The Hong Kong Polytechnic University

Department of Rehabilitation Sciences

# Treatment of Upper Extremity Paresis using Transcutaneous Electrical Stimulation during Acute Stroke

by

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# CERTIFICATE OF ORIGINALITY

The idea of the present investigation is originated from my supervisor, Professor Christina W.Y. HUI-CHAN. The design of the study and the planning of the experiment were resulted from discussions between the author and Professor HUI-CHAN. All experiments in the present investigations were completed solely by the author.

I, Stephanie Suk Yin AU-YEUNG, hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it reproduces no material previously published or written, nor material that has been accepted for the award of any other degree or diploma, except where due acknowledgement has been made in the text.

In addition, ethical approval from the Ethics Committees of The Hong Kong Polytechnic University, Ruttonjee Hospital, Queen Elizabeth Hospital and Kowloon Hospital had been granted for the studies presented in this thesis. Subjects were required to understand the study by the information being read and explained to them as an introduction to the study. Written informed consent was gained prior to the data collection.

AU-YEUNG Suk Yin, Stephanie

# DEDICATION

To my dear father Mr. AU-YEUNG Wing (1929-1994). He educated me through his sincere, caring and positive attitudes to people and his commitments, and his courage, wisdom and perseverance when dealing with overwhelming difficulties.

To my dear mother WONG Kit Fung who has always been caring, patient and supportive to me without limits.

To my sisters, brothers, their families, and my aunt; they always put trust on me and from them my confidence develops.

***To the Lord of creation – He takes care of everything.***

# ABSTRACT

***Introduction:*** Previous randomized controlled trials on people with stroke showed that transcutaneous electrical stimulation (TES) of muscles, nerves or acupuncture points (acupoints) could reduce spasticity and improve muscle strength of lower extremities. Such effects have not been systematically demonstrated in the paretic upper extremities (UE), especially during the acute stage.

***Methods:*** A longitudinal cohort of 57 patients recruited at acute stroke units and receiving conventional rehabilitation (CR) was studied. The course and extent of recovery in the paretic UE in terms of (1) tactile sensation of pressure and two-point discrimination in the index finger, (2) muscle tone measured with the Composite Spasticity Score, (3) muscle strength of shoulder and elbow measured with the Motricity Index, (4) power grip and index pinch strength measured with a dynamometer, and (5) functional ability measured with the Action Research Arm Test, was documented over the first 6 months of stroke. Early clinical characteristics that predicted the recovery of functional dexterity at 6 months were delineated. A double-blind, randomized, placebo-controlled trial then investigated the effectiveness of TES applied to 6 acupoints for promoting recovery in the paretic UE. Patients recruited within 46 hours after stroke onset were randomized to receiving CR alone as controls (n=18), or to the TES (n=28) or placebo-TES (n=20) groups whose subjects were respectively given TES and placebo stimulation in addition to CR. Such treatment was started within 2 days of stroke, given 60 minutes per day, 5 days per week for 4 weeks. Including 19 subjects recruited within 60 hours of stroke and who had been receiving CR as controls, the 3 groups were compared their UE recovery. All subjects were reassessed weekly for the first 4 weeks and then at 1, 2, 3 and 5 months

afterwards. Statistics used were descriptive analyses, logistic regressions and mixed model ANCOVA.

***Results:*** The sensory, motor and functional recovery was rapid in the first 1 to 2 months of stroke. UE muscle strength consistently predicted the recovery of functional dexterity at 6 months post-stroke. The strongest prediction was found at 4 weeks post-stroke, with power grip and index pinch strength being stronger predictors than the shoulder and elbow muscle strength. The TES programme induced better recovery in grip and pinch strength than CR alone when the 1-month treatment ended ($P$ <0.01), and better UE functional ability 3 months afterwards ($P$ ≤0.01). These effects persisted beyond the end of the programme for at least 5 months. Differences between the placebo-TES and the TES or control groups could not be demonstrated in the present study.

***Conclusions:*** (1) The initial 4 weeks of stroke was the time window when rapid motor recovery occurred. (2) Muscle strength in the paretic UE, especially grip and pinch strength 4 weeks after stroke, strongly predicted the return of functional dexterity at 6 months. (3) Adding an early intensive TES programme to CR was effective in promoting greater grip and pinch strength than CR alone as early as 4 weeks after stroke, with carry-over effects lasting for at least 5 months after the programme ended. TES treatment given during acute stroke could be a promising adjunct to CR in promoting motor and functional recovery of a paretic UE.

**Part of the work reported in this thesis has been presented in the following international conferences:**

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| 2-PD | Two-point discrimination |
| ANCOVA | Analysis of covariance |
| ANOVA | Analysis of variance |
| ARAT | Action Research Arm Test |
| BI | The modified Barthel Index |
| C.I. | Confidence interval |
| CSS | Composite Spasticity Score |
| FES | Functional electrical stimulation |
| GRIP | Power grip strength |
| ICC | Intra-class correlation coefficient |
| MI | Motricity Index |
| NCSE | NeuroBehavioral Cognitive Status Examination |
| NIHSS | National Institutes of Health Stroke Scale |
| PINCH | Pinch grip strength |
| PR | Pressure sensibility |
| ROC | Receiver Operating Characteristic |
| TES | Transcutaneous electrical stimulation |
| TENS | Transcutaneous electrical nerve stimulation |
| UE | Upper extremity |
| $W_1$ | 1 week after baseline assessment |
| $W_2$ | 2 weeks after baseline assessment |
| $W_3$ | 3 weeks after baseline assessment |
| $W_4$ | 4 weeks after baseline assessment (1 month post-stroke) |
| $W_8$ | 8 weeks after baseline assessment (2 months post-stroke) |
| $W_{12}$ | 12 weeks after baseline assessment (3 months post-stroke) |
| $W_{16}$ | 16 weeks after baseline assessment (4 months post-stroke) |
| $W_{24}$ | 24 weeks after baseline assessment (6 months post-stroke) |

# *Chapter 1*

## *Introduction*

## 1.1 Epidemiology of Stroke

Stroke, also known as cerebro-vascular accident, has been defined by the World Health Organization's MONICA project as "a sudden onset of focal or global disturbance of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent nonvascular causes" (WHO MONICA Project Principal Investigators 1988). The cerebro-vascular event could be haemorrhagic or ischaemic in nature. 62 to 80 % of stroke events worldwide are ischaemic, due to the occlusion of cerebral arteries by thrombus or emboli (Sudlow and Warlow 1997, Walker et al. 1981, Yip et al. 1997, Zhang et al. 2003). In the Oxfordshire Community Stroke Project which registered 543 patients with cerebral infarct from first stroke (Bamford and Sandercock 1991), 17% of the subjects had cortical and subcortical involvement, 34% had cortical infarct and 25% had lacunar infarcts caused by problems in the deep perforating arteries.

The age- and sex-adjusted incidence rate of stroke in the United States was 259 per 100,000 of population of 1995 (Williams et al. 1999). It is a leading cause of death in most countries (Francescutti et al. 2005, Thorvaldsen et al. 1997). In Hong Kong, the statistics of 2002 showed that there were more than 26,000 hospital admissions diagnosed as stroke under the Tenth Revision of the International Classification of Diseases (ICD-10) codes I60 to I69 (Hospital Authority 2004). With a mortality rate of 33.2 per 100,000 of population, cerebro-vascular disease has been the third highest amongst all causes (Hospital Authority 2004). As in many developed countries (American Heart Association 2005), this mortality rate has been decreasing substantially in recent decades, evidenced by 50% drop amongst men and 38% drop amongst women between 1976 and 1995 (Yu et al. 2000). Survivors of stroke have therefore been increasing in number.

The disease has major impacts on both stroke victims and the society. These impacts are in terms of physical disabilities and psycho-cognitive dysfunctions (Mohr 2004), healthy years lost due to disabilities (Murray and Lopez 1996), as well as health care costs (Dewey et al. 2003, Williams et al. 1999). The American Heart Association reported that stroke is the 7$^{th}$ most costly medical condition in the United States (American Heart Association 2005). The direct and indirect cost of stroke in the U.S. in 2005 was estimated to be US$56.8 billion (American Heart Association 2005). Based on data obtained in Australia's North East Melbourne Stroke Incidence Study, the estimated total lifetime costs of ischaemic stroke are 72% of the costs for all stroke types, amounting US$709.7 millions (Dewey et al. 2003).

## 1.2 Stroke-induced Physical Dysfunctions

The neurological effects of stroke vary. The disease often leads to disorders in the sensory, motor and cognitive systems (Alberts and Horner-Catt 2001, Ferro and Martins 2001, Kim and Choi 1996, Melo and Bogousslavsky 2001, Twitchell 1951). There is abnormal movement control of the extremities (Dewald et al. 2001, Nakayama et al. 1994b, Olney et al. 1991, Woolley 2001) and the trunk (Hsieh et al. 2002), as well as disrupted speech (Pedersen et al. 1995), and bladder and bowel functions (Nakayama et al. 1997). These movement control problems are manifested on the side contralateral to that of the cerebro-vascular lesion, and could occur together with altered sensation (Bowsher 1993, Motomura et al. 1990, Robertson and Jones 1994), abnormal muscle tone and muscle weakness (Twitchell 1951). Studies have shown that in the first week of acute stroke, more than 50% of patients experience difficulties in their activities of daily living (ADL) (Jørgensen et al. 1999),

for example, feeding, self-care (Nakayama et al. 1994a, 1994b), bladder and bowel functions (Nakayama et al. 1997), and ambulation (Jørgensen et al. 1995). Even with rehabilitation, 20 to 50% of survivors remain dependent in ADL 6 months post-stroke (Dombovy et al. 1987, Duncan et al. 1992, Warlow 1998). Among the cohort of subjects in the Copenhagen Stroke Study, 64% were able to walk independently (Jørgensen et al. 1995). Still, 55 to 75% of stroke survivors are left with an affected upper extremity (UE) non-functional (Olsen 1990, Parker et al. 1986, Wade et al. 1983). Broeks and co-workers (1999) found that 73% of a cohort of subjects followed up at 4 years post-onset of stroke still perceived loss of UE function as their major problem. In a study about health-related quality of life after stroke (Williams et al. 1999), functional ability in the paretic UE was identified as one of the three most important concerns.

UE functions involve movements ranging from gross motion of the proximal shoulder, elbow and wrist joints to fine finger dexterity for manipulating of objects (Wing et al. 1996). The complex sensori-motor interactions involved in such movements are supported by the extensive representation of the UE on the sensory and motor cortices as compared to the small cortical representation of the lower extremities or the trunk (Kandel and Jessell 1991). This UE cortical representation is supplied by the middle cerebral artery, which is a common site for cerebro-vascular accidents. Hence, UEs are usually more affected in stroke than lower extremities whose cortical representation is supplied by the anterior cerebral artery (Brust 2000).

### *1.2.1 Impairment and disability in the paretic upper extremity*

#### 1.2.1.1 Sensory impairment

Sensory impairments as a result of stroke involve reduced tactile, temperature

and proprioceptive sensation, or feeling of “pins and needles”, pain and coldness (Bowsher 1993, Hanger and Sainsbury 1996, Wanklyn et al. 1995). For the paretic UE, impaired discriminative sensation of the hand has been reported to be present in 25 to 85 percent of patients (Anderson 1971, Buskirk and Webster 1955, Kim and Choi 1996, Sterzi 1993). This is often of concern because the dexterity of the hand could be affected (Jeannerod et al. 1984, Motomura et al. 1990). Moreover, sensory impairment could also be present in the paretic UE of patients with pure motor stroke (Kim and Choi 1996). Bilateral somatosensory impairment from stroke has also been noted (Carmon 1971). Despite the extensive description about sensory impairment from stroke in the literature, the time course and extent of its recovery remains poorly defined.

1.2.1.2 Abnormal muscle tone

Abnormal muscle tone after stroke could present itself as flaccidity, hypotonicity, or spasticity. Lance (1980) defined spasticity as “a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks, resulting from hyper excitability of the stretch reflex”. It has been shown to reach its peak between 1 to 3 months post-onset of stroke (Thilmann et al. 1991). Although spasticity has been addressed extensively in rehabilitation (Francis et al. 2004, Sommerfeld et al. 2004), its association with motor functions has been controversial. Twitchell (1951), in his observational study, suggested that with recovery of muscle strength, the hyperactive stretch reflex could be suppressed. From a cohort of spastic and nonspastic patients assessed at 3 months after stroke, Sommerfeld and coworkers (2004) found that both groups of patients presented with severe disability at similar rates. Ng and Hui-Chan (2005) further

showed that ankle spasticity did not correlate with Timed-up-and-go time scored in patients with chronic stroke. On the other hand, Formiscano and colleagues (2005) found that subjects with hypotonicity at 3 months post-stroke had delayed motor recovery. Therefore, long-standing flaccidity in the affected UE could affect the recovery of function (Twitchell 1951). Better understanding about the change of muscle tone with time from stroke onset and its relationship with functional recovery in the paretic UE could facilitate the planning of treatment.

#### 1.2.1.3 Reduced muscle strength

Studies have shown that at the onset of stroke, 69 to 90 percent of patients demonstrate muscle weakness in the UE contralateral to the lesion (Bogousslavsky et al. 1988, Bonita and Beaglehole 1988, Nakayama et al. 1994a). The severity of weakness has been shown to be associated with the size of the lesion (Mohr et al. 1993). The distribution of weakness over the proximal and distal muscles of the affected UE, however, is usually similar in extent (Colebatch and Gandevia 1989). Sometimes, the strength of the UE muscles ipsilateral to the side of lesion is also affected (Colebatch and Gandevia 1989, Jones et al. 1989). Studies on the time course of motor recovery of the paretic UE in people receiving rehabilitation have shown that the fastest recovery takes place in the initial 1 to 3 months after the onset of stroke (Duncan et al. 1992, Nakayama et al. 1994a, Wade et al. 1983). However, unlike patients with mild stroke, many patients did not demonstrate a complete return of UE muscle strength (Duncan et al. 1992, Nakayama et al. 1994a).

#### 1.2.1.4 Reduced functional use of the paretic upper extremity

In the acute stage of stroke, many patients demonstrate poor UE function in

basic daily living activities, or indeed any manipulative functions with the affected hand. Nakayama and colleagues (1994b) found that 43% of 421 subjects recruited within one week after stroke onset required partial or total assistance in feeding and personal hygiene activities. Several studies reported that only 25 to 45% patients achieve functional recovery in the affected UE after conventional rehabilitation (Olsen 1990, Parker et al. 1986, Wade et al. 1983). Wade and colleagues (1983) also found that of 56 patients whose paretic UE did not demonstrate any functional ability at admission to rehabilitation, 60% remained with a non-functional UE at the time of a two-year follow-up. In people who had achieved full independence in ADL 4 years after stroke, Broeks and coworkers (1999) found that UE motor function as measured by the Fugl-Meyer arm score accounted for 28% of all variance in UE disability as measured by the Barthel Index. In coping with activities of daily living, compensatory use of the less affected UE was common (Nakayama et al. 1994b). Learned non-use could develop in the paretic UE (Knapp et al. 1958, Wolf et al. 1989).

### *1.2.2 Prognostic indicators to the recovery of upper extremity motor functions*

The severity of the neurological insult associated with a stroke determines the prognosis with respect to mortality and on-going disability in the activities of daily living (Adams et al. 1999). With imaging diagnostic procedures, researchers have shown that the volume of the lesion during the acute stage of infarct is associated with the severity of impairment and disability (Pineiro et al. 2000, Schiemanck et al. 2005). It has been suggested that the laterality of the stroke and the site of the lesion are associated with UE recovery (Katz et al. 1999, Macciocchi et al. 1998). A number of longitudinal studies have also confirmed that muscle strength in the

paretic UE predicts the recovery of muscle strength and disabilities in daily living tasks later on (De Weerdt et al. 1987, Duncan et al. 1992, Wade et al. 1983). The predictive value of spatial perception and of somatosensation in the UE has not been clearly defined. Moreover, the relative importance of these clinical factors intrinsic to the stroke event in influencing the prognosis for UE recovery have not been well established (De Weerdt et al. 1987, Feys et al. 2000, Novack et al. 1987, Prescott et al. 1982, Yavuzer et al. 2001).

## 1.3 Mechanisms of Recovery after Stroke

Spontaneous neurological recovery has been suggested to account for most of the functional recovery demonstrated early post-stroke (Gresham 1986, Heddings et al. 2000, Wade and Hewer 1987). More severe stroke usually implies a longer course of recovery (Duncan and Lai 1997). What are the processes mediating neurological and functional recovery after stroke? Using ischaemic stroke models in animals and investigative procedures involving electro-physiological cortical mapping and neuroimaging techniques, more knowledge has been gathered on the events *governing* the extent of neurological injury and recovery.

### *1.3.1 Ischaemic injury in acute stroke*

In ischaemic stroke, neurological injury starts from the sudden loss of vascular irrigation in the brain resulting from an obstruction within major cerebral blood vessels or small arterioles caused by a thrombus or embolus (Barnett et al. 1992). The human brain needs around 20% of the cardiac output to maintain normal metabolism. When the regional cerebral blood flow (CBF) drops below 50 to 60

percent of normal or the cerebral perfusion pressure falls below 60 mm Hg, a cascade of events leading to brain cell death is triggered (Ahmed et al. 2001). At this threshold value, oxygen and glucose supply to the brain is jeopardized so that the rate of anaerobic glycolysis increases within the affected brain region. The mildly ischaemic tissue is prone to inflammation and electrical depression. When CBF drops to 40 to 50 percent of normal, the sodium and potassium pump involved in the firing of electrical signals in brain cells becomes further compromised. Neurological deficits appear at this point of electrical failure. A quick influx of the cations, $Ca^{2+}$ and $Na^{2+}$ to the intracellular space of neurons begins, while excitatory aminoacids such as glutamate and aspartate are released into the extracellular space. The influx of $Ca^{2+}$ is harmful to neurons because this activates enzymes which degrade neuronal proteins. If the ischaemic process is prolonged and CBF is reduced to 20 to 30 percent of normal, the neurons become overloaded with $Ca^{2+}$. Intracellular swelling increases and irreversible brain tissue damage results. The cytotoxic oedema and extracellular excitatory amino acids from the ischaemic core upset the cerebral perfusion pressure and ionic homeostasis respectively of nearby neurons.

The ischaemic effect in the immediate region of reduced CBF is quick to develop. However, regions surrounding the ischaemic core take some time to become severely affected. The neighbouring region with 40 to 80 percent of normal CBF is called the penumbra, the neurons in it are expressing electrical failure and are at risk of infarction (Ahmed et al. 2001, Baron et al. 1995). If the oxygen supply drops further, so that oedema increases and cerebral perfusion pressure decreases, these penumbral neurons will become vulnerable to irreversible injury.

One important aim of acute stroke management is therefore to ensure perfusion from blood flow and nutrients in cerebral tissues at risk of infarct. It has

been shown that the percentage change of cerebral tissue perfusion in the first 48 hours of ischaemic stroke significantly predicted functional outcomes at 3 months (Baird et al. 1996). Spontaneous neurological recovery in 2 months after the onset of stroke was found to be related to the volume of penumbra which had been reperfused against infarction (Furlan et al. 1996). Early arrest of the ischaemic evolution in the penumbra should salvage brain tissues at risk of hypoxic-related injury and improve the prognosis for recovery (Fisher 1997).

### *1.3.2 Lesion-induced plasticity in the brain*

Neurological injury in the infarct zone becomes irreversible within a very short time. It is thought that neurological recovery involves restitution of function by the non-affected cortical or subcortical pathways (Frost et al. 2003, Nudo et al. 2001, Rothi and Horner 1982). The brain has large capacity for rapid adaptation and reorganization in response to injury (Butefisch et al. 2003, Feydy et al. 2002, Nelles et al. 1999, Weiller et al. 1993). In non-human primates, a combination of changes in cortical excitability and functional connectivity has been found in response to induced cortical infarct (Bütefisch 2004, Xerri et al. 1998). These changes in morphological and functional properties in the brain are the characteristics of brain plasticity (Classen 1998, Donoghue et al. 1996).

#### 1.3.2.1 Reorganization of cortical representation

Functional reorganization of the cortical pathways takes place very early after brain lesion. This might involve resolution of diaschisis, i.e., reactivation of remote neural structures in the brain or spinal cord which are connected with the infarct area but whose function has been suppressed at stroke onset (Nudo et al. 2001, Seitz et al.

1999, Weiller et al. 1992, 1993). The penumbral areas may also contribute to recovery upon reperfusion, with subsequent resorption of intracellular and extracellular oedema and the necrotic tissues (Fisher and Takano 1995).

In a longitudinal study, functional magnetic resonance imaging (fMRI) was used to monitor the temporal changes in task-related brain activation in 8 patients with acute stroke from 2 weeks to 6 and 12 months after stroke onset (Ward et al. 2003). The extent of brain activation was found to match with improvements in UE motor function. In monitoring the progress of 14 patients from 1 to 6 months after unilateral infarct of the middle cerebral artery, Feydy and coworkers (2002) noticed continuous reorganization of cortical networks in both the affected and contralateral hemispheres through serial recording of transcranial magnetic stimulation (TMS) and fMRI. Neuroimaging also revealed various cortical and subcortical regions to have been involved in the functional reorganization of neural networks (Chollet et al. 1991, Cramer et al. 1997, Weiller et al. 1992, 1993). In subjects whose hand movements had recovered after cortical or subcortical infarct, task-related regional CBF was found to have increased in the peri-infarct area, the ipsilateral pre-motor and supplementary motor cortices, bilateral pre-frontal and cingulated cortices, and the contralateral cerebellum. Compared to healthy controls, there was larger volume of activated brain tissues and the hand territory in the sensorimotor cortex of the affected hemisphere was also expanded. Therefore, recruiting neural networks whose functions have former association with the infarct region, or whose pathways serve similar functions is a mechanism for mediating functional reorganization (Aizawa et al. 1991).

1.3.2.2 Plastic adaptations at the neuronal level

It has been suggested that re-establishing brain networks involves unmasking existing but latent synapses (Jacobs and Donoghue 1991, Lee and van Donkelaar 1995), formation of new synapses with intact neurons (Jones 1999, Komitova et al. 2002, Steward 1989), and modulation of synaptic efficacy (Jones 1999). These processes are mediated through downregulation of the inhibitory GABA receptors (Jacobs and Donoghue 1991) and upregulation of the excitatory glutamatergic NMDA receptors (Bütefisch et al. 2000, 2003). The release of synapses from inhibition leads to unmasking of formerly sub-threshold inputs from latent connections. Long-term potentiation of synapses for functional reorganization of neural networks could be facilitated in peri-lesional areas (Hagemann et al. 1998, Mittmann and Eysel 2001).

The synaptic plasticity via inhibitory and excitatory neurotransmitters takes place quickly after brain lesions. Fujioka and colleagues (2004) applied electrophysiological recording techniques to trace the plastic changes in the primary somatosensory cortex of rats after induced focal ischaemia. The peri-infarct areas of the somatosensory cortex were found to increase in neuronal excitability, with the receptive fields expanded as early as one hour post infarct (Fujioka et al. 2004).

### *1.3.3 Use-dependent plasticity*

Long-term potentiation of synapses, a phenomenon of long-lasting increase in synaptic efficacy that is associated with neuronal plastic adaptations after brain lesion, is use-dependent (Bliss and Lømo 1973). Using intracortical micro-stimulation, Nudo and Milliken (1996a, 1996b) mapped changes in the thumb representation area of the primary motor cortex in squirrel monkeys. After induced

infarct in this cortical area, significant reduction of the representation area was observed if the primates were not given training for their affected hands (Friel et al. 2000, Nudo and Milliken 1996a, 1996b). On the other hand, monkeys which had been trained to use the affected hand repetitively while their non-impaired hands were restrained showed recovery of dexterity function to pre-injury levels within two months. The motor cortical representation area of their affected hand was found to have increased and taken over the former elbow and shoulder representation area. Functional reorganization of the un-injured motor cortex was also noted.

Similar use-dependent reorganization of the somatosensory cortex has been reported with induced focal infarct of the sensory representation area of the hand using monkeys (Jenkins and Merzenich 1987, Xerri et al. 1998). Immediately after the induced infarct, areas representing cutaneous reception around the infarct became enlarged (Jenkins and Merzenich 1987). With monkeys trained on object retrieval tasks using the affected fingers repetitively (Xerri et al. 1998), multiple new cutaneous representations of the involved fingers emerged in the affected somatosensory cortex weeks and months after the lesion. However, the hand representation area of the contralateral hemisphere was not changed.

Cortical reorganization has also been well demonstrated in people with chronic stroke after intensive forced-use of the affected UE for 6 hours daily for two weeks (Liepert et al. 2000). fMRI results showed that the cortical activation area for the involved UE muscles had increased together with clinical improvement in UE function. These effects lasted up to six months after the programme ended.

### *1.3.4 Sensory input and plasticity*

Evidence of recovery-associated cortical plasticity has been observed not

only after repetitive *active use* of the affected body parts; even passive movements of a severely impaired UE after stroke could induce reorganization of the sensory and motor cortical networks. Nelles and colleagues (1999) examined the regional CBF of 6 patients with unilateral subcortical infarct using PET. Sequential periods of rest and motor-generated passive movements to the elbow of the paretic UE were introduced while the regional CBF of the brain was measured. Compared to healthy controls, patients showed greater bilateral increases in regional CBF in their sensorimotor cortices and parietal lobes, indicating more neural structure had been activated during passive elbow movements.

Studies on non-human primates (Jenkin et al. 1990) and healthy human subjects (Hamdy et al. 1998, Ridding et al. 2001) have shown that manipulation of sensory inputs can induce long-term cortical reorganization. After two hours of electrical stimulation of the ulnar and radial nerves at the wrist level (using 10 Hz current at an intensity of three times the sensory threshold), the hand representation area of the motor cortex activated by transcranial magnetic stimulation was enlarged (Ridding et al. 2001). Hamdy and colleagues (1998) applied 10 minutes of 10 Hz electrical stimulation to the pharynx of 8 healthy subjects via swallowed electrodes. The topographic motor representation of the pharynx showed an increased area of excitability after the stimulation which lasted at least 30 minutes. McKay and colleagues (2002) also made similar observations in their study of healthy human subjects. They applied a 3-day dual stimulation protocol that included 30 minutes of sub-motor threshold electrical stimulation to the first dorsal interosseous muscle, plus transcranial magnetic stimulation to the cortical motor area of the muscle. After this programme, there was a prolonged increase in the number of active sites and neuronal excitability on the motor cortex associated with finger tapping movements.

### *1.3.5 Factors unfavourable to recovery*

In acute stroke, factors which intensify and prolong the ischaemic cascades could result in more neurological injury. Although plastic reorganization of neural networks is use-dependent, overuse during an early stage of infarct could have unfavourable effects. Kozlowski and coworkers (1996) examined on rats with unilateral surgical lesion of the sensori-motor cortex. Starting very early after brain injury, the rats were forced to use the affected forelimbs in landing after a rear while the ipsilateral forelimb was immobilized in a cast. Compared with control rats either with delayed cast immobization or without immobilization, the experimental rats had significantly less healthy brain tissues remaining, indicating enlargement of their initial cortical lesion (Humm et al. 1998, Kozlowski et al. 1996). Hence, stressful intensive use of the affected limb during the acute stage of stroke might be detrimental to recovery.

Neuronal disconnections at the infarct zones could result in Wallerian degeneration of corticospinal tracts (Fries et al. 1993). Feydy and coworkers (2002) tracked the motor recovery and reorganization of the corticospinal tracts of 14 patients after stroke using fMRI. From 1 to 6 months after stroke onset, the signs of Wallerian degeneration in the corticospinal tracts increased with time. The degree of degeneration was found to be inversely related to the degree of motor function recovery in the contralateral UE. The authors suggested that availability of unimpaired corticospinal tracts might be crucial for recovery from a lesion.

### *1.3.6 Implications for therapies*

In the acute stage of stroke, methods that could attenuate the ischaemic cascades and protect neurons from injury should favour recovery. Under strict

guidelines, antithrombotic and thrombolytic prescriptions have been proven effective in improving neurological outcomes of certain acute ischaemic stroke conditions (Adams et al. 2003, Di Minno et al. 2001). These drugs have to be administered within a limited time window to improve cerebral circulation in the affected brain regions and reperfuse the penumbra (Hill and Hachinski 1998, Ng et al. 2004). Better patient management in stroke units has also resulted in better outcomes in terms of mortality and disability in ADL (Stroke Unit Trialists' Collaboration 1997). Interdisciplinary efforts to control blood pressure (Chamorro et al. 1998), body temperature (Ginsbery and Busto 1998, Jørgensen et al. 1996, Kammersgaard et al. 2002), and hyperglycaemia (Pulsinelli et al. 1983), as well as early mobility (Indredavik et al. 1999, Langhorne and Pollock 2002) might have contributed to favourable effects. Electro-acupuncture has been shown to restrain the excito-toxic cascades in animal studies using induced middle cerebral artery occlusion models (Guo and Cheng 2000, Zhao and Cheng 1997, Zhao et al. 2000). However, evidence for the antitoxic and neuro-protective effects of electro-acupuncture in humans remains pending.

Sensori-motor impairments from stroke make movements difficult. Disuse of the involved body regions would lead to further reductions in functional cortical representation (Nudo and Milliken 1996). It has long been clear that lesion-induced plastic changes in the brain starts early after stroke onset. To reduce the effect of losing synaptic influence from the infarct region and the unfavourable neural adaptations associated with disuse, therapies should start early involving the use of the affected extremity. Such sensori-motor experience has to be of sufficient intensity to enhance synaptic efficiency and to activate latent or alternative pathways to take over or compensate for the function of the lost tissues. On the other hand,

stressful or excessively intensive exercise of the paretic extremities, given too early after induced lesion of the sensori-motor cortex, might be harmful to the damaged brain – at leaset as shown in rat modals (Humm et al. 1998, Kozlowski et al. 1996). Suitable early treatments that augment sensory and motor experience in the paretic extremity need to be designed and tested for efficacy in clients with stroke.

## 1.4 Exercise Therapies

### *1.4.1 Traditional therapies*

Various exercise therapies are used in stroke rehabilitation to reduce the impairments and associated disabilities. Traditional therapies usually target at the neurophysiological effects of stroke, assuming that function can be restored through addressing the underlying impairments (Duncan and Badke 1987). For example, the Bobath or neuro-developmental approach emphasizes normalizing muscle tone and practising normal movement patterns (Bobath 1976, 1990). Proprioceptive neuromuscular facilitation techniques aim at recruiting weaker muscles through activating stronger muscles (Knott and Voss 1968, Voss 1985). These therapies rely on the manual skills of the therapist and her individual preferences. There has not been hard evidence to distinguish the effects of such interventions on motor function recovery from the spontaneous recovery normally taking place after stroke (Dickstein et al. 1986, Gelber 1995, Lincoln et al. 1999, Logigian et al. 1983, Lord and Hall 1986, Duncan et al. 1992). Non-standardized application of these therapies might have led to the general lack of effects observed in the studies which have been reported. Recently, accumulating evidence has highlighted certain characteristics of exercise programmes that account for better outcomes post-stroke.

### *1.4.2 Characteristics of effective exercise therapies*

1.4.2.1 Early therapies

Studies on the effects of rehabilitation therapies have usually involved subjects in their stable phase after stroke, or in the chronic stage after they have already completed conventional rehabilitation. In a meta-analysis of 36 clinical trials involving 3,717 subjects at an average of 7 weeks after stroke when intervention started, Ottenbacher and Jannell (1993) found that earlier initiation of treatment was associated with better functional outcomes. Using a middle cerebral artery occlusion rat model, Biernaskie and coworkers (2004) compared rats exposed to 5 weeks of enriched rehabilitation initiated at day 5, day 14 and day 30 after focal ischaemia. The rats whose intervention started at day 5 post-ischaemia demonstrated the best improvements in functional skills of the affected limbs, together with more dentritic growth in the undamaged cortex. The outcomes in rats given delayed programmes beginning at day 30 post-ischaemia were not different from control rats receiving a conventional programme. These results suggest that the brain responds better to rehabilitation in the early post-stroke period.

1.4.2.2 Intensive therapies

Intensity of treatment is defined in terms of both its amount, frequency and duration (Kisner and Colby 1996). It has been found that more intense treatments produce better functional outcomes (Sunderland et al. 1992, Kwakkel et al. 1999, 2002). After controlling for stroke severity, Bode and coworkers (2004) showed that the amount of rehabilitation therapy predicted the residual functional change in self care and cognition. Kwakkel and colleagues (1999) studied subjects randomized to receive an additional 30 minutes of either task-oriented arm or leg training, 5 days a

week during the first 20 weeks after stroke. The two modes of training resulted in better recovery in dexterity and ADL functions respectively when compared to control subjects whose affected extremities were immobilized over a similar time schedule. The improvement in dexterity, although small in comparison with that from spontaneous recovery, persisted 6 weeks after completion of the programmes (Kwakkel et al. 1999, 2002). In another randomized controlled trial that involved 123 patients recruited within 10 days post-stroke (Rodgers et al. 2003), an additional 30 minutes of combined physiotherapy and occupational therapy to the affected UE, 5 days a week for 6 weeks, resulted in improvements in UE and ADL functions that were not different from those of the controls receiving conventional rehabilitation. Lincoln and colleagues (1999) also reported an additional 10 hours of physiotherapy based on the neuro-developmental approach over a span of 5 weeks produced insignificant effects on UE motor function. The less intensive programmes in the latter two studies might have accounted for the insignificant improvement in UE function. Alternately, it could be a lack of task-specific training.

1.4.2.3 Therapies based on motor learning theories

Motor learning theories for stroke rehabilitation advocate the importance of volitional practice, variability of practice, feedback and practice of specific tasks (Carr and Shepherd 1987, Weinstein 1990). The person under training has to practice the targeted movements or tasks with the affected extremity *actively* and *repetitively* (Basmajian et al. 1982, Butefisch et al. 1995, Crow et al. 1989, Dean and Shepherd 1997, Dickstein et al. 1997, Feys et al. 1998, van der Lee et al. 1999).

That treatment effect is specific to the task trained has been demonstrated by Bütefisch and coworkers (1995). In their multiple baseline study, subjects 3 to 19

weeks after stroke practiced 15 minutes of load-resistive wrist extension, twice per day in addition to conventional rehabilitation. After 3 to 4 weeks of the intervention, they showed significant improvement in the hand grip strength, in the peak force and acceleration of wrist extension, and in UE function as measured with the Rivermead Motor Assessment scale. However, the improvements from another period of additional transcutaneous electrical stimulation to the wrist extensors were not significant. In another randomized controlled trial, subjects with chronic stroke practiced reaching tasks with the paretic UE in sitting (Dean and Shepherd 1997). After two weeks, improvements were found in task-related outcomes including arm reaching and leg loading on the affected side, as well as in sit-to-stand performance when compared to those of the controls, but no effect on walking speed. Hence, treatment effects appeared to be specific to the exercise or task trained.

It has also been suggested that compensation by the less affected UE or the use of adaptive devices beginning at the early stage of stroke would limit the recovery of UE function (Feys et al. 1998, Taub et al. 1999). This has led to experiments in the forced use of the paretic UE in performing structured tasks (Taub et al. 1993, Wolf et al. 1989). This task-related training on the paretic UE was found to be effective in improving its functional ability and dexterity, whether it was applied early (Dromerick et al. 2000) or at the chronic stage of stroke (van der Lee et al. 1999), and with more intensive (Taub et al. 1993, van der Lee et al. 1999) or somewhat less intensive protocols (Page et al. 2001).

Feys and coworkers (1998) have also illustrated the effects of repetitive task practice with the affected UE in a randomized placebo-controlled study. They randomized 100 patients at 2 to 5 weeks post-onset of stroke to receive either the experimental repetitive task training for the paretic UE or short-wave diathermy to

the shoulder as a placebo treatment. In the experimental protocol, subjects sat on forwardly reclined rocking chairs with the paretic hand fixed in a gutter while the rest of the UE was kept in an inflated long arm splint. They then pushed with the paretic UE to rock the chair backward repeatedly for 30 minutes a day, 5 days a week, for 6 weeks. These subjects demonstrated better improvement of the paretic UE in Fugl-Meyer motor scores of the paretic UE at 6 months, 12 months (Feys et al. 1998) and 5 years after stroke (Feys et al. 2004) when compared with those of the control subjects. Moreover, a delayed effect from the experimental programme on UE disability as measured with the Action Research Arm test (ARAT) from the experimental programme was evident in the 5-year follow-up assessment.

### *1.4.3 Limitations of exercise therapies*

It was likely that early, intensive and repetitive sensori-motor experience for the UE could foster improvements in both impairment and disability. However, demonstrations of the efficacy of task-related training in UE recovery have always involved subjects with some volitional movements in the affected UE so that they could practice the tasks repetitively (Duncan 1997, Feys et al. 1998, Kwakkel et al. 1999, Sunderland et al. 1992, Taub et al. 1993, van der Lee et al. 1999). In two recent systematic reviews of clinical trials by Van Peppen and coworkers (2004) and van der Lee's group (2001), the authors commented that, except for constraint-induced movement therapy with strict subject inclusion criteria, evidence supporting the effects of exercise therapies on UE motor functions, such as muscle strength and dexterity was insufficient. Exercise therapies reported were commenced two weeks or longer after stroke onset (Feys 1998, Dromerick et al. 2000) or at the chronic stage of stroke (Basmajian et al. 1982, Butefisch et al. 1995, Crow et al. 1989, Dean

and Shepherd 1997, Whitall et al. 2000, Wolf et al. 1989). It is not clear if implementing exercise therapies earlier would favour functional recovery.

## 1.5 Peripheral Electrical Stimulation

Electrical stimulation is a passive or assisted form of physical therapy modality that could be applied early to extremities with severe paresis after stroke. Monophasic or biphasic pulses of direct current with various combinations of frequency and pulse duration can be applied transcutaneously to selected nerves or muscles via surface electrodes (called "transcutaneous electrical stimulation"), or to acupoints through needles (called "electro-acupuncture").

Levin and Hui-Chan (1993) found that both low and high frequency transcutaneous nerve electrical stimulation (4 Hz and 99 Hz respectively in their study) activated similar types of Aα, Aβ nerve fibres. Although such currents have no effect on motor nerve conduction (Cox et al. 1993), high frequency currents at 110 Hz could reduce sensory nerve conduction velocity (Walsh et al. 1995, 1998, 2000).

It has been suggested that all motor points are acupuncture loci (Liu et al. 1975, Ulett et al. 1998) where skin resistance is low (Heine 1988). Electrical stimulation of acupoints with surface electrodes as transutaneous electrical stimulation (TES) or with needles (electro-acupuncture) has been found to produce similar pain modulating effects (Wang et al. 1992). Moreover, repetitive electrical stimulation of peripheral nerves or acupoints has been reported to activate related cortical sites (Cho et al. 1998, Hui et al. 2000, Yang et al. 1995, Wu et al. 1999) and

induce reorganization of sensori-motor pathways (McKay et al. 2002, Ridding et al. 2001).

### *1.5.1 Transcutaneous electrical stimulation*

Transcutaneous electrical stimulation (TES) has been shown to be effective in alleviating hemiplegic shoulder pain and subluxation (Chantraine et al. 1999, Faghri et al. 1994, Linn et al. 1999, Wang et al. 2000), reducing spasticity (Levin and Hui-Chan 1992, Yan 2002), and improving muscle strength of people with stroke (Baker and Parker 1986, Bowman et al. 1979, Chae et al. 1998, Kraft et al. 1992, Levin and Hui-Chan 1992, Powell et al. 1999, Yan et al. 2005).

#### 1.5.1.1 Effects on abnormal muscle tone

Studies have shown encouraging results on reducing spasticity through electrical stimulation of the affected muscles (Tekeoðlu et al. 1998) or the mixed nerves supplying the spastic muscles (Levin and Hui-Chan 1992, Potisk 1995). With high frequency currents, repetitive stimulation of the common peroneal nerve or sural nerve of the affected lower extremity of subjects with chronic stroke was found to reduce spasticity in the ankle plantarflexors (Levin and Hui-Chan 1992, Potisk 1995). Using a randomized, placebo-controlled design, Hui-Chan and her team showed significant increase in stretch reflex latencies and reduction in spasticity after 45 to 60 minutes of transcutaneous electrical nerve stimulation when compared to the results of placebo stimulation (Hui-Chan and Levin 1993, Levin and Hui-Chan 1992). Low frequency currents of 20 Hz at sub-motor threshold intensity have also shown anti-spastic effects (Walker 1982). More specifically, transcutaneous electrical nerve stimulation produced both segmental and heterosegmental influences

on the hyperactive stretch reflexes (Hui-Chan and Levin 1993). Thus, whether the TES was applied to the median nerve, common peroneal nerve or saphenous nerve, ankle plantarflexor stretch reflex excitability and spasticity could be reduced (Hui-Chan and Levin 1993, Walker 1982). Hui-Chan and Levin (1993) suggested that the effect on spasticity could be attributed to a decrease in the hyperactive stretch reflexes they found.

Yan (2002) has shown that a 3-week programme of 100 Hz TES given to 4 acupoints of the affected lower extremity during acute stroke reduced the development of ankle plantarflexors spasticity. This finding agrees with that of Han and his colleagues (1994) who applied TES to the Hegu (LI4), Zusanli (ST36) and Changshan (B57) acupoints of subjects with spinal cord injury. However, Han and colleagues (1994) and Sonde's group (1998) found that currents of frequencies as low as 2 Hz were not effective in reducing spasticity in the context of their studies.

1.5.1.2 Effects on motor recovery

Electrical stimulation of motor points, acupoints or peripheral nerves at current intensities above the motor threshold elicits contractions of the innervated muscles. In people with chronic stroke, Sonde and colleagues (1998) showed that in addition to conventional rehabilitation, low frequency (1.7 Hz) transcutaneous electrical nerve stimulation to elbow and wrist extensors of the paretic UE given 60 minutes daily for 3 months resulted in greater increases in Fugl Meyer motor scores than were seen among the controls. Wong and co-workers (1999) first reported their study on applying TES at 8 acupuncture points of the paretic extremities in people recruited at 10 to 14 days after stroke onset. In their randomized controlled trial involving 108 subjects, the experimental group received 10 30-minute sessions of

TES at 20-25 Hz and at intensities to elicit muscle contraction, in addition to conventional rehabilitation. These subjects demonstrated better improvements in Fugl Meyer motor scores and ADL functions than the controls receiving only conventional rehabilitation. Interpretation of the results, however, was limited by the lack of double-blind and placebo control, clarification of the randomization procedure, and evidence for carryover effects.

In a randomized placebo-controlled study involving subjects less than 4 weeks after stroke onset, Chae and colleagues (1998) compared the results of TES of the motor points of the affected UE for wrist and finger extension with that of sham stimulation at sensory threshold intensity. The treatment programmes involved 15 1-hour sessions of electrical stimulation with currents at 25-50 Hz. The experimental group was found to have larger gain in Fugl-Meyer UE motor scores, and the effect lasted 4 weeks. Tekeoõlu and colleagues (1998) applied 30 minutes of high frequency electrical stimulation (100 Hz) transcutaneously to the affected triceps and ipsilateral common peroneal nerve of subjects recruited at 1 to 8 months of stroke. After 40 sessions of treatment over 8 weeks, these subjects showed significant improvements in their Barthel Index scores. However, subjects receiving placebo stimulation did not show any improvement.

Intensive electrical stimulation protocols from 30 minutes to 6 hours daily to the paretic UE and given 4 to 8 weeks early within 4 weeks of stroke appear to induce better improvement in muscle strength of the affected UE than that of only conventional rehabilitation (Chantraine et al. 1999, Faghri et al. 1994, Powell et al. 1999, Sonde et al. 1998, Wong et al. 1999). Subjects with less motor impairment at baseline also seem to be a common characteristic in illustrating favourable response to treatment with electrical stimulation (Cauraugh et al. 1992, Francisco et al. 1998,

Gritsenko and Prochazka 2004, Hummelsheim et al. 1997, Kimberley et al. 2004, Kraft et al. 1992, Powell et al. 1999, Sonde et al. 1998). Other effects such as those on shoulder subluxation have been more controversial when applied in acute stroke (Chantraine et al. 1999, Linn et al. 1999). On the other hand, the motor and functional effects from TES have not been consistently shown to last long after the treatment ended (Chae et al. 1998, Chantraine et al. 1999, Linn et al. 1999, Powell et al. 1999, Sonde et al. 1998).

Taken together, the studies reviewed above have shown an improvement in UE muscle strength and UE functional ability with TES to nerves, muscles or acupuncture points of the paretic extremity. Nevertheless, the efficacy of applying TES to the paretic UE in the acute stage for promoting its recovery of motor function and dexterity is still to be confirmed.

### *1.5.2 Electro-acupuncture*

In traditional Chinese medicine (TCM), early application of acupuncture in treatment of stroke has a long history. Since the Tang dynasty, the stimulation of selected body sites, called acupuncture points (termed here "acupoints" from now on) with needles or, more recently, with electricity, has been suggested as a treatment to improve the symptoms (Huang and Yue 1997, Li and Shen 1998) and promote subsequent recovery from stroke (Hu et al. 1993, Hu and Gu 1999, Johansson et al. 1993, Kjendahl et al. 1997, Magnusson et al. 1994, Naeser et al. 1994, Sällström et al. 1996, Si et al. 1998, Zhang and Ni 1998).

In a randomized controlled study, Hu and co-workers (1993) applied a course of electro-acupuncture to patients within 36 hours after stroke onset. They found that compared to subjects with only conventional treatment, 12 sessions of electro-

acupuncture, given 30 to 60 minutes per session for 4 weeks, resulted in better improvement in neurological impairment as measured by the Scandinavian Stroke Scale, and in daily living activities as measured by Barthel Index, especially amongst subjects with poor baseline function. Si and co-workers (1998) conducted a double-blind, randomized controlled trial on 42 subjects within 5 days of stroke. Subjects receiving electro-acupuncture and heparin treatment had better neurological recovery upon discharge when compared with that of the controls who received only drug treatment. Other randomized controlled studies have also reported better motor recovery and quality of life in subjects who completed 20 to 24 sessions of acupuncture over 6 to 10 weeks additional to conventional rehabilitation, with effects lasting as long as one year (Johansson et al. 1993, Kjendahl et al. 1997, Sallstrom et al. 1995). However, the effects might have resulted from the increased additional treatment of the experimental group compared to that of the controls.

The results of another 2 double-blind, randomized, placebo-controlled trials did not support the traditional belief that electro-acupuncture aids recovery from stroke. Gosman-Hedström and co-workers (1998) randomized 104 patients into deep, superficial and no acupuncture treatment groups around one week after stroke onset. The acupuncture treatments were given for 30 minutes each session, twice a week for 10 weeks. Neurological and functional recovery was not different between the deep acupuncture group and the other 2 control groups. Johansson and colleagues (2001) introduced electro-acupuncture to the paretic extremities of patients (n = 48) with moderate to severe stroke at 5 to 10 days after stroke onset. Their 2 control groups were given either low frequency (2 Hz) TES at high current intensity (n = 51) or sub-sensory threshold stimulation from high frequency (80 Hz) currents (n = 51). The treatment protocol for each group was 30 minutes per session,

twice a week for 10 weeks. Again, the changes in motor function (in terms of the Nine Hole Peg Test, Rivermead Mobility Index score and 10-metre walk), ADL function and perceived health were not different among the groups. One might comment that the less frequent treatment protocols could have accounted for the lack of detectable effects. Moreover, more sensitive measurement methods for strength and disability might be required to detect possible effects.

### *1.5.3 Effects of peripheral electrical stimulation on upper extremity recovery – a meta-analysis*

From reports in the literature, peripheral electrical stimulation of motor points, acupoints and peripheral nerves could possibly improve motor impairment of the paretic extremity and ADL performance in patients with stroke. To compare the effectiveness of various treatments in terms of recovery in the paretic UE, a review on the effect sizes of the studies which included a randomized controlled design should provide useful information. Effect size represents "the degree to which the phenomenon is present in the population" (Cohen 1977). It is an index of the difference between two group means relative to the pooled standard deviation in the sample studied. An effect size of 0.2 signifies a small effect, 0.5 a medium effect and 0.8 a large effect.

#### 1.5.3.1 Meta-analysis procedure

The Medline, the CAJ Full-text Database (中國期刊全文數據庫), and BMdisc (中國生物醫學文獻數據庫) were searched with the keywords 'electrical stimulation', 'acupuncture', 'randomized controlled trials', 'recovery' and 'stroke'.

The search covered reports published before January 2001. Reports were selected for inclusion if they met all of the following criteria:

(1) involved patients with a diagnosis of stroke;

(2) reported randomized controlled trials comparing the effects of treatment programmes involving transcutaneous electrical stimulation or electro-acupuncture with the results of conventional stroke management or rehabilitation or placebo stimulation;

(3) involved outcome assessments in terms of specific UE motor impairment in muscle strength and muscle tone, or UE functional ability such as dexterity, or global motor impairment and disability measured with clinical scales which have been published in refereed journals in English or Chinese;

(4) reported data that were readily retrieved for calculating the effect sizes of the outcomes, using the formulae introduced by Hunter and Schmidt (2004) and Wolf (1986) (Appendix I).

1.5.3.2 Results - Effect size of motor impairment and functional ability outcomes

The author (AYS) found a total of 10 studies meeting the screening criteria. Table 1 summarizes the effect sizes from these 10 studies. There were 5 studies of transcutaneous electrical stimulation which involved 283 subjects. The 5 studies of electro-acupuncture involved 276 subjects.

The effect sizes in terms of motor impairment recovery for the 5 studies of transcutaneous electrical stimulation were small to excellent, ranging from 0.14 to 1.62, while the effects on disability in activity functions ranged from 0.15 to 4.44 (Table 1). The unbiased pooled random effect of motor impairment recovery for the 5 studies was 1.05 (95% confidence interval = 0.89- 1.20), and that of the disability

**Table 1: Recovery of stroke-induced dysfunction in the paretic upper extremity: Effects of (a) transcutaneous electrical stimulation, and (b) electro-acupuncture in randomized controlled trials.**

| Authors | Sample size | Type of stroke | Duration of stroke | Treatment protocol | Outcome measures | Effect Size: Motor impairment | Effect Size: Functional ability |
|---|---|---|---|---|---|---|---|
| *(a) Treatment with transcutaneous electrical stimulation* | | | | | | | |
| *# Chae et al. (1998) | E: 14<br>C: 14 | Infarct & haemorrhage | ≤4 weeks | E: FES (25 - 50 Hz), 60 min/day to paretic wrist and finger extensors, 5 days/week, total 15 sessions + CR<br>C: placebo FES with only sensory threshold stimulation + CR | Fugl-Meyer Assessment – upper limb, FIM | 0.78 | 0.15 |
| * Powell et al. (1999) | E: 15<br>C: 18 | Infarct & haemorrhage | 2-4 weeks | E: 90 min FES (20 Hz) to paretic wrist and finger extensors daily for 8 weeks + CR<br>C: CR | Ashworth scale, Isometric wrist extensor strength, ARAT, 9-hole peg test, Rankin scale, BI | - | 1.00 |
| Sonde et al. (1998) | E: 26<br>C: 18 | Not mentioned | 6 – 12 months | E: TENS (1.7 Hz) to wrist and elbow extensors of the paretic extremity, 60 min/day, 5 days/week for 3 months + physiotherapy twice/week<br>C: physiotherapy twice/week | Ashworth scale, Fugl-Meyer Motor Performance Scale, BI | Less severe: 2.81<br>More severe: 0.14 | 0.40 |
| *# Tekeoõlu et al. (1998) | E: 30<br>C: 30 | Not mentioned | 1 – 8 months | E: TENS (100 Hz) to paretic elbow extensor, 30 min/day, 5 days/week. for 8 weeks + CR<br>C: sub-sensory threshold TENS | Ashworth scale, BI | - | 4.44 |
| Wong et al. (1999) | E: 59<br>C: 59 | Infarct & haemorrhage | 10 – 14 days | E: TES (20-25 Hz) on acupoints of limbs, 30 min/day, 5 days/week for 2 weeks + CR<br>C: CR | Brunnstrom staging, FIM | 0.53 | 0.37 |

*(b) Treatment with electro-acupuncture*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *# Gosman-Hedström et al. (1998) | E: 37<br>C: 33 | Infarct | 4 – 10 days | E: EA (2 Hz), 30 min/day, 2 days/week for 10 weeks + CR;<br>C: placebo superficial needling + CR | MAS, NHP, Sundaas Index of ADL | -0.10 | 0.09 |
| Johansson et al. (1993) | E: 38<br>C: 40 | Not mentioned | 4 – 10 days | E: manual + EA (2-5 Hz), 30 min/day, 2 days/week for 10 weeks + CR<br>C: CR | Mobility score (validity unclear), BI, NHP | 0.28 | 1.04 |
| * Kjendahl et al. (1997) | E: 21<br>C: 20 | Infarct & haemorrhage | Median 40 days | Followed up of the study of Sallström and colleagues (1996) | MAS, NHP, Sunnaas Index of ADL | 0.76 | 1.05 |
| * Sallström et al. (1996) | E: 24<br>C: 21 | Infarct & haemorrhage | Median 40 days | E: manual acupuncture, 30 min/day, 3-4 days/week for 6 weeks, EA (2-4 Hz) when indicated + CR<br>C: CR | MAS, NHP, Sundaas Index of ADL | 0.44 | 0.41 |
| Si et al. (1998) | E: 20<br>C: 22 | Infarct | <7 days | E: EA, 5/45 Hz, 30 min/day, 5 days/week until discharge + drug<br>C: drug | Chinese Stroke Scale | 0.91 | - |

* denotes studies with blind assessors; # denotes a placebo-controlled study design; abbreviations in alphabetical order: ADL, activities of daily living; ARAT, Action Research Arm Test; BI, Barthel Index; C, control group; CR, conventional rehabilitation; E, experimental group; EA, electro acupuncture; FES, functional electrical stimulation; FIM, Functional Independent Measurement; MAS, Motor Assessment Scale; NHP, Nottingham Health Profile; SSS, Scandinavian Stroke Scale; TES, transcutaneous electrical stimulation; TENS, transcutaneous electrical nerve stimulation

outcome was 1.25 (95% confidence interval = 1.12-1.39).

For the motor impairment and disability outcomes of the 5 studies on electro-acupuncture, the effect sizes ranged from negative or small (Gosman-Hedström et al. 1998) to excellent (Kjendahl et al. 1997). The unbiased pooled random effect from the 5 studies was small for motor impairment recovery (effect size = 0.44, 95% confidence interval = 0.48-0.64), and medium for disability outcomes (effect size = 0.63, 95% confidence interval = 0.49-0.76).

1.5.3.3 Discussion on the meta-analysis

Previous summaries of research on transcutaneous electrical stimulation (de Kroon et al. 2002, Van Peppen et al. 2004) or acupuncture (Sze et al. 2002) had noted small or no benefits in terms of recovery of motor function after stroke. The present meta-analysis of 10 studies has revealed more information about the effects of peripheral electrical stimulation. The effect sizes in terms of motor impairment and functional recovery produced by transcutaneous electrical stimulation were larger than those by electro-acupuncture. The effect of electro-acupuncture on motor impairment was small. It must be noted that in these studies, motor impairment was measured by clinical composite scales on motor functions of the whole body. Focal improvements such as muscle strength in the paretic hand would be difficult to delineate. Moreover, the limited scoring range could make the scale less sensitive to reveal any improvements made. For example, the three arm items of the Motor Assessment Scale, whose individual item score ranged from 0 to 6, were found having small to moderate sensitivity in detecting the improvement of subjects with stroke (Hsueh and Hsieh 2002). It was also found that intensive electrical stimulation protocols that involved 3 weeks or more of daily treatment had medium

(> 0.5) to large (> 0.8) effect size of outcomes in terms of motor impairment and functional ability. Two of the studies (Chae et al. 1998, Tekeoŏlu et al. 1998) included placebo controls and blind assessors. The protocols that involved less frequent treatment such as 2 days a week (Gosman-Hedström et al. 1998, Johansson et al. 1993) or a shorter treatment period of 3 weeks (Wong et al. 1999) appeared to produce negligible or smaller effects.

## 1.6 Rationale and Objectives of the Study

### *1.6.1 Rationale*

Even today, effective treatments that reliably enhance the recovery of sensation and motor functions in the paretic UE after stroke have not been clearly identified. Task-related training has limited application to the completely paretic UE because the presence of some volitional movements in the extremity is required to practise the tasks actively. Evidence supporting the effectiveness of intensive exercise programmes applied at the rehabilitation or chronic stage of stroke has mainly been obtained from treating people with less impaired upper extremities. Although impairment of somato-sensation is another consequence of stroke, it appears to be less addressed in conventional rehabilitation. There have been only two studies with case study or case-control designs that examined the effects of sensory re-education on sensory recovery in the paretic UE (Carey et al. 1993, Yekutiel and Guttman 1993). Both studies involved subjects with chronic stroke and training in active manipulative tasks. Therefore, with task-related exercises, any treatment-induced recovery in the affected UE could be associated with neuromuscular adaptations driven by repetitive use of the UE.

When applying peripheral electrical stimulation, intensive programmes of daily treatment for 3 or more weeks appear promising (as discussed in section 1.5.3.3). There is evidence for an effect on spasticity. Hypertonicity in the affected extremities was either reduced when peripheral electrical stimulation was applied during chronic stroke (Levin and Hui-Chan 1992, Tekeoŏlu et al. 1998), or was delayed from developing when it was applied at the acute stroke stage (Chae et al. 1998, Kjendahl et al. 1997, Yan 2002, Yan et al. 2005). Studies with intensive programmes of transcutaneous electrical stimulation or electro-acupuncture have also shown improvement of muscle strength of the paretic extremities (Chae et al. 1998, Kjendahl et al. 1997, Levin and Hui-Chan 1992, Powell et al. 1999, Si et al. 1998, Wong et al. 1999, Yan 2002). It has been suggested that these treatment effects resulted from excitation of the large diameter fibres to exert pre-synaptic inhibition of the hyperactive stretch reflex (Levin and Hui-Chan 1993) as well as a decrease in EMG co-contraction (Levin and Hui-Chan 1992, Yan 2002). On the other hand, treatment effects in terms of functional recovery such as dexterity of the hand remain controversial. Moreover, favourable results have mainly been confirmed only shortly after the treatment ceased.

Animal studies with experimental stroke models have shown that electro-acupuncture can reduce acute brain infarct by limiting the release of toxic oxidative enzymes and excitatory amino acids (Guo and Cheng 2000, Jin and Cheng 1998, Zhao and Cheng 1997, Zhao et al. 2000). Based on these findings, early application of electrical stimulation to the acupoints might induce protective effects against neuronal injury during acute stroke. This could lead to less neurological impairment and disability. Equally important is that, based on the growing knowledge in sensory and motor cortical plasticity, repetitive electrical stimulation might be able to

facilitate unmasking of cortical neuronal synapses in acute stroke and induce long-term potentiation of synapses to enhance the recovery process (refer to section 1.3.4).

Indeed, acupoints have rich innervations of muscle spindles, touch and pressure receptors (Wang and Liu 1989). When the UE is mainly paretic during the acute stage of stroke, repetitive stimulation to the acupoints in the UE could stimulate large diameter fibres to provide early sensori-motor experience necessary to guide plastic reorganization of cortical neural networks for UE recovery.

Electrical stimulation programmes reported in the literature have mostly commenced during rehabilitation or the chronic stage of stroke, ranging from 2 weeks to 74 months after stroke onset. Only one study by Hu and coworkers (1993) applied electro-acupuncture within 36 hours after stroke onset as a first treatment. They reported promising recovery in both neurological impairment and ADL function as measured by global clinical outcome measures, when compared to subjects with standard medical treatment and rehabilitation. A few studies involving electrical stimulation of the paretic muscles or the respective nerves have shown localised motor improvement in the muscles (Levin and Hui-Chan 1992, Powell et al. 1999, Yan et al. 2005). It is necessary to delineate the specific effects of electrical stimulation on the recovery of stroke-induced dysfunctions pertaining to the paretic UE under treatment, using reliable and sensitive outcome measurements. Moreover, monitoring the carry-over effects of the treatment would help to confirm its true efficacy.

### *1.6.2 Study objectives and hypotheses*

The main objective of this study was to investigate the effectiveness of an intensive programme of transcutaneous electrical stimulation (TES) of acupoints

during acute stroke in terms of recovery in the paretic UE. The study had two hypotheses:

1. TES applied to acupoints during acute stroke would have resulted in earlier and better recovery of somato-sensation, muscle strength and functional use of the paretic UE;
2. Such early TES therapy would have produced carry-over effects on sensori-motor and functional recovery in the paretic UE.

To date, the characteristics about the recovery of motor functions in the paretic UE after stroke have been referenced with studies more than a decade ago. With the advancement of acute stroke medical management, the time course and extent of recovery in the paretic UE with conventional rehabilitation might have altered. Moreover, an updated knowledge about these characteristics of UE recovery in the local population could be useful reference for the main study. Two other studies were therefore conducted on subjects undergoing conventional stroke management and rehabilitation in local hospitals with the following objectives:

Study 1: To identify characteristics of the time course and extent of sensory and motor function recovery of the paretic UE in the first 6 months of stroke;

Study 2: To identify early clinical characteristics that could predict the recovery of functional dexterity in the paretic UE at 3 and 6 months after stroke.

# *Chapter 2*

## *Methodology*

**Summary**

This thesis has 3 objectives:

(1) To examine the time course and extent of sensory, motor and functional recovery of the paretic UE from within 5 days after stroke onset to 6 months afterwards in patients receiving conventional rehabilitation;

(2) To identify early predictors favourable to the recovery of functional dexterity in the paretic UE;

(3) To determine the effects of a 4-week transcutaneous electrical stimulation (TES) programme applied during the acute stage of stroke on stroke-induced sensori-motor dysfunctions of the paretic UE.

To address objectives (1) and (2), a longitudinal cohort study design was adopted. A double-blind, randomized, placebo-controlled design was used to achieve objective (3). Subjects were recruited from an acute hospital following a set of inclusion-exclusion criteria. They had a diagnosis of first ischaemic stroke and were within 5 days since stroke onset. All of them received conventional rehabilitation (CR). Those subjects who were recruited within the first 46 hours after stroke onset were randomly allocated to 1 of the 3 groups: (1) TES group - Subjects received TES delivered as 200 μsec pulses at 20 Hz and at an intensity 2.5 to 3 times sensory thresholds to 6 acupoints, 60 minutes per day, 5 days per week for 4 weeks; (2) placebo-TES group - Subjects received a similar TES programme but with the circuitry of the TES units removed; or (3) control group - Subjects received only CR. The sample size of each group was calculated a priori based on the pooled effect size of 5 randomized controlled trials in a meta-analysis presented in Chapter 1.

The outcome measurements were assessed on the paretic UE. They included tactile sensation of pressure sensibility and two-point discrimination in the index

finger, muscle tone, muscle strength of the shoulder, elbow, power grip and index pinch grip, and functional ability of the paretic UE in performing grasping, gripping and pinching tasks. The screening and baseline assessments at recruitment were conducted by a research physiotherapist blinded to the treatment allocated at that stage. Follow-up assessments were conducted at 8 time intervals by the investigator (AYS) who was blinded to the allocation of subjects to groups - weekly in the first 4 weeks, then at 8, 12, 16 and 24 weeks after the baseline assessment.

In the pilot study on data repeatability, results of the intra-class correlation coefficients (ICC) confirmed high intra-rater and inter-rater reliability (ICC ≥0.90) for the sensory, muscle strength and functional ability outcomes, and moderate inter-rater reliability (ICC = 0.66) for the measurement of muscle tone.

Statistical methods used to examine the data included descriptive statistics in analysing the baseline characteristics of the subjects, standardized response means (SRM) in illustrating the magnitude of improvement of an outcome measurement, and repeated measures analysis of variance (ANOVA) for within-group changes in the paretic UE across the 24 weeks of assessments. Logistic regressions and Receiver Operating Characteristic (ROC) curves were used to identify the early predictors for return of functional dexterity in the paretic UE. In the main study, mixed model analysis of covariance (ANCOVA) was used in comparisons of the outcome measures among the 3 groups so as to delineate the effects of the TES programme.

## 2.1 Introduction

This chapter describes the methodology to address the 3 objectives listed in Chapter 1. The time course of sensory, motor and functional recovery of the paretic UE of patients receiving conventional rehabilitation (CR) was examined from shortly after stroke onset and followed up to 6 months afterwards with a prospective longitudinal study design. Clinical variables which were predictors for the recovery of useful UE function were then identified in the same cohort. The main study aimed to delineate the effects of an intensive TES programme applied to the paretic UE during the acute stage of stroke. A randomized clinical trial with double-blind, placebo-control design was adopted.

Ethics approval was granted by 3 hospitals of the Hospital Authority. Ruttonjee Hospital was involved where subjects were recruited for the studies on measurement reliability conducted in year 2000. The Queen Elizabeth Hospital and Kowloon Hospital were involved in the studies to address the 3 objectives. They are providing acute stroke management and extended rehabilitation services, respectively, for the central and eastern Kowloon districts in Hong Kong. Data collection started in March 2001 in these 2 hospitals and finished in January 2004 when the last subject completed the 6-month follow-up assessments.

Patients admitted to the medical and acute stroke units of Queen Elizabeth Hospital were screened according to the inclusion and exclusion criteria by a research physiotherapist, who had completed training on both the screening assessment and the outcome measurements. Screening assessments included the patient's medical and premorbid history, muscle strength of the UE contralateral to the side of brain lesion rated by the Motricity Index (MI) (Demeurisse et al. 1980),

and level of consciousness measured by the Glasgow Coma Scale (Teasdale and Jennett 1974).

## 2.2 Subjects

### *2.2.1 Inclusion criteria*

Subjects were included if they

(a) were older than 45 years old,

(b) were experiencing their first stroke,

(c) were diagnosed with an ischaemic type of stroke with unilateral involvement,

(d) had the stroke within 5 days after onset of symptoms;

(e) demonstrated muscle weakness with a score of MI (Demeurisse et al. 1980) less than or equal to 77 in the UE contralateral to the side of brain lesion, i.e., able to work against some manual resistance but weaker than the opposite UE;

(f) had signs of muscle weakness of the paretic UE lasting beyond 1 week after stroke onset.

### *2.2.2 Exclusion criteria*

Subjects were excluded if they

(a) had reduced consciousness indicated by a score of 13 or less on the Glasgow Coma Scale (Teasdale and Jennett 1974);

(b) had neurological deficits lasting less than 24 hours;

(c) had complete recovery of the stroke-induced sensori-motor deficits one week after stroke onset;

(d) had second or recurrent stroke;

(e) presented with severe communication deficits;

(f) had premorbid disability involving the upper body resulted from other neurological, musculoskeletal or cardiopulmonary disorders;

(g) had a cardiac pace-maker of the demand type.

### *2.2.3 Randomization procedure*

Subjects were randomly allocated to 3 groups:

(a) a TES group who received transcutaneous electrical stimulation (TES) applied to 6 acupoints for a total of 20 sessions (section 2.3.1) in addition to conventional rehabilitation (CR) (section 2.3.3);

(b) a placebo-TES group who received placebo TES treatment for 20 sessions in addition to CR (section 2.3.2);

(c) a control group who underwent only CR in the acute and rehabilitation hospitals.

After screening by the research physiotherapist, patients whose condition fulfilled the inclusion-exclusion criteria of recruitment, and who had a stroke within 46 hours after stroke onset, were allocated to 1 of the 3 groups by simple randomization. Simple randomization was carried out by the physiotherapist drawing 1 lot from an envelope containing 3 paper lots - one for each of the TES, placebo-TES and control groups. Subjects who had their stroke onset time beyond 46 hours at recruitment remained receiving CR only as that of the control group. The aims and protocol of the study were explained to all subjects before they signed an informed consent (Appendix II).

### *2.2.4 Sample size and study power*

The sample size for this study was calculated using the Power Analysis of Sample Size (PASS, version 6.0) statistical software package. The effect sizes for strength and for functional outcome were adapted from the summarized unbiased data of the meta-analysis on 5 studies of RCT on transcutaneous electrical stimulation for UE recovery (Chae et al. 1998, Powell et al. 1999, Sonde et al. 1998, Tekeoðlu et al. 1998, Wong et al. 1999) described in Chapter 1, section 1.5.3. For the recovery of UE motor impairment, the summarized unbiased effect size was 1.05 (95% C.I. = 0.89-1.20); that of recovery from the associated disability was 1.25 (95% C.I. = 1.12-1.39). The effect size for motor impairment recovery being smaller was used in the statistical evaluation of the sample size. With an alpha level set as 0.05 and power set as 0.8 ($\beta = 0.20$), the sample size was calculated to be 16 per group for comparisons among 3 groups. Presuming that there would be a drop out rate of 20% subjects during the course of treatment, an extra 3 subjects were recruited to each group, making a total of 19 per group.

## 2.3 Treatment protocol

### *2.3.1 Transcutaneous Electrical Stimulation (TES)*

TES was given to the subjects within 46 hours after their stroke. The treatment was applied for 60 minutes a day, 5 days a week for 4 consecutive weeks for a total of 20 sessions.

TES was applied to 6 acupoints – GB20 (Fengchi) at the sub-occipital region on both sides of the neck, LI 15 (Jianyu), LI 11 (Quchi), LI 10 (Shousanli) and LI 4 (Hegu) of the paretic UE. Figure 2.1 illustrates their locations on the body. A

description of their anatomical positions is listed in Table 2.1. These were acupoints of the *yang* meridian. In traditional Chinese medicine, GB 20 has been commonly treated during very acute stage of stroke to address the conscious level, and to regulate the functioning of *qi* and brain circulation (Ho et al. 1997, Zhang and Ni 1998). LI 15, LI 11, LI 10 and LI 4 of the Large Intestine Meridian are common acupoints in the treatment of stroke-induced UE paresis (Chen et al. 1988, Ho et al. 1997, Qi et al. 1986, Zhang et al. 1987).

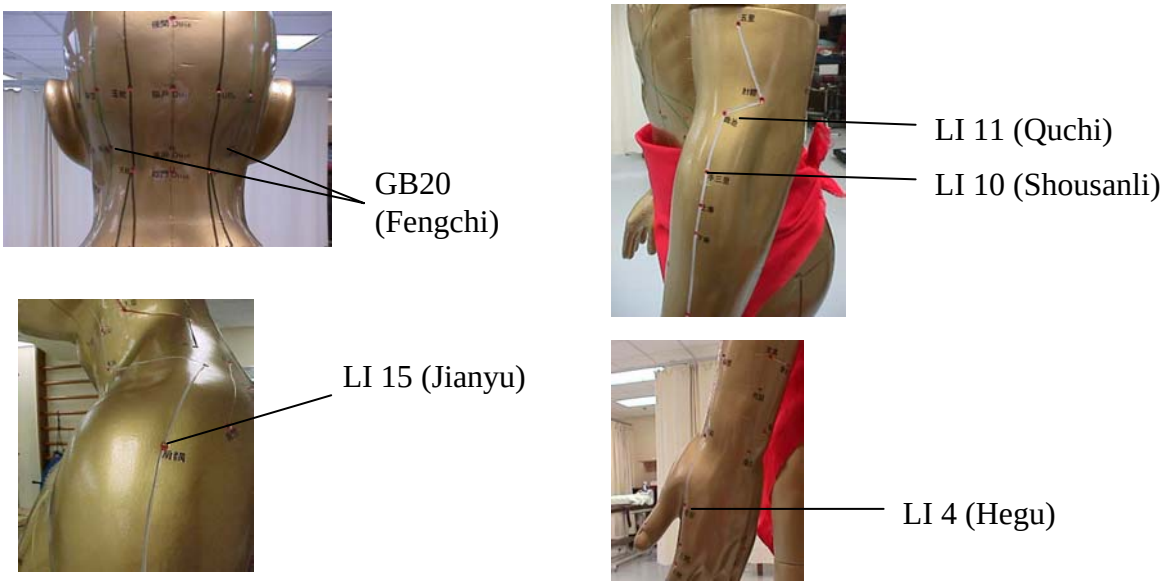


Figure 2.1: The 6 acupoints selected as sites for placement of TES electrodes

**Table 2.1: Anatomical positions of the 6 acupoints to which TES was applied**

| Acupoint | Channel | Anatomical Position |
|---|---|---|
| GB 20 (Fengchi 風池) | Gall bladder meridian of Foot-Shaoyang | Below the occipital bone and located in the depression between the sternocleidomastoid and upper trapezius muscles |
| LI 15 (Jianyu 肩髃) | Large intestine meridian of Hand-Yangming | A point at the antero-inferior depression of the acromion between the anterior and middle fibres of the deltoid muscle located when the arm is in $90^{o}$ of abduction. |
| LI 11 (Quchi 曲池) | Large intestine meridian of Hand-Yangming | A point midway between the lateral end of the cubital crease and the lateral epicondyle of the humerus when the elbow is placed at $90^{o}$ flexion. |
| LI 10 (Shousanli 手三里) | Large intestine meridian of Hand-Yangming | A point two cun distal to LI 11 on an imaginery line which connects the distal radial styloid process and LI 11 |
| LI 4 (Hegu 合谷) | Large intestine meridian of Hand-Yangming | A point on the dorsum of the hand and located lateral to the midpoint of the second metacarpal in the adductor pollicis muscle. |

Stimulation consisted of 200 $\mu$ sec square pulses at 20 Hz and an intensity 2.5 to 3 times sensory thresholds that was maximally tolerable was delivered to the subjects, from 3 channels of 2 TES units (model 120Z®, ITO Co. Ltd., Tokyo, Japan) to the acupoints described above, via 3 pairs of round surface electrodes (Figure 2.2). The electrodes were arranged as follows: the first pair with the cathode on LI 4 and the anode on LI 10, the second pair with the cathode on LI 11 and the anode on LI 15, and the third pair on GB 20 with the cathode and anode respectively on the side contralateral and ipsilateral to the side of brain lesion. At maximal intensity, the stimulation was sufficient to elicit muscle contraction to produce visible wrist movements in most subjects. The maximum stimulation applied to the two GB 20

acupoints that was tolerable to the subjects was lower than that to the other 4 acupoints.

### *2.3.2 Placebo-TES*

Placebo-TES was applied in the same manner as that of TES, except that the electrical circuits of the TES units were disconnected. When the dial was turned on, the green light on the machine was switched on, but unknown to the subjects, there was no current output during the treatment period.

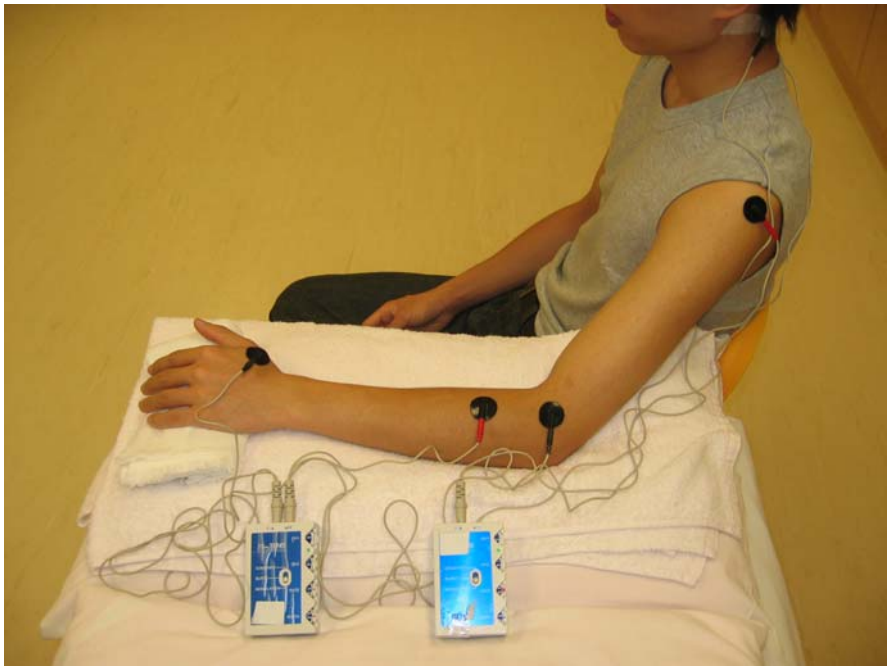

Figure 2.2: The TES units and round carbon electrodes

### *2.3.3 Conventional rehabilitation programme*

The conventional rehabilitation (CR) programme was the usual inpatient and outpatient rehabilitation regime for patients after stroke in Hong Kong. This included the initial short period of daily acute stroke management in the Queen Elizabeth Hospital, followed by 3 to 6 weeks of rehabilitation in the Kowloon Hospital. When the subjects were discharged to their place of residence, the CR programme continued in the outpatient settings, usually at a rate of 2 sessions per week for another 3 to 5 months.

The following description of the CR programme is summarized from a survey conducted in Ruttonjee Hospital of the Hospital Authority, which provides rehabilitation services to patients with stroke from the acute stage as in-patients to the chronic stage as out-patients. The stroke management regime has been similar to that of Queen Elizabeth Hospital and Kowloon Hospital, where patients were recruited for the present study. The in-patient programme included mainly physiotherapy (30 to 60 minutes each day, 5 days a week), occupational therapy (30 minutes once a day for 5 days a week), speech therapy and education on diet when appropriate. The primary objectives in managing stroke during the acute stage were maintaining respiratory function, joint mobility and functional activities in the patient, and providing education to the patient's family or relatives. Treatment included positioning to prevent contractures and pressure sores, active and passive exercises for the chest and limbs, training of balance in sitting and functional activities such as transfer from lying to sitting. Thirty minutes of functional electrical stimulation with Response II was often applied to the paretic lower extremity and occasionally to the paretic upper extremity during the patient's stay in acute stroke wards. In the extended rehabilitation setting, more emphasis was put on

improving patients' functional activities, e.g. dressing, transfer, ambulation and balance in standing and walking. Treatment approaches for improving mobility problems of patients included neuro-developmental approach (Bobath 1976, 1990), motor relearning (Carr and Shepherd 1987), proprioceptive neuromuscular facilitation (Knott and Voss 1968, Voss 1985) and functional electrical stimulation (Baker and Parker 1986, Bowman et al. 1979). At times, sensory re-education was added to those patients with sensory deficits. In order to achieve earlier independence in daily living activities, compensatory movement of the upper limb ipsilateral to the side of lesion was usually taught, while for ambulation, walking aids were usually prescribed when needed early on.

## 2.4 Outcome Measurements and Procedures

### *2.4.1 Measurement battery and intervals*

The research physiotherapist evaluated subjects' performance on these outcome variables in the initial assessment within 24 hours of their recruitment to the study. After informed consent was obtained from a subject, the time of initial assessment from the onset of stroke was recorded in hours. The research physiotherapist recorded the demographic, premorbid and comorbid information, as well as the medical history of each subject. The severity of the neurological insult from stroke was assessed with the National Institutes of Health Stroke Scale (NIHSS) (Brott et al. 1989, Goldstein et al. 1989). Other neurological status such as spatial perceptual impairment and cognition was also assessed. The baseline status of the outcome variables was assessed on the paretic UE. These outcome measurements included: (1) tactile sensation in the distal pulp of the thumb and index finger,

measured by the Semmes-Weinstein Monofilaments® for pressure sensibility and the Mackinnon-Dellon Disk-Criminator™ for two-point discrimination, (2) muscle tone of the elbow flexors evaluated with the Composite Spasticity Score, (3) muscle strength of the paretic UE measured with MI, (4) power grip and index pinch strength measured with a dynamometer, and (5) functional ability of the paretic UE evaluated with the Action Research Arm Test (ARAT). All baseline assessments were conducted within 24 hours after the subjects were recruited. Another physiotherapist (the author AYS) who was not aware of the subjects' allocation to groups reassessed the outcomes at 8 time intervals after the baseline assessment - weekly in the subsequent 4 weeks, and then at 8, 12, 16 and 24 weeks. These reassessment intervals were stated as $W_4$ to $W_{24}$ post-stroke later in the thesis. Note that the clinical characteristics and the outcome variables were measured with tools whose validity and reliability with reference to people with stroke had been documented in literature as highlighted below.

### *2.4.2 Clinical characteristics of stroke*

2.4.2.1 Severity of stroke

The extent of neurological deficits from stroke in the acute stage was measured with a global scale called the National Institutes of Health Stroke Scale (NIHSS) (Brott et al. 1989, Goldstein et al. 1989). The total score of the NIHSS indicates the severity of stroke; the lower the score, the less severe the stroke. The present study adopted the modified version (Goldstein et al. 1989) with a maximum score of 31 from the 13 items of the scale (Appendix III). Goldstein and Samsa (1997) reported that after training with a standardized video recording of patients, professionals who were non-neurologists could conduct the examination with high

intra-rater and inter-rater reliability (intraclass correlation coefficients were 0.93 and 0.95 respectively). Several studies showed that the initial NIHSS score at the acute stage of stroke predicted clinical outcomes with respect to mortality and functional recovery (Adams et al. 1999, Frankel et al. 2000, Muir et al. 1996). In 127 cases of acute ischaemic stroke monitored over 48 hours since admission, DeGraba and colleagues (1999) found that patients with an NIHSS score of 7 or lower showed better chance of early recovery in daily activities, when compared with those having a score greater than 7.

In the present study, the research physiotherapist who performed the screening and recruitment of subjects had been taught by an NIHSS training video. He was the person who conducted the assessment to rate the subjects' initial severity of stroke with NIHSS.

2.4.2.2 Cognition

The cognitive status of subjects was assessed with the Neurobehavioral Cognitive Status Examination (NCSE) (Kiernan et al. 1987). This is a screening test for cognitive dysfunction arising from insults to the cerebral hemispheres. The NCSE assesses 8 domains of cognitive function, namely, level of consciousness, orientation, attention, comprehension of language, visual construction, verbal memory, calculations, and verbal reasoning. It has been found to be sensitive in revealing cognitive impairments resulting from stroke (Osmon et al. 1992), more so than the Mini-Mental State Examination (Mysiw et al. 1989). The cognitive status evaluated with NCSE was also found to predict functional improvement in patients with stroke (Mysiw et al. 1989). In this study, the research physiotherapist

conducted the NCSE test at the bed side of the subjects during their stay in the acute stroke ward in Queen Elizabeth Hospital, when their medical status was stable.

2.4.2.3 Neglect

The presence and degree of neglect or "spatial perceptual deficit" was evaluated with the Line Cancellation Test, which is also called Albert's test (Albert 1973, Fullerton et al. 1986). Studies showed that low scores in this test in the acute stage of stroke predicted poor functional ability at 6 months after stroke onset (Fullerton et al. 1988).

During the test, an A-4 size paper in the landscape orientation was presented to the subject. On the paper were 41 dark lines, each of 2.5 cm in length and drawn with random orientation. There were 20 lines on each side of the midline of the paper, and 1 line in the centre of the paper. Before the test started, the examiner demonstrated to the subject by crossing out this centre line with a pen. Then the subject had to cross out as many lines on the paper as possible. The number of lines being crossed out became the score of the test. The maximum score was therefore 40. In the assessment of visuo-spatial inattention, the Albert's test has been found with good construct validity (Chen and Henderson 1994). In our study, the presence of spatial neglect was defined by 1 or more lines left uncrossed during the test (Albert 1973).

### *2.4.3 Sensation of the paretic upper extremity*

The sensation of the UE contralateral to the side of brain lesion was examined at the distal pulp of the thumb and index finger. Two sensory functions were assessed – pressure sensibility threshold and two-point discrimination.

2.4.3.1 Pressure sensibility threshold (PR)

Pressure (or tactile) sensibility is a type of exteroceptive somatosensation (DeJong 1979). The instrument used to assess this sensory modality is the Semmes-Weinstein Monofilaments® (Figure 2.3). Developed by Semmes and coworkers (1960), this measurement method was reported to have high test-retest reliability in determining pressure threshold (Pearson's correlation = 0.84).

The measurement kit consists of a set of 20 nylon filaments 3.8 cm in length. Each filament is graduated in diameter and calibrated to the logarithm of 10 times force in mg required to bend it, when it is applied perpendicularly to the skin surface under examination. The value of this calibrated graduation ranges from 1.65 to 6.65 which is embossed onto the acrylic rod mounted with the filament of the corresponding diameter. A lower score means better sensibility to contact pressure.

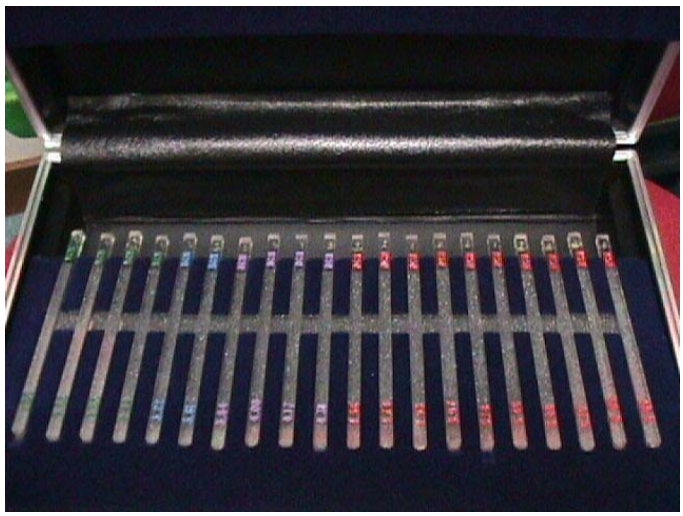

Figure 2.3: The Semmes-Weinstein monofilaments® used to measure the pressure sensibility threshold in fingers

In this study, a value of "7" indicated absence of the sensation even when the skin under test was touched with the thickest filament of 6.65. The Semmes-Weinstein monofilaments® have been shown to yield reproducible force stimuli recorded by a strain-gauge system in both test-retest and inter-tester trials (Bell-Krotoski and Tomancik 1987).

In the present study, subjects rested both upper extremities on a firm support while sitting erect on a chair or in bed during assessment. The filament graduated at 4.31 was applied to the distal pulp of the index finger of the less affected UE ipsilateral to the side of lesion, in order to allow the subject to appreciate the usual sensation in the test. The examiner applied the filament slowly from a distance 2.5 cm above the skin surface of the finger until its tip reached perpendicular to the skin surface, and was bent in a curved shape. After being in contact with the skin surface for about 1.5 second, the filament was slowly lifted off the skin surface. The subject had to report 'yes' immediately upon appreciating the contact of the filament on the skin at the distal pulp of the finger. Once the subject understood the test procedure, he/she was asked to close his/her eyes. The affected UE was then examined with the 4.31 filament on the distal pulp of the thumb first, followed by that of the index finger using the same procedure. If the subject reported 'yes' upon the filament's contact on the skin, the next smaller filament was applied. This procedure continued in a *descending* sequence until the subject could not sense the pressure from the filament being applied to the skin. The filament's graduation was noted as the first pressure threshold value. The procedure was repeated in an *ascending* sequence but started with 2 lightest filaments down the series to confirm no sensation of contact pressure. When the subject reported sensation of the contact pressure again, the graduation of this filament was recorded as the second pressure threshold value. The

PR of the finger was the mean of the 2 graduation values.

2.4.3.2 Two-point discrimination threshold (2-PD)

A score of 2-PD is the smallest distance between 2 stimuli of equal pressure applied simultaneously on the part of the skin when the person is still able to perceive them as 2 distinct stimuli (Kandel and Jessell 1991). This sensibility function of the hand is a somatosensation that combines exteroceptive and proprioceptive sensibilities (DeJong 1979). It has been found to be associated with certain hand functions such as object recognition (Novak et al. 1993, Robertson and Jones 1994). In the present study, the 2-PD threshold of the distal pulp of the thumb and index finger of the paretic UE was determined with the Mackinnon-Dellon Disk-Criminator™ (Dannenbaum and Jones 1993). There were 7 pairs of blunt metal pins as well as 1 single pin mounted on each of the 2 plastic disks (Figure 2.4). The pairs of pins are spaced from 2 to 15 mm apart, which could be read as the scores printed on the 2 disks. The score for the single pin on each disk is recorded as 1. In the present study, a score of "16" represented absence of sensation.

Throughout the assessment procedure, the subject had to keep his/her eyes closed. To begin the assessment, the examiner stabilized the finger to be tested with 1 hand, with the other hand holding the Disk-Criminator™. The pair of pins spaced 5 mm apart was applied perpendicular to the skin of the distal pulp of the thumb, until the skin just became blanch at the area of contact by the two pins. The subject had to report to the examiner whether he/she felt 2 points contacting the skin surface. If the report was correct, the smaller spaced pair of pins from 2 to 5 mm apart alternating with the single pin would be applied randomly to the skin. If the report was incorrect, the pairs of pins spaced larger than 5 mm apart would be used in the

test. The subject continued to indicate to the examiner if he/she could feel 1 stimulus or 2 stimuli. The 2-PD threshold was the smallest distance that the subject was able to feel as 2 distinct stimuli with an accuracy of 80% or more in five trials. In order to let the subject become familiar with the test procedure, trials were conducted on the tip of the subject's thumb ipsilateral to the side of stroke lesion before conducting it on the distal pulp of the thumb and then the index finger of the paretic extremity.

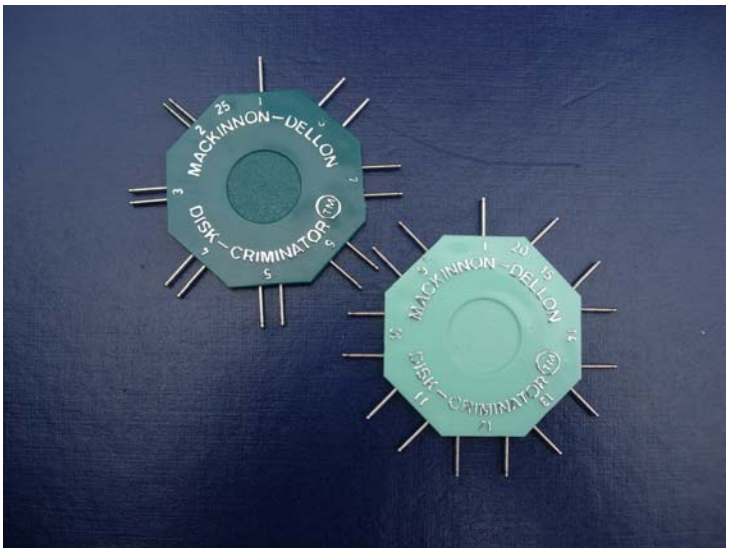


Figure 2.4: The Disk-Criminator™ used to measure the two-point discrimination thresholds in fingers

### *2.4.4 Muscle tone*

The impairment in muscle tone as a result of stroke ranges from no tone (flaccidity) to spasticity over time, due to alterations of tonic and phasic stretch reflexes in the affected muscles (Twitchell 1951). Levin and Hui-Chan (1992) had developed a quasi-quantitate method called the Composite Spasticity Score to measure abnormal muscle tone in the lower extremity of people with hemiparesis (Appendix IV). This clinical measurement of muscle tone consisted of 3 parts: (1) tendon jerk scored on a 5-point scale – a score of 0 as no response, 2 as normal and 4 as maximally hyperactive jerk; (2) resistance to passive stretch of the muscle over the range of joint motion at a fast speed, rated in 5 levels similar to that of the modified Ashworth Scale (Bohannon and Smith 1987) but with the score doubled in weighting – a score of 0 for no resistance, 4 for normal resistance and 8 for maximal resistance against passive stretch; and (3) ankle clonus. Note that this method of scoring muscle tone has been proven to have a high degree of test-retest reliability (ICC = 0.87) in rating spasticity of the lower extremities in subjects with chronic hemiparesis (Levin and Hui-Chan 1993). Gregson and coworkers (2000) who evaluated the muscle tone of elbow flexors in terms of the resistance to passive stretching, also reported high inter- and intra-rater agreement (Kappa statistics $\kappa$ ranged from 0.77 to 0.96 and from 0.77 to 0.83 respectively).

In the present study, the rating of muscle tone of the paretic UE was modified from the Composite Spasticity Score. Muscle tone was examined on the elbow flexors with the subject sitting erect either on a chair with a back support or in bed with the head and trunk supported. The examiner graded the muscle's resistance to passive stretching, i.e., the tonic stretch reflex, and the biceps tendon jerk for its phasic stretch reflex, according to the rating guideline of the Composite Spasticity

Score. A score from 0 to 5 indicated hypotonicity of the muscle; normal tone was scored 6; 7 to 12 indicated hypertonicity or spasticity.

### *2.4.5 Muscle strength*

2.4.5.1 Motricity Index (MI)

The Motricity Index (MI) is a validated measure of strength impairment of the limb muscles of an extremity after stroke (Demeurisse et al. 1980). It was proven to be reliable and sensitive to changes in muscle strength during the course of recovery from acute stroke (Collin and Wade 1990, Sunderland et al. 1989). For the UE, 3 muscle actions were evaluated when the subject rested in a sitting position on a chair or in bed. These include shoulder abduction, elbow flexion and pincer movement of the index finger to the thumb. With reference to the performance of the extremity ipsilateral to the side of lesion, the muscle strength for each action of the affected UE was scored on a 5-point ordinal scale, with weighted scores ranged from 0 for no muscle activity to 33 for normal muscle strength (Demeurisse et al. 1980). The scoring criteria are described in Appendix V. The composite MI score of the UE was the summation of the shoulder-, elbow- and pincer-subscores plus 1 (Demeurisse et al. 1980). A full score of 100 indicates normal strength. This scoring has the advantage of convenience and quick application in patients with acute stroke.

2.4.5.2 Power grip strength (GRIP)

Dynamometry measurement of strength has the advantage of evaluating motor function on a continuous scale, making it more sensitive to detect slight changes of strength in the paretic UE over time or as a result of therapeutic

interventions. Hand grip strength was reported as a good predictor for the return of upper extremity function after stroke (Heller et al. 1987, Sunderland et al. 1989). In 2 prospective studies on patients with acute stroke, Heller's (1987) and Sunderland's groups (1989) found the presence of grip strength in the first month to be a good predictor of early functional recovery of the affected UE. It has also been shown by Colebatch and Gandevia (1989) that the UE ipsilateral to the stroke lesion also presented with weakness. Information from this less affected extremity would not be suitable for reference in evaluating the extent of recovery in the contralateral UE. In the present study, GRIP of the paretic UE contralateral to the side of stroke was measured in kilogramme (kg), using an MIE Digital Dynamometer (MIE Medical Research®).

The MIE Digital Dynamometer was an electronic dynamometer consisting of 2 padded metal bars with a built-in force transducer and a digital force display unit (Figure 2.5). The 2 bars are mounted on a horizontal metal cleat so that they are parallel to each other at a distance of 28 mm apart, a distance considered by all subjects to be comfortable during hand grip assessments. In a pilot test prior to this study, this dynamometer had demonstrated a lower percentage error (less than 8%) in the range of force below 2 kg when compared with that of the JAMAR dynamometer, which had a measurement error of greater than 40% with force below 2kg. The MIE Digital Dynamometer could measure a very small force of only 0.1 kg. Since subjects with acute stroke often present with nil or minimal grip strength, and the smallest recovery of grip strength should be detectable, this equipment was used to measure hand grip strength in the present study.

During the measurement of power grip strength, the subject sat on a chair with back and feet supported, or sat upright in bed with the head and trunk supported.

His/her paretic UE rested by the side of the trunk with the elbow bent in 90$^{o}$ and the forearm in mid-pronation. With the examiner holding the mounting bar of the force transducer, the subject placed the hand to be tested on the 2 metal bars so that the ulnar border of the palm was 2.5 cm from the distal end of the bars. With the digital display of the dynamometer force output turned away from the subject, the latter practised 1 trial grip of the bars using approximately 50% of maximal effort. The subject was then instructed to perform a maximal grip under the examiner's verbal encouragement. The peak grip force was recorded on the digital display of the dynamometer. After a rest of about 30 seconds, another 2 trials of power grip were measured with a brief rest between the trials.


Figure 2.5: The MIE Digital Dynamometer with a force transducer mounted on the metal bars and a digital display of force output

2.4.5.3 Index pinch strength (PINCH)

Pinch strength as an outcome measurement has been adopted in a few intervention studies for recovery of the involved UE (Conforto et al. 2002, Dromerick et al. 2000, Hurvitz et al. 2003). Its measurement by dynamometry has been proven to have good reliability in normal adults (Mathiowetz et al. 1984, 1985).

In the present study, PINCH of the paretic UE was adopted as another outcome measure. The same method as that of GRIP described in the previous section was adopted, except that the subject was instructed to perform maximal pinch grip with the thumb and index finger gripping onto the unpadded end of the 2 bars. When the subject released the pinch grip, the peak force of PINCH was recorded on the digital display of the dynamometer.

### *2.4.6 Functional ability of the paretic upper extremity*

Disability in using the paretic UE was measured with the Action Research Arm Test (ARAT) (De Weerdt and Harrison 1985, Lyle 1981). The set of apparatus used in ARAT is presented in Figure 2.6.

ARAT consists of 19 tasks categorized in 4 sub-tests: grasp (6 tasks), grip (4 tasks), finger pinch (6 tasks), and gross movements (3 tasks) of the involved UE (Lyle 1981) (Appendix VI). In each sub-test, the tasks are arranged in a sequence such that the first task is the most demanding with reference to the strength and movement control required, the second task is the least demanding of the sub-test. From the third task onwards, they are arranged in order of increasing difficulty. The performance in each task is scored on a 4-point scale, with 0 for inability to perform the task, 1 for partial completion, 2 for completion at unusually slow pace or with abnormal synergies, and 3 for normal performance without trick or compensatory

movements. The maximum total score is 57. If a person is able to complete the first task of a sub-test with a full score of 3, he/she would achieve a full score on the sub-test without the need to go through the remaining tasks of the sub-test. However, if he/she scores zero in the most demanding first task, and again zero in the second task which is the least demanding, he/she would score zero for the sub-test without the need to go through the remaining tasks. This arrangement of tasks allows the whole test to be completed in around 8 minutes (DeWeerdt and Harrison 1985).

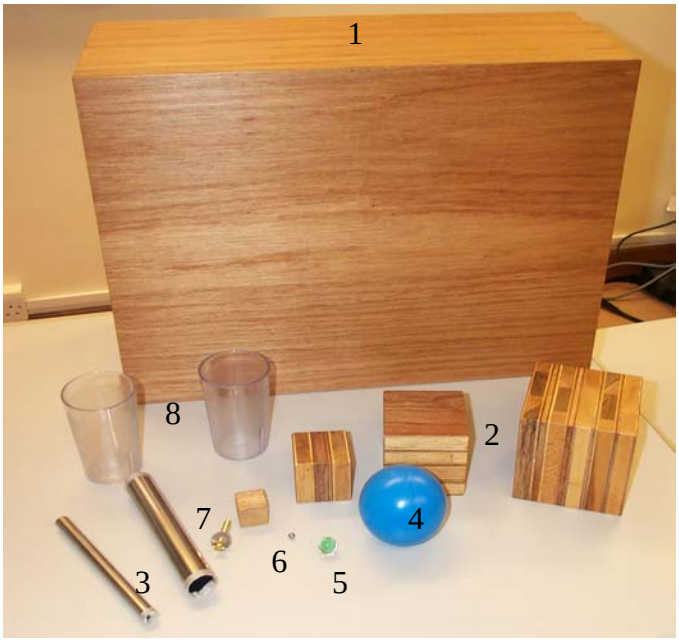


Figure 2.6: The apparatus used in Action Research Arm Test. It includes: (1) a 37 cm high wooden shelf, (2) four wooden cubes of different sizes, (3) two aluminium rods, (4) a cricket ball, (5) a marble, (6) a small ball bearing, (7) a set of nut and bow, (8) two glasses, and a sharpening stone (not shown)

The reliability and validity of ARAT in measuring UE function after stroke have been well proven (Hsieh et al. 1998, Van der Lee and De Groot et al. 2001). Both intra-rater and inter-rater reliability were reported to be very high with ICC values greater than 0.98 (Hsieh et al. 1998, Van der Lee and De Groot et al. 2001). The test was also found to be responsive in detecting changes during recovery from stroke (Hsueh and Hsieh 2002).

## 2.5 Reproducibility of Outcome Measurements

### *2.5.1 Rationale*

Examining the reproducibility of measurement protocols is an important step in research, especially in studies involving repeated measurements and more than 1 rater. Consistency would ensure accuracy of data so that differences in the data recorded at different assessment intervals will be a function of the independent variable of interest rather than of measurement inconsistency.

The outcome measurements in this study had previously been proven valid and reliable in evaluating motor impairments from stroke. There were reports on the reliability of the Composite Spasticity Score (Levin and Hui-Chan 1993), the Motricity Index (Sunderland et al. 1989), and the Action Research Arm Test (Hsieh et al. 1998, Van der Lee and De Groot et al. 2001), when they were applied to people with stroke. For measurements of PR, the Semmes-Weinstein Monofilaments® has been shown to yield reproducible pressure stimuli on selected body parts of healthy subjects with single tester and multi-testers (Bell-Krotoski and Tomancik 1987). Measurement of 2-PD was also found to have high inter-observer reliability from assessments of patients with peripheral nerve injuries (Dellon et al. 1987).

Measurement reliability of both methods on sensation has not yet been reported in clients with stroke

In the present study, there were 2 raters involved in the assessments – the research physiotherapist who carried out the baseline assessment and the author (AYS) who conducted the follow-up assessments as a blind rater. Therefore, an examination of the test-retest or intra-rater reliability, as well as inter-rater reliability was essential.

### *2.5.2 Methods*

2.5.2.1 Subjects

Subjects included in the reliability tests were patients in the extended rehabilitation settings after their transfer from the acute stroke beds, or people with chronic stroke who were more than 6 months post-stroke and attending rehabilitation in out-patient centres. These subjects were recruited by convenience when they satisfied the following inclusion criteria:

(a) had unilateral weakness associated with stroke,

(b) were conscious and medically stable,

(c) could understand instructions of the raters.

Subjects were excluded if they had severe cognitive deficits and a history of neurological or musculoskeletal dysfunctions affecting movements of the paretic UE.

2.5.2.2 Procedure

Data for the reliability tests were collected in the extended rehabilitation units of the Ruttonjee Hospital and Kowloon Hospital. The method and procedure of measuring the outcome variables followed the same as those described in Sections

2.4.3 to 2.4.6. All subjects were assessed with the outcome measures in 2 separate sessions within the same day or the same week for the intra-rater reliability of measurements. Inter-rater reliability of measurements of PR, 2-PD, CSS, MI and ARAT were also examined for the degree of agreement between measurements by the research physiotherapist and the author (AYS). The 2 raters conducted separate measurements on subjects on the same day without knowledge of the scores by each other.

2.5.2.3 Statistics

The SPSS version 11.0 statistical package was used. Intra-rater reliability was evaluated with intra-class correlation coefficients (two-way mixed effect model for absolute agreement), ICC(3,1) for single measurement data, or ICC(3,2) for average data of the measurement trials in each assessment session. For GRIP and PINCH, each assessment involved three recordings of dynamometry measurements (Section 2.4.5.2 and 2.4.5.3). The repeatability of this measurement protocol was examined with intra-class correlation coefficient, ICC(1,1), for the one-way random effect, the result of which provided a rationale for the method selected to process the raw muscle strength data. The inter-rater reliability of measurements of PR, PD, CSS, MI and ARAT by the research physiotherapist and the author (AYS) was examined with intra-class correlation coefficients, two-way random effect model for absolute agreement, ICC(2,1).

### *2.5.3 Results*

2.5.3.1 Pressure sensibility (PR) and two-point discrimination (2-PD) thresholds

Intra-rater reliability. Fourteen subjects (9 male, 5 female) were recruited.

Their mean age was 70.4 years (SD 11.4 years) and the mean duration of their stroke was 7.5 months (SD 5.6 months). Ten subjects had ischaemic stroke and 4 had haemorrhagic stroke. Seven of them had left hemiplegia and the rest had right hemiplegia. Reliability analysis using ICC(3,1) confirmed high intra-rater, or test-retest reliability of PR and 2-PD thresholds (Table 2.2).

Inter-rater reliability. Another 13 subjects (6 males and 7 females), aged 70.3 years (SD 9.3 years), participated in the test of inter-rater reliability. Six of them had left and 7 had right hemiplegia, with a mean of 5.5 weeks (SD 4.3 weeks) post-stroke at the time of assessment. The results confirmed high inter-rater reliability of measurement (Table 2.3).

**Table 2.2: Intra-rater reliability of sensibility measurements**

| n = 14 | Day 1 | Day2 | ICC(3,1) | 95% C.I. |
|---|---|---|---|---|
| Pressure sensibility threshold: | | | | |
| Thumb | 4.1 ± 0.8 | 3.8 ± 0.9 | 0.90 | 0.40-0.97 |
| Index finger | 4.0 ± 0.9 | 3.9 ± 0.9 | 0.94 | 0.84-0.98 |
| Two-point discrimination threshold: | | | | |
| Thumb (mm) | 7.4 ± 5.0 | 6.9 ± 5.1 | 0.94 | 0.83-0.98 |
| Index finger (mm) | 7.3 ± 5.0 | 7.1 ± 5.3 | 0.94 | 0.83-0.98 |

Values are mean ± SD; C.I. denotes confidence interval

**Table 2.3: Inter-rater reliability of the sensibility tests on the index finger**

| n = 13 | Rater 1 | Rater 2 | ICC(2,1) | 95% C.I. |
|---|---|---|---|---|
| Pressure sensibility threshold | 4.6 ± 1.4 | 4.4 ± 1.5 | 0.96 | 0.86-0.99 |
| Two-point discrimination threshold (mm) | 8.0 ± 5.8 | 7.9 ± 6.3 | 0.93 | 0.79-0.98 |

Values are mean ± SD; C.I. denotes confidence interval

2.5.3.2 Muscle tone: the modified Composite Spasticity Score (CSS)

Intra-rater reliability. Eleven subjects (6 males and 5 females) with chronic stroke, aged 61.6 years (SD 7.5 years), participated in the test. Eight of them had left hemiplegia and 3 had right hemiplegia after stroke, with a mean duration of stroke of 38.2 months (SD 33.9 months). Measurements of muscle tone using the CSS were conducted by the same rater on 2 separate sessions, 1 hour apart on the same day. The results confirmed high intra-rater reliability of CSS (Table 2.4).

Inter-rater reliability. Nine of the subjects participated in the intra-rater reliability test were reassessed by 2 raters. They were 4 males and 5 females of mean age 64.7 years (SD 10.8 years). Seven of them had left hemiplegia and 2 had right hemiplegia after stroke, with a mean duration of 70.6 months (SD 120.6 months) after stroke. The rating of muscle tone using CSS was done by the 2 raters separately in the same session. The results confirmed moderate inter-rater reliability with the coefficient of ICC(2,1) equal to 0.66 and a 95% confidence interval of 0.02-0.91 (Table 2.5).

**Table 2.4: Intra-rater reliability of measurement with the modified Composite Spasticity Score (CSS)**

| n = 11 | Day 1 | Day 2 | ICC (3,1) | 95% C.I. |
|---|---|---|---|---|
| CSS subscore: | | | | |
| Resistance to passive elbow extension | 5.3 ± 0.9 | 5.2 ± 1.0 | 0.85 | 0.53-0.96 |
| Elbow jerk | 2.8 ± 0.4 | 2.8 ± 0.4 | 1.00 | - |
| CSS total score | 8.1 ± 1.2 | 8.0 ± 1.3 | 0.91 | 0.71-0.98 |

Values are mean ± SD; C.I. denotes confidence interval.

**Table 2.5: Inter-rater reliability of measurement with the modified Composite Spasticity Score (CSS)**

| n = 9 | Rater 1 | Rater 2 | ICC (2,1) | 95% C.I. |
|---|---|---|---|---|
| CSS subscore: | | | | |
| Resistance to passive elbow extension | 5.2 ± 0.8 | 5.4 ± 1.3 | 0.63 | 0.00-0.90 |
| Elbow jerk | 2.9 ± 0.3 | 2.9 ± 0.8 | 0.68 | 0.04-0.92 |
| CSS total score | 8.1 ± 1.1 | 8.3 ± 2.1 | 0.66 | 0.02-0.91 |

Values are mean ± SD; C.I. denotes confidence interval.

2.5.3.3 Upper extremity muscle strength: Motricity Index (MI)

Intra-rater reliability. Seven subjects (4 males and 3 females) with mean age of 74.4 years (SD 9.6 years) and were 19.1 weeks (SD 6.7 weeks) after stroke, were assessed. Four of them had left hemiplegia and 3 had right hemiplegia. They were assessed twice on separate days of the week. The MI data recorded on the 2 days were exactly the same (mean score 71.7, SD 28.5), giving a correlation coefficient of 1.00.

Inter-rater reliability. Another 15 subjects with stroke (6 males and 9 females, mean age 70.7 years, SD 8.8 years) participated in the inter-rater reliability of this measurement conducted on the same day by the 2 raters. Subjects were on the average 5.3 weeks (SD 4.0 weeks) after stroke, with 6 having left and 9 having right hemiplegia. Results of the intra-class correlation coefficients ICC(2,1) showed high inter-rater reliability of measurements (Table 2.6).

**Table 2.6: Inter-rater reliability of measurement with the Motricity Index (MI)**

| n = 15 | Rater 1 | Rater 2 | ICC (2,1) | 95% C.I. |
|---|---|---|---|---|
| MI subscore: | | | | |
| Shoulder (0-33) | 13.9 ± 9.1 | 13.9 ± 9.1 | 1.00 | 1.00-1.00 |
| Elbow (0-33) | 13.5 ± 8.8 | 12.7 ± 8.4 | 0.92 | 0.79-0.97 |
| Pincer (0-33) | 11.8 ± 13.6 | 13.6 ± 13.1 | 0.96 | 0.87-0.99 |
| MI total score (0-100) | 39.2 ± 29.8 | 40.2 ± 28.8 | 0.98 | 0.94-0.99 |

Values are mean ± SD; C.I. denotes confidence interval

2.5.3.4 Grip strength

Intra-session repeatability. Twelve subjects (7 males and 5 females), aged 71.3 years (SD 12.1 years), with a mean duration of 4.1 weeks (SD 1.9 weeks) after stroke, participated in the repeatability test of the dynamometry measurements of GRIP and PINCH recorded in 1 session. Three trials were performed by each subject. Results of the analysis with ICC(1,1) showed that subjects' performance in the 3 trials was highly repeatable – the intraclass correlation coefficient was 0.99 (95% C.I. = 0.97-0.99) for GRIP and 0.98 (95% C.I. = 0.94-0.99) for PINCH. This high repeatability of performance on dynamometry measurements supported the use of the average value in future data analysis.

Reproducibility of measurement on 2 consecutive days. In order to evaluate the repeatability of dynamometry measurements of strength of power grip and index pinch of patients with stroke during in-patient rehabilitation, a second assessment was conducted on the following day on the same 12 subjects described above.

**Table 2.7: Test-retest reliability of upper extremity strength measured with dynamometry**

| n = 12 | Day 1 | Day2 | ICC(3,2) | 95% C.I. |
|---|---|---|---|---|
| GRIP (kg) | 11.9 ± 8.1 | 11.6 ± 7.7 | 1.00 | 1.00-1.00 |
| PINCH (kg) | 3.8 ± 2.3 | 3.7 ± 2.1 | 0.98 | 0.93-0.99 |

Values are mean ± SD; C.I. denotes confidence interval.

Results again showed very high intra-class correlation coefficients, ICC(3,2), for GRIP and PINCH (Table 2.7).

Intra-rater and inter-rater reliability. Because the measurements of GRIP and PINCH were recorded quantitatively by a (blinded) device – a dynamometer, there was no need for these reliability to be examined.

2.5.3.5 Functional ability of UE: Action Research Arm Test (ARAT)

Intra-rater reliability. Eight subjects (5 males, 3 females; 3 left- and 5 right-sided hemiplegia), with mean age 67.3 years (SD 9.8 years) and a mean duration of 14.1 weeks (SD 10.6 weeks) after stroke, were assessed for test-retest reliability of the measurements in 2 separate sessions on 2 consecutive days. The intra-class correlation coefficients, ICC(3,1), for test-retest reliability were very high for the 2 sub-tests on grip and pinch tasks (ICC = 0.98), followed by grasp (ICC = 0.95) and gross movements (ICC = 0.85). Table 2.8 shows that the test-retest reliability measured with ARAT was high, with an ICC(3,1) of 0.98 and 95% confidence interval of 0.93-1.00.

Inter-rater reliability. Seven other subjects with stroke (3 males and 4 females, mean age 59.6 years, SD 6.4 years) participated in this inter-rater reliability of measurements with ARAT between the 2 raters. The subjects were examined 18.9 ± 6.8 weeks after stroke, with 6 having left hemiplegia and 1 having right hemiplegia. The mean ARAT scores evaluated by the 2 raters were respectively 22.4 (SD 22.0) and 22.1 (SD 21.9). The data agreement was excellent with an intra-class correlation coefficient, ICC(2,1) of 1.00 (95% C.I. = 1.00-1.00).

**Table 2.8: Test-retest reliability of upper extremity function measured with the Action Research Arm Test (ARAT)**

| (n = 8) | Day 1 | Day2 | ICC(3,1) | 95% C.I. |
|---|---|---|---|---|
| ARAT sub-test: | | | | |
| Grasp | 11.1 ± 6.4 | 11.8 ± 6.7 | 0.95 | 0.80-0.99 |
| Grip | 8.6 ± 4.4 | 8.9 ± 4.3 | 0.98 | 0.91-1.00 |
| Pinch | 11.5 ± 7.1 | 11.5 ± 7.7 | 0.98 | 0.92-1.00 |
| Gross movement | 6.1 ± 2.0 | 6.6 ± 2.1 | 0.85 | 0.47-0.97 |
| ARAT total score | 37.4 ± 19.5 | 38.8 ± 20.0 | 0.98 | 0.93-1.00 |

Values are mean ± SD; C.I. denotes confidence interval.

### *2.5.4 Discussion*

In the tests on intra-rater and inter-rater reliability, very high intra-class correlation coefficients were found for measurements of sensibility, muscle strength and functional ability of the paretic UE. The findings for MI and ARAT were in agreement with those reported in the literature for people in acute or chronic stage of stroke (Demeurisse et al. 1980, Hsieh et al. 1998, Sunderland et al. 1989, Van der Lee 2001). The present study demonstrated for the first time that evaluation of sensory impairment with Semmes Weinstein Monofilaments® and Disk-Criminator™ was highly reliable in patients with stroke for measurements involving single or more raters. Levin and Hui-Chan (1993a) have reported high intra-rater reliability (ICC = 0.87) with CSS in measuring the muscle tone of lower extremities in patients with chronic hemiplegia. In the present study, high intra-rater reliability (ICC = 0.91, 95% C.I. = 0.71-0.98) and moderate reliability of measurements between the 2 raters (ICC = 0.66, 95% C.I. = 0.02-0.91) was confirmed.

### *2.5.5 Conclusion*

The measurement protocols of the outcome variables were confirmed to have high intra-rater reliability in patients with stroke. High inter-rater reliability of the measurements was also demonstrated in most protocols although that of CSS was moderately reliable. Note that high intra-and inter-rater reliability of outcome measurements are crucial for detecting within-group and between-group differences due to an intervention.

## 2.6 Statistics

In this thesis, a number of statistical methods were adopted to analyze the data. The Statistical Package for Social Sciences (SPSS) version 11.0 was used. Descriptive statistics were used to analyze the characteristics of the subjects recruited. For the time course of sensory, motor and functional recovery of the paretic UE during acute stroke, repeated measures ANOVA was used in the analysis to detect significant improvement as compared to the baseline measurements (Chapter 3). The magnitude of recovery in the outcome measurements in a defined period post-stroke were examined with standardized response means (SRM). SRM was evaluated as the mean change between two time points per unit of standard deviation of the change (Liang 1995). In identifying the best predictors for the recovery of manual function in the paretic UE after stroke, logistic regressions and Receiver Operating Characteristics curves were applied in the analyses (Chapter 4). To study the effects of early TES programme on the recovery of paretic UE in subjects with acute stroke (Chapter 5), there were comparisons amongst the 3 groups – control, placebo-TES and TES groups. Group differences in the baseline measurements were examined with Chi-square tests for categorical data and one-way analysis of variance (ANOVA) for continuous data. Following intention-to-treat principles (Moher et al. 2001), mixed model repeated measures analysis of covariance was used to test within-group and between-group differences in treatment effects on UE recovery, with variables that were identified as different between groups at baseline used as covariates. The level of significance was adopted as 5% for all statistical tests.

## 2.7 Ethical consideration

TES has been a common modality used by physiotherapists in rehabilitation without notable side-effects being reported in any published study. The present study employed a randomized controlled clinical trial design to test the effects of TES applied to selected acupoints on the recovery of the paretic UE after stroke. The study was approved by the Research Ethics Committee, Department of Rehabilitation Sciences of The Hong Kong Polytechnic University, and the Ethics Committee of Queen Elizabeth Hospital and of Kowloon Hospital. All subjects recruited had to sign an informed consent themselves, or were assisted in signing by their relatives in the subjects' presence before measurements and data collection began. Subjects' personal information was only kept by the research physiotherapist and the author of this study. Their personal identity would not be disclosed in any form. Data collected in this study were only used for academic purpose.

# *Chapter 3*

## *Time Course of Recovery of the Paretic Upper Extremity*

**Summary**

The recovery of stroke-induced upper extremity (UE) paresis has previously been shown to be rapid in the early months after stroke and then plateau. With the advancement of acute stroke management in recent years, the time course and extent of recovery in the paretic UE should be re-examined. This prospective longitudinal study examined the time course of recovery of sensory and motor functions in the paretic UE of subjects receiving conventional rehabilitation (CR) after stroke.

***Methods:*** Subjects receiving CR within 5 days after onset of stroke as well as healthy subjects similar in age were recruited following appropriate inclusion-exclusion criteria. They all underwent assessments of their UE at recruitment, with the stroke subjects at 8 more time intervals – weekly in the first 4 weeks, and at 8, 12, 16 and 24 weeks after the baseline assessment. The outcomes monitored were (1) pressure and two-point discrimination of the index finger pulp of the paretic hand, (2) muscle tone, (3) muscle strength of shoulder and elbow, (4) strength of power grip and index pinch grip, and (5) functional ability of the paretic UE.

***Results:*** 57 subjects with stroke (mean age 69.7 years, SD 10.2 years) and 100 healthy subjects (mean age 69.1 years, SD 8.9 years) completed all assessments. The majority of stroke subjects showed substantial recovery of sensori-motor function during the initial 1 to 2 months after stroke. Sensation in the paretic hand progressed well in most patients, so that by 8 to 16 weeks after the baseline assessment, the mean thresholds of pressure sensibility and two-point discrimination were not different from those of healthy controls. The UE muscle tone became spastic by week 2, and then remained more or less unchanged afterwards. With reference to the standardized response means, the magnitudes of improvement in the muscle strength of shoulder and elbow as well as functional ability of the paretic UE

were larger in the first 3 months post-stroke than in the subsequent 3 months. In contrast, the more distal hand grip strength improved more between 3 and 6 months post-stroke rather than during the first 3 months after stroke onset. At 24 weeks post-stroke, UE proximal muscles had recovered two-thirds of their normal strength, but only one-third of normal hand grip strength. However, 47% of the subjects still had poor UE functional ability, with score on the Action Research Arm Test less than 10.

***Conclusion:*** The results showed that in subjects receiving only CR, there was rapid improvement in sensori-motor functions in the paretic UE first 1 to 2 months after stroke onset compared to the period afterwards. However, the extent of motor recovery after stroke up to 6 months post-stroke was far from optimal. Hence, more effective therapies should be designed to further enhance the recovery of motor functions in the paretic UE, especially in the early stage of stroke.

## 3.1 Introduction

### *3.1.1 Time course of recovery in the paretic upper extremity*

Being a reference for treatment planning and evaluation, the time course of recovery after stroke has been widely researched. Among the longitudinal studies published, the rate of motor function recovery was noted to be fast during the initial 1 to 3 months after stroke onset (Duncan et al. 1994, Jorgensen et al. 1995, Olsen 1989, Wade et al. 1983). Further improvements with time became gradual to plateau afterwards. In tracking the motor function recovery with time, most studies started the baseline measurements when the patients' condition had become stable (Nakayama et al. 1994a, Olsen 1989, Wade et al. 1983). In these studies, composite clinical scores were used to measure sensori-motor impairments, and compensatory strategies were allowed for subjects to perform daily activity tasks in evaluating their disability. The 2 examples were the Fugl-Meyer Assessment Scale and the Barthel Index. With such methods, isolating discrete improvements in sensation from strength of individual muscle group, or functional ability in the paretic UE was not possible. With the recent advancement of acute stroke management (Langhorne et al. 1993, Webb et al. 1995), the time course of recovery after stroke might have changed. Moreover, it has not been clear if sensation, muscle strength and functional ability in the paretic UE have similar time course of recovery. Their extent of recovery following conventional rehabilitation (CR) remained to be investigated.

### *3.1.2 Reference norms for the outcome measurements*

Norm data of sensori-motor functions in UE provide a reference to estimate the extent of recovery in the paretic UE. In this study, certain outcome

measurements were clinical scales for documenting the status of motor functions of the paretic UE. For muscle strength impairment, the Motricity Index of Demeurisse and his team (1980) was used to grade the paretic UE with reference to gravity and the performance of the less affected extremity ipsilateral to the brain lesion. Functional ability of the paretic UE was graded with the Action Research Arm Test (Lyle 1981) according to a 4-level scale with reference to the subject's successful completion of the designated tasks. Note that normal performance was the full score in these 2 scoring systems.

For tactile discrimination and hand grip strength, the UE ipsilateral to the brain lesion was not a suitable normal reference, as this extremity has been shown to demonstrate some sensory and muscle strength impairment (Carmon 1971, Colebatch and Gandevia 1989, Corkin et al. 1970). Up to present, normative values for tactile sensibility thresholds and hand grip strength have been established with non-Chinese subjects. Such sensory thresholds and motor function are known to vary with age, gender, body built, laterality and handedness. In healthy adults, the mean two-point discrimination (2-PD) threshold measured with the Disk-Criminator™ was found to increase with age, by around 3.5 mm in the fingers for subjects with a mean age of 59 years (Kim and Choi 1996), and by 4.4 to 5.6 mm in people more than 60 years old (Desrosiers et al. 1996). The threshold of PR measured with Semmes-Weinstein monofilaments is normally 1.65 to 2.83 for young adults (Bell-Krotoski and Tomancik 1987) and 2.83 to 3.84 for older adults (Desrosiers et al. 1996). The effect of laterality or handedness on tactile discrimination in the hands has not yet been documented (Desrosiers et al. 1996, Kim and Choi 1996, Weinstein and Sersen 1961). However, in a group of 136 subjects aged between 17 to 30 years, Weinstein and Sersen (1961) found that

women had lower PR thresholds in the palms than men. With subjects over 50 years old, 2-PD thresholds in the fingers were lower in females than in males (Desrosiers et al. 1996, Louis et al. 1984). In a study involving 628 healthy adults, hand grip strength was found to deteriorate with age after 40 (Mathiowetz et al. 1985). Balogun and co-workers (1991) also reported similar findings. Moreover, grip strength of the dominant hand is higher than that of the other hand (Hanten et al. 1999). Males have also been shown to have stronger grips than females in people aged 65 years and older (Bassey and Harries 1993).

### *3.1.3 Objectives of the study*

The study reported in this chapter had 3 objectives:

(1) To establish reference norms for tactile discrimination and hand grip strength in the upper extremities of healthy subjects who were similar in age and gender to the patients with stroke recruited in the main study;

(2) To identify the time course of sensori-motor and functional improvements in the paretic UE of subjects receiving conventional stroke rehabilitation in the first 6 months after stroke;

(3) To examine the extent of recovery of sensory, motor and functional abilities in the paretic UE at 6 months post-stroke.

## 3.2 Methods

### 3.2.1 Subjects and procedures

3.2.1.1 Healthy subjects

A convenient sample of healthy subjects was recruited from the community

and from 4 social centres for older people. Three centres were located in the Kowloon Central and Kowloon West districts of Hong Kong, in the same districts that the 2 hospitals in the main study served. One other centre was located in Hong Kong Island East, which had similar population demographics (Census and Statistics Department, 2001).

Subjects were included if they:

(1) were between 45 and 90 years old, and

(2) were right-hand dominant defined by the hand they used during writing.

The exclusion criteria were:

(1) signs or symptoms such as pain in the upper extremities;

(2) a history of orthopaedic or neurological conditions that affected UE functions;

(3) communication disorders or cognitive dysfunctions,

(4) signs or symptoms of musculoskeletal or neurological disease at the time of recruitment.

The research physiotherapist and the author took part in the assessment procedure. After informed consent was obtained from the subjects, their body weight and height were measured. The handedness of the subjects was checked by reference to the hand used in signing the consent form. This preferred hand was considered as the dominant hand in this study. PR and 2-PD, as well as GRIP and PINCH were assessed on both upper extremities. These 4 variables were measured on each subject in a random sequence in 1 session. The equipment used and the methods of measurement were the same as those described in Chapter 2, sections 2.4.3 and 2.4.5.

3.2.1.2 Subjects with stroke

The subjects with stroke discussed in this chapter were recruited from the acute stroke beds of the hospitals and with the inclusion-exclusion criteria described in Chapter 2, sections 2.2.1 and 2.2.2. In fact, they were the patients receiving only CR in the acute hospitals and at subsequent rehabilitation settings of Hong Kong's Hospital Authority (refer to Chapter 2, section 2.3.3).

In tracking the time course of recovery in the paretic UE, assessments to subjects were given by the research physiotherapist at recruitment as baseline, and then at 8 time intervals afterwards by AYS until 6 months post-stroke (once a week during the first month, then at weeks 8, 12, 16 and 24 after the baseline assessment). For the recovery in sensation, PR and 2-PD scores were measured on the thumb and index finger of the paretic hand. For the motor and functional abilities of the paretic UE, muscle tone, muscle strength in the shoulder, elbow, GRIP and PINCH and the UE functional ability were measured. The procedure and methods of measurement were described in sections 2.4.1, 2.4.3 to 2.4.6.

### *3.2.2 Statistics*

Differences between the healthy and stroke groups were examined with t-tests. For changes with time within a group, repeated measures ANOVA was used in the analyses. The level of significance was set at 0.05. In evaluating the magnitude of change over time of the outcome variables, the standardized response mean (SRM) was used. The SRM is a type of effect size (Liang 1995) derived as the ratio of the mean change in a variable between 2 time points to the standard deviation of the changes of the subjects (Desrosiers et al. 2003, Liang 1995). SRM is therefore unitless which takes into account the variance of measurement at 2 time intervals. A

larger SRM value signifies greater recovery during the period. According to the general guidelines of Cohen (1988), an effect size between 0.2 to 0.5 is considered as small, 0.5 to 0.8 as moderate, and >0.8 as large. SRM also allows comparison across the outcome variables (Desrosiers et al. 2003, Kazis et al. 1989).

## 3.3 Results

### *3.3.1 Tactile sensation and grip strength in both upper extremities of healthy, older subjects*

100 subjects, 46 males and 54 females, of mean age 69.1 years (SD 8.9 years, range 48 to 89 years) were recruited. The male and female groups were similar in age, mean body weight and body mass index. Table 3.1 presents descriptive statistics on the subjects and the sensori-motor functions of the 2 genders.

**Table 3.1: Tactile sensation and grip strength of the hands of healthy subjects**

| Variables | | Male (n = 46) | Female (n = 54) |
|---|---|---|---|
| Age, means ± SD (years) | | 69.4 ± 9.4 | 68.9 ± 8.5 |
| Body weight, means ± SD (kg) | | 58.1 ± 10.8 | 58.5 ± 10.6 |
| Body mass index, means ± SD | | 24.1 ± 3.9 | 24.9 ± 3.4 |
| Pressure sensibility threshold, means ± SD | Left | 3.5 ± 0.5 | 3.2 ± 0.4* |
| | Right | 3.6 ± 0.5 | 3.3 ± 0.4* |
| Two-point discrimination threshold, means ± SD (mm) | Left | 3.3 ± 1.1 | 3.4 ± 1.0 |
| | Right | 3.1 ± 1.1 | 3.4 ± 1.0 |
| Power grip strength, means ± SD (kg) | Left | 22.8 ± 6.0 | 16.9 ± 4.2** |
| | Right | 24.9 ± 5.7 | 17.7 ± 3.9** |
| Index pinch strength, means ± SD (kg) | Left | 5.7 ± 1.7 | 5.0 ± 1.5* |
| | Right | 6.2 ± 1.7 | 5.5 ± 1.5* |

*, ** denotes *P*-values <0.05 and <0.001 respectively in a *t*-test comparing male to female subjects

The male and female groups did not differ in their 2-PD thresholds. However, male subjects had higher PR thresholds ($P = 0.01$) and grip strengths ($P < 0.001$ for GRIP and $P = 0.024$ for PINCH) than did the female subjects. There was no difference in PR and 2-PD thresholds between the two hands, but the dominant right hand had a stronger grip.

In this study, the mean scores of PR, 2-PD, GRIP and PINCH of the non-dominant left hand of healthy subjects were adopted as the reference norms for investigating the recovery in the paretic UE of subjects with stroke.

### *3.3.2 Classifying severity of sensory impairment*

In the non-dominant left hand of the healthy subjects, the mean PR threshold of the index finger pulp was 3.3 (SD 0.5), and the mean 2-PD threshold was 3.4 mm (SD 1.0 mm). According to Kim and Choi's (1996) method for categorizing the degree of sensory deficit, a discrimination threshold value equivalent to the norm was classified as "normal". Between the norm and the maximum threshold, values in the lower third of the range were classified as "slightly impaired", within one-third to two-third of the range as "moderate", higher than two-third of the range as "severely impaired". The largest PR threshold measured using Semmes-Weinstein Monofilaments® was 7. PR thresholds of 3.3 or lower would thus be "normal". Threshold values from 3.4 to 4.6 would be "slightly impaired", 4.7 to 5.8 "moderately impaired", and 5.9 or larger "severely impaired". For 2-PD, the largest threshold measured using the Disk-Criminator™ was 16 mm. Threshold values less than 4 mm would be "normal". Values from 4 to 7 mm were "slightly impaired", 8 to 11 mm "moderately impaired", and 12 mm or larger "severely impaired".

### *3.3.3 Recovery in the paretic upper extremity after stroke*

Seventy subjects were recruited in the acute stroke units, with 18 of them being recruited within 46 hours from the onset of stroke. The rest of the subjects were recruited longer than 46 hours but within the first 5 days after stroke. Thirteen subjects were excluded from the analysis: 3 died of a recurrent stroke or stroke complications within the first 4 months, 1 had a recurrent stroke in the third week, 7 subjects left the city or could not be contacted, and 2 refused further follow-up before the week 12 assessment. Analysis with Chi-square tests for categorical data and independent t-tests showed that the demographics and the baseline neurological impairments were not different between the 13 drop-out subjects and the 57 subjects who completed the 6 months of assessments (Table 3.2).

Of the 57 subjects, 25 were female and 32 were male. Their mean age was 69.7 years (SD 10.2 years, range 45 to 90 years). The mean time of baseline assessment was 60.4 hours (SD 25.5 hours) from the onset of stroke, with stroke severity measured as mild to moderate on the NIHSS, with scores ranging from 1 to 15. Thirty-five subjects had stroke to the left hemisphere, resulting in right hemiplegia. Thirty-six subjects had co-morbid stroke risks (Goldstein et al. 2001) such as diabetes mellitus, or cardiac or circulatory dysfunction. There were 57.7% subjects with mild to severe cognitive impairment, with NCSE scores (Mueller et al. 2001) ranging from 20 to 63. The mean length of their hospital stay was 42.0 days (SD 13.3 days, range 5 to 75 days). The following sections describe the time course of recovery of sensory, motor and functional abilities in the paretic UE. The recovery was also compared to the norm of the clinical scores or the normative data established in the group of healthy control who had similar age ($P$ = 0.73) and gender distribution ($P$ = 0.22) as the present patient group (refer to section 3.3.1).

The normal value of GRIP was 19.6 kg (mean, SD 5.9 kg) and that of PINCH was 5.3 kg (mean, SD 1.6 kg).

**Table 3.2: Demographic and baseline characteristics of subjects with stroke**

| Characteristics | Subjects who completed all follow-up assessments (n=57) | Subjects who dropped out (n=13) | *P* |
|---|---|---|---|
| Age, mean ± SD (years) | 69.7 ± 10.2 | 69.4 ± 10.7 | 0.93 |
| Gender - female (%) | 43.9 | 46.2 | 0.88# |
| Comorbidity – stroke risks (%) | 63.2 | 66.7 | 0.82# |
| Hemispheric stroke - left (%) | 61.4 | 46.2 | 0.31# |
| Site of lesion (%) – Lacunar/NAD | 28.6 | 33.3 | 0.53# |
| Cortical | 10.7 | 25.0 | |
| Subcortical | 50.0 | 33.3 | |
| Cortical+Subcortical | 10.7 | 8.3 | |
| Time from stroke onset to first assessment, mean ± SD (hours) | 60.4 ± 25.5 | 50.1 ± 26.9 | 0.20 |
| Stroke severity (NIHSS), mean ± SD | 7.3 ± 2.9 | 7.8 ± 2.6 | 0.58 |
| Cognition (NCSE score), mean ± SD | 57.7 ± 15.1 | 57.1 ± 19.9 | 0.92 |
| Spatial neglect - present (%) | 43.9 | 53.8 | 0.51# |
| Sensibility threshold, mean ± SD: | | | |
| Pressure (range 1.65-7) | 4.1 ± 1.1 | 4.4 ± 1.2 | 0.31 |
| Two-point discrimination (range 2-16), (mm) | 7.6 ± 5.6 | 10.1 ± 5.6 | 0.16 |
| Muscle tone, mean ± SD: | | | |
| Composite Spasticity score (range 0-12) | 5.4 ± 2.5 | 4.8 ± 2.6 | 0.38 |
| Muscle strength, mean ± SD: | | | |
| Motricity Index score (range 0-100) | 34.1 ± 25.8 | 35.8 ± 27.9 | 0.83 |
| Power grip strength (kg) | 1.4 ± 3.7 | 2.7 ± 4.8 | 0.29 |
| Index pinch strength (kg) | 0.5 ± 1.3 | 1.1 ± 2.0 | 0.18 |
| Upper extremity function, mean ± SD: | | | |
| Action Research Arm Test score (range 0-57) | 6.9 ± 14.2 | 8.7 ± 14.6 | 0.68 |
| Barthel Index score (range 0-100), mean ± SD | 41.7 ± 18.6 | 44.5 ± 23.2 | 0.65 |

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; NCSE, Neurobehavioral Cognitive Status Examination score. *P*-values presented are from independent t-tests, except # which denotes the *P*-value of a Chi-square test

3.3.3.1 Tactile discrimination

Figure 3.1 presents the mean PR and 2-PD thresholds in the distal pulp of index finger of the paretic UE as a function of time.

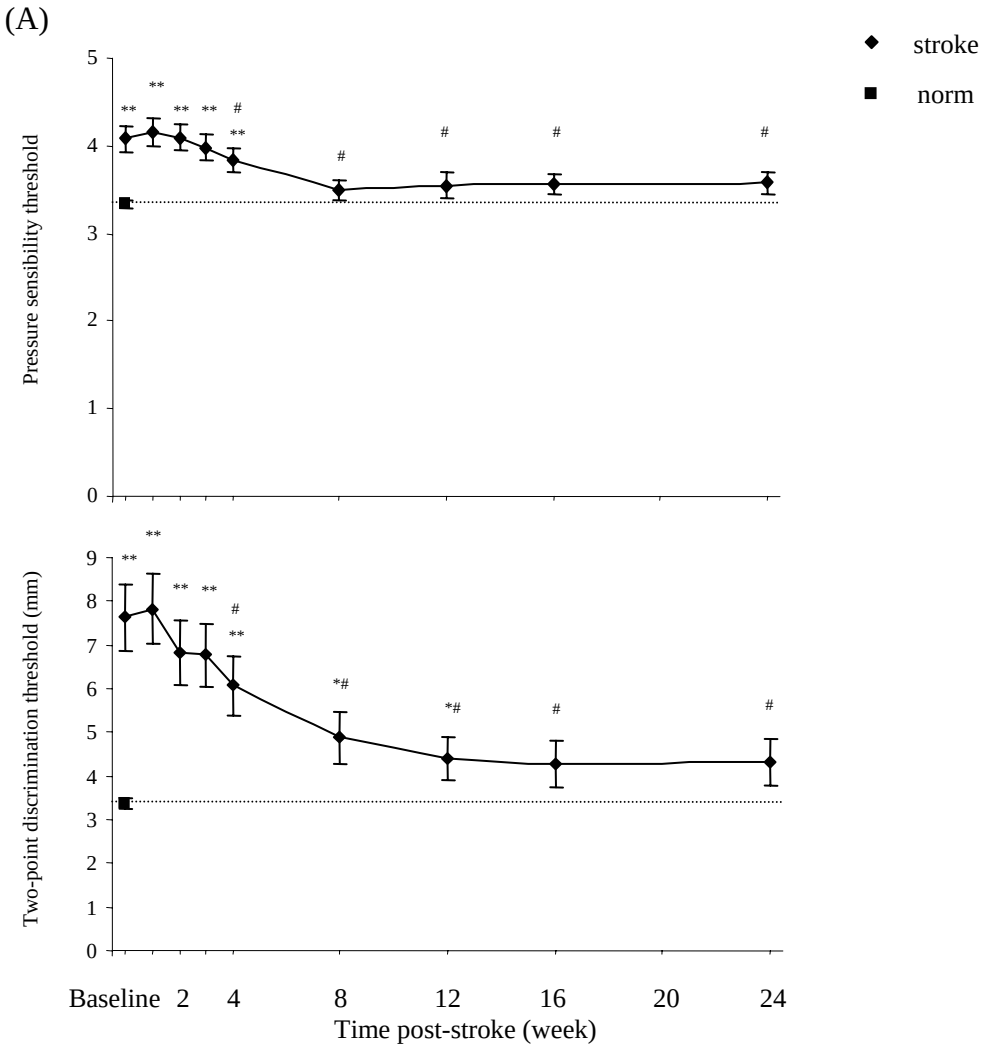


Figure 3.1: Time course of recovery of (A) pressure sensibility and (B) two-point discrimination in the index finger of the paretic upper extremity. Error bars are 1 standard error of the mean; dotted lines mark the level of norm thresholds. * and ** denote $P$ <0.05 and $P$ <0.005 respectively when compared to the normal thresholds, # denotes $P$ <0.05 when compared to the baseline

With reference to the normal PR and 2-PD values, slightly more subjects had impairment in PR at baseline (77.2% of subjects – 61.4% were slightly impaired, 7% moderately impaired and 8.8% severely impaired) when compared to 2-PD (64.9% of subjects – 29.8% were slightly impaired, 3.5% moderately impaired and 31.6% severely impaired).

Improvements in these tactile sensations occurred mainly in the first 2 months after stroke. Both PR and 2-PD showed little or small improvement after the $W_8$ assessment. The results of repeated measures ANOVA showed that PR was significantly improved by $W_4$ ($P = 0.02$) when compared with the baseline status. At $W_8$ assessment, the mean PR threshold was not different from the norm of the healthy subjects ($P = 0.182$, 95% C.I. = -0.08-0.41). For 2-PD, significant improvement from the baseline measurement was found at $W_4$ assessment ($P = 0.006$), and it became not different from the norm by $W_{16}$ ($P = 0.105$, 95% C.I. = -0.19-1.98). At 6 months post-stroke, the percent of subjects with severely impaired PR was slightly reduced to 7%, while only 8.8% remained with severe impairment in 2-PD.

3.3.3.2 Muscle tone

The change of muscle tone with time is presented in Figure 3.2. With reference to normal muscle tone, i.e. a score of 6 on the Composite Spasticity Scale (CSS), 51% subjects had hypotonic or flaccid elbow flexors at recruitment (CSS scores ranged from 1 to 5), while 44% subjects presented with hypertonicity (CSS scores ranged from 7 to 9). Compared with the baseline status, repeated measures ANOVA showed that muscle tone increased significantly as early as week 1 after recruitment ($P = 0.001$). Seventy percent of subjects presented with a spastic UE at

the week 2 assessment (CSS scores ranged from 7 to 9), with the mean CSS score significantly higher than that of normal muscle tone ($P$ = 0.001, 95% C.I. = 0.43-1.54). Muscle tone in the paretic UE was unchanged from $W_4$ to 6 months post-stroke, when 86% of the subjects still had spasticity in the paretic UE (CSS scores ranged from 7 to 12).

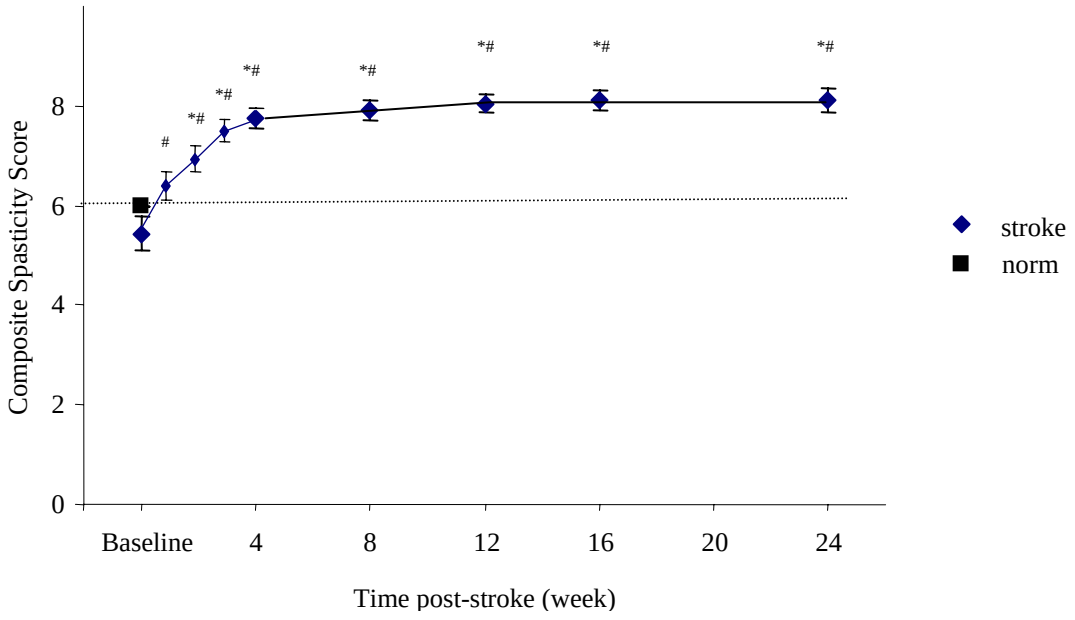


Figure 3.2: Time course of increase in muscle tone in the paretic upper extremity. Error bars are 1 standard error of the mean, the dotted line marks the level of norm score, * and # denote $P \leq 0.001$ when compared to the normal muscle tone and the baseline respectively

3.3.3.3 Muscle strength

At baseline, the average overall muscle strength status of the paretic UE as measured by the Motricity Index (MI) was 34.1 (SD 25.8, range 1 to 77). Sixty percent of the subjects showed marked weakness (MI score <30, full score is 100). Specifically, no more than a flicker of muscle contraction could be detected in the shoulder abductors, the elbow flexors and the finger flexors. Much improvement was observed during the first month post-stroke.

Figure 3.3 (A) presents the changes in the shoulder and elbow MI sub-scores during the 6 months after recruitment. Both muscle strength measures showed a similar time course of improvement. With reference to the baseline status, the improvements in shoulder and elbow muscle strength were significant by week 3 post-stroke ($P$ <0.001). Power grip (GRIP) and index pinch grip (PINCH) strength showed a similar pattern of improvement with time (Figure 3.3B and C). The improvements in MI shoulder and elbow sub-scores, as well as GRIP and PINCH progressed rapidly during the first 4 weeks after the onset of stroke, and became much more gradual after this period.

At 6 months post-stroke, the mean MI sub-scores for the subjects' shoulders and elbows were 19.9 (SD 7.3) and 20.9 (SD 7.6) respectively; both remaining significantly lower than the normal score which was 33 for each of the shoulder and elbow MI subscore. Moreover, their mean GRIP strength was 6.3 kg (SD 7.3 kg) and that of PINCH strength was 1.9 kg (SD 2.3 kg). Comparing to the normal values established with the healthy control (section 3.3.1), the patient subjects had significantly lower GRIP and PINCH strength even at 6 months post-stroke.

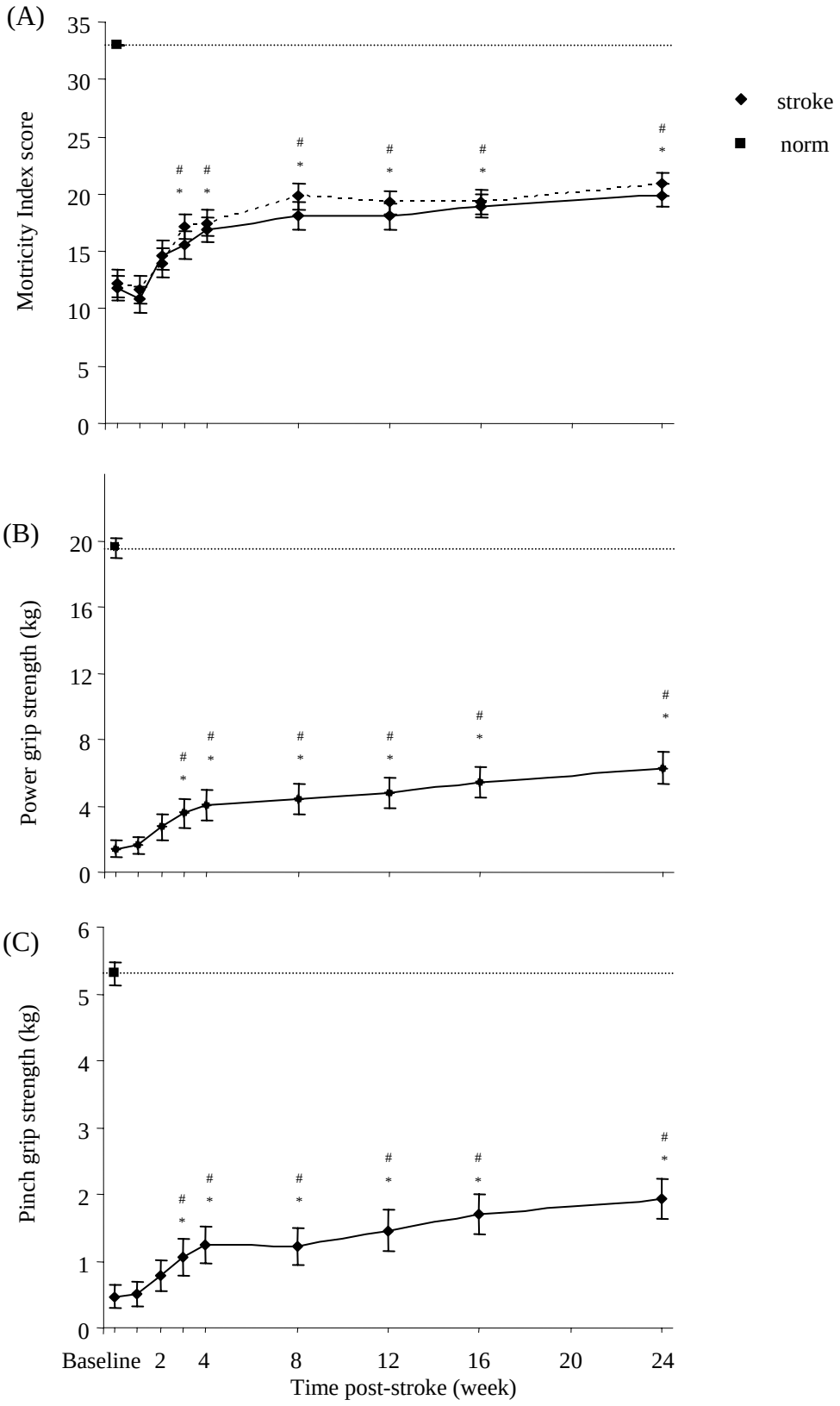


Figure 3.3: Time course of recovery of muscle strength of (A) shoulder abductors (solid line) and elbow flexors (dashed line), (B) power grip, and (C) index pinch of the paretic upper extremity. Error bars are 1 standard error of the mean, the dotted lines mark the levels of norm, * and # denote $P \leq 0.001$ when compared to the norm and the baseline respectively

3.3.3.4 Functional abilities

The median ARAT score of the subjects at recruitment was 0 (mean ARAT score 6.9, SD 14.2). 80.7% of the subjects had poor functional ability (ARAT <10) (Kwakkel et al. 2003) with their paretic UE. Only 5 of the 57 subjects had ARAT scores ≥35, a score signifying the presence of dextrous function such as grasping, gripping and pinching abilities in the paretic UE. With a score of 35, nearly all ARAT tasks could be completed either unusually slowly or with abnormal muscle synergies, although pincer gripping with the ring finger was not yet possible. Figure 3.4 presents the distribution of subjects into the categories of presenting either poor or dextrous UE function, and a third category of fair UE function (ARAT score from 10 to 34).

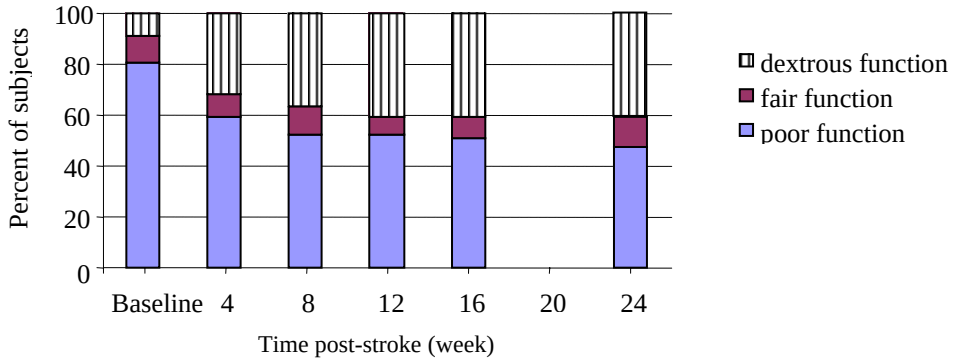


Figure 3.4: Percent of subjects in the 3 categories of upper extremity functional ability

Figure 3.5 shows the improvement in mean ARAT scores over the 6 months of assessments. Significant improvement in UE functional ability was detected at week 3 ($P$ <0.001) when compared to the baseline value. Functional ability improvement was more gradual in the second month, and further improvement almost plateaued with time afterwards. At 6 months post-stroke, 40.4% of the subjects had recovered UE dextrous function, but 47.4% had poor UE function. Note that none of the subjects with poor UE function at baseline assessment could improve to perform UE dextrous function.

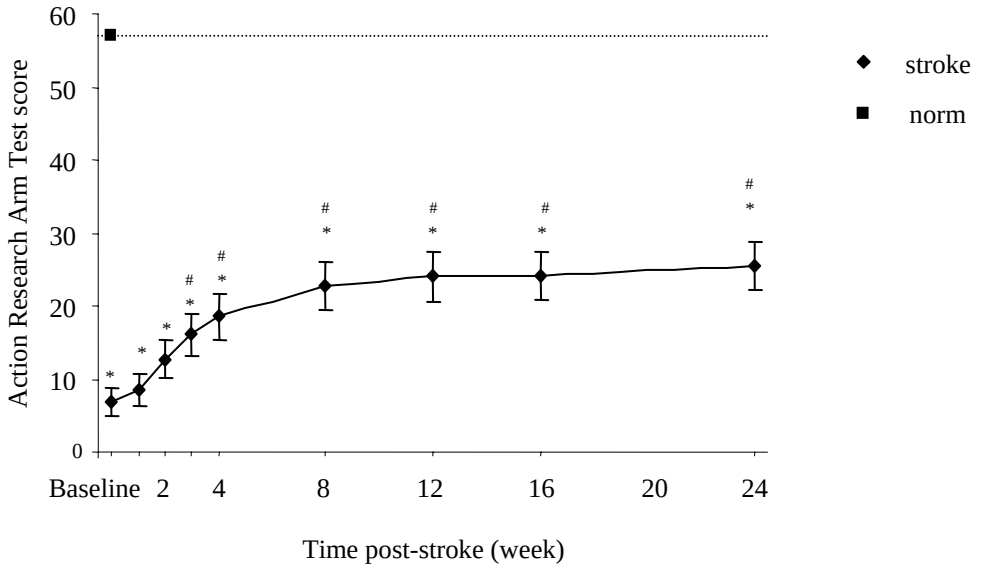


Figure 3.5: Time course of recovery in functional ability of the paretic upper extremity. Error bars are 1 standard error of the mean, the dotted line marks the level of norm, * and # denote $P$ <0.001 when compared to the norm and the baseline respectively

3.3.3.5 Summary of the time course of sensory, motor and functional recovery

A summary of the sensory, motor and functional ability results over the 6 months of assessment together with the norm reference is listed in Appendix VII. Table 3.3 presents the mean changes in the sensori-motor and functional outcomes during 4 periods: between the baseline and $W_4$ assessments, $W_4$ to $W_8$ after stroke, the first 3 months post-stroke, and from 3 to 6 months post-stroke. The magnitudes of the changes are described by the corresponding SRM. Our results show that in the first 4 weeks after stroke, the magnitude of improvements in PR and 2-PD was small compared to that of motor functions. The greatest change was in muscle tone (SRM = 0.84) in this period, while the muscle strength of shoulder and elbow showed slightly greater improvement when compared to hand grip strength. The magnitudes of the improvements in muscle strength (SRM from 0.46 to 0.62) and UE functional ability (SRM = 0.54) were quite similar. During the second month after stroke, i.e., from $W_4$ to $W_8$, the change in muscle tone was minimal and that of muscle strength was smaller than the previous month. However, the improvement in PR was larger (SRM = 0.44) while 2-PD and functional ability continued to improve with rates similar as previous. In general, any improvements in UE sensori-motor functions occurred mostly in the first 3 months post-stroke. Between 3 and 6 months post-stroke, changes in sensation and muscle tone were minimal (SRM $\leq$0.05), and the improvements in muscle strength of shoulder and elbow and UE functional ability were small (SRM ranging from 0.37 to 0.45). On the other hand, improvement in hand grip strength during the later 3 months continued in similar or greater extent (SRM was 0.51 for PINCH and 0.77 for GRIP) compared to the first 3 months post-stroke.

**Table 3.3: Changes in sensori-motor functions of the paretic upper extremity**

| Outcomes | Post-stroke Period | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Baseline to 4 weeks | | 4 to 8 weeks | | Baseline to 3 months | | 3 to 6 months | |
| | Mean change ± SD | SRM | Mean change ± SD | SRM | Mean change ± SD | SRM | Mean change ± SD | SRM |
| Sensibility threshold: | | | | | | | | |
| Pressure sensibility | 0.3 ± 0.9 | 0.29 | 0.3 ± 0.7 | 0.44 | 0.5 ± 0.9 | 0.57 | 0.0 ± 0.5 | 0.05 |
| Two-point discrimination (mm) | 1.6 ± 4.7 | 0.33 | 1.2 ± 3.3 | 0.36 | 3.3 ± 5.2 | 0.63 | 0.1 ± 2.2 | 0.03 |
| Muscle tone: | | | | | | | | |
| Composite Spasticity Scale score | 2.3 ± 2.8 | 0.84 | 0.2 ± 1.1 | 0.15 | 2.6 ± 2.6 | 1.00 | 0.1 ± 1.7 | 0.04 |
| Muscle strength: | | | | | | | | |
| Motricity Index sub-score | | | | | | | | |
| - shoulder | 5.1 ± 8.1 | 0.62 | 1.2 ± 5.2 | 0.23 | 6.2 ± 8.6 | 0.73 | 1.9 ± 5.0 | 0.37 |
| - elbow | 5.3 ± 8.4 | 0.64 | 2.3 ± 4.8 | 0.48 | 7.1 ± 8.0 | 0.88 | 1.6 ± 3.6 | 0.45 |
| Power grip (kg) | 2.6 ± 5.1 | 0.52 | 0.4 ± 1.6 | 0.23 | 3.4 ± 5.8 | 0.59 | 1.5 ± 1.9 | 0.77 |
| Index pinch grip (kg) | 0.8 ± 1.7 | 0.46 | 0.0 ± 1.0 | 0.02 | 1.0 ± 2.0 | 0.49 | 0.5 ± 0.9 | 0.51 |
| Functional ability: | | | | | | | | |
| Action Research Arm Test | 11.7 ± 21.4 | 0.54 | 4.3 ± 7.8 | 0.55 | 17.1 ± 23.7 | 0.72 | 1.5 ± 3.9 | 0.38 |

SRM is a standardized response mean characterizing the change in the outcome variable

## 3.4 Discussion

### *3.4.1 Norms for tactile discrimination and grip strength*

The norm established for PR with the healthy controls was comparable to that reported by Desrosiers and colleagues (1996). However, the 2-PD threshold adopted as a norm in this study was lower than that reported by Kim and Choi (1996). The results confirmed, however, that the dominant and non-dominant hands were similar in tactile discrimination thresholds. They also support the finding that females have lower PR thresholds in the finger than males of similar age (Weinstein and Sersen 1961). In contrast, gender difference was not found to be significant for 2-PD.

This study found that GRIP and PINCH readings were stronger in males than females, and the dominant hands were stronger, agreeing with previous reports in the literature (Bassey and Harries 1993, Hanten et al. 1999).

With the norms for tactile discrimination threshold and hand grip strength established in a sample of subjects similar in age and recruited in residential districts similar to those of the subjects of the main study, these values could be used as normal reference for reviewing sensori-motor recovery of paretic UEs.

### *3.4.2 Time course of recovery in the paretic upper extremity*

In this study, the recovery of the paretic UE as a function of time can be seen in the longitudinal data recorded from 57 subjects from the very acute stage of stroke (within 5 days since stroke onset) to 6 months afterwards. Similar tracking of the time course of recovery from stroke was carried out in western populations more than a decade ago (Duncan et al. 1992, Jorgensen et al. 1995, Kelly-Hayes et al. 1989, Lindmark 1988, Nakayama et al. 1994). Results of our study therefore facilitated an updated review of the recovery process of the paretic UE of patients

who had been receiving conventional medical and rehabilitation management.

3.4.2.1 Period of rapid recovery in the paretic upper extremity

Most subjects showed substantial recovery of all sensori-motor functions of the paretic UE in the initial 3 months, particularly during the first and second month post-stroke. The rate of improvement during the first post-stroke month was better with motor function than with tactile sensation. Such rapid motor recovery early after stroke was also reported by Duncan and coworkers (1992) in their study of 104 patients who were assessed within 2 days from stroke onset. Their patients with moderate to severe stroke continued to show some recovery till 3 months post-stroke. After tracking the recovery of 119 patients with first stroke over 4.5 years, Kelly-Hayes and partners (1989) commented that significant recovery of strength and functional ability after stroke was obvious in the initial 3 months, but any progress became minimal afterwards. Two other studies which followed patients from the acute stage of stroke to 1 year and beyond also revealed similar temporal characteristics of recovery (Lindmark 1988, Wade et al. 1983).

That significant improvement in sensory, motor and functional abilities took place in the first 2 months after stroke could partly be accounted for by spontaneous recovery. During this period, neurons which survive the acute infarct and are connected with the site of the primary infarct could recover from the initial “shock” stage (Seitz et al. 1999), the penumbral regions (brain tissues at risk of infarct) could be reperfused, and extra-cellular and intra-cellular oedema could be resolved. If so, neuronal function could be partly restored, leading to the observed rapid recovery. In addition, brain structures remote from the site of the lesion, i.e., the so-called diaschisis, would have time to become reactivated and take part in restoring function

(Feeny and Baron 1986, Seitz et al. 1999).

Despite nearly 2 decades which had elapsed since previous studies, the subjects in the present study still showed similar rates of recovery in response to conventional management. It is worthwhile to note that the mean length of their in-patient stay was 42.0 days (SD 13.3 days). Most of the subjects continued to attend out-patient rehabilitation once or twice a week for 4 to 6 months. The substantial improvement in all stroke-induced neurological deficits during the first 1 to 2 months might indicate that this period is optimal for neurological recovery, but it may also represent the results of the more intensive daily in-patient rehabilitation programme.

3.4.2.2 Recovery of sensory impairment

This study is the first one to describe the recovery of sensory deficits with time after stroke. Although most patient subjects in our sample were impaired in PR at baseline (77%), there were more subjects had severely impaired 2-PD (32%) than severely impaired PR (8.8%). The somatosensory system involves redundant ascending pathways generating sensation as well as parallel processing of the afferent signals transmitted via these pathways (Kandel and Jessel 1991). This redundancy might explain the near complete recovery in PR in many subjects within the first 2 months of stroke. But on average, 2-PD did not recover to the normal value until 4 months post-stroke. Unlike PR which relies on just perception of tactile pressure at 1 cutaneous site, 2-PD depends on small receptive fields over 2 separate sites and involves more complex processing in the sensory cortex (Kaas 1993). This would demand larger pools of neurons for proper two-point discrimination. A longer period of recovery may therefore be expected. It has also been suggested that 2-PD is associated with hand function (Dellon and Kallman 1983). It should thus be an

important outcome variable to monitor in stroke rehabilitation.

3.4.2.3 Change of muscle tone

Twitchell (1951) in his classic report described the presence of hyperactive tendon reflexes from within 48 hours to the first month of stroke. The present longitudinal study of patients with acute ischaemic stroke over 6 months provides a more detailed picture of changes in muscle tone in the paretic UE with time. The increase in muscle tone took place mainly in the first 4 weeks after stroke. The percentage of subjects with UE spasticity increased from 44% to 70% by week 2 post-stroke, when 21% subjects continued to have a hypotonic UE. The proportion of subjects with hypertonicity increased further to 86% by 6 months post-stroke. Previously, a cohort study by Watkins and coworkers (2002) found that, using the modified Ashworth scale 1 year post-stroke, the prevalence of spasticity was 39% of patients who had suffered a first-ever stroke. Another study of 95 patients showed that only 19% of the cohort had spasticity in the extremities at 3 months after stroke (Sommerfeld et al. 2004). The high incidence of spasticity in the paretic UE observed in the present study might have been due to different emphasis in stroke management as compared to the emphasis in previous studies, or to different methods of muscle tone measurement. Although any direct association of abnormal muscle tone with functional recovery remains unclear, a substantial increase in spasticity in the UE might indicate possible presence of voluntary movements (Twitchell 1951). However, it has also been suggested that complications such as contractures and synergistic movements might develop if spasticity is ignored in stroke treatment (Bobath 1990, O'Dwyer et al. 1996). It would then be important to investigate the predictive value of muscle tone for UE functional recovery so that

rehabilitation goals could be properly set.

3.4.2.4 Recovery in muscle strength and functional ability

In the first month post-stroke, the magnitude of improvement in UE muscle strength in terms of SRM has been larger than that in the second month. The present results also support the observation that the proximal muscles of the shoulder and elbow improve more than the distal hand muscles in the early stage after stroke. This relationship reversed in the period between 3 and 6 months post-stroke, with power grip and index pinch strength showing large (SRM = 0.77) and moderate (SRM = 0.51) effect sizes respectively. In this period, the improvement in shoulder and elbow muscle strength was small in magnitude (SRM $\leq$0.45). At 6 months post-stroke, the mean recovery in muscle strength was only to about two-thirds of the norm in shoulder abductors and elbow flexors, and to around one-third of the norm for the GRIP and PINCH test results.

For UE functional ability, it was recovered to a greater extent during the first 3 months post-stroke (SRM = 0.72). Despite continuous substantial improvements in GRIP and PINCH between 3 and 6 months post-stroke, UE functional ability showed only small improvements (SRM = 0.38) in this period. The improvements in strength of the hand grips seemed not to have transferred to the performance of functional tasks. Conventional rehabilitation might need to address this mismatch in the improvement of muscle strength and functional ability in the paretic UE.

## 3.5 Conclusion

The recovery of the subjects receiving only conventional rehabilitation in

local public hospitals in Hong Kong followed time course similar to that reported in the literature on western populations. Much recovery in sensori-motor functions in the paretic UE took place during the initial 1 to 2 months after stroke. Most subjects showed recovery in tactile sensation to near the normal threshold within the first 4 months after stroke. Recovery of motor functions, on the other hand, was less satisfactory. Most of the subjects had persistent spasticity in the paretic UE. Many of them demonstrated reduced muscle strength and functional ability at 6 months post-stroke. Rehabilitation therapies for the paretic UE should promote motor and functional recovery during the early period after stroke, as well as enhance further recovery during the stage of slow progress beyond.

# *Chapter 4*

## *Predicting the Recovery of Dexterity Function in a Paretic Upper Extremity*

**Summary**

The recovery of motor function in a paretic upper extremity (UE) after stroke is usually complicated by compensatory use of the less affected extremity (Broeks et al. 1999, Nakayama et al. 1994). The longitudinal study reported in Chapter 3 showed that the recovery of functional ability in the paretic UE was fastest in the initial 1 to 2 months after stroke and was slow thereafter. Early predictors of recovery should guide treatment approach in the early stage of rehabilitation. Using a prospective longitudinal design, the present study aimed to identify early clinical characteristics in the first and second month post-stroke which might predict the recovery of dexterity function in the paretic UE 3 and 6 months later.

***Methods:*** The cohort of 57 subjects reported in Chapter 3, who were identified 5 days or less after having suffered a stroke and who were receiving conventional rehabilitation were studied. The recovery of their sensory and motor function was tracked from the time of recruitment to 6 months post-stroke. To identify predictors of the recovery of UE functional ability, multiple binary logistic regression was used to analyze the data. The main outcome measure was dexterity function of the paretic UE in terms of precision grip, which involved grasping, gripping or pinching objects with the hand and fingers, as indicated by a score of ≥35 in the Action Research Arm Test. The predictor candidates included the side and site of the brain infarct, stroke severity, cognition and spatial neglect; and the weekly status of pressure sensibility (PR), two-point discrimination (2-PD), muscle tone, UE muscle strength measured with the Motricity Index, and the strength of power grip and index pinch grip measured with dynamometry. The strength of prediction was evaluated with the Receiver Operating Characteristics (ROC) curve and likelihood ratio test.

***Results:*** The recovery of dexterity function in the paretic UE at 3 and 6 months post-stroke were significantly predicted by 2-PD in week 1 to 3 (odds ratio, OR ranged from 0.51 to 0.83). The weekly status of muscle strength in the paretic UE measured with the Motricity Index in the first 4 weeks post-stroke also consistently predicted the functional outcome of the paretic UE at 3 and 6 months after stroke (OR ≥1.04). After adjusting for the effects of prediction with other predictor candidates, the Motricity Index score at week 4 post-stroke was the strongest predictor, followed by combined 2-PD and Motricity Index score at week 2 post-stroke. At week 4 post-stroke, power grip and index pinch strength were stronger predictors of dexterity function at 3 and 6 months (area under the ROC curve ≥0.95) than the more proximal shoulder and elbow muscle strength (area under the ROC curve ranged from 0.88 to 0.93).

***Conclusion:*** The best early predictors of dexterity function are muscle strength and two-point discrimination in the paretic UE in the first month post-stroke.

## 4.1 Introduction

Survivors of stroke regard upper extremity (UE) function to be important for their quality of life (Williams 1999). Previous studies of people 2 to 3 years after a stroke showed that 25 to 45% of them had experienced some return of function in the affected UE (Olsen 1990, Parker et al. 1986, Wade et al. 1983). However, Broeks and colleagues (1999) reported that 45% of subjects still manifested poor UE function 4 years post-stroke. During daily activities, non-use of the paretic UE with compensation from the less affected side was common (Broeks et al. 1999, Nakayama et al. 1994). Delineating the key predictors of functional recovery in the paretic UE has thus aroused the interest of both clinicians and researchers.

The severity of initial motor impairment in the paretic UE is known to be prognostic for the return of its strength (De Weerdt et al. 1987, Wade et al. 1983). Some studies have also demonstrated that muscle weakness predicts later disability in performing activities of daily living assessed with the Barthel Index (Heller et al. 1987, Shelton and Reding 2001). However, it has been difficult to interpret the exact amount of functional ability recovered in these studies, as the less affected UE was often not restricted from performing the functional tasks during assessments.

Recently, Kwakkel and coworkers (2003) have reported on the probability of regaining dexterity after 6 months in people with a flaccid UE after acute stroke. They used a score of 10 or above on the Action Research Arm Test (full score, 57) as a cut-off for dexterity in functions such as grasp, grip and pinch. Note that such a low cut-off score only captured the presence of gross shoulder and elbow movements, and could therefore lead to false positives for the return of dextrous precision gripping using the hand and fingers.

Apart from muscle strength, the prognostic values of other clinical characteristics such as the side of the stroke lesion (Kwakkel et al. 2003, Macciocchi et al. 1998), perception (Gowland C 1984, Katz et al. 1999, Kwakkel et al. 2003), cognition (Fullerton et al. 1988, Kwakkel et al. 2003), and sensory impairment (Feys et al. 2000, Hendricks et al. 1997, Kusoffsky et al. 1982, Prescott et al. 1982) remains unclear on the basis of research to date (Katrak et al. 1998, Yavuzer et al. 2001). In some of those studies, predictors of UE function were measured in subjects recruited at different times ranging from 1 to 6 weeks after stroke onset (Feys et al. 2000, Gowland 1984, Kwakkel et al. 2003). Since substantial progress could have taken place in the early stage of stroke (Duncan et al. 1992), such variations when the predictor candidates were measured could limit the utility of the results.

The rate of functional recovery after stroke is known to be non-linear, with the most rapid recovery in the initial 1 to 3 months (Duncan et al. 1994, Kwakkel et al. 2004, Nakayama et al. 1994, Wade et al. 1983). Other studies have also noted the greatest improvement in motor impairment and function in the paretic UE takes place in the initial 3 to 6 months post-stroke (Broeks et al. 1999, Lindmark 1988). Results of the longitudinal study reported in Chapter 3 also showed that the recovery of sensori-motor functions in the paretic UE was rapid during the initial 1 to 2 months after stroke. Early predictors for dextrous function in the paretic UE should inform treatment plans for more effective recovery. However, it is not clear which clinical characteristics offer the best predictions of functional outcome at different post-stroke periods. This study therefore aimed to identify the clinical characteristics in the first month after stroke that best predict the return of functional dexterity 3 and 6 months post-stroke.

## 4.2 Subjects and Methods

### *4.2.1 Study Design*

This was a longitudinal prospective cohort study. Ethical approval was obtained from the ethics committees of the university where the study was initiated, as well as that of the acute hospital (Queen Elizabeth Hospital) and the rehabilitation hospital (Kowloon Hospital) where the subjects were recruited and then followed up (see Chapter 2, section 2.7).

### *4.2.2 Subjects*

Subjects were recruited from the acute stroke unit of the Queen Elizabeth Hospital in Hong Kong. The inclusion and exclusion criteria were described in Chapter 2, sections 2.2.1 and 2.2.2.

### *4.2.3 Predictor and outcome variables*

For a description of measurement battery and intervals and how the outcome and predictor variables were measured, please refer to Chapter 2, sections 2.4.1 to 2.4.6.

#### 4.2.3.1 Outcome variable

The main outcome variable to be predicted was the presence of functional dexterity in the paretic UE at 3 and 6 months after the onset of stroke. UE functional ability was measured with the Action Research Arm Test (ARAT) (Lyle 1981). As described in Chapter 2, section 2.4.6, the ARAT consists of 19 tasks categorized into 4 sub-tests: grasp (6 tasks), grip (4 tasks), finger pinch (6 tasks), and gross movements of the shoulder and elbow (3 tasks). The tasks were performed solely by

the paretic UE. The level of performance was rated on a 4-point scale, with 0 for inability to perform the task, 1 for partial completion, 2 for completion with abnormal synergies, and 3 for normal performance. The maximum possible ARAT score was therefore 57 (refer to Appendix VI). This test's validity and reliability in measuring UE function after stroke have been well proven (Hsieh et al. 1998, van der Lee et al. 2001). In the present study, a score of 35 or above was taken to signify the return of functional dexterity in the paretic UE as long as some precision grip and pinch ability was present. This score indicated that at least 17 of the 19 tasks could be completed either slowly or with abnormal synergies (Kwakkel et al. 2003, Lyle 1981), despite pinch grips with the ring finger not being possible.

4.2.3.2 Predictor variables

From previous studies of recovery in the paretic UE (Chapter 1, section 1.2.2), 8 clinical characteristics were selected as candidate predictors. The side of the lesion (1) and (2) the site of the brain infarct were categorized as either lacunar or no obvious lesion, cortical, subcortical, or combined cortical and subcortical (Dromerick and Reding 1995, Kretschman 1986, Shelton and Reding 2001) on the basis of CT or MRI scan reports. (3) The severity of the stroke was rated using the National Institutes of Health Stroke Scale (NIHSS) (Brott et al. 1989, Goldstein and Samsa 1997), with lower scores denoting less severe stroke. (4) Spatial neglect was evaluated by one or more lines being left uncrossed in the Line-cancellation Test (Albert 1973). (5) Cognitive status was assessed using the Neurobehavioral Cognitive Status Examination (Kiernan et al. 1987). This is a validated and sensitive technique for evaluating the cognitive effects of stroke, with scores $\leq$65 indicating impaired cognition (Mueller et al. 2001). (6) Sensation in the paretic UE,

specifically pressure sensibility (PR) and two-point discrimination (2-PD), were measured on the distal pulp of the index finger. (7) Muscle tone in the affected UE was measured in the biceps using the Composite Spasticity Score (Levin and Hui-Chan 1992). This is a validated composite measure of both the phasic and tonic stretch reflexes of the tested muscle, with scores from 0 to 5 indicating hypotonicity, 6 indicating normal tone, and 7 to 12 indicating hypertonicity. (8) Muscle strength in the paretic UE was measured with the composite score of Motricity Index (norm score 100, Demeurisse et al. 1980, refer to Appendix V), as well as the strength of power grip and index pinch grip.

### *4.2.4 Procedures*

The protocols for assessing the candidate predictors of stroke severity and sensori-motor impairment were standardized as has been described in Chapter 2, sections 2.4.2 to 2.4.5. A physiotherapist trained in using the NIHSS assessed the baseline status of all the candidate predictors. The main outcome variable, UE functional ability, was assessed by the author (AYS) using the ARAT 8 times up to 6 months post-stroke (see Chapter 2, section 2.4.1). Neither rater was involved in the conventional rehabilitation programme of these subjects. As reported in Chapter 2, section 2.5, moderate to excellent test-retest and inter-rater reliability were confirmed for the sensation, muscle strength and UE motor function results, with intraclass correlation coefficients ranging from 0.63 to 1.00.

### *4.2.5 Data analysis*

SPSS version 11.0 for Windows was used in the data analyses. Univariate binary logistic regression was applied to assess the strength of association between

the candidate predictors and the presence of functional dexterity in the paretic UE at 3- and 6-months post-stroke. Those candidate predictors showing independent association with the outcome (in terms of odds ratio with $P \leq 0.05$) were selected for model fitting in subsequent multiple logistic regression analyses, using a backward stepwise likelihood ratio approach in 2 steps. The probability for removal of predictors was set at 0.05. Step 1 analysed all the predictors screened by the univariate binary logistic regression; step 2 examined the effects of interactions amongst the predictors as well as model fitting. The overall strength of prediction of the candidate predictors, and the sensitivity and specificity of the prediction models were determined by analyzing the Receiver Operating Characteristics (ROC) curve and the likelihood ratio test.

## 4.3 Results

Seventy subjects were recruited from the acute stroke unit and subsequently followed up in the rehabilitation hospital and in their place of residence. Thirteen subjects were excluded from the regression analyses for various reasons (Chapter 3, section 3.3.3). The baseline characteristics of the 57 subjects who completed 6 months of assessments were not different from those of the drop-outs (see Table 3.2).

### *4.3.1 Clinical variables associated with the return of functional dexterity*

4.3.1.1 Predictor candidates at recruitment

Table 4.1 presents the results of univariate logistic regressions of candidate predictors at recruitment against UE dextrous function (ARAT ≥35) 3 and 6 months after stroke. In such an analysis, a predictor with an odds ratio which was significant

**Table 4.1: Association of the candidate predictors at recruitment with recovery of upper extremity dextrous function (Action Research Arm Test score ≥ 35) at 3 and 6 months post-stroke**

| Predictor Candidates | *3-month functional outcome* | | *6-month functional outcome* | |
|---|---|---|---|---|
| | Odds Ratio (95% C.I.) | *P* | Odds Ratio (95% C.I.) | *P* |
| Hemispheric lesion (with reference to right-sided lesion) | 1.81 (0.59-5.51) | 0.300 | Same results as that for 3-month | |
| Site of lesion : | | 0.051 | | |
| Cortical | 0.46 (0.07-3.09) | 0.420 | | |
| Subcortical | 0.18 (0.05-0.69) | 0.013* | | |
| Cortical & Subcortical | 0.09 (0.01-1.00) | 0.050* | | |
| Stroke Severity | 0.66 (0.51-0.87) | 0.003* | 0.72 (0.57-0.92) | 0.008* |
| Cognition | 1.02 (0.98-1.06) | 0.345 | 1.02 (0.98-1.06) | 0.364 |
| Spatial neglect | 0.97 (0.34-2.83) | 0.962 | 0.97 (0.34-2.83) | 0.962 |
| Sensation: Pressure sensibility | 0.56 (0.30-1.06) | 0.073 | 0.57 (0.30-1.06) | 0.076 |
| Two-point discrimination | 0.84 (0.75-0.96) | 0.007* | 0.85 (0.75-0.96) | 0.008* |
| Upper extremity muscle tone | 1.10 (0.89-1.38) | 0.381 | 1.06 (0.85-1.32) | 0.585 |
| Muscle strength: Motricity Index score | 1.06 (1.03-1.09) | 0.000* | 1.04 (1.02-1.07) | 0.001* |
| Power grip | 1.20 (0.98-1.46) | 0.082 | 1.13 (0.96-1.33) | 0.158 |
| Index pinch grip | 1.56 (0.93-2.62) | 0.095 | 1.31 (0.84-2.03) | 0.232 |

Abbreviation: C.I.=confidence interval; * Denotes values significant at the $P \leq 0.05$ level in univariate binary logistic regression

and greater than 1 would give a favourable prognosis for the return of functional dexterity in the paretic UE, while those significant but less than 1 indicate an adverse prognosis. The table shows that the side of the lesion and the initial levels of cognitive impairment, spatial neglect and muscle tone were not significantly associated with the functional outcome. The 4 variables which showed significant associations were the site of the lesion, the severity of the stroke, initial 2-PD and muscle strength in the paretic UE as measured with the Motricity Index.

4.3.1.2 Muscle tone and functional dexterity

Results of the univariate logistic regression showed there was no significant relationship between muscle tone in the paretic UE up to 2 months post-stroke and the functional outcome at 3 or 6 months post-stroke (Table 4.2).

**Table 4.2: Prediction from muscle tone of UE function at 3 and 6 months post-stroke**

| *Time post-stroke* | *3-month functional outcome* | | *6-month functional outcome* | |
|---|---|---|---|---|
| | Odds Ratio (95% C.I.) | *P* | Odds Ratio (95% C.I.) | *P* |
| *Baseline* | 1.10 (0.89 - 1.38) | 0.381 | 1.06 (0.85-1.32) | 0.585 |
| *Week 1* | 1.15 (0.89 - 1.47) | 0.285 | 0.97 (0.77 - 1.23) | 0.801 |
| *Week 2* | 1.10 (0.84 - 1.43) | 0.484 | 1.10 (0.84 - 1.43) | 0.484 |
| *Week 3* | 0.83 (0.59 - 1.16) | 0.272 | 0.88 (0.63 - 1.21) | 0.428 |
| *Week 4* | 0.73 (0.50 - 1.07) | 0.103 | 0.81 (0.57 - 1.17) | 0.259 |
| *2 months* | 0.72 (0.50 - 1.05) | 0.089 | 0.75 (0.52 - 1.08) | 0.123 |

Abbreviations: C.I.=confidence interval from the univariate logistic regression analysis.

4.3.1.3 Muscle strength as a predictor

Table 4.3 presents the results of regressing initial muscle strength in the paretic UE against functional outcome measures at 3 and 6 months post-stroke. The area under the ROC curve indicates a variable's strength of prediction. At baseline and 2 weeks after recruitment, the Motricity Index shoulder and elbow subscores showed larger ROC curve areas than the strength of power grip or index pinch grip, with the elbow subscore showing the greatest predictive power. At week 4, power grip strength and index pinch strength demonstrated better predictive power to the recovery of functional dexterity than the prediction from shoulder and elbow muscle strength. At 2 months post-stroke, power grip strength continued to be the strongest predictor amongst the muscle strength candidate predictors.

### *4.3.2 The best early predictors of UE functional recovery*

The 4 significant baseline predictors reported in Table 4.1 were entered in the model fitting analysis for the 3- and 6-month functional outcomes using multiple logistic regressions and a stepwise backward likelihood ratio approach. There was no significant interaction of the predictors in terms of functional outcome. Table 4.4 describes the results of the model fitting. At baseline assessment, muscle strength was the only predictor significantly associated with UE dextrous function at 3 months post-stroke (O.R. = 1.06). In the subsequent 3 weeks, the weekly status of muscle strength (O.R. from 1.12 to 1.16) and 2-PD (O.R. from 0.72 to 0.75) together best predicted the functional outcome. However, by $W_4$ and out to 2 months post-stroke, muscle strength became the only strong predictor of UE function at 3 months. Similar findings apply to the prediction of UE dextrous function at 6 months post-stroke. Larger values of the likelihood ratio signify greater strength of the predictor

**Table 4.3: Prediction from muscle strength to functional dexterity at 3 and 6 months post-stroke**

| *Predictors* | *3-month functional outcome* | | | *6-month functional outcome* | | |
|---|---|---|---|---|---|---|
| | Odds Ratio (95% C.I.) | *P** | Area under ROC curve | Odds Ratio (95% C.I.) | *P** | Area under ROC curve |
| *Baseline:* | | | | | | |
| Motricity Index – shoulder subscore | 1.18 (1.07 - 1.31) | 0.001 | 0.79 | 1.12 (1.03 - 1.22) | 0.007 | 0.73 |
| – elbow subscore | 1.17 (1.07 - 1.29) | 0.001 | 0.80 | 1.12 (1.04 - 1.21) | 0.003 | 0.75 |
| Power grip strength | 1.20 (0.98 - 1.46) | 0.082 | 0.67 | 1.13 (0.96 - 1.33) | 0.158 | 0.63 |
| Index pinch grip strength | 1.56 (0.93 - 2.62) | 0.095 | 0.59 | 1.31 (0.84 - 2.03) | 0.232 | 0.55 |
| *Week 2 post-stroke:* | | | | | | |
| Motricity Index – shoulder subscore | 1.33 (1.13 - 1.56) | 0.001 | 0.88 | 1.59 (1.21 - 2.07) | 0.001 | 0.93 |
| – elbow subscore | 1.38 (1.17 - 1.63) | 0.000 | 0.93 | 1.52 (1.21 - 1.91) | 0.000 | 0.95 |
| Power grip strength | 1.64 (1.14 - 2.36) | 0.008 | 0.77 | 2.05 (1.25 - 3.34) | 0.004 | 0.82 |
| Index pinch grip strength | 4.12 (1.40 - 12.09) | 0.010 | 0.75 | 7.33 (1.74 - 30.91) | 0.007 | 0.78 |
| *Week 4 post-stroke:* | | | | | | |
| Motricity Index – shoulder subscore | 1.31 (1.14 - 1.49) | 0.000 | 0.88 | 1.45 (1.21 - 1.74) | 0.000 | 0.93 |
| – elbow subscore | 1.47 (1.22 - 1.76) | 0.000 | 0.93 | 1.67 (1.30 - 2.15) | 0.000 | 0.96 |
| Power grip strength | 2.35 (1.48 - 3.73) | 0.000 | 0.95 | 4.35 (1.89 - 10.01) | 0.001 | 0.97 |
| Index pinch grip strength | 21.48 (4.20 - 109.91) | 0.000 | 0.95 | 90.98 (7.22 - 1147.17) | 0.000 | 0.97 |
| *2 months post-stroke:* | | | | | | |
| Motricity Index – shoulder subscore | 1.25 (1.12 - 1.41) | 0.000 | 0.86 | 1.36 (1.16 - 1.59) | 0.000 | 0.90 |
| – elbow subscore | 1.68 (1.21 - 2.33) | 0.002 | 0.93 | 26.10 (0.00 - - ) | 0.996 | 0.95 |
| Power grip strength | 1.90 (1.32 - 2.72) | 0.001 | 0.96 | 2.82 (1.57 - 5.05) | 0.001 | 0.97 |
| Index pinch grip strength | 4.70 (1.89 - 11.69) | 0.001 | 0.93 | 11.97 (2.88 - 49.80) | 0.001 | 0.94 |

Abbreviation: C.I.=confidence interval; ROC=Receiver Operating Characteristics; * denotes the *P*-value of a univariate logistic regression analysis

**Table 4.4: Best predictors for functional dexterity at 3 and 6 months post-stroke**

| *Best predictors* | Odds Ratio | Likelihood Ratio test | *P* | Sensitivity | Specificity |
|---|---|---|---|---|---|
| *(1) 3-month outcome* | | | | | |
| *Baseline:* UE muscle strength | 1.06 | 21.01 | * | 0.83 | 0.73 |
| *Week 1 post-stroke:* | | | | | |
| UE muscle strength | 1.16 | 37.89 | * | 083 | 0.94 |
| Two-point discrimination | 0.74 | 7.73 | 0.005 | | |
| *Week 2:* | | | | | |
| UE muscle strength | 1.16 | 41.76 | * | 0.96 | 0.87 |
| Two-point discrimination | 0.75 | 5.38 | 0.020 | | |
| *Week 3:* | | | | | |
| UE muscle strength | 1.12 | 30.56 | * | 0.96 | 0.88 |
| Two-point discrimination | 0.72 | 5.34 | 0.021 | | |
| *Week 4:* | | | | | |
| UE muscle strength | 1.18 | 50.98 | * | 0.96 | 0.94 |
| *2 months:* | | | | | |
| UE muscle strength | 1.14 | 45.53 | * | 0.96 | 0.85 |
| *(2) 6-month outcome* | | | | | |
| *Baseline:* UE muscle strength | 1.04 | 13.34 | * | 0.78 | 0.71 |
| *Week 1 post-stroke:* | | | | | |
| UE muscle strength | 1.09 | 24.62 | * | 0.74 | 1.00 |
| Two-point discrimination | 0.83 | 6.12 | 0.013 | | |
| *Week 2:* | | | | | |
| UE muscle strength | 1.45 | 53.12 | * | 1.00 | 0.94 |
| Two-point discrimination | 0.51 | 8.76 | 0.003 | | |
| *Week 3:* | | | | | |
| UE muscle strength | 1.15 | 36.10 | * | 1.00 | 0.91 |
| Two-point discrimination | 0.74 | 4.65 | 0.031 | | |
| *Week 4:* | | | | | |
| UE muscle strength | 454220.78[#] | 74.11 | * | 1.00 | 0.97 |
| *2 months:* | | | | | |
| UE muscle strength | 1.27 | 56.96 | * | 1.00 | 0.88 |

Abbreviation: C.I. = confidence interval, UE = upper extremity. * Denotes significance at $P \leq 0.0005$ in a likelihood ratio test of a multiple logistic regression analysis using the backward likelihood ratio approach. [#] denotes a prediction from UE muscle strength at a cut-off Motricity Index score of 64 clearly demarcate subjects in favour of the presence of functional dexterity (Action Research Arm Test score ≥35) at 6 months post-stroke

models. Muscle strength in the paretic UE at $W_4$ post-stroke was therefore the strongest predictor of functional dexterity at both 3 and 6 months post-stroke.

From analysis of the ROC curves, a Motricity Index score ≥62 for muscle strength in the paretic UE at $W_4$ post-stroke could be considered a cut-off threshold for the return of UE dextrous function at 3 months. This indicator showed high sensitivity (0.96) and specificity (0.94) of prediction. The cut-off Motricity Index score predictive of a satisfactory 6-month functional outcome was 64. The second best model for predicting the 3- and 6-month functional outcome invoked muscle strength and 2-PD results at week 2 post-stroke, which showed sensitivity and specificity of prediction of ≥0.96 and ≥0.87 respectively. The return of UE dextrous function was predicted with a Motricity Index score ≥45 if the 2-PD threshold was normal (3.4 mm). The results suggest that at week 2 post-stroke, 1 mm loss in 2-PD acuity can, statistically speaking, be compensated by a 2 point increase in Motricity Index score in formulating prognosis for UE dextrous function at 3 and 6 months.

## 4.4 Discussion

### *4.4.1 Non-significant predictor candidates*

Previous studies have shown that an adverse prognosis for function in the affected UE after stroke is associated with right hemispheric lesions, spatial neglect and cognitive impairment (Jehkonen et al. 2000, Kwakkel et al. 2003, Macciocchi et al. 1998, Novack et al. 1987). In the study of Kwakkel and co-workers (2003), the prognostic value of the side of stroke and spatial neglect was demonstrated using a homogeneous group (n=102) having poor UE function (ARAT <10) with a median Motricity Index score of 0 for UE strength. Left hemisphere strokes outnumbered

right hemisphere strokes by a proportion of 2 to 3 in in the study group, and half of them had spatial neglect. The present study included subjects who demonstrated a wider range of initial strength impairment at recruitment, with Motricity Index score ranging from 0 to 77. Forty-six of the subjects had poor UE function at recruitment, 39% of them had suffered right-hemisphere strokes, and 44% demonstrated neglect. With this group, the return of functional dexterity was not significantly associated with the side of the stroke lesion, nor with initial neglect. Moreover, their cognitive status had no significant impact on the functional outcome. This was probably due to the nature of the tasks tested, which might not have demanded sufficient planning or analytical thinking during their execution to highlight any relationship.

### *4.4.2 Site of the brain infarcts as a predictor*

A subcortical lesion or a large brain infarct involving both cortical and subcortical structures was found to be marginally significant for predicting functional recovery in the paretic UE at 6 months after stroke ($P$ = 0.013 and 0.050 respectively; Table 4.1). Previous studies have shown that people with total anterior circulation infarcts or lesions involving subcortical structures can expect less UE motor recovery (Duncan et al. 1994, Feys et al. 2000, Shelton and Reding 2001). Using neuroimaging techniques to diagnose acute capsular stroke, Wenzelburger and colleagues (2005) found that lesions in the posterior regions of the internal capsule were associated with chronic dexterity deficits in the affected UE. In the present study, this association could not be demonstrated in the multiple regression analysis. It could be argued that the results have been limited by the small sample in which more subjects had suffered subcortical lesions.

### *4.4.3 Severity of stroke as a predictor*

Severity of stroke has been found to be predictive of the recovery of patients' abilities in their activities of daily living (Adams et al. 1999). However, whether it might also be predictive for the recovery of functional dexterity had never been examined prior to this study. The results show that severity of stroke had an independent association with the functional outcome of the paretic UE, but its strength of prediction became non-significant after adjusting for the effects of other predictors. One reason could be high correlation between severity of stroke and muscle strength in the paretic UE. Nevertheless, the results highlight the need to control for possible confounding effects of severity in clinical trials.

### *4.4.4 Muscle tone was not associated with UE function*

Muscle tone is often considered crucial in governing the recovery of UE motor function (Formisano et al. 2005). In the classic observational study on the recovery of motor function after stroke, Twitchell (1951) commented that early return of finger jerk was prognostic to motor recovery. The cohort in the present study which received only conventional rehabilitation showed that muscle tone in the paretic UE in the first 2 months post-stroke was not a good predictor for the recovery of UE dextrous function (Table 4.2). Sommerfeld and coworkers (2004), who investigated the occurrence of spasticity in 95 patients from week 1 to 3 months post-stroke, found that muscle tone was only weakly associated with the ability to perform motor activities. In the present study, 85% of the subjects (n=48) had spasticity in their paretic biceps by 2 months post-stroke, while only 5 subjects had hypotonic biceps. Based on these results, the traditional emphasis on normalizing

muscle tone (Lennon and Ashburn 2000) to promote the functional dexterity recovery in the paretic UE cannot be justified during the early stages of rehabilitation.

### *4.4.5 Muscle strength as a predictor of functional dexterity*

A study of Sunderland and colleagues (1989) has shown that power grip strength 1 month after stroke can predict recovery in the affected UE. The results of the present study confirm that power grip strength can become a significant predictor by week 2 post-stroke, but not before this, when shoulder and elbow muscle strength are stronger as predictors (Table 4.3). However, power grip and index pinch grip became relatively stronger predictors by week 4 post-stroke. This pattern of predictive power has implications for strategies to reeducate UE functional ability. Improvement in power grip and index pinch strength during the first month after stroke as a result of natural recovery or appropriate treatment should be favourable to later functional recovery in the paretic UE.

### *4.4.6 The best predictors of upper extremity functional recovery*

The results show that strength in the paretic UE was the only consistent early predictor for its functional recovery at 3 and 6 months after stroke onset (Table 4.4). In addition to UE muscle strength, the prediction models in the initial 3 weeks post-stroke also included a significant term for the 2-PD threshold in the paretic hand. The prediction at week 2 was the second strongest after the week 4 model. Duncan and colleagues (1992) have reported that motor and sensory scores on the Fugl-Meyer Assessment at day 5 after stroke together can account for 74% of the variance in the composite scores at 6 months post-stroke. However, it is not possible to

delineate the contribution of UE sensation to the recovery of discrete UE dextrous function from such composite scoring of the sensori-motor functions in both the upper and lower extremity. Other reports on the predictive value of sensation for UE recovery have not provided a clear description of the sensory modality, the method of measurement, or both (De Weerdt et al. 1987, Gowland 1984, Feys et al. 2000, Formisano et al. 2005). In the report of Kwakkel and colleagues (2003), UE proprioception measured by locating the affected thumb in space was not found to be associated with the recovery of UE function at 6-month post-stroke. In contrast, Prescott and colleagues (1982) showed this UE position sense to be predictive of independence in daily activities. Note that deficits in position sense had been reported to be less prevalent than deficits in 2-PD after stroke (Kim and Choi 1996), which could have made it less sensitive in prediction, leading to the contradictory results reported by different investigators.

The present study has confirmed that the 2-PD threshold in the affected hand was a significant early indicator of later recovery in functional dexterity after stroke. Sensory discrimination in the hand is crucial for fine manual skills (Jeannerod et al. 1984, Nudo et al. 2000). Tactile afferent signals in the hand guide force control for precision gripping (Johansson and Westling 1987). Complex movements become difficult to perform when perception of such sensation is degraded, especially in the absence of visual guidance (Jeannerod et al. 1984). Up to now, many therapies for the paretic UE which have proven effective in clinical trials have been targeted at improving motor impairments in the extremity (Bütefisch et al. 1995, Chae et al. 1998, Dean and Shepherd 1997, Dromerick et al. 2000). There have been only a few studies on the effects of sensory retraining programmes for the affected hands after stroke (Carey et al. 1993, Yekutiel and Guttman 1993). A recent report, however,

has shown that a treatment programme to improve somatosensory functions in subjects with pure sensory stroke also improved motor control in their manual task performance (Smania et al. 2003). Moreover, post-stroke brain imaging studies have revealed early sensory and motor cortical reorganization ipsilateral and contralateral to the stroke lesion before clinical recovery has become obvious (Feydy et al. 2002, Nelles et al. 1999). In primates (Friel et al. 2000) and humans (Liepert et al. 2000), neuro-plasticity has been shown to be associated with sensori-motor experience. Because muscle strength together with 2-PD in the paretic UE in the first 3 weeks after stroke was found to be the best predictor for recovery of functional dexterity, such impairments should be addressed early in rehabilitation. Compensatory use of the less involved extremity at an early stage could deprive the paretic UE of practice necessary for sensory, motor and functional improvement.

### *4.4.7 Early predictors of 3- and 6-month outcomes*

The prediction models for functional recovery at 3 and 6 months were similar. This could be explained by the lack of progress in UE functional ability from 3 to 6 months post-stroke, as reflected in the ARAT scores (Appendix VII). Prediction of the 6-month outcome had higher sensitivity and specificity than prediction of 3-month UE function. This finding reinforced the importance of sensory and muscle strength status during the early stage of stroke in governing longer-term functional outcome.

Among subjects recruited within the first 5 days after stroke onset, the relative importance of muscle strength and 2-PD in the paretic UE in the first month in predicting the return of UE function was confirmed. Muscle strength 2 months after stroke was, however, less effective as a predictor. These results support the

suggestion by previous researchers (Duncan et al. 1994, Sunderland et al. 1989, Twitchell 1951) that treatment during a 1-month time window from stroke onset is crucial to recovery. This study has explicitly identified 45 and 64 as the Motricity Index cut-off scores at week 2 and week 4 post-stroke predictive of functional recovery at 6 months. This level of muscle strength could serve as a goal for treatments targeted to recover functional dexterity in patients in stroke patients.

## 4.5 Conclusion

In people who have suffered mild to moderately severe strokes at onset, muscle strength and two-point discrimination in the paretic UE in the first month post-stroke are the best early predictors of the recovery of functional dexterity at 3 and 6 months.

# *Chapter 5*

## *Effects of TES applied to Acupoints during Acute Stroke on Recovery of the Paretic Upper Extremity*

**Summary**

The injured brain has been shown to be capable of plastic reorganization that appears to be facilitated by appropriate sensory input, or as a result of repeated practice of the affected body part. Previous placebo-controlled trials on people with stroke have shown that transcutaneous electrical stimulation (TES) of muscles, nerves or acupuncture points could reduce spasticity and improve muscle strength of the affected lower extremity. However, such treatment effects on the paretic upper extremity (UE) have not been systematically demonstrated, especially when TES was applied during the acute stage. The present study investigated the effects of early TES to acupoints on stroke-induced sensori-motor dysfunctions in a paretic UE using a double-blind, placebo-controlled design.

***Methods:*** Patients within 46 hours after the onset of stroke were randomly allocated to receive either conventional rehabilitation (CR) alone (as control, n=18), TES (n=28), or placebo-TES (n=20). TES was applied to 6 acupoints – GB 20 on both sides of the base of the occiput, and LI 15, LI 11, LI 10 and LI 4 on the paretic UE, 60 minutes per day, 5 days per week for 4 weeks. Five groups of outcome measures were evaluated in the paretic UE: (1) tactile sensibility threshold of pressure (PR) and two-point discrimination (2-PD) in the index finger pulp; (2) muscle tone measured with the Composite Spasticity Index; (3) muscle strength of shoulder abduction and elbow flexion measured with the Motricity Index subscores for shoulder and elbow, (4) power grip and index pinch grip strength measured with an electronic dynamometer; and (5) UE functional ability measured with the Action Research Arm Test. Assessments were made at 9 time intervals: on recruitment, weekly during the subsequent 4 weeks of electrical stimulation, and then monthly until 5 months after treatment ended. In addition to 19 acute stroke subjects being

recruited as controls, mixed-model ANCOVA was used to test the differences in UE recovery among the 3 groups, with the level of significance adjusted to 0.017 in post-hoc analysis for the difference in pair-wise comparisons. Side of stroke, time since onset of stroke at recruitment, and pressure sensibility were the covariates.

***Results:*** No differences were detected among the groups in PR, 2-PD, muscle tone and muscle strength of the shoulder and elbow over time. However, increases in power grip and index pinch strength were significantly greater in the TES group after 4 weeks of electrical stimulation than those of the control group receiving only CR ($P<0.01$). These effects were maintained even up to 5 months after treatment. UE functional ability also showed better improvement in the TES group than the control group ($P\leq0.01$) at 3 and 5 months after the 4-week programme. However, no difference was detected between placebo-TES and TES groups, or between placebo-TES and control groups in the present study.

***Conclusion:*** These results confirmed that adding 4 weeks of intensive TES to the 6 acupoints during acute stroke was more effective in enhancing motor function recovery than conventional rehabilitation alone. Only the TES group showed significantly greater improvements in power grip, index pinch strength and UE functional ability than the control group. Of interest is that these improvements persisted up to 5 months after treatment ended.

## 5.1 Introduction

Improving motor function in a paretic upper extremity (UE) has long been a challenge to clinicians and researchers. Much recovery in a paretic UE has been found to take place in the first 3 months after stroke (Duncan et al. 1992, Nakayama et al. 1994a). However, previous studies have shown that only 25 to 45 percent of people with stroke recover some UE function in response to conventional rehabilitation (Olsen 1990, Parker et al. 1986, Wade et al. 1983). Recovery of UE function is further compromised by compensatory use of the less affected extremity during daily activities (Nakayama et al. 1994b). In fact, people with chronic stroke often perceived the loss of UE function to be a major problem affecting their quality of life (Broeks et al. 1999, Williams and Weinberger et al. 1999).

Most rehabilitation therapies found to improve motor function in the affected UE involved exercising weak muscles against resistive loads (Bütefisch et al. 1995), practising functional tasks repetitively (Dean and Shepherd 1997), or enforcing forced-use of the paretic UE (Dromerick et al. 2000). Randomized controlled trials have only examined the treatment effects in patients who presented some active muscle activity in the paretic UE at baseline (Bütefisch et al. 1995, Dean and Shepherd 1997, Dromerick et al. 2000, Kunkel et al. 1999), during their extended rehabilitation or chronic stage of stroke. In fact, active exercise or task-specific activity employing the paretic UE is normally difficult or impossible for people with acute stroke, especially if they have a severe neurological insult.

Plasticity of the nervous system is one key mechanism mediating post-stroke recovery. Plastic reorganization of neural networks has been found to start early after injury (Jenkins and Merzenich 1987, Xerri et al. 1998). Such morphological and neuronal plastic adaptation has been shown to be use-dependent (Dromerick et al.

2000, Liepert et al. 2000, Nudo and Milliken 1996, Xerri et al. 1998). In rats with induced ischaemic brain injury, the sensitivity of the synaptic activity in the motor cortex in response to an enriched environment was found to decline with time after injury (Biernaskie et al. 2004). This finding suggests that reduced sensori-motor experience of the paretic UE in the early stage of stroke could affect the plastic reorganization in the motor cortex, which might be detrimental to motor recovery.

Kimura (2001) showed that surface electrical stimulation of nerves could activate both muscle spindle and cutaneous afferents. Using cortical mapping techniques, a short course of focussed electrical stimulation applied to selected body parts of healthy subjects was found to increase the excitability of related cortical sites (Hamdy et al. 1998, McKay et al. 2002, Ridding et al. 2001). During acute stroke, transcutaneous electrical stimulation of the paretic UE could be a convenient means of peripheral stimulation which might promote relevant plastic changes at the cortical level.

Indeed, transcutaneous electrical stimulation of muscles or peripheral nerves has been demonstrated to reduce spasticity (Levin & Hui-Chan 1992, 1993), improve muscle strength and promote functional independence in people with stroke (Levin & Hui-Chan 1992, Potisk 1995, Powell et al. 1999, Tekeoõlu et al. 1998, Yan 2002, Yan et al. 2005). Among the studies using randomized, placebo-controlled designs (Levin & Hui-Chan 1992, Tekeoõlu et al. 1998, Yan et al. 2005), only one has examined and demonstrated carry-over effects after 3 weeks of electrical stimulation to the paretic leg given on top of conventional rehabilitation (Yan et al., 2005). Yan and coworkers (2005) showed that spasticity and muscle strength of the weak ankle muscles improved significantly more after 3 weeks of functional electrical stimulation of lower limb muscles than placebo or conventional treatments, with the effects lasting 1

month after the programme ended.

Stimulation of acupoints using needles, either manually or with electric current, is a traditional Chinese medicine (TCM) approach to stroke management. Based on the belief that yin and yan meridians influence bodily functions, a number of acupoints on the limbs and skull have commonly been adopted in treating stroke with acupuncture. Although all motor points are acupoints (Liu et al. 1975, Ulett et al. 1998), the concept behind the choice of acupoints in TCM is not the same as that behind the conventional application of transcutaneous electrical stimulation. The latter is usually targeted at specific weak or spastic muscles, stimulating their motor points or peripheral nerves to generate localized effects on motor function. Acupuncture, by contrast, is applied to body or skull points of selected meridians that mediate *qi* (meaning essence) and blood. Stimulating the acupoints along these meridians, such as the large intestine (LI), stomach (ST) or gall bladder (GB) meridians after stroke, is considered to facilitate the restoration of flow of *qi* and blood (Ho et al. 1997; Chapter 13, pp. 123-130).

In studies using a middle cerebral artery occlusion model in rats (Siu et al. 2004, Zhao et al. 2000), acupuncture applied during acute post-ischaemic reperfusion appeared to limit the neurological insult and increase the amount of anti-oxidants in the injured brain. Early stimulation of acupoints might therefore help control acute ischaemia so as to limit neurological injury. Moreover, acupoints were sites of muscle spindles and slow-adapting touch and pressure receptors (Wang and Liu 1989). With electrical stimulation, acupoints could be a rich source of afferent input to the sensorimotor cortex.

The favourable effects of acupuncture on motor recovery after stroke have been shown in randomized controlled trials, with control subjects receiving only

conventional rehabilitation without inclusion of placebo treatments (Hu et al. 1993, Johansson et al. 1993, Kjendahl et al. 1997, Magnusson et al. 1994, Qi et al. 1986, Sällström et al. 1996, Si et al. 1998, Wong et al. 1999). Contrary to these findings, a randomized, placebo-controlled study involving patients 4 to 10 days after stroke (Gosman-Hedström et al. 1998) could not detect differences in motor or functional recovery between subjects receiving electro-acupuncture and those receiving placebo acupuncture. Their protocol involved 30 minutes of treatment, applied twice a week for 10 weeks, which might not have been sufficiently intense to generate positive effects. Another study applied a similar acupuncture protocol to patients during extended rehabilitation after stroke (Sze et al. 2002). Stationary needles were applied to acupoints for 30 minutes, 2 to 5 times a week for 10 weeks. Again, only small but insignificant improvements in motor function and activities of daily living were found, when compared with subjects receiving conventional rehabilitation.

Can an intensive programme of acupoint stimulation, given early during the acute stage of stroke, be effective in enhancing recovery of stroke-induced motor dysfunction? Unlike acupuncture, transcutaneous electrical stimulation of acupoints could be applied in a non-invasive manner. This study therefore aimed to investigate the effects of intensive treatment with transcutaneous electrical stimulation (TES) of acupoints during acute stroke on the recovery of sensory and motor function in the paretic UE.

## 5.2 Materials and Methods

### *5.2.1 Study design*

This study adopted a double-blind, randomized, placebo-controlled design and

was approved by the local ethics committees of the Queen Elizabeth Hospital, Kowloon Hospital and The Hong Kong Polytechnic University. In Chapter 1, section 1.5.3, an effect size of 1.05 for improving UE muscle strength has been determined from the meta-analysis of 5 randomized controlled studies on transcutaneous electrical stimulation of paretic UE after stroke. Anticipating a 10 to 20% drop-out rate during the study, the estimated sample size was 19 per group for achieving a power of 0.8 in testing differences among 3 groups (Chapter 2, section 2.2.4).

### *5.2.2 Subjects*

Patients admitted to the acute medical wards were screened according to the inclusion and exclusion criteria by a research physiotherapist. They were included if they had suffered a first stroke of the ischaemic type causing weakness in the UE contralateral to the side of stroke, with a Motricity Index score ≤77 out of the full score of 100 (Demeurisse et al. 1980). Subjects had to be older than 45. Exclusion criteria rejected those with a premorbid history of pathologies leading to disabilities in either UE, cardiac pace-makers of the demand type, expressive or receptive aphasia, or a reduced level of consciousness as denoted by a score ≤13 on the Glasgow Coma Scale (Teasdale and Jennett 1974). Subjects were also excluded if their UE weakness disappeared within 1 week after the onset of their stroke.

After their informed consent was obtained, subjects' baseline sensory and motor functions were assessed. Those recruited 46 hours or less after the onset of their stroke were allocated to 1 of the 3 treatment groups by simple randomization (cf. Chapter 2, section 2.2.3). The 3 groups were (1) the controls who received only conventional rehabilitation (CR), (2) the TES group who received additional

transcutaneous electrical stimulation, and (3) the placebo-TES group who received placebo stimulation. Subjects who were recruited beyond 46 hours after the onset of stroke symptoms received only CR.

### *5.2.3 Intervention*

All subjects received similar CR. During their in-patient stay in the two hospitals, CR consisted of physiotherapy (around 60 minutes per session) and occupational therapy (around 30 minutes per session), given 5 to 6 days a week, plus in some cases, speech or a dietician's consultation (refer to Chapter 2, section 2.3.3). Afterwards, rehabilitation continued in out-patient settings for a further 3 to 6 months.

Subjects in the TES and placebo-TES groups were given real or placebo transcutaneous electrical stimulation immediately after the baseline assessment (Chapter 2, section 2.4.1). Four acupoints on the paretic UE contralateral to the side of brain lesion were used, namely, LI 4 (Hegu), LI 10 (Shousanli), LI 11 (Quchi), LI 15 (Jianyu), plus two GB 20 (Fengzhi) points located on either side of the neck at the base of the occiput. A detailed description of the acupoints has already been presented in Table 2.1. Electrical stimulation was applied through 3 pairs of surface electrodes connected to 2 conventional transcutaneous electrical stimulation machines (model 120Z®, ITO Co. Ltd., Tokyo, Japan). Direct current in 200 μsec square pulses at 20 Hz was delivered at maximally tolerable intensity (2.5 to 3 times each subject's sensory threshold) for 60 minutes per session, 5 sessions a week for 4 consecutive weeks. The placebo-TES group received this treatment from the transcutaneous electrical stimulation machines whose electrical circuits had been disconnected.

### *5.2.4 Outcome measurements*

Outcome measurements focussed on sensory and motor functions in the paretic UE, as follows:

(1) tactile sensibility to pressure (PR) and two-point discrimination (2-PD);

(2) muscle tone in the elbow flexors as measured with the modified Composite Spasticity Scale (Levin and Hui-Chan 1992);

(3) muscle strength in shoulder abduction and elbow flexion as measured by the shoulder and elbow sub-scores of the Motricity Index (Demeurisse et al. 1980);

(4) strength of power grip (GRIP) and index pinch grip (PINCH) measured with dynamometry;

(5) functional ability of the paretic UE to perform elevation, grasping, gripping and pinching tasks evaluated with the Action Research Arm Test (Lyle 1981).

These outcome measurements were selected because of their proven validity and test-retest reliability when applied to patients with stroke (Chapter 2, sections 2.5). The methodology has already been described in Chapter 2 (sections 2.4.3 to 2.4.6) and will not be repeated here.

The investigator (AYS) was blinded to the allocation of subjects to groups. She conducted reassessments of the subjects' sensory, motor and functional status once weekly during the first 4 weeks of intervention, then at the end of weeks 8, 12, 16 and 24 after recruitment, which were denoted as $W_8$, $W_{12}$, $W_{16}$ and $W_{24}$ post-stroke. The reassessments were conducted in the hospitals or at the subjects' place of residence.

### *5.2.5 Statistics*

Statistical Package for Social Sciences (SPSS) software version 11.0 was used in the data analysis. Clinical characteristics of the subjects at baseline were analysed with descriptive statistics. To compare the baseline characteristics of the 3 groups, Chi-square tests were applied to categorical data and one-way analysis of variance (ANOVA) to continuous data. The level of significance was set as 5%.

Following intention-to-treat principles (Moher et al. 2001), all subjects recruited into the 3 groups were included in the analysis. To address missing data in the follow-up assessments, mixed model ANOVA (StatSoft, Inc. 2003) was applied to test within-group changes, as well as between-group differences during the 4-week electrical stimulation programme and for 5 months up to $W_{24}$ post-stroke. Assessment intervals and subject group were entered as fixed factors, while each subject was entered as a random factor. At the same time, the baseline outcome measures were entered as covariates, in order to adjust for individual variations at baseline (Norman 1989). In addition, those baseline clinical measures found to be different among the 3 groups were also entered as covariates. When within-group improvement for a particular outcome variable was significant across the 6 months of stroke, post-hoc pair-wise comparisons were carried out. The Bonferroni-adjusted alpha level was set at 0.0125 for comparing the weekly status with the baseline during the first 4 weeks of treatment; while the alpha-level for comparing the 5 time intervals, i.e., $W_4$, $W_8$, $W_{12}$, $W_{16}$ and $W_{24}$ with the baseline was 0.01. When differences in the outcome measures were significant among the 3 groups, post-hoc comparisons was conducted with the Bonferroni-adjusted alpha set as 0.017 (Perneger 1998).

## 5.3 Results

Sixty-six subjects were recruited within 46 hours after the onset of stroke. Upon simple randomization, there were 28 subjects in the TES group, 20 in the placebo-TES group and 18 in the control group. In the TES group, 4 subjects dropped out in the first 2 weeks (2 refused to continue after the first 2 treatment sessions, 1 died of cardiac arrest, and another 1 died of stroke). Two subjects dropped out from the placebo-TES group in the first week (1 transferred to another hospital and 1 fell into coma). Six control group subjects dropped out during the first 3 weeks after recruitment (3 were transferred to other hospitals, 3 others left the city). With the large number of drop-outs in the control group, subjects who met the selection criteria except that they were beyond 46 hours but within 60 hours after stroke onset at recruitment and subsequently had received only CR (n=19) were added to the control group. Though this made the randomized controlled trial less than ideal, these subjects were similar in demographic characteristics and baseline values to the other control subjects who were randomly assigned (Table 5.1).

Figure 5.1 presents the distribution of subjects in the 3 groups and the subsequent follow-up assessments across the 24 weeks of the study. On examining the baseline characteristics of the 3 groups (Table 5.2), there was difference in the composition of hemispheric stroke amongst the groups, with the TENS group having relatively fewer left-sided lesion. The control group had longer time from stroke onset to baseline assessment, and presented with lower mean baseline pressure sensibility thresholds. Noting these baseline differences amongst the groups, side of hemiplegia, time since onset of stroke to baseline assessment, and the baseline pressure sensibility were treated as covariates in the mixed model ANCOVA test of group differences. Twenty-seven subjects in the control group, 16 in the placebo-TES

group and 21 in the TES group completed the 24 weeks of assessments. The baseline neurological profiles of those subjects who dropped out were confirmed to be similar to those who completed the assessments (Appendix VIII). The average length of hospital stay was found to be similar among the control (42.9 days, SD 15.0 days), placebo-TES (43.5 days, SD 27.5 days) and TES groups (41.3 days, SD 18.3 days).

**Table 5.1: Baseline characteristics of the 2 categories of control subjects**

| Characteristics | Time since onset of stroke at recruitment | | *P* |
|---|---|---|---|
| | ≤ 46 hours (n=18) | 47 to < 60 hours (n=19) | |
| Gender - female (%) | 50.0 | 57.9 | 0.63 # |
| Age, mean ± SD (years) | 71.5 ± 9.9 | 69.2 ± 8.1 | 0.45 |
| Comorbid stroke risks (%) | 58.8 | 52.6 | 0.71 # |
| Hemispheric stroke - left (%) | 50.0 | 63.2 | 0.42 # |
| Site of lesion (%) - Lacunar/NAD | 17.6 | 33.3 | |
| Cortical | 0.0 | 16.7 | |
| Subcortical | 64.7 | 44.4 | 0.14 # |
| Cortical+Subcortical | 17.6 | 5.6 | |
| Stroke severity (NIHSS), mean ± SD | 7.3 ± 2.3 | 8.2 ± 2.3 | 0.23 |
| Spatial neglect - present (%) | 33.3 | 15.8 | 0.21 # |

Abbreviations: NIHSS = National Institutes of Health Stroke Scale; *P*-values are results of independent t-tests except that # denotes a *P*-value from analysis using Pearson's Chi-square test.

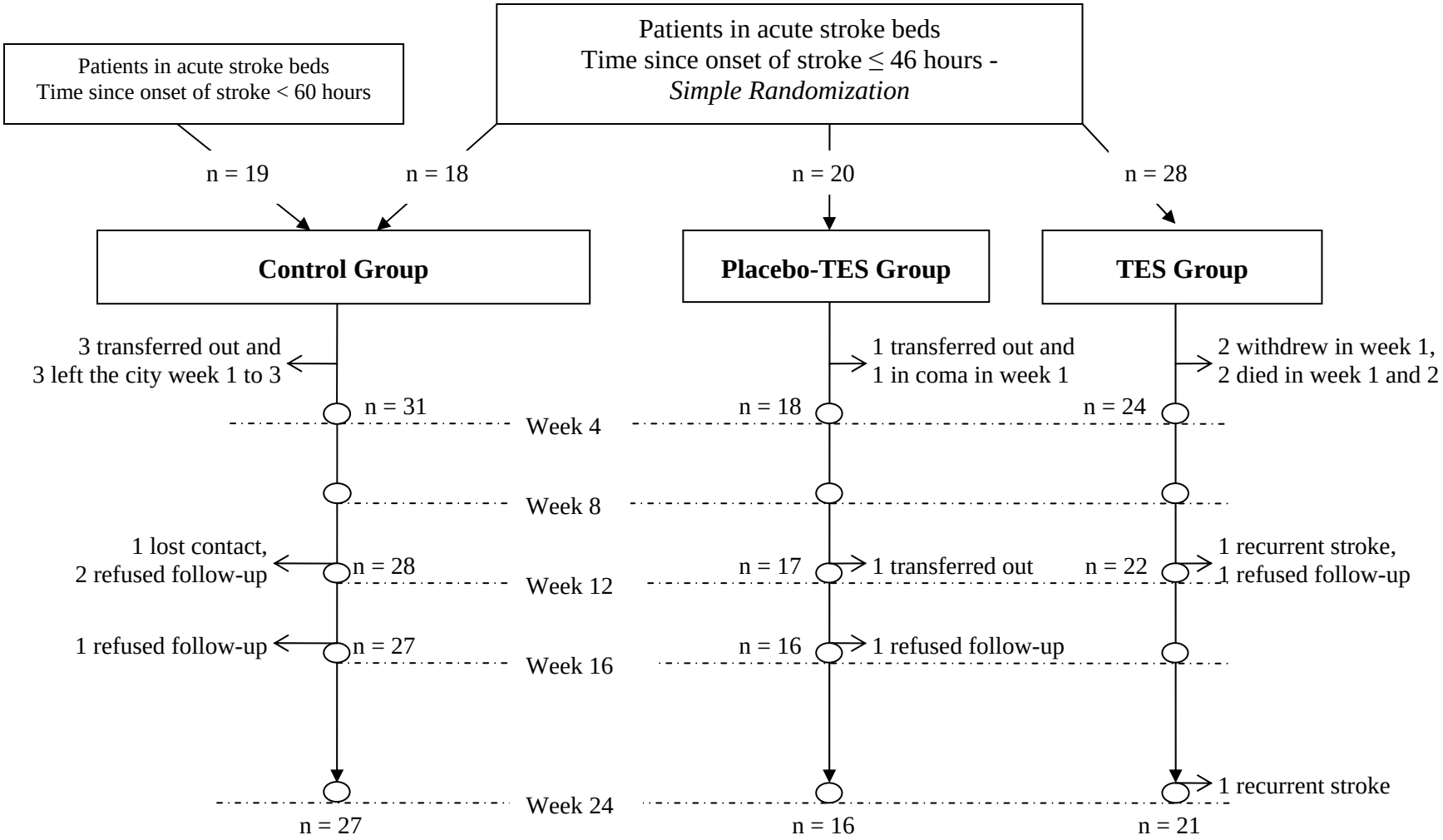


Figure 5.1: Flow chart of the distribution of subjects during the 24 weeks of the study. Control, placebo-TES, TES denote respectively the groups receiving only conventional rehabilitation, placebo and real transcutaneous electrical stimulation in addition to conventional rehabilitation

**Table 5.2: Demographic characteristics and baseline values of the 3 groups**

| Characteristics | Control n=37 | Placebo-TES n=20 | TES n=28 | *P* |
|---|---|---|---|---|
| Gender - female (%) | 54.1 | 50.0 | 42.9 | $0.67_{\#}$ |
| Age, mean ± SD (years) | 70.3 ± 9.0 | 68.4 ± 10.1 | 70.3 ± 10.3 | 0.73 |
| Comorbid stroke risks (%) | 55.6 | 85.0 | 64.3 | $0.08_{\#}$ |
| Hemispheric stroke - left (%) | 56.8 | 45.0 | 21.4 | $0.02_{\#}$ * |
| Site of lesion (%) - Lacunar/NAD | 25.7 | 10.5 | 18.5 | |
| Cortical | 8.6 | 42.1 | 18.5 | |
| Subcortical | 54.3 | 31.6 | 48.1 | $0.12_{\#}$ |
| Cortical+Subcortical | 11.4 | 15.8 | 14.8 | |
| Time from stroke onset to first assessment, mean ± SD (hours) | 41.1 ± 14.8 | 28.9 ± 8.5 | 29.7 ± 8.0 | 0.00* |
| Stroke severity (NIHSS), mean ± SD | 7.8 ± 2.3 | 8.7 ± 3.7 | 8.4 ± 3.9 | 0.55 |
| Cognition: NCSE score, mean ± SD | 54.5 ± 16.9 | 54.7 ± 13.1 | 51.6 ± 19.1 | 0.78 |
| Spatial neglect - present (%) | 41.2 | 65.0 | 56.0 | $0.21_{\#}$ |
| Sensibility threshold, mean ± SD: | | | | |
| Pressure | 4.3 ± 1.3 | 5.0 ± 1.5 | 5.3 ± 1.5 | 0.01* |
| Two-point discrimination (mm) | 8.0 ± 5.8 | 10.6 ± 6.2 | 9.9 ± 6.4 | 0.26 |
| Muscle tone, mean ± SD: | | | | |
| Composite Spasticity Score | 5.7 ± 2.5 | 6.3 ± 2.5 | 5.3 ± 2.8 | 0.42 |
| Muscle strength, mean ± SD: | | | | |
| Motricity Index shoulder subscore (0-33) | 11.5 ± 8.8 | 10.7 ± 8.5 | 11.0 ± 8.5 | 0.94 |
| Motricity Index elbow subscore (0-33) | 11.9 ± 9.1 | 12.2 ± 8.8 | 12.1 ± 10.1 | 0.99 |
| Power grip (kg) | 1.4 ± 3.4 | 1.0 ± 2.7 | 2.0 ± 4.2 | 0.58 |
| Index pinch grip (kg) | 0.4 ± 1.1 | 0.5 ± 1.4 | 0.6 ± 1.4 | 0.79 |
| Upper extremity function, mean ± SD: | | | | |
| Action Research Arm Test score (0-57) | 6.3 ± 13.7 | 3.3 ± 8.4 | 7.5 ± 13.7 | 0.51 |
| Barthel Index score (0-100), mean ± SD | 37.5 ± 16.8 | 36.4 ± 16.7 | 36.8 ± 14.2 | 0.96 |

Control, placebo-TES, TES denote respectively the groups receiving only conventional rehabilitation, placebo and real transcutaneous electrical stimulation additional to conventional rehabilitation, NIHSS = National Institutes of Health Stroke Scale, NCSE = Neurobehavioral Cognitive State Examination. *P*-values are results of one-way ANOVA, except that $_{\#}$ denotes *P*-values from the analysis of Pearson's Chi-square tests, * denotes $P \leq 0.05$.

### *5.3.1 Sensation*

Table 5.3 presents the thresholds of pressure sensibility (PR) and two-point discrimination (2-PD) of the index finger pulp of the paretic UE measured from the time of recruitment to $W_{24}$ post-stroke. Smaller values of PR and 2-PD signify lower thresholds, i.e., greater sensitivity. According to the categorization of sensation status described in Chapter 3 (section 3.3.2), the percent of subjects with impaired PR (threshold ≥3.6) at baseline assessment was 78%, 90% and 93% in the control, placebo-TES and TES groups respectively. For 2-PD in the index finger pulp, 65% of the subjects in the control group showed impairment (threshold greater ≥ 4 mm) at baseline, while the placebo-TES and TES groups respectively had 85% and 71% subjects with impaired 2-PD. Noting that the mean PR data at baseline was different among groups (Table 5.2), this had been treated as a covariate in the analysis of group differences.

With reference to the baseline value, improvements denoted by decreases in PR values with time were significant only in the TES group from $W_{12}$ to $W_{24}$ post-stroke (*P*-values ranged from 0.002 to 0.006). Neither the controls nor the placebo-TES group showed significant within-group changes in PR with time ($P$ >0.03 for controls and $P$ >0.20 for the placebo-TES group). The within-group improvement in 2-PD acuity with time was not significant (Bonferroni adjusted $P$ >0.01) in any of the groups. At $W_4$ assessment when the electrical stimulation programme had just finished, the TES group had improvement in mean PR by 11.6% and 2-PD by 29.0%, both appeared to be larger gain in sensitivity than those in the placebo-TES group (8.5% in PR and 13.5% in 2-PD) and control group (6.1% in PR and 14.8% in 2-PD). However, mixed model ANCOVA could not detect any significant difference in PR and 2-PD acuity by time among the 3 groups at any assessment interval across the 24

weeks of the study.

**Table 5.3: Pressure sensibility (A) and two-point discrimination (B) during the 4-week electrical stimulation programme, and at reassessments after the treatment ended**

| (A) | | Pressure sensibility threshold | | | ANCOVA (group x week) *P*-value[#] |
|---|---|---|---|---|---|
| | *Time post-stroke* | Control | Placebo-TES | TES | |
| *During the 4-week treatment* | Baseline | 4.3 ± 1.3 | 5.0 ± 1.5 | 5.3 ± 1.5 | |
| | Week 1 | 4.3 ± 1.3 | 4.8 ± 1.6 | 4.7 ± 1.6 | |
| | Week 2 | 4.3 ± 1.2 | 4.7 ± 1.6 | 4.8 ± 1.5 | |
| | Week 3 | 4.2 ± 1.2 | 4.9 ± 1.6 | 4.7 ± 1.5 | |
| | Week 4 | 4.0 ± 1.2 | 4.6 ± 1.8 | 4.6 ± 1.5 | 0.225 |
| *Follow-up after treatment* | Week 8 | 3.5 ± 1.0 | 4.5 ± 1.6 | 4.2 ± 1.3 | 0.591 |
| | Week 12 | 3.6 ± 1.2 | 4.2 ± 1.6 | 4.0 ± 1.3 [a] | 0.379 |
| | Week 16 | 3.5 ± 1.0 | 4.1 ± 1.5 | 3.8 ± 1.2 [a] | 0.333 |
| | Week 24 | 3.6 ± 1.0 | 4.3 ± 1.6 | 3.9 ± 1.1 [a] | 0.396 |
| (B) | | Two-point discrimination threshold (mm) | | | ANCOVA (group x week) *P*-value[#] |
| | *Time post-stroke* | Control | Placebo-TES | TES | |
| *During the 4-week treatment* | Baseline | 8.0 ± 5.8 | 10.6 ± 6.2 | 9.9 ± 6.4 | |
| | Week 1 | 7.6 ± 6.3 | 9.1 ± 6.5 | 9.1 ± 6.6 | |
| | Week 2 | 7.8 ± 6.2 | 9.4 ± 6.8 | 8.5 ± 6.4 | |
| | Week 3 | 7.2 ± 5.9 | 9.9 ± 6.7 | 7.6 ± 6.3 | |
| | Week 4 | 6.8 ± 5.8 | 9.2 ± 6.4 | 7.0 ± 6.0 | 0.430 |
| *Follow-up after treatment* | Week 8 | 5.3 ± 4.7 | 7.2 ± 6.3 | 6.2 ± 5.9 | 0.290 |
| | Week 12 | 4.3 ± 3.7 | 6.2 ± 5.7 | 5.2 ± 4.9 | 0.304 |
| | Week 16 | 4.8 ± 4.7 | 5.9 ± 5.8 | 5.4 ± 5.3 | 0.085 |
| | Week 24 | 4.6 ± 4.3 | 7.1 ± 6.3 | 5.7 ± 5.6 | 0.367 |

Values are mean ± SD. Control, placebo-TES, TES denote respectively the groups receiving only conventional rehabilitation, placebo and real transcutaneous electrical stimulation in addition to conventional rehabilitation. [a] $P \leq 0.01$ denotes that the improvement with time was significant within-group with reference to the baseline value from mixed model ANOVA. [#] denotes *P*-values from mixed model ANCOVA for differences in improvements with time among the 3 groups, which were not significant at any assessment interval.

### *5.3.2 Muscle tone*

At baseline assessment, there was no difference among the groups in terms of the percentage of subjects with UE muscle tone that was normal, hypotonic or spastic. A summary of the elbow flexor tone measures using the CSS at all assessment intervals is presented in Table 5.4.

The control group started with a mean CSS score below 6, indicating hypotonicity in the paretic UE. They had increased elbow flexor tone significantly from $W_3$ post-stroke ($P$ <0.001) onwards. The mean CSS of the control group was 8.0 (SD 1.3) at $W_3$ assessment, and 8.8 (SD 1.4) at $W_{24}$ post-stroke, when all except one of the subjects presented with spastic elbow flexors (CSS score >6). The TES group, on average, also presented with UE hypotonicity at baseline, with the mean CSS as 5.3 (SD 2.8). Their muscle tone had significantly increased to 7.17 (SD 1.86) at $W_4$ when the electrical stimulation programme ended ($P$ = 0.005), and to 7.7 (SD 1.8) at $W_{24}$ post-stroke, when 75% of these subjects had spastic elbow flexors. The placebo-TES group had more subjects (65%) with UE spasticity at baseline, and their increases in mean CSS with time were not significant across the 24 weeks of the study. At $W_4$ and $W_{24}$, the percentage of subjects with UE spasticity in this group was 83% and 81% repectively.

Comparing the 3 groups in terms of their muscle tone status across time as measured by CSS, the mixed model ANCOVA did not show any difference among the groups, with $P$-values ranging from 0.945 at the end of the 4-week programme to 0.169 at $W_{24}$ post-stroke.

**Table 5.4: Muscle tone of the elbow flexors during the 4-week electrical stimulation programme, and at reassessments after the programme ended**

| *Time post-stroke* | | Composite Spasticity Score | | | ANCOVA (group x week) *P*-value[#] |
|---|---|---|---|---|---|
| | | Control | Placebo-TES | TES | |
| *During the 4-week treatmnet* | Baseline | 5.7 ± 2.5 | 6.3 ± 2.5 | 5.3 ± 2.8 | |
| | Week 1 | 6.9 ± 2.3 | 6.7 ± 2.5 | 6.0 ± 2.4 | |
| | Week 2 | 7.3 ± 2.1 | 7.4 ± 1.9 | 7.1 ± 1.9 | |
| | Week 3 | 8.0 ± 1.3 [a] | 7.3 ± 2.0 | 7.1 ± 1.8 | |
| | Week 4 | 8.0 ± 1.6 [a] | 7.6 ± 1.6 | 7.2 ± 1.9 [a] | 0.945 |
| *Follow-up after treatment* | Week 8 | 8.0 ± 1.4 [a] | 7.8 ± 1.6 | 7.3 ± 1.8 [a] | 0.778 |
| | Week 12 | 8.1 ± 1.5 [a] | 7.8 ± 1.8 | 7.5 ± 2.0 [a] | 0.823 |
| | Week 16 | 8.5 ± 1.2 [a] | 7.6 ± 1.8 | 7.7 ± 1.6 [a] | 0.697 |
| | Week 24 | 8.8 ± 1.4 [a] | 7.4 ± 1.6 | 7.7 ± 1.8 [a] | 0.169 |

Values are mean ± SD. Control, placebo-TES, TES denote respectively the groups receiving only conventional rehabilitation, placebo and real transcutaneous electrical stimulation in addition to conventional rehabilitation. [a] $P \leq 0.01$ denotes that the change with time was significant within the group with reference to the baseline value according to mixed model ANOVA. [#] denotes *P*-values from mixed model ANCOVA of the differences in improvements with time among the 3 groups, which were not significant at any assessment interval.

### *5.3.3 Muscle strength in the paretic upper extremity*

5.3.3.1 Strength of shoulder and elbow

Table 5.5 presents the strength of the shoulder abductors and elbow flexors as measured by Motricity Index subscores from recruitment (baseline) to $W_{24}$ post-stroke. When compared to the baseline, the within-group improvements in shoulder abduction were significant at $W_{24}$ in the control group ($P \leq 0.01$), and from $W_{12}$ onwards for the TES group. The increase in shoulder abduction strength with time was not significant in the placebo-TES group. The elbow flexor strength was improved significantly by $W_{24}$ assessment for the control group, by $W_{12}$ for the placebo-TES group and by $W_{16}$ for the TES group. Nevertheless, differences in the muscle strength improvements among the 3 groups did not reach significance at any assessment interval.

**Table 5.5: Strength of (A) shoulder abductors and (B) elbow flexors measured with the Motricity Index during the electrical stimulation programme, and at reassessments after the programme ended**

| (A) | | Motricity Index – Shoulder subscore (0-33) | | | ANCOVA (group x week) *P*-value[#] |
|---|---|---|---|---|---|
| *Time post-stroke* | | Control | Placebo-TES | TES | |
| *During the 4-week treatment* | Baseline | 11.5 ± 8.8 | 10.7 ± 8.5 | 11.0 ± 8.5 | |
| | Week 1 | 9.5 ± 8.6 | 14.3 ± 9.6 | 12.4 ± 11.1 | |
| | Week 2 | 13.5 ± 7.9 | 16.0 ± 8.9 | 14.3 ± 11.3 | |
| | Week 3 | 14.2 ± 8.2 | 16.1 ± 8.7 | 15.5 ± 10.7 | |
| | Week 4 | 16.0 ± 8.2 | 16.7 ± 8.0 | 16.3 ± 10.2 | 0.336 |
| *Follow-up after treatment* | Week 8 | 17.1 ± 9.2 | 18.2 ± 7.8 | 18.7 ± 10.9 | 0.669 |
| | Week 12 | 16.1 ± 7.2 | 19.5 ± 11.0 | 19.8 ± 10.9 [a] | 0.078 |
| | Week 16 | 16.9 ± 7.1 | 19.0 ± 10.7 | 20.9 ± 10.3 [a] | 0.168 |
| | Week 24 | 17.9 ± 6.6 [a] | 19.1 ± 10.8 | 19.9 ± 11.1 [a] | 0.643 |

| (B) | | Motricity Index – Elbow subscore (0-33) | | | ANCOVA (group x week) *P*-value[#] |
|---|---|---|---|---|---|
| *Time post-stroke* | | Control | Placebo-TES | TES | |
| *During the 4-week treatment* | Baseline | 11.9 ± 9.1 | 12.2 ± 8.8 | 12.1 ± 10.1 | |
| | Week 1 | 9.5 ± 8.6 | 14.3 ± 11.2 | 12.6 ± 12.0 | |
| | Week 2 | 12.2 ± 9.5 | 15.8 ± 9.5 | 15.2 ± 10.8 | |
| | Week 3 | 15.1 ± 7.9 | 16.4 ± 9.5 | 15.6 ± 11.4 | |
| | Week 4 | 15.2 ± 8.0 | 18.2 ± 8.5 | 16.4 ± 12.3 | 0.541 |
| *Follow-up after treatment* | Week 8 | 17.8 ± 8.1 | 18.4 ± 9.3 | 19.4 ± 11.5 | 0.468 |
| | Week 12 | 17.1 ± 7.1 | 21.8 ± 10.7 [a] | 19.7 ± 11.3 | 0.185 |
| | Week 16 | 16.9 ± 7.8 | 20.8 ± 10.8 | 22.4 ± 9.5 [a] | 0.086 |
| | Week 24 | 19.4 ± 6.7 [a] | 20.6 ± 9.7 | 21.3 ± 9.9 | 0.396 |

Values are mean ± SD. Control, placebo-TES, TES denote respectively the groups receiving only conventional rehabilitation, placebo and real transcutaneous electrical stimulation in addition to conventional rehabilitation. [a] $P \leq 0.01$ denotes that the improvement with time was significant within-group with reference to the baseline value according to mixed model ANOVA. [#] denotes the *P*-values from a mixed model ANCOVA of differences in improvements among the 3 groups which were not significant at any assessment interval.

5.3.3.2 Power grip and index pinch strength

Table 5.6 presents the results of GRIP and PINCH strength for the 3 groups at recruitment to $W_{24}$ post-stroke. Figure 5.2 illustrates the time course of improvement in GRIP and PINCH of the 3 groups over this time period. For the control group, subjects did not show any within-group improvement in either power grip or index pinch strength at any reassessment interval ($P \geq 0.10$). For the placebo-TES group, subjects' within-group improvement in GRIP with time was significant at $W_{12}$ ($P = 0.008$) and $W_{24}$ ($P = 0.009$), but their improvements in PINCH were not significant ($P \geq 0.03$). For the TES group, subjects' improvements in both GRIP and PINCH were significant at $W_{16}$ ($P = 0.003$ for GRIP, and 0.005 for PINCH strength) and $W_{24}$ reassessment ($P = 0.002$ for both GRIP and PINCH strength).

**Table 5.6: Strength of (A) power grip and (B) pinch grip during the 4-week electrical stimulation programme, and at reassessments after the programme ended**

| (A) | | Power grip strength (kg) | | | ANCOVA (group x week) *P*-value[#] |
|---|---|---|---|---|---|
| *Time post-stroke* | | Control | Placebo-TES | TES | |
| *During the 4-week treatment* | Baseline | 1.4 ± 3.4 | 1.0 ± 2.7 | 2.0 ± 4.2 | |
| | Week 1 | 0.8 ± 3.6 | 3.5 ± 5.3 | 4.7 ± 7.1 | |
| | Week 2 | 1.5 ± 3.9 | 4.9 ± 7.0 | 5.5 ± 8.0 | |
| | Week 3 | 1.7 ± 3.5 | 4.5 ± 6.3 | 6.2 ± 8.0 | |
| | Week 4 | 2.1 ± 3.5 | 6.0 ± 7.5 | 6.9 ± 8.4[†] | 0.067 |
| *Follow-up after treatment* | Week 8 | 2.6 ± 4.1 | 6.8 ± 7.6 | 7.4 ± 8.5[†] | 0.013 * |
| | Week 12 | 2.4 ± 3.8 | 7.6 ± 8.1[a] | 7.3 ± 8.0[†] | 0.012 * |
| | Week 16 | 3.4 ± 4.8 | 7.2 ± 8.4 | 9.4 ± 9.2[a†] | 0.021 * |
| | Week 24 | 3.5 ± 4.5 | 7.3 ± 8.0[a] | 9.6 ± 9.0[a†] | 0.011 * |
| (B) | | Pinch strength (kg) | | | ANCOVA (group x week) *P*-value[#] |
| *Time post-stroke* | | Control | Placebo-TES | TES | |
| *During the 4-week programme* | Baseline | 0.4 ± 1.1 | 0.5 ± 1.4 | 0.6 ± 1.4 | |
| | Week 1 | 0.2 ± 1.0 | 1.3 ± 2.4 | 1.3 ± 2.1 | |
| | Week 2 | 0.4 ± 0.9 | 1.5 ± 2.2 | 1.8 ± 2.6 | |
| | Week 3 | 0.4 ± 1.1 | 1.4 ± 1.9 | 1.9 ± 2.4 | |
| | Week 4 | 0.6 ± 1.1 | 1.8 ± 2.2 | 2.3 ± 2.7[†] | 0.015 * |
| *Follow-up post-programme* | Week 8 | 0.7 ± 1.3 | 1.9 ± 2.2 | 2.4 ± 2.8[†] | 0.019 * |
| | Week 12 | 0.7 ± 1.4 | 2.2 ± 2.2 | 2.1 ± 2.5[†] | 0.013 * |
| | Week 16 | 1.0 ± 1.6 | 2.0 ± 2.5 | 2.7 ± 2.7[a†] | 0.057 |
| | Week 24 | 1.0 ± 1.5 | 2.3 ± 2.5 | 3.0 ± 2.7[a†] | 0.008 * |

Values are mean ± SD. Control, placebo-TES, TES denote respectively the groups receiving only conventional rehabilitation, placebo and real transcutaneous electrical stimulation in addition to conventional rehabilitation. [a] denotes significant difference within the group with reference to the baseline value ($P \leq 0.01$) from mixed model ANOVA. [#] denotes *P*-values from mixed model ANCOVA of differences in improvements with time among the 3 groups; * indicates the difference was significant ($P \leq 0.05$); [†] denotes significant difference from control with a Bonferroni-adjusted $P \leq 0.0167$ in post-hoc pair-wise comparison.

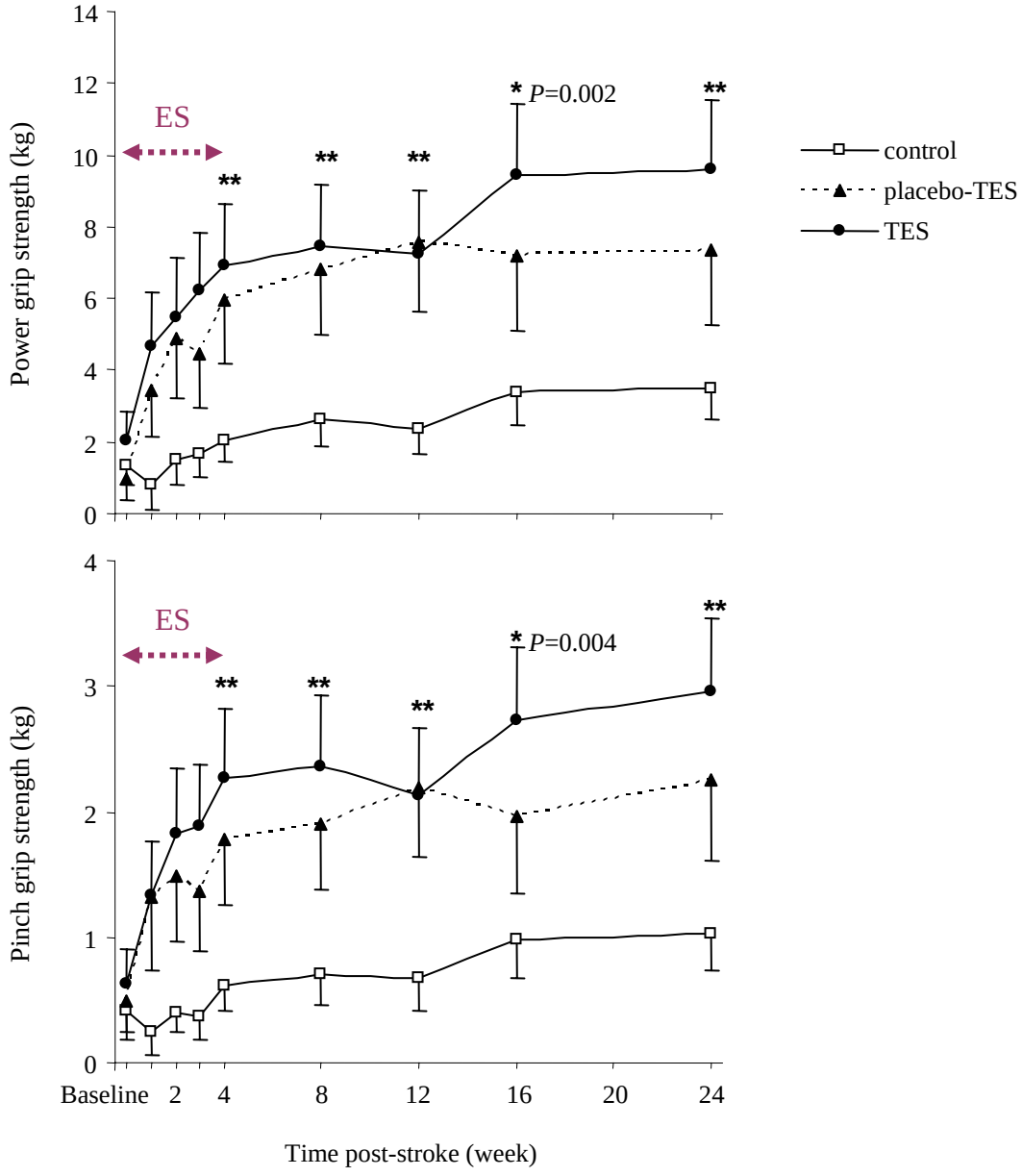


Figure 5.2: The time course of increases in the strength of (A) power grip and (B) pinch grip of the 3 groups. ES marks the 4-week electrical stimulation programme, error bars are 1 SE of the mean. * denotes that the difference between TES and the control groups was significant in post-hoc analysis with reference to a Bonferroni-adjusted *P*-value of 0.0167, and ** denotes $P \leq 0.001$.

Differences in GRIP strength across time among the 3 groups reached significance at $W_8$ ($P$ = 0.013), $W_{12}$ ($P$ = 0.012), $W_{16}$ ($P$ = 0.021) and $W_{24}$ ($P$ = 0.011), but not at $W_4$ ($P$ = 0.067). Significant group differences in PINCH strength were found at $W_4$ ($P$ = 0.015), $W_8$ (P = 0.019), $W_{12}$ (P = 0.013) and $W_{24}$ (P = 0.008) assessments, but not at $W_{16}$ ($P$ = 0.057). Post-hoc analysis revealed that only the TES group showed significantly greater improvements in GRIP and PINCH strength than those of the control group ($P \leq 0.001$). After 4 weeks of electrical stimulation, the effect sizes of the between-group differences were 0.63 and 0.67 for GRIP and PINCH respectively. The placebo-TES group appeared to have greater improvement in GRIP and PINCH strength than that of the controls, but the differences did not reach significance at any reassessment interval (for the differences in GRIP, the *P*-values were 0.185 at $W_4$, 0.032 at $W_8$, 0.02 at $W_{12}$, 0.085 at $W_{16}$ and 0.063 at $W_{24}$ post-stroke; those of PINCH ranged from 0.023 to 0.227 from $W_4$ to $W_{24}$ post-stroke). At the end of the 4-week placebo treatment, the effect sizes of the between-group differences were 0.56 for GRIP and 0.49 for PINCH. There was thus no difference in power grip and index pinch strength across time between placebo-TES and TES groups ($P > 0.60$).

### *5.3.4 Upper extremity function*

At baseline assessment, only a small percentage of the subjects had functional dexterity (ARAT score ≥35) in their paretic UE. Specifically, this was 6.5% of the controls, 5.5% of the placebo-TES group, and 12.5% of the TES group. The percentages were not different among groups (Chi-square statistics, $P$ = 0.38) By $W_{24}$ post-stroke, 5 months after completing the 4-week programme, 52.4% of subjects in the TES group and 41.2% of the placebo-TES group had functional

dexterity, compared to only 22.2% of the controls.

Table 5.7 presents the Action Research Arm Test scores of the paretic UE across the 24 weeks of the study. The within-group improvement with time was significant in both the placebo-TES and the TES groups from $W_8$ post-stroke onwards ($P \leq 0.01$ to 0.005). In contrast, there was no significant change in UE function across the 24 weeks in the control subjects ($P$-values were 0.43 and 0.04 at $W_4$ and $W_{24}$ post-stroke respectively).

**Table 5.7: Functional ability of the paretic upper extremity as measured with the Action Research Arm Test during the 4-week electrical stimulation programme, and at reassessments after the programme ended**

| | | Action Research Arm Test Score | | | ANCOVA (group x week) $P$-value[#] |
|---|---|---|---|---|---|
| | *Time post-stroke* | Control | Placebo-TES | TES | |
| *During the 4-week treatment* | Baseline | 6.3 ± 13.7 | 3.3 ± 8.4 | 7.5 ± 13.7 | |
| | Week 1 | 3.3 ± 10.1 | 14.4 ± 21.1 | 15.1 ± 22.4 | |
| | Week 2 | 8.0 ± 16.1 | 16.5 ± 23.1 | 18.4 ± 23.1 | |
| | Week 3 | 8.9 ± 16.3 | 16.1 ± 21.4 | 18.7 ± 22.9 | |
| | Week 4 | 10.2 ± 16.8 | 22.4 ± 24.4 | 21.9 ± 23.7 | 0.278 |
| *Follow-up after treatment* | Week 8 | 17.3 ± 21.4 | 27.3 ± 25.2 [a] | 27.1 ± 26.0 [a] | 0.200 |
| | Week 12 | 16.9 ± 21.3 | 29.5 ± 24.5 [a] | 28.7 ± 26.2 [a] | 0.135 |
| | Week 16 | 15.4 ± 20.6 | 31.2 ± 25.0 [a] | 33.8 ± 24.9 [a†] | 0.032 * |
| | Week 24 | 17.3 ± 20.9 | 32.6 ± 25.3 [a] | 35.5 ± 25.6 [a†] | 0.051 * |

Values are mean ± SD. Control, placebo-TES, TES denote respectively the groups receiving only conventional rehabilitation, placebo and real transcutaneous electrical stimulation programme in addition to conventional rehabilitation. [a] denotes significant progression within the group with reference to the baseline value ($P \leq 0.01$) from mixed model ANOVA. [#] denotes $P$-values from mixed model ANCOVA for differences in improvements with time among the 3 groups, with * indicating that the difference was significant ($P \leq 0.05$); [†] denotes that the improvement with time was significantly different from that of the control group ($P \leq 0.0167$) in post-hoc pair-wise comparison with Bonferroni adjustment.

Figure 5.3 illustrates the improvement in UE function with time for the 3 groups. Results of the mixed model ANCOVA showed that there was a significant difference in UE function among the 3 groups at $W_{16}$ and $W_{24}$. Post-hoc analysis showed that only the TES group had better improvement in UE function with time than that of the controls (*P*-values were 0.008 and 0.011 at $W_{16}$ and $W_{24}$ respectively). Although both placebo-TES and TES recipients showed improvements of similar extent during the 4-week electrical stimulation programme, the placebo-TES group did not reach significant difference from the controls at either $W_{16}$ or $W_{24}$ (*P*-values were respectively 0.081 and 0.118), or from the TES group (*P* >0.80).

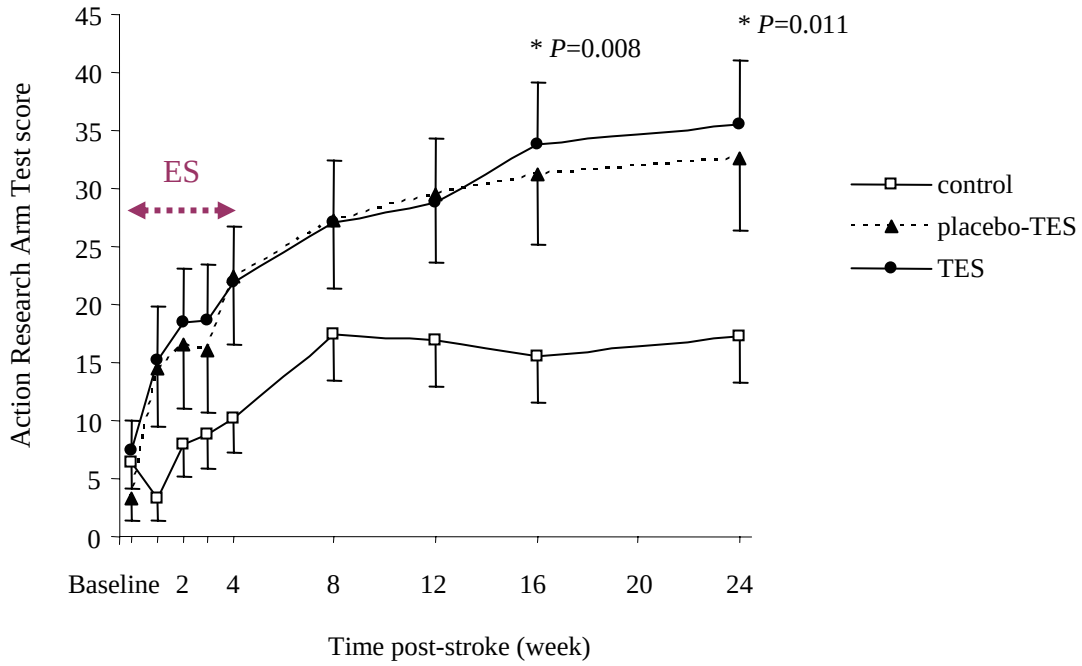


Figure 5.3: The time course of improvement in upper extremity function of the 3 groups. ES marks the 4-week electrical stimulation programme. The error bars are 1 SE of the mean. * denotes significant differences when the TES group was compared to the control group using a post-hoc Bonferroni-adjusted *P*-value as 0.0167.

### *5.3.5 Improvement in motor functions*

In Chapter 3, standardized response means (SRM) (Liang 1995) were adopted to show the effect sizes of an outcome variable between 2 assessment intervals in the sample studied (sub-section 3.3.3.5). This method was applied to examine the characteristics of motor function improvements between measurement intervals in the control, placebo-TES and TES groups. With reference to the baseline status, the overall improvement at 6 months post-stroke was small to moderate in the control group, with the SRM for GRIP, PINCH and functional ability as 0.51, 0.41 and 0.54 respectively. The 6-month effect sizes of motor function recovery were large in both the placebo-TES group (SRM for GRIP, PINCH and UE functional ability were respectively 0.84, 0.75 and 1.22) and the TES group (SRMs were 1.07 and 0.89 respectively for GRIP and PINCH, and 1.21 for UE functional ability).

Table 5.8 presents the SRM values of the respective motor function in the placebo-TES and TES groups for periods between the baseline and $W_4$ assessment, i.e., at the end of the 4-week electrical stimulation programme, as well as between $W_4$ and $W_{24}$ assessment after the electrical stimulation was finished.

For the first 4 weeks of treatment, both placebo-TES and TES groups showed large improvements in GRIP, PINCH and UE functional ability. But unlike the TES group which had SRM values ranging from 0.54 to 0.89 during the 5 months beyond the end of the 4-week treatment, the placebo-TES group had much lower SRM values of all the motor functions (ranging from 0.23 to 0.40) in a similar period after the placebo treatment.

**Table 5.8: Motor function improvements in the placebo-TES and TES groups**

| Period after stroke | Placebo-TES | | TES | |
|---|---|---|---|---|
| | Mean change ± SD | *SRM* | Mean change ± SD | *SRM* |
| *Baseline to week 4* | | | | |
| Power grip (kg) | 4.9 ± 6.4 | *0.76* | 4.5 ± 6.1 | *0.74* |
| Pinch grip (kg) | 1.2 ± 1.8 | *0.68* | 1.5 ± 2.2 | *0.70* |
| Functional ability[#] | 18.8 ± 21.0 | *0.89* | 13.2 ± 19.0 | *0.69* |
| *Week 4 to week 24* | | | | |
| Power grip (kg) | 1.1 ± 4.6 | *0.24* | 2.3 ± 2.6 | *0.89* |
| Index pinch grip (kg) | 0.3 ± 1.4 | *0.23* | 0.6 ± 1.2 | *0.54* |
| Functional ability[#] | 7.4 ± 18.6 | *0.40* | 11.6 ± 15.2 | *0.76* |

SRM is the standardized response mean characterizing the change in the outcome variable (Liang 1995); [#] denotes an outcome expressed as the score on the Action Research Arm Test

### *5.3.6 Summary of results*

Electrical stimulation of the acupoints immediately after stroke did not produce different effects on the time course of recovery of PR, 2-PD and muscle tone in the paretic UE. The TES group showed significantly better recovery in GRIP and PINCH than the control group by the end of the 4-week programme, with the effects persisting up to $W_{24}$ post-stroke. This group also showed better improvement in UE functional ability from $W_{16}$ onwards when compared to the controls. The TES and placebo-TES groups showed similar improvement by $W_4$ when the electrical stimulation programmes ended. Overall, motor function improvements in the placebo-TES group did not reach significant differences from those of TES and control groups.

## 5.4 Discussion

### *5.4.1 Effects of electrical stimulation of acupoints on sensory impairments*

The effects of electrical stimulation on improving stroke-induced sensory impairment have not been extensively studied in previous clinical trials. Yan (2002) attempted to delineate the sensory effects of either functional electrical stimulation or transcutaneous electrical stimulation of the paretic lower extremity in a randomized, placebo-controlled study. Neither of his 2 treatments could induce significant improvement in knee joint proprioception threshold as compared to the controls receiving only standard rehabilitation.

In the present study, within-group improvement was demonstrated only in PR but not in 2-PD in the TES group. In contrast, the sensory improvements with time were not significant in either the placebo-TES or the control group. Note that PR and 2-PD were measured at the distal pulp of the index finger, a hand region densely innervated with mechanoreceptors, and with large receptor field representation in the somatosensory cortex (Kandel and Jessell 1991). When touch stimuli are applied on the index finger pulp, a large area of the primary somatosensory cortex would be involved in encoding the afferent information. Unlike PR, 2-PD demands precise interaction of both excitatory and inhibitory neurons at the spinal, subcortical and cortical levels, such that spatial resolution threshold is eventually encoded in the somatosensory cortex (Gardner et al. 2000). Therefore, impairment in 2-PD as a result of stroke should be more difficult to recover.

Although the time course of sensory recovery was not different among the 3 groups, the TES group appeared to make better gains in PR and 2-PD than the other 2 groups (Table 5.3). The effect sizes of comparisons of the changes in PR and 2-PD between TES and placebo-TES or control groups were small (Cohen's d <0.2 at end

of the 4-week electrical stimulation treatment). A more valid picture of the effects of TES on sensory recovery should require a large sample.

Previous studies have shown that afferent-induced changes in somatosensory cortical representation are dependent on the spatial and temporal properties, as well as the behavioural context of the stimuli (Jenkins et al. 1990, Recanzone et al. 1990, 1992a, 1992b, Sterr et al. 1998, Wang et al. 1995, Wu et al. 2005, Ziemus et al. 2000). In the studies by Recanzone and coworkers (1992a, 1992b), monkeys had to discriminate tactile stimuli of 2 different stimulus frequencies applied to a restricted area of the skin surface of a digit. After training, the representation of the stimulated digit on the somatosensory cortex showed remarkable increases in both the territory and complexity in areas 3a and 3b. In another study, Wu and colleagues (2005) applied electrical stimulation to the median nerve of healthy subjects at supra-threshold current intensity. After 2 hours of stimulation, fMRI mapping revealed the somatosensory cortical representation of the thumb had expanded towards other finger representations (Wu et al. 2005). Hence, an intensive course of electrical stimulation as in the present study should be able to induce similar plastic changes in the somatosensory cortex representation of areas related to the acupoints stimulated.

GB20 is a skull acupoint located in the C2 dermatome. The other 4 acupoints are on the paretic UE itself. LI 15 rests in the autonomous zone of the axillary nerve, LI 11 and LI 10 rest in that of the lateral cutaneous nerve of the forearm, and LI 4 rests within the autonomous zone of the dorsal digital branch of the radial nerve (Devinsky and Feldmann 1988, Gray 1980). These 4 UE acupoints are also located in the C5 and C6 dermatomes on the lateral surface of the shoulder, elbow and forearm, and on the dorsum of the hand respectively. On the other hand, the distal pulp of index finger to which the sensory outcomes were measured lies in the C7

dermatome, with the cutaneous innervation also supplied by the median nerve (Devinsky and Feldmann 1988). Therefore, the finger pulp did not share a common cutaneous innervation with the acupoints. This could have led to the insignificant effects found for the electrical stimulation treatment. In order to evaluate the treatment effects, it is possible that both PR and 2-PD should be examined in skin regions whose cutaneous innervation is similar to that of the acupoints.

It has always been thought that effective sensory retraining of an affected UE after stroke should involve explorative activities using the affected hand. This recommendation has been based on the results of either case-controlled or quasi-experimental research (Carey et al. 1993, Carey and Matyas 2005, Smania et al. 2003, Yekutiel and Guttman 1993). Whether passive stimuli from electrical stimulation of acupoints during acute stroke could enhance sensation recovery warrants further investigation.

### *5.4.2 Effects on muscle tone*

Although spasticity has attracted much attention in treatment after stroke (Francis et al. 2004), the relationship of spasticity and disability has not been clearly established (Sommerfeld et al. 2004). On the other hand, the presence of hypotonicity was found to be associated with delayed motor recovery (Formisano et al. 2005, Twitchell 1951).

Electrical stimulation to the affected muscles (Hummelsheim et al. 1997, Tekeoŏlu et al. 2004, Yan 2002) or the nerve (Levin and Hui-Chan 1992, Potisk et al. 1995) has been found to reduce spasticity in the spastic muscles and improve muscle strength of the paretic antagonists. Usually, currents of 75 to 100 Hz were applied at low intensity in these studies. Yan (2002) has also confirmed that after 3 weeks of

transcutaneous electrical stimulation to 4 acupoints of the paretic leg during acute stroke, a larger percentage of subjects recovered their normal ankle plantarflexor phasic stretch reflex compared to the subjects receiving placebo stimulation. The frequency of the electrical currents applied was also 100 Hz.

In the present placebo-controlled study, most of the subjects presented with hypotonicity (CSS <6) in the paretic UE at baseline, which changed gradually to spasticity 2 weeks after the onset of stroke. The time course of changes in the UE muscle tone of the TES group was not different from that of the placebo-TES or the control group. The lack of difference amongst the groups could be related to the application of relatively low frequency (20 Hz) currents in the present study. In fact, Sonde and coworkers (1998) demonstrated in their randomized, controlled study that 3 months of intensive low frequency TES (1.7 Hz) treatment to the extensors of the paretic elbow and wrist at the chronic stage of stroke did not improve spasticity in the affected UE. Han and colleagues (1994) applied 100 Hz or 2 Hz electrical stimulation for 3 months to acupoints hegu (LI4), zusanli (ST36) and changshan (B57) of people with spinal cord injury. Anti-spastic effect on their legs was demonstrated only after the treatment with high frequency currents.

Up to now, the mechanism through which electrical stimulation improves spasticity has not been fully understood. Hui-Chan and coworkers (Hui-Chan and Levin 1993, Levin and Hui-Chan 1992) found that prolonged segmental or heterosegmental high frequency transcutaneous nerve stimulation could increase the stretch reflex latency and reduce the stretch reflex response magnitude in subjects with chronic stroke. They provided indirect evidence suggesting that large diameter Aα and Aβ afferents that were excited with the electrical stimulation could have enhanced presynaptic inhibition or decreased motoneuronal excitability (Hui-Chan

and Levin 1993). Such mechanisms have so far been found to operate with high frequency electrical stimulation of peripheral nerves (Urasaki et al. 1998).

### *5.4.3 Effects on the recovery of motor functions*

A number of randomized controlled trials on subjects with chronic stroke have shown the effects of intensive, repetitive electrical stimulation in improving motor function, whether the treatment was applied to weakened muscles (Chae et al. 1998, Faghri et al. 1994, Linn et al. 1999, Powell et al. 1999, Sonde et al. 1998, 2000), peripheral nerves that innervate the muscles (Levin and Hui-Chan 1992, Tekeoŏlu et al. 1998), or acupoints (Wong et al. 1999, Yan 2002). In a randomized placebo-controlled study, Yan and coworkers (Yan 2002, Yan et al. 2005) added 3 weeks of electrical stimulation to either acupoints or weak muscles of the paretic leg of subjects receiving conventional rehabilitation after stroke. The experimental groups produced larger increases in ankle dorsiflexion torque than that receiving placebo stimulation. However, Hummelsheim and colleagues (1997) reported that a shorter 2-week electrical stimulation programme to the paretic wrist muscles after stroke did not improve the strength of the wrist muscles or hand grips.

The present study has confirmed that adding an intensive 4-week programme of electrical stimulation to conventional rehabilitation resulted in better improvements in GRIP and PINCH strength than could be obtained by conventional rehabilitation alone. This effect was detected at $W_4$ and persisted after the programme ended. This significant improvement, however, was confined to the power grip and index pinch. It was not found in the paretic shoulder or elbow muscles. One possible reason could be the large variance of strength measurement involved in the Motricity Index, so that a much larger sample would be required to

demonstrate the effect of any treatment on the strength of these more proximal muscles.

There have been controversial findings about the lasting effects of electrical stimulation. For example, Linn and coworkers (1999) introduced very intensive functional electrical stimulation to the affected shoulder early post-stroke. After 4 weeks with 2 to 4 hours of treatment applied daily to the shoulder abductors, the improvement in shoulder subluxation observed at the completion of the programme could not be maintained afterwards. Another 2 studies found that both 3 and 8 weeks of electrical stimulation to the wrist extensors of a paretic UE could improve muscle strength, and that the effects was carried over to 4 weeks (Chae et al. 1998) and 24 weeks (Powell et al 1999) after treatment ended. However, the improvement in terms of UE disability with such programmes has been minimal (Chae et al. 1998, Powell et al. 1999). In the present study, the grip and index pinch strength in the TES group improved much better than that of the control group starting as early as $W_4$, i.e., at the end of the electrical stimulation programme. This effect persisted to $W_{24}$ post-stroke, 5 months after treatment ended. In contrast, grip strength improvement in the placebo-TES group did not reach significant difference from that of the control group at any time interval. The significant and early improvement in grip strength after the TES programme is important, because grip strength at 1 month post-stroke has been proven to predict favourable recovery of UE function, both in this study (Chapter 4) and in the work by Sunderland's group (1989).

### *5.4.4 Treatment-induced plasticity in the motor cortex*

It has been noted that cortical plasticity is one factor contributing to recovery following stroke (Chapter 1). The undamaged cortical and subcortical sites of both

hemispheres, especially the ipsilateral peri-infarct zone and viable corticospinal tracts, were reported to take part in a plastic reorganization process for the restitution and substitution of sensori-motor functions in the damaged hemisphere (Dijkhuizen et al. 2003, Feydy et al. 2002, Nelles et al. 1999, Rothi and Horner 1983). Inputs from the thalamus and the somatosensory cortex, and those via the horizontal intracortical networks to the motor cortex have been identified as crucial for motor cortical plasticity (Hess and Donoghue 1994, Hess et al. 1996, Iriki et al. 1991, Jacobs and Donoghue 1991).

Recently, more and more evidence from studies on animals and human subjects has confirmed that repetitive peripheral electrical stimulation induces plastic changes in the somatosensory, corticomotor, and sensorimotor networks (Hamdy et al. 1998, Golaszewski et al. 2004, Kobayashi et al. 2003, McKay 2002, Nudo et al. 1990, Recanzone et al. 1990, Ridding et al. 2000 and 2001, Stefan et al. 2000). During low intensity peripheral electrical stimulation, Aα and Aβ afferents of muscle spindles and mechanoreceptors provide input to the thalamus via the dorsal column's medial lemniscal pathways, then to the somatosensory cortex, and via horizontal and vertical corticocortical connections to the primary motor cortex (Gardner et al. 2000). Inputs are also directed to the cerebellar cortex and subsequently feedback to the motor cortex.

Studies with physiological mapping techniques have shown that peripheral electrical stimulation increases the excitability of the corticospinal projections to the stimulated muscles and to other muscles with the same sensory topographic representation (Hamdy et al. 1998, Kaelin-Lang et al. 2002, McKay et al. 2002, Ridding 2000 and 2001, Stefan et al. 2000). The motor cortical representation of the muscles also expands. These effects from a single session of electrical stimulation

last from minutes to days afterwards, suggesting that these changes probably involve long-term potentiation-like mechanisms at the synapses (Hamdy et al. 1998, McKay 2002, Ridding et al. 2000). Yan and coworkers (2005b) used fMRI to investigate the cortical sites activated during acupuncture at LI 4. They found that compared to acupuncture at sham points, stimulation at LI 4 activated specific temporal gyri and the cerebellum. Another study showed that stimulation of LI 10 for 10 minutes or longer induced an increase in motor map size (Lo et al. 2005).

The 4 weeks of electrical stimulation applied to acupoints in this study was accompanied by significant improvement in hand grip strength in the paretic UE, and the effects lasted as long as 5 months after the programme ended. This intensive repetitive afferent stimulation might have induced plastic changes in the sensorimotor networks of the undamaged cortical and subcortical regions related to hand grip strength. As functional recovery has been associated with a decrease in the extent of Wallerian degeneration in the corticospinal tracts (Feydy et al. 2002, Nelles et al. 1999), the integrity of these descending pathways might have been better maintained by the early application of an electrical stimulation programme, leading to persistent improvement in UE motor functions.

Training-induced cortical plasticity after stroke has already been widely reported. However, plasticity associated with electrical stimulation has hereto been demonstrated mainly in healthy subjects. No explanation as to how electrical stimulation might promote plasticity leading to functional recovery after stroke has yet been reported in the literature. Recently, Kimberley and coworkers (2004) compared the hand motor function of stroke subjects who had completed an intensive 3-week programme of electromyography-triggered neuromuscular electrical stimulation with that of control subjects who had only practiced active

exercise of the wrist and fingers. Note that the experimental intervention had involved the subjects' active muscle contraction in order to drive the peripheral electrical stimulation treatment. The experimental group showed better motor functions as well as plastic changes in the somatosensory cortex, while the control subjects did not have such plastic changes. In view of this, studies incorporating imaging or physiological mapping techniques are needed to establish a clear picture of the relationship between peripheral electrical stimulation and cortical plasticity in promoting motor recovery post-stroke.

### *5.4.5 Recovery of muscle strength in hand grips but not in proximal muscles*

Previous studies have shown that plastic reorganization in the motor cortex that was induced by electrical nerve stimulation has topographical specificity (Kaelin-Lang et al. 2002, McKay et al. 2002, Ridding et al. 2000 and 2001, Stefan et al. 2000). After 2 hours of electrical stimulation applied to the ulnar nerve at the wrist at a current intensity 2.5 to 3 times the sensory threshold (Ridding et al. 2000 and 2001), or to the motor point of the first dorsal interosseus hand muscle combined with transcranial magnetic stimulation at intensity just eliciting a small motor response in the same muscle (McKay et al. 2002), the amplitudes of motor evoked potentials of those muscles supplied by the same nerve trunk were found to have increased, together with an expansion of their motor cortical maps. A similar stimulation-induced motor response has been noticed in the abductor digiti minimi with C8-T1 innervation, but not in the abductor pollicis brevis supplied by the median nerve (Ridding et al. 2000 and 2001). This difference could be explained by the fact that the afferent projections from the somatosensory cortex to the motor cortex have topographical specificity (Gardner et al. 2000, Kandel and Jessell 1991).

Moreover, the outputs of individual cortical motoneurons could be diverged to multiple muscles, and cortico-motoneurons in overlapping cortical territories could converge to a single muscle, aside from the extensive horizontal interconnections amongst the cortical sub-regions (Cheney and Fetz 1980, Huntly 1991). Therefore, afferent inputs from peripheral electrical stimulation may mediate cortical motoneuronal plasticity with the same somatotopic representation.

In the present study, the acupoints LI 4, LI 10 and LI 11 where the stimulation was applied were supplied by C5 and C6 cutaneous innervation. As described in section 5.5.1, the surface landmark of LI 4 overlays the muscle belly of the bipennate first dorsal interosseus hand muscle whose origin spans from the first and second metacarpal bones to the extensor expansion at the radial base of the proximal phalanx of the index finger. Innervated by C8-T1 of the ulnar nerve, the first dorsal interosseus is involved in index finger abduction, metacarpo-phalangeal joint flexion, interphalangeal joint extension and thumb adduction. Both LI 10 and LI 11 rest on the elbow and forearm region where there are the muscle bellies or musculotendinous junction of supinator, brachioradialis and extensor carpi radialis (Gray 1980). Muscle spindle afferents from these muscles belong to the C5, C6 and C7 nerve roots (Gray 1980). Also noteworthy is that the sensory and motor cortical representation area of the hand and fingers is the largest relative to other parts of the UE. Repetitive electrical stimulation to LI 4, LI 10 and LI 11 acupoints might thus influence a large representation area on the sensory and motor cortex. The associated motoneuronal plastic adaptation might then favour the recovery of GRIP and PINCH strength in the TES group. Although LI 11 and LI 15 fall on the lateral elbow and shoulder, both are small points with reference to the large elbow and shoulder, and are therefore less extensively represented in the sensory and motor

cortices. Any afferent-induced effects from stimulating these 2 acupoints might be insufficient to improve the strength of elbow flexion or shoulder abduction.

### *5.4.6 Latent effects on the recovery of upper extremity functional ability*

Previous studies on electrical stimulation of patients with stroke could not confirm any effect on daily activity or walking speed (Chae et al. 1998, Yan 2002). The TES group in the present study showed better improvements in UE functional ability than the controls. Improved Action Research Arm Test scores were observed at $W_{16}$ and $W_{24}$, i.e., 3 and 5 months after the electrical stimulation programme had finished, starting much later than the effect on grip and pinch strength which reached significant difference from controls at $W_4$. It should be noted that successful performance of the grasping, gripping and pinching tasks of the test demand dexterity in the paretic UE. The 4-week electrical stimulation treatment did not involve any problem-solving components or task training of the paretic UE. As reported in Chapter 4, hand grip strength from $W_4$ post-stroke onwards strongly predicted UE functional ability at 3 months post-stroke. The significantly better time course of UE functional improvement compared to that of the controls is consistent with this prediction model.

### *5.4.7 Effects of augmented therapy time early after stroke*

Although the TES group demonstrated better recovery of motor function than the controls, one might comment that the additional 20 hours of treatment might have accounted for such improvements. Previous studies have shown that enhancing therapy programmes by a significant amount of time appeared to produce better muscle strength, dexterity function and self-care outcomes after stroke (Bode et al.

2004, Kwakkel et al. 1999, Parry et al. 1999, Sunderland et al. 1992). In contrast, Di Lauro and colleagues (2003) have demonstrated that doubling the therapy time for patients during the acute stage of stroke did not result in improved level of dependence in daily living activities. In a meta-analysis, 20 randomized controlled trials that addressed the effects of augmented exercise therapy time after stroke were studied (Kwakkel et al. 2004). The authors concluded that a difference of at least 16 hours within the first 6 months after stroke should make a difference in daily activity outcomes, but not in hand dexterity. The placebo-TES group in this study was given the same amount of treatment as the TES group, but they exhibited no detectable difference in the time course of motor function recovery from that of the controls. So, the present suggested effect from augmented therapy time could only be tested with larger samples in both the placebo-TES and TES groups.

Although another meta-analysis of clinical trials by Ottenbacher and Jannell (1993) has suggested that early initiation of treatment after stroke is associated with better functional improvement, this relationship remains debatable. Nudo and coworkers (1996a, b) found that when monkeys were given an early hand skills retraining programme within 5 days after an induced focal brain infarct, the functional topography representing the hand in the undamaged motor cortex was either maintained or expanded, together with obvious recovery in their hand skill functions. If no training was given after brain lesion, the cortical territory of the affected hand was lost. However, Kozlowski and her group (Kozlowski et al. 1996, Humm et al. 1998) reported adversed effects on the ischaemic injury and subsequent functional recovery in rats given early intensive training. In their experiments, the rats were forced to use their affected forelimbs in activities during the first 15 days after induced brain lesion. Instead of favourable plastic adaptation in the intact

cortical regions, exaggerated brain damage was noted. The authors suggested that early forced-use of the affected limb during acute stroke may be detrimental to functional recovery – at least in rats.

In a randomized controlled trial, Hu and coworkers (1992) have demonstrated favourable neurological recovery when acupuncture is started within 36 hours after the onset of stroke. In the present study, the programme of acupoint stimulation was started within the first 2 days after the onset of stroke. Recovery in hand grip strength and functional ability was enhanced in the TES group throughout the follow-up period up to 6 months post-stroke. Early electrical stimulation of UE acupoints may thus be a promising treatment to facilitate motor recovery during the acute stage of stroke.

### *5.4.8 Motor function recovery after TES and placebo-TES treatment*

Previous placebo-controlled trials of electrical stimulation could not show any effects of placebo stimulation on motor recovery (Chae et al. 1998, Tekeoŏlu et al. 1998). Yan (2002) and colleagues (2005) found that ankle dorsiflexion torque was higher in their experimental group than in the placebo group 1 month after a 3-week electrical stimulation programme being applied to acupoints or weak muscles of the affected leg. However, less intensive protocols which involved 20 sessions of 30-minute electrical stimulation to acupoints over 10 weeks did not produce significant improvements in stroke-induced neurological impairments or disabilities when compared to the outcomes after placebo stimulation or no stimulation (Gosman-Hedström et al. 1998, Johansson et al 2001).

The present study introduced intensive electrical stimulation to 6 UE and skull acupoints starting within 2 days after stroke onset. Both TES and placebo-TES

groups showed significant within-group improvement in UE functional ability, but when compared with those of the control group, only the TES group demonstrated significant improvements in power grip and index pinch strength from $W_4$ onwards (Figure 5.2), and in UE function from $W_{16}$ onwards (Figure 5.3). Although the similar time course of motor function recovery between the TES and placebo-TES groups might be attributed to the small sample size reducing the power of the statistical test, could there be real placebo effects as well?

5.4.8.1 Real placebo effects

Placebos are defined as non-specific factors mediating the response of recipients in a treatment process (Brown 1998, Chaput de Saintonge and Herxheimer 1994). They appear to be especially effective in stress or anxiety afflicted problems such as pain and angina pectoris or the early stage of depression (Brown et al. 1992, Dimond et al. 1960, Turner et al. 1994). Placebo effects depend in part on the individual's expectations about the effects of treatment (Brown 1998). In the present study, it could be the additional 20 hours of treatment the placebo-TES group received during the first 4 weeks. This additional treatment might be particularly meaningful to the subjects during the acute stage, when patients often became anxious about the sudden loss of motor control after stroke, so both physical and psychological support are highly regarded (Liu and Mackenzie 1999).

However, a placebo mechanism is often self-regulating, so the associated treatment gain may be limited (Oh 1994). The placebo-TES group in the present study showed much of their motor function improvement during the 4 weeks of placebo treatment. In this group, the SRM values ranged from 0.23 to 0.40 between $W_4$ and $W_{24}$ post-stroke (Table 5.7), illustrating that the magnitude of any further

motor function recovery was small after the placebo stimulation finished. On the other hand, medium to large gain in grip strength and UE functional ability continued in the TES group during the 5 months after the treatment ended (SRM values ranged from 0.54 to 0.89).

5.4.8.2 Sample size

Noting that the probability of detecting sensori-motor improvement increases as a function of time since the onset of stroke, Duncan and coworkers (1992) have suggested recruiting larger samples for studies on acute stroke. Analysis of the results of this present study using the statistical software NCSS-PASS showed that the minimum sample size needed to detect a difference in motor function between the placebo-TES and control groups at $W_4$ was 30 per group for GRIP (effect size = 0.56), 37 for PINCH (effect size = 0.49) and 29 for UE functional ability (effect size = 0.73). The present study was thus limited by its less than optimal placebo-TES group size (n=20), and the possibility of placebo effects mediating motor function recovery as a result of early TES to acupoints requires further investigation.

5.4.8.3 Attention could mediate motor cortical plasticity

Attention has also been shown to be capable of modulating plasticity in the motor cortex (Rosenkranz and Rothwell 2004, Stefan et al. 2004). In a study of monkeys exposed to a vibration detection task, neurons in their primary somatosensory cortex were found to be excited regardless of whether or not rewards were anticipated (Poranen and Hyvärinen 1982). However, neurons in the secondary somatosensory cortex and the motor cortex were found to become strongly activated only in the reward-anticipated condition. The authors suggested that the attention

triggered by the anticipation of rewards led to enhanced neuronal activity promoting sensorimotor integration for the motor behaviour required to obtain the reward. Stefan (2004) conducted another such experiment with human subjects. During a session of repetitive paired associative stimulation of the abductor pollicis brevis muscle, the motor evoked potential was increased when subjects paid attention to the stimulated hand, but was diminished when attention was directed to the opposite hand. Such neuronal responses were further enhanced when the subjects were looking at the stimulated hand as compared to the condition when the hand was out of sight.

During the 60 minutes of electrical stimulation in this study, subjects in both the TES and placebo-TES groups placed their paretic UE on a support surface so that the UE was within their visual field. This arrangement may have enhanced their attention to the paretic UE, especially to the hand. Whether this increased attention might have augmented the treatment effects would warrant future investigation.

### *5.4.9 Other possible mechanisms for the effects on motor function recovery*

In contrast with previous studies showing only brief persistence of functional gains after treatments were discontinued (Chae et al. 1998, Powell et al. 1999, Yan et al. 2005), the present study demonstrated that improvements in power grip, finger pinch strength and UE functional ability in the TES group persisted during the 5-month period after treatment finished. This long lasting effect might have resulted from earlier control of the ischaemic cascades in response to the early stimulation of the acupoints (c.f. refer back to the review in Chapter 1, section 1.6.1 and subsection here). Several studies using induced infarct models on rats have shown that electroacupuncture can limit free radical expression and induced apopletosis in the

affected brain (Siu et al. 2004, Zhao et al. 2000). The implications of these findings for neurological recovery after stroke are still unknown. Tracing the size of the infarct with diagnostic imaging procedures might allow an estimation of the neuro-protective effects of electrical stimulation early after stroke.

### *5.4.10 Limitations of the present study*

This study included subjects whose severity of ischaemic stroke ranged from mild to moderate as measured with the National Institutes of Stroke Scale (scores at recuitment ranged from 2 to 17), although all of them demonstrated paresis in the contralateral UE. It is unknown if the severity of stroke or the degree of UE paresis would affect response of the paretic UE to the electrical stimulation programme. However, there were no statistical differences among these variables across the 3 groups. Baseline values found to be significantly different among the groups had already been analyzed as covariates. Nevertheless, possible contribution by placebo effects needs to be addressed by further investigation involving a larger sample.

## 5.5 Conclusion

The results of this study support the hypothesis that an intensive 4-week programme of transcutaneous electrical stimulation applied to the 6 acupoints, and started within the first 2 days after the onset of stroke in addition to conventional rehabilitation, can enhance the recovery of motor function in the paretic UE. The TES group demonstrated better recovery than the controls in terms of power grip and index pinch strength which are essential for completing tasks requiring dexterity with the affected extremity. More important was the evidence of carry-over

improvements for as long as 5 months after the programme ended. Possible contribution by placebo effects would require further studies with a larger sample.

# *Chapter 6*

## *Summary and Conclusions*

## 6.1 Introduction

The recovery from stroke-induced motor dysfunction in a paretic UE is often compromised by compensatory use of the less affected UE (Nakayama et al. 1994a). Appropriate early treatment to the paretic UE ideally should enhance its recovery (Biernaskie et al. 2004, Ottenbacher and Jannell 1993). However, training that involves active repetitive use of the paretic UE may not be applicable to all patients during the acute stage of stroke, when most patients experience flaccidity and movement difficulties as a result of the initial neurological shock from the ischaemic brain injury. Transcutaneous electrical stimulation (TES) applied to weak muscles, peripheral nerves or acupuncture points (acupoints) could be an appropriate treatment during this stage. Placebo-controlled trials with stroke patients by Hui-Chan and her group (Levin and Hui-Chan 1992, 1993; Yan 2002, Ng 2005) have shown that electrical stimulation of a paretic lower extremity can result in reduced spasticity and improved strength in the ankle muscles. However, the results of other clinical trials of peripheral electrical stimulation for the recovery of muscle strength and performance in activities of daily living after stroke have been controversial (Gosman-Hedström et al. 1998, Johansson et al. 2001, Kjendahl et al. 1997, Wong et al. 1999). Interpreting the effectiveness of peripheral electrical stimulation after stroke has been complicated by the wide range of methodologies employed in these studies, e.g., single-blind vs. double-blind procedures, the absence of placebo treatment as a control, varied intensity of treatment in terms of treatment duration and frequency, treatment commencing at different times after the onset of stroke, the sensitivity and specificity for detecting possible recovery of the measurement tools

chosen, and questions on the carry over effects. The main study of the thesis addressed the question: Could transcutaneous electrical stimulation (TES) applied early after acute stroke be effective in enhancing sensori-motor and functional recovery in the paretic UE? It involved 2 related studies which tracked the recovery in the paretic UE of subjects with initial ischaemic stroke from within 5 days of the attack to 6 months post-stroke.

## 6.2 Main Findings

### *6.2.1 Study 1: Time course of recovery of the paretic upper extremity*

This preliminary study investigated the recovery of sensory, motor and functional abilities in the paretic UEs of subjects receiving conventional rehabilitation (CR) after stroke. A total of 57 subjects who received only CR after stroke completed 9 assessments from baseline to 6 months post-stroke. The extent of recovery in tactile discriminative sensation, muscle tone, muscle strength and functional ability of the paretic UE was examined with respect to the norms established with 100 healthy subjects. The extent of recovery in each time interval was studied with reference to standardized response means (SRMs). The main findings were:

1. Tactile discriminative sensation measured as pressure sensibility (PR) and two-point discrimination (2-PD) in the paretic hand showed rapid recovery in the initial 1 to 2 months after stroke. In fact, the mean PR and 2-PD scores were not different from the norm by week 8 and week 16 post-stroke, respectively. Further changes between 3 and 6 months post-stroke were minimal (SRM $\leq$0.05).

2. Muscle tone (measured with the Composite Spasticity Score) increased from a hypotonic status at recruitment to a spastic status 2 weeks afterwards. Much of the increase in muscle tone was observed to occur during the first month post-stroke, with a subsequent plateau.

3. Recovery of muscle strength in the paretic UE (measured with the Motricity Index score, power grip and index pinch grip) was fast in the first month post-stroke. Recovery of UE functional ability was faster in the first 2 months post-stroke.

4. The shoulder abductors and elbow flexors of the paretic UE showed faster improvement during the initial 3 months post-stroke (SRM $\geq$0.73) when compared to power grip (SRM = 0.59) and index pinch (SRM = 0.49) strength. In the subsequent 3 months, however, larger gains were observed in power grip and index pinch strength. The SRM was 0.77 for power grip and 0.51 for index pinch strength; that of the shoulder abductors and elbow flexors were 0.37 and 0.45 respectively.

5. After 6 months of CR, the subjects' muscle strength and functional ability in general were still significantly less than the norm, so that the mean muscle strength score was only 2/3 of the norm for shoulder and elbow, and 1/3 of the norms for power grip and index pinch strength. Forty-seven percent of the subjects were left with poor UE function, without any prehensile ability in the paretic hand (ARAT score <10).

The conclusion from this study was that sensori-motor function in the paretic UE showed greater recovery in the initial 1 to 2 months after stroke among patients receiving only CR. Recovery between 3 and 6 months was relatively small or

minimal, although power and pinch grip strength exhibited greater recovery in this later period than in the initial 3 months after stroke. Since the extent of motor function recovery was far from normal even when clients had received conventional rehabilitation, more effective treatments are needed to further enhance the extent of their recovery after stroke.

### *6.2.2 Study 2: Predicting the recovery of functional dexterity in a paretic upper extremity*

The same cohort of subjects with acute stroke reported in Study 1 was examined with the aim of identifying the best early predictors in the initial 2 months post-stroke for the eventual recovery of functional dexterity in a paretic UE. Recovery was defined as the ability to lift objects with a precision grip, indicated by a score ≥35 on the Action Research Arm Test. Initial data were collected on the side and site of the brain infarct, stroke severity (measured with the National Institutes of Health Stroke Scale), cognitive status and spatial neglect, tactile discrimination sensation (PR and 2-PD) of the index finger pulp, muscle tone and muscle strength in the paretic UE (measured with the Motricity Index score), and power grip and index pinch strength in the paretic UE. Data were then collected weekly on the sensori-motor abilities of the paretic UE. These data were analyzed to identify candidate predictors of functional dexterity in the paretic UE at 3 and 6 months post-stroke. The statistic used was univariate logistic regression. Those candidate predictors found significantly associated with the functional outcome were entered to multiple

logistic regressions in order to establish the best predictors of the recovery of functional dexterity in a paretic UE. The main findings were:

1. Muscle tone in the paretic UE recorded from baseline to 2 months was not predictive of its functional outcome.

2. The site of the stroke lesion, especially if the stroke was subcortical (O.R. = 0.18) or involved larger cortical and subcortical area (O.R. = 0.09), as well as stroke severity (O.R. = 0.66) predicted poor recovery of functional dexterity at 3 and 6 months post-stroke.

3. The initial 2-PD (O.R. = 0.84) and Motricity Index scores (O.R. = 1.06), as well as their status during the first month were significantly associated with the recovery of functional dexterity in the paretic UE at 3 and 6 months post-stroke.

4. The association of power grip strength and index pinch strength with functional dexterity became significant at 2 weeks post-stroke and afterwards, with the predictive power strongest at weeks 4 post-stroke (area under the ROC curve >0.90).

5. After adjusting for the effects of prediction with other predictor candidates such as site of stroke lesion and stroke severity, the Motricity Index score at week 4 post-stroke was the strongest predictor of the recovery of functional dexterity at 3 and 6 months post-stroke, followed by combined 2-PD and Motricity Index score at week 2 post-stroke.

6. The sensitivity and specificity of prediction were higher for the 6-month functional outcome than for that at 3 months. Motricity Index scores of 45 at week 2

and of 64 at week 4 were identified as the cut-off values to predict the return of functional dexterity at 6 months post-stroke.

The conclusion from this study was that muscle strength in the paretic UE and to some extent 2-PD in the paretic hand in the first month after stroke gave the best prediction of the eventual recovery of functional dexterity in a paretic UE.

### *6.2.3 Study 3: Effects of transcutaneous electrical stimulation applied to acupoints*

This phase of the study examined the effectiveness of intensive transcutaneous electrical stimulation (TES) applied within 2 days after the onset of stroke in promoting the recovery of sensory, motor and functional abilities in a paretic UE. TES was applied to 6 acupoints (the 2 GB 20 points on either side of the base of the occiput, and LI 15, LI 11, LI 10 and LI 4 on the paretic UE), at 1 hour per day, 5 days a week for 4 weeks. Subjects recruited within 46 hours after stroke onset were randomized in a double-blind placebo-controlled design to receive conventional rehabilitation alone as controls (n=18), TES treatment (n=28) or placebo-TES (n=20) in addition to CR. Nineteen patients who had been recruited within 60 hours after stroke onset and were receiving only CR were added to the control group. The 3 groups were compared their UE recovery in terms of (1) tactile sensation of pressure and two-point discrimination in the index finger pulp, (2) muscle tone, (3) muscle strength in the shoulder and elbow measured with the Motricity Index, (4) power grip and index pinch strength measured with a dynamometer, and (5) functional ability measured with the Action Research Arm Test. All subjects were assessed at

recruitment, then followed up weekly for the first 4 weeks and at 1, 2, 3 and 5 months afterwards. The sensori-motor functioning of the paretic UE was examined with mixed model ANCOVA following intention-to-treat principles. The results revealed that:

1. There was no difference among the 3 groups in terms of their improvement in either PR or 2-PD sensibility at any of the 8 assessment intervals after the baseline assessment.

2. No significant difference was found in the changes in muscle tone, or muscle strength of the shoulder and elbow with time among the groups.

3. TES applied to the 6 acupoints produced significantly greater improvement in power grip and index pinch strength after 4 weeks of treatment when compared to that of subjects receiving only CR ($P$ <0.01). The effects persisted 5 months after the treatment ended.

4. In addition, the TES group showed significantly better recovery than the control group in the UE functional ability measured with the Action Research Arm Test 3 months after the treatment ended ($P \leq 0.01$).

5. The average improvement in the strength of power grip and index pinch as well as functional ability in the paretic UE was not significantly different between the TES and placebo-TES groups at any time studied. The placebo-TES group showed similar effect sizes (measured by SRM) of these outcome variables as the TES group during the 4 weeks of treatment. However, the TES group demonstrated persistent gain in the hand muscle strength after the 4-week electrical stimulation programme ended. In the TES group, the effect sizes over the entire 24 weeks were 1.07 for

power grip and 0.89 for index pinch strength, which tended to be slightly larger than those of the placebo-TES group at 0.84 and 0.75 respectively.

6. Differences in motor function recovery between the placebo-TES and control groups did not reach significance. Based on the effect sizes for the differences in motor function recovery between the placebo-TES recipients and the controls, a larger sample of 29 to 37 subjects per group would be required for delineating possible placebo factors in influencing such recovery in the placebo-TES group.

In summary, our main study confirmed that 4 weeks of intensive TES treatment to 6 acupoints started within 2 days after the onset of stroke, can enhance greater recovery of power grip and index pinch strength than that of CR alone. Moreover, these effects were carried over to at least 5 months after the treatment ended.

## 6.3 Implications for Stroke Rehabilitation

The results of this thesis showed that patients receiving conventional rehabilitation had rapid sensori-motor and functional recovery in the paretic UE in the initial 1 to 2 months after a stroke. Further recovery beyond this period was relatively small and gradual, but power grip and index pinch strength continued to show gradual improvement. More important to note is that motor function of the paretic UE at 6 months post-stroke is still far from normal. Despite advances in acute stroke management in recent decades, the time course of recovery in our local sample

remained similar to that reported in the literature. Therefore, more effective therapies should be developed in order to enhance better motor function recovery in the paretic UE.

Return of functional dexterity in the paretic UE is crucial for more efficient performance of manual tasks in daily life activities. Among the clinical characteristics presented in subjects with acute ischaemic stroke, muscle strength in the paretic UE and to some extent 2-PD in the paretic hand in the first month are the best predictors for the recovery of functional dexterity at 6 months post-stroke. The strongest predictor is the overall UE muscle strength measured with the Motricity Index at week 4 post-stroke. Both power grip and index pinch strength in the paretic UE are stronger predictors than muscle strength in the shoulder or the elbow at week 4 post-stroke. Together, these findings support the importance of early interventions aiming at improving longer-term UE function. Muscle strength impairment, more specifically power grip and index pinch strength, should be addressed in rehabilitation interventions because they are strong prognostic indicators for functional dexterity of the paretic UE later on.

This double-blind, placebo-controlled clinical trial has confirmed that TES applied to 6 acupoints, started within 2 days of stroke and given 60 minutes per day, 5 days per week for 4 weeks, is effective in promoting the recovery of power grip and index pinch strength. This effect was detected at the end of the TES programme (4 weeks after stroke onset) when compared to that from just conventional rehabilitation. It persisted for at least 5 months after the treatment was completed. These results contradict previous negative findings about the effects of TES or acupuncture on

motor or functional improvement (Gosman-Hedström et al. 1998, Johansson et al. 2001, Sze et al. 2002) when comparing with those of conventional rehabilitation. Both hand grip and index pinch strength are prognostic indicators for the recovery of functional dexterity in the paretic UE. Therefore, TES to acupoints using the protocol studied here should be an ideal adjunct to CR treatment to facilitate earlier and greater motor function recovery in the paretic UE.

During the acute stage of stroke, patients spend around 30% of clinical working hours on medical and rehabilitation intervention (see Chapter 2, section 2.3.3, De Wit et al. 2005). They remain inactive during the rest of the time either in bed or sitting idly. The proven effects of additional TES on motor recovery in the paretic UE should warrant its application as a standard treatment for people with mild to moderate ischaemic stroke during the acute stage. Being a non-invasive form of treatment, TES could be applied by the patients themselves or the caregivers according to the present protocol after some training.

## 6.4 Limitations of the Study

Despite the finding of significantly greater motor recovery with TES treatment, the sample size in this study was too small to illustrate possible difference between the effects of placebo-TES and real TES treatment, or between placebo-TES and CR. A larger sample with at least 29 subjects per group is needed to rule out the possibility that a placebo effect could have contributed to the observed treatment effects.

Our subjects were suffering from mild to moderate stroke at the time of recruitment. It is not known if the TES effects observed in these subjects could be generalized to more severely affected patients, or whether the severity of the neurological insult might govern an individual's response to TES treatment. In the future, a larger sample should be recruited to address this issue.

TES treatment appears to have limited effects on improving tactile discrimination in a paretic hand, and on the strength of shoulder abductors and elbow flexors. Because of the large variance found in these variables, more sensitive and/or objective measurement tools should be employed in future experiments. For example, we examined only a small skin area on the distal pulp of the index finger for the effect on sensation after TES. In future studies, tactile discrimination should be examined over a wider representative region of the hand in order to better judge the treatment effects (see Chapter 5, section 5.4.1).

In this study, the effects of TES on motor function have been demonstrated in terms of distal muscle strength and functional ability of the paretic UE, but no significant improvement in muscle tone was found. However, previous randomized clinical trials by Hui-Chan and her group (Levin and Hui-Chan 1992, 1993; Yan et al. 2005, Ng 2005) have shown that spasticity in the lower extremity was improved after TES treatment of the affected muscles, nerves or acupoints. These contradictory results might be related to the electrical stimulation protocol, because low-frequency TES (20Hz) was used in this study, while previous studies used high-frequency TES (99 to 100 Hz). Therefore, the effect of high frequency TES on muscle tone of the paretic UE after stroke needs to be investigated further.

## 6.5 Indications for Future Research

The mechanisms underlying the effects of TES on power grip and index pinch strength, as well as any latent effect on functional ability, should be investigated. Further studies should address the following questions:

1. Are there any changes in cortical activation or neural plastic reorganization in the injured brain during or after TES to acupoints of the paretic UE? If activity is induced in the injured cortex, are there changes in this activity associated with the recovery in the paretic UE observed over time? Can placebo-TES also induce changes in cortical activity? To answer these questions, further studies are required involving electrophysiological or brain imaging procedures such as EEG, transcranial magnetic stimulation, positron emission tomography or functional magnetic resonance imaging. Such techniques should be able to reveal any induced brain activity and test the hypothesized relationship between cortical activity or plasticity and motor function recovery as a result of TES treatment.

2. The acupoints stimulated in this study were 2 skull points (GB 20) and 4 peripheral points on the shoulder (LI 15), the extensor aspect of the paretic forearm (LI 11 and LI 10) and the hand (LI 4). Is the specific effect on the strength of power grip and index pinch strength related to the choice of acupoints used in this study? Could stimulation of the motor points of the relevant muscles of the paretic UE or of the cervical nerve roots at their exit from the cervical spine induce similar effects? Further studies should examine any differences in effects resulting from stimulating different acupoint arrays, and from stimulating non-acupoints.

3. Is the effect of TES on motor function recovery governed by the intensity of treatment? Would the effect be different if the TES treatment were started later after the 1 month time window from the onset of stroke? In order to explain why previous studies have returned negative findings (Gosman-Hedström et al. 1998, Johansson et al. 2001), the effectiveness of the early, intensive TES protocol has to be further validated in randomized controlled trials involving subjects with stroke receiving less intensive or delayed treatment.

4. Is the effect on motor function confined to people with mild or moderate stroke? Does the extent of stroke severity affect the effectiveness of the TES treatment studied here? To enable the examination of possible influence of stroke severity on treatment effects, a study involving stratified randomization of subjects into two categories of stroke severity will be required.

5. Are effects from the present TES protocol confined to the paretic UE? Would the additional treatment applied to the 6 acupoints improve other neurological impairments such as cognition or sensori-motor function in the affected lower extremity? Other possible effects of the TES treatment could be examined with studies tracking their changes over time.

6. Although the two hospitals involved in this study were the largest in Hong Kong providing acute care and rehabilitation to patients with stroke, the treatment effects from the present early intensive TES protocol should be validated further with a multi-centre trial in order to address whether variations in CR between hospitals affect the generalizability of additional TES treatment.

## 6.6 Significance of the Study

With the randomized, placebo-controlled methods, results of this study confirmed that an intensive programme of TES to acupoints, given as early as the first 2 days of mild to moderate ischaemic stroke, promoted greater motor recovery in the paretic UE. This study is the first to show that the TES facilitated the recovery of power grip, index pinch and functional ability of the paretic UE. Although the possibility of placebo effects could not be ruled out, our results showed that only real TES produced continual and further power grip and index pinch strength improvements for at least 5 months after the treatment ended. Since power grip and index pinch strength have been demonstrated to be strong prognostic indicators for the return of functional dexterity 6 months after stroke, our study showed that TES is a valid adjunct treatment to conventional rehabilitation during acute stroke. Because the TES protocol could be taught to the patients or caregivers, it is a low cost treatment approach that could be widely adopted in hospital settings.

# *Appendices*

**Appendix I : Evaluation of Effect Size**

Effect size of the primary outcome of a study (Hunter and Schmidt 2004, p.277, Wolf 1986, pp.23-56):

$$\text{Effect size (d)} = \frac{\text{(change in Experimental group – change in Control group)}}{\text{within-group standard deviation}}$$

Unbiased pooled effect size of a number of studies in the meta-analysis (Hunter and Schmidt 2004, pp.284-285):

$$\text{Unbiased pooled effect size} = \frac{\text{Mean of d across studies}}{1 + 0.75/(\text{mean sample size across studies} - 3)}$$

## Appendix II : Consent Forms

### (1) Electrical Stimulation Treatment (English and Chinese version)

**INTRODUCTION**

The Department of Rehabilitation Sciences of The Hong Kong Polytechnic University would like to invite you to participate in a research project on the effects of transcutaneous electrical stimulation on recovery of the paralyzed arm in patients with stroke.

Transcutaneous electrical stimulation is a common physical therapeutic modality. In this study, your weak arm will be given the electrical stimulation treatment one hour per day, five days per week during your rehabilitation in the first four weeks after stroke. To evaluate your arm's progress, there will be regular assessments in the coming six months. The assessment will include sensation, movement and strength of your arm, and your ability in performing some tasks of daily activities, e.g., dressing, feeding. The procedures for both the assessment and treatment are safe.

All your personal information will be kept confidential and will only be used for academic and research purpose. If you participate in this research study and have any queries about it, you are welcome to raise them to the investigator Au-Yeung Suk Yin Stephanie (Tel: 2766 / 9680 ). You can also write to the Research Ethics Committee, the Department of Rehabilitation Sciences of The Hong Kong Polytechnic University.

Your participation in this research is voluntary. You may refuse to participate, or withdraw your participation in this research any time you feel like without prejudice against your present or future care in the hospital and rehabilitation units.

Your participation in this research may assist in improving the future treatment of stroke clients. Your acceptance of this invitation would be very much appreciated.

Sincerely,

Stephanie Au-Yeung
Assistant Professor
Department of Rehabilitation Sciences
Hong Kong Polytechnic University

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**CONSENT FORM**

I _____ (H.K. Identity Card Number: _____) consent to participate in the research on the effects of electrotherapy on the recovery of the paralyzed arm after stroke which is conducted by the Department of Rehabilitation Sciences of the Hong Kong Polytechnic University. I have understood the aim, nature and procedure of the research. I have been given the chance to ask about the research and my queries have been answered to my satisfaction.

Signature : _____ Date: _____

Witness: _____ Date: _____

Research Personnel: _____ Date : _____

# 穴位透皮神經電刺激對中風病人的偏癱上肢復原研究

## 研究簡介

香港理工大學康復治療科學系,現誠邀閣下參加有關透皮神經電刺激對中風後的偏癱上肢復原的研究。

透皮神經電刺激乃常用之物理治療項目。在是項研究中,閣下的偏癱上肢在康復療程初期的四星期內,接受每星期五天、每天一小時之透皮神經電刺激電療。為檢驗閣下因電療達至的效果,閣下將在今後六個月接受定期檢查。檢查包括感覺、肌力、活動及日常生活功能,例如穿衣、進食等的測驗。每次檢查大約一個小時。透皮神經電刺激在同類研究中並沒有已知的危險,整個檢查過程亦十分安全。

閣下之個人資料將會保密及只作學術及研究用途。若閣下在參加此研究期間有任何疑問,可隨時向負責人歐陽淑賢提出(電話:2766 / 9680 ),或致函香港理工大學康復治療科學系之研究道德委員會。

閣下是自願參與是項研究,閣下可隨時拒絕參與或退出此研究,並且不會影響閣下在院內的治療。

若閣下願意參加是項研究,對將來改進治療上肢於中風後的活動障礙有極大的幫助。謝謝!

香港理工大學助理教授

歐陽淑賢 上

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## 同意書

本人 _____ (身份證號碼 _____ )願意參加由香港理工大學康復治療科學系進行有關電療對中風患者上肢康復的研究。本人已瞭解整個研究的目的、內容及程式,並已獲得提問的機會,亦得到滿意的解釋。

簽名: _____ 日期: _____

見證人: _____ 日期: _____

研究員: _____ 日期: _____

## (2) Conventional Rehabilitation (English and Chinese version)

**INTRODUCTION**

The Department of Rehabilitation Sciences of the Hong Kong Polytechnic University would like to invite you to participate in a research project on the recovery of the paralyzed arm of patients after stroke.

You will receive conventional rehabilitation treatments given by the Hospital in this study. The progress of your weak arm will be assessed regularly in the coming six months. The assessment will include sensation, movement and strength of your arm, and your ability in performing some tasks of daily activities, e.g., dressing, feeding. Each assessment will take about one hour to complete. The assessment procedure is safe.

All your personal information will be kept confidential and will only be used for academic and research purpose. If you participate in this research study and have any queries about it, you are welcome to raise them to the investigator Au-Yeung Suk Yin Stephanie (Tel: 2766 / 9680 ). You can also write to the Research Ethics Committee, the Department of Rehabilitation Sciences of The Hong Kong Polytechnic University.

Your participation in this research is voluntary. You may refuse to participate, or withdraw your participation in this research any time you feel like without prejudice against your present or future care in the hospital and rehabilitation units.

Your participation in this research would assist in improving the future treatment of stroke clients. Your acceptance of this invitation would be very much appreciated.

Sincerely,

Stephanie Au-Yeung
Assistant Professor
Department of Rehabilitation Sciences
Hong Kong Polytechnic University

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**CONSENT FORM**

I _____ (H.K. Identity Card Number: _____)
consent to participate in the research on treatment strategies to improve movement problems of the arm in patients with stroke which is conducted by the Department of Rehabilitation Sciences of the Hong Kong Polytechnic University. I have understood the aim, nature and procedure of the research. I have been given the chance to ask about the research and my queries have been answered to my satisfaction.

Signature : _____ Date: _____

Witness: _____ Date: _____

Research Personnel: _____ Date: _____

# 中風病人的偏癱上肢復原研究

## 研究簡介

香港理工大學康復治療科學系,現誠邀閣下參加有關中風後的偏癱上肢復原的研究。此項研究將有助改良治療上肢於中風後的活動障礙。

在是項研究期內,閣下會接受由醫院提供的康復治療。在今後六個月內，閣下上肢的復原情況會有定期檢查。檢查內容包括感覺、活動及日常生活功能，例如穿衣、進食等的測驗。每次檢查大約一個小時。整個檢查過程是十分安全的。

閣下之個人資料將會保密及只作學術及研究用途。

若閣下在參加此研究期間有任何疑問,可隨時向負責人歐陽淑賢提出(電話：2766 / 9680 ), 或致函香港理工大學康復治療科學系之研究道德委員會。閣下是自願參與是項研究, 閣下可隨時拒絕參與或退出此研究, 並且不會影響閣下在院內的治療。

若閣下願意參加是項研究，對將來改進治療上肢於中風後的活動障礙有極大的幫助。謝謝！

香港理工大學助理教授

歐陽淑賢 上

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## 同意書

本人 _____ (身份證號碼 _____) 願意參加由香港理工大學康復治療科學系進行有關康復治療對中風患者上肢康復的研究。本人已瞭解整個研究的目的、內容及程式，並已獲得提問的機會，亦得到滿意的解釋。

簽名： _____ 日期： _____

見證人： _____ 日期： _____

研究員： _____ 日期： _____

## **Appendix III** : National Institutes of Health Stroke Scale (NIHSS)

| Test | Score |
|---|---|
| Level of consciousness | ❑ 0 = alert, keenly responsive<br>❑ 1 = drowsy, but arousable by minor stimulation to obey, answer, or respond<br>❑ 2 = requires repeated stimulation to attend, or lethargic or obtunded requiring strong or painful stimulation to make movements (not steoeotyped)<br>❑ 3 = responds only with reflex motor or autonomic effects, or totally unresponsive, flaccid, reflexless |
| Level of consciousness questions (the patient is asked what month it is and his / her age; only the initial answer is graded) | ❑ 0 = answers both correctly<br>❑ 1 = answers one correctly<br>❑ 2 = answers both incorrectly or unable to speak |
| Level of consciousness commands (the patient is instructed to open / close his/her hand/eyes; only initial response are graded; credit is given if an unequivocal attempt is made but not completed) | ❑ 0 = obeys both correctly<br>❑ 1 = obeys one correctly<br>❑ 2 = incorrect |
| Best gaze: extraocular movements | ❑ 0 = normal<br>❑ 1 = partial gaze palsy; score is given when gaze is abnormal in one or both eyes, but where forced deviation or total gaze paresis is not present<br>❑ 2 = forced deviation or total gaze paresis not overcome by the oculocephalic maneuver |
| Visual fields (test for hemianopia using moving fingers on confrontation with both of patient's eyes open; double simultaneous stimulation is also performed; use visual threat where level of consciousness or comprehension limit testing, but score 1 only if clear-cut asymmetry is found; complete hemianopia (score=2) is recorded for dense loss of response extending to within 5 to 10 degrees of fixation | ❑ 0 = no visual loss<br>❑ 1 = partial hemianopia<br>❑ 2 = complete hemianopia |
| Facial palsy | ❑ 0 = normal<br>❑ 1 = minor<br>❑ 2 = partial (total/ near total paralysis of lower face)<br>❑ 3 = complete paralysis in upper and lower face |
| Motor arm (patient is examined with arms outstretched at 90 degrees if sitting, or at 45 degrees if supine; request full effort for 10s; If consciousness or comprehension are abnormal, cue the patient by actively lifting his or her arms into position as the request for effort is orally given; only the weaker limb is graded) | ❑ 0 = limb holds $90^o$ for full 10 seconds<br>❑ 1 = limb holds $90^o$ position but drifts before full 10 seconds<br>❑ 2 = limb can't hold $90^o$ position but some effort against gravity<br>❑ 3 = limb falls, no effort against gravity |
| Motor leg (while supine, patient is asked to maintain weaker leg at 30 degrees for 5s; if consciousness or comprehension are abnormal, cue the patient by actively lifting the leg into position as the request for effort is orally given) | ❑ 0 = leg holds $30^o$ position for 5 seconds<br>❑ 1 = limb holds $30^o$ position but drifts by end of 5 seconds<br>❑ 2 = limb can't hold $90^o$ position for 5 seconds, but there is some effort against gravity<br>❑ 3 = leg falls to bed immediately with no effort against gravity |
| Limb ataxia | ❑ 0 = absent<br>❑ 1 = ataxia is present in one limb<br>❑ 2 = ataxia is present in two limbs |
| Sensory (test with pin; when consciousness or comprehension are subnormal, score sensation normal unless deficit is clearly recognized [eg. by clear cut grimace asymmetry, withdrawl asymmetry]; only hemisensory losses are counted as abnormal) | ❑ 0 = normal, no sensation loss<br>❑ 1 = mild to moderate, patient feels pinprick is less sharp or is dull on the affected side, or there is a loss of superficial pain with pinprick but patient is aware of being touched<br>❑ 2 = severe-to-total sensation loss, the patient is not aware of being touched |
| Neglect | ❑ 0 = no neglect<br>❑ 1 = visual, tactile or auditory hemi-inattention<br>❑ 2 = profound hemi-inattention to more than one modality |
| Dysarthria | ❑ 0 = normal<br>❑ 1 = mild to moderate, patient slurs at least some words, and at worst, can be understood with some difficulty<br>❑ 2 = patient's speech is so slurred as to be unintelligible |
| Language (the patient is asked to name the items on the naming sheet and is then asked to read from the reading sheet [see "subjects and methods" section]; comprehension is judged from responses to all of the commands in the preceding general neurologic examination) | ❑ 0 = normal<br>❑ 1 = mild to moderate aphasia, as follows, naming errors, word-finding errors, paraphasias, and / or impairment of comprehension/ expression disability<br>❑ 2 = severe aphasia, fully developed Broca's or Wernicke's aphasia<br>❑ 3 = mute or global aphasia |

## **Appendix IV** : Composite Spasticity Score (CSS)

The CSS was developed by Levin and Hui-Chan (1992). In this study, a modified version has been used which consists of (1) phasic stretch reflex expressed as biceps tendon jerk for the upper extremity (UE), and (2) tonic stretch reflex expressed as resistance to passive full range of elbow extension which is doubly weighted.

**Scoring guidline:**

***Biceps tendon jerk***

| | |
|---|---|
| No jerk elicited | 0 |
| Minimal response (hypoactive jerk) | 1 |
| Normal response | 2 |
| Moderately hyperactive response | 3 |
| Maximally hyperactive response | 4 |

***Resistance to passive stretch of elbow flexors during elbow extension***

| | |
|---|---|
| No resistance during movement | 0 |
| Slight resistance | 2 |
| Normal resistance | 4 |
| Moderately increased resistance | 6 |
| Maximally increased resistance | 8 |

| | | |
|---|---|---|
| **Total score** | 0 | : flaccidity |
| | 1–5 | : hypotonicity |
| | 6 | : normal tone |
| | 7-12 | : hypotonicity/spasticity |

## Appendix V : Motricity Index (MI) for Evaluating Muscle Strength in the Upper Extremity

This assessment is conducted with the subject sitting erect on a chair with back, thighs and feet supported, or in bed with the head, trunk and legs supported. Motor function of the upper extremity is the summation of scores obtained in tests 1 to 3 plus 1 (Demeurisse et al. 1980). A score of 100 represents full motor function (strength).

**Scoring Guidelines:**

**Test 1. Pincer grip** – tested with a 2.5 cm cube placed between the thumb and index finger (Figure I-A)

| | | |
|---|---|---|
| Score: | 0 | no movement |
| | 11 | beginning of prehension |
| | 19 | grips cube, but unable to hold against gravity |
| | 22 | grips cube and holds against gravity, but not against a weak pull from the examiner |
| | 26 | grips cube against a pull from the examiner, but weaker than the other extremity |
| | 33 | normal strength of pincer grip |

**Test 2. Voluntary elbow flexion –** the arm rests by the side of the body with the elbow at $90^{o}$ flexion; the elbow then demonstrates voluntary flexion (Figure I-B)

**Test 3. Shoulder abduction** – starting with the arm by the side of the body and abducting to $90^{o}$ (Figure I-C)

| | | |
|---|---|---|
| Score: | 0 | no movement |
| | 9 | palpable contraction in the muscle for the intended movement, but movement is not seen |
| | 14 | movement seen, but not full range/against gravity |
| | 19 | movement with full range against gravity, but not against resistance |
| | 25 | movement against resistance, but weaker than the other side |
| | 33 | movement against resistance with normal power as that of the other side |

(A) (B) (C)

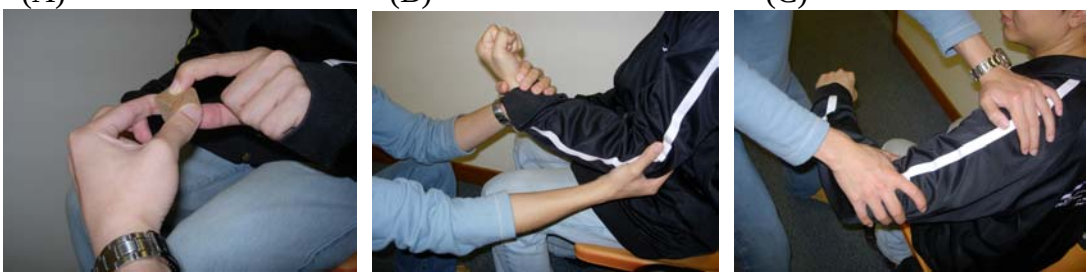

Figure I: Scoring muscle strength of the upper extremity with Motritcity Index: (A) pincer grip on the wooden cube, (B) elbow flexion, and (C) shoulder abduction

## Appendix VI : The Action Research Arm Test (ARAT)

Developed by Lyle (1981), this test on the functional ability of the upper extremity has 19 tasks assigned to four subtests. The method of scoring is described below. Note that the first task in each subtest is the most demanding, the second task is the least demanding, with the remaining tasks in ascending order of difficulty.

**Subtest 1: Grasp** (6 tasks)

Lift the designated object over 37 cm from the lower shelf to the top shelf

(1) 10.0 cm wooden cube
(2) 2.5 cm wooden cube
(3) 5.0 cm wooden cube
(4) 7.5 cm wooden cube
(5) cricket ball
(6) sharpening stone

**Subtest 2: Grip** (4 tasks)

(7) pour water from one glass into another
(8) displace an alloy tube (2.5 cm in diameter) from one side of the table to the other
(9) displace an alloy tube (1 cm in diameter) from one side of the table to the other
(10) put a washer over a bolt

**Subtest 3: Pinch** (6 tasks)

Pick up a marble or ball bearing (indicated below) from the lower shelf, and lift it over 37 cm to put it on the top shelf using the fingers as follow:

(11) a 6-mm ball bearing between ring finger and thumb
(12) a marble between index finger and thumb
(13) a 6-mm ball bearing between middle finger and thumb
(14) a 6-mm ball bearing between index finger and thumb
(15) a marble between ring finger and thumb
(16) a marble between middle finger and thumb

**Subtest 4: Gross Movement** (3 tasks)

(17) place hand behind head
(18) place hand on top of head
(19) bring hand to mouth

**Score:**

0 cannot perform any part of the test
1 can perform test partially
2 can complete test but with an abnormally long time or great difficulty
3 can perform test normally

**Appendix VII : A Comparison Between the Sensori-motor Functions of the Paretic Upper Extremity and the Respective Normal Scores**

| | Pressure sensibility threshold | Two-point discrimination threshold (mm) | Muscle tone (Composite Spasticity Score) | Upper extremity muscle strength (Motricity Index Score) | Power grip strength (kg) | Pinch grip strength (kg) | Upper extremity functional ability (Action Research Arm Test score) |
|---|---|---|---|---|---|---|---|
| Healthy controls (n=100) | 3.3 ± 0.5 | 3.4 ± 1.0 | 6 | 100 | 19.6 ± 5.9 | 5.3 ± 1.6 | 57 |
| Subjects with stroke (n=57): | | | | | | | |
| *Time post-stroke –* | | | | | | | |
| Baseline | 4.1 ± 1.1$^{***}$ | 7.6 ± 5.7$^{***}$ | 5.4 ± 2.5 | 34.1 ± 25.8$^{***}$ | 1.4 ± 3.7$^{***}$ | 0.5 ± 1.3$^{***}$ | 6.9 ± 14.2$^{***}$ |
| 1 week | 4.2 ± 1.2$^{***}$ | 8.0 ± 6.1$^{***}$ | 6.4 ± 2.3 | 32.2 ± 26.5$^{***}$ | 1.6 ± 3.9$^{***}$ | 0.5 ± 1.4$^{***}$ | 8.5 ± 16.3$^{***}$ |
| 2 weeks | 4.1 ± 1.1$^{***}$ | 6.8 ± 5.6$^{***}$ | 7.0 ± 2.1$^{**}$ | 41.5 ± 29.4$^{***}$ | 2.7 ± 5.7$^{***}$ | 0.8 ± 1.7$^{***}$ | 12.7 ± 20.0$^{***}$ |
| 3 weeks | 4.0 ± 1.1$^{***}$ | 6.8 ± 5.5$^{***}$ | 7.6 ± 1.7$^{***}$ | 46.9 ± 27.8$^{***}$ | 3.6 ± 6.5$^{***}$ | 1.1 ± 2.1$^{***}$ | 16.1 ± 21.7$^{***}$ |
| 4 weeks | 3.8 ± 1.1$^{**}$ | 6.1 ± 5.2$^{***}$ | 7.8 ± 1.5$^{***}$ | 49.5 ± 27.9$^{***}$ | 4.0 ± 6.8$^{***}$ | 1.2 ± 2.1$^{***}$ | 18.5 ± 23.1$^{***}$ |
| 2 months | 3.5 ± 0.9 | 4.9 ± 4.5$^{*}$ | 7.9 ± 1.5$^{***}$ | 55.2 ± 28.3$^{***}$ | 4.4 ± 7.0$^{***}$ | 1.2 ± 2.1$^{***}$ | 22.8 ± 24.8$^{***}$ |
| 3 months | 3.6 ± 1.1 | 4.4 ± 3.7$^{*}$ | 8.0 ± 1.4$^{***}$ | 55.6 ± 27.1$^{***}$ | 4.8 ± 7.1$^{***}$ | 1.5 ± 2.3$^{***}$ | 24.0 ± 25.1$^{***}$ |
| 4 months | 3.6 ± 0.9 | 4.3 ± 4.0 | 8.1 ± 1.5$^{***}$ | 58.1 ± 25.8$^{***}$ | 5.4 ± 6.9$^{***}$ | 1.7 ± 2.3$^{***}$ | 24.2 ± 24.9$^{***}$ |
| 6 months | 3.6 ± 0.9 | 4.3 ± 3.9 | 8.1 ± 1.8$^{***}$ | 62.8 ± 23.9$^{***}$ | 6.3 ± 7.3$^{***}$ | 1.9 ± 2.3$^{***}$ | 25.5 ± 24.9$^{***}$ |

Values are mean ± SD, $^{*}$ denotes $P$ <0.05, $^{**}$ denotes $P$ <0.005, $^{***}$ denotes $P$ <0.0005 in $t$-tests comparing the difference between the subjects with stroke and the healthy group

**Appendix VIII : A Comparison of the Baseline Characteristics Between the Dropouts and Subjects Completing the 6-month Assessments**

| Characteristics | Subjects | | *P* |
|---|---|---|---|
| | Dropped-out (n=21) | Completed the 6-month assessments (n=64) | |
| Gender - female (%) | 47.6 | 50.0 | 0.85 # |
| Age, mean ± SD (years) | 70.0 ± 9.7 | 69.8 ± 9.7 | 0.95 |
| Comorbid stroke risks (%) | 75.0 | 62.5 | 0.31# |
| Hemispheric stroke - left (%) | 28.6 | 46.9 | 0.14# |
| Site of lesion (%) - Lacunar/NAD | 22.2 | 19.0 | |
| Cortical | 22.2 | 19.0 | |
| Subcortical | 44.4 | 47.6 | 0.96# |
| Cortical+Subcortical | 11.1 | 14.3 | |
| Cognition: NCSE score, mean ± SD | 49.9 ± 23.4 | 54.4 ± 15.1 | 0.52 |
| Stroke severity (NIHSS), mean ± SD | 8.7 ± 3.4 | 8.0 ± 3.2 | 0.44 |
| Sensibility threshold, mean ± SD: | | | |
| Pressure | 4.9 ± 1.5 | 4.7 ± 1.5 | 0.73 |
| Two-point discrimination (mm) | 9.6 ± 5.7 | 9.1 ± 6.3 | 0.73 |
| Muscle tone, mean ± SD: | | | |
| Composite Spasticity Score | 5.3 ± 2.8 | 5.8 ± 2.5 | 0.51 |
| Muscle strength, mean ± SD: | | | |
| Motricity Index shoulder subscore (0-33) | 10.5 ± 9.9 | 11.3 ± 8.1 | 0.72 |
| Motricity Index elbow subscore (0-33) | 11.7 ± 9.8 | 12.1 ± 9.2 | 0.85 |
| Power grip (kg) | 1.4 ± 3.4 | 1.5 ± 3.6 | 0.91 |
| Index pinch grip (kg) | 0.4 ± 1.0 | 0.5 ± 1.3 | 0.65 |
| Upper extremity function, mean ± SD: | | | |
| Action Research Arm Test score (0-57) | 6.5 ± 12.0 | 5.8 ± 12.9 | 0.84 |
| Barthel Index score (0-100), mean ± SD | 38.0 ± 19.2 | 36.7 ± 14.7 | 0.76 |

Abbreviations: NIHSS = National Institutes of Health Stroke Scale, NCSE = Neurobehavioral Cognitive State Examination. *P*-values are results of one-way ANOVA, except that # denotes *P*-values from the analysis of Pearson's Chi-square tests.

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