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DEQI

AND

ASSOCIATED PHYSIOLOGICAL CHANGES

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Ph.D

The Hong Kong

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DEQI
and
ASSOCIATED PHYSIOLOGICAL CHANGES

By

YU TAI WAI DAVID

A thesis submitted in partial fulfilment of the requirements

for the degree of

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CERTIFICATE OF ORIGINALITY

The idea of the present investigations and planning of the experiments were the result of discussions between YU Tai Wai David and Professor Alice JONES.

I hereby declare that this thesis is my own work and that, to the best 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.

Signed:

Name: YU Tai Wai David

DEDICATION

This thesis is dedicated to my wife Tammy

and children Kelvin and Jason

For their endless love, support and encouragement and always stood by me and dealt with all of my absence from family occasions with a smile

ABSTRACT

Acupuncture has been widely used in China for thousands of years. One of the fundamental characteristics of acupuncture is "obtaining *qi*" during acupuncture, known as *deqi*. Based on Traditional Chinese Medicine (TCM) concepts, *qi* must flow in appropriate strength and quality along body meridians so that health can be maintained. It is believed that the flow of *qi* can successfully be altered by the acupuncture technique only if *deqi* is elicited during the technique. There are a number of studies in Western medicine that have attempted to quantify *deqi* sensations. The Massachusetts General Hospital Acupuncture Sensation Scale (MASS) appears to be the most comprehensive assessment tool in measuring/reporting needle sensations. However, the validity and reliability of MASS have not been properly established. Furthermore, MASS is an English instrument and the precise Chinese terms that best describe the *deqi* sensation in the Chinese population have not been determined. Therefore, the first aim of this doctoral thesis is to establish and validate a Chinese version of the MASS and to test its psychometric properties.

The first study was a methodological and exploratory study. The English version of MASS was first translated into Chinese using standardized forward-backward translation procedures. Content validity was conducted by 9 experts in acupuncture. The "pre-final" Chinese version of MASS (C-MASS) was then administered to 30 acupuncture-naïve healthy subjects. Electroacupuncture was then performed on the right Hegu (LI4) and Quichi (LI11) for 30 min. Test-retest reliability measurement was administered again 1-2 weeks later. Construct validity was examined by

comparing the C-MASS and the Short-form McGill Pain Questionnaire (SF-MPQ). The construct validity was further assessed by the principle component analysis. Results of this study showed that the C-MASS demonstrated a content validity ratio on relevance and importance which ranged from -0.04 to 1.00. Convergent validity was demonstrated by its significant association with the sensory dimension of the SF-MPQ (γ=0.63, $p<0.05$). Discriminant validity was demonstrated by its low association with the affective dimension of the SF-MPQ (γ=-0.3, p=0.111). A five-factor structure for the C-MASS was established by factor analysis. The C-MASS had good internal consistency (Cronbach's α = 0.71) and test-retest reliability (ICC= 0.92). Further analysis of the structure suggested that the descriptor "sharp pain" was not related to *deqi* sensations and was therefore deleted from the inventory. A new instrument, namely, the Modified Massachusetts General Hospital Acupuncture Sensation Scale Chinese version (C-MMASS), was compiled.

Reports on the relationship between *deqi* intensity and changes in autonomic nervous system (ANS) activity are scanty. The second study in this doctoral thesis therefore aims to investigate modulation in the ANS (as reflected by changes in heart rate variability) and cardiovascular changes associated with *deqi* and to determine any relationship that might exist between *deqi* intensity and such changes. This second study was a single blinded, randomized, placebo, controlled trial. Thirty-six subjects (19 males), aged 34.5±4.6 years, were randomly assigned to Group 1 - electro-acupuncture at 2 Hz, 0.4 ms to right LI4 and LI11 for 30 min.; Group 2 - electro-acupuncture stimulation to bilateral knee caps; or Group 3 - sham electro-acupuncture to right LI4 and LI11 but over Duoderm® pads. Heart rate (HR), mean arterial blood pressure (MAP) and heart rate variability by low/high frequency spectral analysis (LF/H/F) were recorded 5 min before, during and 5 min after the

intervention. Needle sensations were quantified by C-MMASS, and the C-MMASS *index* was computed. Results of this second study showed that there was a significant increase in LF/HF, MAP and HR in Group 1. A small and significant increase in LF/HF was observed in Group 2 but the changes in MAP and HR in Group 2 and 3 were not significant. The C-MMASS index was highest in Group 1 (5.3±1.3), moderate in Group 2 (3.5±0.7) and lowest in Group 3 (0.77±0.2). A positive correlation between the *deqi* intensity and changes in LF/HF, MAP and HR was observed. This study suggests that during the electroacupuncture procedure, *deqi* is associated with changes in cardiovascular parameters and the *deqi* intensity increases with an increase in sympathetic discharge of the ANS.

While positive effects of acupuncture have been acknowledged by many studies, adverse effects associated with the application of acupuncture have also been reported. These include transmission of infectious disease, organ puncture such as pneumothorax, cardiac tamponade, and broken needles with remnants migrating to other locations. Therefore, non-invasive techniques including acupressure and laser acupuncture, have become "safer" alternatives. Recently the application of Transcutaneous Electrical Nerve Stimulation over Acupoints (Acu-TENS) was reported in association with improved clinical outcomes. Whether Acu-TENS is associated with acupoint sensations similar to *deqi* experienced during acupuncture, has not been investigated. The third study therefore investigates whether acupoint sensations were experienced during Acu-TENS and whether such sensations were associated with any concomitant changes in ANS activity. The third study was a single blinded, randomized, controlled trial. Thirty-six healthy subjects were randomly assigned to either Experimental Group (Acu-TENS on LI4 and LI11); Control Group (Acu-TENS to bilateral knee caps); or Placebo Group (Sham

Acu-TENS on right LI4 and LI11). Results of this study demonstrated that subjects in the Experimental Group showed significant increase in HR (73.5±6.3 to 75.9±6.7 bpm, p=0.027), MAP (88.5±4.5 to 91.0±4.1mmHg, p=0.004), SDNN (143.36± 8.58 to 153.69±7.64 ms, p=0.002) and LF/HF (1.26±0.19 to 1.31±0.21, p=0.037) during the intervention. The Control Group showed significant increase in SDNN (140.21±8.72 to 143.39±9.47ms, p=0.009) and LF/HF (1.21±0.09 to 1.23±0.12, p=0.033). There were no significant physiological changes in Placebo Group. Overall C-MMASS index for Experimental, Control and Placebo groups were 3.23±0.3, 2.14±0.6 and 0.29±0.32 respectively. Between-group difference was statistically significant ($F=139.24$, $df=2$, $p<0.05$). However, correlation analysis did not support any association between sensation intensity and cardiovascular response in any groups (γ ranged from -0.36 to 0.25). This study therefore confirmed that "acupoint sensations" were experienced when Acu-TENS was applied to LI4 and LI11 but such sensations were not associated with cardiovascular changes in response to the stimulation.

Acu-TENS applied to the acupoint Dingchuan has been reported to be effective in reducing dyspnoea sensation and improving forced expiratory flow in 1 second (FEV_1) in patients with COPD and asthma. The relationship between Acu-TENS, *deqi*, and induced autonomic responses has not been reported. It was unclear whether the reported effects of Acu-TENS over Dingchuan in patients with COPD or asthma were associated with *deqi* or sympathetic modulation. The last project in this thesis therefore presents a case study on the application of Acu-TENS over LI4 and LI11 (acupoints that influence autonomic activity), in two patients with COPD; one emphysema predominant and the other asthma. The specific aim of the case study is to see whether Acu-TENS over LI4 and LI11 has any effect on FEV_1, *deqi* (acupoint sensation) and autonomic nervous system activity modulation.

The last project involved application of TENS to LI4 and LI11 for 45 minutes in two patients. One diagnosed with COPD but predominant with emphysema (Patient A) (male, 67 years old) and the other with predominant asthma characteristics (Patient B) (male, 65 years old). Both patients attended the laboratory three times, two weeks apart. At each visit, spirometry lung function assessment, 6 minute walk test (6MWT), resting heart rate, blood pressure, respiratory rate and SpO_2 were recorded, and BODE index was computed. At the second visit, Acu-TENS was applied over LI4 and LI11 for 45 minutes. During the intervention, heart rate (HR) was monitored continuously. At 5 minute intervals, mean arterial blood pressure (MAP) and heart rate variability [low/high frequency (LF/H/F) and standard deviation of the NN interval (SDNN)] were computed. Immediately after Acu-TENS, patients were asked to complete C-MMASS for quantification of the acupoint sensations during the electrical stimulation and the C-MMASS index was computed.

Results of this observational study showed that Patient A demonstrated an increase in 6-minute walk distance (6MWD) by 10.3% and an increase in FEV_1 by 5.3%. MAP was elevated throughout the intervention period but heart rate and the SGRQ-HK score and remained unchanged. Analysis of heart rate variability showed that LF/HF ratio increased by 10.5% and maintained an increase of 3.9%, at 5 minutes after stimulation. SDNN increased by 11.6% and remained raised by 6.1% until the end of the intervention. The overall C-MMASS score was 3.34. For Patient B, the increase in 6MWD was by 14.1% and increase in FEV_1 was nearly 9.3%. Effects on SGRQ-HK score, HR and MAP were similar to Patient A. LF/HF ratio increased by 8.2% and remained elevated by 3.5% after stimulation, and SDNN increased by 8.8% and remained 1.9% above baseline after Acu-TENS. The overall C-MMASS was 3.59. There were no overall changes in BODE Index and SGRQ-HK scores. While data

were only from 2 patients, therefore, the results are far from conclusive. Further studies with larger sample size and inclusion of control groups are necessary for meaningful investigation of the role of Acu-TENS and its associated mechanisms in the management of patients with COPD.

In summary, the work involved in this thesis included development of a valid and reliable Chinese version of an international tool to quantify *deqi* sensations; further work then showed that acupuncture to LI4 and LI11 increased sympathetic ANS activity and *deqi* was positively correlated with such physiological changes. Furthermore, application of a non-invasive modality Acu-TENS to LI4 and LI11 suggested that Acu-TENS is associated with increase in autonomic activity, but the acupoint sensations experienced are not associated with such responses. Lastly, clinical application of Acu-TENS to patients with COPD showed improved FEV_1 and 6MWD after 45 minutes of Acu-TENS, associated with increase in ANS activity. The work on this thesis suggests that the role of Acu-TENS in patients with COPD warrants further investigation.

PUBLICATIONS ARISNG FROM THE THESIS

PUBLISHED PAPERS

1. DTW Yu, AYM Jones. Development and Validation of the Chinese Version of the Massachusetts General Hospital Acupuncture Sensation Scale: an exploratory and methodological study. *Acupuncture in Medicine* 2012;30:214-221.
2. DTW Yu, AYM Jones. Physiological Changes Associated with *Deqi* during Electro-acupuncture to LI4 and LI11 – a Randomized Placebo-controlled Trial. *Acupuncture in Medicine* 2013;31:143-150.
3. DTW Yu, AYM Jones. Are physiological changes experienced by healthy subjects during Acu-TENS associated with acupoint sensations? *Acupuncture in Medicine* 2014;32:28-36.

CONFERENCE PRESENTATION

1. "Heart Rate Variability Noninvasive Electrocardiographic Method to Assess the Modulation of the Autonomic Nervous System" Hong Kong Physiotherapy Association Annual Conference, 2009
2. "Complementary and Alternative Medicine in the Management of Breathlessness" The Hong Kong Thoracic Society Annual Congress, 2013

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Appendix 20 Patient consent form of the case study (Chinese)

LIST OF ABBREVIATIONS

Acu-TENS	Transcutaneous electrical nerve stimulation applied over acupoints
ANOVA	Analysis of variance
ANS	Autonomic nervous system
ASS	Acupuncture Sensation Scale
ATS	American Thoracic Society
BODE index	Body-mass index, airflow obstruction, dyspnoea, and exercise capacity index
bps	Burst per second
cAMP	Cyclic adenosine monophosphate
CI	Confidence interval
C-MMASS	Modified Massachusetts General Hospital Acupuncture Sensation Scale Chinese version
COPD	Chronic Obstructive Pulmonary Disease
CRQ	Chronic Respiratory Disease Questionnaire
CVR	Content validity ratio
DBP	Diastolic blood pressure
DLCO	Single-breath diffusing capacity of the lung for carbon monoxide
EADL	Nottingham Extended Activities of Daily Living
EELV	End-expiratory lung volume
ECG	Electrocardiogram
df	Degree of freedom

FEV_1	Forced expiratory volume in one second
$\%FEV_1$	Percentage of the predicted forced expiratory volume in one second
FFT	Fast Fourier Transformation
FVC	Forced vital capacity
fMRI	Functional magnetic resonance imaging
GOLD	Global initial for chronic obstructive pulmonary disease
HRCT	High resolution commuted tomography
HF	High frequency
HR	Heart rate
HRV	Heart rate variability
Hz	Hertz
ICC	Intraclass correlation coefficient
LF	Low frequency
LF/HF	Low frequency to high frequency ratio
LSD	Least significant difference
MAP	Mean arterial pressure
MASS	Massachusetts General Hospital Acupuncture Sensation Scale
MGH	Massachusetts General Hospital
min	Minutes
mm	Minimeter
mmHg	Mini mercury
ms	Minisecond
$PaCO_2$	Partial pressure of carbon dioxide in the blood
PaO_2	Partial pressure of oxygen in the blood

PCA	Principle component analysis
PET	Positron Emission Tomography
PPI	Present pain intensity
pps	Pulse per second
rMSSD	The square root of the mean squared differences of successive R-R intervals
RPD	Rate of perceived dyspnoea
RPE	Rate of perceived exertion
SASS	Subjective Acupuncture Sensation Scale
SBP	Systolic blood pressure
SD	Standard deviation
SDNN	Standard Deviation of Normal-to-Normal Intervals
SF-MPQ	Short-form McGill Pain Questionnaire
SGRQ	St. George's Respiratory Questionnaire
SpO_2	Saturation level of oxygen in hemoglobin (pulse oximeter)
SPSS	Statistical Package for Social Sciences
TENS	Transcutaneous electrical nerve stimulation
TCM	Traditional Chinese medicine
VAS	Visual analogue scale
γ	Pearson's product moment correlation coefficient
μs	Microsecond
6MWT	Six-minute walk test
6MWD	Six-minute walk test distance covered

CHAPTER 1

Introduction

1.1 Background

Management of diseases and maintenance of health in Traditional Chinese Medicine (TCM) is believed to be through the regulation of "*qi*" (a vital force or energy which circulates between organs along different meridians or channels) and the balance of y*in* and *yang* (two opposite but interconnected forces) in the body. *Qi* must flow along the meridians with sufficient strength for health to be maintained (Kaptchuk, 2002; Vickers et al 2002). The flow of *qi* can be manipulated by inserting a needle into specific points (acupuncture points or acupoints) located along the meridians (Kaptchuk, 2002; Vickers et al, 2002), a technique known as Acupuncture. Acupuncture has been used in China for thousands of years for restoration of health (Kaptchuk, 2002; Kong et al, 2007). During the acupuncture process, the individual may experience some unusual sensations, such as soreness, numbness, heaviness, pressure sensation, and even heat or coldness around the point of stimulation; this type of sensation at the acupoint is referred as "*deqi*" and is thought to indicate that the *qi* is appropriately *tapped* and the body is in the process of re-establishing homeostasis (Stux, 1987; Kong et al, 2007). Four standard needle-sensations were reported when *deqi* is achieved, these are soreness, distension, heaviness and numbness (Vincent et al, 1989; Park et al, 2005; Kong et al, 2007). To quantify the *deqi* sensation, Kong and his coworkers developed an acupuncture sensation scale, namely the Massachusetts General Hospital Acupuncture Sensation Scale (MASS) (Kong et al, 2005). However, although this tool appears to be a comprehensive tool in assessment of acupuncture point sensations, validity and reliability of the MASS has not been established. Furthermore, the terms that described the sensations used in the scale are in English, and application of the MASS in a Chinese population may not produce accurate results. Therefore there is a need to develop a validated Chinese

version of the MASS such that this tool can be appropriately applied to the Chinese population; this objective thus forms the basis of the first study in this thesis.

Increased blood β-endorphin (Abenyakar et al, 1994) and modulation of the autonomic nervous system (ANS) activities (Knardahl, et al 1998; Haker et al, 2000) are believed to be associated with the working mechanism of acupuncture. Modulation of brain activities has also been shown to be associated with acupuncture, and deactivation the cortico-limbic region of the brain during the *deqi* experience was reported (Hsieh et al, 2001; Huang et al, 2012; Hui et al, 1999; Hui et al, 2005). The relationship between the intensity of *deqi* sensations, physiological changes, and changes in ANS activities however has not been investigated. The second aim of this thesis therefore undertakes to investigate the relationship between *deqi,* cardiovascular physiological changes, as well as changes in heart rate variability (which reflects changes in ANS activities), during an electro-acupuncture stimulation procedure.

While acupuncture is effective, this technique is invasive and adverse effects have been reported. These include transmission of infectious disease, pneumothorax and other problems associated with organ punctures, cardiac tamponade and broken needles with remnants migrating to other locations (Kaptchuk, 2002; Vickers et al, 2002). Stimulation of acupuncture points by non-invasive methods therefore become potential useful alternatives. Non-invasive acupuncture-like techniques, such as laser acupuncture (Morton et al 1993, Gruber et al 2002) and acupressure (Maa et al 1997, Maa et al 2003, Wu et al 2004, Tsay et al 2005) have been used for management of shortness of breath in patients with asthma, chronic obstructive pulmonary disease (COPD) or cancer-related breathlessness.

More recently, Transcutaneous Electric Nerve Stimulation (TENS) applied over acupoints (Acu-TENS) has also been employed for management of breathlessness in patients with COPD and asthma (Lau and Jones, 2008; Ngai et al, 2009; Ngai et al, 2011). Acu-TENS at Neiguan (PC-6) was shown to prevent nausea and vomiting after anesthesia (Zarate et al, 2001; Habib et al, 2006) and facilitate recovery of resting heart rate after high intensity treadmill exercise (Cheung et al, 2007). Recent studies on Acu-TENS also showed that this technique is effective in facilitating early haemodynamic recovery after open-heart surgery (Ng et al 2012), relieving labor pain (Chao et al, 2007; Peng et al, 2010), reducing blood pressure changes in normal healthy subjects (Zhang et al, 2009; Jones et al, 2011), and decreasing airway resistance (Chan et al, 2012). However, the working mechanism for Acu-TENS remains inconclusive. Many of the above studies proposed that the effectiveness of Acu-TENS is associated with increased blood β-endorphin level or modulation of ANS activity. While *deqi* appears to be necessary for positive therapeutic effects to prevail during acupuncture, whether distinct acupuncture point sensations similar to *deqi* are experienced during Acu-TENS has not been investigated. The third aim of this thesis therefore attempts to investigate whether *deqi* is experienced during the non-invasive Acu-TENS modality and whether such sensation is associated with changes in the ANS.

As previously mentioned, there were many clinical studies which demonstrated the positive effect of Acu-TENS on lung function in patients with COPD or asthma, but whether *deqi* and ANS modulation is associated with such changes after Acu-TENS has not been reported. The final project of this thesis presents a case study which explored the effect of Acu-TENS on *deqi,* ANS modulation and lung function.

1.2 Outline of the thesis

The first chapter of this thesis describes the rationale for the need to develop a valid and reliable Chinese version of the MASS, and to explore the relationship between *deqi* sensation and any associated physiological changes and changes in ANS activities during electro-acupuncture and Acu-TENS.

A review of the literature that investigates description and quantification of acupoint sensations (*deqi*), and highlights the gap in this research area is presented in Chapter 2.

Chapter 3 describes the instrument and outcome measures adopted in this thesis. The process of developing the Hong Kong Chinese version of the MASS and the psychometric properties of this translated version was presented in Chapter 4. Chapter 5 reports the investigation of the relationship between *deqi* intensity and physiological changes as well as changes in ANS activity as reflected by heart rate variability during electro-acupuncture on LI4 and LI11 in normal healthy subjects. Chapter 6 describes the work involved in exploration of the relationship between acupoint sensations and application of Acu-TENS on LI4 and LI11. A case study on the physiological and ANS changes during Acu-TENS on LI4 and LI11 in two typical patients with COPD was presented in Chapter 7 and conclusion of the work involved in this study was presented in Chapter 8. All references referred in the text are listed in Chapter 9.

1.3 Objectives of the thesis

Specific objectives of this thesis include:

1.3.1 To develop a valid and reliable Chinese version of the MASS

1.3.2 To investigate any cardiovascular changes and modulation of the ANS associated with electro-acupuncture

1.3.3 To determine whether any physiological and ANS changes mentioned in 1.3.2 have any association with the *deqi* sensations

1.3.4 To determine the correlation between the intensity of the *deqi* sensations and the physiological and ANS responses

1.3.5 To determine where *deqi* experience is experienced during the non-invasive modality of Acu-TENS

1.3.6 To investigate the relationship between intensity of the *deqi* sensation and any associated cardiovascular physiological changes and ANS responses during Acu-TENS

1.4 Hypotheses of the studies

Hypothesis of the work involved in this theses include:

1.4.1 Electro-acupuncture to LI4 and LI11 in normal healthy subjects will lead to significant changes in cardiovascular parameter and associate with changes in the autonomic nervous system

1.4.2 There is positive correlation between the intensity of *deqi* sensations elicited by electro-acupuncture on LI4 and LI11 and cardiovascular and ANS changes in normal healthy subjects

1.4.3 Acupoint sensations similar to those described as *Deqi* is experienced by subjects receiving Acu-TENS to LI4 and LI11

1.4.4 Acu-TENS to LI4 and LI11 in normal healthy subjects is associated with significant cardiovascular and ANS changes

1.4.5 There is positive correlation between the intensity of *deqi* sensations elicited by Acu-TENS to LI4 and LI11 and cardiovascular and ANS changes in normal healthy subjects

1.4.6 Acu-TENS to LI4 and LI11 in patients COPD is associated with significant changes in cardiovascular parameters, modulation in ANS, improved forced expiratory flow in 1 second and improved 6-minute walk distance

CHAPTER 2

Literature Review

2.1 Proposed mechanisms of acupuncture

Acupuncture, a simple modality used in China for more than two thousand years for management of diseases, has become increasingly popular in Western countries as an alternative management for pain and chronic disorders (Langevin et al, 2001).

The word "Acupuncture" is derived from the Latin: *acus* (needle) and *punctus* (insertion). It is a procedure which generally involves insertion of steel, silver, or gold needles into specific acupuncture points or acupoints (Cabýoglu & Ergene 2006). According to the classic theory of Chinese medicine, acupoints are linked together in a network of "meridians" running longitudinally along the surface of the body (Langevin et al, 2002).

Acupuncture meridians are "channels" through which "meridian *qi*" or energy flows (Kaptchuk, 2002). Disruption of the meridian channel network is believed to be associated with disease, and needling of acupuncture points is thought to be able to "awaken and modulate" *qi* in the meridian so as to regulate and restore the *yin-yang* balance in the body (Kong et al, 2007).

2.1.1 The meridians

Acupuncture meridians are believed to be a network in the body which connects peripheral tissues to each other as well as to central viscera (Kaptchuk, 2002). Modern acupuncture charts indicate 12 principal meridians "connecting" the limbs to the trunk and head. In addition, there are "accessory" meridians as well as deep "internal branches", starting at specific points on the principal meridians and reaching internal organs. The *Yang* meridians include large intestine, stomach, small intestine, gall bladder, triple warmer, and bladder; and the *Yin* meridians are the lung, spleen, heart,

kidney, pericardium and liver meridians (Langevin et al, 2002). Although there are no actual "physical" channels connecting the internal organs and the peripheral tissues, some investigators suggested that these acupuncture meridians are believed to be located along fascial planes between muscles, or between a muscle and bone or tendon (Langevin et al, 2002).

2.1.2 The acupoints

Under the concept of Chinese medicine, acupoints are "points" where access to some deeper tissue components can be gained through insertion of a needle (O'Connor and Bensky, 1981). Acupoints are mostly located along the meridians, although "extra" points outside the meridian system also exist. In Western medicine, acupoints are believed to be located where the nerve enters a muscle, at midpoint of a muscle, or at the enthesis where the muscle joins with the bone. In western literature, acupoints are viewed to be associated with neurovascular bundles (Bossy, 1984), neuromuscular attachments (Liu et al, 1975; Gunn et al, 1976; Dung, 1984), and various types of sensory nerve endings (Ciczek et al, 1985). It was suggested that acupoints are located in areas of high density of nerve endings (Liu Et al, 1975; Gunn et al, 1976). More recent researches have suggested that acupoints have lower electrical impedance compared to other tissues (Falk et al, 2000; Egot-Lemaire et al 2011).

2.1.3 *Deqi* – Acupoint sensations

Manipulation of *qi* either manually or electrically through the acupuncture technique is believed to be successful when *qi* is 'tapped' (obtained). *Qi* has to be "awakened" or modulated in the meridians in order for *yin* and *yang* to be regulated (Kong et al, 2007). In western medicine, the concept of "restoration of balance of *yin-yang"* is explained by modulation of the sympathetic and parasympathetic outputs of the autonomic nervous system (ANS) (Kaptchuk, 2002; Anderson and Lundeberg, 1995; Huang et al, 2011) and *deqi* is believed to be associated with such mechanism (Stux, 1987; Kong et al, 2007).

Deqi is believed to be elicited by manual manipulation of the inserted needle in rotation or up-and-down movements, and distinct sensations are reported to be felt by the recipient of acupuncture at the area surrounding the needle (Kong et al, 2007). When *deqi* is perceived by the recipient, the acupuncturist could also perceive a distinct needle sensation, as if the tissue around the needle is being "grasped", with increasing resistance to further motion of the manipulated needle (Stux, 1987; Langevin et al, 2001). This sensation is referred as 'needle grasp' (Langevin et al 2001) and described as "like a fish biting a fishing line" (Kong et al, 2007). Langevin's group reported that, their microscopic observation revealed that while *deqi* was experienced by the recipients, mechanical coupling of needle insertion and manipulation (such as twisting, pistoning) resulted in winding of the connective tissue around the needle's shaft, an action of 'grasping' the needle; they proposed that the "needle grasp" generates a mechanical signal through pulling of collagen fibers during needle manipulation, allowing mechano-transduction of the signal to the connective tissue cells. The authors proposed that the downstream effects of this

mechanical signal may include release of growth factors, cytokines, vasoactive substances, degradative enzymes, modification of extracellular matrix, amplification and propagation of the signal along connective tissue planes (Langevin et al, 2001).

2.1.3.1 Proposed mechanisms of *deqi*

Stimulation of blood vessels, nerves, tendons and the periosteum can all evoke variable sensations (Kong et al, 2007). For example, stimulation of nerve tissues produce numbness, stimulation of muscle produces soreness, distension or pain (Kong et al, 2007). Therefore, complex sensations which include soreness, distension, numbness, heaviness, and possibly pain may be perceived by recipients of acupuncture. In addition, if meridians exist on a connective tissue plane, it is possible that any contraction of connective tissue can set up a wave of sensory mechanoreceptor stimulation that propagates along the connective tissue plane. The phenomenon of "propagated sensation" was proposed to explain the slow spreading of *deqi* sensation along the course of an acupuncture meridian, as reported by recipients of acupuncture (Langevin et al, 2002).

A recent meta-analysis on the effect of acupuncture on the human brain using functional magnetic resonance imaging (fMRI) confirmed that acupuncture stimuli is associated with modulation of brain activities, through activation of the supramarginal gyrus, secondary somatosensory cortex, pre-supplementary motor area, middle cingulate gyrus, insula, thalamus and precentral gyrus. Acupuncture stimulation was also shown to be associated with deactivation of pregenual anterior cingulate, posterior cingulate cortex, subgenual cortex, amygdale/ hippocampal formation, ventromedial prefrontal cortex and nucleus accumbens of the limbic region (Huang et al, 2012). As the central outflow of ANS is coordinated in the medulla oblongata and

regulated by the limbic system (Ueyama, 2012), it is possible that acupuncture stimulation may induce changes in the ANS via modulation of the cerebro-cerebellar limbic system.

Deqi sensations were also shown to be associated with changes in brain activities. One recent randomized controlled trial confirmed that subjects who experienced *deqi* sensations during acupuncture demonstrated reduced activity in the limbic/sub-cortical structures compared to the group that did not experience *deqi* (Asghar et al, 2010). This study provides important data which suggest a relationship between acupoint sensations and brain activities.

2.1.3.2 *Deqi* and its association with the autonomic nervous system

Acupuncture is believed to be associated with modulation of the ANS activities leading to changes in physiological parameters as a consequence. There is also an increasing research interest to determine any association between *deqi* sensation and physiological parameters. Several studies have investigated the physiological responses of acupuncture specifically when subjects experienced *deqi* (Knardahl et al, 1998; Haker et al 2000; Kimura et al, 2006); however, the results reported were inconsistent. The study conducted by Knardahl and his coworkers showed that when electro-acupuncture was performed on Hegu (LI4) and Quichi (LI11), there was a significant increase in muscle sympathetic nerve activity when subjects experienced *deqi.* In addition, there was a small increase in heart rate and mean arterial pressure during the stimulation; however there were no overall physiological changes after the stimulation (Knardahl et al, 1998). The study conducted by Kimura also showed that manual acupuncture to Hegu (LI4) resulted in significant increase in skin sympathetic nerve activity (Kimura et al, 2006). Haker and coworkers, however, found that

acupuncture stimulation to Hegu (LI4) induced a significant increase in the high-frequency component of the heart rate variability measured, suggesting increased in parasympathetic (rather than sympathetic) activity following acupuncture (Haker et al, 2000). While the duration and pattern of stimulation were similar in these studies, the major limitation of these studies was a small sample size; with only 7 subjects in Knardahl's study and 12 in both Haker's and Kimura's studies (Knardahl et al, 1998; Haker et al, 2000; Kimura et al, 2006). Therefore, there is a need for a randomized-placebo-controlled study with a larger sample size for appropriate evaluation of the relationship between physiological and ANS responses to acupuncture, and especially when *deqi* is experienced.

2.2 Quantification of *Deqi* sensations

As mentioned earlier in this chapter, under the concept of TCM, "*Deqi*" is thought to indicate that the body is in a process of re-establishment of homeostasis (Mao et al, 2007). Many TCM practitioners believe that *deqi* is essential to achieve the therapeutic effect of acupuncture (Kaptchuk, 2002; MacPherson & Asghar, 2006). Nevertheless, scientists are skeptical about the concept of *qi* (Hsu, 1996). It was argued that *qi* is invisible and relied solely on subjective report from the acupuncture recipients, similarly, acupuncturists' reports on their patients' sensations are possibly biased preconceptions of "what one ought to feel" rather than what the patient actually felt. Thus in Western medicine, rather than following the concept of *qi*, the alleged therapeutic effects of acupuncture are explained by endorphin-release, relaxation or placebo effects (Hsu, 1996).

Four standard needle sensations were often reported when *deqi* is achieved, these include soreness, distension, heaviness and numbness (Vincent et al, 1989; Park et al,

2005; Kong et al, 2007). Sensations including aching, pressure, fullness, tingling, warmth/coolness, itching, water/air flow; insect crawling and radiating were also reported by some patients (Kong et al, 2007).

The first attempt to quantify needle sensations was the Acupuncture Sensation Scale (ASS) developed by Vincent and his coworkers (Vincent et al, 1989). This scale was developed by adopting the McGill Pain Questionnaire with the help of 10 practicing acupuncturists. One hundred and twenty-five patients were asked to rate the sensations experienced during acupuncture administration; to identify the component of the scale, the authors used "Principal Component Analysis" for factor extraction in their Factor analysis. Seven components of the *deqi* sensations were identified from the scale: dull-heavy, general intensity dimension, spreading, stinging, hot, sharp and electric sensations.

In 2002, Park and his colleagues (Park et al, 2005) performed a similar study in a cohort of 38 healthy, acupuncture-naïve female Koreans. The subjects first completed the McGill Pain Questionnaire based on their expectations of acupuncture. Then the subjects underwent a 30-second intervention which involved needle insertion, stimulation and removal at Hegu (LI4); and were then required to complete the questionnaire again. The results indicated that *deqi* sensation was more complex than the general pain dimension. Although the subjects expected to feel sensations such as hurting, penetrating, sharpness, tingling, pricking, and stinging with acupuncture, they actually reported aching, spreading, radiating, pricking, and stinging for more than 60% of the time during acupuncture (Park et al, 2005). While the McGill Pain Questionnaire measures pain, yet acupuncturists usually try to avoid inducing sharp pain (Kong et al, 2007) with the procedure; hence, the McGill Pain scale is deemed

unable to accurately account for a patient's experience with acupuncture needling (Kong et al 2007).

In 2006, MacPherson and coworkers (MacPherson and Asghar, 2006) invited 29 international acupuncture experts to complete a questionnaire listed with 25 sensations deemed to be related to acupuncture. Experts were asked to categorize the sensations associated with either *deqi* or acute pain expected at the needling site. The results showed that 7 sensations were considered to be associated with *deqi*, these were aching, dull, heavy, numb, radiating, spreading, and tingling. The drawback of this study however is that only the opinion of the acupuncturists, but not the recipients of acupuncture, were sought.

In 2007, Mao and his colleagues (Mao et al, 2007) developed a questionnaire and conducted a survey involving 200 patients at six outpatient acupuncture clinics in Beijing, China. Results of the survey showed that the most common terms referred to needling sensations were "distended" (94%), "soreness" (81%) and "numbness" (78%). Eighty-two percent of subjects believed that the needling sensation was very important for acupuncture treatment. However, the survey was conducted in an out-patient clinic in China where native Chinese usually have a great deal of cultural familiarity with acupuncture. Hence the result of the survey on *deqi* sensations may not be applicable to other cultures (Mao et al, 2007).

Kong and his coworkers (Kong et al, 2005) developed a Subjective Acupuncture Sensation Scale (SASS) to investigate acupuncture point sensations. This scale consisted of nine items, namely tingling, heavy, aching, numb, burning, throbbing, stabbing, fullness and soreness. These items were based on the literature as well as the authors' experience. This scale was later revised into the Massachusetts General

Hospital Acupuncture Sensation Scale (MASS) (Kong et al, 2007). The MASS consists of 12 descriptors that are related to *deqi* sensations. They are soreness, aching, deep pressure, heaviness, fullness/distension, tingling, numbness, sharp pain, dull pain, warmth, cold and throbbing. As the MASS forms the basis of the first study of this thesis, more detailed description of the MASS will be discussed in the next chapter.

A review of the literature suggests that MASS appears to be the most comprehensive tool in quantification of *deqi*, however the validity and reliability of this instrument has not been established. Furthermore, the wordings used for description of acupoint sensations in the MASS are in English, the precise Chinese terms that describe *deqi* sensations have not been determined. Therefore, there is a need to develop a validated Chinese version of the MASS such that this instrument can be appropriately used by the patients whose primary language is Chinese.

2.3 Acu-TENS

While acupuncture is effective, it is an invasive modality and carries risks of transmission of infectious disease, lung puncture (pneumothorax) and other problems such as organ punctures, cardiac tamponade, and broken needles with remnants migrating to other locations (Lao, 1996; Vickers, et al., 2002). Application of transcutaneous electrical nervous stimulation (TENS) over acupoints, referred to as "Acu-TENS", has been reported to influence clinical outcomes, including regulation of blood pressure (Jones, et al 2011; Ng et al, 2012), reduction of shortness of breath and improvement of lung function (Lau and Jones, 2008; Ngai et al, 2009; Ngai et al, 2010; Ngai et al, 2011) as well as reduction of nausea after cesarean delivery (Habib et al, 2006).

TENS is a non-invasive modality commonly employed in pain management (Melzack et al, 1983). There is evidence to suggest that the frequency, intensity and pulse duration of the stimulation are associated with stimulation of different pain fibers. High frequency (>50 Hz) and low intensity (no motor contraction) stimulation is commonly used for the management of acute pain. This form of stimulation is referred as "Conventional TENS". Melzack and Wall (1965) suggested that pain signal is transmitted to the thalamus and cerebral cortex via A-δ fibers the C fibres. It is postulated that high frequency TENS stimulates large diameter non-noxious afferent (Aβ) fibers thus suppressed the central transmission of the nociceptive information to the cortex; that is, closing the "gate" of nociceptive signal transmission (Melzack et al, 1965). High-frequency TENS also specifically activates δ-opioid receptors, explaining the role of TENS in reduction of hyperalgesia (Sluka et al, 1999; Kalra et al, 2001).

Low frequency (<10 Hz) and high intensity (with muscle contraction) stimulation parameters is referred as "Acupuncture like TENS" (Robinson et al, 1995) and is for the management of chronic pain. Low-frequency TENS was reported to specifically activates μ-opioid receptors. In addition, it is believed that low frequency TENS is be able to activate the endogenous analgesia system from the ascending reticular system to the cortex, and induce the release of endogenous opioid peptides including endorphin and enkephalin in blood as well as the cerebrospinal fluid (Facchinetti et al, 1984; Han et al, 1991).

Authors of Acu-TENS studies proposed that application of TENS over acupuncture points could lead to positive clinical outcomes similar to that of acupuncture (Lau and Jones 2008; Ngai et al 2009; Ngai et al, 2011). However,

whether the subjects would experience *deqi* sensation during Acu-TENS, similar to that during acupuncture, has not been investigated. Hence, if a valid and reliable tool to quantify the *deqi* sensation is developed, this tool could be used to quantify the *deqi* sensation during application of Acu-TENS. Results of such study would also add to the existing knowledge of the working mechanism of Acu-TENS.

2.3.1 Proposed working mechanism of Acu-TENS

2.3.1.1 Acu-TENS and β-endorphin levels

There is much evidence to support that opioid drugs reduce dyspnoea (Abernethy et al, 2003; Qaseem et al, 2008; Mahler et al, 2010). Opioids are able to depress spontaneous respiratory drive and modulate cortical activities, as they do in suppression of pain sensation (Parshall et al, 2012) and thus opioids have also been shown to reduce the discomfort of dyspnoea (Banzett et al, 2011). Several studies also showed endogenous opioids are also able to modulate dyspnoea, similar to administration of opiates (Kirsch JL et al, 1989; Nishino et al, 2005; Mahler et al, 2009). Moreover, it has been suggested that endogenous opioids are able to suppress hyperpnoea (Thoren et al, 1990; Greer et al, 1995; Takita et al, 1997). Application of Acu-TENS for 45-min, 5-days/week for 4 weeks over Dingchuan (Ex-B1) in patients with COPD has demonstrated significant reduction of dyspnoea sensation and improved FEV_1, and these effects were associated with an increase in blood β-endorphin level (Ngai et al, 2010, Ngai et al, 2011). There is evidence to support that β-endorphin act on μ-opioid receptors (Chen et al, 1992) and these receptors are located in the rhythm-generating component of the respiratory centre. Since the μ-opioid receptors are involved in reduction of respiratory frequency (Takita et al, 1997), it can help to suppress hyperpnoea. In addition, since hyperpnoea is associated

with airway constriction (Hallstrand et al, 2005), it is thus possible that release of endogenous opioid may induce bronchodilation by relaxing the smooth muscle of the airway and hence improve the FEV_1 and dyspnoea score (Ngai et al, 2009, Ngai et al, 2010; Ngai et al, 2011).

2.3.1.2 Acu-TENS and associated changes in the autonomic nervous system activities

Several studies had shown that Acu-TENS would alter the ANS activities. Application of Acu-TENS on PC6 (Neiguan) was shown to facilitate return of resting heart rate after intensive exercise in healthy subjects (Cheung and Jones, 2007). The authors proposed that the effect of Acu-TENS was due to modulation of the autonomic nervous system. Arai and coworkers suggested that TENS on Jianshi (PC5) and Neiguan (PC6) in patients undergoing Caesarean section might have augmented sympathetic tone by increasing cardiac function and vascular tone and alleviating hypotension after spinal anaesthesia (Arai et al, 2007). Application of Acu-TENS to Neiguan (PC6) was later shown to be able to augment blood pressure and associated with a faster return to preoperative resting HR in patients after open-heart surgery (Ng et al, 2012). Ng and coworkers proposed that these physiological changes might be due to induced vagal stimulation and/or inhibition of sympathetic neural activity (Ng et al, 2012). A study conducted by Lau and Jones revealed that a single session of Acu-TENS on Dingchuan (Ex-B1) significantly increase FEV_1 and decrease dyspnoea in patients with COPD. The authors also proposed that the Acu-TENS induces signal transmission similar to acupuncture, and influencing vagal afferents via hypothalamic stimulation, and effecting sympathetic and parasympathetic output (Lau and Jones, 2008). While the authors of several studies on Acu-TENS proposed that Acu-TENS is

associated with modulation of ANS activities, the relationship between Acu-TENS and associated ANS responses have not been reported.

2.4 Role of acupoint stimulation on management of Chronic Obstructive Pulmonary Disease (COPD)

COPD is the fourth leading cause of death in the world (World Health Report 2000). The burden of COPD management in Hong Kong is as high as reported globally. In Hong Kong, COPD ranked second as a respiratory cause for hospitalization and inpatient bed-days (Ko et al, 2008). Management of COPD is costly, especially in the elderly; as the majority of the health-care costs arise from hospitalization (Chan-Yeung et al, 2008; Ko et al, 2008; Lau and Jones, 2008). The most disabling symptom of COPD is dyspnoea, which is also the main reason for deterioration of quality of life in this patient cohort (Chan-Yeung et al, 2008; Ko et al, 2008; Lau and Jones, 2008). The principal aim of management of COPD is thus reduction of dyspnoea. While pharmacological intervention is the mainstay of management, recently there are increasing interests in the use of Acu-TENS for reduction of dyspnoea in patients with COPD. A single session of Acu-TENS on Dingchuan (Ex-B1) for 45 minutes was shown to significantly improve FEV_1 and reduce dyspnoea in patients with COPD (Lau and Jones, 2008). Moreover, studies conducted by Ngai and coworkers also showed that either single session of 45 minutes Acu-TENS (Ngai et al, 2011) or daily Acu-TENS applied for 4-week (Ngai et al, 2010) could significantly improve FEV_1 and dyspnoea with a concurrent increase in plasma β-endorphin level in patients with COPD. However, none of these studies report whether acupoint sensations or *deqi* was experienced during Acu-TENS. Furthermore, the physiological changes and the ANS activities changes during the

Acu-TENS were also not assessed. There is therefore, a need to investigate whether Acu-TENS to Hegu (LI4) and Quichi (LI11) - acupuncture points that are commonly used for investigation of ANS activities, are able to elicit positive clinical effects which improve lung function and reduce dyspnoea in patients with COPD.

A review of the literature presented above demonstrates the gap in research areas of quantification of *deqi* and relationship between acupuncture, Acu-TENS, *deqi* and associated cardiovascular and ANS responses; this forms the rationales for the work of this thesis outlined in the last section of Chapter One.

CHAPTER 3

Outcome Measurements

The projects included in this thesis involve development of a validated Chinese version of the Massachusetts General Hospital Acupuncture Sensation Scales (MASS), an instrument that measures *deqi* sensation; and with the help of this instrument, to investigate the relationship between *deqi* sensation and its associated cardiovascular physiological parameters, as well as any effect on modulation of the ANS. This chapter describes the MASS instrument; the short form McGill Pain questionnaire used for validation of a Chinese version of the MASS; instruments involved in the measurement of heart rate and blood pressure; as well as description of analysis of heart rate variability which reflects changes in ANS activities. Outcome measures adopted for evaluation of the clinical effects of Acu-TENS on patients with asthma and COPD are also described.

3.1 The Massachusetts General Hospital Acupuncture Sensation Scales (MASS)

The MASS was modified from a preliminary acupuncture sensation scale, namely the Subjective Acupuncture Sensation Scale (SASS), which was established by Kong and his coworkers in 2005 (Kong et al, 2005). The SASS listed 9 sensations: stabbing, throbbing, tingling, burning, heaviness, fullness, numbness, soreness, and aching. As reported by the authors, selection of these descriptors was based on description of *deqi* sensations reported in traditional literature and contemporary books (Kong et al, 2005). In this scale, one blank supplementary row was included for subjects to describe in their own words, perceptions other than the 9 descriptors. Each of these 10 elements on the SASS was presented on a 10cm bar with anchored with

words “none”, “mild”, “moderate” and “severe”, spaced evenly on the continuum. The authors investigated the relationship between the *deqi* sensation induced by acupuncture and the perceived therapeutic effects of acupuncture on 11 healthy, acupuncture-naïve subjects. Results of Kong’s study showed that acupoint sensation or *deqi* sensation is in fact rather complex and subjects nominated multiple descriptors during different modes of acupuncture stimulation (manual, electroacupuncture and placebo). This study also demonstrated significant correlation between analgesia and intensity ratings of numbness and soreness, but not with intensity of stabbing, throbbing, tingling, burning, heaviness, fullness, or aching. The authors concluded the SASS is a reasonable tool to measure sensations evoked by acupuncture stimulation (Kong et al, 2005; Kong et al, 2007).

To allow a wider range of application for the SASS, Kong and his coworkers further modified the SASS, and in 2007, they established another acupuncture sensation scale, the Massachusetts General Hospital (MGH) Acupuncture Sensation Scale (MASS); this scale expanded the 10 SASS descriptors to 13 (Appendix 1), and the major modifications included:

a) Replacing “stabbing” and “burning” by “sharp pain”, as the authors considered that sharp pain could occur during acupuncture during certain conditions.
b) Addition of descriptors “warmth” and “coolness”, as several subjects reported such sensation when *deqi* was experienced. Besides, as explained by the authors, these sensations were also frequently mentioned in ancient literature (*Suwen,* chapter 45).
c) The descriptor “dull pain” was also added based on the study conducted by MacPherson and colleagues (MacPherson and Asghar, 2006) which reported that

dull ache is one of the most common sensations associated with *deqi*.

The MASS thus has 13 descriptors: soreness, aching, deep pressure, heaviness, fullness/distension, tingling, numbness, sharp pain, dull pain, warmth, cold, throbbing and one supplementary row at the end for subjects to describe perceptions in their own words.

Despite the MASS being a newly developed tool for objective measurement of *deqi*, however, validity and reliability of MASS as an accurate tool for measurement of *deqi* have not yet been properly established.

3.2 Short-form McGill Pain Questionnaire

The Short-form McGill Pain Questionnaire (SF-MPQ) (Melack 1987) is an abbreviated version of the MPQ originally designed by Melzack (Melzack, 1975). The SF-MPQ is a self-reported scale derived from the original McGill Pain Questionnaire. The main component of the SF-MPQ consists of 15 descriptors (11 sensory; 4 affective) which are rated on a 4-point Likert scale: 0 = none, 1 = mild, 2 = moderate or 3 = severe. Three pain scores are derived from the sum of the intensity rank values of the words chosen for sensory, affective and total descriptors. The SF-MPQ also includes the Present Pain Intensity (PPI) index of the standard MPQ and a visual analogue scale (VAS). The PPI index is a scale from 0 (*no pain*) to 5 (*excruciating*). One was referred as *sensory*, which described the nociceptive pain experience of the individual, and the other was referred as *affective*, which described the emotional impact of the nociceptive pain experience (Appendix 2).

3.3 Physiological measurements - heart rate, blood pressure and heart rate variability measurements

3.3.1 Measurement of heart rate (HR) and blood pressure (BP)

The digit patient monitor (Mindray PM-8000 Express Patient Monitor, Bio-Medical Electricity, Hamburg, Germany) was used to monitor heart rate and blood pressure in subjects receiving electroacupuncture of Acu-TENS described in this thesis. Machine calibration was carried out according to the standard procedure suggested by the manufacturer before data collection. The patient monitor was tested against the "Human Physiological Signals Simulator" to ensure that the displayed heart rate and blood pressure values were consistent with the parameters set up on the simulator.

3.3.2 Heart rate variability (HRV) measurement - assessment of ANS changes

Traditionally, there are various methods available for assessment of changes in the ANS. These include cardiovascular reflex tests (Korner et al, 1976; Ewing et al, 1980, Robotis et al, 1994), biochemical (Wellman et al, 1990; Richards et al, 1999) and scintigraphic tests (Lown et al 1976). However, these techniques involve complicated procedures and are not commonly used in a clinical environment (Sztajzel 2004). In the recent decade, there is increasing popularity in the use of noninvasive techniques which use information from the electrocardiogram (ECG) as markers of autonomic modulation of heart activities; these include analyses of Heart Rate Variability (HRV) (Van Ravenswaaij-Arts et al 1993; Stein et al 1994), baroreflex sensitivity (La Rovere et al, 1998), QT interval (Schwartz et al, 1978) and

heart rate turbulence (Schmidt et al, 1999). Among these techniques, analysis of the HRV has emerged as a simple, noninvasive method to evaluate the sympatho-vagal balance at the sinoatrial level (Sztajzel 2004). The project in this thesis adopts standard measurement of ECG signals for analysis of HRV which reflect changes in ANS activity. Measurement and analysis of HRV is described below.

3.3.2.1 Measurement and analysis of HRV

The heart rate (HR) and the ECG signals were recorded continuously during acupuncture and Acu-TENS interventions. The ECG signals were analyzed by Chart™5 Pro for Window. These signals were simultaneously recorded by the PowerLab 16/30 (ADInstruments Pty Ltd. NSW, Australia) for data acquisition and further analysis. Analysis of HRV consists of a series of measurements of successive R-R intervals; information of autonomic tone is provided through analysis of the "variations" of the R-R intervals (sinus origin) (Van Ravenswaaij-Arts et al, 1993). Such variations can be analyzed in two ways: by calculation of indices based on statistical investigation of R-R intervals (time domain analysis) (Tsuuji et al, 1996); or by spectral (frequency domain) analysis of an array of R-R intervals (Parer et al, 1985).

3.3.2.1.1 Time domain analysis

Time domain analysis is the investigation of the intervals between adjacent normal R waves (NN intervals) of electrocardiogram recorded over a period of time. Analysis of NN intervals can be extrapolated via "statistical" or "geometric" method (Akselrod et al, 1985; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

Statistical analysis of the NN intervals examines variation of sinus depolarization, common variables of interests are standard deviation of all R-R (NN) intervals recorded over a time period (SDNN) and standard deviation of averaged 5-minute NN intervals (SDANN); other parameters derived from statistical analysis of NN intervals are displayed in Table 3.1 below (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

Table 3.1 Time Domain Measures of HRV calculated over 24 hours

Variables	***Units***	***Reference values*** *(Sztajzel, 2004)*	**Description**
SDNN	ms	141$\pm$39	Standard deviation of all normal to normal R-R (NN) intervals
SDANN	ms	127$\pm$35	Standard Deviation of averaged of NN intervals of 5-minute segments of the entire recording
rMSSD	ms	27$\pm$12	Square root of the mean of the sum of squares of differences between adjacent NN intervals
NN50 count		Not available	The number of NN intervals differing by >50 ms from the preceding interval
pNN50	%	9$\pm$7	NN50 count divided by the total number of all NN intervals

Adapted from Sztajzel, 2004 and Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996

Another method of examining the NN intervals is the 'Geometric method'. Histograms of NN intervals are derived or constructed from recorded NN intervals. HRV can be analyzed in different geometrical forms, for example, the 24-hour histogram, the HRV triangular index and its modification, the triangular interpolation of NN interval histogram, and the method based on Lorenz plot of NN or Poincaré plots (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Kleiger, et al 1987; Kleiger et al, 1992, Kleiger, et al 2005). The 24-hour histogram evaluates the relationship between the total number of R-R intervals detected and R-R interval variation in the 24 hour. The triangular HRV index (Figure 3.1) examines the triangular peak of the histogram. The base of the triangle corresponds to the volume or expanse of R-R interval variability, the height of the triangle represents the most frequently observed duration of R-R intervals, and the area of the triangle resembles the total number of all R-R intervals.

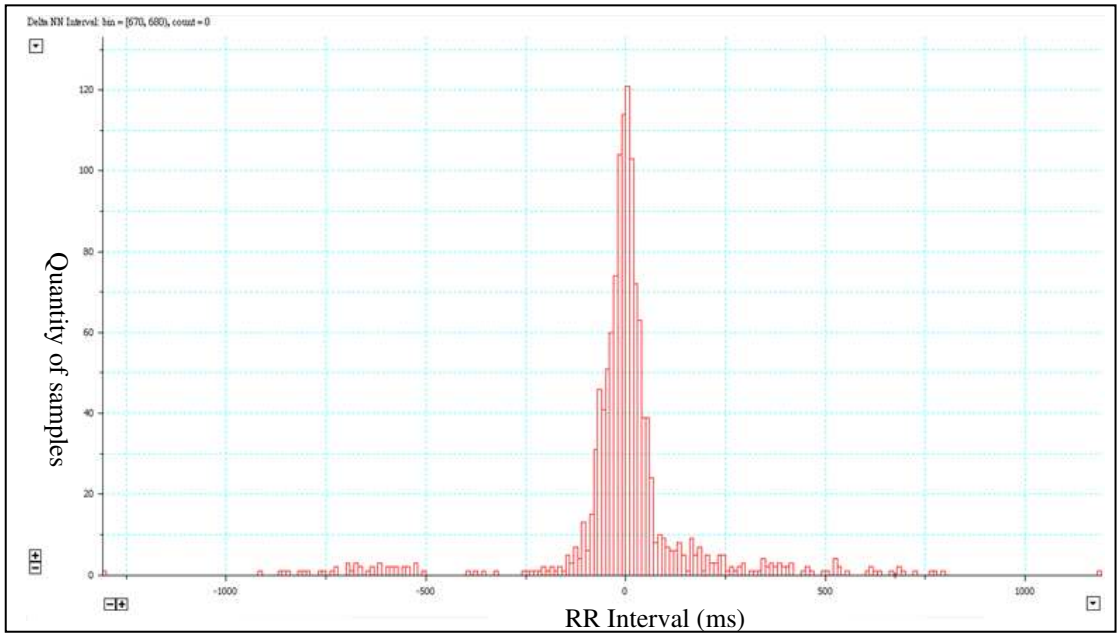


Figure 3.1 The triangular HRV index [Quantity of samples plot against RR intervals (ms)]

The Task Force of the European Society of Cardiology and the North American of Pacing and Electrophysiology has recommended the use of four metrics of the time domain analysis for HRV assessments: SDNN, SDANN, rMSSD and the HRV triangular index. Of these, the simplest variable to be calculated is the SDNN - the square root of the variance (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996; Sztajzel 2004). SDNN reflects all the cyclic components responsible for variability in the period of ECG recording, and mathematically variance is equal to total power of spectral analysis (Kleiger et al, 1987; Bigger et al 1988; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). The triangular HRV index is used as an estimation of the overall HRV (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996; Sztajzel 2004).

3.3.2.1.2 Frequency domain analysis

Under Frequency domain (Power Spectral Density) analysis, the periodic oscillations of the heart rate signal is examined in terms of frequencies and amplitudes; the basic information of how power (i.e. variance) distributes as a function of frequency is presented (Cripps et al, 1991; Kleiger et al, 1992; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996; Hnathova et al, 1995). Power spectral analysis is calculated by the Fast Fourier Transformation (FFT) method, characterized by discrete peaks of different frequency components (autoregression estimation). In other words, cyclic fluctuation of R-R intervals is quantified by the FFT or autoregression technique. FFT is commonly used in clinical conditions because of the simplicity of the algorithm

employed and the high processing speed (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). The process involves measurement of the R-R intervals based on ECG recording and a tachogram is established. By using the Power Spectral Density analysis, the tachogram is analyzed. The time signals are then transformed to frequency signals and then presented in different spectral frequencies by FFT (Figures 3.2, 3.3).

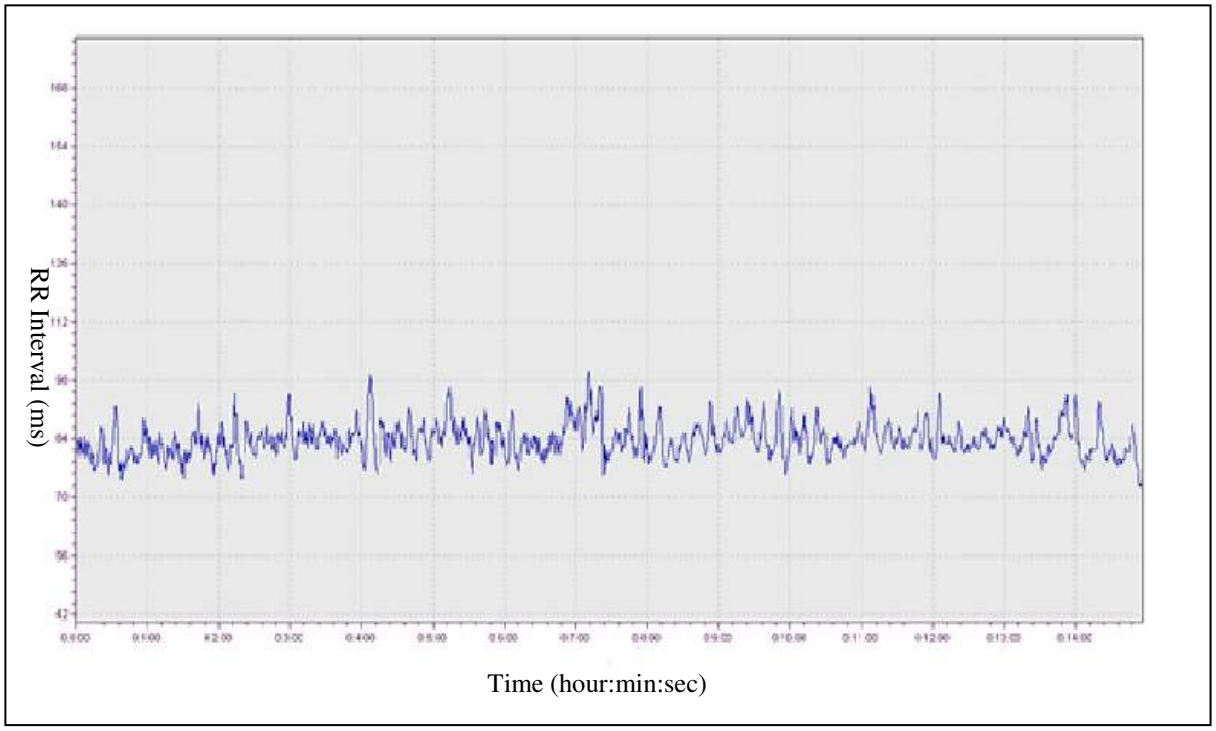


Figure 3.2 Interval tachogram - RR interval (ms) plots against the time

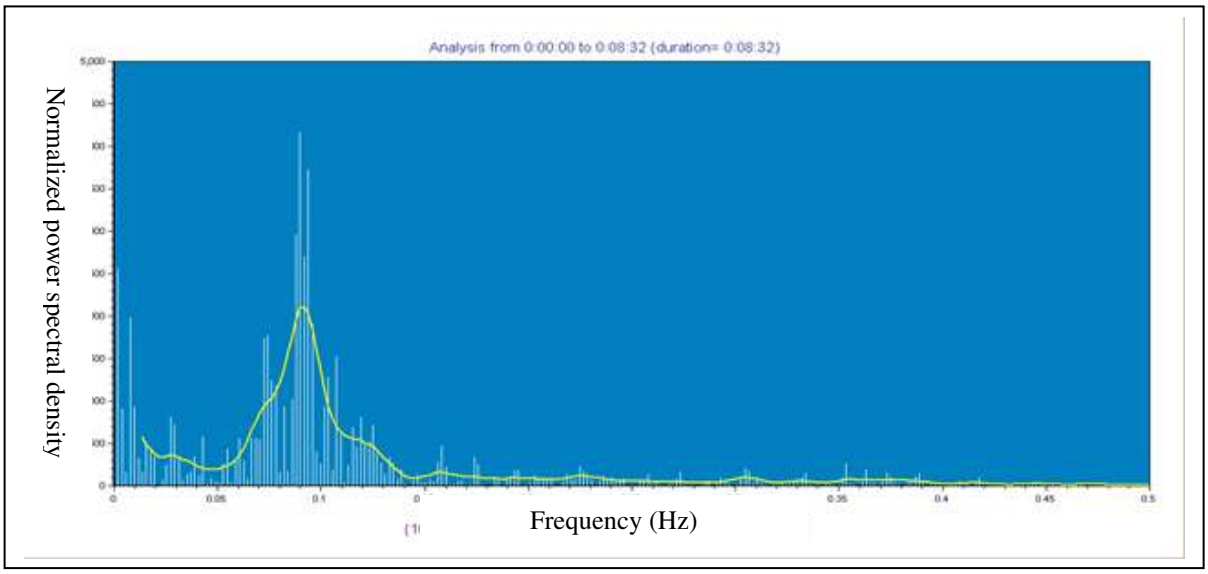


Figure 3.3 Power spectral components displayed after the Fast Fourier Transformation (FFT) [Normalized power spectral density plots against the Frequency (Hz)]

Spectral analysis can be performed on short-term laboratory studies or long-term recordings. In short-term recordings, 3 main spectral components are distinguished from segments recorded from 2 to 5 minutes (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Very often, standard 5-minute ECG segments are analyzed and the 3 frequency bands identified (Cripps et al, 1991); these are: a) very low frequency component (VLF) with frequency range <0.003-0.04Hz, b) low frequency component (LF) with frequency range 0.04-0.15Hz and c) high frequency component (HF) with frequency range 0.15-0.4Hz (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Sztajzel, 2004).

For long-term recordings, the sequences of NN intervals in the entire 24 hour period are analyzed. The result will include an ultra-low frequency component (ULF) with the frequency <0.003Hz, in addition to VLF, LF and HF components (Task

Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Sztajzel, 2004). The implications of different frequency components are listed in Table 3.2 below.

Table 3.2 Implications of different frequency components

Variables	***Units***	***Description***	***Reference values (Sztajzel, 2004)***	**Clinical implications**
ULF	ms^2	Ultra low frequency	Not available	Reflection of circadian and neuroendocrine rhythms
VLF	ms^2	Very low frequency	Not available	Major determinant of physical activity, proposed as marker of sympathetic activity
LF	ms^2	Low frequency	791±563	Controversial in interpretation. Maybe interpreted as a measure of sympathetic modulation, OR a combination of sympathetic and parasympathetic activity.
HF	ms^2	High frequency	229±282	Marker of vagal modulation. This component is respiration mediated and is associated with the frequency of breathing
LF/HF ratio		Ratio of low-high frequency power	4.61±2.33	Reflects the global sympatho-vagal balance or a measure of such balance

Adapted from Sztajzel, 2004

3.4 Assessment of dyspnoea

Assessment of dyspnoea is essential as an outcome marker of efficacy of intervention in management of respiratory disorder. At present, there exist numerous tools for classifying and characterizing dyspnoea. Among these, the Medical Research Council (MRC) Scale and a subjective dyspnoea score are most commonly used in a clinical environment.

3.4.1 The Modified Medical Research Council (MMRC) Scale

Defined in 1959 by Fletcher et al (Fletcher et al, 1959), the Medical Research Council (MRC) scale is the first clinical scale for the determination of dyspnea. This is a 5-point scale based on the sensation of breathing difficulty experienced by the patient during daily life activities and it allows the patients to indicate the extent to which their breathlessness affects their mobility (Bestall et al, 1999). The modified MRC dyspnoea scale MMRC) is a questionnaire that consists of five statements about perceived breathlessness:

Grade 0, “I only get breathless with strenuous exercise”;

Grade 1, “I get short of breath when hurrying on the level or up a slight hill”;

Grade 2, “I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level”;

Grade 3, “I stop for breath after walking 100 yards or after a few minutes on the level”;

Grade 4, “ I am too breathless to leave the house or I am breathlessness when dressing” (Appendix 3).

A significant association between MMRC scale and shuttle distance, scores of the St. George's Respiratory Questionnaire (SGRQ) and Chronic Respiratory Disease Questionnaire (CRQ), mood state, and Nottingham Extended Activities of Daily Living (EADL) scale was reported (Bestall et al 1999). Multiple logistic regression of relevant data showed that the determinants of disability appeared to vary with the person's level of disability. Exercise is found to be a significant covariate at MMRC grades 4 and 5. Variation of 1 point in the scale nevertheless signifies a perceived clinical improvement (de Torres et al, 2002).

3.4.2 The rate of perceived dyspnoea (RPD)

The precursor of the RPD is the rate of perceived exertion (RPE). RPE is a categorical scale with verbal descriptors (termed anchors) associated to a score that rates the perceived level of exertion (Borg 1970). The principle of the scale - composed of 15 levels, from 6 to 20 - is based on the notion that during physical exercise, a close correlation exists between heart rate (HR) and workload: the scores of the RPE have in fact been translated from values of HR during exercise tests in subjects with normal health, where the score 6 corresponds to 60 beats/min (medium resting HR) and the score 200 to an extreme of the spectrum, i.e. 200 beats/min (considered as the maximum HR attainable at exercise peak) (Borg 1970). The verbal anchors create categories of sensation with which subjects can easily identify: "moderate intensity" is placed at the center of the scale, "strong" and "weak" symmetrically at the two ends of the scale (Appendix 4).

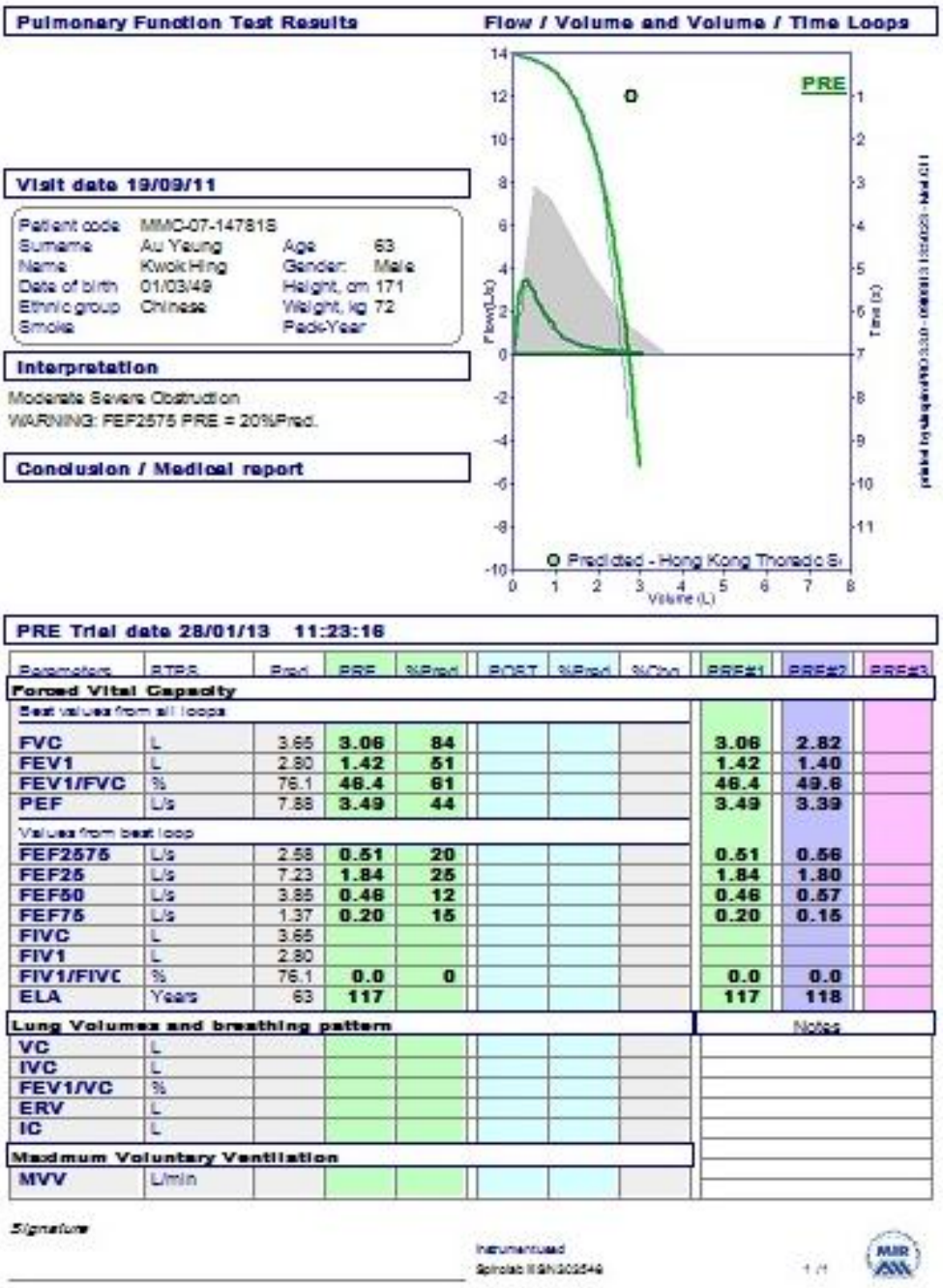
In Hong Kong, the modified Borg Scale (Mahler et al, 1987) for perceived exertion was adapted for measurement of dyspnoea (RPD). This consisted of a

vertical scale labeled 0-10, with corresponding verbal expressions of progressively increasing perceived sensation intensity (Appendix 5).

3.5 Pulmonary function Test

Pulmonary function tests adopted in this thesis were performed using a spirometer (SpiroLab III, MIR, Roma, Italy) in a standardized position (Miller et al, 2005) (Figure 3.4) . All data were analyzed by the *winspiro PRO* software. The percentage of predicted FEV_1 (%FEV_1) was obtained from the recorded FEV_1 divided by the FEV_1 of the published norm, with reference to the patient's gender, age and height (Ip et al, 2006) (Figure 3.5).

Figure 3.4 A patient is performing a lung function test



Pulmonary Function Test Results

Flow / Volume and Volume / Time Loops

PRE

O Predicted - Hong Kong Thoracic Si

Flow(L/s)

Volume (L)

Time (s)

Visit date 19/09/11

Patient code	MMC-07-14781S		
Surname	Au Yeung	Age	63
Name	Kwok Hing	Gender	Male
Date of birth	01/03/49	Height, cm	171
Ethnic group	Chinese	Weight, kg	72
Smoke		Pack-Year	

Interpretation

Moderate Severe Obstruction
WARNING: FEF2575 PRE = 20%Pred.

Conclusion / Medical report

PRE Trial date 28/01/13 11:23:16

Parameters	BTPS	Pred	PRE	%Pred	POST	%Pred	%Chg	PRE#1	PRE#2	PRE#3
Forced Vital Capacity										
Best values from all loops										
FVC	L	3.65	**3.06**	**84**				**3.06**	**2.82**	
FEV1	L	2.80	**1.42**	**51**				**1.42**	**1.40**	
FEV1/FVC	%	76.1	**46.4**	**61**				**46.4**	**49.6**	
PEF	L/s	7.88	**3.49**	**44**				**3.49**	**3.39**	
Values from best loop										
FEF2575	L/s	2.58	**0.51**	**20**				**0.51**	**0.56**	
FEF25	L/s	7.23	**1.84**	**25**				**1.84**	**1.80**	
FEF50	L/s	3.85	**0.46**	**12**				**0.46**	**0.57**	
FEF75	L/s	1.37	**0.20**	**15**				**0.20**	**0.15**	
FIVC	L	3.65								
FIV1	L	2.80								
FIV1/FIVC	%	76.1	**0.0**	**0**				**0.0**	**0.0**	
ELA	Years	63	**117**					**117**	**118**	
Lung Volumes and breathing pattern								Notes		
VC	L									
IVC	L									
FEV1/VC	%									
ERV	L									
IC	L									
Maximum Voluntary Ventilation										
MVV	L/min									

Signature

Instrumentused
Spirolab III SN:302549

1 / 1

Figure 3.5 A printout report of the Lung function test from a subject

3.6 Six-minute walk test (6MWT)

The six-minute walk test is one of the common tests for assessing exercise capacity for patients with cardiopulmonary diseases (American Thoracic Society, 2002). According to the guidelines suggested by the American Thoracic Society (2002), the test would be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The walking course was 30 m in length. The length of the corridor would be marked every 3 m. The turnaround point was marked with a cone.

The 6MWT conducted is conducted on the basis of the greatest distance covered by the subject in 6 minutes. Patients are allowed to rest during the 6 minutes, if necessary. During the test, a stopwatch is used for timing and in studies reported in this study, a Nonin 3100 WristOx oximeter (Minnesota, USA) was used for recording of oxygen saturation (SpO_2) and pulse rate. Each subject was allowed to perform the test twice to obtain the best result. The first and second trials were 15 minutes apart so that subjects would have enough rest before attempting the second trial (American Thoracic Society, 2002) (Figure 3.6).

Figure 3.6 A patient is performing the 6-minute walk test

3.7 BODE Index

The BODE index, which integrates body mass index, airflow limitation (forced expiratory volume in one second), dyspnoea and 6-min walk distance, predicts mortality in patients with COPD. The BODE index is a multi-dimensional 10-point scale in which the higher scores indicate a higher risk of death (Celli et al, 2004). The hazard ratio for death from any cause per one-point increase in the BODE score was 1.34, and the hazard ratio for death from respiratory causes was 1.62 (Celli et al, 2004) (Appendix 6). The BODE index has also be used as a predictor of hospitalization for COPD (Ong et al, 2005) and to reflect the effects of pulmonary rehabilitation (Cote et al, 2005).

3.8 Health-related quality of life – the St. George's Respiratory Questionnaire (SGRQ)

The St. George's Respiratory Questionnaire (SGRQ) is a self-administered questionnaire designed to measure quality of life covering three areas (symptoms, activity and impacts) in patients with COPD. Component score of each domain and a total score will be calculated. The higher the score indicates poorer quality of life. A validated Chinese version, the SGRQ-HK (Yu et al, 2004) (Appendix 7) is available and was used for the assessment of quality of life for patients with COPD (Please see Chapter 7).

CHAPTER 4

Development and Validation of the Chinese Version of the Massachusetts General Hospital Acupuncture Sensation Scale: an exploratory and methodological study

(published in *Acupuncture in Medicine* 2012;30:214-221) – Appendix 8

4.1 Introduction

Acupuncture has been widely used in China for thousands of years (Diehl et al, 1997; Eisenberg et al, 1998; Kaptchuk 2002). One of the fundamental characteristics of acupuncture is "obtaining of *qi*" during acupuncture, known as *deqi*. Based on the concept of Traditional Chinese Medicine TCM), *qi* must flow in correct strength and quality along the meridians so that health can be maintained. Restoration of health can only be achieved if the acupuncture technique is able to elicit *deqi*, thereby able to alter the flow of *qi* (Kaptchuk 2002; Vickers et al, 2002). Several studies tried to relate the therapeutic effectiveness of acupuncture when subjects experienced *deqi* (Kaptchuk 2002; Lai 1997; Langevin et al, 2001; Kong et al, 2007). However, solid evidence linking to this relationship is still lacking (Kong et al, 2007).

When *deqi* occurs, both the acupuncturist and the subject may experience some "unusual" sensations around the needle. The acupuncturist may perceive heaviness or tenseness around the needle when *qi* arrives (Seem et al, 2003). However, the feelings of the acupuncturist are more often subjected to biased preconceptions of "what one ought to feel" and thus hold greater likelihood of a biased subjective report (Hsu, 1996). In recent years, researchers are more concerned about the sensations from the subjects. One of the major reasons may be due to the rising popularity of using electroacupuncture in most of the clinical studies (Kong et al, 2007). Standard needle sensations experienced by the subjects are described as soreness, distension, heaviness and numbness (Vincent et al, 1989; Park et al, 2005; MacPherson and Asghar, 2006). Nevertheless, there is still no standard method in measuring the needle sensations at present. This may hinder the further investigation on the therapeutic effect of acupuncture.

In the last two decades, a number of studies have attempted to quantify *deqi* sensations (Vincent et al, 1989; Park et al, 2005; MacPherson and Asghar, 2006). Vincent and colleagues adopted the McGill Pain Questionnaire and created a scale of 20 adjectives describing possible acupuncture sensations (Vincent et al, 1989). In 2005, Park et al modified Vincent and colleagues' work by adding 5 extra descriptions of the sensation scale (Park et al, 2005). However, both of these scales have limitations because they measure a range of sensations that include pain as well as *deqi*. In 2006, a panel of 29 international acupuncture experts was involved in MacPherson and Asghar's study who categorized 25 sensations during acupuncture as associated with *deqi* and acute pain at the needling site (MacPherson and Asghar 2006). However, the above study quantified *deqi* sensations based on the acupuncturists rather than the patient/subject's perception.

In order to address the complexity involved in accurately assessing the acupuncture sensations, an inventory incorporating various *deqi* sensations was developed by Kong and coworkers in 2005, namely the "Subjective Acupuncture Sensation Scale" (SASS). The SASS listed 9 sensations based on *deqi* sensations reported in traditional literature (Kong et al, 2005). Each of the elements was presented on a 10-cm bar with the anchor words "none", "mild", "moderate", and "severe" spaced evenly on the continuum. Subjects were asked to quantity their sensations at each point by rating the intensity with which they experienced after acupuncture. The authors demonstrated that there were significant correlations between numbness and soreness items of the SASS (Kong et al, 2005). In order to apply SASS to a wider range of research projects, Kong and his coworkers further expanded the descriptors in the SASS, and this became the Massachusetts General Hospital Acupuncture Sensation Scale (MASS) (Appendix 1) (Kong et al, 2007). The

descriptors in MASS include soreness, aching deep pressure, heaviness, fullness/distension, tingling, numbness, sharp pain, dull pain, warmth, cold, throbbing, plus one blank supplementary row left for subjects to describe perceptions in their own words. The MASS Index is then calculated and used to quantify the intensity of the needle sensations experienced by a subject. The MASS also included two supplementary scales for measuring spreading of the acupuncture sensation and anxiety (Kong et al, 2007).

With the increasing trend of investigating how acupuncture works in clinical research, a valid and reliable instrument is essential so that objective information on *deqi* sensations can be provided. The establishment of the MASS involved extensive review of relevant literature and it seems to be the most comprehensive assessment tool in measuring the needle sensations. MASS has been used in studies that involved acupuncture sensations measurement (Salih et al, 2010; Napadow et al, 2009). The validity and reliability of the MASS, however, have not been properly established. Additionally, the precise Chinese language terms that best describe the *deqi* sensation have not been determined. The objectives of the study were to establish a Chinese version of the MASS and to test its psychometric properties.

4.2 Methodology

The study was an exploratory, methodological study that involved two phases. Ethics approval was granted by the Human Subjects Ethics Committee of the Hong Kong Polytechnic University involved (Project ID: HSEARS20080514001). The nature of the study was explained to the subjects and written consent obtained prior to data collection (Appendix 9 and 10 for the samples of the Chinese and English

consent forms). All procedures were conducted in accordance with the Declaration of Helsinki.

4.2.1 Phase I: Cultural adaptation of the Massachusetts General Hospital Acupuncture Sensation Scale and assessment of content validity

Permission was obtained from the original authors of the MASS before the initiation of the study. The translation process was divided into 5 stages and was mainly based on the guidelines that described by Beaton et al (Beaton et al, 2000) and Wild et al (Wild et al, 2005).

The first stage was the forward translation of the MASS into two independent Chinese versions by a Physiotherapist and a professionally trained translator whose mother tongue is Chinese. The professionally trained translator has no medical or clinical background (naïve translator).

The second stage involved the synthesis of the results of the translations. The translated versions were compared and any ambiguous wordings were identified. Then, a single Chinese version of the MASS was first established.

The third stage was the back translation stage. It involved another two independent translators with Physiotherapy and TCM backgrounds and they translated the Chinese version into English.

In the fourth stage, a panel of committee consisting of one professor from a local university, 7 Physiotherapists and 2 nursing staff working in regional hospitals examined the preliminary versions in terms of the degree of agreement on the importance and relevance of each item on the Chinese version of the MASS to *deqi*

sensation. All the committee members are bilingual individuals with Chinese as their mother tongue. Six of them had a Master level in acupuncture studies and 4 had a Bachelor degree in TCM. They had an average of 9 years of clinical experience in acupuncture. They were asked to rate each item on a 5-point scale from "strongly agree" to "strongly disagree" (Appendix 11). The Content Validity Ratio (CVR) was then computed. The CVR = (ne – N/2) / (N/2), where 'ne' refers to the number of subject matter that the experts considered as essential measurement items, and N is the total number of experts in the panel. The CVR range between –1.00 and +1.00, where a CVR of 0.00 means that 50% of the panel believes the item to be essential. With an expert panel of 10 members, a 0.60 CVR was required to meet a 0.05 significance level of importance (Lawshe, 1975). The prefinal version was then established based on the results on the degree of agreement on the importance and relevance in content validity measurement.

In the fifth stage, the prefinal version was pilot-tested on ten normal healthy young subjects who were naïve to acupuncture and had no prior knowledge on the original MASS. They received electroacupuncture on right Hegu (LI4) and Quichi (LI11) (see Phase II below) and they were asked to complete the prefinal Chinese version of the MASS. Subjects were asked to select from this prefinal version that best describe the sensations during electroacupuncture. In computing the MASS index, the subject's individual MASS rating scales were ordered from highest to lowest intensity, and the MASS index was calculated according to the following equation:

$$\text{MASS Index} = \frac{\sum_{i=1}^{n} (1/2)^i R_i}{1 - (1/2)^n}$$

Where R indicates the ratings for different sensations from highest to lowest; n represents the number of *deqi* sensations on the MASS questionnaire (Kong et al, 2007).

Based on the feedback obtained from the subjects who participated in the pilot testing, minor modifications were made to the inventory to further improve its clarity. The final Chinese version, the C-MASS (Appendix 12), was adopted and was used to examine the reliability and construct validity in this study.

4.2.2 Phase II: Validation of the C-MASS

4.2.2.1 Subjects' selection and sample size estimation

Subject inclusion criteria for this study included people of under 40 years of age, right-handed, with normal health, naïve with acupuncture, and able to understand both Chinese and English, as the subjects were required to complete the Short-form McGill Pain Questionnaire (English version). Subjects with known neurological, cardiovascular and psychological disorders were excluded. Convenience sampling method was adopted. All subjects were invited to a face-to-face interview and demographic data were collected after written consent was obtained.

The software PASS 2008 was used for sample size calculation (www.ncss.com/pass.html). Sample estimation was based on the intraclass correlation coefficient (ICC) obtained during the pilot test-retest reliability study. Preliminary results showed that the test-retest reliability was good with the ICC exceeding 0.95. Therefore, if the ICC was set at 0.95 at Type I error of 5% and power of 80%, 30 subjects were required.

4.2.2.2 Procedures for electroacupuncture administration

The acupuncture points Hegu (LI4) and Quichi (LI11) of the right arm were selected as appropriate points for stimulation. All subjects were in a sitting position with both arms supported by a pillow. After the acupoints were located, isopropyl alcohol was applied for disinfection. Then two 40mm × 0.25mm single-use, sterile, prepacked stainless needles with guide tubes were inserted into the Hegu (L14) and Quichi (LI11) points. The needles were inserted for about 0.5 inch and then manually manipulated until *deqi* sensation was reported. In this study, *deqi* was defined as sensations perceived by the subjects as "soreness / numbness / distension / heaviness" at intensity around a moderate level. This was to ensure that proper acupoints were located and the subjects could identify types of sensations when *deqi* arrived. In order to standardize the stimulation throughout the stimulation period, electroacupuncture was used in the present study. Two electrodes were attached to the needles and connected to an electroacupuncture device (ITO, ES-160, Hannover, Germany). Electrical stimulation was then applied for 30 minutes at a frequency of 2Hz, pulse duration at 0.6 – 0.8ms (Kong et al, 2005) (Figure 4.1). The intensity of the electrical stimulation was increased gradually to moderate level using a 10-point Visual analog scale (Wewers and Lowe, 1990). Subjects were checked every 5 minutes and the intensity was readjusted so as to ascertain that needle sensation was present.

Figure 4.1 Electroacupuncture to right LI4 and LI11

After the electroacupuncture stimulation, the subjects were asked to quantify their acupuncture sensations by first completing the C-MASS and then the Short-Form McGill Pain Questionnaire (SF-MPQ) (Melzack, 1987). Those who experienced *deqi* sensation at a moderate level during electroacupuncture in this session were invited back 1-2 weeks later for test-retest reliability measurement. This period was chosen because it was relatively long enough to minimize the chance of recalling the answers but short enough to minimize the probability of the subjects having undergone real change on the domain of interest (Portney and Watkins, 2009). Similar to the first assessment session, the subjects received electroacupuncture on right Hegu (LI4) and Quichi (LI11) in the second session and then required to quantify the *deqi* with the C-MASS. The MASS index obtained at the first visit was compared with the second visit for the test-retest reliability assessment.

4.2.2.3 The Short-form McGill Pain Questionnaire (SF-MPQ)

The SF-MPQ is designed to provide a brief measurement of pain (Melzack, 1987). It is a 2-factor inventory (sensory and affective) constructs for measurement of pain. The SF-MPQ consists of 15 descriptors (11 sensory and 4 affective) rated on an intensity scale as 0 = none, 1 = mild, 2 = moderate or 3 = severe.

4.3 Statistical analysis

Descriptive statistics was performed to indicate the intensity of each needle sensation. Construct validity was examined by comparing the C-MASS and the SF-MPQ. It was hypothesized that items in C-MASS would be highly correlated with the sensory component but not with affective component of the SF-MPQ. Correlation matrices were created between the items of C-MASS and SF-MPQ. The data were compared by Pearson product-moment coefficient of correlation γ. A correlation coefficient above 0.50 to 0.75 indicates a moderate to good relationship, above 0.75 was considered as good to excellent relationship. The observed values of γ should be greater than or equal to the tabled value to achieve a significance level (Portney and Watkins, 2009).

The construct validity was further assessed by principle component analysis (PCA) of the C-MASS. A correlation matrix of all the items was created. The factor was extracted for factor analysis by two criteria: factors with eigenvalues greater than 1 and the Scree test criterion, obtained by plotting the eigenvalues against the number of factors. A factor loading of greater than 0.40 was considered significant. Orthogonal rotation using varimax rotation was used for the rotation of factors to improve the spatial structure of the variables so that distinct factors would be more

visible (Portney and Watkins, 2009). Naming of factors was based on those items which had the highest factor loading in each factor (Portney and Watkins, 2009).

For reliability, the internal consistency of the C-MASS was assessed using Cronbach's α coefficient which was considered reliable if it approached 0.70 (Portney and Watkins, 2009). To examine the test-retest reliability, ICC two-way random model were computed. ICCs above 0.75 were indicative of good reliability whereas those between 0.5 and 0.75 were considered moderate reliability (Portney and Watkins, 2009). The level of significance was set at 0.05 for all analyses. All of the statistical analyses were performed using SPSS V.17.0 software (SPSS, In., Chicago, Illinois, USA).

4.4 Results

4.4.1 Phase I: Assessment of content validity

The degree of agreement on the importance and relevance of each item associated with *deqi* sensation is shown in Table 4.1 and Table 4.2. It was found that the CVR of all items ranged from -0.4 to 1.0.

Table 4.1 Results of content validity of the prefinal Chinese version of the MASS ("Importance" content associated with *deqi* sensation) (n=11)

	Strongly agree (%)	Agree (%)	Total % of agree	Neutral (%)	Disagree (%)	Strongly disagree (%)	Total % of disagree	CVR
Soreness	70	30	100	0	0	0	0	1.0
Aching	20	60	80	0	20	0	20	0.6
Deep pressure	20	40	60	10	20	10	30	0.2
Heaviness	40	50	90	10	0	0	0	0.8
Fullness/distension	50	40	90	10	0	0	0	0.8
Tingling	40	40	80	10	10	0	10	0.6
Numbness	50	30	80	20	0	0	0	0.6
Sharp pain	20	30	50	20	20	10	30	0.0
Dull pain	60	40	100	0	0	0	0	1.0
Warmth	10	40	50	20	30	0	30	0
Cold	10	20	30	30	40	0	40	-0.4
Throbbing	40	40	80	20	0	0	0	0.6
Other (subject defined)	70	30	100	0	0	0	0	1.0
Overall agreement	38.5	37.7	76.2	11.5	10.8	1.5	12.3	

CVR = Content Validity Ratio

Table 4.2 Content validity of the prefinal Chinese version of the MASS ("Relevance" to content of *deqi* sensation) (n=11)

	Strongly agree (%)	Agree (%)	Total % of agree	Neutral (%)	Disagree (%)	Strongly disagree (%)	Total % of disagree	CVR
Soreness	80	20	100	0	0	0	0	1.0
Aching	30	40	70	10	20	0	20	0.4
Deep pressure	40	10	50	20	20	0	20	0.0
Heaviness	70	20	90	10	0	0	0	0.8
Fullness/distension	70	20	90	10	0	0	0	0.8
Tingling	50	30	80	20	0	0	0	0.6
Numbness	60	30	90	0	10	0	10	0.8
Sharp pain	30	0	30	10	20	40	60	-0.4
Dull pain	70	30	100	0	0	0	0	1.0
Warmth	40	30	70	30	0	0	0	0.4
Cold	30	10	40	20	30	10	40	-0.2
Throbbing	40	40	80	10	10	0	10	0.6
Other (subject defined)	90	10	100	0	0	0	0	1.0
Overall agreement	53.8	22.3	76.1	11.5	8.5	3.8	12.3	

CVR= Content Validity Ratio

4.4.2 Phase II: Validation of the C-MASS

4.4.2.1 Subject characteristics

Thirty normal healthy subjects were recruited by convenience sampling (18 men, 12 women). The mean age was 34.1 (±3.81) years. Three subjects experienced only a very low level of "soreness / numbness / distension / heaviness" and were considered not achieved *deqi* in the first session of electroacupuncture. These subjects were excluded from the analysis as inclusion of vague and uncertain sensation from these subjects was considered inappropriate. Therefore, only 27 subjects were invited to receive the electroacupuncture stimulation again for the test-retest reliability assessment at one to two weeks after the first session. A comparison of the intensity of various *deqi* sensations during the first and second sessions is displayed in Table 4.3. The result showed that fullness/distension, soreness, numbness, dull pain and aching scored highest among the 13 sensations. No subject added any other sensations in the blank row provided. The mean MASS index obtained in the first and second assessment sessions were 4.4(±1.3) and 4.7(±1.1) respectively.

Table 4.3 Comparison of different needle sensations intensity between Time 1 and Time 2 and Test-retest Reliability of the C-MASS (n=27)

	Sensation Intensity		Test-retest Reliability of the C-MASS			
	Time 1 Mean (±SD)	Time 2 Mean (±SD)	$ICC_{3,1}$	95% CI Lower Bound	95% CI Upper Bound	p-value
Soreness	6.9 (±1.3)	7.6 (±0.9)	0.62	0.16	0.83	0.009*
Aching	5.9 (±1.6)	6.3 (±1.4)	0.98	0.95	0.99	<0.001*
Deep pressure	3.2 (±1.5)	3.4 (±1.5)	0.96	0.91	0.98	<0.001*
Heaviness	6.0 (±1.4)	6.6 (±0.9)	0.55	0.01	0.88	0.024*
Fullness/distension	7.4 (±1.2)	7.9 (±0.8)	0.73	0.41	0.88	0.001*
Tingling	4.0 (±1.8)	4.4 (±1.4)	0.89	0.77	0.95	<0.001*
Numbness	6.3 (±1.3)	6.5 (±1.1)	0.97	0.92	0.98	<0.001*
Sharp pain	3.2 (±1.7)	4.0 (±1.7)	0.79	0.54	0.91	<0.001*
Dull pain	6.1 (±1.5)	5.9 (±1.4)	0.98	0.95	0.99	<0.001*
Warmth	0.2 (±0.4)	0.2 (±0.4)	0.96	0.91	0.98	<0.001*
Cold	0.2 (+0.4)	0.2(±0.4)	0.96	0.91	0.98	<0.001*
Throbbing	3.4 (±1.4)	3.1 (±1.2)	0.96	0.91	0.98	<0.001*
Other (subject defined)	0.0	0.0	0.92	0.83	0.96	<0.001*
Overall MASS Index	4.4 (±1.2)	4.7 (±1.1)	0.92	0.83	0.96	<0.001*

CI = Confidence Interval, ICC = Intraclass correlation coefficient
* indicate statistical significance ($p<0.05$)

4.4.2.2 Validity analysis

The C-MASS showed moderate correlation with the overall SF-MPQ score with the Pearson's product moment correlation coefficient γ=0.56, p=0.001. A significant correlation was observed when the C-MASS was compared with the sensory dimension of the SF-MPQ (Pearson's product moment correlation coefficient γ=0.63, p<0.05) but not with the affective dimension of the SF-MPQ (Pearson's product moment correlation coefficient γ=-0.3, p=0.111).

For factor analysis, based on the criterion of an eigenvalue of more than 1, the data yield 5 factors and explained 77% of variance. Therefore, the results suggested there were 5 factors among the 13 sensations of the C-MASS (Table 4.4). Naming of factors was based on locating the highest factor loading in the factor. Therefore, Factor 1 was labelled as "soreness"; Factor 2 was labelled as "heaviness"; Factor 3 was labelled as "fullness"; Factor 4 was labelled as 'dull pain" and Factor 5 was labelled as "numbness".

Table 4.4 Factor analysis on C-MASS (n=27)

Items	Factors				
	Soreness	**Heaviness**	**Fullness**	**Dull pain**	**Numbness**
Factor 1	-	-	-	-	-
Soreness	0.90[§]	-	-	-	-
Aching	0.81	-	-	-	-
Pressure	0.53	-	-	-	-
Factor 2	-	-	-	-	-
Heaviness	-	0.87[§]	-	-	-
Warmth	0.43	0.67	-	-	-
Factor 3	-	-	-	-	-
Throbbing	-	-	0.65	-	-
Fullness	-	0.59	0.92[§]	-	-
Factor 4	-	-	-	-	-
Pressure	-	-	-	0.54	-
dull pain	-	0.40	-	0.67[§]	-
Factor 5	-	-	-	-	-
Tingling	0.41	0.86	-	-	0.45
Numbness	-	-	-	-	0.79[§]
sharp pain	-	-	-	-	0.77

(Only factor loading > 0.4 was displayed); [§]highest factor loading in the factor

4.4.2.3 Internal consistency and test-retest reliability measurements

The overall Cronbach's α of the C-MASS was calculated as 0.71 (Table 4.5). For test-retest reliability, 3 subjects did not meet the criteria of achieving *deqi* sensation during the first session of electroacupuncture and were thus excluded from the test-retest reliability assessment. Based on the data of the 27 subjects, the test-retest reliability of individual items of the C-MASS was moderate to excellent ($ICC_{3,1}$= 0.55-0.98) and that of the MASS index was excellent ($ICC_{3,1}$ = 0.92) (Table 4.3).

Table 4.5 Item-Total Statistics of the C-MASS (n=27)

	Scale Mean if Item Deleted	Scale Variance if Item Deleted	Corrected Item-Total Correlation	Squared Multiple Correlation	Cronbach's Alpha if Item Deleted
Soreness	27.23	52.94	0.39	0.76	0.69
Aching	27.43	52.12	0.38	0.87	0.69
Pressure	27.97	55.62	0.31	0.69	0.70
Heaviness	26.80	54.03	0.40	0.69	0.69
Fullness	27.53	46.33	0.47	0.72	0.68
Tingling	29.17	56.28	0.48	0.82	0.69
Numbness	26.20	50.99	0.48	0.56	0.68
Sharp pain	28.43	56.19	0.40	0.44	0.69
Dull pain	26.43	51.29	0.34	0.73	0.70
Warmth	29.20	54.92	0.36	0.71	0.69
Cold	30.20	63.41	-0.10	0.61	0.73
Throbbing	29.13	56.46	0.30	0.82	0.70
Other (patient specific)	30.26	61.03	0.14	0.62	0.71

4.5 Discussion

This study examined the measurement properties of the translated version of the MASS as an inventory of needle sensations associated with *deqi*. The results demonstrated that the translated version is a valid and reliable instrument for the assessment of needle sensations in Hong Kong Chinese people receiving electro-acupuncture.

In the forward translation process, two translators carried out independent forward translations of the instrument to ensure that the translations could be compared, enabling detection of errors and divergent interpretation of ambiguous items in the original, thus reducing the potential bias (Wild et al, 2005). This study also adopted two back translations that were carried out in parallel so as to ensure that the quality of the translation is literally and conceptually the same as the original one (Beaton et al, 2000; Wild et al, 2005). The major discrepancy was on the translation of “aching” and “dull pain” as both terms are semantically and pragmatically similar in Chinese translation. The reconciliation between the two forward translators was the conclusion that ‘aching’ and ‘dull pain’ should both be used in the Chinese version.

The convergent validity and the discriminant validity of the C-MASS were established by comparing with the SF-MPQ. The overall C-MASS score has moderate correlation with the overall score of the SF-MPQ. Since 4 of the items in the sensory dimension of the SF-MPQ have the same description as the MASS, a stronger correlation was therefore observed if the C-MASS was compared with the sensory dimension of the SF-MPQ (convergent validity). However, as any affective effect from acupuncture was not expected, it is reasonable that only minimal correlation was

observed when the C-MASS was compared with the affective dimension of the SF-MPQ (discriminant validity).

The original developers of the SASS conducted a Principle Component Analysis (PCA) which supported the partition of 3 factors among the 9 sensations (Kong et al, 2007). When PCA was performed on the C-MASS in this study, 5 factors were extracted under the "eigenvalues greater than 1" rule. These 5 factors explained 77% of the total variance. Factor analysis performed in this study confirmed that the C-MASS is a 5-factor scale. The factors identified (soreness, heaviness, fullness, dull pain and numbness) are in fact similar to those reported in most TCM literature as the "standard" *deqi* sensations perceived (Kaptchuk 2002; Vickers et al, 2002; Kong et al, 2007). Results of this study showed that the test-retest reliability of the C-MASS was high.

From the opinions of the content experts, most of the items of the C-MASS were found to be important and relevant in relation to the content of *deqi* measurement with "deep pressure", "sharp pain", "warmth" and "cold" being the exception. These items have a low CVR. Previous studies supported that "pressure" appeared to be an important characterization of *deqi* (Napadow et al, 2009; Hui et al, 2005; Hui et al, 2007), whereas "warmth and coolness" sensations are frequently considered as important associates of health in ancient TCM literature (*Suwen*, Chapter 54) (Kong et al, 2007). According to Suwen (Chapter 54), a patient with "excess" syndrome would feel coldness under the needle when the *yin qi* arrives; however, a patient with "deficient" syndrome would feel warmth under the needle when the *yang qi* arrives (Kong et al, 2007). This study showed that the subject cohort involved did not experience any 'cold' sensation or only experienced low level of 'warmth' sensation

during acupuncture needling. This is probably because subjects in this cohort were young and healthy and thus less sensitive these sensations, which dominate only when there is an imbalance of *qi* in their healthy status. In view of this, it was considered that "warmth" and "cold" are important components of the *deqi* sensations to be included in the instrument.

However, although the original MASS includes "sharp pain" as one of the descriptors, it was not considered as a sensation associated with *deqi* by the original authors of MASS and others (MacPherson and Asghar, 2006; Kong et al, 2007). A recent pilot survey on the perception of *deqi* by Chinese and American acupuncturists also revealed that 50% participants classified "sharp pain" as "not *deqi*" and 42% believed it was harmful (Hui et al, 2011). This study showed that with "sharp pain" removed from the scale, the overall Cronbach's α only decreased by 0.02, indicating that the overall homogenicity of the scale was not much affected (Table 4.5). The test-retest reliability was still maintained excellent with the $ICC_{3,1}$ increased from 0.92 to 0.93 ($p<0.001$). The modified version also showed moderate correlation with the overall SF-MPQ score ($\gamma=0.53$, $p=0.03$) and sensory dimension of the SF-MPQ ($\gamma=0.6$, $p<0.001$). The five-factor structure was also preserved and it explained 79.6% of the total variance. Since the validity and reliability of the modified scale was not much affected if 'sharp pain' was removed, it was considered that it would be appropriate for the descriptor 'sharp pain' to be removed from the C-MASS for assessment of needle sensation associated with *deqi*. As the instrument now is one descriptor short of the original MASS, this Chinese version was thus renamed as the 'Modified' Massachusetts General Hospital Acupuncture Sensation Scale, Chinese version (C-MMASS). The C-MMASS is a 12-item measure that includes soreness, aching, deep pressure, heaviness, full/distension, tingling, numbness, dull pain, warmth, cold,

throbbing and the one supplementary row at the end for subjects to describe perceptions in their own words (Appendix 13).

Deqi sensations are complex and highly individualized. In addition, the intensity and nature of deqi sensations are determined by many factors such as patient constitution, types of needle, acupoints, needling and allied techniques (Bovey 2006). In this study, all these confounding factors were minimized by including only young healthy subjects, only one type of acupuncture needle was used, only the Hegu (LI4) and Quichi (LI11) points were chosen for stimulation, acupuncture performed by the same trained physiotherapist and a fixed protocol used in electroacupuncture.

4.6 Limitations of the study

There are several limitations in this study. First, only healthy subjects at age below 40 were recruited. Therefore, generalization of the result findings to other age groups of Hong Kong Chinese would not be deemed appropriate. Secondly, the present study only adopted the Hegu (LI4) and Quichi (LI11) acupoints, as they are the classical acupoints commonly used for investigation of *deqi*. It may be possible that other distinct needle sensations could be elicited if different acupoints of other meridians were stimulated. Thirdly, the present study did not use non-acupoints for comparison. Hence, the sensations related to skin piercing and tissue damage could not be distinguished from real acupuncture sensation elicited by acupoints stimulation. Lastly, manual and sham acupuncture were generally used in acupuncture studies that involved *deqi* sensations measurement (Streitberger et al, 1998; Kong et al, 2005). However, these groups were not included for comparison in this study. It is anticipated that subjects may rate the needle sensations differently, since manual,

sham and electro acupuncture may work through different mechanism and, thus, may affect the same individual on the perception of needle sensations (Kong et al, 2005).

4.7 Conclusion

Deqi is an important concept as it may well influence the therapeutic effect of acupuncture. Developing a valid and reliable tool to measure needle sensations is an important step towards a better understanding of the basic mechanisms underlying the reported therapeutic effects. While there has been no standardized, valid and reliable tool to quantify *deqi*, this study has established a Chinese version from the MASS and have it modified to be a valid tool for assessment of needle sensation associated with *deqi*. This study has also shown that this Chinese version of MASS has good repeatability, producing consistent scores over a period of time, as well as good internal consistency. The five-factor structure of the translated version was also established. Further study with the involvement of manual acupuncture and sham acupuncture as study groups may confer greater applicability of the C-MMASS in the quantifying *deqi* in acupuncture in the future.

CHAPTER 5

Physiological Changes Associated with *Deqi* during Electro-acupuncture to LI4 and LI11 – a Randomized Placebo-controlled Trial

(published in *Acupuncture in Medicine* 2013;31:143-150) - Appendix 14

5.1 Introduction

Chapter 4 described in detail the development of a valid and reliable instrument for quantification of *deqi* / acupoints sensations that can be widely appreciated in a Chinese speaking population. To further explore the relationship between the intensity of *deqi* sensation and its association with ANS activities, a second study in this doctoral thesis aimed to investigate modulation in the ANS (as reflected by changes in heart rate variability) and cardiovascular changes associated with *deqi* and to determine any relationship that might exist between *deqi* intensity and such changes.

According to the conceptual framework of Traditional Chinese Medicine (TCM), it was believed that disharmony and imbalance between *yin* and *yang* and disruption of *qi* (energy) flow along the energy channels (meridians) may affect health (Kaptchuk 2002). Through stimulation of acupuncture points, the flow of *qi* is believed to be modulated, leading to restoration of health. When *qi* is 'tapped' by acupuncture, the subject may experience distinct sensations known as *deqi* (Kong et al, 2005; Park et al, 2005; MacPherson and Asghar 2006; Kong et al, 2007). These sensations are considered to be essential for effective acupuncture stimulation (Lao 1996; Langevin et al, 2001; Kaptchuk 2002), though solid evidence is still lacking (Kong et al, 2007).

In Western medicine, the concept of 'restoration of balance of *yin–yang*' is explained by modulation of the sympathetic and parasympathetic outputs of the autonomic nervous system (ANS) (Anderson and Lundeberg, 1995; Kaptchuk 2002; Huang et al, 2011). Currently, heart rate variability (HRV) is commonly used to determine effects on modulation of the ANS in acupuncture studies (Haker et al, 2000; Sztajzel 2004, Saki et al, 2007). However, reports on whether acupuncture activates or

suppresses the sympathetic or parasympathetic outputs have been inconsistent. For example, acupuncture to Dazhui (GV14), Neiguan (PC6) (Li et al, 2003) and BL15 (Hsu et al, 2006) were shown to facilitate parasympathetic and suppress sympathetic activities whereas stimulation of Hegu (LI4) showed significant increase in sympathetic activity (Knardahl et al, 1998; Kimura et al, 2006). Furthermore, reports on the relationship between the acupuncture sensations intensity and changes in the ANS activities are scarce. Whether these sensations are necessary to evoke changes in the ANS, and whether stimulation to non-acupuncture points could produce similar ANS changes, have not been investigated. The aims of this study were to investigate the physiological responses associated with acupuncture sensations during electro-stimulation of acupuncture points and to determine the correlation between the intensity of these sensations and such responses. The Population, Intervention, Comparator, Outcome (PICO) format adopted being: P=Normal healthy subjects; I=Electro-acupuncture; C=True electro-acupuncture to non-acupoints and Sham electro-acupuncture to acupoints and O=Physiological and sensory responses.

5.2 Methodology

This study adopted a randomised, placebo-controlled trial design. Approval to conduct the study was granted by the Human Subjects Ethics Subcommittee of The Hong Kong Polytechnic University (project ID: HSEARS20110510001).

5.2.1 Sample size estimation

Sample size for this study was determined based on the data of the previous study in quantifying the *deqi* sensation. With an expectation of the effect size to be "medium" (Cohen's d = 0.3), and with the power set at 0.8, Type I error of 5%, the

standard deviation was approximately 2.00. Using a statistical software PASS (2008), 36 subjects were estimated to be appropriate for this study.

5.2.2 Subjects

A convenience sampling method was adopted for subject recruitment. Inclusion criteria included normal health without known cardiovascular, respiratory, neurological or psychological dysfunction; naïve to acupuncture and ability to read Chinese. Subjects with medical disorders or those required to take medications that might affect the cardiovascular system within 1 week prior to the study, or with uncomfortable sensations of the upper and lower limbs, were excluded. All subjects were informed of the aims of the study. Written consent was obtained from each subject prior to data collection (Patient consent forms in Chinese and English versions are displayed in Appendices 15 and 16 respectively).

5.2.3 Randomization

Recruited subjects were randomly assigned to one of three groups and blinded to the other two groups. Three sets of group numbers were generated by computer and placed in opaque sealed envelopes. Subjects were asked to draw one envelope that contained a random group number. The drawn envelope was then opened by an independent investigator who did not participate in the study process. For Group 1, electroacupuncture was applied to right Hegu (LI4) and Quichi (LI11). These two points were selected since they are most frequently reported in clinical studies associated with the ANS activity (Lin et al, 1981; Haker et al, 2000). For Group 2, electroacupuncture was applied to a point at 10 mm below each patellar, that is, into the patellar tendons where there are no acupuncture points. For Group 3, four

Duoderm pads (ConvaTec, Skillman, New Jersey, USA), of size 10mm×10mm were stacked up to approximately 5 mm and applied to right Hegu (LI4) and Quichi (LI11) respectively. Subjects were told that the purpose of the Duoderm pads was mainly for acupuncture point identification. Acupuncture needles were then inserted 3–4 mm into the Duoderm pads and the investigator was cautious to ensure the needle did not touch the skin (Figures 5.1-5.4). This is to ensure that electrical current would not be transmitted to the skin. The output light remained active, however, flashing in a manner similar to the other two groups. Subjects were told that with the electrical frequency applied, they may or may not feel any needle sensation.

Figure 5.1 True Electro-acupuncture to right Hegu (LI4) and Quichi (LI11) (Group 1)

Figure 5.2 True Electro-acupuncture to left and right knee caps (Group 2)

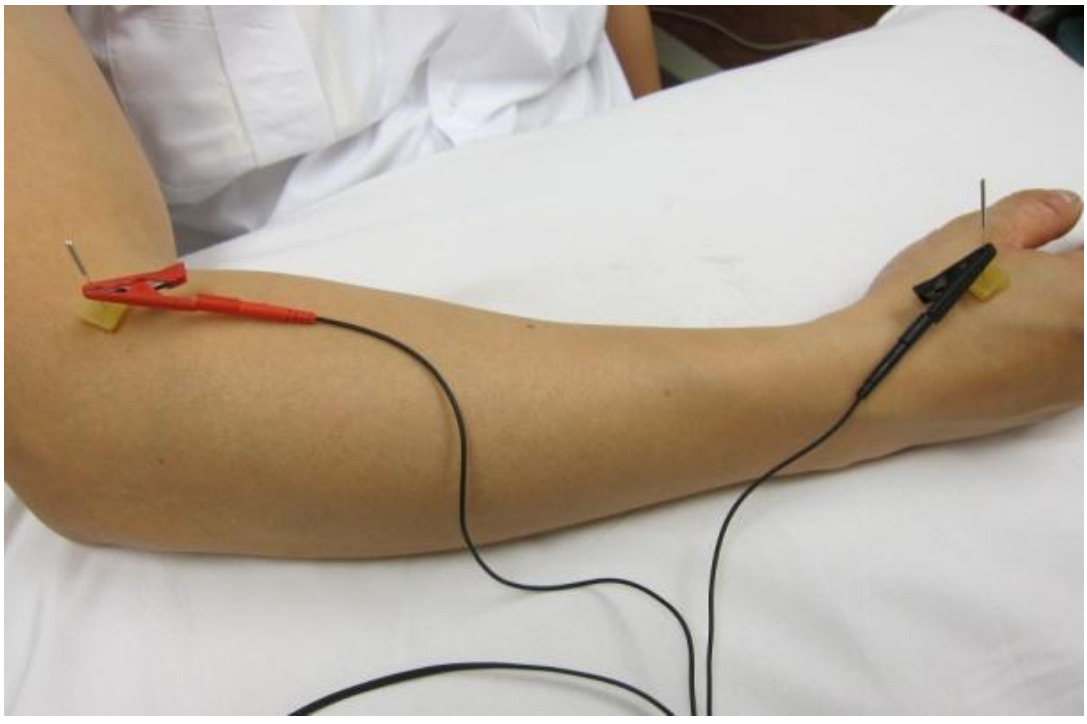


Figure 5.3 Sham electro-acupuncture on right Hegu (LI4) and Quichi (LI11) over the DuoDerm® pads (Group 3)

Figure 5.4 Close up view of the DuoDerm® pad

5.2.4 Procedures

Subjects were asked to refrain from consumption of caffeinated drinks, smoking or strenuous physical activities on the experiment day. All measurements were taken between 16:00 to 18:00 so as to minimize the circadian effect on the ANS. Subjects were instructed to relax and breathe regularly to minimize any effect of the respiration on HRV indices (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996, Kleiger et al, 2005).

Upon arrival at the laboratory, subjects were asked to rest in a sitting position for 30 min. Baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels were then recorded using a digital blood pressure monitor (Mindray PM-8000 Express Patient Monitor, Bio-Medical Electricity, Hamburg, Germany). Three electrocardiogram (ECG) electrodes were placed over the left and right clavicles and left upper quadrant of the abdomen and were connected to a digital patient monitoring device (Mindray PM-8000) for recording HR and HRV during the intervention. After that, acupuncture points were located and sterilised by isopropyl alcohol. Two 30 mm×0.25 mm single-use, sterile, prepacked stainless needles with guide tubes were inserted into the Hegu (LI4) and Quichi (LI11) points (Group 1), bilateral patellae (Group 2) and to the Duoderm pads over LI4 and LI11 (Group 3). The depth of needle penetration was about 10 mm for groups 1 and 2, and 3–4 mm for Group 3. Manual twirling was used during needle insertion. Subjects were asked if they could feel any needle sensation, but were also told that they might or might not feel any needle sensation. Once appropriate needle insertion was established, two electrodes were then attached to the needles and connected to an electroacupuncture device (ITO,

ES-160, Hannover, Germany). Electrical stimulation was applied for 30 min at a frequency of 2 Hz, pulse duration at 0.4ms. These parameters were adopted following a study by Knardahl et al (Knardahl et al, 1998). It was believed that low-frequency (LF) electroacupuncture has an effect on the ANS by modulating the sympathetic nerves (Stener-Victorin et al, 2004). The intensity for Groups 1 and 2 was gradually increased (approximately 10 mA to 25 mA) until the subjects felt the intensity was at a moderate level using a 10-point visual analogue scale (Wewers and Lowe, 1990) (strong sensation but without feeling discomfort). All subjects were made aware that the output light was flashing. Subjects were checked every 5 min and the intensity was readjusted if necessary. At the end of the 30 min stimulation, the subjects were asked to complete the Hong Kong Chinese version of the Modified Massachusetts General Hospital Acupuncture Sensation Scale (C-MMASS) (Yu et al, 2012) for quantification of the acupuncture sensations during the electrical stimulation. At 5 min after the electrical stimulation, blood pressures, HR and HRV data were again recorded (Figure 5.5)

Figure 5.5 Setup of the study (for Group 1)

5.3 Measurements

5.3.1 Mean arterial pressure and heart rate

SBP and DBP were recorded before inserting the acupuncture needles (before stimulation); every 5 min for 30 min during the electroacupuncture; and at 5 min after the electroacupuncture (after stimulation). The mean arterial blood pressure (MAP) was computed by using the formula DBP+(SBP−DBP)/3.

The HR and the ECG signals were recorded continuously during the electrical stimulation. The ECG signals were analysed using Chart™ 5 Pro for Windows. These signals were simultaneously recorded using a PowerLab 16/30 device (**ADI**nstruments Pty Ltd, Bella Vista, New South Wales, Australia) for data acquisition and further analysis.

5.3.2 Heart rate variability

Recorded ECG signals were subjected to power spectral analysis using the fast Fourier transformation technique. The low LF component of the power spectrum of the HRV is defined as the power between 0.03 and 0.15 Hz, and is interpreted as a measure of sympathetic modulation (Sztajzel 2004). The parasympathetic outflow is estimated as the high frequency (HF) component (0.15–0.5 Hz). The global sympathovagal balance was expressed by a ratio of LF to HF components (LF/HF). A high value of the LF/HF ratio reflects domination of the sympathetic system (Sztajzel 2004; Stener-Victorin et al, 2004; Kleiger et al, 2005).

5.3.3 Acupuncture sensation measurement

The C-MMASS consists of 12 descriptors of sensation and includes soreness, aching, deep pressure, heaviness, fullness/distension, tingling, numbness, dull pain, warmth, cold, throbbing, plus a blank supplementary row left for subjects to describe their own perceptions (Yu et al, 2012). Each descriptor is presented on a 10 cm bar, anchored with numerical scores 0–10 and with the words 'none', 'mild', 'moderate' and 'severe' spaced evenly along the continuum. Immediately after the acupuncture stimulation, subjects were asked to quantify the sensations by rating the intensity for each descriptor that they may have experienced. The C-MMASS index was then calculated and was used to quantify the overall intensity of the acupuncture sensations experienced.

5.4 Statistical Analysis

Using the analysis and sample size software PASS 2008 (http://www.ncss.com/pass.html), and based on results of the previous study on *deqi* measurement (Yu et al, 2012), to achieve a medium effect size, power of 0.8, and produce a two-sided 95% CI with a width equal to 0.987 and SD of 2.00, a total sample size of 36 subjects was required and 12 subjects were allocated to each group. All statistical analyses were conducted using the statistical software SPSS for Windows V.17 (SPSS, Chicago, Illinois, USA). Data including age, resting HR, MAP and LF/HF ratio were compared among the three groups using one-way analysis of variance (ANOVA). Categorical data such as gender were compared by χ^2 analysis.

The HR, MAP and LF/HF of the three groups before, during and after electroacupuncture were compared by one-way repeated ANOVA with post-hoc pairwise comparison and Bonferroni adjustment. Moreover, an exploratory correlation analysis using Spearman's correlation was performed between the overall C-MMASS index, mean LF/HF, HR and MAP in each group. The level of significance was set at 0.05 for all analyses. A CONSORT diagram of the study is illustrated in Figure 5.6.

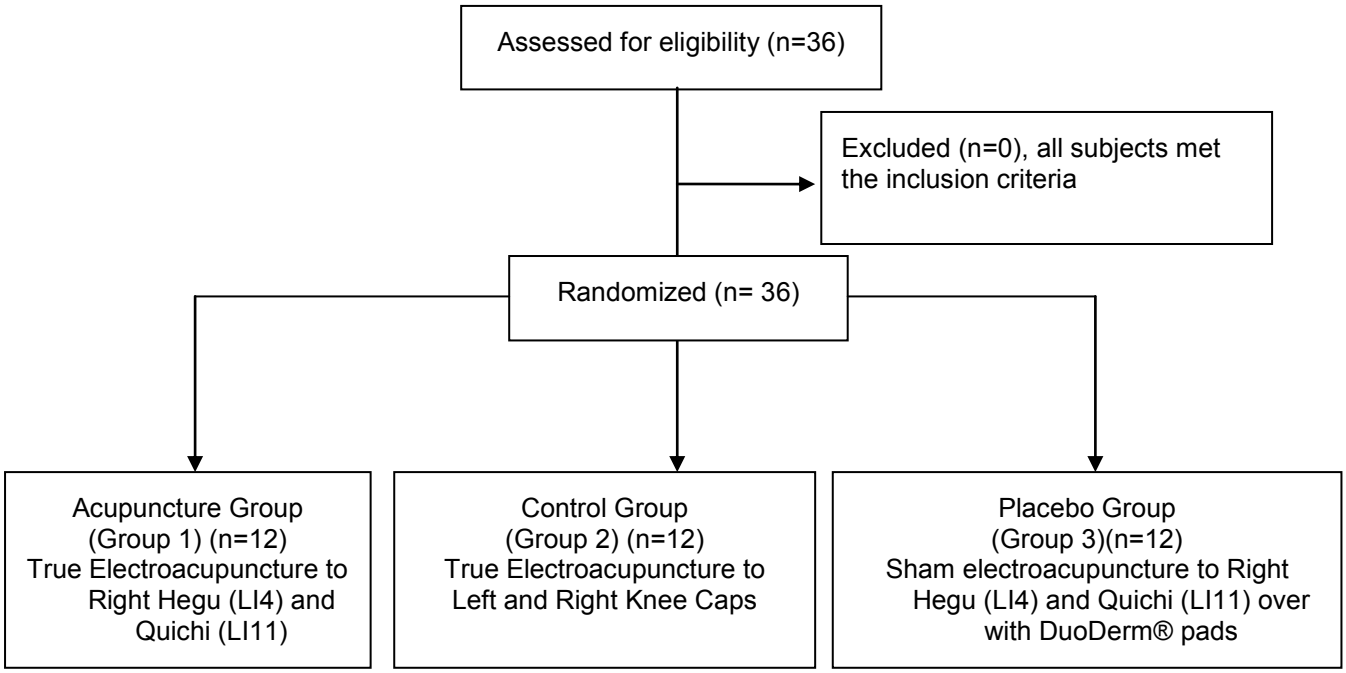


Figure 5.6 CONSORT diagram of the experiment

5.5 Results

A total of 36 subjects (19 men, 17 women), with a mean (±SD) age of 34.5 (±4.6) years, were recruited. There were no significant differences in baseline demographic and physiological variables among the three groups.

5.5.1 Changes in mean arterial blood pressure

A significant increase in MAP from a baseline of 84.6 (±2.6) mmHg to 90.0 (±0.9) mmHg was observed during acupuncture stimulation in Group 1 subjects ($p<0.05$). Such an increase failed to maintain statistical significance at 5 min after the stimulation ($p=0.058$). In Group 2, the MAP demonstrated a slight, non-significant increase at the initial onset of stimulation but then gradually returned to baseline and remained stable for the rest of the observation period ($p=0.058$). For Group 3, no significant changes in MAP were observed during or after the stimulation period ($p=0.599$; Table 5.1). There were significant between-group differences between Group 1 and Group 2 (mean difference=1.75±7.82mmHg, $p=0.035$) and between Group 1 and Group 3 (mean difference=4.21±4.3mmHg, $p=0.009$) during acupuncture stimulation. However, the between-group difference between Group 2 and Group 3 was not significant ($p=0.34$).

Table 5.1 Mean arterial blood pressure before, during, and at 5 minutes post intervention (n=36)

	Pre-stimulation	Stimulation period						5-min. post-stimulation
		5 min	10 min	15 min	20 min	25 min	30 min	
Group 1 (n=12)	84.6 (±2.6)	89.0 (±4.2)*	89.8 (±4.6)*	90.8 (±4.6)*	91.0 (±4.4*)	90.3 (±4.1)*	89.1 (±3.7)*	87.4 (±3.7)
Group 2 (n=12)	86.7 (±4.4)	88.6 (±5.6)	89.2 (±5.7)	88.8 (±5.6)	88.8 (±5.0)	87.5 (±3.5)	86.6 (±3.8)	86.0 (±3.7)
Group 3 (n=12)	85.5 (±6.7)	85.2 (±4.3)	84.7 (±6.2)	84.6 (±6.9)	84.9 (±7.2)	85.3 (±7.1)	85.8 (±9.4)	84.2 (±8.9)

Group 1= True electro-acupuncture to right Hegu (L4) and Qui (LI11); Group 2 = True electro-acupuncture to bilateral knee caps; Group 3 = Sham electro-acupuncture to right Hegu (LI4) and Quichi (LI11) *p<0.05

5.5.2 Changes in heart rate

For subjects in Group 1, there was a significant increase in HR in the initial period of stimulation (p=0.035); the HR gradually slowed down for the rest of the stimulation. No significant changes in HR were observed in subjects in Group 2 (p=0.12) or Group 3 (p=0.242; Table 5.2). There were significant between-group differences between Group 1 and Group 2 (mean difference=6.03±8.6bpm, p=0.043) and between Group 1 and Group 3 (mean difference=8.77±10.8bpm, p=0.02) during acupuncture stimulation. However, the between-group difference between Group 2 and Group 3 was not significant (p=0.35).

Table 5.2 Mean heart rate before, during and at 5 minutes post intervention (n=36)

	Pre-stimulation	Stimulation period						5-min. post-stimulation
		5 min	10 min	15 min	20 min	25 min	30 min	
Group 1 (n=12)	75.9 (±7.9)	80.1 (±7.8)*	81.7 (±8.2)*	81.5 (±7.9)*	80.9 (±7.2)	80.8 (±6.3)	79.5 (±6.7)	78.1 (±7.5)
Group 2 (n=12)	73.0 (±5.1)	75.7 (±5.1)	75.5 (±6.5)	76.0 (±6.3)	75.2 (±5.8)	73.3 (±6.1)	72.8 (±5.9)	71.7 (±5.6)
Group 3 (n=12)	73.5 (±7.1)	73.3 (±7.5)	72.6 (±8.1)	71.8 (±6.5)	72.6 (±5.1)	72.7 (±4.2)	72.7 (±3.9)	72.0 (±4.8)

Group 1= True electro-acupuncture to right Hegu (L4) and Quichi (LI11); Group 2 = True electro-acupuncture to bilateral knee caps; Group 3 = Sham electro-acupuncture to right Hegu (LI4) and Quichi (LI11) *p<0.05

5.5.3 Changes in autonomic nervous system activities

The computed LF/HF was highest in Group 1 during electroacupuncture stimulation when compared to the other two groups (p=0.001) and this ratio decreased at 5 min after the stimulation but still remained significantly higher than the baseline value (p=0.002). Subjects in Group 2 also showed a significant increase in LF/HF during stimulation when compared with the baseline (p=0.01). The ratio remained

slightly higher than baseline at 5 min after the stimulation; however, this was not statistically significant (p=0.084). There was a slight but insignificant increase in LF/HF during (p=0.412) and at 5 min after (p=0.375) the stimulation in Group 3 (Table 5.3).

Table 5.3 LF/HF before, during and at 5 minutes post intervention (n=36)

	LF / HF		
	Pre-stimulation	Stimulation	Post-stimulation
Group 1 (n=12)	0.69±0.21	2.31±1.09*	1.33±0.56*
Group 2 (n=12)	0.60±0.30	1.23±0.51*	0.77±0.23
Group 3 (n=12)	0.83±0.11	0.84±0.17	0.84±0.13

Group 1= True electro-acupuncture to right Hegu (L4) and Quichi (LI11); Group 2 = True electro-acupuncture to bilateral knee caps; Group 3 = Sham electro-acupuncture to right Hegu (LI4) and Quichi (LI11); LF = low frequency; HF = high frequency *p<0.05

5.5.4 Intensity of acupuncture sensations during stimulation

Figure 5.7 shows the mean intensity of each descriptor in the C-MMASS reported by the three groups. The overall C-MMASS index of Group 1, Group 2 and Group 3 were 5.3 (±1.3), 3.5 (±0.7) and 0.77 (±0.2), respectively. There was a significant difference in the C-MMASS among the three groups (F=69.92. df=2, p<0.05). Post-hoc analysis with Bonferroni adjustment showed that there was a significant difference in the C-MMASS index between Group 1 and 2 (p<0.05, CI=1.00 to 3.04). In Group 1, dull pain, fullness/distension, aching, numbness and tingling were the most frequent sensations reported. The majority of the ratings were in the mild to moderate range. In Group 2, the strongest sensations were reported for tingling and soreness. For Group 3, the strongest sensations were recorded in fullness/distension and tingling. No subject opted to add any new descriptors in the blank row provided.

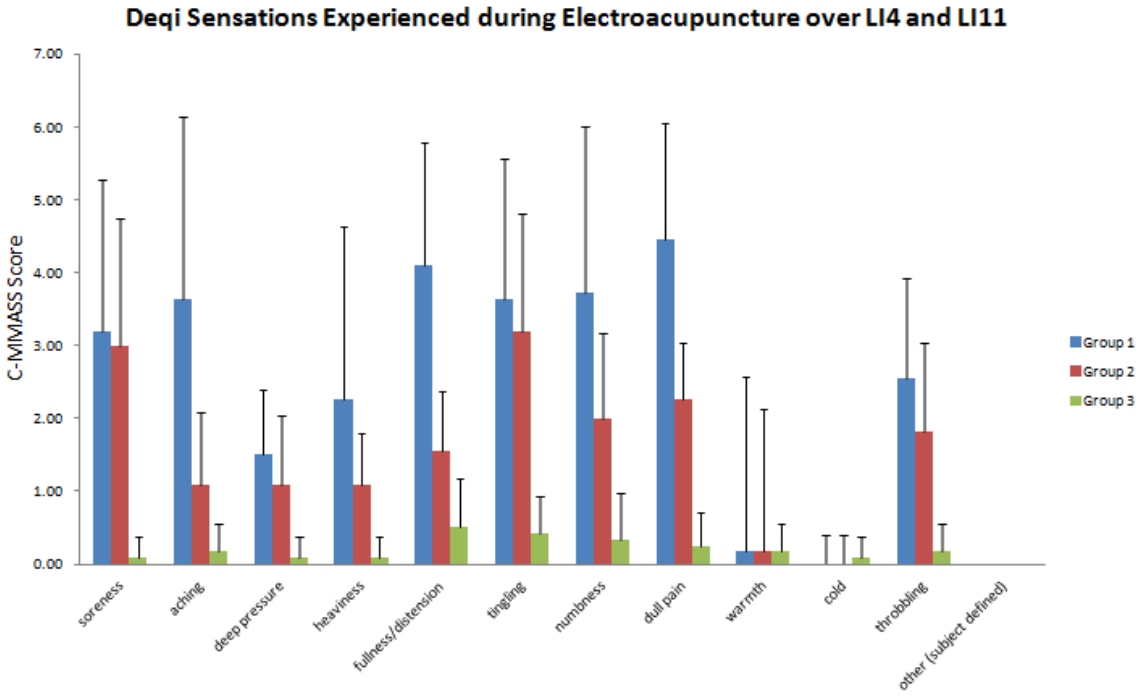


Figure 5.7 Mean intensity of needle sensations expressed by C-MMASS score, reported by Group 1, Group 2 and Group 3

Group 1= True electro-acupuncture to right Hegu (L4) and Quichi (LI11); Group 2 = True electro-acupuncture to bilateral knee caps; Group 3 = Sham electro-acupuncture to right Hegu (LI4) and Quichi (LI11)
C-MMASS = Modified Massachusetts General Hospital Acupuncture Sensation Scale Chinese version

5.5.5. Association between acupuncture sensations and the physiological responses

Correlation analysis between the overall C-MMASS score and physiological responses (HR, MAP, LF/HF) revealed a strong correlation between the intensity of acupuncture sensations and the LF/HF (γ=0.89 p<0.001), MAP (γ=0.78, p=0.018) and mean HR (γ=0.71, p=0.023) in Group 1. Moderate correlation was found between the acupuncture sensations intensity and LF/HF (γ=0.65, p=0.029) and MAP (γ=0.58, p=0.049) but not with the HR (γ=0.33, p=0.083) in Group 2. There was a very low association between the acupuncture sensations intensity and the physiological

responses in Group 3 (γ=0.17, p=0.589 for LF/HF; γ=0.25, p=0.528 for MAP; γ=0.11, p=0.734 for HR).

Table 5.4 summarizes the correlation between individual C-MMASS descriptors and the physiological responses in each group. The result showed that fullness/distension, tingling, numbness, dull pain and aching had stronger correlation with the changes in physiological responses than other acupuncture sensations. Similar associations were observed in Group 2, except there was no strong correlation between the acupuncture sensations and the changes in HR. In Group 3, there were no correlations between any descriptors and physiological parameters.

Table 5.4 Correlation between individual C-MMASS descriptors and the physiological parameters (n=36)

	Group 1 (n=12)			Group 2 (n=12)			Group 3 (n=12)		
	MAP	HR	LF/HF	MAP	HR	LF/HF	MAP	HR	LF/HF
soreness	0.55*	0.67*	0.78*	0.52*	0.36	0.73*	0.14	0.10	0.08
aching	0.66*	0.66*	0.81*	0.33	0.31	0.52*	0.20	0.13	0.19
deep pressure	0.33	0.36	0.43	0.39	0.33	0.53*	0.16	0.10	0.32
heaviness	0.56*	0.52*	0.63*	0.43	0.38	0.52*	0.16	0.09	0.21
fullness/distension	0.84*	0.79*	0.88*	0.55*	0.22	0.66*	0.26	0.11	0.26
tingling	0.82*	0.77*	0.82*	0.62*	0.32	0.72*	0.24	0.16	0.22
numbness	0.83*	0.73*	0.82*	0.51*	0.26	0.62*	0.22	0.12	0.31
dull pain	0.78*	0.74*	0.93*	0.51*	0.22	0.66*	0.22	0.13	0.26
warmth	0.21	0.19	0.23	0.26	0.18	0.22	0.21	0.06	0.16
cold	§	§	§	§	§	§	0.17	0.11	0.16
throbbing	0.77*	0.55*	0.68*	0.60*	0.34	0.60*	0.24	0.21	0.37
Other (subject define)	§	§	§	§	§	§	§	§	§

LF = low frequency; HF = high frequency; MAP = Mean arterial pressure; HR = Heart rate; C-MMASS = Modified Massachusetts General Hospital Acupuncture Sensation Scale Chinese version
*p<0.05 § = unable to perform correlation analysis due to small number

5.6 Discussion

There is evidence that ANS activities can be modulated by acupuncture. The current study demonstrated that electroacupuncture to Hegu (LI4) and Quichi (LI11) induced significant sympathetic discharge. In fact, responses to acupuncture stimuli encompass a broad network of regions consistent with somatosensory, affective and cognitive processing in the brain. A recent meta-analysis on the effect of acupuncture on the human brain using functional MRI (fMRI) confirmed that verum acupuncture stimuli can modulate the brain activities by activating the supramarginal gyrus, secondary somatosensory cortex, pre-supplementary motor area, middle cingulate gyrus, insula, thalamus and precentral gyrus. Acupuncture stimulation, however, was associated with deactivation of the pregenual anterior cingulate, posterior cingulate cortex, subgenual cortex, amygdale/hippocampal formation, ventromedial prefrontal cortex and nucleus accumbens of the limbic region (Huang et al, 2012). As the central outflow of the ANS is coordinated in the medulla oblongata and regulated by the limbic system (Ueyama 2012), it is possible that acupuncture stimulation may induce changes in the ANS via modulation of the cerebrocerebellar limbic system.

Reports on whether acupuncture induces dominant changes in sympathetic or parasympathetic activities are inconsistent. Results of this study showed that LF electroacupuncture to Hegu (LI4) and Quichi (LI11) evoked sympathetic discharge. There are several explanations for this observation. Firstly, studies have shown that electroacupuncture stimulation applied to Hegu (LI4), at an intensity where the subject experienced strong acupuncture sensations, led to activation of the hypothalamus (Hsieh et al, 2001; Napadow et al, 2007). It is known that activation of the hypothalamus is associated with increase of sympathetic vasomotor activity (De

Wardener, 2001; Marsh et al, 2003; Napadow et al, 2007). Subjects in the present study who received electroacupuncture over LI4 and LI11 experienced rather strong sensations as reflected by the high C-MMASS score; therefore, it is possible that the ANS activity induced was associated with modulation of brain activity. Secondly, the increase in sympathetic discharge seen in this study could also be related to the acupuncture point specificity theory (Huang et al, 2011). Some authors believed that *yin* is the parasympathetic division and *yang* is the sympathetic division of the ANS (Tjen-A-Looi et al, 2004). Since Hegu (LI4) and Quichi (LI11) lie along the Large Intestine yang meridian (Paton et al, 2005), it is logical to believe that stimulation of these acupuncture points would enhance the sympathetic activities leading to an increase in mean MAP and HR. Since all subjects were naïve to acupuncture, the initial exposure to an experimental trial with electroacupuncture may lead to an increase in anxiety-induced sympathetic activity. However, the amplitude of sympathetic discharge recorded during electrical stimulation over the patella points (non-acupuncture points) was far less than actual electroacupuncture over LI4 and LI11, as demonstrated by a statistical significant between-group difference in MAP, HR and LF/HF changes, this suggests the *deqi* sensation as well as physiological parameters such as heart rate and MAP could in part explained by the actual "acupoints effect", and not a result of mere electrical stimulation. Nevertheless, this study is not able to conclude whether electroacupuncture stimulation to Hegu (LI4) and Quichi (LI11) would only associate with an 'increase' in sympathetic discharge; it is possible that acupuncture could shift sympathetic or parasympathetic activities to either direction in order to maintain and restore the homeostasis of the body system. For instance, low frequency electroacupuncture to abdominal muscle demonstrated a significant decrease in muscle sympathetic activity in patients with polycystic ovary

syndrome, a condition associated with increased sympathetic activities (Stemer-Victorin et al, 2009).

The results of this study also show an interesting relationship between acupuncture sensations, changes in HR and MAP and an increase in sympathetic discharge. In this study, the majority of the subjects who received electrical stimulation experienced sensations of dull pain, fullness/distension, aching and numbness regardless of acupuncture point or non-acupuncture point stimulation. These sensations are predominately conveyed by Aδ and Aβ fast conducting fibres (Wang et al, 1985). Signals of the sensations will rapidly lead to an increase in impulses generated by mechanosensitive receptors of high and low threshold, resulting in afferent input to the central nervous system (Benham and Johnson, 2010), in turn affecting the ANS. This probably explains the positive correlation observed between acupuncture sensation intensity and the extent of ANS changes. The findings of this study suggest that acupuncture sensations are associated with changes in the ANS.

In the present study, electroacupuncture and not manual acupuncture was chosen. This is because the former technique is becoming more popular and commonly reported in clinical trials and research studies (Kong et al, 2007). Also, the parameters for electroacupuncture stimulation could easily be standardised throughout the study duration. Moreover, an interesting finding of this study is that while acupuncture sensations are strongly associated with stimulation of the acupuncture point, similar sensations including dull pain, fullness/distension, aching and numbness and soreness were also reported with non-acupuncture point stimulation, although the reported intensity of these sensations were higher during electrical stimulation over

acupuncture points compared to non-acupuncture points. While evidence for the anatomical existence of acupuncture points is not compelling (Ying et al, 2010), it is believed that acupuncture points are located where nerves enter a muscle, the midpoint of the muscle, or at the enthesis where the muscle joins with the bone (Ying et al, 2010). Stimulation of nerve branches will produce numbness, and stimulation of muscles will produce soreness and distension (Kong et al, 2007). This probably explains the higher intensity of sensations experienced by subjects in Group 1.

The use of sham electroacupuncture as placebo control group is common in acupuncture studies. Such techniques include using retractable acupuncture needles (Kaptchuk 2002; Kong et al, 2005, Enblom et al, 2008; Streitberger and Kleinhenz, 1998) or insertion of the needle subcutaneously (Knardahl et al, 1998; Haker et al, 2000; Li et al, 2005). Nevertheless, both techniques have drawbacks. Pressing the skin with a retractable needle could activate the sensory pathways despite the type and strength of sensory input differing from traditional acupuncture (Huang et al, 2011). However, insertion of a needle subcutaneously may induce an increase of the cutaneous blood flow and may also excite nociceptive primary afferents (Kolzenburg and Handwerker, 1994; Li et al, 2005). This afferent nerve activity can have pronounced effects on the functional connectivity in the brain, resulting in a 'limbic touch response' (Lund et al, 2009; Huang et al, 2011). This study therefore employed a new placebo method in our study. Insertion of the needle into the Duoderm pads mimics the acupuncture techniques without exertion of excessive mechanical pressure on the skin or penetration of the skin. Interestingly, some subjects still experienced mild needle sensations in Group 3. As explained by Salih and coworkers, the elicitation of acupuncture sensations without cutaneous sensory input could be due to expectancy, awareness, focusing of attention on the acupuncture points, or general

treatment settings by the subjects. All these could reinforce subjects' expectation that they would feel something during the interventions (Salih et al, 2010). The slight increase in LF/HF in the placebo group could be the result of the subject's anxiety, expectation or focused attention to the points, as an increase in awareness of spontaneous activity of motoneurons could lead to an increase in the muscle and skin sympathetic nerve activity (Hagbarth and Vallbo, 1967).

5.7 Limitations of the study

The major limitation of this study was the lack of a group that received electroacupuncture but elicited no acupuncture point sensations. Such a group may be ideally possible when the subjects are anaesthetized while receiving acupuncture. This current study however showed that subjects could experience some acupuncture point sensations even without actual acupuncture stimulation. Another limitation of this study is the small sample size and that the sample consisted only of healthy subjects who can reliably sense and report the needle sensations. In this regard, further studies involving the above mentioned 'ideal' group, and with a larger sample size, are necessary to further investigate the relationship between acupuncture and its associated physiological effects.

5.8 Conclusions

This current study confirmed that electroacupuncture to Hegu (LI4) and Quichi (LI11) is likely to be associated with an increase in sympathetic discharge of the ANS. The results of the study suggest the notion that acupuncture sensations are associated with changes in the ANS. The intensity of acupuncture sensation was positively correlated with haemodynamic and ANS changes.

CHAPTER 6

Are physiological changes experienced by healthy subjects during Acu-TENS associated with acupoint sensations?

(published in *Acupuncture in Medicine* 2014;32:28-36) – Appendix 17

6.1 Introduction

The work described in Chapter 5 suggests that during the electroacupuncture procedure, *deqi* is associated with changes in cardiovascular parameters and the *deqi* intensity increases with an increase in sympathetic discharge of the ANS. While positive effects of acupuncture have been acknowledged by many studies, adverse effects associated with the application of acupuncture have also been reported. Therefore, non-invasive techniques including acupressure and laser acupuncture, have become "safer" alternatives. The application of Transcutaneous Electrical Nerve Stimulation over Acupoints (Acu-TENS), an non-invasive modality, was recently reported in association with improved clinical outcomes. However, whether Acu-TENS is associated with acupoint sensations similar to *deqi* experienced during acupuncture has not been investigated. This chapter describes a third study in this thesis which investigates whether acupoint sensations were experienced during Acu-TENS and whether such sensations were associated with any concomitant changes in ANS activity.

Complementary treatments are receiving increased attention as a choice for health maintenance. Traditional Chinese Medicine (TCM) practitioners believe acupuncture is able to modulate qi flow and restore the *yin–yang* balance, and hence health can be maintained (Kaptchuk 2002; Vickers et al, 2002). In Western medicine, acupuncture concepts have been explained as a regulation of the autonomic nervous system (ANS), revitalising and balancing the body's homeostasis through modulation of the sympathetic and parasympathetic systems (Lin and Chen, 1994; Kong et al, 2007). Analysis of heart rate variability (HRV), has become a common measurement parameter in many acupuncture studies (Haker et al, 2000; Chang et al, 2005; Li et al,

2005; Backer et al, 2008; Jeong et al, 2008; Park et al, 2008).

While positive effects of acupuncture have been acknowledged by many studies, its associated adverse effects have also been reported (White et al, 2001; Lao et al, 2003). Thus, non-invasive techniques including acupressure (Arai et al, 2008; Arai et al, 2011) and laser acupuncture (Gruber et al, 2002) have been seen as 'safer' alternatives. Transcutaneous electrical nerve stimulation (TENS) applied over acupuncture points (Acu-TENS), has been reported to be effective in reducing dyspnoea in patients with chronic obstructive pulmonary disease (COPD) (Lau and Jones, 2008; Ngai et al, 2012), facilitate early haemodynamic recovery after open heart surgery (Ng et al, 2012), relieve labour pain (Chao et al, 2007; Peng et al, 2010) and reduce blood pressure changes in normal healthy subjects (Zhang et al, 2009; Jones et al, 2011). Acu-TENS is also associated with an increase in blood β-endorphin level (Ngai et al, 2010; Ngai et al, 2011), a decrease in airway resistance (Chan et al, 2012) and is possibly associated with regulation of the ANS (Ngai et al, 2010; Ngai et al, 2011; Chan et al, 2012).

Comparative investigation of the mechanism of action of Acu-TENS and acupuncture continues, but a fundamental criterion for effective acupuncture, '*deqi*', has not been examined during Acu-TENS. In TCM terms, *deqi* is a unique sensation that indicates an appropriate psychophysical response to acupuncture (Kaptchuk 2002; Vickers et al, 2002). In Western medicine, the *deqi* sensation is thought to indicate stimulation of the ANS via modulation of the cerebrocerebellar limbic system (Huang et al, 2012; Ueyama, 2012). Based on previous reports on Acu-TENS (Lau and Jones, 2008; Ngai et al, 2011), this study hypothesized that Acu-TENS can induce ANS changes similar to acupuncture; however, whether acupuncture point sensations

described as *deqi* are necessary for the ANS changes elicited during Acu-TENS has not been investigated. This study therefore aims to investigate acupuncture point sensations experienced during Acu-TENS and whether such sensations are associated with any concomitant changes in ANS activity. The Population, Intervention, Comparator, Outcome (PICO) format adopted being: P=Normal healthy subjects; I=Acu-TENS; C=True Acu-TENS on non-acupoints and Sham Acu-TENS to acupoints and O=Physiological and sensory responses.

6.2 Methods

6.2.1 Sample size estimation

Sample size for this study was determined based on the data of the previous study in quantifying the *deqi* sensation (Yu et al 2012). With an expectation of the effect size to be "medium" (Cohen's d = 0.3), and with the power set at 0.8, Type I error of 5%, the standard deviation was approximately 2.00 and produced a 2-sided 95% CI with a width equal to 0.987. Using a statistical software PASS (2008) (http://www.ncss.com/pass.html), 36 subjects was estimated to be appropriate for this study.

6.2.2 Subjects

This study adopted a single-blinded (patient-blinded), randomised, controlled trial design. Ethics approval was obtained from the Human Subjects Review Committee of the Hong Kong Polytechnic University (Project ID: HSEARS20110510001) and was carried out within the ethical standards set forth in the Helsinki Declaration of 1975. Written consent was obtained from all participants (Appendix 18 – Chinese and Appendix 19 - English version). Normal healthy subjects

who were naïve to TENS or acupuncture or Acu-TENS and able to read Chinese were recruited. Subjects were excluded if they had a history of cardiopulmonary, neurological and psychological disorders, or if they required any medication for cardiovascular, neurological or psychological conditions within 1 week prior to the study.

6.2.3 Randomization procedure

Subjects were randomly assigned to one of the three groups using sequentially numbered, opaque sealed envelope simple randomisation method (Altman and Schulz, 2001). A total of 12 sheets of paper were marked with 'Experimental group', 12 sheets with 'Control group' and 12 sheets with 'Placebo group', and the sheets were then put into 36 opaque envelopes (1 sheet per envelope), which were then sealed. The deck of envelopes was shuffled thoroughly by an independent assistant. Then, the front of each envelope was marked sequentially with the numbers 1–36. These envelopes were then placed in numerical order in a plastic container. Each subject was asked to draw an envelope, which was then opened by an independent investigator.

6.2.4 Experimental procedure

On arrival at the laboratory, subjects were asked to rest for 30 min in a sitting position to establish a steady cardiopulmonary state. Subjects were instructed to breathe normally, to minimise any effect of respiration on HRV. All measurements were taken between 16:00 and 18:00 to minimise the circadian effect on the ANS (Agelink et al, 2001).

Systolic and diastolic blood pressures were taken on the left arm by a digital patient monitor (Mindray PM-8000 Express Patient Monitor, Bio-Medical Electricity,

Hamburg, Germany). The mean arterial pressure (MAP) was recorded. Electrocardiogram (ECG) electrodes were applied over left and right clavicles and left upper quadrant of abdomen and then connected to the digital patient monitor device. HR was continuously monitored. The ECG signals were analysed by Chart™5 Pro for Windows. The ECG signals were transferred to the PowerLab 16/30 (**ADI**nstruments Pty Ltd., New South Wales, Australia) for data acquisition and analysis of the HRV.

MAP, HR and HRV parameters were measured at 5 min before the intervention, every 5 min for 45 min during the intervention and at the 5th minute after the stimulation. Data recorded during the 45 min intervention were averaged for analysis. Immediately after the intervention, subjects were asked to complete the Hong Kong Chinese version of the Massachusetts General Hospital Acupuncture Sensation Scale (C-MMASS) (Yu et al, 2012) to quantify the acupuncture point stimulation sensations.

6.2.5 HRV measurement

The HRV was analysed in accordance with the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). For frequency domain analysis, power spectral analysis was performed by the Fast Fourier Transformation technique (Agelink et al, 2001; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Low frequency (LF), defined as the power between 0.03 and 0.15 Hz, mainly represents sympathetic modulation; high frequency (HF), defined as the power between 0.15 and 0.5 Hz, is regarded as an index of vagal (parasympathetic)

modulation; the ratio LF/HF reflects the global sympathovagal balance of the body (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Sztajzel, 2004). For the time domain analysis, the recorded SD of the NN interval (SDNN) is referred to as the global index of the HRV (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Sztajzel, 2004).

6.2.6 Points location and preparation

The locations of the right Hegu (LI4) and Quichi (LI11) points and the apex of patella were identified by a trained physiotherapist. Isopropyl alcohol was applied for skin preparation after locating the points. Two self-adhesive ECG electrodes (F-601 SKINTACT) were then placed over the acupuncture points and attached to a dual channel portable TENS unit (120z Dual Channel TENS, EMS Physio Ltd, Oxfordshire, UK). The pulse frequency and pulse width of the TENS were set at 2 Hz and 200ms, respectively, with the intensity adjusted to the subject's maximum tolerable level short of muscle contraction. Total duration of stimulation was 45 min (Ngai et al, 2010; Ngai et al, 2011; Chan et al, 2012).

6.2.7 Intervention protocols

All interventions were conducted in the sitting position. For the Experimental Group, subjects received Acu-TENS over the right Hegu (LI4) and Quichi (LI11) points (Figure 6.1); for the Control Group, subjects received TENS over the apex of bilateral kneecaps (Figure 6.2); for the Placebo Group, subjects received the same protocol as the Experimental group and TENS but the points were covered with non-conducting plastics of the same size as the TENS electrodes, such that no

electrical current would pass through the skin (Figure 6.3 and 6.4). Subjects were informed that they might or might not feel the electrical stimulation depending on the pulse frequency used.

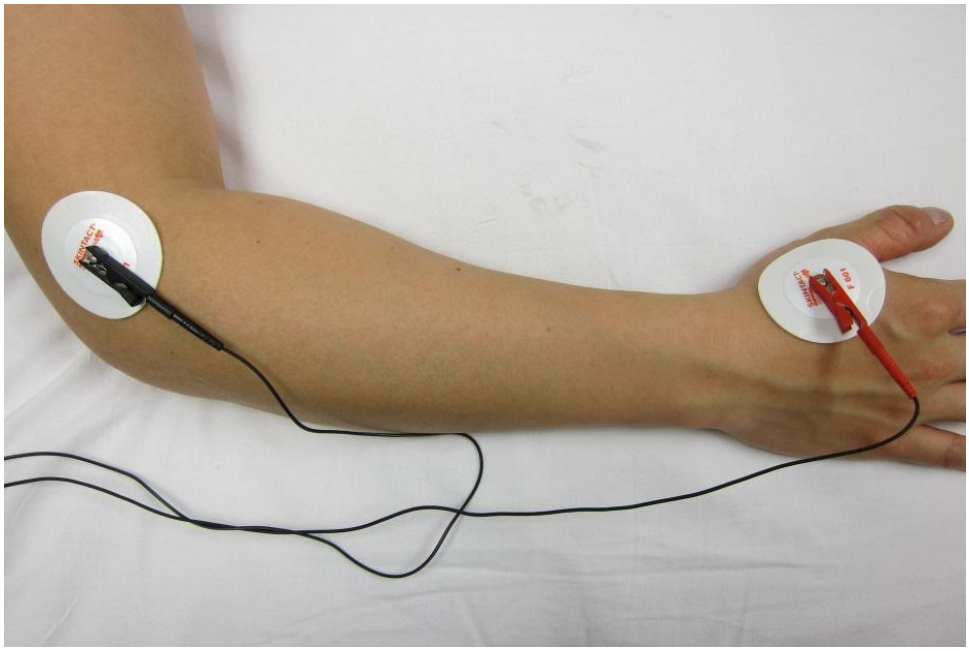


Figure 6.1 Acu-TENS to right LI4 and LI11 (Experimental Group)

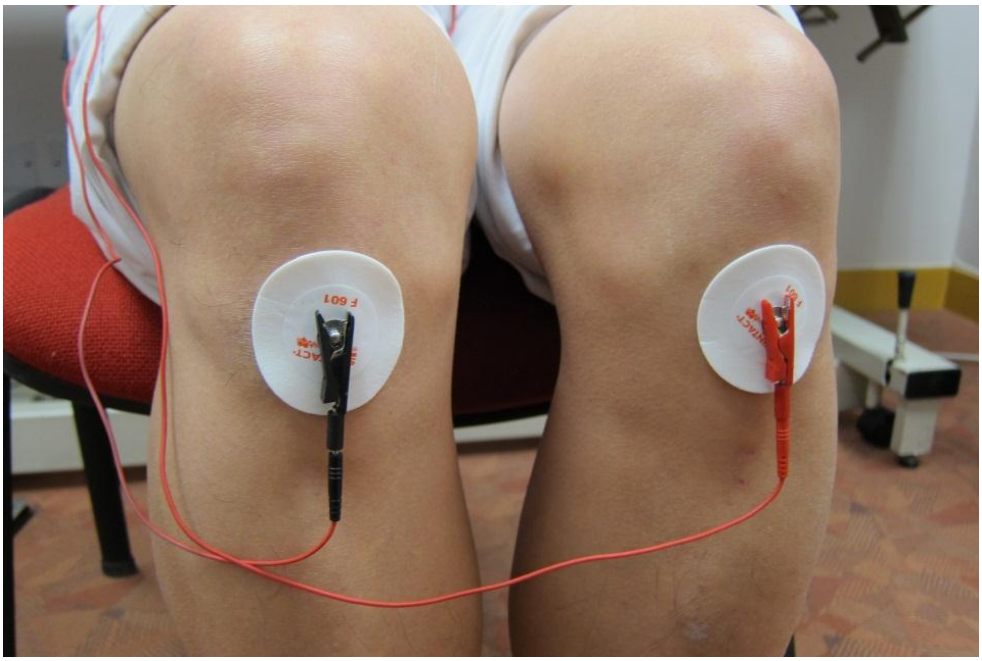


Figure 6.2 TENS applied to bilateral knee caps (Control Group)

Figure 6.3 TENS applied over non-conductive plastic films on the right LI4 and LI11 (Placebo Group)

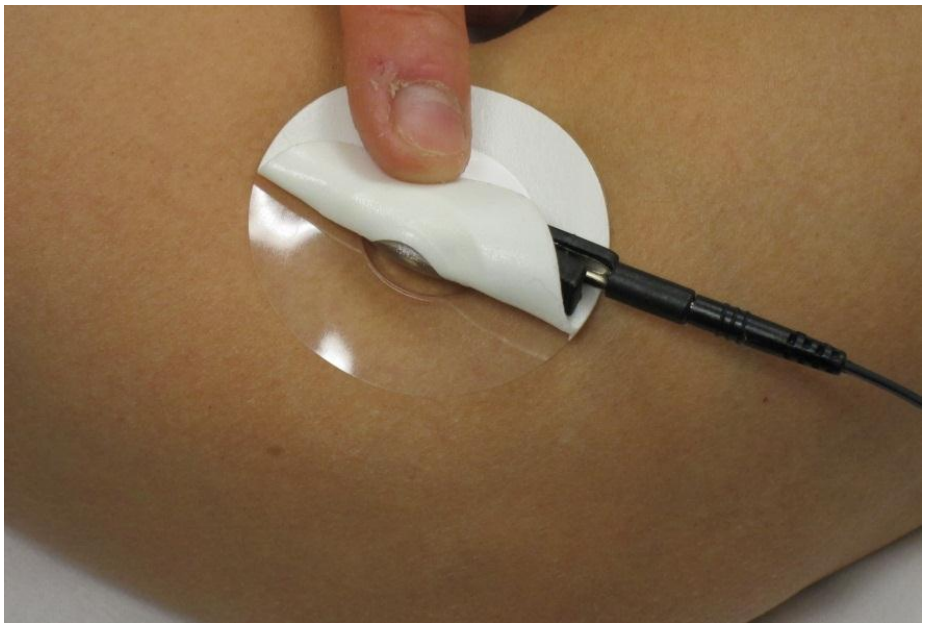


Figure 6.4 Close-up view of TENS applied over non-conductive plastic films on the right LI4 and LI11 (Placebo Group)

6.2.8 Modified Massachusetts General Hospital Acupuncture Sensation Scale, Chinese Version

The C-MMASS consists of 12 descriptors of sensation, including soreness, aching, deep pressure, heaviness, fullness/distension, tingling, numbness, dull pain, warmth, cold, throbbing plus a blank supplementary row left for subjects to describe their own perceptions (Yu et al, 2012). Each descriptor is presented on a 10-cm bar, anchored with numerical scores 0–10 and with the words 'none', 'mild', 'moderate' and 'severe' spaced evenly along the continuum. Immediately after the 45-min intervention, subjects were asked to quantify the sensations experienced by rating the intensity for each descriptor. The C-MMASS index was then calculated (Yu et al, 2012) and was used to quantify the overall intensity of the acupuncture sensations experienced.

6.3 Statistical analysis

All statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) V.17.0 for Windows. Demographic and baseline data were compared among the three groups using one-way analysis of variance (ANOVA). The within-group change in HR, MAP, LF/HF, SDNN and the C-MMASS index of the groups at before, during and after intervention were analysed by one-way repeated ANOVA. Between-group differences were analysed by one-way ANOVA with post hoc pairwise comparison and least significant difference (LSD) adjustment. The null hypothesis was rejected if the calculated F ratio exceeds the critical value with $p<0.05$. An exploratory correlation analysis using Spearman's correlation was performed

between the overall C-MMASS index, mean MAP, HR, SDNN and LF/HF in each group. The level of significance was set at 0.05 for all analyses. A CONSORT diagram of the study procedure was showed in Figure 6.5.

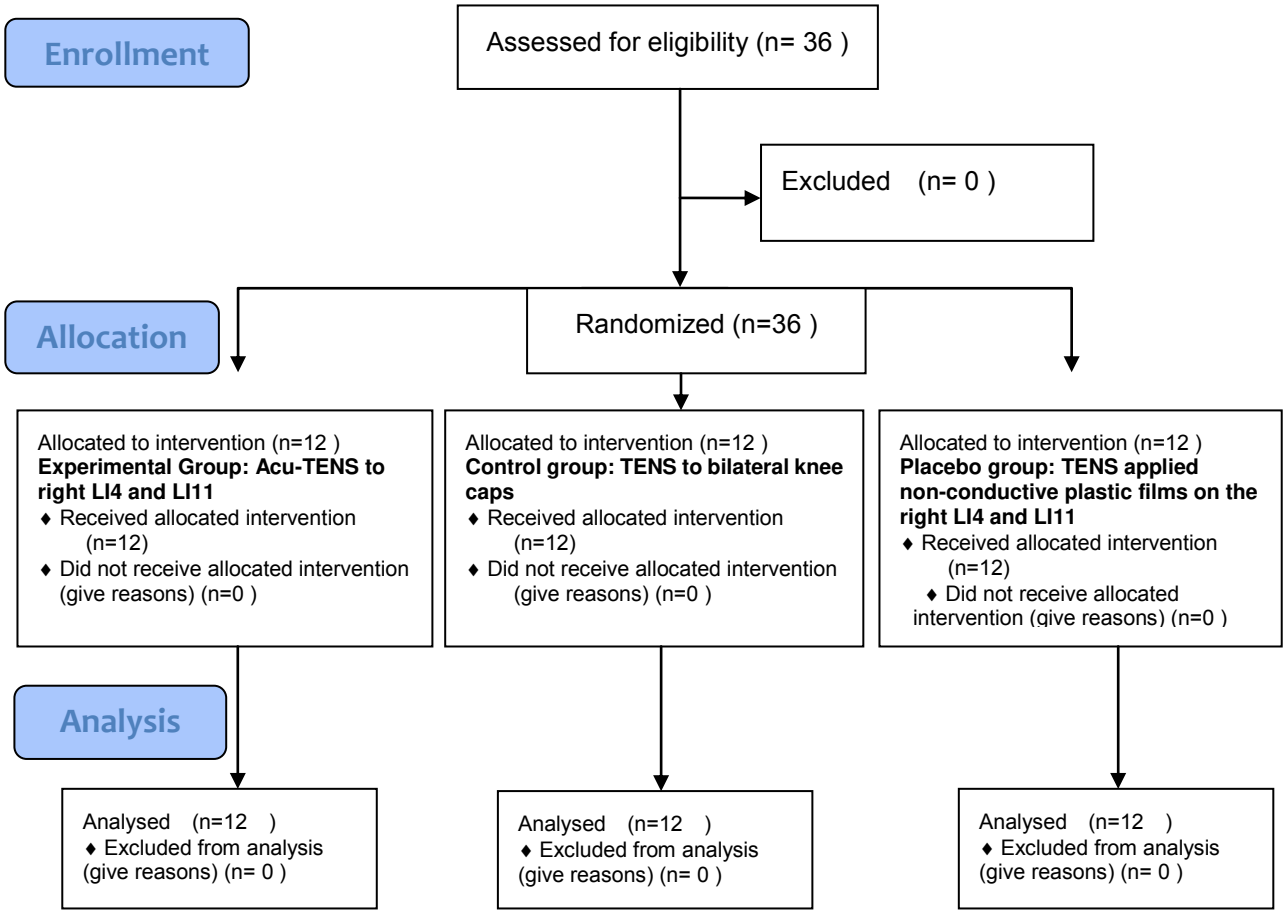


Figure 6.5 A CONSORT diagram of the experiment set up

6.4 Results

In all, 36 participants (22 men and 14 women) were recruited for this study, mean age (±SD) = 32.8(±2.1) years.

6.4.1 Blood pressure changes

The MAP increased significantly from 88.5(±4.5)mmHg to 91.0(±4.1)mmHg during Acu-TENS in the Experimental Group (p=0.004); at 5 min after intervention, the MAP returned to 89.3(±4.6)mmHg and was still slightly higher than baseline but did not reach statistical significance (p=0.898). There was no significant change in MAP for the Control [from 88.7 (±5.9) mmHg to 89.6 (±5.8) mmHg] (p=0.315) or the Placebo Groups [86.6 (±5.7) mmHg to 87.1 (±5.4) mmHg] (p=0.3) during the stimulation (Figure 6.6). There were significant between-group differences between Experimental Group and Control Group (mean difference=1.49±9.52mmHg, p=0.024) and between Experimental Group and Placebo Group (mean difference=4.88±5.14mmHg, $p<0.05$) during Acu-TENS stimulation. However, the between-group difference between Control Group and Placebo Group was not statistically significant (p=0.064).

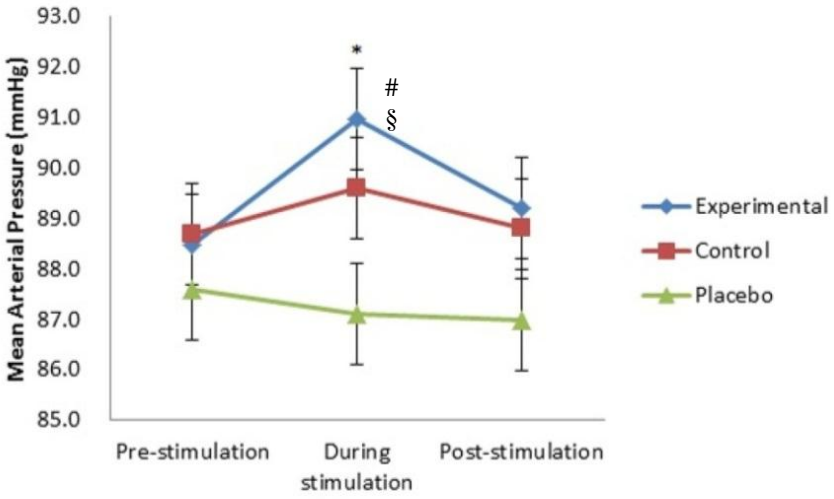


Figure 6.6 Changes in Mean Arterial Pressure at various measurement time points in the three groups

Experimental Group: Acu-TENS to right Hegu (LI4) and Quichi (LI11); Control Group: TENS to bilateral knee caps; Placebo Group: TENS applied to non-conductive plastic films on the right LI4 and LI11
*p<0.05 (Within group difference in Experimental Group)
#p<0.05 (Between-group difference - Experimental and Control Group)
§ p<0.05 (Between-group difference - Experimental and Placebo Group)

6.4.2 Heart rate changes

The HR increased significantly from 73.5(±6.3) bpm to 75.9(±6.7) bpm during Acu-TENS in the Experimental Group (p=0.027) and gradually returned to baseline [74.6(±8.4) bpm] post stimulation. There was also a slight increase in HR in the Control Group from 73.0(±4.5) bpm to 74.2(±3.7) bpm during the stimulation period, but this was not statistically significant (p=0.57); the HR returned to baseline at 5 min after the stimulation. For the Placebo Group, there was no significant changes in HR [from 72.1(±6.9)bpm to 71.6(±4.7)bpm] throughout the stimulation period (p=0.831) (Figure 6.7). The increase in HR during Acu-TENS was significantly higher in the Experimental Group compared to the Control group, the mean between-group

difference being 4.83±7.2bpm (p=0.044); likewise, the between-group difference in change of HR between Experimental Group and Placebo Group was 8.1±8.8bpm (p=0.046). However, the between-group difference between Control Group and Placebo Group was insignificant (p=0.087).

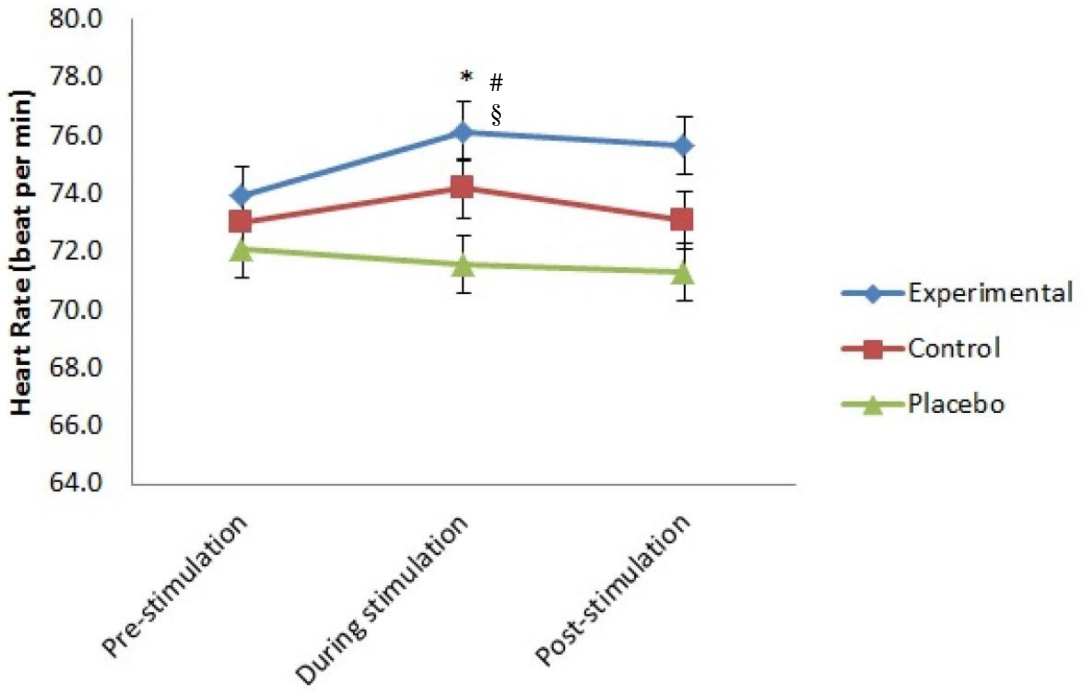


Figure 6.7 Heart rate changes at various measurment time points in the three groups

Experimental Group: Acu-TENS to right Hegu (LI4) and Quichi (LI11); Control Group: TENS to bilateral knee caps; Placebo Group: TENS applied to non-conductive plastic films on the right (Hegu (LI4) and Quichi (LI11)
*p<0.05 (Within gp difference in Experimental Group)
#p<0.05 (Difference between Experimental Group and Control Group)
§ p<0.05 (Difference between Experimental Group and Placebo Group)

6.4.3 SDNN changes

The SDNN increased from 143.36(±8.58)ms to 153.69(±7.64)ms in the Experimental Group during stimulation (p=0.002); at 5 min post stimulation, it remained higher than the baseline value by 6.31ms (p=0.037). For the Control Group, the SDNN increased from 140.21(±8.72)ms to 143.39(±9.47)ms during the stimulation (p=0.009); at 5 min post stimulation, it was 2.46ms higher than the baseline but the change was not statistically significant (p=0.068). For the Placebo Group, there was no significant change in SDNN during or after the stimulation [144.3 (±10.19)ms to 144.23(±10.23)ms] (Figure 6.8). A significant between-group difference in the SDNN during the stimulation was found among the three groups (F=4.06, df=2, p=0.027). Post hoc analysis with LSD adjustment showed there was a significant difference in the SDNN between the Experimental and Control Groups (mean between-group difference=9.7±12.49ms, p=0.013, 95%CI 2.3 to 18.3) and between the Experimental and Placebo Groups, (mean between-group difference= 7.73±11.1ms, p=0.029, 95%CI 0.97 to 17.0). There was also a significant main effect for Acu-TENS on SDNN (F=19.068, $p<0.05$) and a significant interaction effect between Acu-TENS and the period of stimulation (F=7.91, $p<0.05$).

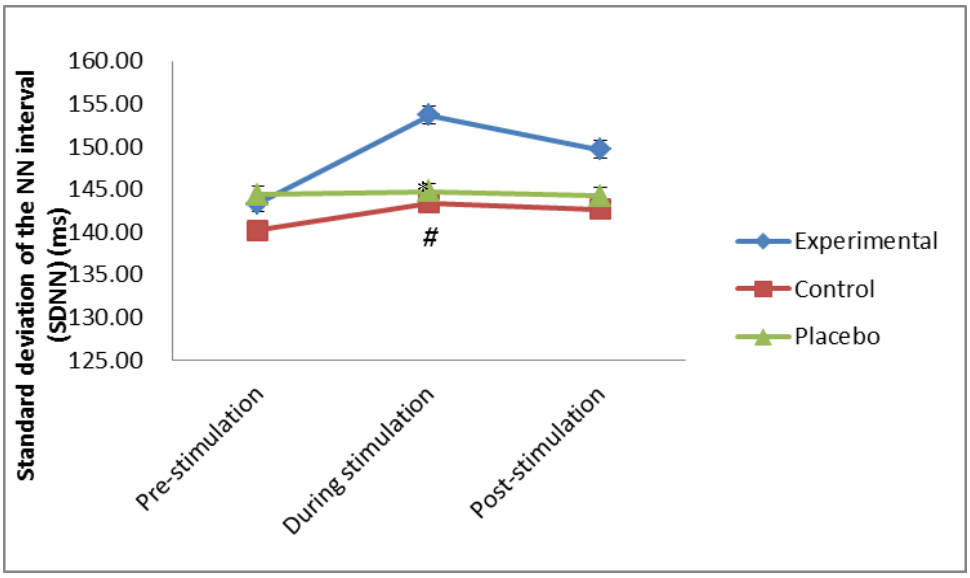


Figure 6.8 SDNN changes in different groups

Experimental Group: Acu-TENS to right Hegu (LI4) and Quichi (LI11); Control Group: TENS to bilateral knee caps; Placebo Group: TENS applied non-conductive plastic films on the right Hegu (LI4) and Quichi (LI11)
SDNN = standard deviation of the NN interval
*p<0.05 (Difference of SDNN between the Experiemtnal Group and the Conrol Group during Acu-TENS)
#p<0.05 (Difference of SDNN between the Experiemtnal Group and the Placebo Group during Acu-TENS)

6.4.4 LF/HF changes

The LF/HF increased from 1.26(±0.19) to 1.32(±0.21) during Acu-TENS (p=0.019) and at 5 min after the stimulation [1.30(±0.17)] (p=0.037). There was a small but statistically significant increase in LF/HF in the Control Group during the stimulation period [from 1.21(±0.09) to 1.23(±0.12)] (p=0.033). This ratio returned to baseline 5 min after the stimulation. Changes in this ratio were not significant in the Placebo group, where the LF/HF remained at 1.23(±0.11) throughout the intervention (Figure 6.9). A significant between-group difference in the LF/HF was found during the stimulation period (F=11.25, df=2, p=0.03). Post hoc analysis with LSD adjustment showed there was a significant difference in the LF/HF between the

experimental and Control groups (p=0.02, 95%CI 0.45 to 2.2) and between the Experimental and Placebo groups (p=0.017, 95%CI 0.4 to 2.3). Furthermore, there was a significant primary effect for Acu-TENS on LF/HF (F=2.73, p=0.044) while there was no significant interaction effect between Acu-TENS and the period of stimulation (F=0.411, p=0.72).

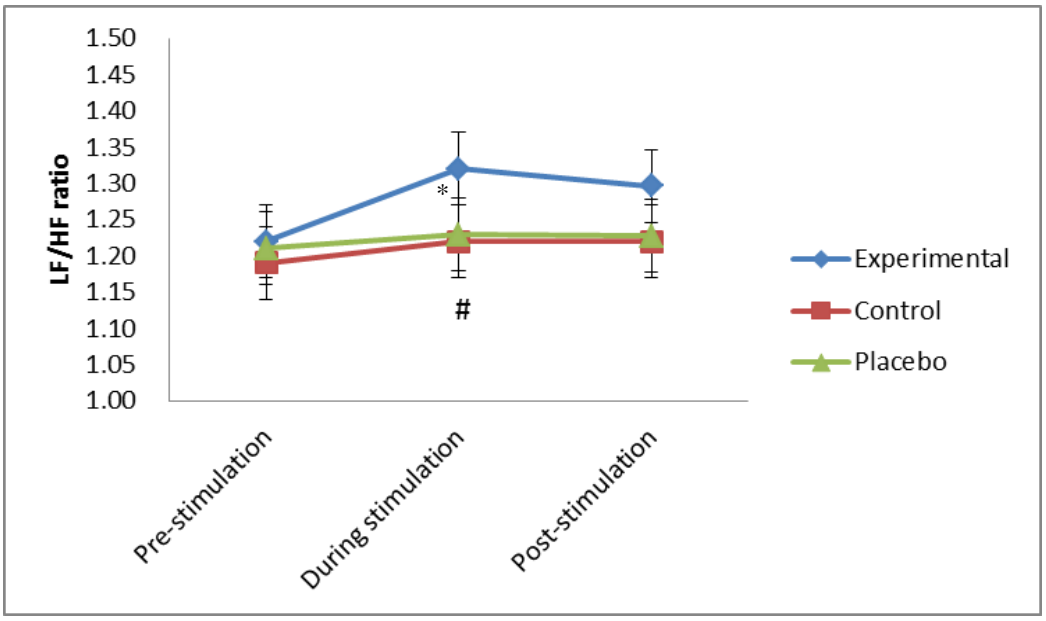


Figure 6.9 LF/HF ratio changes in different groups

Experimental Group: Acu-TENS to right Hegu (LI4) and Quichi (LI11); Control group: TENS to bilateral knee caps; Placebo Group: TENS applied non-conductive plastic films on the right Hegu (LI4) and Quichi (LI11)
LF = Low frequency; HF = High frequency
*p<0.05 (Different of LF/HF betweeb the Experiemtnal Group and the Control Group during Acu-TENS)
#p<0.05 (Different of LF/HF betweeb the Experiemtnal Group and the Placebo Group during Acu-TENS)

6.4.5 Intensity of acupuncture point sensations perceived during intervention

There was a significant difference in the C-MMASS index among the three groups (F=139.24, df=2, p<0.05); with the overall C-MMASS indices of the Experimental, Control and Placebo groups being 3.23(±0.3), 2.14(±0.6) and 0.29(±0.32), respectively. Post hoc analysis with LSD adjustment showed that there

was a significant difference in the C-MMASS index between the experimental and control groups (mean difference=1.09 ±0.85, $p<0.05$, 95%CI 0.72 to 1.45) and between the experimental and placebo groups (mean difference=2.94±1.1, $p<0.05$, 95%CI 2.57 to 3.30). In the Experimental Group, the three descriptors recorded with highest ratings were throbbing, soreness and fullness/distension. For the control group, the three strongest sensations recorded were tingling, throbbing and numbness. For the Placebo Group, the strongest sensation recorded was tingling. No subject opted to add any new descriptors in the blank row provided (Figure 6.10).

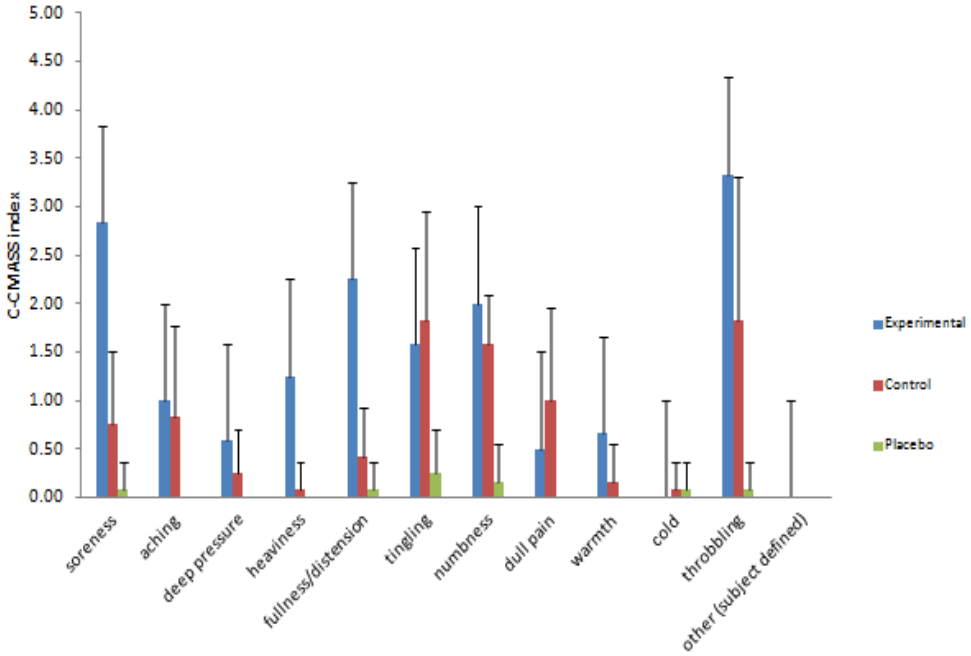


Figure 6.10 Intensity of sensations expressed by C-MMASS index score reported by different groups

Experimental Group: Acu-TENS to right Hegu (LI4) and Quichi (LI11); Control Group: TENS to bilateral knee caps; Placebo Group: TENS applied non-conductive plastic films on the right Hegu (LI4) and Quichi (LI11)
C-MMASS = Modified Massachusetts General Hospital Acupuncture Sensation Scale Chinese version

6.4.6 Association between C-MMASS score and the physiological responses

Correlation analysis between the overall C-MMASS index score and HR, MAP, SDNN and LF/HF revealed a very low association between the intensity of sensations and any of the recorded physiologic responses in all groups (Table 6.1).

Table 6.1 Correlation between C-MMASS and the physiological responses

C-MMASS Score	*MAP*	*HR*	*SDNN*	*LF/HF*
Experimental Group	-0.16 (p=0.62)	0.08 (p=0.81)	-0.32 (p=0.32)	-0.06 (p=0.85)
Control Group	-0.42 (p=0.17)	-0.06 (p=0.86)	-0.36 (p=0.6)	-0.07 (p=0.12)
Placebo Group	-0.26 (p=0.41)	0.25 (p=0.15)	0.08 (p=0.81)	0.09 (p=0.76)

Experimental Group: Acu-TENS to right Hegu (LI4) and Quichi (LI11); Control Group: TENS to bilateral knee caps; Placebo Group: TENS applied to non-conductive plastic films on the right Hegu (LI4) and Quichi (LI11)

C-MMASS = Modified Massachusetts General Hospital Acupuncture Sensation Scale Chinese version
MAP = Mean arterial blood pressure
HR = Heart rate
SDNN = standard deviation of the NN interval
LF = Low frequency;
HF = High frequency

6.5 Discussion

This is the first study to report a relationship between Acu-TENS and acupuncture point sensations, similar to *deqi* reported in the literature (Wang et al, 1985; Hui et al, 2007; Kong et al, 2007). The results show that acupuncture point sensations were experienced by the healthy subjects and were strongest during Acu-TENS, compared to non-acupuncture point and placebo stimulations.

Deqi is believed to be an indispensable component of effective acupuncture (Kong et al, 2007). Previous studies have shown that *deqi* sensation is associated with regulation of blood flow (Sandberg et al, 2003; Kuo et al, 2004; Hui et al, 2005; Sandberg et al, 2005; Huang et al, 2012), changes in neuronal activity in different areas of the brain (Hsieh et al, 2001; Napdow et al, 2007; Napdow et al, 2009), changes in ANS activities (Knardahl et al, 1998; Haker et al, 2000; Li et al, 2003; Hsu et al, 2006; Kimura et al, 2006; Saki et al, 2007; Choi et al, 2012; Yu and Jones, 2013) and an increase in pain threshold (Choi et al, 2012). A survey conducted by the British Acupuncture Council on 574 members revealed that 87% of acupuncturists would aim to attain *deqi* during acupuncture (MacPherson et al, 2001). The work presented in Chapter 5 demonstrated that needle electroacupuncture to Hegu (LI4) and Quichi (LI11) increases sympathetic discharge, which was strongly associated with acupuncture point sensations (Yu and Jones, 2012). Insertion of the needle into the acupuncture points, together with the needle-twirling manoeuvre, lead to muscle tension, trembling, twitching and spasm; this in turn stimulates muscle proprioceptors and gives rise to distinct needle sensations (Li et al, 2004). Such sensory inputs modulate ANS activities by regulating the brain activity through deactivation of the cerebrocerebellar limbic systems (Huang et al, 2012). TENS, however, stimulates the

human body through a different mechanism. TENS induces cutaneous stimulation through burst train mode, low pulse frequency, electrical activity (Sluka and Walsh, 2003; Jones et al, 2011). Application of TENS to acupuncture points may induce acupuncture point sensations through electrical stimulation of the particular acupuncture point.

The results of this current study demonstrate that subjects in the Experimental Group experienced strong sensations of throbbing, soreness, fullness and distension, similar to the sensations described during needle acupuncture. The C-MMASS score was also reported to be highest in the Experimental Group, moderate in the Control Group and minimal in the Placebo Group. Anatomically, acupuncture points are areas with a high density of nerve endings and lower electrical impedance compared to other tissues (Liu et al, 1975; Gunn et al, 1976; Falk et al, 2000; Egot-Lemaire et al, 2011). It is possible that the 'sensation' experienced by subjects in the Experimental and Control Groups was due to electrical current stimulation. The lower C-MMASS score recorded in the Control Group may be a consequence of a lower density of nerve endings in the patella region, eliciting weaker sensations compared to stimulation of actual acupuncture points. However, the acupuncture point sensations reported in the Control Group were different from those reported by the Acu-TENS group. The dominant sensation reported by the Control Group was tingling, numbness and throbbing. This could be sensation of electrical stimulation rather than *deqi*. It is therefore possible that the 'acupuncture point effect' could at least, in part, account for the high C-MMASS score recorded in subjects in the Experimental Group, and not just have arisen as a consequence of current stimulation. However, this study also suggests that the acupuncture point sensations, with descriptive features similar to *deqi*, are not associated with ANS changes induced during Acu-TENS.

It is interesting to note that although there should be no electrical stimulation occurring in the Placebo group, some subjects still reported mild sensations of tingling, soreness, fullness/distension and throbbing during the intervention. A previous report has also shown that placebo Acu-TENS over Dingchuan (EX-B1) could increase forced expiratory volume in 1 second (FEV_1), reduce respiratory rate and dyspnoea score in patients with COPD (Ngai et al, 2011), and reduce airway resistance in healthy individuals after exercise (Chan et al, 2012). It is postulated that despite a novel placebo method of impeded electrical current to the skin was employed in this study, tactile sensations over the site of electrode placement were still experienced. It is possible that when one is focused on a certain body area, one could become aware of spontaneous activity of motorneurons or peripheral sensory afferents (Hagbarth and Valbo, 1967). Furthermore, there is evidence to suggest that complex medical interventions or medical devices have high placebo effects (Paterson et al, 2005). The intervention procedures in this study required complex setup and frequent subject–practitioner contacts; therefore, the subjects in the placebo group may have a high expectation that contributed to the slight distinct sensations experienced.

Previous studies have demonstrated that 30-minute of TENS to Hegu (LI4) and Sanyinjao (Sp6) significantly reduced pain during the first stage of labour and such pain relief was associated with decreased sympathetic tone (Chao et al, 2007). The reduction of sympathetic discharge associated with TENS was proposed to be through the release of opioid peptides in the central nervous system (Han et al, 2004; Chao et al 2007). On the contrary, this present study demonstrated an increase in sympathetic discharge when Acu-TENS was applied to LI4 and LI11. It may be possible that Acu-TENS has a bidirectional effect when acupuncture points are stimulated;

acupuncture was shown to be able to raise blood pressure in haemorrhagic patients with low blood pressure (Syuu et al, 2003) and yet able to lower blood pressure in patients with hypertension (Macklin et al, 2006; Yin et al, 2007); as the subjects in the present study were healthy individuals, they did not require modulation of the parasympathetic tone to induce a calming effect. Another explanation for the increase in sympathetic activities induced is that, as Hegu (LI4) and Quichi (LI11) are located in the Large Intestine meridian—believed to be the sympathetic division of the ANS (Delius et al, 1972), it is possible that stimulation of the acupuncture points on the *yang* meridian will increase the sympathetic discharge. Furthermore, it was previously reported that naturally occurring sympathetic action potentials occur in bursts trains (Delius et al, 1972). A burst mode TENS with the intensity at the maximal tolerable level was used in this current study; this may have facilitated sympathetic discharge. This may also explain why when TENS was applied to non-acupuncture points, an increase in sympathetic activities was also demonstrated although to a much lesser extent when compared with Acu-TENS.

6.6 Limitations of the study

One limitation is the small sample size in the present study; however, data from the present study have produced a satisfactory medium effect size and thus the findings are considered to be valid.

If stimulation were applied to bilateral Hegu (LI4) and Quichi (LI11), the acupuncture point stimulation effect could be stronger. However, it is important to prevent occlusion of the circulation to the left forearm by the blood pressure cuff, especially during the inflation phase, as it may consequently perturb the fidelity of the Acu-TENS effects on the acupuncture points.

Lastly, direct measurement of sympathetic activities such as muscle sympathetic activity and evaluation of the plasma catecholamine level (Mark et al, 1985) could help to provide more concrete evidence to demonstrate the association between Acu-TENS and sympathetic outflow.

6.7 Conclusions

This is the first study to investigate the relationship between acupuncture point sensations and Acu-TENS. This study showed that acupuncture point sensations were experienced during Acu-TENS to Hegu (LI4) and Quichi (LI11); however, as the intensity of the sensations was not correlated with the physiological responses induced, it was concluded that acupuncture point sensations are not associated with the physiological responses evoked during Acu-TENS.

CHAPTER 7

Acu-TENS - acupuncture point sensations and ANS changes in patients with COPD – a case study

7.1 Introduction

The previous two chapters described the relationship between acupuncture and Acu-TENS with *deqi* sensation, changes in cardiovascular physiological parameters and modulation of ANS activities. As reported in the last chapter, Acu-TENS to Hegu (LI4) and Quichi (LI11) is associated with an increase in sympathetic discharge; it is therefore hypothesized that Acu-TENS may have an effect on the ANS similar to "sympathomimetic" drugs that relieve dyspnoea, and if so, Acu-TENS to Hegu (LI4) and Quichi (LI11) could potentially relieve dyspnoea in patients with COPD. There is already evidence which supports that application of Acu-TENS to Dingchuan (EX-B1) in patients with COPD improves FEV_1 and reduces dyspnoea (Lau and Jones 2008, Ngai et al 2010); and that application of Acu-TENS simultaneously to EX-B1 and Lieque (LU7) reduces decline of FEV_1 following exercise training in patients with asthma (Ngai et al, 2009). However, unlike LI4 and LI11, EX-B1 and LU7 are acupoints recognized in TCM as "specific" points for management of shortness of breath. Furthermore, in these previous studies, the relationship between Acu-TENS and *deqi* sensation or the role of Acu-TENS in modulation of ANS activities have not been investigated.

It is a known fact that COPD is a leading cause of morbidity and mortality, and this condition remains a major public health problem globally (Murray et al, 1997). In Hong Kong, the prevalence of COPD is high and about 10% of older population is diagnosed with COPD (Woo et al, 1997). With dyspnoea being the major debilitating symptom that affects patients with COPD (Parshall et al, 2012), further investigation of the role of Acu-TENS, a non-invasive modality, and its associated mechanism on dyspnoea management is warranted.

The characteristic pathological changes associated with COPD result from permanent structural damages to the airways, lung parenchyma and pulmonary vasculature (Hogg, 2004). Patients with a pattern of parenchymal destruction leading to airflow limitation and decreased efficiency in gas exchange are classified as emphysema (GOLD, 2014). Structural changes in the pulmonary system can also result from chronic asthma, a condition where airflow limitation is the main presentation. Adults with asthma were found to have a 12-fold higher risk of acquiring COPD (Silva et al, 2004). Often COPD patients exhibit a mixture of pathological pulmonary changes associated with both emphysema and asthma (Jeffery 1998). Those with pathology mainly associated with airway and alveolar destruction are classified as "emphysema predominant" COPD and those with pathological airway narrowing and diffuse wheeze are classified as "asthma predominant" COPD.

While previous studies have shown that Acu-TENS improved FEV_1 in patients with chronic respiratory conditions, the degree of improvement however varied between patients with asthma and those with COPD. A study by Lau and Jones (2008) showed that FEV_1 improved by 10.5% after Acu-TENS to EX-B1 in patients with Stage I and II COPD; and similar to Lau & Jones' findings, Ngai et al (2010) demonstrated an 8.2% increase in FEV_1 after 45-minute Acu-TENS to EX-B1 in patients with severe COPD. Though statistically significant, the change in FEV_1 in patients with asthma after Acu-TENS was however only 1.3% (Ngai et al 2009). Such differences could be due to the different pathology involved in the patients. The distinctive role of Acu-TENS in patients with emphysema or asthma should be further explored.

As illustrated above, previous clinical studies demonstrated Acu-TENS was able to reduce dyspnoea in patients with COPD, but only the use of acupoints Dingchuan (EX-B1) and Lique (LU7) were reported; these studies however did not investigate whether *deqi* or acupoints sensations are associated with Acu-TENS. On the other hand, the previous work described in this thesis, has shown that Acu-TENS to Hegu (LI4) and Quichi (LI11) induced significant sympathetic modulation in subjects with normal health; it is therefore possible that LI4 and LI11, other than Dingchuan (EX-B1) and Lieque (LU7), can also reduce dyspnoea with concomitant increase in FEV_1 in patients with chronic respiratory illness, and furthermore, may possibly induce associated acupoints sensation. It was therefore decided a snapshot of the effect of Acu-TENS over LI4 and LI11 on FEV_1, *deqi* (acupoint sensation) and autonomic nervous system activity modulation, employed in a patient with COPD, may provide some information or insight to future studies on the role of Acu-TENS and its associated mechanism, in the management of patients with COPD .

7.2 Methodology

7.2.1 Patients selection

This study adopted a single-case study design. At the Physiotherapy Department of Queen Elizabeth Hospital where this study was conducted, patients diagnosed with COPD were identified as COPD with “emphysema predominant” or with “asthma predominant”. Emphysema predominant was confirmed by high-resolution commuted tomography (HRCT) scan and single-breath diffusing capacity of the lung for carbon monoxide (DLCO). Asthma predominant was diagnosed if the patient has diffuse wheezing over both lungs and with an increase in FEV_1 of at least 12% and 200 mL in absolute term after the administration of bronchodilator (Brusasco et al, 2005).

Two patients attending follow up at the respiratory clinic that satisfied the following criteria were invited to participate in the case study: 1) with diagnosis as COPD with predominant emphysema (or COPD with predominant asthma); 2) COPD of stage III or IV according to the GOLD Classification (GOLD, 2013); 3) naïve to Acu-TENS; and 4) able to understand, speak and read Cantonese. Patients were not considered for invitation if they were: 1) on medications including vasodilators, angiotensin-converting enzymes inhibitors and anti-hypertensive agents; 2) with cardiovascular, musculoskeletal, endocrine and neurological disorders. The two selected patients were explained the nature of the case study and a signed consent form for participation in the study (Appendix 20) was obtained prior to data collection.

7.2.2 Experimental procedures

The two selected patients were required to attend the Physiotherapy Department at Queen Elizabeth Hospital three times but on different days, so they did not meet each other. Both patients were asked to refrain from caffeine drink, smoking or strenuous physical activities on the day of the visit. Treatment with aminophylline, inhaled β_2-agoinst and steroid, medications was also discontinued for 24 hour before the visit (Volterrani et al, 1994). All measurements were taken on the day of the visit at between 4 o'clock to 6 o'clock in the afternoon so as to minimize the circadian effect on the ANS. Each visit was two weeks apart (wash-out period). The assessments for all visits were identical. Acu-TENS to LI4 and LI11 for 45 minutes was performed at the second visit. Hence, these subjects served as their own control and any changes of the outcome measures would most likely be due to the intervention with Acu-TENS.

At the first visit, demographic data including gender, age, medical history, smoking history and exercise habit were recorded. Systolic and diastolic blood pressures were taken on the left arm by a digital patient monitor (Mindray PM-8000 Express Patient Monitor, Bio-Medical Electricity, Hamburg, Germany). The mean arterial pressure (MAP) was recorded. Electrocardiogram (ECG) electrodes were placed over left and right clavicles and left upper quadrant of abdomen and then connected to the digital patient monitor device. HR was continuously monitored. The ECG signals were analysed by Chart™5 Pro for Windows. MAP, HR and heart rate variability (HRV) parameters were measured at rest as baseline and then every 5 min for 50 min.

Body mass index (BMI) was then obtained with the ratio of body mass in kilogram (kg) to the square of body height in meter (m) (http://www.nhlbi.nih.gov/guidelines/obesity/BMI/bmicalc.htm). After that, forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were measured using a spirometer (SpiroLab III, MIR, Roma, Italy) in the standardized procedure (Miller et al, 2005). Next, the level of dyspnoea was measured using the Medical Research Council (MRC) scale described in Chapter 3. Then, the patients were requested to perform a 6-minute walk test (6MWT) according to the recommendation from the ATS (American Thoracic Society, 2002). The distance completed in the 6 minutes (6MWD) was recorded. Lastly, the patient was also asked to complete the Hong Kong Chinese version of the St. George's Respiratory Questionnaire (SGRQ-HK) (Yu et al, 2004) for assessment of their quality of life.

At the second visit, all procedures were the same as the first visit except that after the baseline measurement of MAP, HR and HRV, Acu-TENS (detailed

parameters described under Section 7.3.8 below) was applied to right Hegu (LI4) and Quichi (LI11) for 45 mins. MAP, HR and HRV parameters were measured continuously every 5 min for the 45 min. After the intervention, MAP, HR and HRV were measured again at the 5th minute post intervention. Immediately after the stimulation, the patients were requested to perform the pulmonary function test and they were also asked to complete the Hong Kong Chinese version of the Modified Massachusetts General Hospital Acupuncture Sensation Scale (C-MMASS) (Yu et al, 2012) for quantification of the acupoint sensations during the electrical stimulation.

At the third visit, the assessment procedures were again exactly the same as the first one. The whole experimental procedures is summarized and displayed in Figure 7.1.

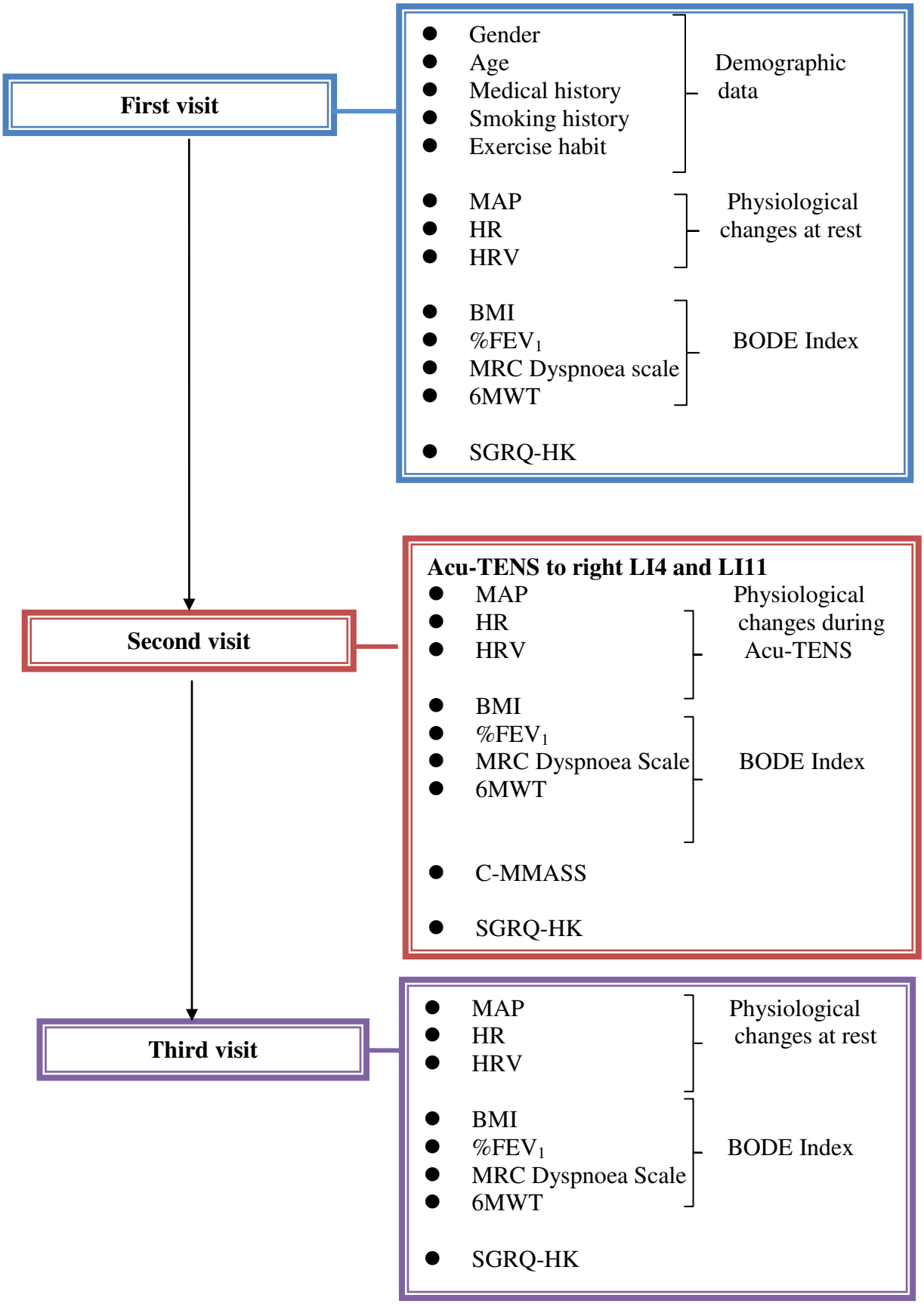


Figure 7.1 Measurements taken from the two patients during their three visits

7.3 Measurements

7.3.1 Mean arterial pressure and heart rate

Systolic (SBP) and diastolic blood pressure (DBP) were recorded every 5 minutes for 50 minutes using a digital blood pressure monitor (Mindray PM-8000 Express Patient Monitor, Bio-Medical Electricity, Hamburg, Germany). The mean arterial blood pressure (MAP) was computed by using the formula DBP + (SBP – DBP)/3.

The HR and the ECG signals were recorded continuously. The ECG signals were transferred to the PowerLab 16/30 (**ADI**nstruments Pty Ltd., New South Wales, Australia) for data acquisition and analysis of the HRV.

7.3.2 Heart rate variability (HRV)

The HRV was analyzed in accordance with the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Agelink et al, 2001). For frequency domain analysis, power spectral analysis was performed by the Fast Fourier Transformation technique. Individual RR intervals were transformed into bands of different frequency ranging from 0 to 0.5Hz. Low frequency (LF) is defined as the power between 0.03 to 0.15Hz (mainly represents sympathetic modulation). High frequency (HF) is defined as the power between 0.15 to 0.5Hz, (regarded as an index of vagal /parasympathetic modulation). The LF/HF ratio reflects the global sympatho-vagal balance of the body (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996;

Agelink et al, 2001). A higher LF/HF ratio reflects domination of the sympathetic system, while lower ratio values reflect dominance of the parasympathetic system. As for time domain analysis, the standard deviation of the NN interval (SDNN) was recorded as the global index of the HRV (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Sztajel, 2004). During measurement of HRV, the patient was instructed to relax and breathe normally, in order to minimize any respiratory effects on HRV indices (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Kleiger et al, 2005).

7.3.3 Pulmonary function test

Pulmonary function test was performed using a spirometer (SpiroLab III, MIR, Roma, Italy) at every visit. At the second visit, pulmonary function test was performed immediately after 45-minute Acu-TENS. The reliability of the spirometer was established with a 3-L syringe before data collection. The FVC and FEV_1 were obtained from the display of the spirometer. The percentage of predicted FEV_1 (%FEV_1) was obtained from the recorded FEV_1 divided by the FEV_1 of the published norm, with reference to the patient's gender, age and height (Ip et al, 2006).

7.3.4 Measurement of dyspnoea

The Modified Medical Research Council Scale (Appendix 3) was used to measure the level of dyspnoea. This is a 5-point scale based on the sensation of breathing difficulty experienced by the patient during daily life activities and it allows the patients to indicate the extent to which their breathlessness affects their mobility (Bestall et al, 1999).

7.3.5 Six-minute walk test

The 6MWT was conducted on the basis of the greatest distance covered by the patients in 6 minutes. Patients were allowed to rest during the 6 minutes, if necessary (ATS, 2002). Each subject was allowed to perform the test twice to obtain the best result. The first and second trials were 15 minutes apart so that subjects would have enough rest before attempting the second trial. During the test, a stopwatch was used for timing and an oximeter (Nonin 3100 WristOx, Minnesota, USA) for oxygen saturation (SpO2) and pulse rate measurements. In addition, the rate of perceived dyspnoea using the Modified Borg Scale (Appendix 5) was also measured at the end of the 6MWT (ATS, 2002)

7.3.6 Quantification of acupoint sensations

The C-MMASS is valid and reliable tool to quantify acupoint sensations or *deqi* (Chapter 4). After the patient completed the C-MMASS, the C-MMASS Index was then calculated.

7.3.7 Assessment of health-related quality of life

The Hong Kong Chinese version of the SGRQ (Yu et al, 2004) (Appendix 8) was used to assess the psychosocial health of these two patients. The SGRQ-HK consists of 50 items accessing three components: “Symptoms”, “Activity” and “Impact”. A “Total” score is also formulated. The scores range from 0 to 100. The lower the “Total” and or component scores, the better the quality of life being represented (Yu et al, 2004). A change in “Total” score of four units is consistent with a clinically significant change in quality of life of the patient (Jones, 2005)

7.3.8 Points location and preparation

All interventions were conducted in the sitting position. The locations of the right Hegu (LI4) and Quichi (LI11) for stimulation were identified by the investigator. Hegu (LI4) and Quichi (LI11) were located as described in Chapter 4, section 4.2.2.2, page 49 of this thesis. Preparation of the acupoints was similar to that reported in Chapter 4. Two self-adhesive ECG electrodes (F-601 SKINTACT®) were then placed over the acupoints and attached to a dual channel portable TENS unit (120z Dual Channel TENS, EMS Physio Ltd, Oxfordshire, England). The pulse frequency and pulse width of the TENS were set at 2Hz and 200μs respectively with the intensity set at subject's maximum tolerable level without discomfort and short of muscle contraction. Total duration of stimulation was 45 minutes (Ngai et al, 2010; Ngai et al, 2011; Chan et al, 2012).

7.4 Data Analysis

The MAP, HR, LF/HF ratio and SDNN recorded at every 5-minute for the 45 minutes (with or without intervention), for each of these two patients during the three visits were plotted for visual analysis of level and trend (Wolery and Ezell, 1993).

7.5 Results

7.5.1 Patient characteristics

Patient A, diagnosed with "COPD predominant with emphysema", was a 67-year old man and was an ex-smoker. He had quitted smoking for more than 10 years; was a retired accountant and living with his wife. Emphysema predominant was confirmed by high-resolution commuted tomography (HRCT) scan and the DLCO value of this

patient was 13.47ml/min/mmHg (55% predicted). He had a history of repeated admissions (3 times between June 2012 to June 2013) due to acute exacerbation of COPD. Chest X-ray showed lung hyperinflated chest with normal heart size. FEV_1 measured was 0.95L which was 38% of the predicted value. The FEV_1 improved from 0.95L to 1L after administration of bronchodilator. Arterial blood gas revealed a normal PaO_2 and $PaCO_2$ (pH 7.4; PO_2 11kPa; PCO_2 5.6kPa; $HCO3^-$ 24 mEq/L; BE 1; SaO_2 96%) at rest on room air and did not require supplemental oxygen at rest. He complained of shortness of breath when performing level ground walking and could only manage one city-block for about 5 minutes and required frequent rests. This patient occasionally required assistance during bathing.

Patient B, diagnosed with "COPD predominant with asthma", was a of 65 years old man, an ex-smoker for more than 5 years and a retired salesman. He had regular follow-up at the Specialist Out-patient of the regional hospital without hospital admission record. Clinically, the patient presented with nocturnal cough, shortness of breath on exertion (mainly chest tightness) and audible wheeze on forceful expiration and prolonged expiratory phase. On auscultation, there was diffuse wheeze all over the lung fields. The FEV_1 measured was 1.1L which was 43% of the predicted value. Pulmonary function test showed reversibility element as there was 12% improvement in FEV_1 following administration of salbutamol (improve from 1.1L to 1.23L after the administration of bronchodilator). Chest X-ray showed slight lung hyperinflation with normal heart size. Arterial blood gas revealed normal PaO_2 and $PaCO_2$ at rest on room air (pH 7.43; PO2 13kPa; PCO2 5.1kPa; HCO3- 22 mEq/L; BE 1; SaO2 97%). This patient did not require supplemental oxygen. This patient claimed that the asthmatic symptoms were well controlled by inhaled corticosteroid together with long and short acting β_2-agoinsts. The patient mainly complained of shortness of breath when

performing strenuous activities such as brisk walking or climbing uphill. He was able to manage all activities of daily living independently.

7.5.2 BODE Index, BMI, dyspnoea score, FEV_1 and 6MWD over the 3 visits

There was no change in the BODE index for both patients (Table 7.1). Sub-analysis of the BODE index parameters revealed that the BMI score was also stable for both patients over the 3 visits (Figure 7.2). While there was no change in the MMRC dyspnoea score for Patient A (COPD with predominant emphysema), the MMRC score for Patient B reduced from "2" recorded in the 1st visit to "1" in the 2nd and 3rd visit.

Table 7.1 BODE Index recorded at the three visits for Patients A (COPD with predominant emphysema) and Patient B (COPD with predominant asthma)

	Patient A (COPD with predominant emphysema)			**Patient B (COPD with predominant asthma)**		
	1st visit	**2nd visit**	**3rd visit**	**1st visit**	**2nd visit**	**3rd visit**
BMI (kg/m^2)	20.83	20.83	20.83	19.29	19.29	19.29
%FEV_1	38	40	39	43	47	44
MMRC Scale	3	3	3	2	1	1
6MWD (m)	253	279	256	368	420	393
BODE Index	6	6	6	4	4	4

BMI: Body mass index; % FEV_1: Percentage of predicted forced expiratory volume in one second; MMRC: Modified Medical Research Council; 6MWD: Six-minute walk test distance covered

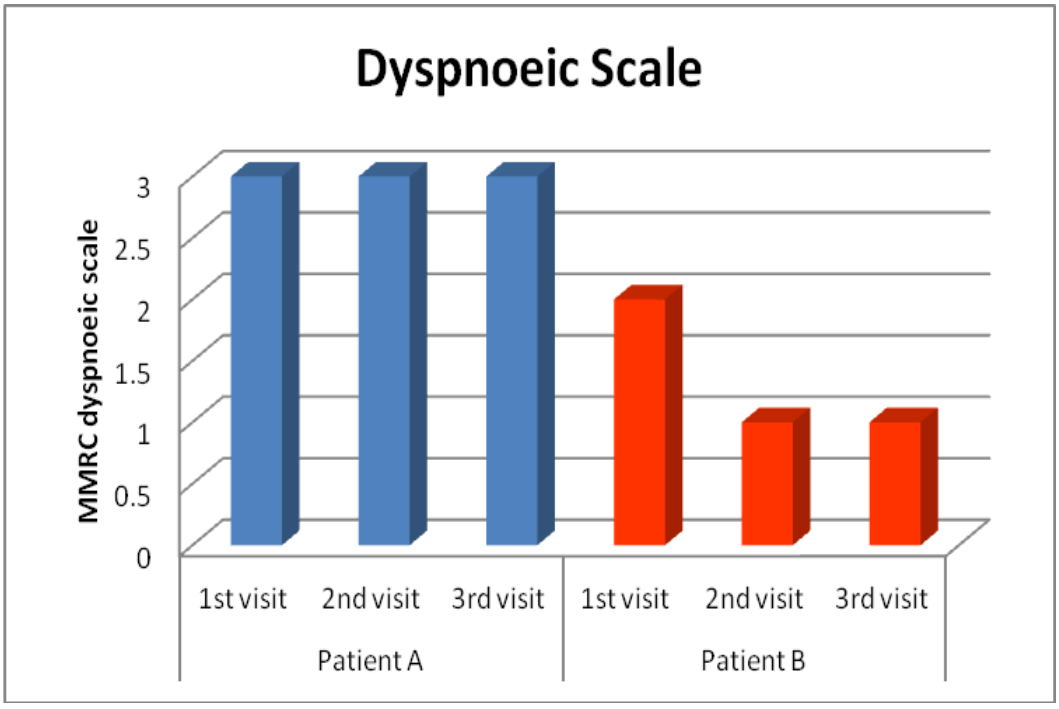


Figure 7.2 MMRC dyspnoeic scale of the two patients at the three visits

Patient A: Patient diagnosed with COPD predominant with emphysema
Patient B: Patient diagnosed with COPD predominant with asthma
MMRC: Modified Medical Research Council

Compared to baseline measurement at the first visit, the % predicted FEV_1 increased by 5.3% after Acu-TENS (2^{nd} visit) (FEV_1 increased from 0.95L to 1.0L) in Patient A, and maintained slightly increased by 2.6% at the 3^{rd} visit (Figure 7.3) (FEV_1 = 0.97L). In patient B, the % predicted FEV_1 increased by 9.3% after Acu-TENS (2^{nd} visit) (FEV_1 increased from 1.1L 1.2L) and increased by 2.3% (1.13L) at the 3^{rd} visit (Figure 7.3).

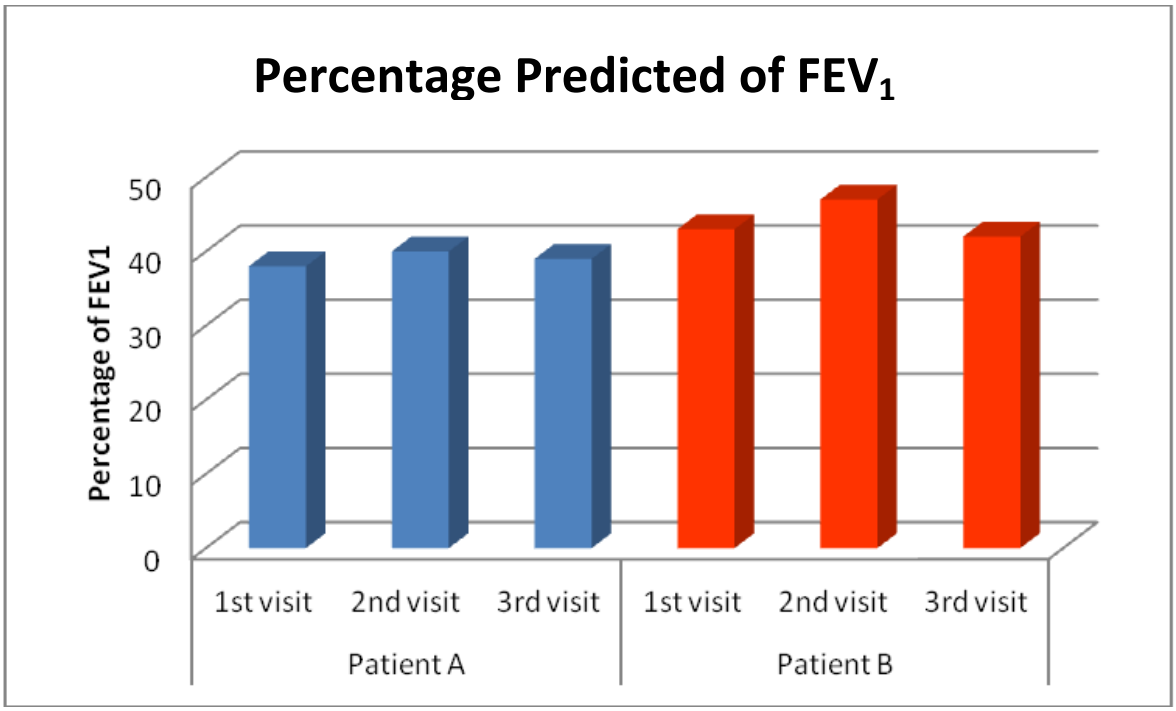


Figure 7.3 % predicted FEV_1 measured at the 3 visits in both patients

Patient A: Patient diagnosed with COPD predominant with emphysema
Patient B: Patient diagnosed with COPD predominant with asthma

Both patients showed improvement in the 6MWD in the 2nd (after Acu-TENS) and 3rd visit. The improvement was 10.3% after Acu-TENS and maintained increased by 1.1% at the 3rd visit in Patient A. In Patient B, the 6MWD improved by 14.1% and 6.8% at the 2nd and the 3rd visit respectively (Figure 7.4). There were no significant changes in SpO_2, and for both patients, the RPD score after the 6MWT was lower after Acu-TENS (Table 7.2).

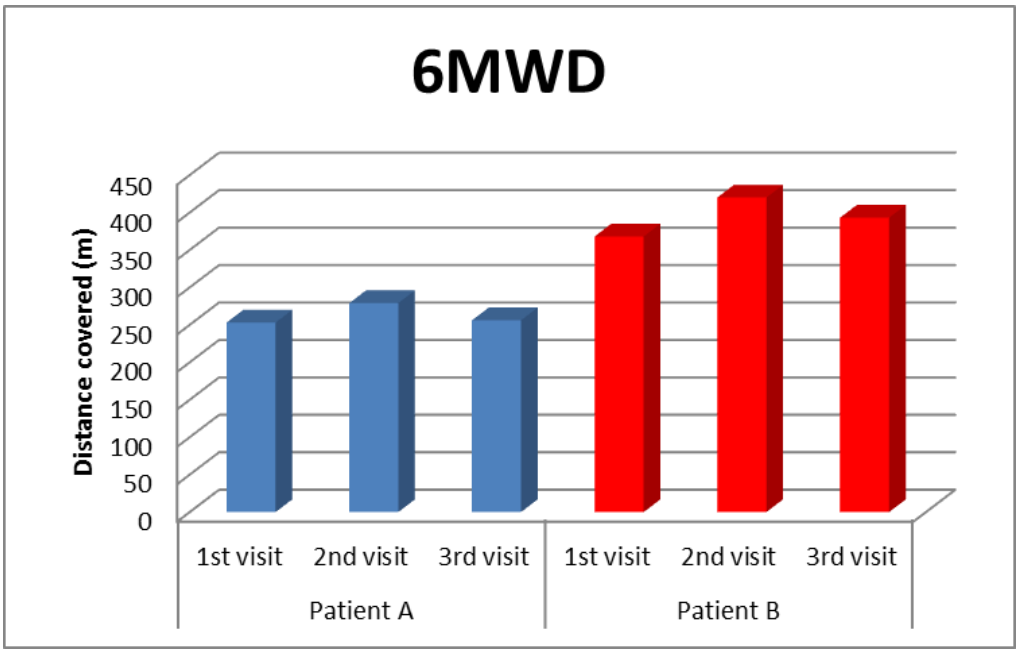


Figure 7.4 6MWD recorded for both patients at the three visits

Patient A: Patient diagnosed with COPD predominant with emphysema
Patient B: Patient diagnosed with COPD predominant with asthma

Table 7.2 Rate of perceived dyspnoea (RPD) and oxygen saturation (SpO_2) at the end of 6MWD at the three visits for Patient A (COPD with predominant emphysema) and Patient B (COPD with predominant asthma)

	Patient A (COPD with predominant emphysema)			**Patient B (COPD with predominant asthma)**		
	1st visit	**2nd visit**	**3rd visit**	**1st visit**	**2nd visit**	**3rd visit**
RPD (0-10)	6	5	6	4	2	3
SpO_2 (%)	92	92	92	94	93	93

RPE: Rate of perceived exertion; SpO_2: Oxygen saturation

7.5.3 Changes in SGRQ-HK scores

There were only minimal changes of the "Symptoms", "Activities" and "Impact" subscale of the SGRQ-HK score over the 3 visits in both patients. For Patient A, the differences in scores between the 1st visit and the 2nd visit and between the 1st visit and the 3rd visit ranged from -1.13 to 1.77; the "Total" score decreased by 0.55 unit at the 2nd visit and 0.6 unit at the 3rd visit. In Patient B, the differences in the scores were slightly more, and ranged between -0.42 to 0.17 unit; the "Total" score decreased by 0.41 unit at the 2nd visit and 0.34 unit at the 3rd visit.

Since there were less than 4 units in variation of the "Total" score for both patients, it was considered that there was no change in health-related quality of life in either patient throughout the visits (Table 7.3, Figure 7.5).

Table 7.3 Changes in SGRQ-HK scores at the three visits for Patients A and B

	Patient A (COPD predominant with emphysema)			**Patient B (COPD predominant with asthma)**		
	1st visit	**2nd visit**	**3rd visit**	**1st visit**	**2nd visit**	**3rd visit**
Symptoms	57.39	56.26	56.83	59.25	58.95	59.42
Activities	84.12	84.63	83.29	12.4	12.4	12.2
Impact	23.37	23.40	25.14	8.96	8.62	8.54
Total	48.16	47.61	47.56	19.79	19.38	19.45

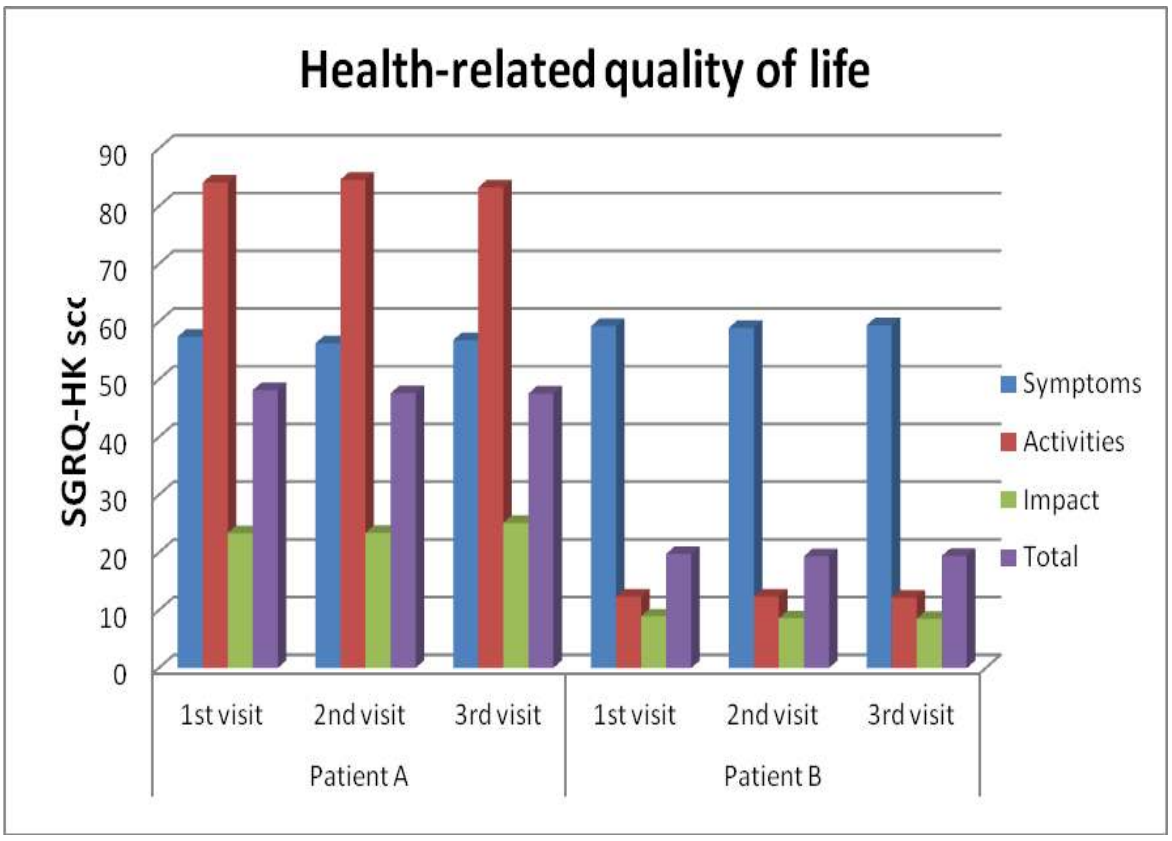
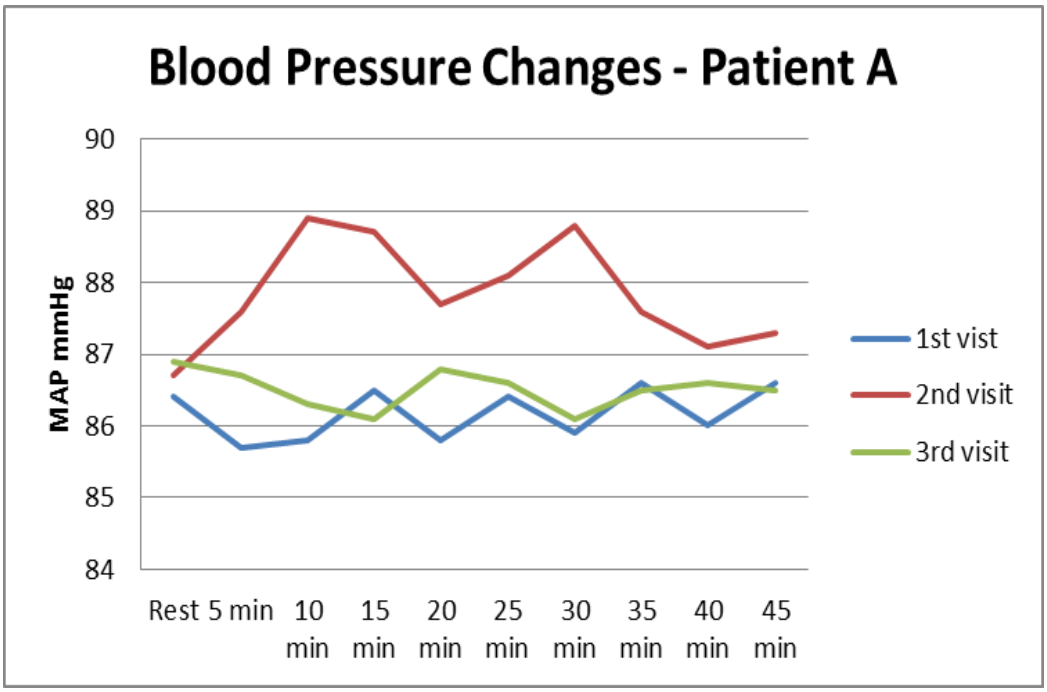


Figure 7.5 Changes in SGRQ-HK scores for Patients A and B at the three visits

SGRQ-HK: Hong Kong Chinese version of the St. George's Respiratory Questionnaire
Patient A: Patient diagnosed with COPD predominant with emphysema
Patient B: Patient diagnosed with COPD predominant with asthma

7.5.4 Blood pressure and heart rate changes recorded at the three visits

The pattern of change in MAP and HR recorded in both patients were similar. Both MAP and HR recorded during the first and third visits were stable throughout the measurement periods but appeared to be higher during the 45-minute Acu-TENS intervention at the second visit (Figures 7.6 and 7.7).



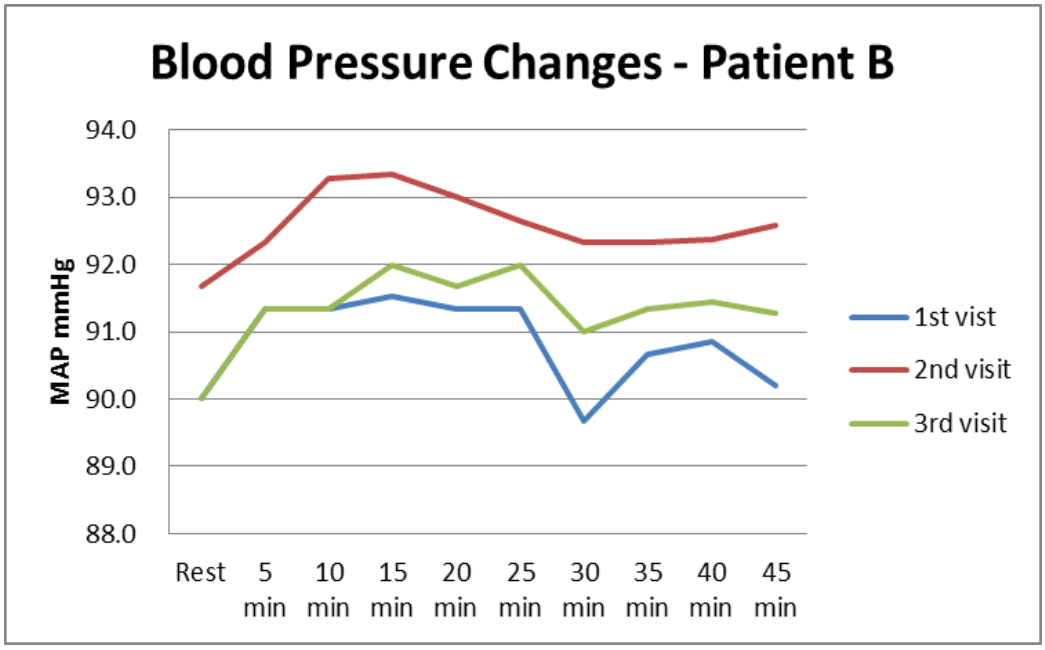
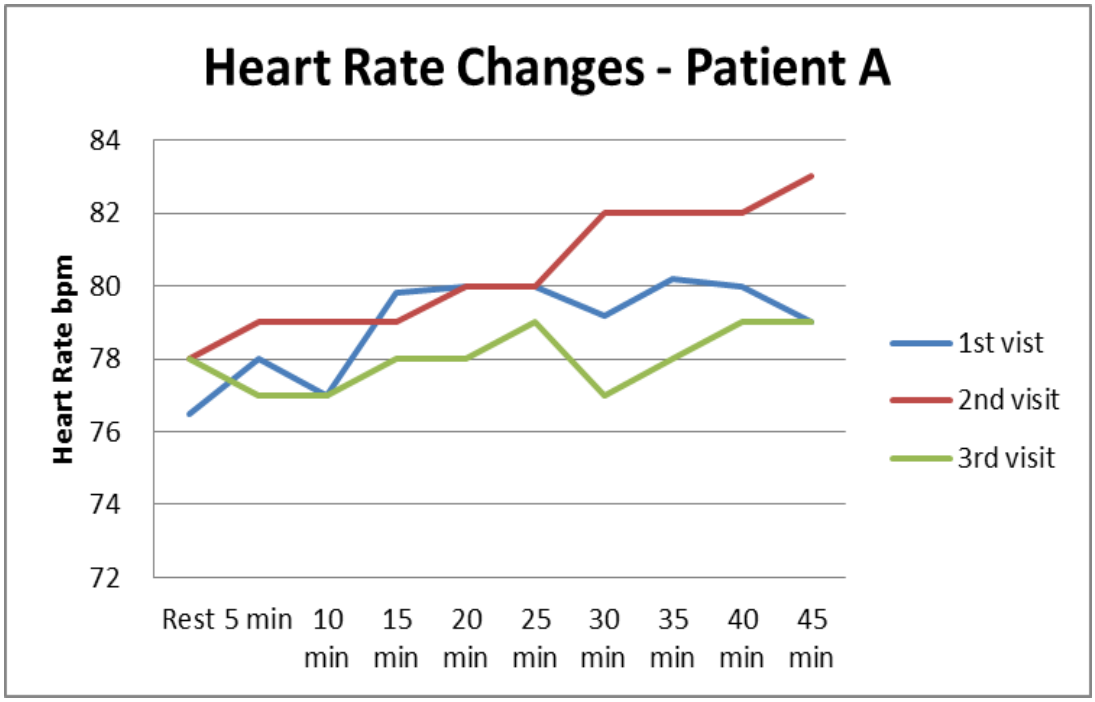


Figure 7.6 Blood pressure changes at various measurement points for both patients

Patient A: Patient diagnosed with COPD predominant with emphysema
Patient B: Patient diagnosed with COPD predominant with asthma
MAP: Mean arterial blood pressure



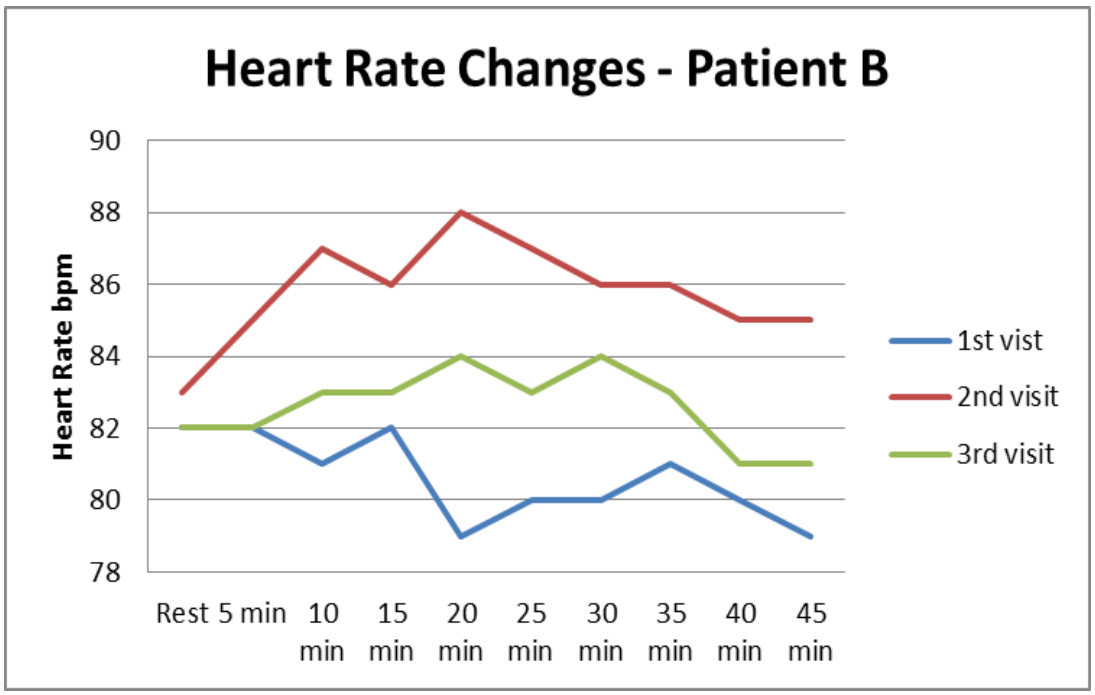
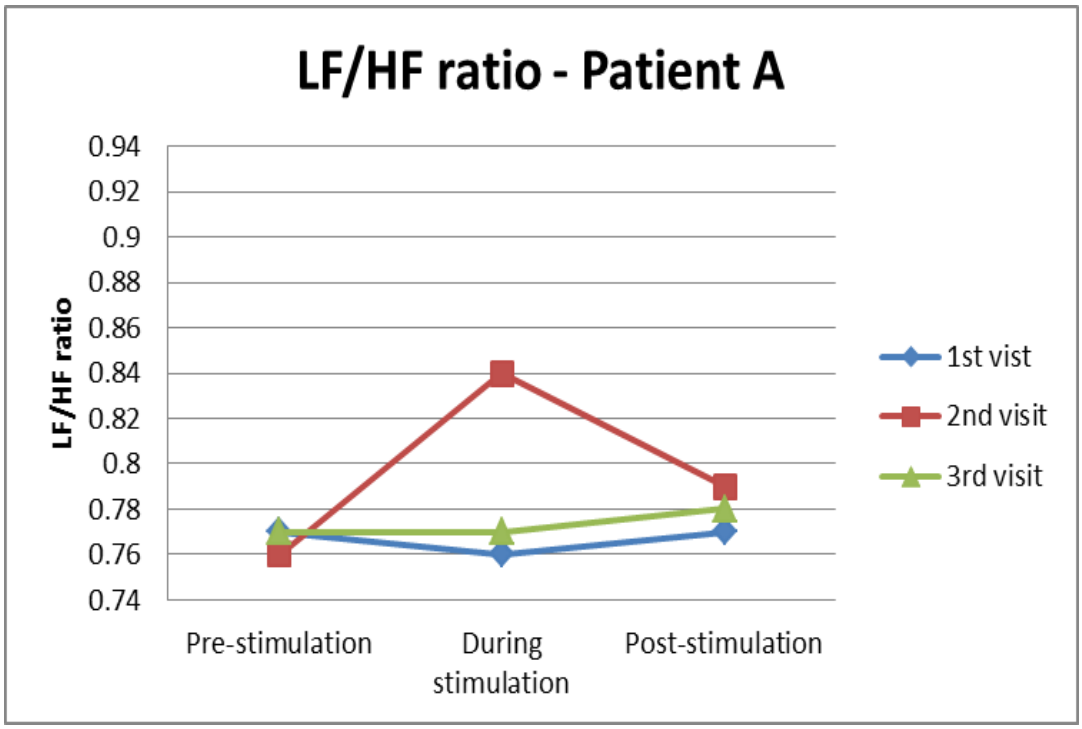


Figure 7.7 Heart rate changes at various measurement points for both patients

Patient A: Patient diagnosed with COPD predominant with emphysema
Patient B: Patient diagnosed with COPD predominant with asthma

7.5.5 Changes in Heart rate variability at the three visits

The LF/HF ratio for both patients increased during Acu-TENS and remained higher than baseline at the end of stimulation. The percentage increase during Acu-TENS was 10.5% in Patient A and 8.2% in Patient B. At the end of Acu-TENS, the LF/HF ratio remained 3.9% higher than baseline in Patient A and 3.5% in Patient B. Similarly SDNN increased by 11.6% in Patient A and 8.8% in Patient B during Acu-TENS, and remained higher than baseline by 6.1% in Patient A and 1.9% in Patient B after the stimulation (Figures 7.8, 7.9).



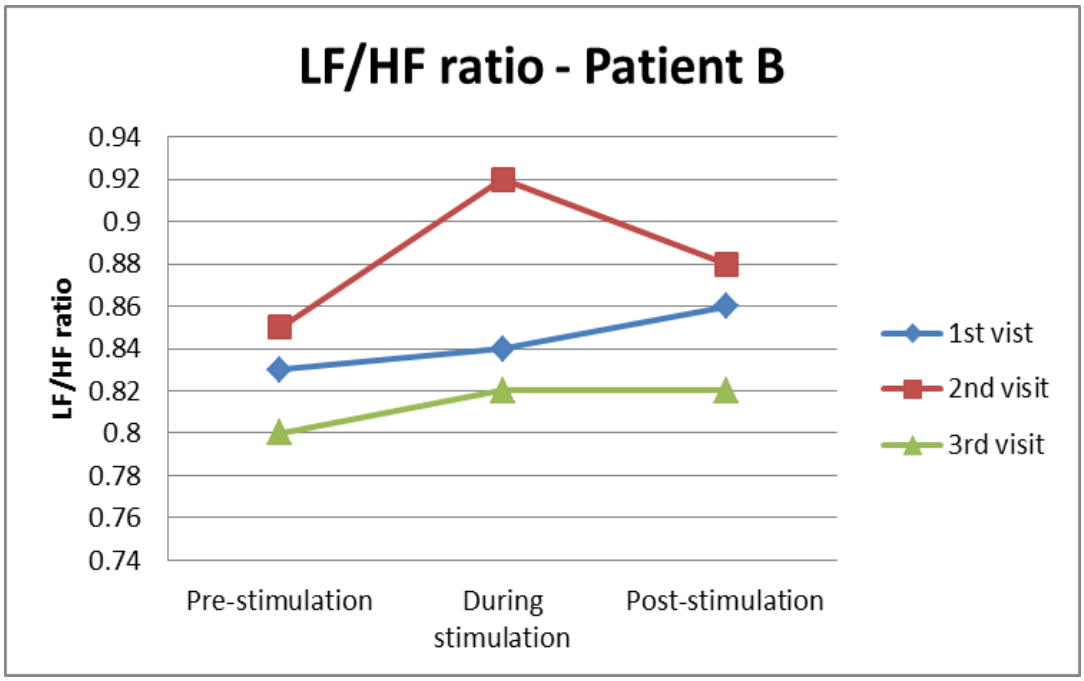
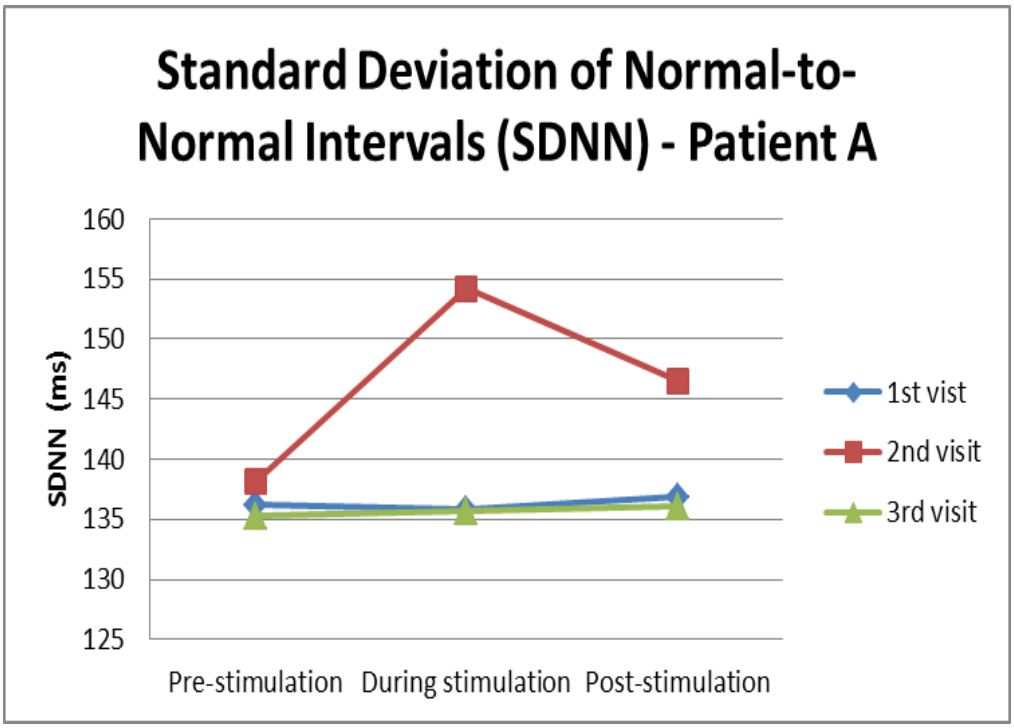


Figure 7.8 Changes in LF/HF ratio at various measurement points for both patients

Patient A: Patient diagnosed with COPD predominant with emphysema
Patient B: Patient diagnosed with COPD predominant with asthma
HF: High frequency LF: Low frequency



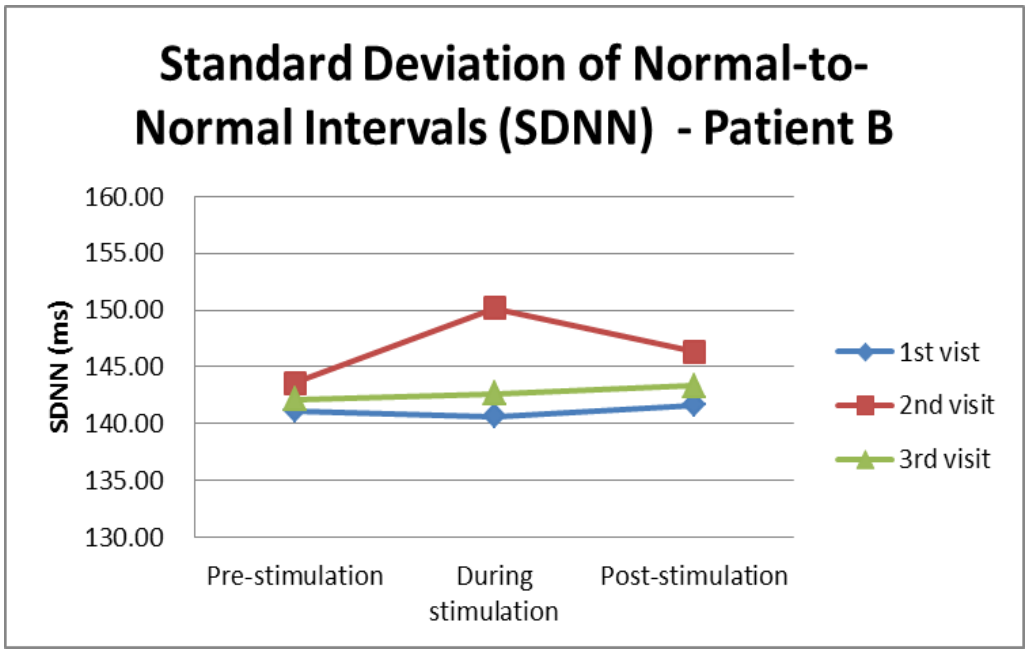


Figure 7.9 Changes in SDNN at various measurement points for both patients

Patient A: Patient diagnosed with COPD predominant with emphysema
Patient B: Patient diagnosed with COPD predominant with asthma
HF: High frrequency LF: Low frequency

7.5.6 Acupoint sensations during Acu-TENS

Figure 7.10 shows the acupoint sensations perceived by Patient A and Patient B during Acu-TENS to LI4 and LI11. Patient A experienced stronger tingling, throbbing and numbness sensations during Acu-TENS. While Patient B experienced stronger sesnsations on aching, throbbing and numbness during the intervention. The C-MMASS index score for Patient A was 3.34 and 3.59 for Patient B.

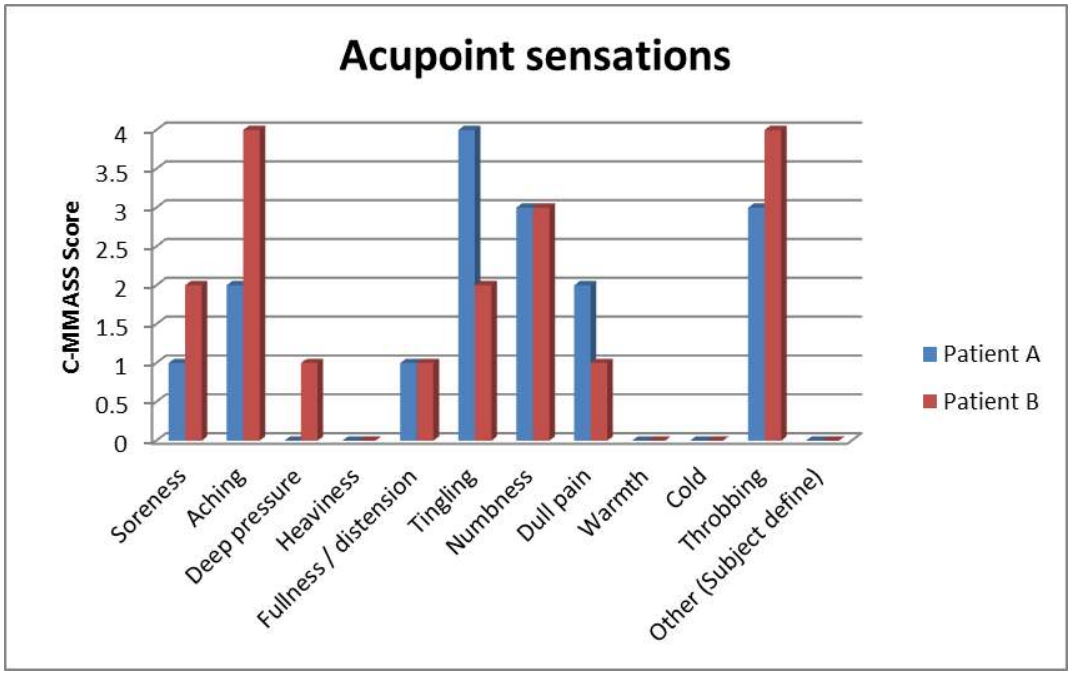


Figure 7.10 C-MMASS index score reported by both patients

C-MMASS = Modified Massachusetts General Hospital Acupuncture Sensation Scale Chinese version
Patient A: Patient diagnosed with COPD predominant with emphysema
Patient B: Patient diagnosed with COPD predominant with asthma

7.6 Discussion

The aim of this case study was an attempt to detect some initial indications on the effect of Acu-TENS on Hegu (LI4) and Quichi (LI11) on two patients with COPD, one predominent with emphysema and one with asthma. It appeared that 45 minutes of Acu-TENS to patients with COPD could result in an immediate increase in sympathetic discharge as reflected by increased LF/HF ratio and SDNN, irrespective of whether the patient's condidtion was predominant with asthma or with emphysema. This case study also suggests that Acu-TENS to LI4 and LI11 could associate with an increase in FEV_1 as well as improve 6MWD. Furthermore, similar to the findings presented in Chapter 6, both patients experienced distinct acupuncture point sensations during Acu-TENS.

7.6.1 Changes in FEV_1 associated with Acu-TENS

This case study showed that 45 min of Acu-TENS improved FEV_1 by 5.3% in the patient with predominant emphysema, this is much less than the 10.5% increase demonstrated by Lau and Jones (2008) and 8.2% increase demonstrated by Ngai et al 2010. The percentage increase in FEV_1 was over 9% in the patient predominant with asthma in this case study, this is much more than the 1.3% reported by Ngai et al 2009. Direct comparison of the absolute percentage increase in FEV_1 between studies may not be appropriate; as unlike to previous studies, the acupoints used in this case study were LI4 and LI11, instead of EX-B1 or Lieque (LU7). According to the "*acupuncture point specificity*" theory (Huang w et al, 2011), stimulation of different points could result in different effects. EX-B1 and LU7 are considered to be 'specific' point for strengthening lung *qi* and spleen *qi* and accompanied with bronchodilation effect (Zhao et al, 2002). LI4 and LI11 are however acupoints normally used for

management of pain (Kong et al, 2005) rather than pulmonary diseases. Furthermore, the severity of the pathological conditions could affect the effect of Acu-TENS intervention. In Lau and Jones' study, the subject cohort recruited were Stage I or II COPD patients with the baseline % predicted FEV_1 at 69%. In the present case study, the two patients recruited were with Stage III COPD and baseline $\%FEV_1$ of 38% and 43% respectively. It is probable that the extent of bronchodilation induced by Acu-TENS in severe and very serve patients was less obvious compare to that of mild to moderate COPD patients (Berger and Smith, 1988; Hay et al, 1992). The improvement in clinical outcomes demonstrated in these two patients could possibly be a consequence of bronchodilation through increased sympathetic discharge evoked by Acu-TENS. Although, this is obviously pure speculation as only two patients were involved in this pilot study. Be that as it may, the relationship between Acu-TENS and airway resistance has been reported (Chan et al 2012). Stimulation of β2-adrenergic receptor of the sympathetic nervous system causes relaxation of the airway smooth muscle and resulting in bronchodilation (McCorry, 2007), thus it is probable that the bronchodilation effect observed in this case study was a consequence of the increased sympathetic discharge as reflected by increased LF/HF ratio and SDNN.

7.6.2 Changes in 6MWD associated with Acu-TENS

This case study showed that there is an increase in 6MWD after Acu-TENS in both patients. The minimal clinical significance of 6MWD in COPD patients was reported to be 25 m (Holland et al, 2010). The improvement in the patient with predominant emphysema in this case study was 36 m and that for the patient with predominant asthma was 38 m, thus the improvement in 6MWD associated with

Acu-TENS appeared to be of clinical significance. As Acu-TENS was also shown to be associated with an improvement in FEV_1 in these two patients, it is possible that the improvement of FEV_1 and reduced dyspnoea sensation (reflected by reduced RPD scores after the 6MWT after Acu-TENS) was the reason for improvement in 6MWD.

7.6.3 Changes in BODE index and SGRQ-HK

Although there were improvement in both % predicted FEV_1 and 6MWD in both patients, there were no overall changes in BODE index. For BODE index to change, there needs to be significant improvement in $\%FEV_1$ and 6MWD. For example, the FEV_1 has to increase by approximately 32% or the 6MWD increase by 38% in Patient A in order to decrease one point of the BODE index. Similarly, the $\%FEV_1$ has to increase by 16% so as to effect a change in one BODE index point in Patient B. Hence, such expectation is not expected with one session of Acu-TENS.

Unlike the study conducted by Ngai et al (2010), there was no obvious change in SGRQ-HK scores in both patients. A reduction of SGRQ score of more than 4 points is considered to clinically significant (Jones et al, 2005). In Ngai's study, daily Acu-TENS to EX-B1 for 4 weeks produced a significant improvement in the "Total" score and "Activity" component score of the SGRQ. This is probably because at least 4 weeks of continuous intervention is required for Acu-TENS to exert an adjunctive role and cumulative effect in enhancing the activity level in patients with COPD.

7.6.4 *Deqi* sensation associated with Acu-TENS

In accord with the previous work reported in this theses (Chapter 6), this case study further confirmed that subjects experienced distinct acupoint sensations,

similar to *deqi*, during Acu-TENS to LI4 and LI11. As mentioned in the previous chapter, the intensity of the acupoint sensations was not correlated with the physiological response. The physiological changes such as increase in sympathetic discharge in normal healthy subjects may purely due to electrical stimulation on particular acupuncture point (Yu et al 2013). Whether acupuncture sensation experienced by these two COPD patients during Acu-TENS is necessary for any changes in the ANS remains unknown, as the sample size is too small for this evaluation. Further study with larger sample size is required to confirm such observation.

7.7 Limitations of the study

The results of this pilot case study provides a snapshot of the possible role of Acu-TENS over LI4 and LI11; but as only two patients were involved, and there was no control comparator, no clinical inference nor conclusion can be drawn. Another major limitation is that β-endrophin level was not measured in these two patients, thus it is not known at all whether stimulation of LI4 and LI11 is able to increase β-endrophin level similar to stimulation of EX-B1 or LU7. Although no clinical inference can be drawn from this pilot case study, the preliminary results suggest that further investigation of the role of Acu-TENS over LI4 and LI11, in comparison to stimulation over EX-B1 and LU7, particularly in the area of *deqi* sensation and modulation of ANS activity, is warranted.

7.8 Conclusion

An immediate increase in $\%FEV_1$ and 6MWD after 45 min of Acu-TENS to LI4 and LI11 was demonstrated in in two patients with COPD. These changes appeared to

be associated with an increase in sympathetic discharge as reflected by an observable increase in LF/HF ratio and SDNN in these two patients. Furthermore, these two patients also experienced acupoint sensations that were similar to *deqi* in acupuncture. This case study supports the need for further investigation of the role, and working mechanism of Acu-TENS in management of patients with different respiratory pathology and at different severity level.

CHAPTER 8

General Summary and Conclusion

8.1 Summary of findings

Acupuncture has been used in China for more than 2000 years for restoration of health. Modulation of *qi* flow and regulation of *ying-yang* balance are believed to be successful only if *deqi* sensation is elicited during the acupuncture technique. The first project involved in this thesis reported the need to develop a valid and reliable tool to quantify *deqi* sensations; and subsequently, based on the Massachusetts General Hospital Acupuncture Sensation Scale (MASS), a Chinese version C-MMASS was established. This 12-descriptor C-MMASS was shown to be a valid and reliable to report acupuncture point sensations associated with *deqi* among healthy young Chinese people. This tool was then used in subsequent studies involved in this thesis for quantifying acupuncture point sensations during acupuncture and Acu-TENS.

The concept of *yin and yang* is explained by modulation of the sympathetic and parasympathetic outputs of the ANS in western medicine. Chapter 5 reports that 30-minute acupuncture stimulation to right Hegu (LI4) and Quichi (LI11) was associated with significant increase in heart rate and mean arterial blood pressure in normal healthy subjects; there was also concurrent increase in sympathetic discharge of the ANS as reflected by an increase in the LF/HF ratio during the stimulation. Subjects who received real acupuncture experienced a high intensity of *deqi* sensations. This is the first study that reports the association between *deqi* sensation, changes in cardiovascular parameters and modulation of ANS activities.

Various clinical studies in recent years have demonstrated that Acu-TENS, a non-invasive technique with application of TENS to acupoints, was able to reduce dyspnoea and airway resistance, as well as improve FEV_1 in patients with asthma and COPD. These studies suggested that the effect of Acu-TENS may be similar to

acupuncture, but whether *deqi* was experienced during Acu-TENS was not investigated. The work reported in Chapter 6 suggested that 45-minute Acu-TENS to right Hegu (LI4) and Quichi (LI11) induced a slight but significant increase in heart rate and mean arterial blood pressure during Acu-TENS; and in addition, the LF/HF and the SDNN index also increased significantly, suggesting Acu-TENS to LI4 and LI11 facilitated sympathetic discharge of the ANS in normal healthy subjects. This is the first study to report that acupoints sensations, similar to *deqi,* could also be experienced during Acu-TENS. However, unlike acupuncture, there was low association between acupuncture point sensations intensity and the ANS changes during Acu-TENS.

Both studies described in Chapter 5 and Chapter 6 were young and healthy subjects, it is of note that if older subjects were recruited in the studies, baseline physiological data and HRV index would be rather different from the younger cohort of subjects in these studies. For example the mean blood pressure and resting heart rate in an older population will be higher than younger subjects. In addition, an older subject cohort may have co-morbidities such as arterial hypertension, diabetes, coronary heart disease or arrhythmia. Furthermore, HRV index decreases with age. To eliminate co-morbidities and varied baseline physiological parameters in the subject cohort, thus young subject cohorts with normal health were recruited for the studies described in this thesis.

Chapter 7 provides a snapshot of how the knowledge gained from the work described in this thesis may be applied in the clinical setting. The case study described in Chapter 7 illustrates the possible clinical role of Acu-TENS to unilateral Hegu (LI4) and Quichi (LI11) in two patients with COPD. It appears that Acu-TENS to these

points produced similar physiological and ANS changes as reported in Chapters 5 and 6. This study also showed that a single session of Acu-TENS to LI4 and LI11 could possibly improve FEV_1 and 6MWD in patients with COPD. While there were obvious limitations associated with this case study (as reported in Section 7.7), this small case study provides an indication that further studies which explore the role of Acu-TENS to different acupoints, its relationship with deqi sensation, possible associated mechanisms such as modulation of ANS, in a large sample population of patients with COPD, is warranted.

8.2 Future plan

As explained in the previous paragraph, further studies to explore the role of Acu-TENS in management of patients with COPD are warranted. Characteristics of such future studies perhaps should focus on:

- a randomized-controlled trial with inclusion of a control group that receive Acu-TENS to knee-cap (non-acupoints), as well as a placebo group that receive Acu-TENS to actual acupoints but no electrical stimulation
- larger sample size population of people with COPD and sample size estimation can be based on the results in Chapter 6. For example, with the Cohen's *d* equals to 0.32, a medium effect will be expected in Acu-TENS study in patients with COPD. To achieve a medium effect size at Type I error of 5% and power of 80%, 36 subjects were required. If 10% attrition rate is added, then a minimum of 40 subjects will be required.
- Acupoint consideration – future studies can aim to compare the associated deqi sensation, modulation of ANS activities, and β-endorphin level, between Acu-TENS to EX-B1 and LI4+ LU7.

8.3 Clinical implications and overall conclusion

In conclusion, the results of the work described in this thesis demonstrated that acupuncture and Acu-TENS are associated with an immediate modulation of the sympathetic and parasympathetic activities of the ANS. *Deqi* sensations elicited by acupuncture to LI4 and LI11 were associated with physiological and ANS activities changes. However, the acupoint sensations elicited by Acu-TENS had low association with the changes in ANS activities. Nevertheless, Acu-TENS to LI4 and LI11 appears to be able to facilitate increased sympathetic discharge, and associated with improved FEV_1 and reduction of dyspnoea in patients with COPD, irrespective of whether the characteristic of their condition was predominant with asthma or emphysema. Since previous studies have demonstrated that Acu-TENS to Dingchuan (Ex-B1) can improve clinical outcomes in patients with COPD, synergy effect may be possible if Dingchuan (Ex-B1), Hegu (LI4) and Quichi (LI11) are stimulated simultaneously to achieve a better clinical outcomes. Further investigation in this aspect is warranted.

Acu-TENS is a simple and non-invasive modality and this study has further supported the promising potential of Acu-TENS in improving dyspnoea and physical activity level in patients with COPD. In addition, application of Acu-TENS does not require a trained acupuncturist, and it can be easily be taught to the carer of the patient; thus Acu-TENS may be a useful adjunct in the management of dyspnoea in patients with COPD. The working mechanism of Acu-TENS and its role in management of respiratory diseases warrants further investigation.

CHAPTER 9

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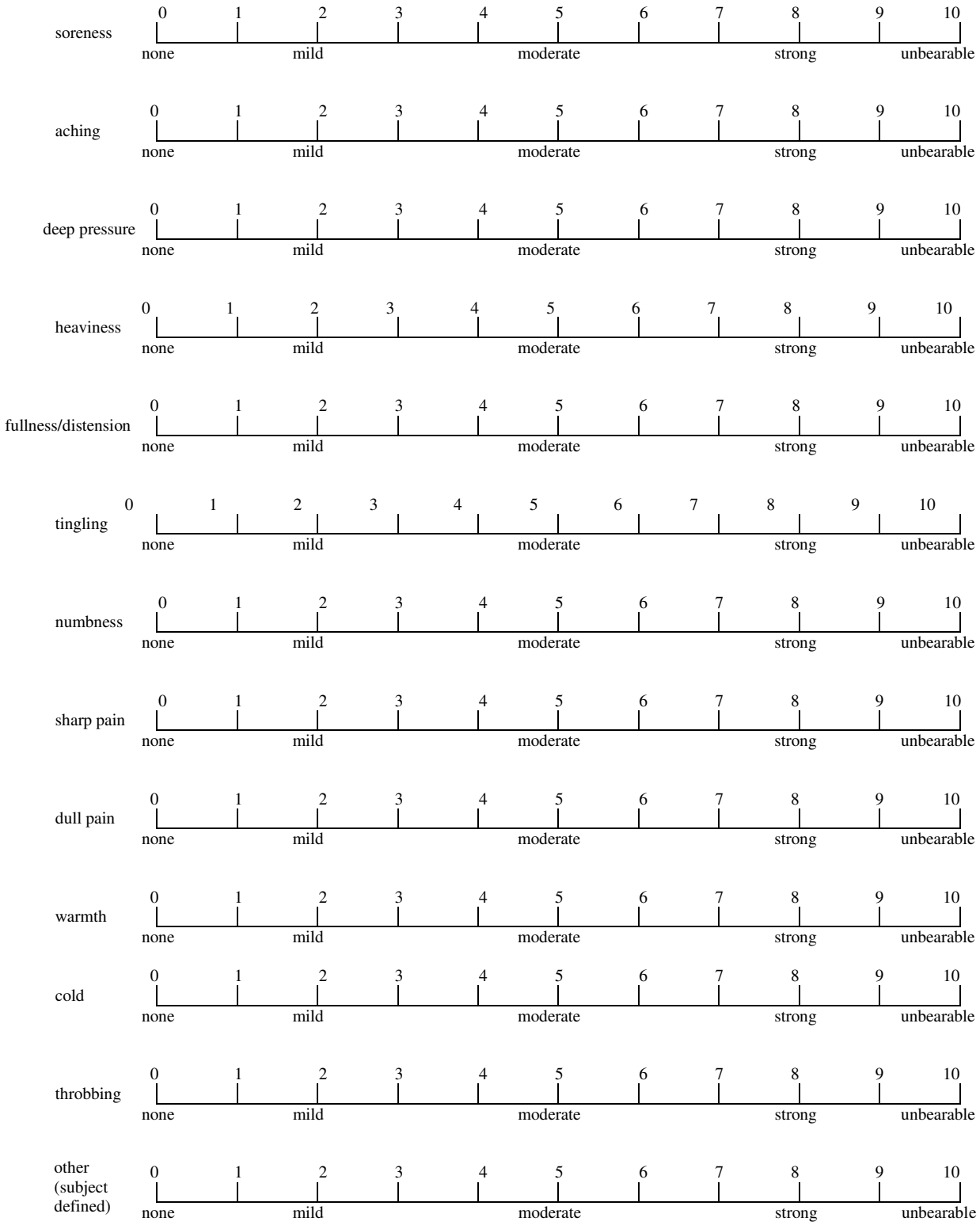
APPENDIX 1

The Massachusetts General Hospital Acupuncture

Sensation Scales

The Massachusetts General Hospital Acupuncture Sensation Scales



APPENDIX 2

Short-form McGill Pain Questionnaire

SHORT-FORM McGILL PAIN QUESTIONNAIRE

PATIENT'S NAME_____ DATE

Instructions: Since you have reported that one of your problems is **physical pain**, the purpose of this checklist is for you to give us an idea about what your **physical pain** feels like. Each of the words in the left column describes a quality or characteristic that pain can have. So, for each pain quality in the left column, check the number in that row that tells how much of that specific quality your pain has. Rate every pain quality.

PAIN QUALITY	NONE	MILD	MODERATE	SEVERE
1. Throbbing	(0)_____	(1)_____	(2)_____	(3)_____
2. Shooting	(0)_____	(1)_____	(2)_____	(3)_____
3. Stabbing	(0)_____	(1)_____	(2)_____	(3)_____
4. Sharp	(0)_____	(1)_____	(2)_____	(3)_____
5. Cramping	(0)_____	(1)_____	(2)_____	(3)_____
6. Gnawing	(0)_____	(1)_____	(2)_____	(3)_____
7. Hot-burning	(0)_____	(1)_____	(2)_____	(3)_____
8. Aching	(0)_____	(1)_____	(2)_____	(3)_____
9. Heavy	(0)_____	(1)_____	(2)_____	(3)_____
10. Tender	(0)_____	(1)_____	(2)_____	(3)_____
11. Splitting	(0)_____	(1)_____	(2)_____	(3)_____
12. Tiring-exhausting	(0)_____	(1)_____	(2)_____	(3)_____
13. Sickening	(0)_____	(1)_____	(2)_____	(3)_____
14. Fearful	(0)_____	(1)_____	(2)_____	(3)_____
15. Punishing-cruel	(0)_____	(1)_____	(2)_____	(3)_____

A. PLEASE MAKE AN "X" ON THE LINE BELOW TO SHOW HOW BAD YOUR PAIN IS RIGHT NOW.

NO PAIN |——————————————————————————————| WORST POSSIBLE PAIN

B. PLEASE CHECK THE ONE DESCRIPTOR BELOW THAT BEST DESCRIBES YOUR PRESENT PAIN.

0 NO PAIN _____
1 MILD _____
2 DISCOMFORTING _____
3 DISTRESSING _____
4 HORRIBLE _____
5 EXCRUCIATING _____

C. IS YOUR PAIN ?

(check one word)

_____ Brief
_____ Intermittent
_____ Continuous

Note: Adapted with permission from the "Short Form McGill Pain Questionnaire". Copyright 1987 Ronald Melzack.

S = ___/33 A/E = ___/12

APPENDIX 3

Modified Medical Research Council Scale

Medical Research Council Scale

Grade	Description of Breathlessness
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on the level or up a slight hill
2	I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level
3	I stop for breath after walking 100 yards or after a few minutes on the level
4	I am too breathless to leave the house or I am breathless when dressing

APPENDIX 4

Rate of Perceived Exertion

Rate of Perceived Exertion

6	**NO EXERTION AT ALL**
7	**EXTREMELY LIGHT**
8	
9	**VERY LIGHT**
10	
11	**LIGHT**
12	
13	**SOMEWHAT HARD**
14	
15	**HARD/HEAVY**
16	
17	**VERY HARD**
18	
19	**EXTREMELY HARD**
20	**MAXIMAL EXERTION**

APPENDIX 5

Modified Borg Scale

Modified Borg Scale

0	**NOTHING AT ALL (just noticeable)**
0.5	**VERY VERY SLIGHT**
1	**VERY SLIGHT**
2	**SLIGHT**
3	**MODERATE**
4	**SOMEWHAT SEVERE**
5	**SEVERE**
6	
7	**VERY SEVERE**
8	
9	**VERY VERY SEVERE (almost maximal)**
10	**MAXIMAL**

APPENDIX 6

BODE Index

BODE Index

Variable	Points on BODE Index			
	0	**1**	**2**	**3**
FEV_1 (% of predicted)†	≥65	50-64	36-49	≤35
Distance walked in 6 min (m)	≥350	250-349	150-249	≤149
MMRC dyspnoea scale‡	0-1	2	3	4
Body-mass index ∫	>21	≤21		

The total possible vales range from 0 to 10. FEV_1 denotes forced expiratory volume in one second.

† The FEV_1 categories are based on stages identified by the American Thoracic Society.

‡ Scores on the modified Medical Research Council (MMRC) dyspnoea scale can range 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or become breathless when dressing or undressing.

∫ The values for body-mass index were 0 or 1 because of the inflection point in the inverse relation between survival and body-mass index at a value of 21.

APPENDIX 7

Hong Kong Chinese version of the St. George's Respiratory Questionnaire in patients with COPD

聖 佐 治 胸 肺 科 問 卷

這份問卷設計的目的在於了解更多你的氣喘情況 / 毛病 / 問題及它如何影響你的生活，藉以找出你最大的問題。

請細閱問卷的指示。如遇上不明白的地方，可隨時發問。答題時，無須花時過久選擇答案。

姓名：_____

性別： 男 / 女

身份証號碼：_____

年齡：_____

日期：_____

甲部

有關在上年度胸肺問題對你的影響。請於每題中選出一個最適當的答案，並於❑內加上✓號。

	每星期差不多每天	每星期有多天	每星期有幾天	每當肺部受感染	沒有
一. 於過去十二個月內，我咳嗽的頻密程度是：	❑	❑	❑	❑	❑
二. 於過去十二個月內，我有痰的日子是：	❑	❑	❑	❑	❑
三. 於過去十二個月內，我感到呼吸困難的次數：	❑	❑	❑	❑	❑
四. 於過去十二個月內，我遇上「牽哈」的日子：	❑	❑	❑	❑	❑

五. 於過去十二個月內，你有多少次嚴重的胸肺病發作？

超過三次❑　三次❑　二次❑　一次❑　沒有❑

六. 最嚴重的一次胸肺病發維持了多久？

(若題五選擇答案 ‘沒有’ ，不用作答此題)

一星期或以上❑ 三天或以上❑ 一至兩天❑ 少於一天❑

七. 於過去十二個月內每星期你平均有多少天沒有被胸肺問題困擾？

沒有❑ 一至兩天❑ 三至四天❑ 幾乎每天❑ 每天❑

八. 若遇有「牽哈」時，是否在朝早較為嚴重？

不是❑ 是❑

乙部

(一) 你會怎樣形容你的胸肺情況？
(請選擇最適當的答案，並在❑內加上✓號。)

- 是我最要緊的問題 ---------- ❑
- 給我構成甚多問題 ---------- ❑
- 給我構成一些問題 ---------- ❑
- 沒有構成問題 ---------- ❑

若你曾有受薪工作，請在以下✓最適當的答案。

- 我的胸肺問題令我要停止工作 ---------- ❑
- 我的胸肺問題影響我的工作或令我要轉換工作 ----- ❑
- 我的胸肺問題不影響我的工作 ---------- ❑

(二) 在近期有甚麼活動常導致你感到氣喘。
(請在每一項中選擇**是**或否，並於❑內加上✓號)

	是	否
• 坐或躺臥 ----------	❑	❑
• 梳洗或更衣 ----------	❑	❑
• 在家中步行 ----------	❑	❑
• 在戶外走平路 ----------	❑	❑
• 上一層樓梯 ----------	❑	❑
• 行山 ----------	❑	❑
• 做運動或比賽 ----------	❑	❑

(三) 以下問題是關於近期咳嗽和氣喘的情況。
(請在每一項中選擇<u>是</u>或<u>否</u>，並於❑內加上✓號)

	是	否
• 我的咳嗽令我感到不適 ----------	❑	❑
• 我的咳嗽令我感到疲倦 ----------	❑	❑
• 說話時，我感到透不過氣來 ----------	❑	❑
• 彎腰時，我感到透不過氣來 ----------	❑	❑
• 我的咳嗽或呼吸問題影響我的睡眠 ----------	❑	❑
• 我容易感到精力耗盡 ----------	❑	❑

(四) 以下問題是關於近期你的胸肺問題對你構成的其他影響。
(請在每一項中選擇<u>是</u>或<u>否</u>，並於❑內加上✓號)

	是	否
• 在公眾場合中，我的咳嗽或呼吸問題令我感到尷尬 ----------	❑	❑
• 我的胸肺問題令家人，朋友及鄰居感到討厭 --	❑	❑
• 當我不能控制呼吸時，我便會驚惶失措 --------	❑	❑
• 我覺得不能控制自己的胸肺問題 ----------	❑	❑
• 我不期望自己的胸肺情況會好轉 ----------	❑	❑
• 我因自己的胸問題而變得脆弱或無用 ----------	❑	❑
• 運動對我來說是不安全的 ----------	❑	❑
• 一切對於我來說都感到吃力 ----------	❑	❑

(五) 以下問題是關於藥物治療的情況。若你沒有使用藥物治療，請跳去第六節。
(請在每一項中選擇<u>是</u>或<u>否</u>，並於❑內加上✓號)

	是	否
• 我的藥物對我幫助不大 ----------	❑	❑
• 在公眾場所用藥令我感到尷尬 ----------	❑	❑
• 我對所用的藥物有不良的副作用 ----------	❑	❑
• 我的藥物對我的生活造成很多干擾 ----------	❑	❑

(六) 以下問題是關於你的活動如何被你的呼吸問題困擾。
(請在每一項中選擇<u>是</u>或<u>否</u>，並於❑內加上✓號)

	是	否
• 我梳洗或更衣需時良久 ----------	❑	❑
• 我不能洗澡或淋浴，或需時良久 ----------	❑	❑
• 我步行較其他人慢，或需要中途休息 ----------	❑	❑
• 工作時，例如料理家務，需時良久或要中途休息 ----------	❑	❑
• 若我要上一層樓梯，也要慢慢步上或停下來 --	❑	❑
• 若我趕急或快步走路，也要停下來或慢下來 --	❑	❑
• 我的呼吸問題令我難做到，例如：行山，挽東西上樓梯，輕便的園藝如除草，跳舞，打保齡球或打高爾夫球等 ----------	❑	❑
• 我的呼吸問題令我難做到，例如：挽重物，在花園翻泥，緩步跑或以每小時五英里的速度步行，打網球或游泳等 -----	❑	❑
• 我的呼吸問題令我難做到，例如：十分粗重的工作，跑步，踏單車，快速地游泳或進行比賽性的運動 ----------	❑	❑

(七) 以下問題目的是想知道你的胸肺問題如何影響你的日常生活。

(註：因呼吸問題導致你不能做某些事才在「是」的❑內加上✓號)

	是	否
• 令我不能做運動或比賽 ----------	❑	❑
• 令我不能外出消遣或娛樂 ----------	❑	❑
• 令我不能外出購物 ----------	❑	❑
• 令我不能做家務 ----------	❑	❑
• 令我不能走動離開我的床或椅子太遠 ----------	❑	❑

以下有一系列其他活動可能因你的胸肺問題令你做不到。(你不用在每項中作出回應，它們純屬例子，目的只在於提醒你怎樣被呼吸問題影響自己)。

例：

- 外出散步或拖狗
- 在家中作事或園中工作
- 行房
- 外出消遣，去教堂或去娛樂場所
- 在天氣差的日子出外或進入煙霧瀰漫的房間
- 探訪親友或和小孩子玩耍

請在下面填上其他因你的胸肺問題導致你做不到的重要活動：

_____

_____

_____

_____

請在以下選出一項答案最能描述胸肺問題對你的影響：

- 它不阻礙我做任何我喜歡做的事 ---------- ❑
- 它阻礙我做一至兩件我喜歡做的事 ---------- ❑
- 它阻礙我做很多我喜歡做的事 ---------- ❑
- 它阻礙我做一切我喜歡做的事 ---------- ❑

— 完 —

多謝你的合作填完此份問卷。
離開前，請覆查是否已作答所有問題，並把問卷交回物理治療師。

*** Direct translated from The St. George's Respiratory Questionnaire - P.W. Jones , F.H. Quirk and M. Baveystoc**

APPENDIX 8

Development and Validation of the Chinese Version of the Massachusetts General Hospital Acupuncture Sensation Scale: an exploratory and methodological study

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Development and validation of the Chinese version of the Massachusetts General Hospital Acupuncture Sensation Scale: an exploratory and methodological study

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► Additional material is published online only. To view these files please visit the journal online (http://aim.bmj.com/content/early/recent).

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Abstract

Background The Massachusetts General Hospital Acupuncture Sensation Scale (MASS) is a tool to measure needle sensations. The aims of the present study were to develop a Chinese version and to assess its psychometric properties.

Methods This study was a methodological and exploratory study. The English version of the MASS was translated into Chinese using standardised translation procedures. Content validity was conducted by nine acupuncture experts. The prefinal Chinese version (C-MASS) was then administered to 30 acupuncture-naïve, healthy subjects. Electroacupuncture was performed on the right LI4 and LI11 acupoints for 30 min. A test–retest reliability measurement was administered 1–2 weeks later. Construct validity was examined by comparing results from C-MASS and the Short-Form McGill Pain Questionnaire (SF-MPQ). The construct validity was further assessed by the principle component analysis.

Results C-MASS demonstrated a content validity ratio on relevance and importance from −0.04 to 1.00. Convergent validity was demonstrated by its significant association with the sensory dimension of SF-MPQ (γ=0.63, $p<0.05$). Discriminant validity was demonstrated by its low association with the affective dimension of SF-MPQ (γ=−0.3, $p=0.111$). A five-factor structure of C-MASS was established by factor analysis. C-MASS demonstrated good internal consistency (Cronbach's α=0.71) and test–retest reliability (intraclass correlation coefficient=0.92). Since the descriptor 'sharp pain' was not a valid needle sensation related to *deqi*, this was removed from C-MASS. We renamed the scale as the Modified MASS-Chinese version (C-MMASS).

Conclusions A 12-descriptor C-MMASS was established and shown to be a reliable and valid tool in reporting needle sensations associated with *deqi* among healthy young Chinese people.

INTRODUCTION

Acupuncture has been widely used in China for thousands of years.[1–3] One of the fundamental characteristics of acupuncture is to 'obtain *qi*' during acupuncture, a sensation referred to as '*deqi*'. Based on the concept of traditional Chinese medicine (TCM), *qi* must flow in correct strength and quality along the meridians so that health can be maintained. It was believed that restoration of health can only be achieved if the acupuncture technique is able to elicit *deqi*, thereby allowing the flow of *qi* to be altered.[3 4] While investigations of the relationship between the therapeutic effectiveness of acupuncture and the *deqi* experience have been reported in the literature,[3 5–7] scientific evidence to support such a relationship is still lacking.[7]

When *deqi* occurs, the acupuncturist and the subject may experience some 'unusual' sensations around the needle. The acupuncturist may perceive heaviness or tenseness around the needle when *qi* arrives.[8] However, the feelings of the acupuncturist are more often subjected to biased preconceptions of 'what one ought to feel' and thus hold greater likelihood of a biased subjective report.[9] In recent years, researchers have focused more on sensations perceived by the subjects. Standard needle sensations associated with *deqi* experienced by the subjects are described as soreness, distension, heaviness and numbness.[10–12] Nevertheless, there is still no standard method in measurement and quantifying *deqi* sensations at present.

Over the last two decades, a number of studies have attempted to quantify *deqi* sensations.[10–12] Vincent and colleagues adopted the McGill Pain Questionnaire and created a new scale of 20 adjectives describing possible acupuncture sensations.[10] In 2005, Park *et al* modified Vincent and colleagues' work by adding five extra descriptions of the sensation scale.[11] However, these scales have limitations because both of these instruments measure a range of sensations that include pain as well as *deqi*. In 2006, a panel of 29 international acupuncture experts were involved in MacPherson and Asghar's study, which categorised 25 sensations during acupuncture as associated with *deqi* and acute pain at the needling site.[12] However, the above study quantified *deqi* sensations based on the acupuncturists rather than the patient's/subject's perception.

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To address the complexity involved in accurately assessing the acupuncture sensations, Kong and coworkers developed the 'Subjective Acupuncture Sensation Scale' (SASS), an inventory incorporating various sensations associated with *deqi*.[13] The SASS listed nine descriptors of sensations associated with *deqi* sensations reported in the traditional literature.[13] Each of the elements was presented on a 10-cm bar with the anchor words 'none', 'mild', 'moderate' and 'severe' spaced evenly along the continuum. Subjects were asked to quantity their sensations at each point by rating the intensity with which they experienced after acupuncture. The authors demonstrated that there were significant correlations between numbness and soreness items of the SASS.[13] In order to apply SASS to a wider range of research projects, Kong and his coworkers further expanded the descriptors in the SASS, and this became the Massachusetts General Hospital Acupuncture Sensation Scale (MASS) (Appendix 1).[7] The descriptors in MASS include soreness, aching deep pressure, heaviness, fullness/distension, tingling, numbness, sharp pain, dull pain, warmth, cold, throbbing, plus a blank supplementary row left for subjects to describe perceptions in their own words. The MASS index is then calculated and used to quantify the intensity of the needle sensations experienced by a subject. The MASS also included two supplementary scales for measurement of spreading of the acupuncture sensation and anxiety.[7]

Establishment of the MASS involved extensive review of relevant literature and appears to be the most comprehensive assessment tool in measuring the needle sensations. The MASS has subsequently been used for measurement of acupuncture sensations.[14 15] The validity and reliability of the MASS, however, have not been properly established. Furthermore, the precise Chinese language terms that best describe the needle sensation have not been determined. If optimal needle sensation is essential for achieving positive acupuncture effects, it is necessary to have a valid and reliable instrument to be used in the clinical setting to systematically quantify and document the needle sensation associated with *deqi*, as this could be an important factor that determines the treatment effect of acupuncture intervention. The objectives of the present study therefore were to establish a Chinese version of the MASS and to test its psychometric properties.

METHODS

The study was an exploratory, methodological study that involved two phases. Ethics approval was granted by the Human Subjects Ethics Committee of the university involved. The nature of the study was explained to the subjects and written consent obtained prior to data collection. All procedures were conducted in accordance with the Declaration of Helsinki.

Phase I: cultural adaptation of the MASS and assessment of content validity

Permission was obtained from the original authors of the MASS before the initiation of the study. The translation process was divided into five stages and was mainly based on the guidelines that described by Beaton *et al*[16] and Wild *et al*.[17]

The first stage was the forward translation of the MASS into two independent Chinese versions by a physiotherapist and a professionally trained translator whose mother tongue is Chinese. The professionally trained translator had no medical or clinical background (naïve translator).

The second stage involved the synthesis of the results of the translations. The translated versions were compared and any ambiguous wordings were identified. Thus, a single Chinese version of the MASS was first established.

The third stage was the back translation stage. This involved another two independent translators with physiotherapy and TCM backgrounds and they translated the Chinese version into English.

In the fourth stage, a panel consisting of a professor from a local university, seven physiotherapists and two nursing staff examined the preliminary versions in terms of the degree of agreement on the importance and relevance of each item on the Chinese version of the MASS to *deqi* sensation. All the committee members were bilingual individuals with Chinese as their mother tongue. Six of them had a Master's degree in acupuncture studies and four had a Bachelor's degree in TCM. They had an average of 9 years of clinical experience in acupuncture. They were asked to rate each item on a five-point scale from 'strongly agree' to 'strongly disagree'. The content validity ratio (CVR) was then computed. The CVR=(ne–N/2)/(N/2), where 'ne' refers to the number of subject matter that the experts considered as essential measurement items and N is the total number of experts in the panel. The CVR ranged between −1.00 and +1.00, where a CVR of 0.00 means that 50% of the panel believes the item to be essential. With an expert panel of 10 members, a 0.60 CVR was required to meet a 0.05 significance level of importance.[18] The prefinal version was then established based on the results on the degree of agreement on the importance and relevance in content validity measurement.

In the fifth stage, the prefinal version was pilot tested on 10 normal healthy young subjects who were naïve to acupuncture and had no prior knowledge of the original MASS. They received electroacupuncture on the right Hegu (LI4) and Quichi (LI11) acupoints (see phase II below) and they were asked to complete the prefinal Chinese version of the MASS. Subjects were asked to select from this prefinal version that best describe the sensations during electroacupuncture. In computing the MASS index, the subject's individual MASS rating scales were ordered from highest to lowest intensity, and the MASS index was calculated according to the following equation:

$$\text{MASS index} = \frac{\sum_{i=1}^{n} (1/2)^{i} R_i}{1-(1/2)^{n}}$$

Where R indicates the ratings for different sensations from highest to lowest and n represents the number of *deqi* sensations on the MASS questionnaire.[7]

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Based on the feedback obtained from the subjects who participated in the pilot testing, minor modifications were made to the inventory to further improve its clarity. The final Chinese version, the C-MASS, was adopted and used to examine the reliability and construct validity in this study.

Phase II: validation of the C-MASS

Subjects' selection and sample size estimation

Subject inclusion criteria included people of under 40 years of age, right-handed, with normal health, naïve to acupuncture, and able to understand Chinese and English, as the subjects were also required to complete the Short-Form McGill Pain Questionnaire (SF-MPQ) (English version). Subjects with known neurological, cardiovascular and psychological disorders were excluded. A convenience sampling method was adopted. Subjects were invited to a face-to-face interview and demographic data collected.

The software PASS 2008 was used for sample size calculation (www.ncss.com/pass.html). Sample estimation was based on the intraclass correlation coefficient (ICC) obtained during the pilot test–retest reliability study. Preliminary results showed that the test–retest reliability was good, with the ICC exceeding 0.95. Therefore, if the ICC was set at 0.95 with a type I error of 5% and power of 80%, 30 subjects were required.

Procedures for electroacupuncture administration

The acupuncture points Hegu (LI4) and Quichi (LI11) of the right arm were selected as appropriate points for stimulation. All subjects were in a sitting position with both arms supported by a pillow. After the acupoints were located, isopropyl alcohol was applied for disinfection. Then, two 40 mm×0.25 mm single-use, sterile, prepacked stainless needles with guide tubes were inserted into the LI4 and LI11 points. The needles were inserted for about 0.5 inch and then manually manipulated until *deqi* sensation was reported. In this study, *deqi* was defined as sensations perceived by the subjects as 'soreness/numbness/distension/heaviness' at intensity around a moderate level. This was to ensure that proper acupoints were located and the subjects could identify the types of sensations when *deqi* arrived. In order to standardise the stimulation throughout the stimulation period, electroacupuncture was used in the present study. Two electrodes were attached to the needles and connected to an electroacupuncture device (ITO, EX-160, Hannover, Germany). Electrical stimulation was then applied for 30 min at a frequency of 2 Hz, pulse duration at 0.6–0.8 ms.[13] The intensity of electrical stimulation was increased gradually to a moderate level using a 10-point visual analogue scale.[19] Subjects were checked every 5 min and the intensity was readjusted so as to ascertain that *deqi* sensation was present.

After the electroacupuncture stimulation, the subjects were asked to quantify their acupuncture sensations by first completing the C-MASS and then the SF-MPQ.[20] Those who experienced *deqi* sensation at a moderate level during electroacupuncture in this session were invited back 1–2 weeks later for a test–retest reliability measurement. This period was chosen because it was relatively long enough to minimise the chance of recalling the answers but short enough to minimise the probability of the subjects having undergone real change on the domain of interest.[21] Similar to the first assessment session, the subjects received electroacupuncture on the right LI4 and LI11 points in the second session and were then required to quantify *deqi* with the C-MASS. The MASS index obtained at the first visit was compared with that obtained at the second visit for the test–retest reliability assessment.

The Short-Form McGill Pain Questionnaire

The SF-MPQ is designed to provide a brief measurement of pain.[20] It is a two-factor inventory (sensory and affective) construct for measurement of pain. The SF-MPQ consists of 15 descriptors (11 sensory and 4 affective) rated on an intensity scale as 0=none, 1=mild, 2=moderate or 3=severe.

Statistical analysis

Descriptive statistics were performed to indicate the intensity of each needle sensation. Construct validity was examined by comparing the C-MASS and the SF-MPQ. It was hypothesised that items in C-MASS would be highly correlated with the sensory component but not with the affective component of the SF-MPQ. Correlation matrices were created between the items of C-MASS and SF-MPQ. The data were compared by Pearson product-moment coefficient of correlation γ. A correlation coefficient above 0.50 to 0.75 indicates a moderate to good relationship, above 0.75 was considered as good to excellent relationship. The observed values of γ should be greater than or equal to the tabled value to achieve a significance level.[21]

The construct validity was further assessed by principle component analysis (PCA) of the C-MASS. A correlation matrix of all the items was created. The factor was extracted for factor analysis by two criteria: factors with eigenvalues greater than 1 and the Scree test criterion, obtained by plotting the eigenvalues against the number of factors. A factor loading of greater than 0.40 was considered significant. Orthogonal rotation using varimax rotation was used for the rotation of factors to improve the spatial structure of the variables so that distinct factors would be more visible.[21] Naming of factors was based on those items that had the highest factor loading in each factor.[21]

For reliability, the internal consistency of the C-MASS was assessed using Cronbach's α coefficient, which was considered reliable if it approached 0.70.[21] To examine the test–retest reliability, ICC two-way random model were computed. ICCs above 0.75 were indicative of good reliability whereas those between 0.5 and 0.75 were considered moderate reliability.[21] The level of significance was set at 0.05 for all analyses. All of the statistical analyses were performed using SPSS V.17.0 software (SPSS, Chicago, Illinois, USA).

RESULTS

Phase I: assessment of content validity

The degree of agreement on the importance and relevance of each item associated with *deqi* sensation is shown in

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table 1 and table 2. It was found that the CVR of all items ranged from −0.4 to 1.0.

Phase II: validation of the C-MASS

Subject characteristics

A total of 30 normal healthy subjects were recruited by convenience sampling (18 men, 12 women). The mean age was 34.1 ±3.81 years. Three subjects experienced only a very low level of 'soreness/numbness/distension/heaviness' at the required intensity and were considered not to have achieved *deqi* in the first session of electroacupuncture. These subjects were excluded from the analysis as inclusion of vague and uncertain sensations from these subjects was considered inappropriate. Therefore, only 27 subjects were invited to receive the electroacupuncture stimulation again for the test–retest reliability assessment at 1–2 weeks after the first session. A comparison of the intensity of various *deqi* sensations during the first and second sessions is displayed in table 3. The results showed that fullness/distension, soreness, numbness, dull pain and aching scored highest among the 13 sensations. No subject added any other sensations in the blank row provided. The mean MASS index obtained in the first and second assessment sessions were 4.4 (SD=1.3) and 4.7 (SD=1.1) respectively.

Validity analysis

The C-MASS showed moderate correlation with the overall SF-MPQ score with the Pearson's product moment correlation coefficient γ=0.56, p=0.001. A significant correlation was observed when the C-MASS was compared

Table 1 Results of content validity of the prefinal Chinese version of the Massachusetts General Hospital Acupuncture Sensation Scale ('importance' content associated with deqi sensation) (n=11)

	Strongly agree (%)	Agree (%)	Total percentage of agreement	Neutral (%)	Disagree (%)	Strongly disagree (%)	Total percentage of disagreement	CVR
Soreness	70	30	100	0	0	0	0	1.0
Aching	20	60	80	0	20	0	20	0.6
Deep pressure	20	40	60	10	20	10	30	0.2
Heaviness	40	50	90	10	0	0	0	0.8
Fullness/distension	50	40	90	10	0	0	0	0.8
Tingling	40	40	80	10	10	0	10	0.6
Numbness	50	30	80	20	0	0	0	0.6
Sharp pain	20	30	50	20	20	10	30	0.0
Dull pain	60	40	100	0	0	0	0	1.0
Warmth	10	40	50	20	30	0	30	0
Cold	10	20	30	30	40	0	40	−0.4
Throbbing	40	40	80	20	0	0	0	0.6
Other (subject defined)	70	30	100	0	0	0	0	1.0
Overall agreement	38.5	37.7	76.2	11.5	10.8	1.5	12.3	

CVR, content validity ratio.

Table 2 Content validity of the prefinal Chinese version of the Massachusetts General Hospital Acupuncture Sensation Scale ('relevance' to content of deqi sensation) (n=11)

	Strongly agree (%)	Agree (%)	Total percentage of agreement	Neutral (%)	Disagree (%)	Strongly disagree (%)	Total percentage of disagreement	CVR
Soreness	80	20	100	0	0	0	0	1.0
Aching	30	40	70	10	20	0	20	0.4
Deep pressure	40	10	50	20	20	0	20	0.0
Heaviness	70	20	90	10	0	0	0	0.8
Fullness/distension	70	20	90	10	0	0	0	0.8
Tingling	50	30	80	20	0	0	0	0.6
Numbness	60	30	90	0	10	0	10	0.8
Sharp pain	30	0	30	10	20	40	60	−0.4
Dull pain	70	30	100	0	0	0	0	1.0
Warmth	40	30	70	30	0	0	0	0.4
Cold	30	10	40	20	30	10	40	−0.2
Throbbing	40	40	80	10	10	0	10	0.6
Other (subject defined)	90	10	100	0	0	0	0	1.0
Overall agreement	53.8	22.3	76.1	11.5	8.5	3.8	12.3	

CVR, content validity ratio.

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Table 3 Comparison of different deqi sensations intensity between time 1 and time 2 and test–retest reliability of the C-MASS (n=27)

	Sensation intensity		Test–retest reliability of the C-MASS			
				95% CI		
	Time 1 mean (±SD)	Time 2 mean (±SD)	$ICC_{3,1}$	Lower Bound	Upper Bound	p Value
Soreness	6.9 (±1.3)	7.6 (±0.9)	0.62	0.16	0.83	0.009*
Aching	5.9 (±1.6)	6.3 (±1.4)	0.98	0.95	0.99	<0.001*
Deep pressure	3.2 (±1.5)	3.4 (±1.5)	0.96	0.91	0.98	<0.001*
Heaviness	6.0 (±1.4)	6.6 (±0.9)	0.55	0.01	0.88	0.024*
Fullness/distension	7.4 (±1.2)	7.9 (±0.8)	0.73	0.41	0.88	0.001*
Tingling	4.0 (±1.8)	4.4 (±1.4)	0.89	0.77	0.95	<0.001*
Numbness	6.3 (±1.3)	6.5 (±1.1)	0.97	0.92	0.98	<0.001*
Sharp pain	3.2 (±1.7)	4.0 (±1.7)	0.79	0.54	0.91	<0.001*
Dull pain	6.1 (±1.5)	5.9 (±1.4)	0.98	0.95	0.99	<0.001*
Warmth	0.2 (±0.4)	0.2 (±0.4)	0.96	0.91	0.98	<0.001*
Cold	0.2 (+0.4)	0.2(±0.4)	0.96	0.91	0.98	<0.001*
Throbbing	3.4 (±1.4)	3.1 (±1.2)	0.96	0.91	0.98	<0.001*
Other (subject defined)	0.0 (±0.3)	0.0 (±0.2)	0.92	0.83	0.96	<0.001*
Overall MASS index	4.4 (±1.2)	4.7 (±1.1)	0.92	0.83	0.96	<0.001*

*Indicate statistical significance (p<0.05).
C-MASS, Massachusetts General Hospital Acupuncture Sensation Scale Chinese version; ICC, intraclass correlation coefficient.

with the sensory dimension of the SF-MPQ (Pearson's product moment correlation coefficient γ=0.63, p<0.05) but not with the affective dimension of the SF-MPQ (Pearson's product moment correlation coefficient γ=−0.3, p=0.111).

For factor analysis, based on the criterion of an eigenvalue of more than 1, the data yield five factors and explained 77% of variance. Therefore, the results suggested there were 5 factors among the 13 sensations of the C-MASS (table 4). Naming of factors was based on locating the highest factor loading in the factor. Therefore, factor 1 was labelled as 'soreness', factor 2 was labelled as 'heaviness', factor 3 was labelled as 'fullness', factor 4 was labelled as 'dull pain' and factor 5 was labelled as 'numbness'.

Internal consistency and test–retest reliability measurements

The overall Cronbach's α of the C-MASS was calculated as 0.71 (table 5). For test–retest reliability, three subjects did not meet the criteria of achieving *deqi* sensation during the first session of electroacupuncture and were thus excluded from the test–retest reliability assessment. Based on the data of the 27 subjects, the test–retest reliability of individual items of the C-MASS was moderate to excellent ($ICC_{3,1}$=0.55–0.98) and that of the MASS index was excellent ($ICC_{3,1}$=0.92) (table 3).

DISCUSSION

This study examined the measurement properties of the translated version of the MASS as an inventory of needle sensations associated with *deqi*. The results demonstrated that the translated version is a valid and reliable instrument for the assessment of needle sensations in Hong Kong Chinese people receiving electroacupuncture.

In the forward translation process, two translators carried out independent forward translations of the instrument to ensure that the translations could be compared, enabling detection of errors and divergent interpretation of ambiguous items in the original, thus reducing the potential bias.[17] Our study also adopted two back translations that were carried out in parallel so as to ensure that the quality of the translation is literally and conceptually the same as the original one.[16 17] The major discrepancy was on the translation of 'aching' and 'dull pain' as both terms are semantically and pragmatically similar in the Chinese translation. The reconciliation between the two forward translators was the conclusion that 'aching' and 'dull pain' should both be used in the Chinese version.

The convergent validity and the discriminant validity of the C-MASS were established by comparing with the SF-MPQ. The overall C-MASS score has moderate correlation with the overall score of the SF-MPQ. Since four of the items in the sensory dimension of the SF-MPQ have the same description as the MASS, a stronger correlation was therefore observed if the C-MASS was compared with the sensory dimension of the SF-MPQ (convergent validity). However, as we did not expect any affective effect from acupuncture, it is reasonable that only minimal correlation was observed when the C-MASS was compared with the affective dimension of the SF-MPQ (discriminant validity).

The original developers of the SASS conducted a PCA that supported the partition of three factors among the nine sensations.[7] When PCA was performed on the C-MASS in this study, five factors were extracted under the 'eigenvalues greater than 1' rule. These five factors explained 77% of the total variance. Factor analysis performed in

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Table 4 Factor analysis on Massachusetts General Hospital Acupuncture Sensation Scale Chinese version (n=27)

	Factors				
Items	**Soreness**	**Heaviness**	**Fullness**	**Dull pain**	**Numbness**
Factor 1	–	–	–	–	–
Soreness	0.90*	–	–	–	–
Aching	0.81	–	–	–	–
Pressure	0.53	–	–	–	–
Factor 2	–	–	–	–	–
Heaviness	–	0.87*	–	–	–
Warmth	0.43	0.67	–	–	–
Factor 3	–	–	–	–	–
Throbbing	–	–	0.65	–	–
Fullness	–	0.59	0.92*	–	–
Factor 4	–	–	–	–	–
Pressure	–	–	–	0.54	–
Dull pain	–	0.40	–	0.67*	–
Factor 5	–	–	–	–	–
Tingling	0.41	0.86	–	–	0.45
Numbness	–	–	–	–	0.79*
Sharp pain	–	–	–	–	0.77

Only factor loading >0.4 was displayed.
*Highest factor loading in the factor.

Table 5 Item-total statistics of the Massachusetts General Hospital Acupuncture Sensation Scale Chinese version (n=27)

	Scale mean if item deleted	**Scale variance if item deleted**	**Corrected item-total correlation**	**Squared multiple correlation**	**Cronbach's α if item deleted**
Soreness	27.23	52.94	0.39	0.76	0.69
Aching	27.43	52.12	0.38	0.87	0.69
Pressure	27.97	55.62	0.31	0.69	0.70
Heaviness	26.80	54.03	0.40	0.69	0.69
Fullness	27.53	46.33	0.47	0.72	0.68
Tingling	29.17	56.28	0.48	0.82	0.69
Numbness	26.20	50.99	0.48	0.56	0.68
Sharp pain	28.43	56.19	0.40	0.44	0.69
Dull pain	26.43	51.29	0.34	0.73	0.70
Warmth	29.20	54.92	0.36	0.71	0.69
Cold	30.20	63.41	−0.10	0.61	0.73
Throbbing	29.13	56.46	0.30	0.82	0.70
Other (patient specific)	30.26	61.03	0.14	0.62	0.71

this study confirmed that the C-MASS is a five-factor scale. The factors we identified (soreness, heaviness, fullness, dull pain and numbness) are in fact similar to those reported in most TCM literature as the 'standard' *deqi* sensations perceived.[3 4 7] The results of this study showed that the test–retest reliability of the C-MASS was high.

From the opinions of the content experts, most of the items in the C-MASS were found to be important and relevant in relation to the content of *deqi* measurement, with 'deep pressure', 'sharp pain', 'warmth' and 'cold' being the exception. These items have a low CVR. Previous studies supported that 'pressure' appeared to be an important characterisation of *deqi*,[15 22 23] whereas 'warmth and coolness' sensations are frequently considered as important associates of health in ancient TCM literature (*Suwen*, Chapter 54).[7] According to *Suwen* (Chapter 54), a patient with 'excess' syndrome would feel coldness under the needle when the *yin qi* arrives; however, a patient with 'deficient' syndrome would feel warmth under the needle when the *yang qi* arrives.[7] Our study showed that our subject cohort did not experience any 'cold' sensation or only experienced low level of 'warmth' sensation during acupuncture needling. This is probably because our subjects were young and healthy and thus less sensitive to these sensations, which dominate only when there is an imbalance of *qi* in their health status. In view of the above,

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we considered deep pressure, warmth and cold sensations are important components of the *deqi* sensations to be included in the instrument.

However, although the original MASS includes 'sharp pain' as one of the descriptors, it is not considered as a sensation associated with *deqi* by the original authors of MASS and others.[7 12 24] A recent pilot survey on the perception of *deqi* by Chinese and American acupuncturists also revealed that 50% participants classified 'sharp pain' as 'not *deqi*' and 42% believed it was harmful.[24] Our study showed that with 'sharp pain' removed from the scale, the overall Cronbach's α only decreased by 0.02, indicating that the overall homogenicity of the scale was not affected (table 5). The test–retest reliability was still maintained excellent with the $ICC_{3,1}$ increased from 0.92 to 0.93 ($p<0.001$). The modified version also showed moderate correlation with the overall SF-MPQ score ($\gamma=0.53$, $p=0.03$) and sensory dimension of the SF-MPQ ($\gamma=0.6$, $p<0.001$). The five-factor structure was also preserved and it explained 79.6% of the total variance. Since the validity and reliability of the modified scale was not much affected if 'sharp pain' was removed, we consider that it would be appropriate for the descriptor 'sharp pain' to be removed from the C-MASS for assessment of needle sensation associated with *deqi*. As the instrument now is one descriptor short of the original MASS, we thus renamed this Chinese version the 'Modified' Massachusetts General Hospital Acupuncture Sensation Scale, Chinese version (C-MMASS). The C-MMASS is a 12-item measure that includes soreness, aching, deep pressure, heaviness, full/distension, tingling, numbness, dull pain, warmth, cold, throbbing and the one supplementary row at the end for subjects to describe perceptions in their own words (appendix 2).

Deqi sensations are complex and highly individualised. In addition, the intensity and nature of *deqi* sensations are determined by many factors such as patient constitution, types of needle, acupoints, needling and allied techniques.[25] In our study, we have minimised all these confounding factors by including only young healthy subjects, only one type of acupuncture needle was used, only the LI4 and LI11 points were chosen for stimulation, acupuncture performed by the same trained physiotherapist and a fixed protocol used in electroacupuncture.

Limitations of the study

There are several limitations in our study. First, we have only recruited healthy subjects aged below 40. Therefore, generalisation of the findings to other age groups of Hong Kong Chinese would not be deemed appropriate. Secondly, the present study only adopted the LI4 and LI11 acupoints, as they are the classical acupoints commonly used for investigation of *deqi.* It may be possible that other distinct needle sensations could be elicited if different acupoints of other meridians were stimulated. Thirdly, the present study did not use non-acupoints for comparison. Hence, we could not distinguish the sensations related to skin piercing and tissue damage from real acupuncture sensation elicited by acupoint stimulation. Lastly, manual and sham acupuncture were generally used in acupuncture studies that involved *deqi* sensations measurement.[13 25] However, our study had not included these groups for comparison. We anticipate that subjects may rate the needle sensations differently, since manual, sham and electroacupuncture may work through different mechanisms and, thus, may affect the same individual differently in the perception of needle sensations.[13]

Summary points

- The MASS is an accepted method of objectively scoring the sensation of *de qi*.
- We have produced a Chinese version and then shown it to be valid and reliable.

CONCLUSIONS

Deqi is an important concept as it may well influence the therapeutic effect of acupuncture. Developing a valid and reliable tool to quantify needle sensations is an important step towards a better understanding of the basic mechanisms underlying the reported therapeutic effects. While there has been no standardised, valid and reliable tool to quantify the *deqi*, our study has established a Chinese version from the MASS and modified it. We demonstrated that this is a valid tool for assessment of needle sensation associated with *deqi*. This study has also shown that this Chinese version of MASS has good repeatability, producing consistent scores over a period of time, as well as good internal consistency. The five-factor structure of the translated version was also established. Further study with the involvement of manual acupuncture and sham acupuncture as study groups may confer greater applicability of the C-MMASS in quantifying *deqi* in acupuncture in the future.

Contributors All authors were involved in the study design. DTWY and AYMJ were responsible for the conduct of the study and drafting the manuscript. MYCP performed statistical analysis.

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Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the Human Subjects Ethics Committee of the Hong Kong Polytechnic University (HSEARS20080514001).

Provenance and peer review Not commissioned; externally peer reviewed.

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Development and validation of the Chinese version of the Massachusetts General Hospital Acupuncture Sensation Scale: an exploratory and methodological study

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APPENDIX 9

Patient Consent Form of the 1st Study (Chinese)

香港理工大學康復治療科學系科研同意書

科研題目：建立麻薩諸塞醫院針灸感覺級別表 -香港中文版
科研人員：余大為先生
導師：鍾斯綺文教授 (香港理工大學康復治療學系)

科研內容：此項科研之目的，是為了建立麻薩諸塞醫院針灸感覺級別表 (香港中文版)。台端須到理工大學 ST402 室進行此研究。進行研究當日， 台端須停止飲用含咖啡鹼之飲料。進行研究時，研究員會為 台端右手掌及手脛進行三十分鐘穴位透皮神經電療，其間我們將量度 台端的血壓、心跳率及心跳率的變化。穴位透皮神經電療完畢後， 台端須填寫一份感覺級別表問卷，以反映針灸電療時之感覺。

對項目參與人仕和社會的益處：透過這項研究，能讓我們理解針灸電療電療與得氣之關係，及了解人體對針灸電療電療的生理變化。

潛在危險性：根據過往研究所知，此等針灸電療電療並無危險或不良副作用， 台端只會在穴位處或有針刺、麻痺、脹痛等感覺，此等感覺會於廿四小時內消失。進行針灸電療電療時， 台端或會感到痛楚，部份人士或會引致不適，但我們會採取適當的措施來減低此等風險。

保密: 所有用於本研究之資料將會根據法例保密，此項研究之結果可能被發表，若此項研究之結果被發表，可辨認 台端的資料將會絕對保密。

自願參予及退出: 台端 參予此項研究純屬自願性質， 台端有權拒絕參予此項研究並且不會因此而導致任何懲罰或不公平對待， 台端有權隨時退出，而此舉不會受到任何懲罰或不公平對待。與此同時，研究員或學術監督可無須得到同意而隨時終止此研究。

同意書：
本人_____已瞭解此次研究的具體情況。本人願意參加此次研究, 本人有權在任何時候、無任何原因放棄參與此次研究, 而此舉不會導致我受到任何懲罰或不公平對待。本人明白參加此研究課題的潛在危險性，以及本人的資料將不會洩露給與此研究無關的人員，我的名字或相片不會出現在任何出版物上。

本人可以用電話 27666749 來聯繫此次研究課題負責人，鍾斯綺文教授。若本人對此研究人員有任何投訴，可以聯繫梁女士（部門科研委員會秘書），電話：27665397。本人亦明白，參與此研究課題需要本人簽署一份同意書。

簽名（參與者）： 日期：

簽名（證人）： 日期：

APPENDIX 10

Patient Consent Form of the 1st Study (English)

The Hong Kong Polytechnic University
Department of Rehabilitation

Research Project Informed Consent Form

Title: Development of Modified Massachusetts Hospital Acupuncture Sensations Scale - Hong Kong Chinese Version

Principle investigator: Mr. David Yu Tai-Wai

Supervisor: Professor Alice Jones, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University

You are being invited to participate a research study to develop the a scale to quantify deqi sensation through electroacupuncture to acupuncture points. The findings in this study can help us to understand how our body responses to acupuncture.

Procedure:
You are requested to attend the Cardiopulmonary Laboratory (ST 402) at the Hong Kong Polytechnic University for data measurement. At the date of data measurement, you should refrain from any caffeine drink such as coffee, tea or soft drink. During the study, electroacupuncture will be performed on your right hand and elbow. And you will receive 45 minutes electroacupuncture. During the stimulation, your blood pressure, heart rate and heart rate changes will be measured. After the stimulation, you are required to fill in one sensation scale so as to record your sensations during the study.

Benefits: By completion of this study, we can have deeper understanding the relationship between electroacupuncture and *deqi* and will add to the knowledge base of the role of electroacupuncture in the management of body functions.

Risk and discomforts: There is no known hazard or side effects of electroacupuncture except you may feel some unusual sensations such as tingling, numbness or fullness sensations etc around the site of stimulation. During stimulation, you may also find pain around the acupuncture points. We will take all precautions to minimize any risks.

Confidentiality
All documents and information pertaining to this research study will be kept confidential in accordance with local laws and regulations. The results of this study may be published. If any data is published, your name will not be identified.

Voluntary participation and withdrawal
Your participation in this study is entirely voluntary, and refusal to participate will involve no penalty or loss of benefits to you. You may discontinue your participation at any time without penalty or loss of benefits. Your participation in this study may be stopped at any time by the assessor, principal investigator without your consent.

Consent:

I, _____, have been explained the details of this study. I voluntarily consent to participate in this study. I understand that I can withdraw from this study at any time without giving reasons, and my withdrawal will not lead to any punishment or prejudice against me. I am aware of any potential risk in joining this study. I also understand that my personal information will not be disclosed to people who are not related to this study and my name or photograph will not appear on any publications resulted from this study.

I can contact the chief investigator, Professor Alice JONES at telephone 27666749 for any questions about this study. If I have complaints related to the investigator(s), I can contact Mrs Michelle LEUNG, secretary of Departmental Research Committee, at 27665397. I know I will be given a signed copy of this consent form.

Signature (subject): Date:

_____ _____

Signature (witness): Date:

_____ _____

APPENDIX 11

Rating Form for Content Validity Measurement

Rating Form for Content validity measurement

Please indicate by putting a "√ "of the items below that you think are "Importance" to reflect Deqi sensations

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
酸痛					
疼痛					
壓迫感					
沉重感					
脹痛感					
針刺感					
麻痺感					
強烈刺痛					
淵痛					
溫暖感					
凍感					
跳動					
其他 (請明確說明)					

Please indicate by putting a "√ "of the items below that you think are "Relevance" to reflect Deqi sensations

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
酸痛					
疼痛					
壓迫感					
沉重感					
脹痛感					
針刺感					
麻痺感					
強烈刺痛					
淵痛					
溫暖感					
凍感					
跳動					
其他 (請明確說明)					

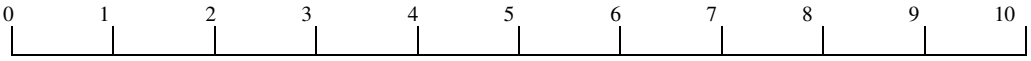
APPENDIX 12

Chinese Version of The Massachusetts General Hospital Acupuncture Sensation Scales

麻薩諸塞醫院針灸感覺級別表

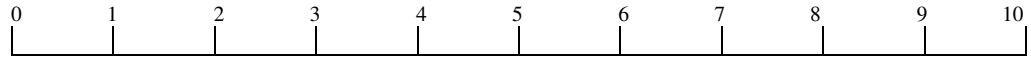
麻薩諸塞醫院針灸感覺級別表

酸痛



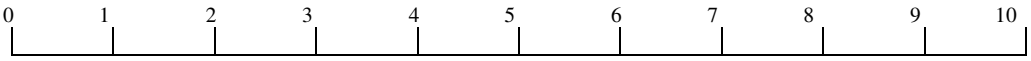
沒有感覺　輕微的　中等的　強烈的　不能忍受的

疼痛



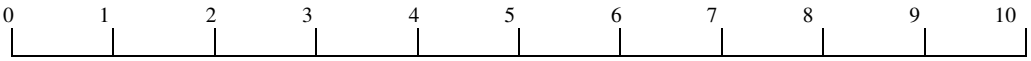
沒有感覺　輕微的　中等的　強烈的　不能忍受的

壓迫感



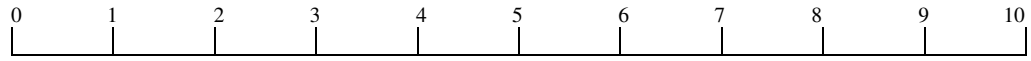
沒有感覺　輕微的　中等的　強烈的　不能忍受的

沉重感



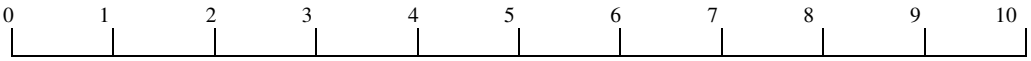
沒有感覺　輕微的　中等的　強烈的　不能忍受的

脹痛感



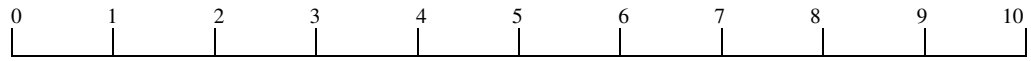
沒有感覺　輕微的　中等的　強烈的　不能忍受的

針刺感



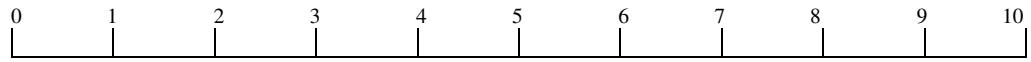
沒有感覺　輕微的　中等的　強烈的　不能忍受的

麻痺感



沒有感覺　輕微的　中等的　強烈的　不能忍受的

強烈刺痛



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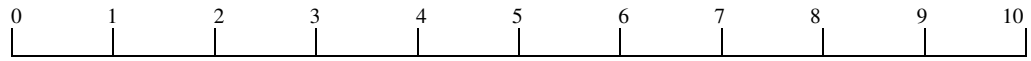

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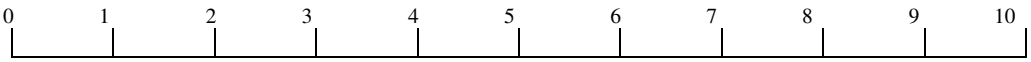

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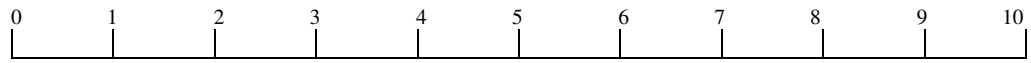

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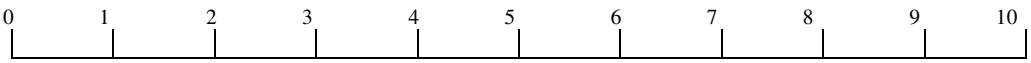

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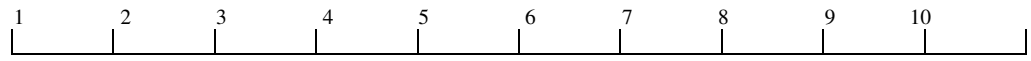

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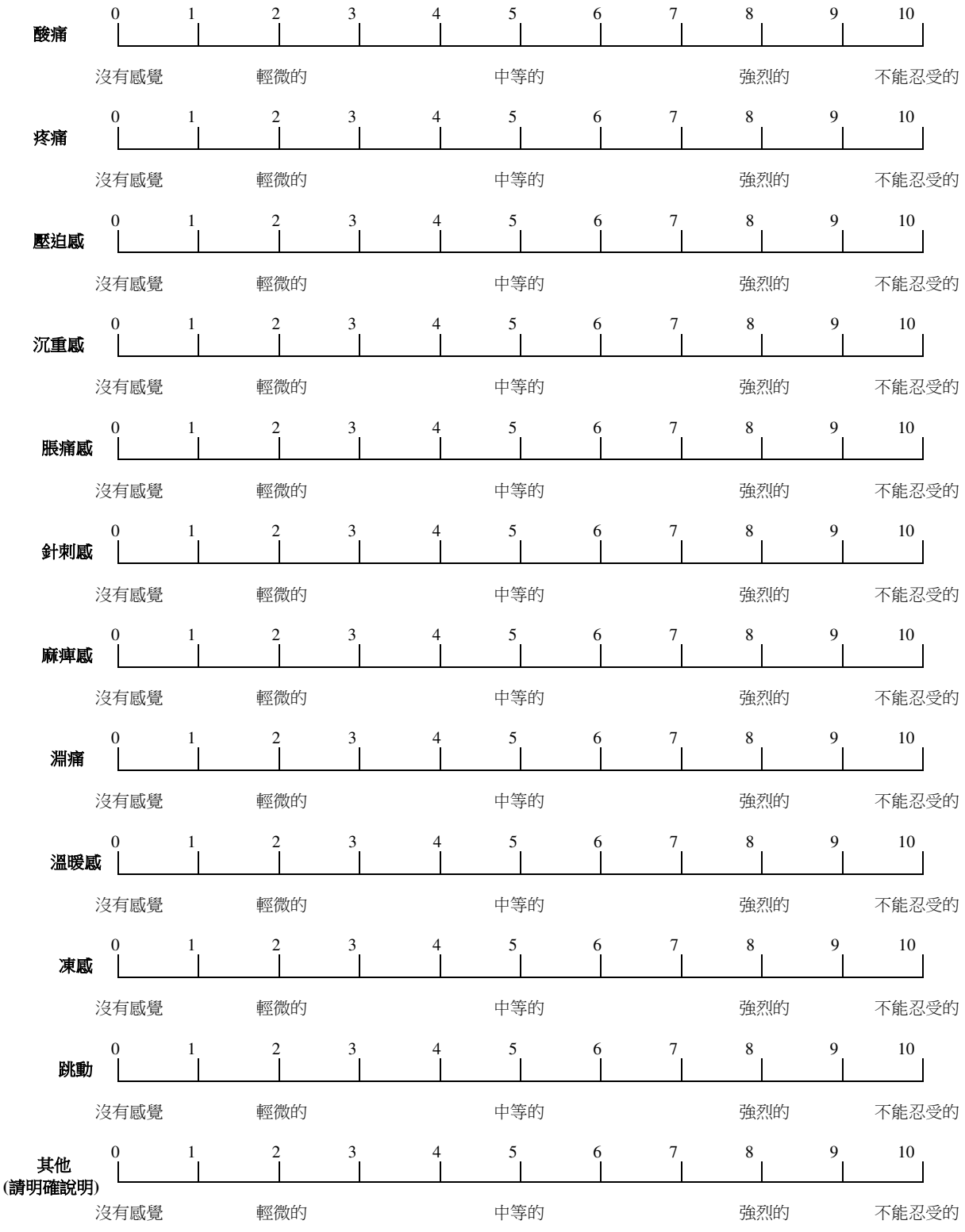
APPENDIX 13

Modified Massachusetts General Hospital Acupuncture Sensation Scales (Chinese Version)

針灸感覺級別表(香港改良版)

針灸感覺級別表(香港改良版)



APPENDIX 14

Physiological Changes Associated with Deqi during Electro-acupuncture to LI4 and LI11 – a Randomized Placebo-controlled Trial

(published in *Acupuncture in Medicine* 2013;31:143-150)

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Physiological changes associated with *de qi* during electroacupuncture to LI4 and LI11: a randomised, placebo-controlled trial

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ABSTRACT

Background Studies on the relationship between *de qi* intensity and activity changes in the autonomic nervous system (ANS) are scarce. This study investigates the physiological responses associated with *de qi*. The relationship between *de qi* intensity and such responses was determined.

Method This was a single-blinded, randomised, placebo-controlled trial. A total of 36 subjects (19 men, 17 women), aged 34.5±4.6 years, were randomly assigned to group 1 (electroacupuncture at 2 Hz, 0.4 ms to right LI4 and LI11 for 30 min), group 2 (electroacupuncture stimulation to bilateral patellae) or group 3 (sham electroacupuncture to right LI4 and LI11 but over Duoderm pads). Heart rate (HR), mean arterial blood pressure (MAP) and HR variability by low/high frequency (LF/HF) were recorded 5 min before, during and 5 min after the intervention. Needle sensations were quantified by the Modified Massachusetts General Hospital Acupuncture Sensation Scale – Chinese version (C-MMASS) and the C-MMASS index was computed.

Results A significant increase in LF/HF, MAP and HR was observed in group 1. A small and significant increase in LF/HF was observed in group 2 but the changes in MAP and HR in groups 2 and 3 were not significant. The C-MMASS index was highest in group 1 (5.3±1.3), moderate in group 2 (3.5±0.7) and lowest in group 3 (0.77±0.2). A positive correlation between *de qi* intensity and changes in LF/HF, MAP and HR was observed.

Conclusions This study suggests that *de qi* is associated with physiological changes, and that *de qi* intensity increases with an increase in sympathetic discharge of the ANS.

INTRODUCTION

According to the conceptual framework of Traditional Chinese Medicine (TCM), it was believed that disharmony and imbalance between *yin* and *yang* and disruption of *qi* (energy) flow along the energy channels (meridians) may affect health.[1] Through stimulation of acupuncture points, the flow of *qi* is believed to be modulated, leading to restoration of health. When *qi* is 'tapped' by acupuncture, the subject may experience distinct sensations known as *de qi*.[2–5] These sensations are considered to be essential for effective acupuncture stimulation,[1 6 7] though solid evidence is still lacking.[2]

In Western medicine, the concept of 'restoration of balance of *yin–yang*' is explained by modulation of the sympathetic and parasympathetic outputs of the autonomic nervous system (ANS).[1 8 9] Currently, heart rate variability (HRV) is commonly used to determine effects on modulation of the ANS in acupuncture studies.[10–12] However, reports on whether acupuncture activates or suppresses the sympathetic or parasympathetic outputs have been inconsistent. For example, acupuncture to GV14, PC6[13] and BL15[14] were shown to facilitate parasympathetic and suppress sympathetic activities whereas stimulation of LI4 showed significant increase in sympathetic activity.[15 16] Furthermore, reports on the relationship between the acupuncture sensations intensity and changes in the ANS activities are scarce. Whether these sensations are necessary to evoke changes in the ANS, and whether stimulation to non-acupuncture points could produce similar ANS changes, have not been investigated.

The aims of this study were to investigate the physiological responses associated with acupuncture sensations during electrostimulation of acupuncture points and to determine the correlation between the intensity of these sensations and such responses.

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METHODOLOGY

This study adopted a randomised, placebo-controlled trial design. Approval to conduct the study was granted by the Human Subjects Ethics Subcommittee of The Hong Kong Polytechnic University (project ID: HSEARS20110510001).

Subjects

A convenience sampling method was adopted for subject recruitment. Inclusion criteria included normal health without known cardiovascular, respiratory, neurological or psychological dysfunction; naïve to acupuncture and ability to read Chinese. Subjects with medical disorders or those required to take medications that might affect the cardiovascular system within 1 week prior to the study, or with uncomfortable sensations of the upper and lower limbs, were excluded. All subjects were informed of the aims of the study. Written consent was obtained from each subject prior to data collection.

Randomisation

Recruited subjects were randomly assigned to one of three groups and blinded to the other two groups. Three sets of group numbers were generated by computer and placed in opaque sealed envelopes. Subjects were asked to draw one envelope that contained a random group number. The drawn envelope was then opened by an independent investigator who did not participate in the study process.

For group 1, electroacupuncture was applied to right LI4 and LI11. These two points were selected since they are most frequently reported in clinical studies associated with the ANS activity.[11 17] For group 2, electroacupuncture was applied to a point at 10 mm below each patellar, that is, into the patellar tendons where there are no acupuncture points. For group 3, four Duoderm pads (ConvaTec, Skillman, New Jersey, USA), of size 10 mm×10 mm were stacked up to approximately 5 mm and applied to right LI4 and LI11 respectively. Subjects were told that the purpose of the Duoderm pads was mainly for acupuncture point identification. Acupuncture needles were then inserted 3–4 mm into the Duoderm pads and the investigator was cautious to ensure the needle did not touch the skin (figure 1). This is to ensure that electrical current would not be transmitted to the skin. The output light remained active, however, flashing in a manner similar to the other two groups. Subjects were told that with the electrical frequency applied, they may or may not feel any needle sensation.

Procedures

Subjects were asked to refrain from consumption of caffeinated drinks, smoking or strenuous physical activities on the experiment day. All measurements were taken between 16:00 to 18:00 so as to minimise the circadian effect on the ANS. Subjects were instructed to relax and breathe regularly to minimise any effect of the respiration on HRV indices.[18 19]

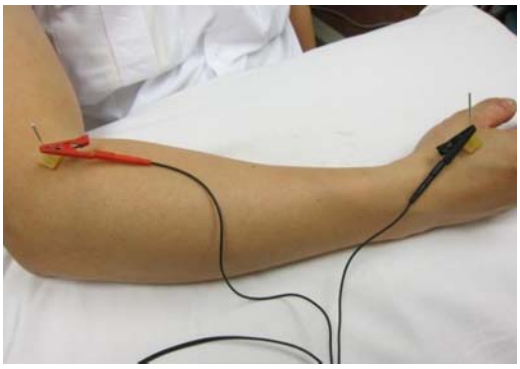

Figure 1 Sham electroacupuncture on right LI4 and LI11 over the Duoderm pads (group 3).

Upon arrival at the laboratory, subjects were asked to rest in a sitting position for 30 min. Baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels were then recorded using a digital blood pressure monitor (Mindray PM-8000 Express Patient Monitor, Bio-Medical Electricity, Hamburg, Germany). Three electrocardiogram (ECG) electrodes were placed over the left and right clavicles and left upper quadrant of the abdomen and were connected to a digital patient monitoring device (Mindray PM-8000) for recording HR and HRV during the intervention. After that, acupuncture points were located and sterilised by isopropyl alcohol. Two 30 mm×0.25 mm single-use, sterile, prepacked stainless needles with guide tubes were inserted into the LI4 and LI11 points (group 1), bilateral patellae (group 2) and to the Duoderm pads over LI4 and LI11 (group 3). The depth of needle penetration was about 10 mm for groups 1 and 2, and 3–4 mm for group 3. Manual twirling was used during needle insertion. Subjects were asked if they could feel any needle sensation, but were also told that they might or might not feel any needle sensation. Once appropriate needle insertion was established, two electrodes were then attached to the needles and connected to an electroacupuncture device (ITO, ES-160, Hannover, Germany). Electrical stimulation was applied for 30 min at a frequency of 2 Hz, pulse duration at 0.4 ms. These parameters were adopted following a study by Knardahl *et al*.[15] It was believed that low-frequency (LF) electroacupuncture has an effect on the ANS by modulating the sympathetic nerves.[20] The intensity for groups 1 and 2 was gradually increased (approximately 10 mA to 25 mA) until the subjects felt the intensity was at a moderate level using a 10-point visual analogue scale[21] (strong sensation but without feeling discomfort). All subjects were made aware that the output light was flashing. Subjects were checked every 5 min and the intensity was readjusted if necessary. At the end of the 30 min

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stimulation, the subjects were asked to complete the Hong Kong Chinese version of the Modified Massachusetts General Hospital Acupuncture Sensation Scale (C-MMASS)[22] for quantification of the acupuncture sensations during the electrical stimulation. At 5 min after the electrical stimulation, blood pressures, HR and HRV data were again recorded.

MEASUREMENTS

Mean arterial pressure and HR

SBP and DBP were recorded before inserting the acupuncture needles (before stimulation); every 5 min for 30 min during the electroacupuncture; and at 5 min after the electroacupuncture (after stimulation). The mean arterial blood pressure (MAP) was computed by using the formula DBP+(SBP−DBP)/3.

The HR and the ECG signals were recorded continuously during the electrical stimulation. The ECG signals were analysed using Chart 5 Pro for Windows. These signals were simultaneously recorded using a PowerLab 16/30 device (ADInstruments Pty Ltd, Bella Vista, New South Wales, Australia) for data acquisition and further analysis.

Heart rate variability

Recorded ECG signals were subjected to power spectral analysis using the fast Fourier transformation technique. The low LF component of the power spectrum of the HRV is defined as the power between 0.03 and 0.15 Hz, and is interpreted as a measure of sympathetic modulation.[10] The parasympathetic outflow is estimated as the high frequency (HF) component (0.15–0.5 Hz). The global sympathovagal balance was expressed by a ratio of LF to HF components (LF/HF). A high value of the LF/HF ratio reflects domination of the sympathetic system.[10 19 20]

Acupuncture sensation measurement

The C-MMASS consists of 12 descriptors of sensation and includes soreness, aching, deep pressure, heaviness, fullness/distension, tingling, numbness, dull pain, warmth, cold, throbbing, plus a blank supplementary row left for subjects to describe their own perceptions.[22] Each descriptor is presented on a 10 cm bar, anchored with numerical scores 0–10 and with the words 'none', 'mild', 'moderate' and 'severe' spaced evenly along the continuum. Immediately after the acupuncture stimulation, subjects were asked to quantify the sensations by rating the intensity for each descriptor that they may have experienced. The C-MMASS index was then calculated and was used to quantify the overall intensity of the acupuncture sensations experienced.

STATISTICAL ANALYSIS

Using the analysis and sample size software PASS 2008 (http://www.ncss.com/pass.html), and based on results of our previous study on *de qi* measurement,[22] to achieve a medium effect size, power of 0.8, and produce a two-sided 95% CI with a width equal to 0.987 and SD of 2.00, a total sample size of 36 subjects was required and 12 subjects were allocated to each group.

All statistical analyses were conducted using the statistical software SPSS for Windows V.17 (SPSS, Chicago, Illinois, USA). Data including age, resting HR, MAP and LF/HF ratio were compared among the three groups using one-way analysis of variance (ANOVA). Categorical data such as gender were compared by χ^2 analysis.

The HR, MAP and LF/HF of the three groups before, during and after electroacupuncture were compared by one-way repeated ANOVA with post-hoc pairwise comparison and Bonferroni adjustment. Moreover, an exploratory correlation analysis using Spearman's correlation was performed between the overall C-MMASS index, mean LF/HF, HR and MAP in each group. The level of significance was set at 0.05 for all analyses.

RESULTS

A total of 36 subjects (19 men, 17 women), with a mean age of 34.5±4.6 years, were recruited. There were no significant differences in baseline demographic and physiological variables among the three groups.

Changes in mean arterial blood pressure

A significant increase in MAP from a baseline of 84.6 (±2.6) mm Hg to 90.0(±0.9) mm Hg was observed during acupuncture stimulation in group 1 subjects ($p<0.05$). Such an increase failed to maintain statistical significance at 5 min after the stimulation ($p=0.058$). In group 2, the MAP demonstrated a slight, non-significant increase at the initial onset of stimulation but then gradually returned to baseline and remained stable for the rest of the observation period ($p=0.058$). For group 3, no significant changes in MAP were observed during or after the stimulation period ($p=0.599$; table 1).

Changes in heart rate

For subjects in group 1, there was a significant increase in HR in the initial period of stimulation ($p=0.035$); the HR gradually slowed down for the rest of the stimulation. No significant changes in HR were observed in subjects in group 2 ($p=0.12$) or group 3 ($p=0.242$; table 2).

Changes in autonomic nervous system activities

The computed LF/HF was highest in group 1 during electroacupuncture stimulation when compared to the other two groups ($p=0.001$) and this ratio decreased at 5 min after the stimulation but still remained significantly higher than the baseline value ($p=0.002$). Subjects in group 2 also showed a significant increase in LF/HF during stimulation when compared with the

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Table 1 Mean arterial blood pressure before, during and at 5 min post intervention (n=36)

		Stimulation period						
	Before stimulation	5 min	10 min	15 min	20 min	25 min	30 min	5 min post stimulation
Group 1 (n=12)	84.6 (±2.6)	89.0 (±4.2)*	89.8 (±4.6)*	90.8 (±4.6)*	91.0 (±4.4*)	90.3 (±4.1)*	89.1 (±3.7)*	87.4 (±3.7)
Group 2 (n=12)	86.7 (±4.4)	88.6 (±5.6)	89.2 (±5.7)	88.8 (±5.6)	88.8 (±5.0)	87.5 (±3.5)	86.6 (±3.8)	86.0 (±3.7)
Group 3 (n=12)	85.5 (±6.7)	85.2 (±4.3)	84.7 (±6.2)	84.6 (±6.9)	84.9 (±7.2)	85.3 (±7.1)	85.8 (±9.4)	84.2 (±8.9)

Group 1, true electroacupuncture to right L4 and LI11; group 2, true electroacupuncture to bilateral patellae; group 3=sham electroacupuncture to right LI4 and LI11.
*p<0.05.

baseline (p=0.01). The ratio remained slightly higher than baseline at 5 min after the stimulation; however, this was not statistically significant (p=0.084). There was a slight but insignificant increase in LF/HF during (p=0.412) and at 5 min after (p=0.375) the stimulation in group 3 (table 3).

Intensity of acupuncture sensations during stimulation

Figure 2 shows the mean intensity of each descriptor in the C-MMASS reported by the three groups. The overall C-MMASS index of group 1, group 2 and group 3 were 5.3±1.3, 3.5±0.7 and 0.77±0.2, respectively. There was a significant difference in the C-MMASS among the three groups (F=69.92. df=2, p<0.05). Post-hoc analysis with Bonferroni adjustment showed that there was a significant difference in the C-MMASS index between group 1 and 2 (p<0.05, CI=1.00 to 3.04). In group 1, dull pain, fullness/distension, aching, numbness and tingling were the most frequent sensations reported. The majority of the ratings were in the mild to moderate range. In group 2, the strongest sensations were reported for tingling and soreness. For group 3, the strongest sensations were recorded in fullness/distension and tingling. No subject opted to add any new descriptors in the blank row provided.

Association between acupuncture sensations and the physiological responses

Correlation analysis between the overall C-MMASS score and physiological responses (HR, MAP, LF/HF) revealed a strong correlation between the intensity of acupuncture sensations and the LF/HF (γ=0.89, p<0.001), MAP (γ=0.78, p=0.018) and mean HR (γ=0.71, p=0.023) in group 1. Moderate correlation was found between the acupuncture sensations intensity and LF/HF (γ=0.65, p=0.029) and MAP (γ=0.58, p=0.049) but not with the HR (γ=0.33, p=0.083) in group 2. There was a very low association between the acupuncture sensations intensity and the physiological responses in group 3 (γ=0.17, p=0.589 for LF/HF; γ=0.25, p=0.528 for MAP; γ=0.11, p=0.734 for HR).

Supplementary table S4 (web only) summarises the correlation between individual C-MMASS descriptors and the physiological responses in each group. The result showed that fullness/distension, tingling, numbness, dull pain and aching had stronger correlation with the changes in physiological responses than other acupuncture sensations. Similar associations were observed in group 2, except there was no strong correlation between the acupuncture sensations and the changes in HR. In group 3, there were no correlations between any descriptors and physiological parameters.

DISCUSSION

There is evidence that ANS activities can be modulated by acupuncture. The current study demonstrated that electroacupuncture to LI4 and LI11 induced significant sympathetic discharge. In fact, responses to acupuncture stimuli encompass a broad network of regions consistent with somatosensory, affective and cognitive processing in the brain. A recent meta-analysis on the effect of acupuncture on the human brain using functional MRI (fMRI) confirmed that verum acupuncture stimuli can modulate the

Table 2 Mean heart rate before, during and at 5 min post intervention (n=36)

		Stimulation period						
	Before stimulation	5 min	10 min	15 min	20 min	25 min	30 min	5 min post stimulation
Group 1 (n=12)	75.9 (±7.9)	80.1 (±7.8)*	81.7 (±8.2)*	81.5 (±7.9)*	80.9 (±7.2)	80.8 (±6.3)	79.5 (±6.7)	78.1 (±7.5)
Group 2 (n=12)	73.0 (±5.1)	75.7 (±5.1)	75.5 (±6.5)	76.0 (±6.3)	75.2 (±5.8)	73.3 (±6.1)	72.8 (±5.9)	71.7 (±5.6)
Group 3 (n=12)	73.5 (±7.1)	73.3 (±7.5)	72.6 (±8.1)	71.8 (±6.5)	72.6 (±5.1)	72.7 (±4.2)	72.7 (±3.9)	72.0 (±4.8)

Group 1, true electroacupuncture to right L4 and LI11; group 2, true electroacupuncture to bilateral patellae; group 3, sham electroacupuncture to right LI4 and LI11.
*p<0.05.

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Table 3 LF/HF before, during and at 5 min post intervention (n=36)

	LF/HF		
	Before stimulation	During stimulation	After stimulation
Group 1 (n=12)	0.69±0.21	2.31±1.09*	1.33±0.56*
Group 2 (n=12)	0.60±0.30	1.23±0.51*	0.77±0.23
Group 3 (n=12)	0.83±0.11	0.84±0.17	0.84±0.13

Group 1, true electroacupuncture to right L4 and LI11; group 2, true electroacupuncture to bilateral patellae; group 3, sham electroacupuncture to right LI4 and LI11.
*p<0.05.
HF, high frequency; LF, low frequency.

brain activities by activating the supramarginal gyrus, secondary somatosensory cortex, pre-supplementary motor area, middle cingulate gyrus, insula, thalamus and precentral gyrus. Acupuncture stimulation, however, was associated with deactivation of the pregenual anterior cingulate, posterior cingulate cortex, subgenual cortex, amygdale/hippocampal formation, ventromedial prefrontal cortex and nucleus accumbens of the limbic region.[23] As the central outflow of the ANS is coordinated in the medulla oblongata and regulated by the limbic system,[24] it is possible that acupuncture stimulation may induce changes in the ANS via modulation of the cerebrocerebellar limbic system.

Reports on whether acupuncture induces dominant changes in sympathetic or parasympathetic activities are inconsistent. Our results showed that LF electroacupuncture to LI4 and LI11 evoked sympathetic discharge. We offer several explanations for this observation. Firstly, studies have shown that electroacupuncture stimulation applied to LI4, at an intensity where the subject experienced strong acupuncture sensations, led to activation of the hypothalamus.[25 26] It is known that activation of the hypothalamus is associated with increase of sympathetic vasomotor activity.[26–28] Our subjects who received electroacupuncture experienced rather strong sensations as reflected by the high C-MMASS score; therefore, we believe that the ANS activity induced was associated with modulation of brain activity. Secondly, the increase in sympathetic discharge seen in this study could also be related to the acupuncture point specificity theory.[9] Some authors believed that *yin* is the parasympathetic division and *yang* is the sympathetic division of the ANS.[29] Since LI4 and LI11 lie along the Large Intestine *yang* meridian,[30] it is logical to believe that stimulation of these acupuncture points would enhance the sympathetic activities leading to an increase in mean MAP and HR. Furthermore, since all subjects were naïve to acupuncture, the initial exposure to an experimental trial with electroacupuncture may lead to an increase in anxiety-induced sympathetic activity. Nevertheless, we are unable to conclude whether electroacupuncture stimulation to LI4 and LI11 would only associate with an 'increase' in sympathetic discharge; it is possible that acupuncture could shift sympathetic or parasympathetic activities to either direction in order to maintain and restore the homeostasis of the body system. For instance, LF electroacupuncture to abdominal muscle demonstrated a significant decrease in muscle sympathetic activity in patients with polycystic ovary syndrome, a condition associated with increased sympathetic activities.[31]

Our results also show an interesting relationship between acupuncture sensations, changes in HR and MAP and an increase in sympathetic discharge. In our study, the majority of the subjects who received

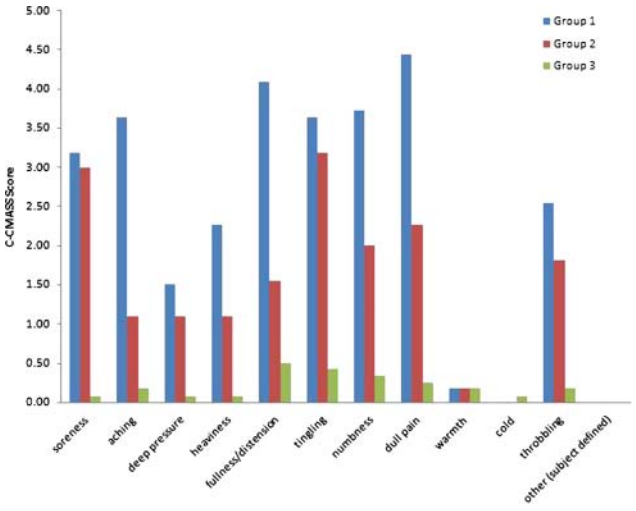

Figure 2 Mean intensity of needle sensations expressed by C-MMASS score, reported by group 1, group 2 and group 3. Group 1, true electroacupuncture to right L4 and LI11; group 2, true electroacupuncture to bilateral patellae; group 3, sham electroacupuncture to right LI4 and LI11. C-MMASS, Modified Massachusetts General Hospital Acupuncture Sensation Scale – Chinese version.

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electrical stimulation experienced sensations of dull pain, fullness/distension, aching and numbness regardless of acupuncture point or non-acupuncture point stimulation. These sensations are predominately conveyed by Aδ and Aβ fast conducting fibres.[32] Signals of the sensations will rapidly lead to an increase in impulses generated by mechanosensitive receptors of high and low threshold, resulting in afferent input to the central nervous system,[33] in turn affecting the ANS. This probably explains the positive correlation observed between acupuncture sensation intensity and the extent of ANS changes. Our findings suggest that acupuncture sensations are associated with changes in the ANS.

In the present study, electroacupuncture and not manual acupuncture was chosen. This is because the former technique is becoming more popular and commonly reported in clinical trials and research studies.[2] Also, the parameters for electroacupuncture stimulation could easily be standardised throughout the study duration. Moreover, an interesting finding of this study is that while acupuncture sensations are strongly associated with stimulation of the acupuncture point, similar sensations including dull pain, fullness/distension, aching and numbness and soreness were also reported with non-acupuncture point stimulation, although the reported intensity of these sensations were higher during electrical stimulation over acupuncture points compared to non-acupuncture points. While evidence for the anatomical existence of acupuncture points is not compelling,[34] it is believed that acupuncture points are located where nerves enter a muscle, the midpoint of the muscle, or at the enthesis where the muscle joins with the bone.[35] Stimulation of nerve branches will produce numbness, and stimulation of muscles will produce soreness and distension.[2] This probably explains the higher intensity of sensations experienced by subjects in group 1.

The use of sham electroacupuncture as placebo-control group is common in acupuncture studies. Such techniques include using retractable acupuncture needles[1 3 36 37] or insertion of the needle subcutaneously.[11 15 38] Nevertheless, both techniques have drawbacks. Pressing the skin with a retractable needle could activate the sensory pathways despite the type and strength of sensory input differing from traditional acupuncture.[9] However, insertion of a needle subcutaneously may induce an increase of the cutaneous blood flow and may also excite nociceptive primary afferents.[38 39] This afferent nerve activity can have pronounced effects on the functional connectivity in the brain, resulting in a 'limbic touch response'.[9 40] We therefore employed a new placebo method in our study. Insertion of the needle into the Duoderm pads mimics the acupuncture techniques without exertion of excessive mechanical pressure on the skin or penetration of the skin. Interestingly, some subjects still experienced mild needle sensations in group 3. As explained by Salih and coworkers, the elicitation of acupuncture sensations without cutaneous sensory input could be due to expectancy, awareness, focusing of attention on the acupuncture points, or general treatment settings by the subjects. All these could reinforce subjects' expectation that they would feel something during the interventions.[41] The slight increase in LF/HF in the placebo group could be the result of the subject's anxiety, expectation or focused attention to the points, as an increase in awareness of spontaneous activity of motoneurons could lead to an increase in the muscle and skin sympathetic nerve activity.[42]

LIMITATIONS OF THE STUDY

The major limitation of this study was the lack of a group that received electroacupuncture but elicited no acupuncture point sensations. Such a group may be ideally possible when the subjects are anaesthetised while receiving acupuncture. This current study however showed that subjects could experience some acupuncture point sensations even without actual acupuncture stimulation. Another limitation of our study is the small sample size and that our sample consisted only of healthy subjects who can reliably sense and report the needle sensations. We suggest that studies involving the above mentioned 'ideal' group, and with a larger sample size, are necessary to further investigate the relationship between acupuncture and its associated physiological effects.

CONCLUSIONS

This current study confirmed that electroacupuncture to LI4 and LI11 is likely to be associated with an increase in sympathetic discharge of the ANS. The results of the study suggest the notion that acupuncture sensations are associated with changes in the ANS. The intensity of acupuncture sensation was positively correlated with haemodynamic and ANS changes.

Summary points

- Acupuncture may generate the *de qi* sensation.
- Acupuncture may also influence the autonomic nervous system.
- Both were measured in an experiment with healthy volunteers and found to be correlated.

Contributors All authors were involved in the study design. TWDY and AYMJ were responsible for the conduct of the study and drafting the manuscript. TWDY performed the statistical analysis.

Competing interests None.

Patient consent Obtained.

Ethics approval Ethics Committee, the Hong Kong Polytechnic University.

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Physiological changes associated with de qi during electroacupuncture to LI4 and LI11: a randomised, placebo-controlled trial

David Tai Wai Yu and Alice Yee Men Jones

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APPENDIX 15

Patient Consent Form the 2nd Study (Chinese)

香港理工大學康復治療科學系科研同意書

科研題目：針灸電療時得氣與生理變化之關係
科研人員：余大為先生
導師：鍾斯綺文教授 (香港理工大學康復治療學系)

科研內容：此項科研之目的，是了解針灸電療時得氣與生理變化之關係。台端須到理工大學 ST402 室進行此研究。進行研究當日， 台端須停止飲用含咖啡鹼之飲料。進行研究時，研究員會為 台端右手掌及手腳進行三十分鐘針灸電療，其間我們將量度 台端的血壓、心跳率及心跳率的變化。針灸電療完畢後， 台端須填寫一份感覺級別表問卷，以反映針灸電療時之感覺。

對項目參與人仕和社會的益處：透過這項研究，能讓我們理解針灸電療與得氣之關係，及了解人體對針灸電療的生理變化。

潛在危險性：根據過往研究所知，此等針灸電療並無危險或不良副作用， 台端只會在穴位處或有針刺、麻痺、脹痛等感覺，此等感覺會於廿四小時內消失。進行針灸電療時， 台端或會感到痛楚，部份人士或會引致不適，但我們會採取適當的措施來減低此等風險。

保密: 所有用於本研究之資料將會根據法例保密，此項研究之結果可能被發表，若此項研究之結果被發表，可辨認 台端的資料將會絕對保密。

自願參予及退出: 台端 參予此項研究純屬自願性質， 台端有權拒絕參予此項研究並且不會因此而導致任何懲罰或不公平對待， 台端有權隨時退出，而此舉不會受到任何懲罰或不公平對待。與此同時，研究員或學術監督可無須得到同意而隨時終止此研究。

同意書：
本人_____已瞭解此次研究的具體情況。本人願意參加此次研究, 本人有權在任何時候、無任何原因放棄參與此次研究, 而此舉不會導致我受到任何懲罰或不公平對待。本人明白參加此研究課題的潛在危險性，以及本人的資料將不會洩露給與此研究無關的人員，我的名字或相片不會出現在任何出版物上。
本人可以用電話 27666749 來聯繫此次研究課題負責人，鍾斯綺文教授。若本人對此研究人員有任何投訴，可以聯繫梁女士（部門科研委員會秘書），電話：27665397。本人亦明白，參與此研究課題需要本人簽署一份同意書。

簽名（參與者）： 日期：

簽名（證人）： 日期：

APPENDIX 16

Patient Consent Form the 2nd Study (English)

The Hong Kong Polytechnic University
Department of Rehabilitation

Research Project Informed Consent Form

Title: Physiological Changes Associated with *Deqi* During Electro-acupuncture to LI4 and LI11 – a Randomized Placebo-controlled Trial

Principle investigator: Mr. David Yu Tai-Wai

Supervisor: Professor Alice Jones, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University

You are being invited to participate a research study to investigate whether the physiological changes by electroacupuncture is associated with *deqi*. The findings in this study can help us to understand how our body responses to electroacupuncture.

Procedure:
You are requested to attend the Cardiopulmonary Laboratory (ST 402) at the Hong Kong Polytechnic University for data measurement. At the date of data measurement, you should refrain from any caffeine drink such as coffee, tea or soft drink. During the study, electroacupuncture will be performed on your right hand and elbow. And you will receive 30 minutes electroacupuncture. During the stimulation, your blood pressure, heart rate and heart rate changes will be measured. After the stimulation, you are required to fill in one sensation scale so as to record your sensations during the study.

Benefits: By completion of this study, we can have deeper understanding the relationship between electroacupuncture and *deqi* and will add to the knowledge base of the role of electroacupuncture and *deqi* in the management of body functions.

Risk and discomforts: There is no known hazard or side effects of electroacupuncture except you may feel some unusual sensations such as tingling, numbness or fullness sensations etc around the site of stimulation. During stimulation, you may also find pain around the acupuncture points. We will take all precautions to minimize any risks.

Confidentiality
All documents and information pertaining to this research study will be kept confidential in accordance with local laws and regulations. The results of this study may be published. If any data is published, your name will not be identified.

Voluntary participation and withdrawal
Your participation in this study is entirely voluntary, and refusal to participate will involve no penalty or loss of benefits to you. You may discontinue your participation at any time without penalty or loss of benefits. Your participation in this study may be stopped at any time by the assessor, principal investigator without your consent.

Consent:

I, _____, have been explained the details of this study. I voluntarily consent to participate in this study. I understand that I can withdraw from this study at any time without giving reasons, and my withdrawal will not lead to any punishment or prejudice against me. I am aware of any potential risk in joining this study. I also understand that my personal information will not be disclosed to people who are not related to this study and my name or photograph will not appear on any publications resulted from this study.

I can contact the chief investigator, Professor Alice JONES at telephone 27666749 for any questions about this study. If I have complaints related to the investigator(s), I can contact Mrs Michelle LEUNG, secretary of Departmental Research Committee, at 27665397. I know I will be given a signed copy of this consent form.

Signature (subject): Date:

_____ _____

Signature (witness): Date:

_____ _____

APPENDIX 17

Are physiological changes experienced by healthy subjects during Acu-TENS associated with acupoint sensations?

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Are physiological changes experienced by healthy subjects during acu-TENS associated with acupuncture point sensations?

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ABSTRACT

Background Transcutaneous electrical nerve stimulation over acupuncture points (acu-TENS) has been reported to improve clinical outcomes. The objectives of the present study were to investigate whether acupuncture point sensations were experienced during acu-TENS, and whether such sensations were associated with any concomitant changes in autonomic nervous system activity.

Methods This study adopted a single-blinded, randomised, controlled trial methodology. A total of 36 healthy subjects were randomly assigned to an experimental group (acu-TENS on right LI4 and LI11 points); control group (acu-TENS to bilateral kneecaps); or placebo group (sham acu-TENS on right LI4 and LI11 points). Heart rate (HR), mean arterial blood pressure (MAP), SD of the NN interval (SDNN) and low frequency to high frequency ratio (LF/HF) were measured before, during and after intervention. The Hong Kong Chinese version of the Massachusetts General Hospital Acupuncture Sensation Scale (C-MMASS) index was used for quantifying the acupuncture point stimulation sensations.

Results The experimental group showed a significant increase in HR (mean (SD) 73.5 (6.3) to 75.9 (6.7) bpm, p=0.027), MAP (88.5 (4.5) to 91.0 (4.1) mm Hg, p=0.004), SDNN (143.36 (8.58) to 153.69 (7.64) ms, p=0.002) and LF/HF (1.26 (0.19) to 1.31 (0.21), p=0.037) during the intervention. The control group showed a significant increase in SDNN (140.21 (8.72) to 143.39 (9.47) ms, p=0.009) and LF/HF (1.21 (0.09) to 1.23 (0.12), p=0.033). There were no significant physiological changes in the placebo group. Overall C-MMASS indices for the experimental, control and placebo groups were 3.23 (0.3), 2.14 (0.6) and 0.29 (0.32), respectively. The between-group difference was statistically significant (F=139.24, df=2, p<0.05). However, correlation analysis did not support any association between sensation intensity and physiological responses in any groups (γ ranged from −0.36 to 0.25).

Conclusions This study showed that 'acupuncture point sensations' were experienced during acu-TENS to LI4 and LI11, but such sensations were not associated with physiological responses induced during the stimulation.

INTRODUCTION

Complementary treatments are receiving increased attention as a choice for health maintenance. Traditional Chinese Medicine (TCM) practitioners believe acupuncture is able to modulate *qi* flow and restore the *yin–yang* balance, and hence health can be maintained.[1 2] In Western medicine, acupuncture concepts have been explained as a regulation of the autonomic nervous system (ANS), revitalising and balancing the body's homeostasis through modulation of the sympathetic and parasympathetic systems.[3 4] Analysis of heart rate variability (HRV), has become a common measurement parameter in many acupuncture studies.[5–10]

While positive effects of acupuncture have been acknowledged by many studies, its associated adverse effects have also been reported.[11 12] Thus, non-invasive techniques including acupressure[13 14] and laser acupuncture[15] have been seen as 'safer' alternatives. Transcutaneous electrical nerve stimulation (TENS) applied over acupuncture points (acu-TENS), has been reported to be effective in reducing dyspnoea in patients with chronic obstructive pulmonary disease (COPD),[16 17] facilitate early haemodynamic recovery after open heart surgery,[18] relieve labour pain[19 20] and reduce blood pressure changes in normal healthy subjects.[21 22] Acu-TENS is

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also associated with an increase in blood β-endorphin level,[17 23] a decrease in airway resistance[24] and is possibly associated with regulation of the ANS.[17 23 24]

Comparative investigation of the mechanism of action of acu-TENS and acupuncture continues, but a fundamental criterion for effective acupuncture, '*de qi*', has not been examined during acu-TENS. In TCM terms, *de qi* is a unique sensation that indicates an appropriate psychophysical response to acupuncture.[1 2] In Western medicine, the *de qi* sensation is thought to indicate stimulation of the ANS via modulation of the cerebrocerebellar limbic system.[25 26] Based on previous reports on acu-TENS,[16 17] we hypothesise that acu-TENS can induce ANS changes similar to acupuncture; however, whether acupuncture point sensations described as *de qi* are necessary for the ANS changes elicited during acu-TENS has not been investigated. This study therefore aims to investigate acupuncture point sensations experienced during acu-TENS and whether such sensations are associated with any concomitant changes in ANS activity.

METHODS

Subjects

This study adopted a single-blinded (patient-blinded), randomised, controlled trial design. Ethics approval was obtained from the Human Subjects Review Committee of the involved university (Project ID: HSEARS20110510001) and was carried out within the ethical standards set forth in the Helsinki Declaration of 1975. Written consent was obtained from all participants. Normal healthy subjects who were naïve to TENS or acupuncture or acu-TENS and able to read Chinese were recruited. Subjects were excluded if they had a history of cardiopulmonary, neurological and psychological disorders, or if they required any medication for cardiovascular, neurological or psychological conditions within 1 week prior to the study.

Sample size calculation

Using the analysis and sample size software PASS 2008 (http://www.ncss.com/pass.html), and based on the results of our previous study on *de qi* measurement,[27] to achieve a medium effect size, power of 0.8 and produce a 2-sided 95% CI with a width equal to 0.987 and SD of 2.00, a total sample size of 36 subjects was considered appropriate for the study.

Randomisation procedure

Subjects were randomly assigned to one of the three groups using sequentially numbered, opaque sealed envelope simple randomisation method.[28] A total of 12 sheets of paper were marked with 'experimental group', 12 sheets with 'control group' and 12 sheets with 'placebo group', and the sheets were then put into 36 opaque envelopes (1 sheet per envelope), which were then sealed. The deck of envelopes was shuffled thoroughly by an independent assistant. Then, the front of each envelope was marked sequentially with the numbers 1–36. These envelopes were then placed in numerical order in a plastic container. Each subject was asked to draw an envelope, which was then opened by an independent investigator.

Experimental procedure

On arrival at the laboratory, subjects were asked to rest for 30 min in a sitting position to establish a steady cardiopulmonary state. Subjects were instructed to breathe normally, to minimise any effect of respiration on HRV. All measurements were taken between 16:00 and 18:00 to minimise the circadian effect on the ANS.[29]

Systolic and diastolic blood pressures were taken on the left arm by a digital patient monitor (Mindray PM-8000 Express Patient Monitor, Bio-Medical Electricity, Hamburg, Germany). The mean arterial pressure (MAP) was recorded. Electrocardiogram (ECG) electrodes were applied over left and right clavicles and left upper quadrant of abdomen and then connected to the digital patient monitor device. HR was continuously monitored. The ECG signals were analysed by Chart 5 Pro for Windows. The ECG signals were transferred to the PowerLab 16/30 (ADInstruments Pty Ltd., New South Wales, Australia) for data acquisition and analysis of the HRV.

MAP, HR and HRV parameters were measured at 5 min before the intervention, every 5 min for 45 min during the intervention and at the 5th minute after the stimulation. Data recorded during the 45 min intervention were averaged for analysis. Immediately after the intervention, subjects were asked to complete the Hong Kong Chinese version of the Massachusetts General Hospital Acupuncture Sensation Scale (C-MMASS)[27] to quantify the acupuncture point stimulation sensations.

HRV measurement

The HRV was analysed in accordance with the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[30] For frequency domain analysis, power spectral analysis was performed by the Fast Fourier Transformation technique.[29 30] Low frequency (LF), defined as the power between 0.03 and 0.15 Hz, mainly represents sympathetic modulation; high frequency (HF), defined as the power between 0.15 and 0.5 Hz, is regarded as an index of vagal (parasympathetic) modulation; the ratio LF/HF reflects the global sympathovagal balance of the body.[30 31] For the time domain analysis, the recorded SD of the NN interval (SDNN) is referred to as the global index of the HRV.[29 30 31]

Point location and preparation

The locations of the right LI4 and LI11 points and the apex of patella were identified by a trained physiotherapist. Isopropyl alcohol was applied for skin

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preparation after locating the points. Two self-adhesive ECG electrodes (F-601 SKINTACT) were then placed over the acupuncture points and attached to a dual channel portable TENS unit (120z Dual Channel TENS, EMS Physio Ltd, Oxfordshire, UK). The pulse frequency and pulse width of the TENS were set at 2 Hz and 200 ms, respectively, with the intensity adjusted to the subject's maximum tolerable level short of muscle contraction. Total duration of stimulation was 45 min.[17 23 24]

Intervention protocols

All interventions were conducted in the sitting position. For the experimental group, subjects received acu-TENS over the right LI4 and LI11 points; for the control group, subjects received TENS over the apex of bilateral kneecaps; for the placebo group, subjects received the same protocol as the experimental group and TENS but the points were covered with non-conducting plastics of the same size as the TENS electrodes, such that no electrical current would pass through the skin. Subjects were informed that they might or might not feel the electrical stimulation depending on the pulse frequency used.

Modified Massachusetts General Hospital Acupuncture Sensation Scale, Chinese version

The C-MMASS consists of 12 descriptors of sensation, including soreness, aching, deep pressure, heaviness, fullness/distension, tingling, numbness, dull pain, warmth, cold, throbbing, plus a blank supplementary row left for subjects to describe their own perceptions.[27] Each descriptor is presented on a 10-cm bar, anchored with numerical scores 0–10 and with the words 'none', 'mild', 'moderate' and 'severe' spaced evenly along the continuum. Immediately after the 45-min intervention, subjects were asked to quantify the sensations experienced by rating the intensity for each descriptor. The C-MMASS index was then calculated[27] and was used to quantify the overall intensity of the acupuncture sensations experienced.

Statistical analysis

All statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) V.17.0 for Windows. Demographic and baseline data were compared among the three groups using one-way analysis of variance (ANOVA). The within-group change in HR, MAP, LF/HF, SDNN and the C-MMASS index of the groups at before, during and after intervention were analysed by one-way repeated ANOVA. Between-group differences were analysed by one-way ANOVA with post hoc pairwise comparison and least significant difference (LSD) adjustment. The null hypothesis was rejected if the calculated F ratio exceeds the critical value with $p<0.05$. An exploratory correlation analysis using Spearman's correlation was performed between the overall C-MMASS index, mean MAP, HR, SDNN and LF/HF in each group. The level of significance was set at 0.05 for all analyses.

RESULTS

In all, 36 participants (22 men and 14 women) were recruited for this study (mean (SD): age 32.8 (2.1) years).

Blood pressure changes

The MAP increased significantly from 88.5 (4.5) mm Hg to 91.0 (4.1) mm Hg during acu-TENS in the experimental group ($p=0.004$); at 5 min after intervention, the MAP returned to 89.3 (4.6) mm Hg and was still slightly higher than baseline but did not reach statistical significance ($p=0.898$). There was no significant change in MAP for the control (from 88.7 (5.9) mm Hg to 89.6 (5.8) mm Hg) ($p=0.315$) or the placebo groups (86.6 (5.7) mm Hg to 87.1 (5.4) mm Hg) ($p=0.3$) during the stimulation (figure 1).

Heart rate changes

The HR increased significantly from 73.5 (6.3) bpm to 75.9 (6.7) bpm during acu-TENS in the experimental group ($p=0.027$) and gradually returned to baseline (74.6 (8.4) bpm) post stimulation. There was also a slight increase in HR in the control group from 73.0 (4.5) bpm to 74.2 (3.7) bpm during the stimulation period, but this was not statistically significant ($p=0.57$); the HR returned to baseline at 5 min after the stimulation. For the placebo group, there was no significant changes in HR (from 72.1 (6.9) bpm to

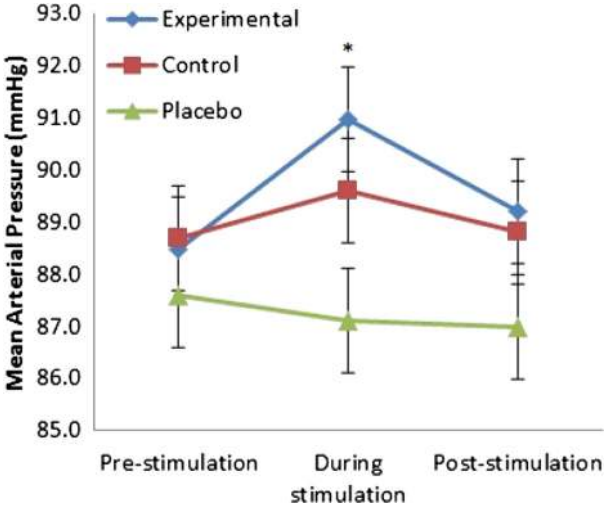

Figure 1 Changes in mean arterial pressure at various measurement timepoints in the three groups. Experimental group: transcutaneous electrical nerve stimulation over acupuncture points (acu-TENS) to right LI4 and LI11 points; control group: TENS to bilateral kneecaps; placebo group: TENS applied to non-conductive plastic films on the right LI4 and LI11 points. *Difference of mean arterial pressure between prestimulation and during stimulation in the experimental group ($p<0.05$).

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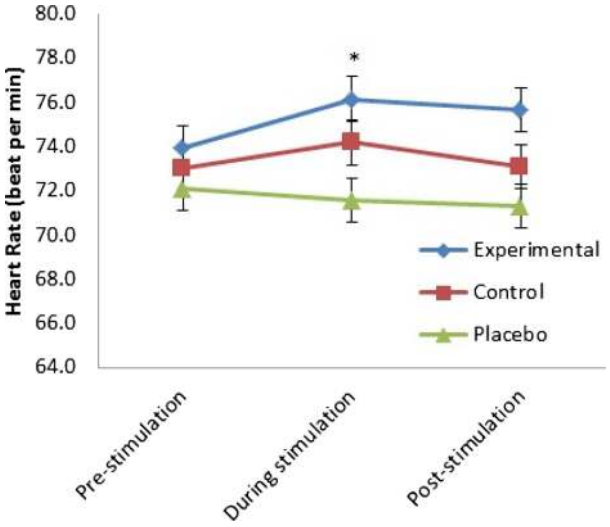

Figure 2 Heart rate changes at various measurement timepoints in the three groups. Experimental group: transcutaneous electrical nerve stimulation over acupuncture points (acu-TENS) to right LI4 and LI11 points; control group: TENS to bilateral kneecaps; placebo group: TENS applied to non-conductive plastic films on the right LI4 and LI11 points. *Difference of heart rate between prestimulation and during stimulation in the experimental group (p<0.05).

71.6 (4.7) bpm) throughout the stimulation period (p=0.831) (figure 2).

SDNN changes

The SDNN increased from 143.36 (8.58) ms to 153.69 (7.64) ms in the experimental group during stimulation (p=0.002); at 5 min post stimulation, it remained higher than the baseline value by 6.31 ms (p=0.037). For the control group, the SDNN increased from 140.21 (8.72) ms to 143.39 (9.47) ms during the stimulation (p=0.009); at 5 min post stimulation, it was 2.46 ms higher than the baseline but the change was not statistically significant (p=0.068). For the placebo group, there was no significant change in SDNN during or after the stimulation (144.38 (10.19) ms to 144.23 (10.23) ms), (figure 3). A significant between-group difference in the SDNN during the stimulation was found among the three groups (F=4.06, df=2, p=0.027). Post hoc analysis with LSD adjustment showed there was a significant difference in the SDNN between the experimental and control groups (p=0.013, CI 2.3 to 18.3) and between the experimental and placebo groups (p=0.029, CI 0.97 to 17.0). There was also a significant main effect for acu-TENS on SDNN (F=19.068, p<0.05) and a significant interaction effect between acu-TENS and the period of stimulation (F=7.91, p<0.05).

LF/HF changes

The LF/HF increased from 1.26 (0.19) to 1.32 (0.21) during acu-TENS (p=0.019) and at 5 min after the

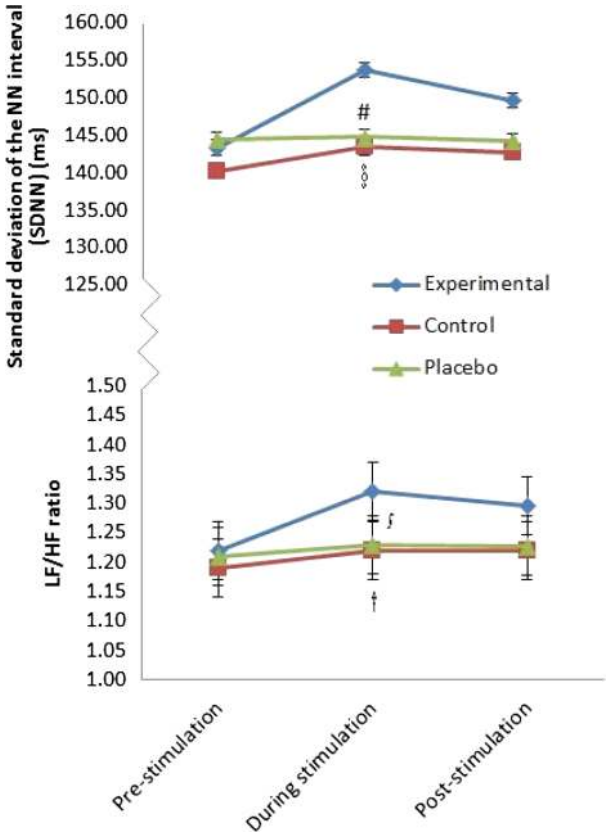

Figure 3 SDNN and LF/HF changes at various measurement timepoints in the three groups. Experimental group: transcutaneous electrical nerve stimulation over acupuncture points (acu-TENS) to right LI4 and LI11 points; control group: TENS to bilateral kneecaps; placebo group: TENS applied non-conductive plastic films on the right LI4 and LI11 points. #Difference of SDNN between the experimental group and the control group during acu-TENS (p<0.05). §Difference of SDNN between the experimental group and the placebo group during acu-TENS (p<0.05). ∫Difference of LF/HF between the experimental group and the control group during acu-TENS (p<0.05). †Difference of LF/HF between the experimental group and the placebo group during acu-TENS (p<0.05). HF, high frequency; LF, low frequency; SDNN, standard deviation of the NN interval.

stimulation (1.30 (0.17)) (p=0.037). There was a small but statistically significant increase in LF/HF in the control group during the stimulation period (from 1.21 (0.09) to 1.23 (0.12)) (p=0.033). This ratio returned to baseline 5 min after the stimulation. Changes in this ratio were not significant in the placebo group, where the LF/HF remained at 1.23 (0.11) throughout the intervention (figure 3). A significant between-group difference in the LF/HF was found during the stimulation period (F=11.25, df=2, p=0.03). Post hoc analysis with LSD adjustment showed there was a significant difference in the LF/HF between the experimental and control groups (p=0.02, CI 0.45 to 2.2) and between the experimental and placebo groups (p=0.017, CI 0.4 to 2.3). Furthermore, there was a significant primary effect for acu-TENS on LF/HF (F=2.73, p=0.044) while there

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was no significant interaction effect between acu-TENS and the period of stimulation (F=0.411, p=0.72).

Intensity of acupuncture point sensations perceived during intervention

There was a significant difference in the C-MMASS index among the three groups (F=139.24, df=2, p<0.05); with the overall C-MMASS indices of the experimental, control and placebo groups being 3.23 (0.3), 2.14 (0.6) and 0.29 (0.32), respectively. Post hoc analysis with LSD adjustment showed that there was a significant difference in the C-MMASS index between the experimental and control groups (p<0.05, CI 0.72 to 1.45) and between the experimental and placebo groups (p<0.05, CI 2.57 to 3.30). In the experimental group, the three descriptors recorded with highest ratings were throbbing, soreness and fullness/distension. For the control group, the three strongest sensations recorded were tingling, throbbing and numbness. For the placebo group, the strongest sensation recorded was tingling. No subject opted to add any new descriptors in the blank row provided (figure 4).

Association between C-MMASS score and the physiological responses

Correlation analysis between the overall C-MMASS index score and HR, MAP, SDNN and LF/HF revealed a very low association between the intensity of sensations and any of the recorded physiological responses in all groups (table 1).

DISCUSSION

This is the first study to report a relationship between acu-TENS and acupuncture point sensations, similar to *de qi* reported in the literature.[3 32 33] The results show that acupuncture point sensations were experienced by our healthy cohort and were strongest during acu-TENS, compared to non-acupuncture point and placebo stimulations.

De qi is believed to be an indispensable component of effective acupuncture.[3] Previous studies have shown that *de qi* sensation is associated with regulation of blood flow,[34–38] changes in neuronal activity in different areas of the brain,[39–41] changes in ANS activities[42–48] and an increase in pain threshold.[49] A survey conducted by the British Acupuncture Council on 574 members revealed that 87% of acupuncturists would aim to attain *de qi* during acupuncture.[50] Our previous work demonstrated that needle electroacupuncture to LI4 and LI11 increases sympathetic discharge, which was strongly associated with acupuncture point sensations.[42] Insertion of the needle into the acupuncture points, together with the needle-twirling manoeuvre, lead to muscle tension, trembling, twitching and spasm; this in turn stimulates muscle proprioceptors and gives rise to distinct needle sensations.[51] Such sensory inputs modulate ANS activities by regulating the brain activity through deactivation of the cerebrocerebellar limbic systems.[34] TENS, however, stimulates the human body through a different mechanism. TENS induces cutaneous stimulation through burst train mode, low pulse frequency, electrical activity.[22 52] Application of TENS to acupuncture points may induce acupuncture point sensations

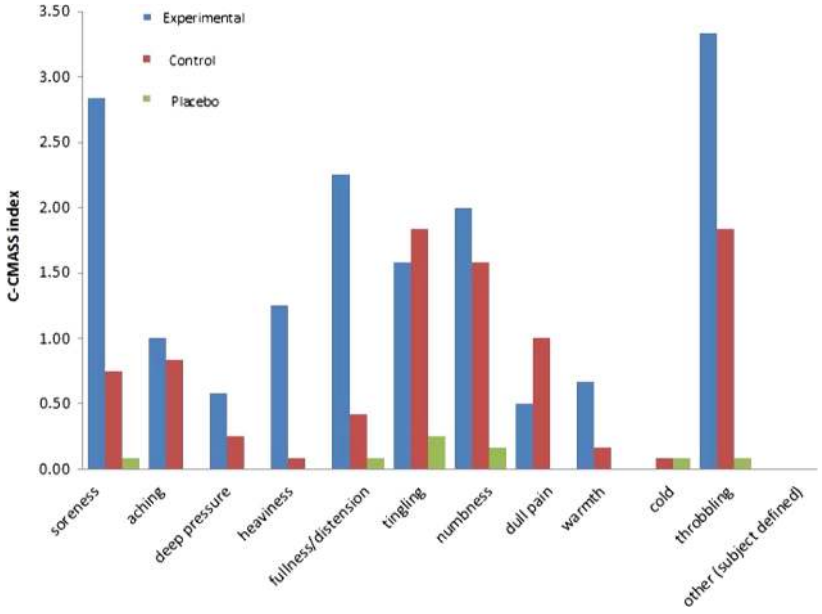

Figure 4 Intensity of sensations expressed by C-MMASS index score reported by different groups. Experimental group: transcutaneous electrical nerve stimulation over acupuncture points (acu-TENS) to right LI4 and LI11 points; control group: TENS to bilateral kneecaps; placebo group: TENS applied non-conductive plastic films on the right LI4 and LI11 points. C-MMASS, Modified Massachusetts General Hospital Acupuncture Sensation Scale, Chinese version.

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Table 1 Correlation between C-MMASS and the physiological responses

C-MMASS score	MAP	HR	SDNN	LF/HF
Experimental group	−0.16 (p=0.62)	0.08 (p=0.81)	−0.32 (p=0.32)	−0.06 (p=0.85)
Control group	−0.42 (p=0.17)	−0.06 (p=0.86)	−0.36 (p=0.6)	−0.07 (p=0.12)
Placebo group	−0.26 (p=0.41)	0.25 (p=0.15)	0.08 (p=0.81)	0.09 (p=0.76)

Experimental group: acu-TENS to right LI4 and LI11 points; control group: TENS to bilateral kneecaps; placebo group: TENS applied to non-conductive plastic films on the right LI4 and LI11 points.
Acu-TENS, transcutaneous electrical nerve stimulation over acupuncture points; C-MMASS, Modified Massachusetts General Hospital Acupuncture Sensation Scale, Chinese version; HF, High frequency; HR, heart rate; LF, low frequency; MAP, mean arterial blood pressure; SDNN, SD of the NN interval.

through electrical stimulation of the particular acupuncture point.

The results of this current study demonstrate that subjects in the experimental group experienced strong sensations of throbbing, soreness, fullness and distension, similar to the sensations described during needle acupuncture. The C-MMASS score was also reported to be highest in the experimental group, moderate in the control group and minimal in the placebo group. Anatomically, acupuncture points are areas with a high density of nerve endings and lower electrical impedance compared to other tissues.[53–56] It is possible that the 'sensation' experienced by subjects in the experimental and control groups was due to electrical current stimulation. The lower C-MMASS score recorded in the control group may be a consequence of a lower density of nerve endings in the patella region, eliciting weaker sensations compared to stimulation of actual acupuncture points. However, the acupuncture point sensations reported in the control group were different from those reported by the acu-TENS group. The dominant sensation reported by our control group was tingling, numbness and throbbing. This could be sensation of electrical stimulation rather than *de qi*. It is therefore our postulation that the 'acupuncture point effect' could at least, in part, account for the high C-MMASS score recorded in our subjects in the experimental group, and not just have arisen as a consequence of current stimulation. However, this study also suggests that the acupuncture point sensations, with descriptive features similar to *de qi*, are not associated with ANS changes induced during acu-TENS.

It is interesting to note that although there should be no electrical stimulation occurring in the placebo group, some subjects still reported mild sensations of tingling, soreness, fullness/distension and throbbing during the intervention. A previous report has also shown that placebo acu-TENS over *Dingchuan* (EX-B1) could increase forced expiratory volume in 1 second (FEV_1), reduce respiratory rate and dyspnoea score in patients with COPD,[17] and reduce airway resistance in healthy individuals after exercise.[24] Our speculation is that despite our novel placebo method of impeded electrical current to the skin, tactile sensations over the site of electrode placement were still experienced. It is possible that when one is focused on a certain body area, one could become aware of spontaneous activity of motorneurons or peripheral sensory afferents.[57] Furthermore, there is evidence to suggest that complex medical interventions or medical devices have high placebo effects.[58] The intervention procedures in this study required complex setup and frequent subject–practitioner contacts; therefore, the subjects in the placebo group may have a high expectation that contributed to the slight distinct sensations experienced.

In contrast to other studies which showed that TENS decreased sympathetic tone by providing powerful analgesic effects through the release of opioid peptides in the central nervous system,[23 59–61] our study demonstrated an increase in sympathetic discharge when acu-TENS was applied to LI4 and LI11. It may be possible that acu-TENS has a bidirectional effect when acupuncture points are stimulated; as our subjects were healthy individuals, they did not require modulation of the parasympathetic tone to induce a calming effect. Another explanation for the increase in sympathetic activities induced is that, as LI4 and LI11 are located in the Large Intestine meridian—believed to be the sympathetic division of the ANS,[62] it is possible that stimulation of the acupuncture points on the *yang* meridian will increase the sympathetic discharge. Furthermore, it was previously reported that naturally occurring sympathetic action potentials occur in bursts trains.[62] A burst mode TENS with the intensity at the maximal tolerable level was used in this current study; this may have facilitated sympathetic discharge. This may also explain why when TENS was applied to non-acupuncture points, an increase in sympathetic activities was also demonstrated although to a much lesser extent when compared with acu-TENS.

Limitations of the study

One limitation of our study is the small sample size; however, our data have produced a satisfactory medium effect size and thus we consider our findings to be valid.

If stimulation were applied to bilateral LI4 and LI11, the acupuncture point stimulation effect could be stronger. However, we were mindful to prevent occlusion of the circulation to the left forearm arm by the blood pressure cuff, especially during the inflation

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phase, as it may consequently perturb the fidelity of the acu-TENS effects on the acupuncture points.

Lastly, direct measurement of sympathetic activities such as muscle sympathetic activity and evaluation of the plasma catecholamine level[63] could help to provide more concrete evidence to demonstrate the association between acu-TENS and sympathetic outflow.

CONCLUSIONS

This is the first study to investigate the relationship between acupuncture point sensations and acu-TENS. This study showed that acupuncture point sensations were experienced during acu-TENS to LI4 and LI11; however, as the intensity of the sensations was not correlated with the physiological responses induced, we conclude that acupuncture point sensations are not associated with the physiological responses evoked during acu-TENS.

Summary points

- When using transcutaneous electrical nerve stimulation (TENS), the relationship between sensation and physiological response is unknown.
- We compared TENS at acupuncture points with TENS at a control site and placebo TENS.
- Real TENS generated physiological responses, but these were not correlated to sensation.

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Contributors All authors were involved in the study design. TWDY and AYMJ were responsible for the conduct of the study and drafting the manuscript. TWDY performed statistical analysis.

Competing interests None.

Ethics approval Human Subjects Review Committee of the Hong Kong Polytechnic University (Project ID: HSEARS20110510001).

Provenance and peer review Not commissioned; externally peer reviewed.

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Are physiological changes experienced by healthy subjects during acu-TENS associated with acupuncture point sensations?

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APPENDIX 18

Patient Consent Form of the 3rd Study (Chinese)

香港理工大學康復治療科學系科研同意書

科研題目：穴位透皮神經刺激電療能否如針灸般達至得氣及生理之變化?
科研人員：余大為先生
導師：鍾斯綺文教授 (香港理工大學康復治療學系)

科研內容：此項科研之目的，是了解**穴位透皮神經電刺激電療**能否如針灸般達至得氣感覺及生理之變化。台端須到理工大學 ST402 室進行此研究。進行研究當日， 台端須停止飲用含咖啡鹼之飲料。進行研究時，研究員會為 台端右手掌及手腳進行四十五分鐘穴位透皮神經電療，其間我們將量度 台端的血壓、心跳率及心跳率的變化。穴位透皮神經電療完畢後， 台端須填寫一份感覺級別表問卷，以反映穴位透皮神經電療時之感覺。

對項目參與人仕和社會的益處：透過這項研究，能讓我們理解穴位透皮神經電療與得氣之關係，及了解人體對穴位透皮神經電療的生理變化。

潛在危險性:根據過往研究所知,此等穴位透皮神經電療並無危險或不良副作用，台端只會在穴位處或有針刺、麻痺、脹痛等感覺,此等感覺會於廿四小時內消失。進行穴位透皮神經電療時， 台端或會感到痛楚，部份人士或會引致不適，但我們會採取適當的措施來減低此等風險。

保密: 所有用於本研究之資料將會根據法例保密，此項研究之結果可能被發表，若此項研究之結果被發表，可辨認 台端的資料將會絕對保密。

自願參予及退出: 台端 參予此項研究純屬自願性質， 台端有權拒絕參予此項研究並且不會因此而導致任何懲罰或不公平對待， 台端有權隨時退出，而此舉不會受到任何懲罰或不公平對待。與此同時，研究員或學術監督可無須得到同意而隨時終止此研究。

同意書：
本人_____已瞭解此次研究的具體情況。本人願意參加此次研究, 本人有權在任何時候、無任何原因放棄參與此次研究, 而此舉不會導致我受到任何懲罰或不公平對待。本人明白參加此研究課題的潛在危險性，以及本人的資料將不會洩露給與此研究無關的人員，我的名字或相片不會出現在任何出版物上。

本人可以用電話 27666749 來聯繫此次研究課題負責人，鍾斯綺文教授。若本人對此研究人員有任何投訴，可以聯繫梁女士（部門科研委員會秘書），電話：27665397。本人亦明白，參與此研究課題需要本人簽署一份同意書。

簽名（參與者）： 日期：

簽名（證人）： 日期：

Appendix 19

Patient Consent Form of the 3rd Study (English)

The Hong Kong Polytechnic University
Department of Rehabilitation

Research Project Informed Consent Form

Title: Are Physiological Changes Experienced by Healthy Subjects During Acu-TENS Associated with Acupoint Sensations?

Principle investigator: Mr. David Yu Tai-Wai

Supervisor: Professor Alice Jones, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University

You are being invited to participate a research study to investigate whether *deqi* can be elicited through Transcutaneous Electrical Nerve Stimulation (TENS) to acupuncture points (Acu-TENS). The findings in this study can help us to understand how our body responses to Acu-TENS.

Procedure:
You are requested to attend the Cardiopulmonary Laboratory (ST 402) at the Hong Kong Polytechnic University for data measurement. At the date of data measurement, you should refrain from any caffeine drink such as coffee, tea or soft drink. During the study, Acu-TENS will be performed on your right hand and elbow. And you will receive 45 minutes Acu-TENS. During the stimulation, your blood pressure, heart rate and heart rate changes will be measured. After the stimulation, you are required to fill in one sensation scale so as to record your sensations during the study.

Benefits: By completion of this study, we can have deeper understanding the relationship between Acu-TENS and *deqi* and will add to the knowledge base of the role of Acu-TENS in management of body functions.

Risk and discomforts: There is no known hazard or side effects of Acu-TENS except you may feel some unusual sensations such as tingling, numbness or fullness sensations etc around the site of stimulation. During stimulation, you may also find pain around the acupuncture points. We will take all precautions to minimize any risks.

Confidentiality
All documents and information pertaining to this research study will be kept confidential in accordance with local laws and regulations. The results of this study may be published. If any data is published, your name will not be identified.

Voluntary participation and withdrawal
Your participation in this study is entirely voluntary, and refusal to participate will involve no penalty or loss of benefits to you. You may discontinue your participation at any time without penalty or loss of benefits. Your participation in this study may be stopped at any time by the assessor, principal investigator without your consent.

Consent:

I, _____, have been explained the details of this study. I voluntarily consent to participate in this study. I understand that I can withdraw from this study at any time without giving reasons, and my withdrawal will not lead to any punishment or prejudice against me. I am aware of any potential risk in joining this study. I also understand that my personal information will not be disclosed to people who are not related to this study and my name or photograph will not appear on any publications resulted from this study.

I can contact the chief investigator, Professor Alice JONES at telephone 27666749 for any questions about this study. If I have complaints related to the investigator(s), I can contact Mrs Michelle LEUNG, secretary of Departmental Research Committee, at 27665397. I know I will be given a signed copy of this consent form.

Signature (subject): Date:

_____ _____

Signature (witness): Date:

_____ _____

Appendix 20

Patient Consent Form (Chinese)

香港理工大學康復治療科學系科研同意書

科研題目：穴位透皮神經刺激電療對慢性阻塞性肺病患者生理之變化
科研人員：余大為先生
導師：鍾斯綺文教授 (香港理工大學康復治療學系)

科研內容：此項科研之目的，是了解**穴位透皮神經電刺激電療**能否如針灸般達至得氣感覺及生理之變化。台端須到伊利沙伯醫院物理治療部進行此研究。進行研究當日， 台端須停止飲用含咖啡鹼之飲料及停止劇烈活動，參與者亦須進行研究當日前二十四小時，停止服用口服式或噴霧式氣管舒張劑及類固醇。進行研究時，研究員會為 台端右手掌及手腑進行四十五分鐘穴位透皮神經電療，其間我們將量度 台端的血壓、心跳率及心跳率的變化。穴位透皮神經電療完畢後， 台端須填寫一份感覺級別表問卷，以反映穴位透皮神經電療時之感覺。
對項目參與人仕和社會的益處：透過這項研究，能讓我們理解穴位透皮神經電療與得氣之關係，及了解患有慢性阻塞性肺病的患者對穴位透皮神經電療的生理變化。

潛在危險性：根據過往研究所知，此等穴位透皮神經電療並無危險或不良副作用，台端只會在穴位處或有針刺、麻痺、脹痛等感覺，此等感覺會於廿四小時內消失。進行穴位透皮神經電療時， 台端或會感到痛楚，部份人士或會引致不適，但我們會採取適當的措施來減低此等風險。

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