage for the functional data was obtained using 41 contiguous interleaved 3-mm axial slices. Each functional session consisted of 100 functional volumes.

2.2.3.1. Functional MRI

All patients were assessed using the NIHSS, 6th item of NIHSS, MAS and mRS in the fMRI group. Before fMRI investigation a goniometer was used to measure the range of motion of passive ankle plantar and dorsiflexion. During the 400-second-long functional MRI sessions, 40-second-long active and passive blocks were employed (a total of 10 block pairs, beginning with a passive block). In the passive block, no stimulus was applied, whereas in the active block, slow continuous passive motion (CPM) of the left or right foot was carried out by the physiotherapist for 40 seconds. The effects of the passive movement of the left versus the right foot were investigated in separate sessions.

For each subject, two fMRI investigations for both the left and right foot movement paradigm were applied. Between these measurements, 30-minute session of continuous passive motion was performed on the paretic leg by our passive motion device.

2.2.3.2. Image Processing

Assessment of the scans was done with the help of our co-authors of the article published in the European Neurology Journal (Vér et al., European Neurology, 2016;76(3-4):132-142.).

Lateralization of brain lesions during the image processing was made uniform by applying mirroring technique: prior to processing the left and right sides of the structural and functional images of patients with left hemispheric lesion were swapped, so that in all the images lesions were on the right side only. This step allowed us to conduct a pooled population-level statistical analysis of all patients without the need of splitting the population into two cohorts based on the side of the stroke.

FMRI time series were motion corrected using the intra-modal motion correction utility of the functional MRI of the brain software library (FSL). The first three volumes of each data set were discarded from further analysis to allow for T1 equilibration effects. The brain extraction utility of FSL was used to remove non-brain areas from both the functional and structural scans. For each fMRI session, a "noise region" was delineated by the analysis of the temporal signal-to-noise ratio of BOLD signals, and five principal noise components were extracted from the data following the component-based noise correction method (CompCor).

The resulting preprocessed fMRI data were non-linearly co-registered to the brain extracted anatomical image and then spatially transformed to the symmetric template of Montreal Neurological Institute (MNI) 152 space using linear and non-linear registration utilities of the FSL package, to achieve spatial correspondences for group analysis.

2.2.3.3. Statistical analysis of fMRI group

FMRI group's statistical analysis was done with the help of our co-authors of the article published in the European Neurology Journal (Vér et al., European Neurology, 2016;76(3-4):132-142.).

A total of 12 patients were included in the fMRI group in compliance with the selection criteria, however, two patients had to be excluded from the statistical analysis: one due to claustrophobia which developed in the course of MRI, and the other due to extreme head movements related to stimuli received during the fMRI recording.

Before statistical analysis, an isotropic Gaussian smoothing with 8-mm Full Width at Half Maximum (FWHM) was applied to the functional images. The data was then analyzed within a general linear model (GLM) framework. In the voxel-wise GLM-based first-level analysis we incorporated seven explanatory variables: the hypothesis for the stimulus according to the block design, the temporal derivate thereof (to allow for slight variations in timing), and the five

principal noise component time courses based on the noise correction analysis. We convolved the predictor of interest with a double-gamma hemodynamic response function.

The resulting statistical parametric maps were analysed on the population level with two second-level, fixed-effect models corresponding to the healthy (non-paretic) and paretic ankle motion stimulations denoted respectively by healthy and paretic ankle passive motion. In line with the paired-sample design, within-subject variance was modelled with a factor variable encoding the session repetition, i.e. whether the scan was taken before or after the continuous passive motion therapy. Four population-level statistical parametric images were constructed according to both stimuli and two sessions: two mean activations of healthy and paretic motion evaluated from first-session fMRI data and two increased activation maps calculated by a two-sample paired t-test using repeated measurements. Statistical parametric images were corrected for multiple comparison using Gaussian Random Field theory and cluster probability thresholding. Clusters were defined by a z-value threshold of 3.1 ($p_{uncorrected} < 0.001$), and activation clusters having a probability of less than 0.05 were discarded. The emphasized activation clusters were identified by the atlas toolbox of FSL view software and the database of Harvard-Oxford cortical and subcortical structural atlases.

2.2.3.4. Prevention and correction of fMRI image motion artifacts

2.2.3.4.1. The role of the physiotherapist in the prevention and reduction of fMRI image motion artifacts

One alternative solution for the prevention of head motions is to reduce possibility of movements during scanning.

Patient education plays a key role here. During the enrolment process the physiotherapist was to inform the patient very carefully. The therapist had to give a detailed description of the purpose and the procedures of the study. Apart from general information (like it was non-invasive, painless, no radiation was involved, or whether the patients had any metal implant in their body), other aspects had to be touched upon before taking MRI scans, aspects that may lead to significant head movements; therefore along with other basic questions patients were also asked whether they had claustrophobia.

If the patients said they did not know of it, or were not sure, more questions followed asking them whether they felt scared of being enclosed, or being restricted, or feared confined spaces. Presence of the physiotherapist normally has a calming effect in unfamiliar surroundings.

It was one of the basic questions too, whether the patient was able to lie motionless for longer periods, or whether they had an organ system problem (e.g. discus hernia induced pain), which made maintaining a supine position for a longer period impossible. During patient enrolment involving neuroimaging all of this is one of the responsibilities of physiotherapists so that extreme head movements or failure of imaging examinations can be avoided.

The pelvis was fixed with a strap for the scans. Both lower limbs were stabilized with sand sacks and beside the physiotherapist who carried out the passive moving of the ankle, radiographers manually fixed the mobilized and the contralateral lower limb. This way the physiotherapist and the radiographers were able to minimize the extent of the expected head movements during scanning.

2.2.3.4.2. Movement correction techniques and population level analysis

The first author and co-authors of our article published in the Journal of Neuroimaging helped with the application of movement correction techniques and their analysis. (Aranyi et al, Journal of Neuroimaging, 17 Nov 2016).

Another alternative solution apart from preventing and reducing movements during scanning is correction of the artifacts caused by movements during processing the scans.

We applied several different techniques to correct signals of fMRI scans. In case of passive ankle movement special attention must be paid to motion artifacts, as movement in the scanner may coincide with the task on hand and may well cover the BOLD sign value that indirectly measures neurological activity.

In cooperation with the staff of the Medical Imaging Institute at the University of Debrecen, Faculty of General Medicine, we have worked out a population level method that may improve the result of the group level analysis by modelling the effects of stimulus correlated motions.

2.2.3.4.3. Correlations of motion parameters and clinical parameters

Head motion during fMRI scanning was characterized with a so called RMS (root-mean-squared) curve, which depicts the extent of motion in millimeters calculated by the motion correction software of the FSL program package.

We have derived the following five different parameters from head motion changes in time that describe the patient’s movement during fMRI testing:

- RMS.scan = all movements (the higher, the more movement performed)
- RMS.task = sum of movements during passive ankle movement (the higher, the more movement performed)
- RMS.rest = sum of movements in the rest period (the higher, the more movement performed)
- RMS.diff = statistical difference of the movements between rest and passive ankle movement defined with the Wilcoxon-rank-sum test. The higher the difference between the involuntary head motion during rest and during passive ankle movement the higher this parameter will be.
- RMS.dyn = rate of movements during passive ankle movement and during rest periods (RMStask/RMSrest).

We compared the RMS parameters defined above with themselves and with other patient specific parameters using correlation techniques.

2.2.4. The motion sensor device

The motion sensor and method of calculation were prepared by Gábor Szima, electrical engineer (Diaware LTD) according to the objectives of the study

In the period prior to our own development, studies had used accelometers available on the market, which measure duration of movement. In our study we used our own proprietary motion sensor, which mainly differs from available devices in the unit of activity and method of its calculation.

The device, which measures activity, is made up of two main parts, a triaxial accelometer capable of sensing motion in all three dimensions of space (X, Y, and Z) and a measuring device containing the signal processing unit.

The measured acceleration data are transferred by radiofrequency to the data collector unit with a radius of operation of 100m. The accelometer equipped with a radio transmitter runs on two AAA batteries or an accumulator battery, the data collector is connected to the mains power source and placed on the patient's nightstand. The meter does not emit signals continuously, only in 1/8 of the time, thus the mean emission power is also 1/8 of the current operational power. Maximum mean emission power is 12.8 mW, which is approximately 1-2 mW, supposing the data collector is located directly adjacent to the patient. This does not cause

any health injury. A transmission cable is needed to download the data onto a personal computer.

Derivation of the acceleration-time function recorded by the device is performed with our own proprietary software, and the new graph is integrated at the time intervals preset by our team (1 second - 1 day). We call the unit thus gained amount of movement, which is a physical quantity created by our team and its unit is m/s^2. In our case the amount of movement is used in the everyday sense of the word, i.e. the movement needed to move the limb in order to change its position within a certain unit of time.

During processing the following mathematical operations are used:

$$\int_{t1}^{t2} \frac{\Delta\sqrt{(a_x^2 + a_y^2 + a_z^2)}}{\Delta t}$$

Mathematically in short:

$$\int_{t1}^{t2} \frac{\Delta a}{\Delta t}$$

The accelometer needed a cover which is:

- shockproof
- resistant to water and/or other contaminants
- its size does not in any way restrict the patient while it is worn
- comfortable to wear
- sterilizable.

The protective covers of the accelometer designed according to our purposes were made in collaboration with Gábor Kovács and Zoltán Nyisztor, both mechanics (Ortoprofil LLC.).

The protective cover of the accelometer:

- is made of shockproof plastic
- is water resistant
- is 6×6×3 cm in size
- can be attached to the wrist of the patient with a single use Velcro strap
- is fully sterilizable.

An improved and miniaturized version of our device is a chip with a water resistant and sterilizable capsule complete with a triaxial accelometer chip, a FRAM storage unit for the measured parameters, a power supply and a 3 Volt button cell. The triaxial accelometer sensor is capable of recording values ranging from -5g to 5g. The sensor weighs approximately 100 grams. The meter measures the acceleration of a limb 50 times per second and records the

measurements with a precision of a hundredth of a second. The storage unit is capable of recording the acceleration data of about a week's period. The sensor is located in a 3,5 x 3,5 x 2,5 cm water resistant capsule, which can be attached to either limb with the help of a flexible strap A transmission cable is needed to download and feed the data collected by the motion sensor to a personal computer into the software of the system.

2.2.4.1. Validation of the motion sensor device

A type Alice 3 polysomnograph from Respironics was used to record muscle tone in the biceps muscles. Surface EMG electrodes were fixed on the bicepses bilaterally on the thickest part of the muscles. We simultaneously collected muscle tone and amount of movement (AOM) data during movements of varying intensity. We performed 15 measurements on healthy individuals.

The surface EMG electrodes were fixed on the participant's biceps muscles' thickest parts, the movement monitors were fixed on the wrists bilaterally. Forty-five-second-long active periods were evaluated. During the active period the participants performed forearm movements of different intensity; only elbow flexion were allowed.

2.2.4.2. The measurement procedure

We started measurements after the morning investigations and physicians' rounds. We informed the patients about the purpose and methodology of the study and asked them to sign an informed consent form. The study was carried out within seven days of the ischemic or hemorrhagic stroke. We took a detailed history of each patient, we defined handedness (left- or right-handed), and assessed the results of CT scans and lab tests. The measuring device was attached to both upper limbs of the patient, 3-5 cm above the wrist joint and measured the amount of movement for 24 hours. The device was only removed during personal hygiene activities. The following values of scales were determined prior to the actual measuring:

Current functional condition and severity of stroke can be defined with the help of the National Institute of Health Stroke Scale and the European Stroke Scale.

The higher the score on the NIHSS scale, one of the most frequently used scales, the worse the patient's functional condition. The highest score is 33.

The European Stroke Scale, similar to the NIHSS scale helps assess severity of the stroke and the functional condition of the patient; in case of the upper limbs not only capacity of holding the upper limb, and capability of lower arm pronation are scored, but also whether the patient

is able to lift the arm, extend the wrist, create a circle with thumb and pointer finger and what muscle power is used for this. The highest score on the European Stroke Scale is consistent with a very good neurological status. Minimum score is 0, maximum is 100.

The statistical package Stata was used for data analysis. We considered correlations or effects significant if the p-value was <0.05 (StataCorp. 2009).

3. RESULTS

3.1. The effect of manual and ankle passive motion device therapy for paretic ankle and foot joints

3.1.1. Results in the Manual (M) group

No significant changes could be detected in the ankle's mean plantar (p=0.349) and dorsiflexion (p=0.456).
The improvement of equinovalgus deformity (p=0.485) and Modified Ashworth Scale (p=0.499) was not significant. The mean NIHSS score improved significantly (p=0.046). The improvement of the 6th item (NIHSS) (p=0.055) and mRS (p=0.157) did not reach the level of significance (p=0.055) after the treatment period.

3.1.2. Results in the Manual+Device (M+D) group

The ankle's mean plantar flexion range increased significantly by 3.41 (SD=5.19) degrees (p<0.001) and the dorsiflexion also improved significantly by 1.15 (SD=2.71) degrees (p=0.019). The mean flexible equinovalgus deformity decreased by -5.12 (SD=8.02) degrees (p<0.001). The Modified Ashworth Scale score improved by 0.53 (1.12) points (p<0.001). The mean NIHSS score improved significantly by -2.27 (SD=2.47) points (p<0,001). The mean 6th item (NIHSS) score decreased significantly by -0.76 (SD=0.56) points (p<0,001) and the mRS score improved significantly by -0.61 (0.57) points (p<0,001).

Because of the higher mean age of M group, NIHSS score and sex differences in the distribution, the analysis has been performed so as to adjust the values for age, sex and baseline parameters. The results were consistent with the results of the unadjusted analysis, and did not add to the information already available. Therefore, we have decided to present the data resulting from the more simple analysis, which can be easily and more directly interpreted.

3.2. The effect of manual and ankle passive motion device therapy for brain activity

3.2.1. The effect of manual and ankle passive motion device therapy for brain regions

Processing of the scans and the statistical analysis was done with the help of our co-authors of the article published in the European Neurology Journal (Vér et al., European Neurology, 2016;76(3-4):132-142.).

In the statistical analysis of first-session (pre-training) data, we found that both the healthy and paretic ankle motion stimuli activated the contralateral primary motor (M1) and primary somatosensory (S1) cortex. Furthermore, we observed activated voxels (with z=7.0 maximal value) in the small part of the supplementary motor area (SMA) during the paretic ankle motion in contrast to healthy ankle motion.

Overlapping activity in the anterior division of the supramarginal gyrus (aSMG) and secondary somatosensory/parietal operculum cortex (S2) were found contralaterally in the case of healthy ankle motion, and ipsilaterally during paretic ankle motion. In the case of healthy ankle motion, a third ipsilateral activation cluster was also detected, overlapping the part of the posterior division of the superior temporal gyrus (pSTG) and insular region of S2. Comparing data from two fMRI sessions (before and after treatment) revealed increased activation in the post-treatment session both for healthy and paretic ankle motion. In the case of healthy ankle motion, we found only one cluster in the superior frontal gyrus (SFG) near the cluster-significance threshold ($p_{cluster}<0.0413$) with a size of 2.5 cm^3, and z=4.1 peak activity. During the paretic ankle passive motion, two bilaterally located clusters were observed in the anterior division of the parahippocampal gyrus (aPHCG) connected with the activated area of the posterior division of the inferior temporal gyrus (pITG).

3.2.2. Prevention and correction of motion artifacts in fMRI scans

3.2.2.1. RMS-parameter selection

The first author and co-authors of our article published in the Journal of Neuroimaging helped with the application of movement correction techniques and their analysis. (Aranyi et al, Journal of Neuroimaging, 17 Nov 2016)

For selection a suitable in-scanner head movement parameter for 2^{nd} level analysis we investigated the correlations of the five introduced RMS-parameters (RMS.scan, RMS.rest, RMS.task, RMS.diff and RMS.dyn) and the clinical scores of subjects. We focused on the

correlation values of the parameters evaluated by goniometer, because they measure the degree of range of motion of passive ankle plantar and dorsiflexion. High correlation value with these parameters indicate which RMS-parameters are useful for describing the relationship between the patient's pathological condition and their in-scanner movement. The correlation analysis revealed a strong correlation on the paretic side stimulus between RMS.diff with plantar and dorsal flexion with correlation coefficients r = -0.63 and r = -0.52 respectively and so we selected this parameter for the further analysis.

This parameter, as opposed to all others, is able to clearly distinguish ankle movement ability between healthy and paretic legs. Using the RMS.diff parameter we can model motion variability of individual subjects in our group-level statistical analysis.

3.3. Developing and testing motion sensors on paretic upper limbs

3.3.1. Results of validation

The linear regression model confirmed a significant correlation ($p<0.0001$) between the data collected by the motion sensor and those collected by the polysomnograph EMG sensors.

3.3.2. Comparison of motion intensity of upper limbs of stroke patients and controls

Based on data measured by triaxial motion sensors and confirmed by t-test results, intensity of motion of upper limbs of controls is significantly higher than that of paretic limbs of stroke patients ($p=0,001$). There is however, hardly any difference between intensity of motion measured in upper limbs of controls ($p=0,001$).

In case of stroke patients the ratio of intensity of motion of paretic and healthy upper limbs is significantly smaller than the ratio of intensity of motion of dominant and non-dominant upper limbs of healthy controls ($p = 0,0195$). In case of healthy controls the dominant limb was considered to be the “uninjured” upper limb, as the amount of movement is higher in the dominant upper limb.

3.3.3. Correlation of values with the NIHSS scale

Activity of the injured upper limb of paretic patients calculated with Kruskal-Wallis test shows a significant correlation with the scores of the NIHSS scale ($p=0.0049$): the higher the scores on the scale the lower the amount of movement of the paretic upper limb.

We found a significant correlation between the scores of the NIHSS scale and the intensity of motion of the non-paretic upper limbs of patients too ($p = 0.0066$). In case of paretic patients the higher the NIHSS score, the less the patients move their non-paretic upper limb.

3.3.4. Our results and the ESS scale

We measured the condition of 9 patients with ESS. There was no correlation between the scores of the ESS scale and the amount of movement of the injured upper limb ($p = 0.1106$). On the non-paretic side the amount of movement of the upper limb significantly correlated with the ESS score ($p = 0.0344$): the lower the score on the scale the less the patients move their healthy limb. Multiple linear regression models were used to investigate the correlation.

3.3.5. Our results and the state of consciousness

Investigated with multiple linear regression method a significant correlation was found with the motion intensity of the paretic upper limb ($p = 0.0382$), the motion intensity of the non-paretic upper limb ($p = 0.0064$) and the state of consciousness of stroke patients. When the state of consciousness of patients deteriorates, the patients move their paretic and uninjured upper limb less and less. With the improvement of the state of consciousness the amount of movement of both the uninjured and the paretic upper limb increases.

4. DISCUSSION

4.1. The effect of manual and ankle passive motion device therapy for paretic ankle and foot joints

Our scientific work comprised two clinical studies on post stroke patients.
In the first part of our study we analyzed the effect of our own device, developed and tested for the passive movement of paretic ankles, on the locomotion system of acute stroke patients and we used functional magnetic resonance (fMRI) imaging to define which brain regions are activated by passive movement. We also tested a new fMRI paradigm and investigated the role of the physiotherapist in motion correction during fMRI scanning.

Lack of health care professionals is a serious problem in the Hungarian Health Care System. Based on the Yearbook of Health Statistics for the year 2013 issued by the Hungarian Central Statistical Office the number of physiotherapists („number of all occupied jobs”) in Hungary was 2280 (15.5% of which were self-employed). Though the Hungarian Association

of Physiotherapists does not have accurate statistical data, based on their information maximum 1 or 2 physiotherapists can be assumed to have worked in neurological departments in 2015.

In the acute stages of stroke passive movement is a frequently applied conservative therapeutic method. It can be carried out manually but also mechanically.
Manual passive movement for the therapist is tiresome and intensity of movement will decrease after a few repetitions. Therapists use alternating force and rhythm to move the joints and judge subjectively at which point the "endpoint" is reached.

That is why continuous passive motion devices are of crucial importance. The devices move the given joint in a specified motion range, with specified intensity approaching the pain threshold. Using them may:

- prevent the development of deep vein thrombosis and contractures;
- resolve spasticity;
- facilitate active exercise;
- send stimuli to the cerebral cortex on a continuous basis during passive movement.

This way the problem of physiotherapy at weekends can partially be solved, since the parameters preset by the therapist can be applied by the care personnel as well. The use of the device at weekends is primarily recommended for the movement of distal joints, as the selective mobility of these is the hardest to regain, and it is at these points that the majority of pathological positions and deformities develop.

Insisting on using continuous passive motion devices is not aimed at replacing the work of physiotherapists. Their work cannot be replaced by instruments and devices, because during therapy there is the human touch, the interaction, which means that therapists heal by their professional knowledge, empathy and personality.
The use of continuous passive motion devices is recommended for the therapeutic benefit of the patients, and in order to make the work of therapists easier and more effective. The biggest benefit of treatment with the device is – just as with fast spreading and costly robot therapies – the relatively high number of repetitions. Setting the device to maximum speed the ankle joint is moved over the maximum range of motion (altogether 60 grades) seven times per minute and four times per minute when the speed is at its lowest. This means that during a half hour treatment period at maximum speed the ankle is moved 210 times while at minimum speed 120 times.

Continuous passive motion devices for the movement of joints are costly, ranging from 1 300 000 to 2 500 000 Ft gross, as seen at the websites http://artromot.hu/artromot-rehabilitacio/artromot-cpm-keszulekek (downloaded 05 January 2017). The device is available for sale from medical aid distributors, or from health care companies, or for rent. Purchase options for ankle-foot continuous passive motion devices in Hungary are rather restricted; only two types of devices were on sale in the past months. Advantages of the device *Artromot SP3* available in the home market:

- intuitive manual operator with symbols for simple usage,
- both inversion and eversion motions are possible,
- additional functions: a chip card with patient specific settings, several treatment programs can be selected (warm up, break, …),
- the patient can program it via manual control too.

Drawbacks of *Artromot SP3*:

- weight: 11 kg,
- purchase price: ~ 1 500 000 HUF,
- relatively large size 78 x 42 x 39,5 cm,
- treatment in a sitting position,
- only the leg and foot rests can be disinfected:

http://artromot.hu/artromot-cpm-keszulekek/ormed-artromot-sp3 (downloaded 05 January 2017).

Advantages of *Kinetec Breva*:

- both inversion and eversion motions are possible,
- to be used in either a sitting or a lying position,
- several treatment programs can be selected (warm up, break…),
- patients can program it via manual control too.

Drawbacks of *Kinetec Breva*:

- weight: 12,5 kg,
- purchase price: ~ 1 400 000 HUF,
- size: 56 x 37 x 45 cm:

http://www.pharmics.hu/hu/termek/boka-mozgato (downloaded 05 January 2017).

Advantages of our device as compared to Artromot SP3 and Kinetec Breva:

- weight: 7 kg, easier for the therapist to move and lift,

- size: 25 x 52 x 45 cm,
- purchase price: 500 000 HUF + VAT,
- fully sterilizable.

Drawbacks of our device as compared to Artromot SP3 and Kinetec Breva:

- may perform movement in one plane only (plantar – and dorsiflexion),
- to be used ”only” in supine position (but for acute stroke patients it is optimal),
- only one treatment program is possible,
- no manual control for patients.

Continuous passive motion devices are primarily used in the first days post orthopedic surgeries, as well as in rehabilitation units for the treatment of orthopedic, traumatological, and CNS (after stroke, traumatic and non-traumatic brain injuries) patients and particularly widely spread are the devices for the mobilization of the lower limb, primarily the hip and knee.

Based on the literature and our experiences continuous passive motion devices, and other such based on the same principle are normally used in early rehabilitation or on chronic stroke patients for treatment and/or scientific research. However, treatment with continuous passive motion devices initiated within 24 or 24-48 hours post stroke significantly contributes to tercier prevention and may prevent complications (flexible and rigid deformity, increase in tone, deep vein thrombosis, etc.).

Some research groups have already done some studies into effects of ankle motion devices based on similar principles in post stroke patients. The main differences of their devices compared to ours is their mechanical structure, and that some devices perform stretching at the end point of the range of motion for a few seconds. Some of these work groups studied only short term effects of a single treatment of the paretic ankle.

Zhang et al. investigated the short term effect of a single 30 minute treatment on chronic stroke patients. They found that as a result of the treatment the passive plantar- and dorsiflexion range increased, while Gao’s team detected an increase in the passive plantar- and dorsiflexion range after a 60 minute treatment. Their results in unison with our observations confirm that treatment of the ankle with the continuous passive motion device improves the passive range of motion of the paretic ankle joint.

The disadvantage of their devices however is, that they are big, portable only with difficulty if at all, and treatments are carried out with the patient seated, which is not exactly optimal in an acute stroke unit. Our results confirm the conclusions Zhang et al. drew; by using a portable, low budget device working on a simple principle in a clinical or home setting on a regular basis may improve efficiency of the motion therapy.

Our results confirm the observation of Selles et al., who, like our team, investigated the effects of multiple treatments (3x45 minutes a week for four weeks) on the paretic ankle. They found significant increase of passive plantar and dorsiflexion range in post stroke patients. The drawback of their device can be ascribed to its mechanical structure too, in that it is big, treatment is done with the patient in a sitting position, and it is not appropriate for bedside treatment.

Our observations confirm the results of Wu et al. too, in that the increased tone of the paretic ankle can be reduced by using the continuous passive motion device on the ankle. Score reduction in the Ashworth scale was detected upon 1x15 minute treatment and the scores of the visual analogue scale (VAS) regarding severity of spasticity have also improved significantly. The basic principle of the device is very simple. Treatment is provided in a standing up position, the patient stands on a platform, which moves the knee joint during the treatment at a constant speed (9sec/circle) in the direction of dorsiflexion (efficacy of treatment is helped by the body weight of the patient) while the patient holds on to a bar. At the end of the range the device holds the ankle joint in dorsiflexion for 1 second. This simple, cheap device has proved to be effective and is practical for chronic patients and those able to stand. The majority of acute stroke patients, however, is not eligible for this treatment as hemorrhagic stroke patients cannot be made to stand up directly after the stroke, and some of them are not able to stand up and hold themselves due to muscle weakness, and ischemic stroke patients' medical condition as well as their muscle power does not allow them to endure a fifteen minute treatment period standing up. This is the reason why only devices that can be used at the bedside are viable options.

As no studies investigating similar clinical parameters (PROM, MAS) have been conducted, our results cannot be compared with other studies, however, other authors have also reported beneficial effects of passive motion devices in moving the ankle. According to Bressel and McNair static stretching and continuous passive motion reduces ankle stiffness.

Zhao et al. found that a six week (3 times a week) treatment with an intelligent stretching device increased the elasticity of the calf muscles while decreasing stiffness of the gastrocnemius muscle in children with paresis. The technical parameters of the device (big, non-portable,

treatment of patients in a sitting position) would not make this a likely candidate for acute stroke units either.

In the acute phase of stroke reducing the chance of developing deep vein thrombosis should also be aimed at. According to some estimates incidence of deep vein thrombosis is 160 per 100 000 people. It occurs most frequently (90%) in the vessels of the lower limb, but in bedridden patients the upper limb may also be involved. The incidence grows with growing age (under 15 the incidence rate is 5/100 000, while over 80 it is 450-600/100 000). Lack of limb movement dramatically increases the chance of developing deep vein thrombosis.
If somebody becomes temporarily or permanently incapable of movement due to some illness, surgery or injury, it is a good enough indication to consider prevention, and take measures to avoid deep vein thrombosis. A German research group investigated in a randomized, controlled study of 227 subjects, how the device performing dorsiflexion and plantar flexion of the ankle joint (combined with a heparin regimen) affected the incidence of deep vein thrombosis in patients with spinal or lower limb injury. Prevalence of thrombosis among control subjects, who were given physiotherapy (breathing exercises, isometric muscle exercises etc.) combined with heparin, was 25%, (29 out of 116), whereas in the study group where therapy was supplemented with continuous passive motion device, only 3.6 % (4 out of 111). Results of their study confirm that a passive motion device moving the ankle can effectively prevent deep vein thrombosis too. Based on their short description the device cannot be programmed, and treatment specifications cannot be adapted to patients' individual parameters (individual range of motion, muscle tone etc.).
In our study none of the patients treated with the passive motion device on the ankle joint developed deep vein thrombosis.

The operating principles of the application of passive ankle movement and stretching devices used in the above mentioned literature are partly different from those of our device, but our results confirm the beneficial effects of passive ankle movement studied by research groups earlier in that it increases range of motion of the paretic ankle joint and reduces increased muscle tone.

4.2. The effect of manual and ankle passive motion device therapy for brain activity

4.2.1. The effect of manual and ankle passive motion device therapy for brain regions

We also studied the effect of therapy applied with the passive motion device on the hemodynamic responses that are related to the nervous activity of the brain.

There are fMRI studies in the literature that address the effect of passive movement of the ankle joint on the nervous activity of the brain in healthy participants; however, there is limited knowledge on the effect in stroke patients.

Our results demonstrate the passive movement of a paretic ankle generating activation in the contralateral S1, M1 and SMA areas, and the ipsilateral supramarginal gyrus and S2 area. In contrast to our observation, Enzinger et al. also described activation during paretic ankle passive movement in the contralateral sensorimotor cortex, but they did not report the differences between peak activations of S1 and M1. We have shown that the peak activity in M1 was lower than in S1 during paretic ankle motion in contrast to the healthy ankle motion where these values were almost equal.

We hypothesize that passive movement as sensory information (such as continuous tactile perception) and as a motor task contributes to motor learning and motor function. Additionally, it can facilitate active movement. In our study, the repetitions of fMRI scans in healthy versus paretic ankle motion differs: in the former case the second session was simple repeated measurement, while in the latter case 30-minute-long therapy was performed using our CPM device between the scans. This difference explains why the two increased activation patterns differ. We found increased activity in the superior frontal gyrus (MNI coordinates: 4, 42, 44) in the repeated measurement compared to the first session during healthy ankle motion. The between-sessions therapy resulted in higher activity bilaterally in the anterior division of the parahippocampal gyrus (aPHG). Adhikari et al. investigated the neural basis of movement synchronization through a finger-tapping fMRI study. They described greater brain activity during tapping rate deceleration in the cerebellum, superior temporal gyrus and parahippocampal gyrus. We hypothesize that the detected increased activity in the aPHG after the mid-session training may be related to the motion synchronization learning process.

4.2.2. Prevention and correction of motion artifacts in fMRI scans

In this study phase we investigated motion correction strategies for fMRI at individual-level analysis, and we introduced a technique to account for patient head movement at population-level.

It is known, that different groups of subjects can have different amount of movement based on the stimulus, resulting in various confounds on the data, which we have to consider, and it is particularly challenging to reduce motion artifacts in stroke.

We assume that during activation, stimulus-correlated motion effects can either amplify or interfere with neural activity. Thus stimulus-correlated motion can cause false-positive activation in task-based fMRI, and the extent of motion-artifacts will not be equally distributed throughout the population. This might appear as a systematic error in fMRI studies investigating the neural correlates of the above mentioned clinical stroke parameters and introduce a bias in the analysis.

We found strong negative relationship between RMS.diff and two clinical scores that are related to the ability of ankle movement: plantar flexion and dorsiflexion. This may be a systematic connection in ischemic stroke studies, where movement of a limb is involved in the task-based fMRI examination.

Lower plantar and dorsal flexion of the ankle means lesser ability to move patients' legs, causing more in-scanner movement during the task.

The explanation for the development of motion artifacts may be that due to post stroke immobility (there is no, or weakened muscle function, the patient is unable to actively move the joint) and increased muscle tone (we detected increased muscle tone in seven patients), it is harder for the physiotherapist to move the patients' joints since ankle stiffness and increased muscle tone create a higher resistance during passive movement, which means that on the one hand of the physiotherapist has to exert more power during movement of the ankle and on the other he or she has to apply more power to stabilize the lower leg. The power exercised by the mobilizing and stabilizing hands is not always even, the hands may tire after a few movements, the movement output will fluctuate, and as a result, the lower limb, the trunk or the head may move.

In case of post stroke patients this may result in a bigger involuntary movement of the head during passive movement of the ankle joint, which will consequently lead to the appearance of motion artifacts.

We concluded that stimulus-correlated motion artifacts in passive-movement task-based fMRI measurements are related to clinical symptoms of stroke and corresponding limited passive range of motions. These motion artifacts might appear as a systematic confound in fMRI studies where the neural correlates of stroke is investigated.

4.2.3. Summary of important results and conclusions

- We have proved the significance of post stroke equinovalgus deformity and the useful conservative treatment method of equinovalgus within 24 hours post stroke, because the impact of immobility can already be observed in the first 24 hours after the stroke in the structure of muscles and tendons.

  Continuous passive ankle movement in one of the planes (plantar to dorsiflexion) has a beneficial effect on the severity of flexible equinovalgus deformity.
- We have substantiated the efficacy of treatment with a device as additional treatment to manual passive movement. On the basis of the literature and our results the conclusion can be drawn that in case of acute and chronic stroke patients the ankle movement increases the range of motion of the paretic ankle joint and reduces increased muscle tone already after a few treatment sessions.
- We have proved that along with the improvement of clinical parameters of the locomotion system, change will not only occur locally in the joint, or in the muscle tone, but treatment with passive ankle motion will have an impact on the regions of the brain responsible for motion coordination.
- We have stated that a parameter from among the fMRI signals can be distinguished that is related to the severity of the stroke patient's condition.
- The limitations of our study include the reduced sample size (which is acceptable for rehabilitation studies), and the significant additive effect of the motion rendered by the device during the motion therapy session, which the authors have demonstrated that has no advantage over the manual therapy because of the different total motion time (45 vs. 15 minutes) if the human factors are omitted (tiring and variable intensity). The results confirm the additive effect rendered by the device, however, the advantage of the motion provided by the device has not been demonstrated over the manual passive motion.

  The limitations of the comparative study of the effect of the manual and device-provided passive motion are the small sample size and the lack of control group as well as the lack of information on the length of the effect of the treatment.

  We do not know how long the effect of the treatment lasts. May further improvement be expected in the case of a long-term treatment, or does the treatment have no effect beyond a point?

  We do not know how permanent the flow changes are, but it is the subject of another longitudinal study of ours.

- As a result of our research and development we are recommending for serial production an ankle moving device which complies with all indispensable criteria of stroke patients:
    - It is easy to use;
    - It can be used in a lying position on the bed of the patient;
    - It does not need the cooperation of the patient;
    - It can be used in septic circumstances as well because it can be disinfected;
    - It is light and portable;
    - It is safe, does not cause injuries and there is no danger of electrocution;
    - Upon sensing resistance it will automatically stop and give a sound signal;
    - It is appropriate for supplementing manual therapies to prevent;
    - it can be used on both legs irrespective of the patient's individual features (edema in the lower leg, obesity or leanness of patients);
    - it is comfortable.

4.3. Development and testing of a motion sensor device on paretic upper limbs

In the second phase of our study our work group collected concrete data and did scientific investigations with their own proprietary device to quantitatively measure reduced mobility.

In the period before our innovation, studies used accelometers already available on the market capable of measuring duration of the movement. In our study we used our own proprietary motion sensor, which differs from the available devices mostly in the unit of activity and its method of calculation. Instead of duration of movement we calculated the integral of speed of change in acceleration values per predefined time intervals.

We concluded that mean intensity of motion of the upper limbs of controls is higher (p=0,001) than that of the stroke patient group, and also that the intensity of motion of the two upper limbs differ only slightly in favor of the dominant upper limb (p=0,001).

The rate of intensity of motion of the healthy and paretic upper limbs is smaller than that of the upper limbs in the control group ($p = 0.0195$). This finding confirms the results of Lang et al. in that stroke patients use both their paretic and healthy upper limbs less than subjects in the control group.

We found a distinctly significant correlation between the amount of movement of paretic and healthy upper limbs of stroke patients and NIHSS scale scores. With respect to a more severe stroke condition as defined by the NIHSS scale, the amount of movement of both

the paretic ($p = 0.0049$), and the healthy limb ($p = 0.0066$) is less. Our results are in line with those of Gebruers et al., who found significant correlation between data collected with the accelometer and NIHSS scores in acute stroke patients. We have not found any correlation between ESS score and the intensity of motion of the paretic upper limb ($p = 0.1106$), although ESS score and data measured on the upper arm with a device actually did confirm correlation ($p = 0.0344$). Further investigation of this phenomenon is needed on a bigger cohorts.

According to our expectations the state of consciousness had an impact on the amount of movement of the upper limbs. If the level of consciousness deteriorated, the intensity of motion of both upper limbs decreased. Surveying the literature we were not able to find a publication which would have investigated the correlation between the amount of movement of the upper limbs and state of consciousness of acute stroke patients, but this phenomenon also supports the sensitivity of the measurements made with our device.

The data collected with our device show that the more severe the grade of handicap post stroke, the less patients move their healthy and paretic upper limbs.

The post stroke patients with disabilities become more passive and the amount of movement of their normal limbs decreases as well.

The data measured with the device demonstrates a fluctuation of the amount of movement of the hemi paretic upper limb with the times of the day.

In sum, the study has found that the triaxial accelometer we developed is capable of assessing motor injuries. The device that we developed and tested may become routinely applied in neurology departments for the assessment of the condition of patients and for the follow up of the efficacy of their rehabilitation.

The software of our device can be adapted according to the group of patients we want to examine, and monitor with respect to the improvement of their condition:

- It can be used for tracking the efficiency of medicinal and non-medicinal therapy before and after therapy;
- In case of Parkinson's disease, the severity and change of severity of symptoms-(tremor, bradykinesia and dyskinesia) can be assessed;
- It can be used to monitor levodopa induced dyskinesia;
- In case of multiple sclerosis patients the device can objectively examine the physical activity of patients;
- By using the appropriate software in case of epileptic seizures, (which is capable of differentiating between everyday limb movements and those during tonic-clonic

seizures) a seizure can be detected in time and localization of its onset can be determined. Joining this function with an alarm function early recognition of an episode and initiation of an emergency call will be possible just like decrease or even prevention of dangers presented by the episode;

- Follow-up of consciousness and improvement of motion therapy of patients after traumas, thoracic-abdominal surgeries, orthopedic surgeries and neurosurgeries;
- By establishing monitoring points (hospital bed, door of the patient's room, door of the ward, entrance of the institute) wandering off of children, disturbed or dementia patients can be prevented, as the system will immediately signal when the patient leaves the ward or the institute.

Health care is a high risk area as adverse events, which are rather the consequence of the treatment than that of the basic disease, may lead to death or cause serious complications, suffering for the patient. Many health care institutes in Hungary fall short of expectations regarding patient safety and patient safety procedures. Therefore, devices and systems need to be introduced that aim to reduce the incidence of adverse events (tripping, falling off, wandering off) and their consequences (injuries, death).

Devices available on the market for monitoring patients operate mostly by the patient's pressing a button in case of an emergency, the device does not signal tripping, or falling off, or motionless conditions, therefore pressing a button is not an optimal solution for disturbed or dementia patients, moreover its use for the event of losing consciousness is obviously not an option. Such being the case, devices need to be developed and tested that automatically alert the operating personnel of emergencies. We have taken the first steps in order to improve our present system and our objective is to create a reliable patient monitoring system that would take patients' rights into consideration

4.3.1. Summary of the main results and conclusions

- We have developed a motion sensor on post stroke patients and tested it in clinical circumstances.
- We validated our device with a device already accepted and applied in the clinical practice, and we could confirm reliability of the device.
- Our device is sensitive as proven by its capacity of differentiating between amounts of movement: dominant vs non-dominant upper limb, paretic vs healthy upper limb.
- Its measuring sensitivity makes it appropriate for tracking consciousness of patients.

- In case of some neurological illnesses it may help monitor medicinal and non-medicinal therapies, and rehabilitation, as well as improving their efficacy.
- The device can be used in septic conditions because it is water resistant, sterilizable and comes with a shockproof cover.
- By improving the hardware and the software of our device not only assessment of the current condition of the patients can be carried out, but also a patient monitoring system may be established that may help prevent adverse events, like tripping, falling off, wandering off, injury and death.
- The limitations of our study include the small sample size, and that the validation of the device was not done by an independent laboratory.

5. SUMMARY

Due to continuously growing shortage of human resource in Hungarian health care, it is necessary to develop and test economical methods which help both diagnostic and therapeutic activities of the human resource. Post-stroke muscular weakness, spasticity and pathological posture of the paretic lower limb may cause ankle and foot deformity and disharmony of the gait.

- Our team have developed an electronically controlled device which performs plantar flexion and dorsiflexion with personalised action radius, and which is in summary better and more suitable (although not in every aspect) for treating acute stroke patients than any other device available on the Hungarian market or in the literature. The device is suitable for serial production.
- We analysed the effect of our passive ankle mobilising device (developed by ourselves and tested in clinical setting) on the locomotor system, and examined by functional magnetic resonance (fMRI) device which areas of the cerebral cortex are activated by passive movement. Our results show that in the acute phase of stroke:
    - treatment by an ankle passive motion device has significant additive effect in the treatment of the paretic ankle and foot;
    - in addition to the improvement of the clinical parameters of the locomotor system, changes occur not only in the joint or in the muscle tone, but the treatment performed with the ankle mobiliser also has effect on certain areas of the brain;
    - the fMRI signals include a motion parameter which is in relation to the severity of the state of the stroke patient.
- We have developed, validated and clinically tested an accelerometer which enables us to objectively assess and track the state of stroke patients. Advantages of our device:
    - it makes possible the assessing of the patient's current state by measuring their quantity of motion,
    - it sensitively indicates the differences between quantities of motion (dominant vs. non-dominant or paretic vs. healthy upper limb),
    - it is suitable for tracking the consciousness of the patient,
    - in cases of certain neurological diseases, it may help make the follow-up and improve the effectiveness of both pharmacological and non-pharmacological therapies as well as rehabilitation,

- it may be used in septic circumstances as well because its casing is waterproof, shockproof and sterilisable.

6.1. List of publications related to the thesis

Registry number: DEENK/297/2016.PL
Subject: PhD Publikációs Lista

Candidate: Csilla Vér
Neptun ID: IKYBS6
Doctoral School: Doctoral School of Neurosciences

List of publications related to the dissertation

1. Aranyi, C., Opposits, G., Nagy, M., Berényi, E., **Vér, C.**, Csiba, L., Katona, P., Spisák, T., Emri, M.: Population-level Correction of Systematic Motion Artifacts in fMRI in Patients with Ischemic Stroke.
   J. Neuroimaging. *"Accepted by Publisher"*, 2016.
   IF: 1.625 (2015)
2. **Vér, C.**, Emri, M., Spisák, T., Berényi, E., Kovács, K., Katona, P., Balkay, L., Menyhárt, L., Kardos, L., Csiba, L.: The Effect of Passive Movement for Paretic Ankle-Foot and Brain Activity in Post-Stroke Patients.
   Eur. Neurol. 76 (3-4), 132-142, 2016.
   DOI: http://dx.doi.org/10.1159/000448033
   IF: 1.403 (2015)

List of other publications

3. **Vér, C.**, Hofgárt, G., Szima, G., Kovács, G., Nyisztor, Z., Kardos, L., Csiba, L.: Saját fejlesztésű mozgásérzékelővel szerzett tapasztalataink.
Ideggyogy. Szle. 66 (1-2), 29-34, 2013.
IF: 0.343

4. Hofgárt, G., **Vér, C.**, Csiba, L.: Antikoagulálás a gyakorlatban.
Orv. Hetil. 153 (19), 732-736, 2012.
DOI: http://dx.doi.org/10.1556/OH.2012.29357

Total IF of journals (all publications): 3,371
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6.2. List of abstracts related to the thesis

G. Hofgárt, **C. Vér,** G. Szima, L. Csiba:
Observations with a new movement-monitoring device in rehabilitation of stroke patients Cerebrovascular Diseases. -31 : Suppl.2 (2011), p. 189-190. -Cerebrovasc. Dis. -1015-9770.

C. Vér, G. Hofgárt, L. Menyhárt, A. Kiss, L. Ábrahám, G. Kovács, Z. Nyisztor, L. Csiba: Prevention of lower limb spasticity and immobilization complications with passive mobilization in acute stroke patients. European Journal Of Neurology . – 19 (2012), p. 572. IF: 3.692

Vér Cs., Hofgárt G., Menyhárt L., Kardos L., Csiba L.: Saját fejlesztésű boka mobilizáló készülékkel szerzett tapasztalataink post stroke betegeken. Vascularis Neurológia. 2013. 5. évf. (1. Supplementum) 47.

Vér Cs., Emri M., Spisák T., Berényi E., Kovács K., Katona P., Balkay L., Menyhárt L., Kardos L., Csiba L.: A passzív boka mobilizálás hatása a mozgás szervrendszerre és az agyi aktivitásra akut stroke betegeken. Vascularis Neurológia. 2015. 7. évf. (1. Supplementum) 68.

6.3. List of conference presentations and posters related to the thesis

C. Vér, G. Hofgárt, G. Szima, L. Kardos, L. Csiba: Observations with a new movement monitoring device in rehabilitation of stroke patients. 15th EFNS Congress, Budapest
Critical care and rehabilitation. Poster Session 2. 2011.09.08.

C. Vér, G. Hofgárt, L. Menyhárt, A. Kiss, L. Ábrahám, G. Kovács, Z. Nyisztor, L. Csiba: Prevention of lower limb's spasticity and the immobilization's complications with passive mobilize device in rehabilitation of acute stroke patients. 16th EFNS Congress, Stockholm Critical care and rehabilitation. Poster Session 2. 2012.09.10. 14:30

Vér C., Hofgárt G., Menyhárt L., Kardos L., Csiba L.: Alsóvégtag mobilizáló és stimuláló készülék fejlesztése akut stroke betegek rehabilitációjában. Előadás. Új diagnosztikus és rehabilitációs kezdeményezések neurológiai betegségekben mini szimpózium, Hotel Eger. 2012. Szeptember 22.

Vér Cs., Hofgárt G., Menyhárt L., Kardos L., Csiba L.: Alsóvégtag mobilizáló és stimuláló készülék fejlesztése és tesztelése akut stroke betegek rehabilitációjában. Előadás. Magyar Ideg- és Elmeorvosok Társaságának XXXV. Vándorgyűlése, Debrecen, 2012. november 23. 11:15

Vér Cs., Hofgárt G., Menyhárt L., Kardos L., Csiba L.: Sajátfejlesztésű alsóvégtag mobilizáló és stimuláló készülékkel szerzett tapasztalataink akut stroke betegeken. Poszter. Magyar Ideg- és Elmeorvosok Társaságának XXXV. Vándorgyűlése, Debrecen, 2012. november 22-24. 2012. november 22-24.

Vér Cs., Hofgárt G., Menyhárt L., Kardos L., Csiba L.: Saját fejlesztésű boka mobilizáló készülékkel szerzett tapasztalataink post stroke betegeken. Poszter. Magyar Stroke Társaság XI. Konferenciája, Nyíregyháza, 2013.szeptember 5-7.

C. Vér, G. Hofgárt, L. Menyhárt, K. Kovács, M. Emri, E. Berényi, L. Csiba: Investigation of brain activity with functional magnetic resonance imaging after passive moving in post stroke patients. Joint

Congress of European Neurology. Istanbul, Poster session 2. 2014. 06. 01.

Katona P., Aranyi Cs., **Vér Cs.,** Csiba L., Berényi E., Emri M., Kovács K.: Poststroke betegek passzív lábmozgatása során aktiválódó motoros hálózat karakterizálása fMRI mérések segítségével. Magyar Neuroradiológus Társaság 22. Kongresszusa, Hajdúszoboszló, 2014. november 6-8. 5.

Kovács K., **Vér Cs.,** Csiba L., Spisák T., Berényi E., Katona P., Emri M.: Paretikus stroke betegek agyi aktivitáskülönbségeinek kimutatása fMRI vizsgálattal. Magyar Neuroradiológus Társaság 22. Kongresszusa, Hajdúszoboszló, 2014. november 6-8.

Vér Cs., Emri M., Spisák T., Berényi E., Kovács K., Katona P., Balkay L., Menyhárt L., Kardos L., Csiba L.: A passzív boka mobilizálás hatása a mozgás szervrendszerre és az agyi aktivitásra akut stroke betegeken. A Magyar Stroke Társaság XII. konferenciája és a Magyar Neuroszonológiai Társaság konferenciája, Sopron, 2015.09.17-19. *The best poster award.*

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