THE HONG KONG POLYTECHNIC UNIVERSITY

SCHOOL OF NURSING

DEVELOPING AN OBJECTIVE TRADITIONAL CHINESE MEDICINE PULSE DIAGNOSTIC MODEL IN ESSENTIAL HYPERTENSION

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A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy

July 2009

CERTIFICATE OF ORIGINALITY

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

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Abstract

Background: Traditional Chinese medicine (TCM) pulse diagnosis is used to assess the health status of patients in TCM consultation. However, the low inter-rater reliability of pulse diagnosis among TCM doctors does not fit well with evidence-based practice. Developing an objective and reliable standard for TCM pulse diagnosis has thus become a pressing issue.

Aim: The aim of this doctoral work was to develop an objective and reliable standard for TCM pulse diagnosis in hypertensive patients.

Method: A correlational study design was used and a dice model was formulated to integrate the concepts of pulse in TCM and modern medicine. The independent variable was the arterial pulse, and the dependent variable was essential hypertension. Normotensive and hypertensive subjects were recruited.

A TCM doctor rated the eight elements (depth, rate, regularity, width, length, smoothness, stiffness, and strength) at the six locations (left and right cun, guan, and chi) on a visual analogue scale. A validated pulse acquisition device was used to acquire the arterial pressure waveforms at the six locations. Sixteen physical parameters (amppeak, h_3/h_1, h_4/h_1, h_5/h_1, h_1/t_1, W/t, t, t_1/t, t_4/t, t_5/t, A_T, A_S, A_D, pamax, Δ80%pamax, and SD-PPI) were generated from the waveforms. Univariate analysis, regression analysis, and an artificial neural network (ANN) were used to analyze the data. A p-value of less than 0.05 denoted statistical significance.

Results: Group and location had a significant effect on both the eight elements and the physical parameters. Depth, width, length, smoothness, stiffness, and strength differed significantly among the six locations ($p < 0.05$). The hypertensive subjects had irregular, larger, longer, rougher, and stiffer pulse, and their pulse at left chi was more floating.

For the physical parameters, only t_1/t, h_5/h_1, and pamax differed significantly across the six locations ($p < 0.01$). A_T, A_S, A_D, amppeak, and h_1/t_1 at left and right guan and Δ80%pamax at left and right cun were significantly larger in the hypertensive group ($p < 0.01$).

The nonlinear relationship among the eight elements and the physical parameters at the six locations was identified using an ANN. The r-squared of the models ranged from 0.60 to 0.80. The accuracy of the differentiation models for hypertension was around 80%.

Discussion: The significant differences in the eight elements and the physical parameters among locations and between groups give new insight into the role of organs other than the heart in hypertension.

The nonlinear relationship among the eight elements and the physical parameters at the six locations indicates that this is a fruitful direction for future study.

For the differentiation model of hypertension, the results substantiate the recent postulation in TCM on hypertension. It may help to simplify the complicated process of syndrome differentiation in hypertension.

Conclusion: This thesis reports the first study to demonstrate the nonlinear relationship of the eight elements and the physical parameters at the six locations, and the first to differentiate hypertension using the eight elements at the six locations. With further verification, the findings could pave the way for the development of an objective, reliable, and TCM-specific pulse diagnosis standard.

Acknowledgements

Having completed my study, I must extend my heartfelt thanks to several people. First and foremost, I would like to express my gratitude to my two supervisors, Professor Joanne Chung and Dr. Fan Ka Lun, for their support and guidance during the study. They always put me first in their busy schedules and provided me with much inspiration and psychological support.

Special thanks also go to Professor Thomas Wong, who was the founder of the ASD and without whom this study would never have got off the ground. I would also like to thank Dr. William Cheung, Mr. Lau Yin Ki, and Mr. Ken Leung of the ASD and CIDH teams for their technical support. The study would not have been possible without their efforts to develop the necessary hardware and software. I am also grateful to the other members of the ASD and CIDH teams for creating a peaceful and harmonious environment from which I could draw comfort when I faced difficulties.

Thank you also to Dr. Anthony Wong and Mr. Sonny Tse for their guidance and advice on the topic of statistics and traditional Chinese medicine. I am indebted to

Mr. Lau Tak Sung, a Chinese medical doctor working at the Beijing-Hong Kong Chinese medical clinic of the Hong Kong Polytechnic University, for sparing his precious time to help me perform the pulse diagnosis during the data collection.

Ms Chen Jinghan, Ms Alice Ng, and Mr. Simon Lam generously shared their experience in conducting research with me, and gave me some good suggestions when I came up against obstacles.

Least but not the least, I am truly grateful for the patience of my family, who never once complained of my negligence when I was absorbed in conducting the study. Without their understanding, I would have never been able to finish this thesis.

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CHAPTER ONE

INTRODUCTION

1.1 Background

Hypertension is a chronic health problem and a known risk factor for cardio-cerebro-vascular morbidity and mortality (American Heart Association, 2009). There are two types of hypertension, essential and secondary hypertension. Essential hypertension, which is idiopathic in origin, constitutes over 90 percent of hypertensive cases while secondary hypertension is induced by an identifiable cause, e.g. kidney disease, diabetes mellitus (Zerwekh, Claborn, Gaglione, & Miller, 2006). In this thesis, “hypertension” refers to essential hypertension, unless stated otherwise.

Hypertension is managed differently in modern medicine and traditional Chinese medicine (TCM). In modern medicine, hypertension is assessed by systolic and diastolic blood pressure in the brachial artery (National Heart Lung and Blood

Institute [NHLBI], 2004), and is treated with medication to alleviate symptoms (Knowledge Wharton, 2007). In TCM, hypertension is assessed by palpating the pulse in the radial arteries of both wrists, a technique called TCM pulse diagnosis (中醫脈診). The purpose of TCM pulse diagnosis is to assess the harmonization of Yin and Yang of the body, and disharmony between Yin and Yang is regarded as the cause of hypertension (Lewith, 2009). The merit of TCM pulse diagnosis in assessing hypertension is that it can detect the disharmony of Yin and Yang before hypertension has developed, which means that hypertension can be treated from its origin based on the result of the pulse diagnosis. To improve the prevention of hypertension, this thesis investigates the relationship between hypertension and TCM pulse diagnosis.

1.2 TCM pulse diagnosis

TCM pulse diagnosis is used to assess a patient's current health status, and to give prognoses on and evaluate the efficacy of TCM therapies. It reveals the state of health of the organs by assessing the flow of qi and blood in both wrists. Pulse conditions (脈象) at six locations are the outcome indicators of a TCM pulse diagnosis, each of which is composed of eight fundamental elements, including depth, rate, regularity, width, length, smoothness, stiffness, and strength (Wei, 1981; Xu & Niu, 2003). The six locations where the health of organs is assessed are the left and right cun (寸), guan (關), and chi (尺).

TCM doctors are taught to interpret what they feel during pulse palpation in the same way, yet discrepancies in the pulse conditions diagnosed by doctors nevertheless occur (King, Cobbin, Walsh, & Ryan, 2002; Yoon, Koga, & Matsumoto, 1986). Further, the incongruence of TCM theories with modern scientific theories limits the use of TCM pulse diagnosis in research and clinical practice. It is posited that the lack of an objective and reliable standard of TCM pulse diagnosis is the reason for its limited use. Thus, if TCM pulse diagnosis is to be more widely used, then the pulse conditions must be accurately quantified. By quantifying the eight elements at the six locations, the work presented in this thesis substantiates TCM pulse diagnosis and thereby affirms it as an objective and reliable clinical indicator for assessing the prognoses and evaluating the efficacy of TCM therapies.

1.3 Quantification of pulse conditions

Various approaches are used to quantify pulse conditions. Linear analytical methods are mostly used to examine the relationship between pulse condition and the arterial pressure waveform, and several pulse conditions that are variously described as floating (浮), sunken (沉), string-like (弦), and slippery (滑) are found to be associated with measurable physical parameters of the arterial pressure waveform in the time (Fei, 2003; Huang & Sun, 1995; Niu, Yang, Fu, Liu, & Liu, 1994) and frequency domains (Wang & Xiang, 1998; Xu, Wang, & Zhang, 2002). Some researchers have analyzed the relationship between pulse condition and the arterial pressure waveform using nonlinear analytical methods, such as fuzzy inference and artificial neural network (ANN). However, limited work has been carried out on quantifying the eight elements at the six locations.

The eight elements at the six locations are the core component of TCM pulse diagnosis, and constitute the uniqueness of TCM pulse diagnosis. It is important to emphasize that retaining the uniqueness of TCM pulse diagnosis in the quantification process is a prerequisite for the appropriate evaluation of TCM therapies (Cai, 1988; Hui, 1999; Jia, 2008; World Health Organization Western Pacific Region, 2000). However, the researcher questions the ability of current approaches to embrace this uniqueness.

1.4 Aim and Objectives

The aim of this study is to quantify pulse condition based on the eight elements at the six locations in people with hypertension. To achieve this aim, the following objectives are set.

i. To examine the difference in the magnitude of the eight elements (depth, rate, regularity, width, length, smoothness, stiffness, and strength) at the six locations (left and right cun, guan, and chi) in hypertensive and normotensive patients.

ii. To examine the difference in the magnitude of the arterial pressure waveform in the time domain at the six locations in hypertensive and normotensive patients.

iii. To investigate the relationship among the eight elements and the arterial pressure waveform in the time domain at the six locations.

iv. To differentiate hypertension from normotension using the eight elements at the six locations.

1.5 Research questions

In accordance with the aim and objectives, four overarching research questions are posed.

i. Are there any differences in the eight elements at the six locations between normotensive and hypertensive patients?

ii. Are there any differences in the arterial pressure waveform in the time domain between normotensive and hypertensive patients?

iii. What are the relationships among the eight elements and the arterial pressure waveform in the time domain at the six locations?

iv. Is it possible to differentiate hypertension from normotension using the eight elements at the six locations?

1.6 Hypotheses

The three null hypotheses of the thesis are as follows.

i. There are no differences in the eight elements at the six locations between normotensive and hypertensive patients.
ii. There are no differences in the arterial pressure waveform in the time domain at the six locations between normotensive and hypertensive patients.
iii. The eight elements at the six locations cannot differentiate hypertension from normotension.

The corresponding three alternate hypotheses are as follows.

i. The eight elements at the six locations are different in normotensive and hypertensive patients.
ii. The arterial pressure waveforms in the time domain at the six locations are different in normotensive and hypertensive patients.

iii. The eight elements at the six locations can differentiate hypertension from normotension.

1.7 Assumptions

First, it is assumed that a TCM doctor will rate the intensity of the eight elements with the same standard across the six locations. Second, it is assumed that a TCM doctor's pulse palpation truly reflects the sensation of his or her finger.

1.8 Variables

In this thesis, the arterial pulse is the independent variable and hypertension is the dependent variable.

1.9 Definition of terms

For the sake of clarity, the following terms are defined.

i. Organs (臟): A TCM term referring to the viscera, which constitute the liver, the heart, the kidneys, the spleen, and the lungs.

ii. Arterial pulse: pulse at the radial artery.

iii. Arterial pressure waveform: pressure waveform acquired at the radial artery.

iv. Pulse diagnosis (脈診): A TCM term referring to pulse assessment.

v. Pulse condition (脈象): A TCM term referring to the overall quality of the pulse as felt by a TCM doctor when palpating the radial artery at an individual location.

1.10Delimitations

First, during pulse acquisition, the forearm and tonometer holder were designed to minimize motion artifacts, but fine movements such as the twitching of a thumb or finger may still have slightly affected the quality of the arterial pressure waveform. Second, the eight elements are the inherent subjective judgment of the magnitude of the pulse by a TCM doctor.

1.11 Organization of the Thesis

The remainder of this thesis is organized as follows. Chapter Two describes the concept of pulse assessment in TCM and in modern medicine. Chapter Three reviews studies on the quantification of pulse condition. A dice model is postulated as a conceptual framework for the quantification of pulse condition in hypertension and is presented in Chapter Four. The methodology of this study and the preparatory work undertaken before conducting the study are described in Chapter Five. The results of a pilot study and its implications for the main study are discussed in Chapter Six, followed by the results of the main study in Chapter Seven. A discussion and explanation of the limitations of the main study are given in Chapter Eight. Finally, a summary and the conclusions of the thesis are presented in Chapter Nine.

CHAPTER TWO

LITERATURE REVIEW ON PULSE ASSESSMENT IN TRADITIONAL CHINESE MEDICINE AND MODERN MEDICINE

2.1 Introduction

Pulse is the most fundamental sign of life (O'Rourke, 1971). Both traditional Chinese medicine (TCM) and modern medicine consider pulse assessment to be a crucial component in patient consultation (Maciocia, 1989). However, the way in which pulse is assessed depends on how it is conceptualized. This chapter explores the concepts of pulse from the TCM and modern medical perspectives.

The chapter starts with an explanation of Yin Yang theory. It then describes the interpretation of pulse in both streams of medicine and compares the outcome parameters of pulse assessment.

2.2 Yin Yang Theory

The earliest Chinese classic documenting Yin Yang theory is that of Yi Jing, which is the oldest Chinese classic explicating change and permanence in the universe. Figure 2-1 depicts the famous symbol "Taiji Symbol" (太極圖) that illustrates this theory.

Figure 2-1 Taiji Symbol (Adopted from Maciocia, 1989, p.5)

This symbol encapsulates two relationships of the universe: The relationship between Yin and Yang and the relationship between the parts (Yin and Yang) with that of the whole (Taiji circle). The black represents Yin and the white represents Yang. Yin and Yang are not mutually exclusive, but rather are the two poles of a continuum, together conceptualizing the nature of all matters in the universe.

The sinuous shapes represent the dynamic movement of Yin and Yang. Yin and Yang are a complementary pair in all matters and are always relative to each other. They are intergenerating, intersupporting-consuming, intertransforming, and mutually restricting (Maciocia, 1989). The small black and white circles represent the intergeneration of Yin and Yang. The whole, which is absolute in nature, is thus composed of Yin and Yang, and is represented by the large circle made up of the black and white sinuous shapes. Yin and Yang always strive for balance and the ultimate goal of Yin Yang harmony. This theory deeply influences the concept of health and pulse in TCM and in modern medicine.

2.3 Pulse in TCM

The concept of qi (氣) in TCM stems from Taoism, and encompasses everything in the universe. Jing Yue Quan Shu (景岳全書) stated that “human life depends upon this qi” (as cited in Wiseman & Ellis, 1995, p.17). Health is perceived as the harmonization of Yin qi and Yang qi. For example, Su Wen (素問) stated that “disharmony between qi and blood causes all kinds of diseases” (as cited in Li &

Liu, 2005, p. 665). The principle of health management in TCM is thus to harmonize Yin and Yang.

Pulse embraces qi, blood, and the vessels. Si Yan Ju Yao (四言舉要) stated that "Mai Nai Xie Mai, Qi Xie Zhi Xian, Xie Zhi Sui Dao…" ("脈乃血脈，氣血之先，血之隧道…") (as cited in Ma & Yan, 2001, p.277). Qi is the primary substance for growth and development, and refers to both the refined nutritive substance and physiological activities within the body (World Health Organization [WHO], 2007). Refined nutritive substance is the Yin qi, and encompasses the essence, blood, body fluid, and organs. Yang qi is the physiological activities of organs, which in TCM are categorized as qi movement and qi transformation (Wiseman & Ellis, 1995).

Qi movement is the flow of qi in four directions, that is, ascending, descending, exiting, and entering. It is the prerequisite for qi transformation, which is the mutual transformation of essence, qi, blood, and body fluids. The proper flow of qi in these four directions depends on the interaction of the organs. The liver, the heart, the lungs, the spleen, and the kidneys are the Yin form of qi, whereas qi movement and qi transformation are the Yang form of qi and their functions. The smooth flow of qi and blood storage is the function of the liver. The heart governs the blood and the vessels and pumps blood into the vessels. The lungs assist the movement of qi and the blood. The spleen mutually transforms qi and the blood, and the kidneys store essential qi, which is the basis for growth and development (Liu & Guo, 2002; Maciocia, 1989; Wiseman & Ellis, 1995).

Blood, as a Yin form of qi, is responsible for nourishing the body. Blood flowing within the vessels relies on the support of qi, and qi flowing within and outside the vessels requires nourishment from the blood. Qi and the blood are thus a complementary Yin and Yang pair that possesses all of the properties of Yin and Yang (Liu & Guo, 2002). Two Chinese sayings summarize their relationship: “Qi is the commander of blood” and “Blood is the mother of qi.” The former explains the engendering, moving, and holding action of qi on the blood, and the latter explains that qi relies on blood for growth and development, and so too the physiological activities of the body.

Qi is abstract and invisible, but crucial to life. Pulse is a medium that reflects the harmony of Yin and Yang qi in all parts of the body. Wang, Chang, Wu, Hsu, and Wang (1991) established the "Blood Pressure Wave Resonance Theory" to explain how pulse reflects qi and health.

2.3.1 Blood Pressure Wave Resonance Theory

Blood pressure wave resonance theory was proposed Wang, Chang, et al. (1991) to explain the mechanism of TCM pulse diagnosis using the concept of the coupling resonance of the aorta and organs. A physical model was established to explain the effect of organs on blood pressure waves in term of harmonics, in which a blood pressure wave is the summation of incident waves generated by the heart and their reflected waves from peripheral sites on the body. Harmonics are the frequency components of blood pressure waves. Eleven harmonics have been identified, each of which relates to a specific organ. Table 2-1 shows the eleven harmonics and their corresponding organs.

Table 2-1 Harmonics and corresponding organs (Wang, 2002)

	Organs										
	Heart	Liver	Kidneys	Spleen	Lungs	Stomach	Gallbladder	Bladder	Large intestine	Tripler burners	Small intestine
Harmonic	C_0	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}

Harmonics C_0 to C_5 occupy most of the pulse energy, which indicates that the heart, liver, kidneys, spleen, lungs, and stomach have a decisive influence on pulse (Zhang, Wang, Chen, Ke, & Wang, 1995).

Resonance is a term that is used in physics to describe the tendency of a system to oscillate at its maximum amplitude with a specific frequency (Oxford University Press, 2007, para 1d). When the circulatory system is resonant with the organs, it greatly facilitates the propagation of the blood pressure wave propagation along the arterial system by minimizing the resistance to the high-frequency components of the wave. This then enhances the blood flow through the organs and reduces the load on the heart (Nichols & O'Rourke, 1998; Wang, Chang, et al., 1991).

The intrinsic properties of the organs are important determinants of resonance in the circulatory system (Wang, Chang, et al., 1991; Wang Lin, Chang, Chen, Hsiu, & Wang, 1997; Young, Wang, Chang, & Kuo, 1992). The number of arterioles and capillaries, the distribution of arterioles and capillaries within an organ, the tissues surrounding the organ, the length of the arteries connecting the organ to the aorta, and the distance of the organ from the central arteries are all intrinsic factors affecting an organ and its associated acupoints, and hence the frequency range of reflection and oscillation with the aorta (Wang, Chang, et al.; Young et al.).

Each organ and its associated acupoints only allow a specific frequency range to pass through and reflect to the central artery (Wang, Hsu, Chen, Jan, & Wang Lin, 1994; Wang, & Wang Lin, 1992; Wang Lin et al., 1997; Yu, Wang Lin, & Wang, 1994). In a healthy condition, an organ will oscillate with the aorta to achieve a resonant condition within its chosen frequency range. The reflected waves at this frequency range reflect strongly to the aorta and so facilitate the propagation of the blood pressure wave. However, when an organ"s health is compromised, it cannot oscillate with the aorta, and the reflected waves at this frequency range are dampened and the blood pressure wave propagation affected.

This theory explains the mechanism of TCM pulse diagnosis from a physical perspective, and suggests that the state of health of the organs can be assessed through pulse assessment because a pulse is composed of frequency components that are specific to their related organs. Lu, Cheng, Lin Wang, and Wang (1996) conducted a study to examine the correlations of the eleven harmonics and people with abnormal liver function in 85 subjects, and found that harmonic C_1, C_4, and C_6 had a significant correlation with abnormal liver function. Lu (2006) conducted a similar study and supported these findings. Lu, Lin Wang, and Wang (1999) examined the correlations of the harmonics and liver cirrhosis, and found that C_3 was a significant indicator of the disease.

2.4. Pulse in modern medicine

Pulse, blood pressure, and blood pressure waves are conceptualized differently in modern medicine, and are terms used to describe the flow of blood. Pulse is taken to be “the rhythmic beating or vibrating movement” (Myers, 2009, p.1553), blood pressure is “the pressure exerted on the wall of arteries, veins and chambers of the heart by the circulating volume of blood” (Myers, p. 231), and pressure wave is a term used in physics to describe a type of elastic wave that travels through elastic solids and liquids. In cardiovascular physiology, blood pressure waves are produced by the rhythmic expansion and contraction of the heart during a cardiac cycle, pulse is the product of the blood pressure wave propagation along the arteries, and blood pressure is thus the pressure generated by the heart on the arterial system during the blood pressure wave propagation. Pulse or blood pressure originates from the circulatory system, and is regulated by other physiological systems. The process of regulating blood pressure in response to the internal and external environment is called homeostasis.

2.4.1 Blood pressure regulation and homeostasis

The concept of homeostasis emerged in the nineteenth century. Kieser (1779-1862) believed that Yin and Yang were the two forces controlling all living things (as cited in Tseui, 1989). Later in the nineteenth century, Claude Bernard (1813-1878) discovered that the body maintained itself in a constant state with respect to external and internal factors, and highlighted the importance of keeping the internal environment constant for maintaining good health (as cited in Tseui). Cannon (1871-1945) called this phenomenon homeostasis, and defined it as the maintenance of static or constant conditions in the internal environment of the body (as cited in Tseui).

The sympathetic nervous system and the parasympathetic nervous system form a complementary pair in the autonomous nervous system, analogous to that of Yang and Yin, to regulate blood pressure. Figure 2-2 shows the mechanism of blood pressure regulation inside the body.

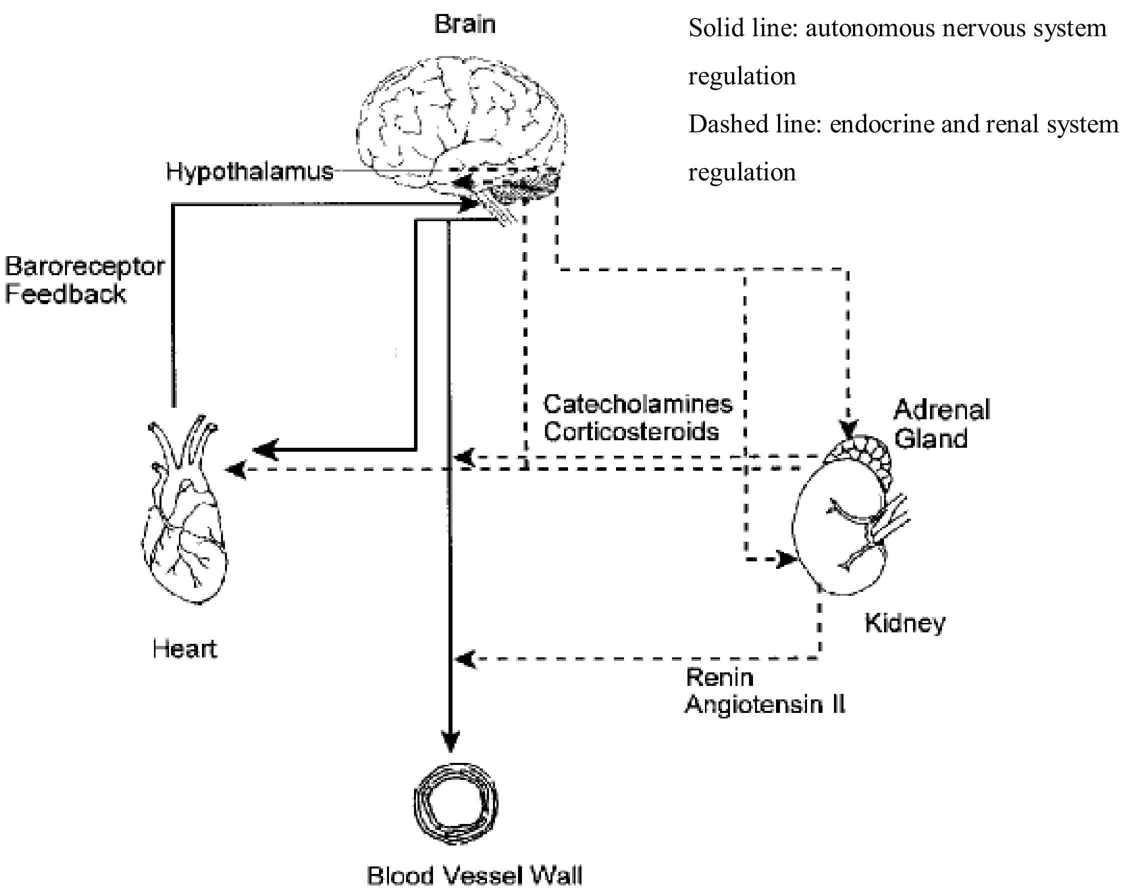

Figure 2-2 Diagrammatic presentation of blood pressure regulation (Modified from Larkin, Semenchuk, Frazer, Suchday, & Taylor, 2008)

The major physiological systems involved in regulating blood pressure are the endocrine system, the nervous system, and the renal system. Baroreceptors located in the carotid artery and the aorta act as detectors of blood pressure changes in the circulatory system. When blood pressure is high, a neural signal is sent to the parasympathetic nervous system to reduce the high pressure by lessening the heart rate. Similarly, when blood pressure is low, a neural signal is sent to the sympathetic nervous system to initiate vasoconstriction. The endocrine system is involved in releasing the appropriate hormones, that is, catecholamines and corticosteroids from the adrenal gland and rennin and angiotensin II from the kidneys, in these processes to regulate blood pressure (Larkin et al., 2008).

2.4.2 Pulse generated by the circulatory system

The periodic contraction and relaxation of the left ventricle provides the mechanical force to expel blood from the heart to the arteries. The contraction of the left ventricle is known as the systole and its relaxation as the diastole. A cardiac cycle refers to one complete sequence of ventricular contraction and relaxation (Mohrman & Heller, 1997).

After blood is pushed into arteries, the viscoelastic properties of the arteries determine the contour of the blood pressure wave. There are two types of arteries: elastic and muscular. The main difference between them lies in the amount of collagenous fibers present. The aorta is an elastic artery and is highly distensible, as it possesses less collagenous fibers. It distends greatly with increased intra-arterial pressure in normal circumstances, but under some conditions in which intra-arterial pressure exceeds the normal range, such as in hypertension, collagenous fibers are gradually recruited and the aorta becomes less distensible. Peripheral arteries, such as the radial artery, are muscular arteries that do not distend much under any circumstances, as they possess relatively more collagenous fibers and are stiffer than the elastic arteries. The stiffness gradient of both the aorta and the radial artery decreases when the intra-arterial pressure exceeds the normal range (O'Rourke, 1999), and this stiffness gradient thus influences the velocity of the wave reflection.

2.4.2.1 Wave reflection

Wave reflection can occur at any peripheral sites of the body, and represents the reflection of incident waves from the peripheries to the aorta. Arterial pulse is the summation of the incident waves and reflected waves within a cardiac cycle. Wave reflection depends on the dimensions and branching patterns of the peripheral arteries. Under normal circumstances, all reflected waves occur during the diastole. This helps to raise blood pressure in the early diastole and boost coronary perfusion without increasing systolic blood pressure (Vlachopoulos & O'Rourke, 2000).

The upper part and lower part of the body are the two main sites at which wave reflection takes place. Usually, the reflected waves from the upper body arrive at the aorta earlier than those from the lower body (Vlachopoulos & O'Rourke, 2000). However, aging and pathological changes cause the aorta to stiffen. A stiffer aorta accelerates the wave reflection and leads to the earlier return of the reflected waves. These early returned waves move progressively into the systole and augment the systolic blood pressure. This is undesirable, as augmented systolic blood pressure increases the ventricular load and decreases the coronary perfusion (Vlachopoulos & O'Rourke).

2.5 Outcome parameters of pulse assessment in TCM

Pulse conditions at six locations are the physiological parameters of a TCM pulse assessment, and indicate the location (病位), nature (病性), and interaction of pathogens and the healthy qi of a patient (病勢). The pulse conditions are classified into one of three categories of the Eight Principles (八綱) used to diagnose health status in TCM. The three categories are interior and exterior, cold and heat, and deficiency and excess, which operationalize the location, the nature, and the interaction of pathogens and healthy qi, respectively. Each category is formed by a complementary Yin and Yang pair. Interior, cold, and deficiency are the Yin half of the pair, whereas are exterior, heat, and excess are the Yang.

2.5.1 Wrist pulse taking method (寸口診法)

Wrist pulse (寸口) is the commonest region for assessing pulse. It is the radial arteries in the left and right wrists. It is first suggested in Nan Jing (難經) and further elaborated in Mai Jing (脈經). Wrist pulse is chosen by TCM doctors as the artery for pulse assessment because it is closely associated with the other eleven meridians. In Nan Jing, it states that „Shi Er Jie Dong Mai, Du Qu Cun Kou Yi Jue Wu Zang Liu Fu Siǐ Sheng Ji Xiong Zhi Fa, He Wei Ye? Ran Cun Kou Zhe, Mai Zhi Da Hui, Shou Tai Yin Zhi Mai Dong Ye.‟ ("十二皆動脈，獨取寸口，以決五臟六腑死生吉凶之法，何謂也? 然寸口者，脈之大會，手太陰之脈動也。") (Li, trans. 1999). Wrist pulse is the artery of the lung meridian, the assessment of wrist pulse means that the health of the organs can be detected.

Long before Nan Jing, Nei Jing (內經) has documented the assessment of pulse at wrist pulse. In Su Wen, it states that „Wei Wei Shui Gu Zhi Hai, Liu Fu Zhi Da Yuan Ye, Wu Wei Ru Kou, Cang Yu Wei Yi Yang Wu Zang Qi, Qi Kou Yi Da Yin Ye. Shi Yi Wu Zang Liu Fu Zhi Qi Wei, Jie Chu Yu Wei. Bian Jian Yu Qi Kou.‟ ("胃爲水谷之海，六腑之大源也，五味入口，藏於胃以養五臟氣，氣

口亦大陰也。是以五臟六腑之氣味，皆出於胃。變見於氣口。”) (Li & Liu, 2005). The above paragraph implies that blood in all arteries and meridians must pass through the lung. Only after being combined with and diffused by lung qi, blood can nourish the organs and convey essence to skin and hair. At that time, Quan Shen Bian Zhen Fa (全身遍診法) is used for pulse assessment, wrist pulse is only one of the sites in pulse assessment. In Quan Shen Bian Zhen Fa, pulses are assessed at upper, middle and lower parts of the body, it is called three positions (三部). At each part, three pulses are assessed at three sites. For example, at the middle part, pulses at Lie Que (Lu 7), Jing Qu (Lu 8) and Tai Yuan (Lu 9) , He Gu (Li 4) and Shen Men (Ht 7). Nine indicators (九候) are referred as the assessment of three pulses at three parts.

In wrist pulse taking method, its three positions and nine indicators are different from that mentioned in Nei Jing. Nan Jing describes three positions as cun, guan and chi which are the three locations at wrist pulse for pulse assessment. Nine indicators are interpreted as the three levels of depth of a pulse at each location, i.e. floating, middle and deep. Nan Jing states that „San Bu Zhe, Cun Guan Chi Ye, Jiu Hou Zhe, Fu Zhong Chen Ye.‟ (“三部者，寸關尺也，九候者，浮中沉

也。”) (Li, trans. 1999). It means that at each location, the location of the disease (病位) is assessed by applying superficial, middle and deep pressure.

Beside, Nan Jing has interpreted the length of cun, guan and chi and described their nature according to Yin Yang Theory. It defines the length of the wrist pulse as 1.9 inch, cun is 0.9 inch and chi is 1 inch. It states that „Cun Wei Yang, Chi Wei Yin, Yin De Chi Nei Yi Cun, Yang De Cun Nei Jiu Fen.‟ (“寸爲陽，尺爲陰，陰得尺內一寸，陽得寸內九分。”) (Li, trans. 1999). It does not define the length of guan. Guan is the boundary of cun and chi. Later in Mai Jing, it clearly defines cun, guan and chi. It states that „Cong Yu Ji Zhi Gao Gu Que Xing Yi Cun, Qi Zhong Ming Yue Cun Kou, Cong Cun Zhi Chi, Ming Wei Chi Ze, Gu Yue Chi Cun, Cun Hou Chi Qian Ming Yue Guan. Yang Chu Yin Ru, Yi Guan Wei Jie, Yang Chu San Fen, Yin Ru San Fen. Gu Yue San Yin San Yang.‟ (“從魚際至高骨卻行一寸，其中名曰寸口，從寸至尺，名爲尺澤，故曰尺寸，寸後尺前名曰關。陽出陰入，以關爲界，陽出三分，陰入三分。故曰三陰三陽。”) (Wang, 2002). It clearly states that 1 inch from guan to Yu Ji (Lu 10) is cun while 1 inch from guan to Chi Ze (Lu 5) is chi. Guan is the summation of 0.3 inch of cun and chi. Therefore, chi are 0.7 inch while cun and guan are 0.6 inch.

The inch in the ancient China is not the same as the one in mathematics. It is defined by Zhong Zhi Tong Shen Cun (中指同身寸). The inch is defined as the length of the middle phalange of an individual.

2.5.2 Pulse condition

Pulse itself is objective, but pulse condition is subjective. It is the quality of pulse as felt by a TCM doctor, and thus represents the subjective judgment of that doctor. More than 30 pulse conditions have been documented in Chinese medical texts. Some of them, e.g. floating, rapid, string-like are single pulse condition (單脈) which describes one element of a pulse condition. Others describe more than one element of a pulse condition which is called compound pulse condition (複脈). For example, replete is the composite of forceful, long, large and stiff (Fei, 2003).

Nei Jing describes over 30 types, e.g. large (大), small (小), long (長), short (短), slippery (滑), rough (澀), sunken (沉), slow (遲), rapid (數), strong (盛), tough (堅), soft (軟), moderate (緩), hurried (急), vacuous (虛), replete(實), scattered (散), intermittent (代), fine (細), weak (弱). Mai Jing documents 24 types which are floating (浮), sunken (沉), hollow (芤), large (洪), small (細), skipping (促), tight (緊), rapid (數), stirred(動), slippery (滑), weak (弱), string-like (弦), faint (微) , soft (軟), dissipated (散), moderate (緩), slow (遲), bound (結), drumskin (革), replete (實), intermittent (代), vacuous (虛), rough (澀) and hidden (伏). The 28 pulse conditions most commonly used in clinical practice come from Bin Hu Mai Xue (瀕湖脈學) (Li, trans 1998) and Zhen Jia Zhen Gyan (診家正眼) (Li, 1997). They are floating (浮), sunken (沉), slow (遲), rapid (數), surging (洪), fine (細), vacuous (虛), replete (實), long (長), short (短), slippery (滑), rough (澀), string-like (弦), tight (緊), soggy (濡), moderate (緩), faint (微), weak (弱), dissipated (散), hollow (芤), drumskin (革), firm (牢), hidden (伏), stirred (動), intermittent (代), bound (結), skipping (促), and racing (疾).

Descriptions of pulse conditions in Chinese medical texts are mostly qualitative, and are often illustrated by similes and poems. For instance, the slippery is compared to "beads rolling" ("如珠漼漼然，往來流利卻還前") and the string-like is like pressing the string of a musical instrument ("端直似絲弦") (Li, trans. 1998). A few of the descriptions, such as the rapid, the slow, the floating, and the sunken, are quantitative. The rapid and the slow describe the rate of a pulse, and can be quantified by the number of beats per breath. The floating and the sunken describe the depth of a pulse, and can be quantified by shu (菽), the unit of weight used during the Warring States period (403-221BC) of ancient China, with floating corresponding to three shu and sunken nine shu (Li, trans. 1999).

Using analogies and poems to describe pulse condition is subject to the interpretation of the TCM doctor. For example, the string-like may be described as like pressing the string of a musical instrument ("端直似絲弦") and the tight as like pressing a rope ("舉如轉索切如繩"), but the feeling of a string or a rope depends on the sensitivity of one‟s fingers. Qualifying words such as "a bit," "average," and "very" are used to describe the intensity of a pulse. For example, the difference between the fine and the faint is that the fine is a little bit stronger than the faint. "A little" is countable, but cannot precisely determine how much of this "little" differentiates the fine from the faint.

Descriptions of pulse conditions also overlap (Ma & Yan, 2001; Yang & Chen, 1999). Some pulse conditions describe a single dimension of pulse. The floating, for example, describes the depth of a pulse, whereas the rapid describes the rate of a pulse. Others describe two or more dimensions. The firm means string-like, long, replete, surging, and sunken, whereas the drumskin is string-like, large, rapid, and hollow. The number of dimensions that a pulse assessment should encompass is controversial. Floating or sunken and slow or rapid are the two pairs of dimensions suggested in Bin Hu Mai Xue (Li, trans 1998). Nan Jing (Li, trans 1999) and Mai Jing (Wang, 2002), in contrast, proposed three dimensions: floating or sunken, slippery or rough, and long or short. Nei Jing (Li & Liu, 2005) described three dimensions: slippery or rough, slow or rapid, and surging or fine, whereas Fei (2003) suggested floating or sunken, slow or rapid, and vacuous or replete.

It is suggested that there are two reasons for the obscurity of descriptions of pulse condition. First, TCM doctors are accustomed to assessing pulse by their own perception, rather than on a rational basis (Guan, 2001). Second, there are no concise and precise standards to guide TCM doctors in the diagnosis of pulse condition. It is likely that these two reasons are the causes of the low inter-rater and intra-rater reliability of pulse assessments by TCM doctors found by Craddock (1997) and Krass (1990) (as cited in King et al., 2002). As evidence-based practice emphasizes consistency of outcome (Water, n.d.), the low reliability of pulse assessments by TCM doctors reported in the literature demonstrates the need to standardize pulse diagnosis in TCM.

2.5.2.1 Eight Elements

Zhou Xuehai‟s (1856-1906) early attempt to standardize pulse condition is a milestone in the quantification of TCM pulse diagnosis. He proposed that each pulse condition should have four elements. “Wei Shu Xing Shi Zhe, Zheng Mai Zhi Ti Wang. Qiu Ming Mai Li Zhe, Xu Xian Jiang Wei Shu Xing Shi Jiang De Zhen Qie, Ge Zhong Mai Xiang Liao Ran, Bu Bi Ju Ni Mai Ming” (“位數形勢者，正脈之提網。求明脈理者，須先將位、數、形、勢講得真切，各種脈象了然，不必拘泥脈名。”) (as cited in Huang, 2007, p. 31). He explicitly stated that position, frequency, shape, and trend are the four main elements of pulse condition, and that each pulse condition description should contain these four elements.

Various scholars have elaborated on this idea (Fei, 2003; Li, 2005; Liu, Wang, & He, 1997; Luo, 1983; Wei, 1981; Xu & Niu, 2003), and have extended the original four elements to eight: depth, rate, regularity, width, length, smoothness, stiffness, and strength. Each pulse condition should contain these eight elements with different intensities (Fei ; Liu et al.; Wei; Xu & Niu).

Rate is the number of beats per breath. The definition of regularity is similar to that in modern medicine, it describes rhythm of a pulse condition. Rate and regularity gives information on the nature of a disease, whether heat or cold (Deng & Guo, 1983). Depth is defined as the vertical position of a pulse, and indicates the location of a disease, whether interior or exterior (Deng & Guo). Width and length describe the shape of a pulse, where width is defined as the intensity of a pulsation and length is defined as the range in which the pulsation can be sensed across the cun, guan, and chi (Fei, 2003). Smoothness is defined as the slickness of a pulse, stiffness is defined as the sensation of arterial elasticity, and strength is defined as the change in forcefulness of a pulse in response to a change of applied pressure (Deng & Guo). Width, length, smoothness, stiffness, and strength also describe the interaction of a pathogen and healthy qi in the body (Fei). The eight elements so described thus provide a basis for quantifying pulse condition.

2.5.3 Organ distribution at the six locations

Assignment of the organs to the six locations differs across Chinese medical texts. Nan Jing is the first pulse classic touching on the distribution of the organs at the six locations. Its two sayings “Xin Fei Ju Fu, Shen Gan Ju Chen, Pi Zai Bing Zhong.” (“心肺俱浮，腎肝俱沉，脾在並中。”) and “Mai You San Bu, Bu You Si Jing.” (“脈有三部，部有四經。”) (Li, trans. 1999), summarize the sequence of the organs at the six locations and describe that each location contains two meridians. Mai Jing further elaborates on the idea of Nan Jing and summaries the distribution of the organs with the saying – “Gan Xin Chu Zuo, Pi Wei Chu You, Shen Yu Ming Men Ju Chu Chi Bu.” (“肝心出左，脾胃出右，腎與命門俱出尺部。”) (Wang, 2002). TCM doctors thus follow these two pulse classics to define the distribution of the organs at wrist pulse. Figure 2-3 shows the distribution of the organs at the six locations.

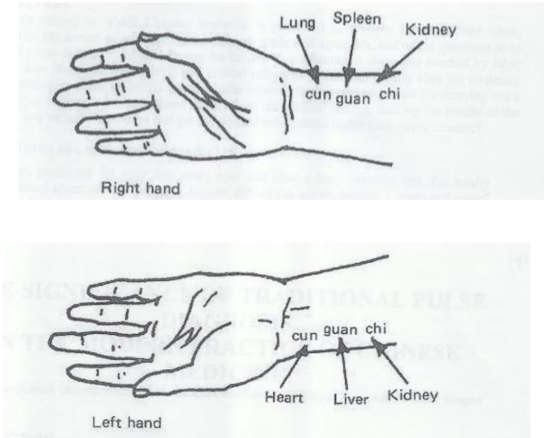

Figure 2-3 Distribution of the organs at the wrist pulse (Adapted from Dharmananda, n.d.)

Left cun, guan, and chi are the locations used to assess the Yin form of qi (the blood), whereas right cun, guan, and chi assess the Yang form of qi (the qi). The heart, liver, and kidneys are assessed at the left cun, guan, and chi, whereas the lungs, spleen and kidneys are assessed at the right cun, guan, and chi. Both the left and right chi can be used to assess the kidneys: the left chi indicates the health of the kidneys, whereas the right chi represents their physiological function, which is referred to as the lifegate. The lifegate is the place where qi transformation originates, and is the root of life (WHO, 2007).

Chinese medical texts detail different pulse conditions for the six locations. This has caused great controversy, as some argue that cun, guan, and chi rest on the same artery and that the distance among them is so short that it is impossible to discern any difference in pulse condition between them.

From the clinical perspective, it has been argued that the manipulation of a TCM doctor during pulse assessment is the key factor that causes the different pulse conditions to appear at the six locations (Yan & Ma, 1999). A TCM doctor applies different pressure to the six locations, either individually or simultaneously, to feel the changes in the pulse quality, and the changes resulting from these different pressures may be the reason for the differences in pulse condition.

Several studies have been conducted to investigate the difference in the arterial pulse at the six locations. Chang (2005) conducted a study investigating the arterial pulse at the six locations in patients with left heart failure, and found that the left ventricular ejection fraction was positively correlated with $h_1$at right cun in floating level and right guan in middle level, and negatively correlated with h_1 at left cun in middle level and right chi in sunken level. Cardiac output was positively correlated with h_1 at left guan in floating level and left chi in middle level, and was negatively correlated with h_1 at right guan in middle level and at right cun in sunken level. Yang et al. (2006) found that patients with congestive heart failure displayed an arterial pressure waveform at left cun that was significantly different from that in healthy people when different pressure was applied at the six locations. These studies demonstrated that the arterial pulse at the six locations differed across health states. Huang (2007) postulated that the radial artery at the six locations possesses a different number of neuroreceptors, and that the thresholds of these neuroreceptors, which respond to the neural signals sent out from the autonomous nervous system, would vary under different pathophysiological conditions. However, no studies have been conducted to verify this hypothesis.

2.6 Outcome parameters of pulse assessment in modern medicine

The sphygmograph introduced by Marey in 1860 is the chief outcome parameter of pulse assessment in modern medicine (Kelly et al., 1989), and consists of an arterial pressure waveform that is acquired by a validated pulse acquisition device. Arterial applanation tonometry is the most popular method used to acquire the sphygmograph, with the radial artery at the wrist being the common location for pulse assessment.

2.6.1 Arterial applanation tonometry

Applanation tonometry was originally applied to measure intra-ocular pressure. Applanation means "to flatten" and tonometry means pressure measurement (Townsend, 2007). Figure 2-4 illustrates the application of a tonometer over the radial artery.

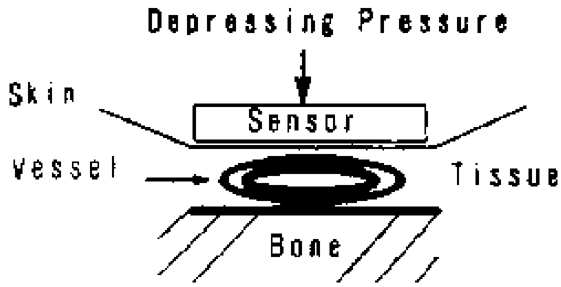

Figure 2-4 Principle of arterial tonometry (Narimatsu & Ohmori, 1992)

To ensure accurate pulse acquisition, three conditions must be satisfied. The radial artery must be fully flattened, the tonometer must be placed over the center of the flattened artery, and the artery must be supported by a rigid structure, such as the radius bone beneath the radial artery (Mattys & Verdonck, 2002; Sato, Nishinaga, Kawamoto, Ozawa, & Takatsuji, 1993; Vlachopoulos & O'Rourke, 2000). This balances the inherent circumferential forces and means that the pressure registered by the tonometer is exactly the same as the intra-arterial pressure (Mattys & Verdonck; Sato et al.). In practice, the radial artery cannot be fully flattened because of interference from the underlying bones and tissues, and it has been reported that the measurement error is strongly dependent on the degree of flattening of the radial artery (Mattys & Verdonck). To compensate for this shortcoming, calibration with cuff sphygmomanometry is required to rescale the arterial pressure waveform to its original amplitude (Mattys & Verdonck). This method has been validated by Kelly et al. (1989).

2.6.2 Arterial pressure waveform

In modern medicine, the rate, rhythm, and contour of the arterial pulse are assessed. Rate is the number of beats per minute, and rhythm refers to the regularity of the arterial pulse in terms of its contour and the interval between pulses. The contour of an arterial pulse is examined from the arterial pressure waveform (Figure 2-5), which possesses four prominent features: a percussion wave, tidal wave, incisura, and dicrotic wave.

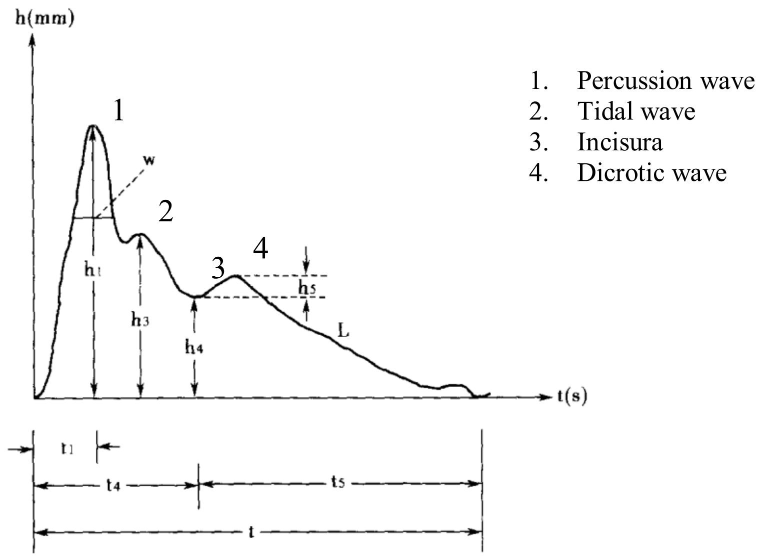

Figure 2-5 A typical arterial pressure waveform (Adapted from Fei, 2003, p.163)

The percussion wave is a sharp peak occurring in the early systole that is associated with ventricular ejection (O'Rourke, 1971). Incisura is a sharp downward deflection associated with the closure of the aortic valve at the end of ventricular systole, which occurs because a small volume of aortic blood flows backward to fill the aortic valve leaflets as they close (Morhman & Heller, 1997). Both the tidal and dicrotic waves are associated with reflected waves: the tidal wave is associated with reflected waves from the upper body and the dicrotic wave with reflected waves from the lower body (O'Rourke).

Systolic blood pressure is the pressure exerted on the arterial wall in the systolic period, whereas diastolic blood pressure is the pressure exerted on the arterial wall in the diastolic period. In addition to these two pressures, other physical parameters of the arterial pressure waveform can be used to assess pulse and hence cardiovascular function. Table 2-2 summarizes the common physical parameters used to determine cardiovascular function and their physiological implications (Fei, 2003; Huang & Sun, 1995).

Table 2-2 Physiological implications of the physical parameters of the arterial pressure waveform

Physical Parameters	**Physiological Implications**
h_1	Systolic function Aortic compliance
h_3	Arterial stiffness
h_4	Peripheral resistance
h_5	Aortic compliance
t	Duration of one cardiac cycle
t_1	Duration of rapid systolic ejection
t_4	Duration of the systolic phase
t_5	Duration of the diastolic phase
A_T	Area of a cardiac cycle
A_S	Area of a systole
A_D	Area of a diastole
W	Duration of high systolic blood pressure
h_1/t_1	Systolic slope
h_3/h_1	Arterial stiffness
h_4/h_1	Resistance index
h_5/h_1	Arterial stiffness Function of the aortic valve
t_4/t_5	Related to pulse rate
W/t	Arterial stiffness
t_1/t	Systolic function
$(t_4-t_1)/t$	Related to cardiac output

Systolic blood pressure and diastolic blood pressure are usually used to classify hypertension (NHLBI, 2004), and other physical parameters have seldom been used in clinical practice since the invention of the sphygmomanometer. Mahomed (1872) pointed out that the arterial pressure waveform conveys valuable information (as cited in O'Rourke, Pauca, & Jiang, 2000), as it does not only reflect cardiovascular health, but also the health of other organs. Mahomed (1874, 1877, as cited in O'Rourke et al., p.507) also demonstrated the effect of hypertension on the arterial pressure waveform, and used the waveform to describe essential hypertension and differentiate it from the waveform produced in the presence of chronic nephritis.

Several studies have compared the arterial pressure waveform in different health states, and have echoed the findings of Mahomed (1874, 1877, as cited in O'Rourke et al., 2000). Hu, Liu, and Chen (1998) investigated the relationship between the arterial pressure waveform and liver disease in 116 patients with liver disease and 50 healthy people as a control group. The physical parameters h_1, h_4, h_4/h_1, W, t, W/t, A_T, A_S, and A_D were extracted from the arterial pressure waveform for data analysis, and the results demonstrated a significant difference between the two groups. Lau and Chwang (2000) compared the arterial pressure waveform in healthy people and people with renal and cardiac diseases, and reported that in 97% of the arterial pressure waveforms of the healthy participants the tidal wave occurred in the late systole. The healthy participants also had a greater systolic ascending and descending slope than the participants with renal and cardiac diseases. Three kinds of arterial pressure waveform were found in the renal patients: the tidal wave appearing in the systolic slope, the tidal wave appearing in the percussion wave, a complete absence of the tidal wave and a waveform with a smooth round head. The arterial pressure waveform in the patients with cardiac disease was also significantly more irregular than that in the other two groups, and four kinds of arterial pressure waveform were identified: irregular, a waveform with a round head, an insignificant tidal waveform just after the percussion wave, and no tidal wave. Wang, Li, Guo, Chen, and Han (2000) explored the difference in arterial pressure waveform in healthy and essential hypertensive groups. One hundred and seventy six patients with essential hypertension were recruited and 118 healthy people were recruited for the healthy group. A significant difference in h_3/h_1, h_4/h_1, and W/t was found between the groups. These studies substantiate the applicability of the arterial pressure waveform for assessing the health of the organs in addition its usual use in determining cardiovascular health.

2.7 Conclusion

This review summarizes the concepts of pulse in TCM and modern medicine. It highlights how Yin Yang theory is essentially the fundamental theory underpinning both streams of medicine, with the balance of Yin and Yang being the main principle of health management. The only difference between the two streams of medicine is the way in which they present this concept. TCM, which is influenced by Taoism, holds qi to be the basic substance of pulse, and the balance of Yin qi and Yang qi to be the ultimate goal of health management. In modern medicine, this concept is presented as homeostasis, and is explained from a biochemical perspective.

Both streams of medicine also believe that pulse conveys much information about health. TCM uses a subjective approach to describe this information – the quality of the pulse as felt by a TCM doctor. This is condemned by some for being unreliable and subjective, because an objective and precise standard is not available to guide TCM doctors in diagnosing pulse condition. Modern medicine describes pulse using an objective approach – that of the sphygmograph. Although the sphygmograph is mostly confined to use in diagnosing cardiovascular diseases, studies have shown that the health information that it conveys goes beyond its current clinical application.

The review clearly indicates that there are some shortcomings in TCM pulse diagnosis. However, this thesis posits that these shortcomings can be compensated by the advanced technology of modern medicine, and specifically the development of an objective standard of TCM pulse diagnosis with the use of a sphygmograph.

Since the 1950s, much research has been carried out to quantify pulse conditions. Reviewing these studies has helped to modify the study design of this doctoral work. An extensive review of the literature is presented in Chapter Three, along with a critique of current study approaches and the identification of their strengths and weaknesses.

CHAPTER THREE

LITERATURE REVIEW ON THE QUANTIFICATION OF PULSE CONDITION IN HYPERTENSION

3.1 Introduction

To quantify means to measure or determine an amount of something (Oxford University Press, 2007, para 1). It can be subjective, such as a TCM doctor feeling a pulse, or objective, such as the arterial pressure waveform. This chapter reviews the literature on the quantification and briefly the qualification of pulse condition, in particular in hypertension.

The relevancy of the content and appropriateness of various rating scales for the qualification of pulse condition are discussed, and the selection of variables for the quantification of pulse condition is explored. The various statistical approaches to the quantification of pulse condition are then deliberated.

3.2 Qualification

The literature shows that there is much confusion about the assessment of pulse in TCM, mainly due to the ambiguous descriptions of pulse condition in Chinese medical texts (Dharmananda, n.d.). To tackle this problem, an appropriate content and rating scale must be chosen to measure pulse condition that is both relevant and adheres to the fundamental concepts of pulse assessment in TCM. Several studies have been carried out in this regard. King et al. (2002) developed a measurement scale to standardize TCM pulse assessment. However, their scale does not reflect pulse condition adequately for several reasons. First, the six items included in the scale –depth, width, force, relative force, rhythm, and pulse occlusion –are not widely accepted as core items in TCM pulse assessment. Appropriate rating scales should include the six locations, as a complete TCM pulse assessment must include the eight elements at the six locations. Second, the definitions of the items are abstract. For example, force is defined as the overall intensity of a pulse and relative force is defined as a subtler version with overall force. Third, the scale is an ordinal scale that is anchored with descriptors to measure the items. For example, depth is measured at three levels: superficial, middle, and deep. However, an ordinal scale is not a sufficiently sensitive measure, as there are an insufficient number of available response categories to rate the items (Chung, 1998), and the words used to describe each ordinal level are not universal. Further, as the items have not been well quantified, using an ordinal scale would not reflect the actual sensation perceived by a TCM doctor.

It is proposed that at the preliminary stage of quantifying pulse condition, the sensation of pulse perceived by a TCM doctor should be genuinely reflected to minimize the influence of subjective judgment on a rating scale.

3.3 Quantification

In the qualification of pulse condition, the eight elements are measured unidimensionally. It is hypothesized that the eight elements are related to the arterial pressure waveform and that their intensity is a composite of the physical parameters of the arterial pressure waveform. Relating the eight elements to these physical parameters would thus make them quantitively measurable. Much research has been carried out on the quantification of pulse condition. Measurement of the arterial pressure waveform in the time domain and frequency domain are the two main approaches currently used, but due to the disparity of research aims, methodologies, and statistical approaches, the results of existing studies in this area are incomparable.

3.3.1 Time domain

The time domain is widely used in cardiovascular research (Vlachopoulos & O'Rourke, 2000) and is also popularly used in the quantification of pulse condition (Sun, Yu, Wang, Fu, & Xia, 2003). Time domain analysis looks at the arterial pressure waveform with respect to time, and a time domain graph shows how the arterial pressure waveform changes over time. Figure 3-1 shows a typical arterial pressure waveform.

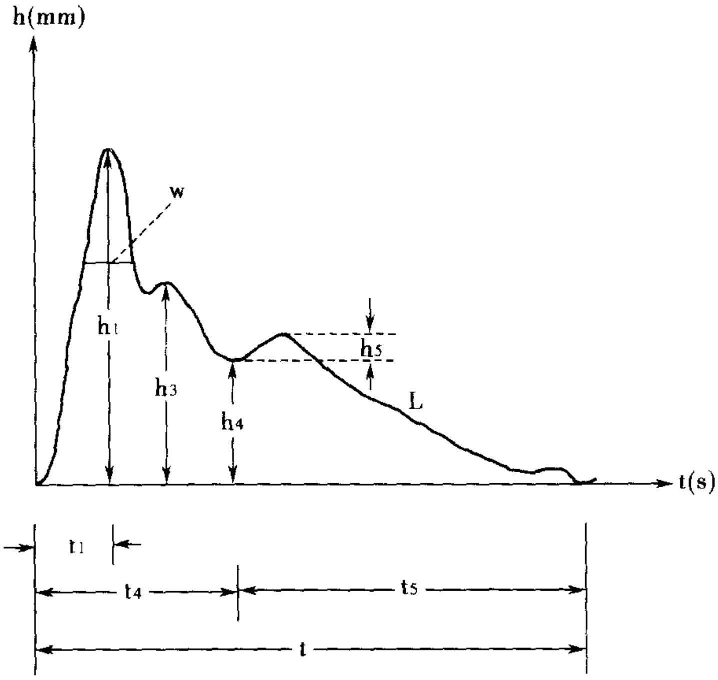

Figure 3-1 A typical arterial pressure waveform (Adapted from Fei, 2003, p.163)

In time domain, researchers extracted physical parameters from the arterial pressure waveform, such as h_1, h_3, and generate new parameters from them. Yoon, Lee, and Sah (2000) proposed three parameters to measure depth, width, and strength. Depth was measured by the hold-down pressure with the relatively largest h_1 (Pamax). The maximum average h_1 (h_1) was used to quantify width, and strength was measured by the pressure difference at the 80% maximum average h_1 (△80%pamax). These three parameters have gained some acceptance as standard parameters for the measurement of depth, width, and strength (Fei, 2003; Li, 2005).

The advantage of using the time domain for the quantification of pulse condition is that most of the physical parameters related to it have physiological meanings.

Exploring their relationship with the eight elements should thus help to understand the elements from a modern medical perspective.

Many studies have demonstrated the association between the physical parameters of the arterial pressure waveform in time domain and the eight elements (Chen, 2008; Fei, 2003; Huang, 2007; Huang & Sun, 1995; Xu, Wang, Zhang, Li, et al., 2003; Yang & Niu, 2006; Yoon et al., 2000; Zhang, Niu, Yang, & Si, 2008; Zheng, Wang, & Wang, 1994; Zhu et al., 2007). Depth has been associated with pamax, rate with t, and regularity with the interval between two individual arterial pressure waveforms and the consistency of the contour of the waveforms. Width has been associated with h_4/h_1, t_1, and h_1. The surging has been found to have a smaller h_4/h_1 and t_1 and a larger h_1. Length has been associated with h_1 at cun, guan, and chi. The short was observed to have small h_1, although association with the other physical parameters in the arterial pressure waveform was indiscernible. Smoothness has been related to W/t, h_4/h_1, t_1, h_5, and h_5/h_1. A smaller h_4/h_1 and a larger h_5 have been observed for the slippery, and h_3/h_1, h_4/h_1, and h_5/h_1 are associated with stiffness. A larger h_3/h_1 and h_4/h_1, and a smaller h_5/h_1 have been observed for the string-like. Four types of arterial pressure waveform have been identified for the string-like: lower h_1 than h_3, h_3 equal to h_1, h_3 higher than h_1, and h_3 merged with h_1. Strength is associated with a Δ80% pamax. Some of these observations have been explained in terms of hemodynamic, For example, the string-like was found to be caused by an increase in arterial stiffness and peripheral resistance, whereas width was determined by blood velocity, cardiac output, peripheral resistance, the diameter of the radial artery, and the spatial movement of the radial artery. Length has been related to the rate of arterial dilatation.

The incongruence of the results of these studies means that their postulations cannot be substantiated. Fei (2003) reported that the superficial and deep levels of depth ranged from 25 to 175g and 100 to 250g, respectively. According to Xu, Wang, Zhang, Li, et al. (2003), the range of the superficial, middle, and deep levels was smaller than 100g, 100-200g, and greater than 200g, respectively. In these studies, depth is reported as a unit of force, whereas in other studies report as a unit of pressure (Chen, 2008; Huang & Sun, 1995). Huang and Sun reported that the superficial, middle, and deep levels ranged from 10 to 40 mmHg, from 50 to 80 mmHg, and 90-120 mmHg respectively, whereas Chen reported ranges of 89.8 to 157.7 mmHg, 151.9 to 222.9 mmHg, and 279.3 mmHg for the superficial, middle, and deep levels, respectively. In terms of smoothness, Huang and Sun characterized the slippery as having t_1 within the range of 0.07 to 0.09s, h_5 larger than 2 mm, obvious h_3, and h_4/h_1 smaller than 0.50, whereas Fei found that the slippery was characterized as having W/t smaller than 0.20, an h_4/h_1 smaller than 0.40, and h_5/h_1 larger than 0.10.

There appear to be four reasons for such inconsistency. First, none of the studies reports the surface area of the sensor used. As force varies with the surface area of a sensor with the same hold-down pressure, the lack of this information makes the results incomparable. Second, the characteristics of the subjects in the studies may have affected the results. Age, gender, and weight are all factors that affect pulse condition (Fei, 2003; Huang & Sun, 1995), yet these studies report no demographic data on the subjects. Hence, it is not possible to rule out that the incongruence is due to the diversity of the subjects. Third, there is no protocol that standardizes the pulse acquisition procedure, and few of the studies reported the procedure that they used to acquire the waveform. To mimic a TCM pulse assessment, the arterial pressure waveform is acquired with different hold-down pressure applied to the radial artery. Two procedures for pulse acquisition are known. Huang (2007) developed a formula to calculate how much hold-down pressure should be used for the superficial, middle, deep, and hidden levels of depth in women and men. He also proposed that the ratio of actual body weight over ideal body weight is the determinant of the hold-down pressure (Table 3-1).

Table 3-1 Weight ratio and corresponding hold-down pressure

(Actual weight)/(Ideal weight)	***Hold-down Pressure at Different Levels of Depth***			
	Superficial	Middle	Deep	Hidden
< 0.8	50g	100g	200g	300g
0.8 – 1.0	70g	130g	250g	400g
1.0 – 1.2	100g	180g	300g	450g
> 1.2	150g	230g	350g	550g

Although several studies have adopted this protocol to acquire the waveform (Chang, 2005; Tyan, Chang, Chen, & Hsu, 2001; Yang et al., 2006), the rationale for quantifying depth in this way is not explicated, and its credibility is thus suspect. The other procedure is that of Fei (2003), who applied pressure from 0 g to 250 g at 50g intervals for each pulse acquisition. However, the interval of 50 g may be too wide, and does not allow for any change in the waveform within this interval.

Fourth, there is no standard measurement for the eight elements. The majority of the aforementioned studies focused on pulse condition rather than the eight elements. However, as each pulse condition embraces all eight elements with different intensities, even if the other seven elements have the same intensity, variation in one element will lead to a different waveform for the same pulse condition. Moreover, the sensation of a TCM doctor to the eight elements has not been standardized, and variation among the TCM doctors participating in the studies will inevitably have led to different results.

3.3.2 Frequency domain

The frequency domain can be used to analyze pulse condition based on the energy distribution of the arterial pressure waveform (Cassidy, 2002). A frequency domain graph comprises two parts –amplitude versus frequency and phase versus frequency – and is converted from the time domain of the arterial pressure waveform using a transform, which is a pair of mathematical operators used to carry out a conversion. Fast Fourier transform is an example of a commonly used transform in signal processing. Usually, the amplitude versus frequency graph is examined in studies of pulse condition. A graph showing only the amplitude and frequency is called a power spectrum (Figure 3-2).

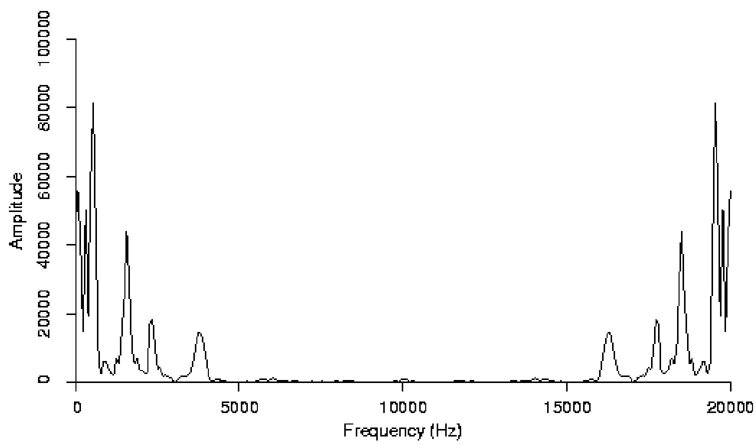

Figure 3-2 Example of a power spectrum (Adapted from Cassidy, 2002)

The y-axis of a power spectrum graph, which is labeled "amplitude" represents the power of the frequency, whereas the x-axis shows the "frequency" in Hertz (Hz). An harmonic is the frequency component of an arterial pressure waveform.

The majority of the studies that use the frequency domain to analyze the arterial pulse have focused on differentiating diseases (Fu & Lai, 1989; Wang, Luo, Xiang, & Yang, 2001; Zhang & Yang, 2005), examining the power spectrum in relation to the meridians (經絡) (Wang, 2000; Wang, Bau, Hsu, & Lin Wang, 2000), and investigating the relationship among disease, syndrome, and channels (Kuo, Chiu, et al., 2004; Kuo, Lo, & Wang, 2001; Lu, 2006; Lu, Cheng, et al., 1996; Lu, Lin Wang, et al., 1999; Su et al., 2000; Wang, Hsu, Chiang, & Lin Wang, 1996). Only a few studies have explored the characteristics of the power spectrum for different pulse conditions (Wang & Xiang, 1998; Xu et al., 2002).

Wang and Xiang (1998) discovered that the power spectrum differed markedly for the normal (平), the slippery, the string-like, and the slow-intermittent . In general, the power spectrum of all pulse conditions decreased with increasing frequency and the frequency range was within 0 to 40Hz. However, the power spectrum of the normal was smoother than that of the other three pulse conditions. The slippery had more than ten harmonics, whereas the normal had eight harmonics. The string-like and the slow-intermittent had three to five harmonics. The frequency of the normal was distributed within the 25Hz range. The percentage of energy distributed below 10Hz was 99% for the normal and 97% for the string-like, and that distributed below 5Hz was 90.2% for the moderate, 83.7% for the slippery, and 60.9% for the string-like. Forty-five percent of the energy was distributed below 1 Hz for the moderate and 16% for the string-like. These findings suggest that the frequency of the normal falls within the 1 to 5Hz range, and that frequencies below 1 Hz and over 10 Hz may indicate illness. Xu et al. (2002) suggested that counting the number of harmonics in the power spectrum could be used to differentiate pulse conditions. Their study reported that the slippery possessed three main harmonics that were much higher than those of the normal, and the drumskin had two main harmonics. The amplitude of the harmonics in the normal decreased with increasing frequency. The reasons for the different results for the slippery are the same as those proposed for the time domain quantification.

Both the time domain and frequency domain are based on the arterial pressure waveform, but differ in the way in which they interpret it. Although the available evidence supporting the applicability of the frequency domain to quantify pulse condition is weaker than that supporting the use of the time domain, this may simply due be to the lack of studies on the frequency domain. However, the time domain is to a certain extent more advantageous than the frequency domain for quantifying pulse condition because the physical parameters in the time domain have physiological meanings, which means that the physiological implications of the eight elements could be revealed if their relationship with these physical parameters were traced. It is thus more prudent and beneficial to adopt the time domain in the quantification of pulse condition.

3.4 Statistical approaches

Regression analysis is commonly used in medical research for function approximation and classification (Kleinbaum, Kupper, & Chambless, 1982; Sargent, 2001). To the best of the researcher's knowledge, no studies have examined the relationships among the physical parameters and the eight elements or the relationships among the eight elements at the six locations and hypertension using regression analysis. However, it has been suggested that more advanced statistical techniques, such as fuzzy inference and artificial neural network (ANN) may be more appropriate for modeling these relationships (Hu, 1996; Lu, Shi, Xing, & Cao, 2007; Yu, 2006).

Fuzzy inference is a modeling technique that is based on fuzzy set theory. Fuzzy set theory deals with the degree of truth in a vaguely defined set, where truth is represented as a value that ranges from 0 to 1. Lee, Suzuki, Adachi, and Umeno (1993) used fuzzy inference to assess the health state of a subject with renal problems before and after taking herbal medicine. The arterial pressure waveform was acquired at the right chi, and the physical parameters in the time domain were used to construct the fuzzy model. The results showed that the model could successfully predict the prognosis for a patient. The authors thus proposed applying fuzzy inference to assess health status using pulse condition.

ANN is a nonlinear statistical modeling technique commonly used in the modeling of complex nonlinear relationships among independent variables and dependent variables (Sargent, 2001; Zhang, 2000;). It resembles regression analysis, but has much more flexibility because it is not restricted by any statistical assumptions or prespecified algorithms. In other words, ANN is a self-adaptive and data-driven modeling technique (Wu et al., 1993; Zhang). The presence of hidden layers in the network greatly increases its capacity to deal with various complicated relationship. Figure 3-3 shows the basic architecture of an ANN.

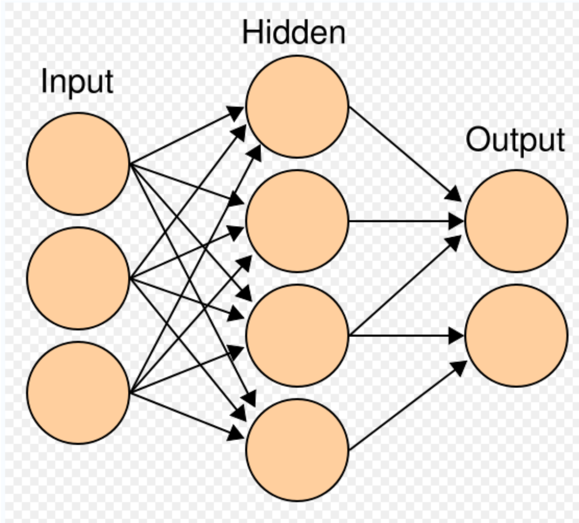

Figure 3-3 Basic architecture of an ANN (Adapted from Wikipedia, 2009)

The architecture shown in Figure 3-3 is commonly used in the type of ANN known as a multilayer perceptron. This consists of an input layer, a hidden layer, and an output layer. The input layer and output layer also appear in the architecture of linear regression, but the distinguishing characteristic of an ANN is the hidden layer in between the input and output layers. The number of hidden layers can be manipulated by the researcher until a satisfactory result is obtained. The input layer contains input neurons, which represent the number of independent variables in the study. The output neurons in the output layer are the dependent variables. The number of hidden neurons in the hidden layer(s) and the number of hidden layers in the model are determined by trial and error using the sum-squared error in function approximation and the cross entropy function in classification. The cross entropy function can be regarded as analogous to the likelihood function in logistic regression (Zhang, 2000). They are the cost functions that determine when to stop training the model.

Backpropagation is the most popular training algorithm for ANNs. This utilizes the steepest gradient descent in a multilayer perceptron to minimize the sum-squared error. The steepest gradient descent is a mathematical algorithm that locates the local minimum of a function by taking steps proportional to the negative of the gradient of the function at the current point. In backpropagation, the weights of the hidden and input neurons are modified according to the sum-squared error fed back from the output neurons until the mean squared error is minimized.

Wang and Xiang (2001) compared the accuracy of fuzzy inference and ANN in predicting pulse condition. They reported the successful application of ANN in identifying the normal, the string-like, the slippery, and the fine, and showed that ANN had a 87% predictive accuracy, which was 12% higher than that of fuzzy inference. Xu, Meng, and Wang (2007) compared the predictive accuracy of traditional ANN and fuzzy neural network in predicting eight pulse conditions. Three traditional ANNs using backpropagation were developed, each of which had 3 layers: an input layer, a hidden layer, and an output layer. The input neurons were seventeen physical parameters of the arterial pressure waveform in the time domain and the output neurons were the eight pulse conditions, which were, however, not specified. The number of hidden neurons used in the three traditional ANNs were 10, 15, and 20. The fuzzy neural network was a composite of four sub-fuzzy neural networks, and was used to model seventeen physical parameters and the four elements (position, frequency, shape and trend) proposed by Zhou Xuehai (1856-1906) (as cited in Huang, 2007) separately. The four sub-fuzzy neural networks were then combined to predict the eight pulse conditions. The three traditional ANNs obtained 86-88% accuracy, but the fuzzy neural network outperformed these networks by 4%. They concluded that it was beneficial to combine fuzzy inference and ANN to quantify pulse conditions.

The successful application of these advanced statistical techniques for quantifying pulse conditions is encouraging, and at least indicates that the various pulse conditions have a physiological basis. However, medical research emphasizes the explanatory power of a model, and values statistical techniques with a high explanatory power (Hart & Wyatt, 1990; Lisboa, 2002; Silver & Hurwitz, 1996). According to these criteria, ANN can be condemned as black box (Sargent, 2001), which means that the internal knowledge of the system cannot readily known by researchers (Hart & Wyatt).

The main rationale for using either ANN or fuzzy inference to quantify pulse condition is that pulse condition is subjective and highly complex. It is argued in this thesis that the complexity of this quantification is due to the fact that the basis of pulse condition is not well studied. Every complex relationship is built on simpler relations. The eight elements have been identified as the basic elements that make up a pulse condition. It is thus posited that clarifying the relationship among the eight elements and the physical parameters of the time domain of the arterial pressure waveform will provide more insight into the physiology of pulse condition. It has also been suggested that ANN should only be used when other statistical methods with higher explanatory power, such as regression analysis, are unable to establish a relationship (Hart & Wyatt, 1990). As no studies have reported the applicability of regression analysis in modeling the aforementioned relationships, this thesis explores the use of both regression analysis and ANN to quantify pulse condition and the eight elements in relation to the arterial pressure waveform in the time domain.

3.5 Conclusion

A handful of studies have been conducted to quantify pulse condition in TCM, and especially to quantify the eight elements at the six locations. These studies use both the time domain and frequency domain of the arterial pressure waveform, but there appears to be more evidence to support the association of the time domain and pulse condition. Furthermore, the physiological meanings of the physical parameters of the time domain could provide a physiological basis for the quantification of pulse condition. The time domain is thus chosen in this doctoral work to quantify pulse condition.

In terms of statistical approaches, no studies have reported the applicability of regression analysis to model the relationship among the physical parameters of the time domain and the eight elements in pulse condition quantification. This doctoral work thus explores the relationship using both regression analysis and ANN.

To guide the study approach in this doctoral work, a conceptual framework has been formulated, and is presented in the next chapter.

CHAPTER FOUR

CONCEPTUAL FRAMEWORK FOR TRADITIONAL CHINESE MEDICINE PULSE DIAGNOSIS

4.1 Introduction

A conceptual framework is the conceptual underpinning of a study (Polit, Beck, & Hungler, 2001). The purpose of formulating a conceptual framework is to provide a conceptual perspective about the interrelated phenomena under investigation, in this case the concepts of pulse and health in TCM and modern medicine (Polit et al.). A dice model has been formulated in this thesis to explain the interconnection and interrelation between the arterial pulse and the eight elements of pulse condition at the six locations, and between the eight elements at the six locations and health status in TCM. This framework serves as the backbone of this doctoral work to quantify pulse condition at six locations in hypertensive patients.

The dice model comprises two levels. Level one includes the arterial pulse and the eight elements at the six locations, and level two covers the eight elements at the six locations and health status in TCM. More specifically, level one deals with the sensation of the arterial pulse as perceived by a TCM doctor, and level two gives an interpretation of the eight elements at the six locations to determine health status. These two concepts are interconnected. The symbolic meaning of a dice and a dice roll with respect to the arterial pulse and the health status in TCM are explicated in this chapter, and the dependent and independent variables in the two levels are described.

4.2 Arterial pulse and the eight elements at the six locations

It is postulated that the eight elements are influenced by the arterial pulse at the six locations (left and right cun, guan, and chi). The arterial pulse at the six locations is an independent variable. An independent variable is a condition, intervention, or characteristic that predicts or causes a given outcome (Portney & Watkins, 2000). There are two types of independent variables: active variables and attribute variables. An active variable is a variable that is manipulated by the researcher so that subjects are assigned to a certain level of that variable, whereas an attribute variable is a variable that the researcher is unable to assign to subjects, but must instead observe in a naturalistic way. The arterial pulse at the six locations is an attribute variable, and is operationalized as the arterial pressure waveform at the six locations.

A dependent variable is a response or effect that is presumed to vary depending on the independent variable (Portney & Watkins, 2000). Depth, rate, regularity, width, length, smoothness, stiffness, and strength are the eight elements of pulse condition at the six locations. The intensity of each element is determined by the sensation of the arterial pulse perceived by a TCM doctor. Thus, the eight elements at the six locations are the dependent variables, and are operationalized as a rating along a continuum with Yin and Yang at the extremes.

Specifically, depth is operationalized as the vertical position of the arterial pulse, and is rated along a continuum with the deepest being Yin and the most floating being Yang. Rate is the number of beats in a minute, with the slowest being Yin and the most rapid being Yang. Regularity is the rhythm of the arterial pulse, which is categorized as either regular or irregular. Width is the intensity of the arterial pulse, with the smallest being Yin and the largest being Yang. Length is the range of the arterial pulse that can be sensed across cun, guan, and chi, with the shortest being Yin and the longest being Yang. Smoothness is the slickness of the arterial pulse, where the roughest is Yin and the smoothest is Yang. Stiffness is the elasticity of the radial artery, with the least stiff being Yin and the stiffest being Yang. Finally, strength is the forcefulness of the arterial pulse relative to the change in pressure applied by a TCM doctor, with the least forceful being Yin and the most forceful being Yang.

4.3 The eight elements at the six locations and health status

In TCM pulse diagnosis, health status is determined by the pulse condition at the six locations, with each location reflecting the health status of a specific organ. Left cun, guan, and chi reflect the health status of the heart, the liver, and the kidneys, whereas right cun, guan, and chi reflect the health status of the lungs, the spleen, and the kidneys (lifegate). The eight elements are the assessment criteria for the health status of the organs. The eight elements at the six locations are thus the independent variables in the second level of the dice model.

Health status is the outcome measure of TCM pulse diagnosis, and is a composite measure of the health status of the organs. Health status is the dependent variable in the second level of the model, and is operationalized as denoting hypertension or normotension.

4.4 The dice model

In the model, a dice is used to embody the intertwining and cascading relationship among the arterial pulse, the eight elements at the six locations, and health status (Figure 4-1). Figure 4-1 shows a diagrammatic presentation of the dice model.

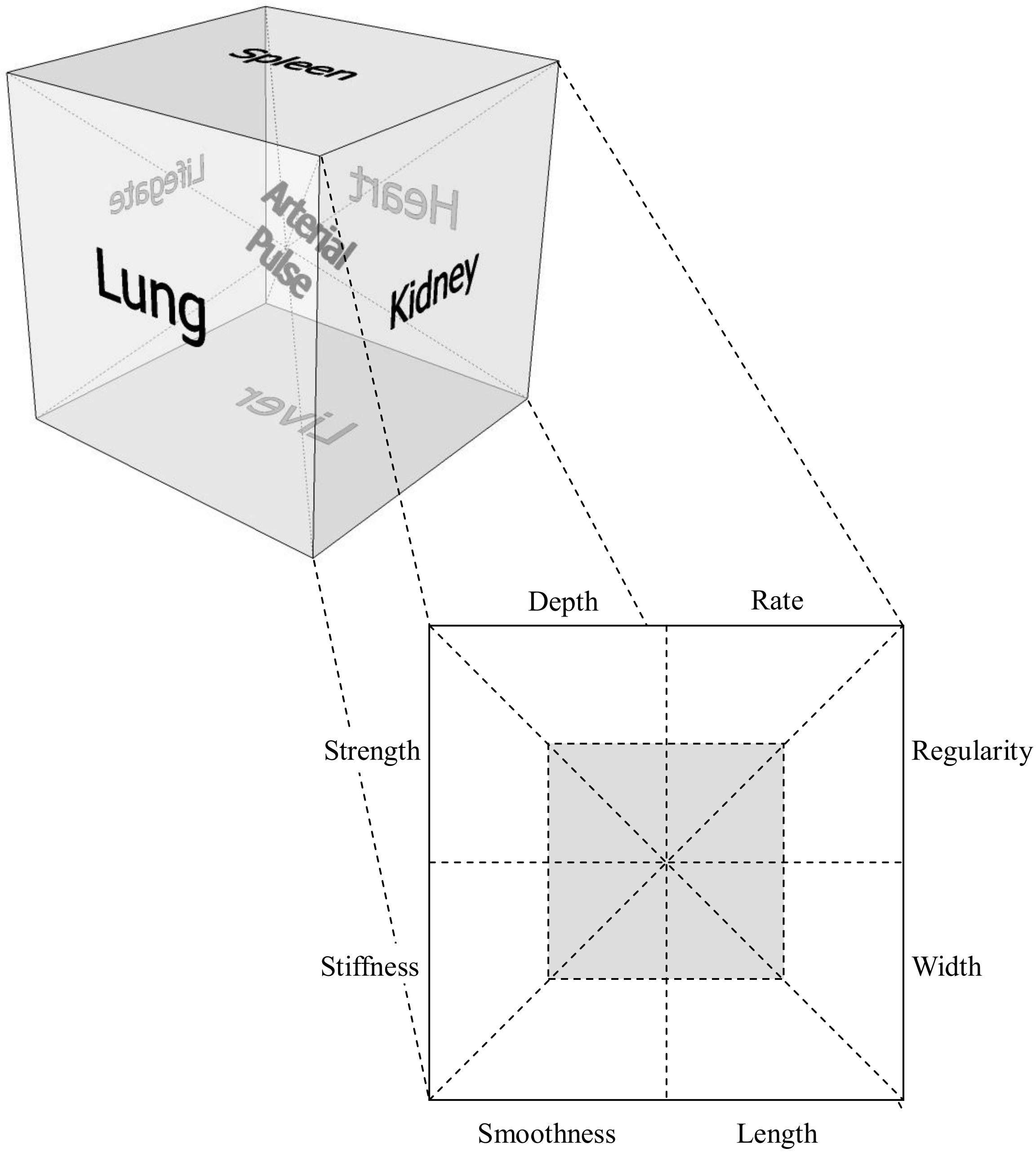

Figure 4-1 The dice model

4.4.1 Assumptions

The dice model is formulated under three assumptions. The first is that the eight elements carry the same weight in the assessment of overall pulse condition. Second, the mid-point along a continuum indicates the balance of Yin and Yang. Third, the six locations have the same weight in determining health status.

4.4.2 Symbolic meaning

The dice is analogous to the concept of health in TCM. Health is perceived as the balance of Yin and Yang, which in turn relies on the individual functioning and interaction of the organs. The six pyramids that make up a dice are thus analogous to the organs at the six locations.

The inside of the dice represents the blood flow within the organs, the combination of which constitutes the arterial pulse. Hence, any change in the blood flow from any of the organs is reflected in the arterial pulse. By assessing the six pyramids, the health status of the organs and thus overall health status can be revealed.

4.4.2.1 Position of the six organs

As has been stated, the six pyramids represent the six locations where the pulse is assessed by a TCM doctor. The lungs and the heart, the liver and the spleen, the kidneys and the lifegate are arranged in opposite pyramids according to their role in overall health. This arrangement is based on the notion that left cun, guan, and chi assess the blood, which is Yin in nature, whereas right cun, guan, and chi assess qi, which is Yang in nature. The position of the organs arranged in the dice thus adheres to Yin Yang theory.

4.4.2.2 The eight elements

Each pyramid is made up of the eight elements. The enlarged square to the lower right of Figure 4-1 shows the interrelation of the eight elements. Each element is a complementary Yin-Yang pair. According to Yin Yang theory, Yin always represents the inside and Yang the outside. Thus, the black square indicating the

Yin nature of the elements is the core of the pyramid, and the white square indicating their Yang nature is the outer part of the pyramid.

The intensity of the eight elements depends on the arterial pulse. The combined intensity of the eight elements thus indicates the health status of the organ denoted by that pyramid.

4.4.2.3 Interconnection in the dice model

The dice model of TCM pulse diagnosis is inspired by the Taiji symbol. The dotted line that links the six pyramids together symbolizes the interchanging and dynamic relationship among the organs. In the model, the Yin and Yang of each element, the eight elements in each pyramids, and the six pyramids of the dice are connected with dotted lines, which means that they are Yin and Yang composites and are always interchanging and balancing one another. The solid outline of the dice represents the absolute of health, just as the Taiji circle represents the world. Health is not expandable or reducible: it is only the health status that can be altered, which is determined by the interaction of Yin and Yang in the body.

4.4.3 Analogy between a dice roll and health status

To further elaborate the dice model, a roll of the dice is taken as analogous to health status. With a balanced or "fair" dice, the probability of rolling each pyramid is equal, because the areas and weights of the pyramids are identical. A "fair" dice is thus analogous to a healthy status, in which the blood flow within the organs is normal, the wave reflection and wave resonance occur in the proper way, the intensity of the eight elements is around the mid-point of the continuum and forms a regular shape in the middle of the pyramid, and the six pyramids are equal and balanced. Yin and Yang are balanced and harmony is attained.

However, if any one of the pyramids is intentionally altered in terms of its area or weight, then the dice is no longer "fair" and can be called a loaded dice. With a loaded dice, the probability of rolling each pyramid is unequal, and varies with the area and weight of the pyramids. A loaded dice is analogous to an unhealthy status, in which the abnormal functioning of any of the organs affects the wave reflection and wave resonance within the circulatory system, blood flow is altered, and thus the weight of the pyramid representing that organ is altered. The arterial pulse changes in accordance with the health status of the organ, and thus the intensity of the eight elements also changes. The pyramid formed by the eight elements is no longer regular, but is smaller or larger and skewed. An imbalance thus occurs in the six pyramids, Yin and Yang are imbalanced, and health is compromised.

4.5 Significance of the dice model in this thesis

The objectives and hypotheses set in this thesis are based on the dice model. The relationships between the arterial pulse and the eight elements at the six locations are examined to provide a modern scientific explanation for the eight elements. The relationships established are then used to develop an objective standard for the eight elements, and the differentiation of blood pressure state using the eight elements at the six locations is explored. The resulting differentiation model can be used as an outcome indicator for blood pressure assessment in TCM.

4.6 Conclusion

In this chapter, a dice model is presented that illustrates the interrelation and interconnection of the concepts of pulse and health in TCM and modern medicine. The two levels of the framework have been described, and the dependent and independent variables in each level specified and operationalized. The intertwining and cascading relationship among the arterial pulse, the eight elements, the six locations and health have been depicted and explained explicitly. Several hypotheses based on this model are verified in this doctoral work. As an appropriately structured study design is crucial to the validity of the results, the next chapter describes in detail the study method used in this doctoral work.

CHAPTER FIVE

METHODOLOGY

5.1 Introduction

The appropriate selection of a study design, sampling method, data collection procedure, and statistical methods for data analysis is crucial, as these elements affect the internal and external validity of the results of a study. Internal validity reflects the appropriate use of statistical procedures for analyzing data (Portney & Watkins, 2000), including the validity and reliability of the instruments used, the subject selection, and the statistical methods chosen. External validity concerns the generalizability of the results beyond the study (Portney & Watkins). In this chapter, the method used to conduct the study reported in this thesis is delineated in detail. The study design, subject recruitment, data collection, and data analysis procedures are described and justified. The reliability and validity of the instruments used is reported, and the procedure and results of the reliability and validity tests are described.

5.2 Justification of the research approach: Correlational research

Correlational research is a kind of exploratory research that investigates the relationships among a set of factors and predicts what these relationships suggest

(Portney & Watkins, 2000). This study examined the interrelationship among the arterial pulse, the eight elements at the six locations, and hypertension in the dice model, and thus the correlational study approach was chosen.

5.3 Subject recruitment

The issue of external validity is of prime concern in subject selection. As the main objective of the study was to investigate the relationship among the eight elements at the six locations and hypertension, the generalizability of the findings to other populations is not a concern. However, to ensure the internal validity of the results, extraneous variables such as age, gender, and body weight that are associated with the arterial pulse (Fei, 2003; Huang & Sun, 1995; Zhao, 2001) were controlled using a control group.

Two groups of subjects were examined in this study: a hypertensive and a normotensive group. Volunteer subjects were recruited by quota sampling through e-mail and posters on the university campus, in community health centers and hospitals, and advertisements placed in newspapers. Quota sampling was used to ensure the homogeneity of the subjects across the two groups. Inclusion and exclusion criteria were specified to govern the subject selection. Inclusion criteria are the primary traits of the target population and exclusion criteria are those factors that would preclude someone from being a subject (Portney & Watkins, 2000) because their inclusion could potentially confound the results.

5.3.1 Normotensive group

The inclusion criteria for the normotensive group were as follows.

i. Aged 18 or over, and

ii. Normal blood pressure, that is, a systolic blood pressure of less than 120 mmHg and a diastolic blood pressure of less than 80 mmHg in a resting condition (NHLBI, 2004).

The exclusion criteria were as follows.

i. Pregnant,

ii. Any physical, sensory, or cognitive impairment,

iii. Suffering from a chronic disease, for example, cardiovascular disease, diabetes mellitus, renal disease, or liver disease,

iv. Suffering from an infectious diseases, and

v. Currently taking medication, including prescriptions from a medical doctor, herbal medicine, or over-the-counter drugs.

5.3.2 Hypertensive group

The inclusion criteria were as follows.

i. Aged 18 or over,

ii. Diagnosed hypertension, and

iii. Systolic blood pressure of greater than or equal to 140 mmHg and/or a diastolic blood pressure of greater than or equal to 90 mmHg in a resting condition (NHLBI, 2004).

The exclusion criteria were as follows.

i. Pregnant,

ii. Any physical, sensory, or cognitive impairment,

iii. Suffering from a chronic disease other than hypertension, for example, cardiovascular disease, diabetes mellitus, renal disease, or liver disease,

iv. Suffering from an infectious disease, and

v. Currently taking medication other than prescriptions for hypertension, including prescriptions from a medical doctor, herbal medicine, or over-the-counter drugs.

Potential subjects were screened for eligibility by phone. The screening items were age, gender, body weight, body height, and the selection criteria. If a potential subject met the selection criteria, then the data collection procedure was described and the potential harm of the study explained.

Subjects eligible for the hypertensive group were asked whether they would be able to stop taking anti-hypertensive drugs one day before the appointment, and were informed of the potential side effects of ceasing antihypertensive medication. If the hypertensive subjects felt uncomfortable on the day of ceasing medication, then they were told to resume medication and to phone the researcher to cancel the appointment. If they felt uncomfortable during the data collection, they were sent to the campus clinic for medical advice.

The subjects were also told that if their systolic and diastolic blood pressure did not meet the selection criteria when measured on the day of data collection, they could not participate in the study. After giving this information and seeking verbal consent from the recruited subjects, an appointment was booked.

5.4 Demographic data, hemodynamic, and anthropometric parameters

Demographic data and data on certain hemodynamic and anthropometric parameters were collected to compare the homogeneity of the subjects in the normotensive and hypertensive groups.

5.4.1 Demographic data

Studies have shown that the arterial pulse differs in young-, middle-, and old-age groups (Fei, 2003). In this study, age was categorized into young adulthood (18-34 years), middle age (35-64 years), and old age (≥ 65 years). The purpose of this categorization was to intentionally balance the number of subjects in the three groups to minimize the confounding effect of age.

Gender is another extraneous variable that can affect the arterial pulse. The number of male and female in normotensive and hypertensive group was thus balance to cancel out the confounding effect of this variable.

5.4.2 Hemodynamic parameters

5.4.2.1 Systolic and diastolic blood pressure

Systolic blood pressure and diastolic blood pressure were measured at the left and right brachial artery in millimeters of mercury (mmHg). Blood pressure was measured at both the left and right side because there would be a significant difference in the left and right blood pressure in subjects with vascular disease. It is suggested in the literature that blood pressure be measured at both sides to determine whether the difference in systolic blood pressure and diastolic blood pressure are greater than 20 mmHg and 10 mmHg, respectively (Beever, Lip, & O'Brien, 2001).

5.4.2.2 Pulse rate

Pulse rate was measured manually at the wrist in beats per minute (bpm) for one minute to ensure that a subject was in a stable condition and could undergo the data collection procedure.

5.4.3 Anthropometric parameters

Body mass index (BMI) was measured to reflect the weight of a subject relative to height. This measure is universally used in clinical practice to identify weight problems. Body mass was calculated by weight over height squared in kilograms per meter squared (kg/m^2) and categorized into three groups – underweight, normal, and overweight according to the Asian standard (Choo, 2002). A BMI of less than 18.50 is categorized as underweight, between 18.50 and 22.99 as normal, and over 22.99 as overweight.

5.5 Independent and dependent variables

5.5.1 Arterial pulse

Arterial pulse was operationalized as the arterial pressure waveform in the time domain. Sixteen physical parameters were generated from the arterial pressure waveform, including pamax, Δ80%pamax, amppeak, h_3/h_1, h_4/h_1, h_5/h_1, h_1/t_1, W/t,

t, t_1/t, t_4/t, t_5/t, A_T, A_S, A_D, and SD-PPI. Their operational definitions are given in Table 5-1, where "average" is defined as the mean of seven to ten arterial pressure waveforms in a tracing.

Table 5-1 Sixteen physical parameters and their operational definitions

Physical Parameter	***Operational Definition***
Pamax	The hold-down pressure with the relatively largest amppeak compared with tracings of the arterial pressure waveform acquired at different hold-down pressures at the same location.
Amppeak	The average global maxima of the arterial pressure waveform at pamax.
Δ80%pamax	The difference in the hold-down pressures at 80% amppeak
h_3/h_1	The average ratio of the amplitude of the tidal wave to the amplitude of the percussion wave at pamax.
h_4/h_1	The average ratio of the amplitude of the incisura to the amplitude of the percussion wave at pamax.
h_5/h_1	The average ratio of the amplitude of the dicrotic wave measured vertically from the incisura to the amplitude of the percussion wave at pamax.
h_1/t_1	The average ratio of the amplitude of the percussion wave to the time of rapid systolic ejection at pamax.
W/t	The average ratio of the duration of 2/3 h_1 to the time of one complete arterial pressure waveform at pamax.

Table 5-1 Sixteen physical parameters and their operational definitions (Con't)

Physical Parameter	***Operational Definition***
t	Duration of one cardiac cycle.
t_1/t	The average ratio of the duration of rapid systolic ejection to the duration of one complete arterial pressure waveform at pamax.
t_4/t	The average ratio of the duration of the systolic phase to the duration of one complete arterial pressure waveform at pamax.
t_5/t	The average ratio of the duration of the diastolic phase to the duration of one complete arterial pressure waveform at pamax.
A_T	The average total area of one complete arterial pressure waveform at pamax.
A_S	The average area of the systolic phase at pamax.
A_D	The average area of the diastolic phase at pamax.
SD-PPI	The standard deviation of seven to ten peak-to-peak intervals at pamax.

5.5.2 The eight elements

Depth, rate, width, length, smoothness, stiffness, and strength were measured using a visual analogue scale (VAS). Depth is the score on a VAS that measures the vertical position of a pulse. Rate is the VAS score that measures the number of beats per minute. Width is the VAS score that measures the intensity of a pulse. Length is the VAS score that measures the palpable range of a pulse across cun, guan, and chi. Smoothness is the VAS score that measures the slickness of a pulse. Stiffness is the VAS score that measures the elasticity of the radial artery. Strength is the VAS score that measures the forcefulness of a pulse relative to changes of pressure applied during the pulse assessment. Regularity is a categorical variable, and is categorized as 0 for a regular pulse and 1 for an irregular pulse in terms of the interval and contour of the arterial pressure waveform.

5.5.3 The six locations

The six locations at which pulse was assessed were left and right cun, guan, and chi, and were measured and marked with a skin marker. The procedure used to locate the six locations was as follows.

1. Measure the second segment of the subject's middle finger to obtain the unit "inch" of the subject.
2. Locate guan, which is central to the radial styloid.
3. Locate cun, which is one inch from guan in the direction of the hand.
4. Locate chi, which is one inch from guan in the direction of the arm.
5. Starting from guan, measure 0.3 inch to cun and to chi. The total 0.6 inch is the area of guan.
6. The remaining 0.7 inch to the proximal side is chi and the remaining 0.6 inch to the distal side is cun.

5.6 Instrument

Reliable measurement depends on the validity and the reliability of the measurement instruments (Portney & Watkins, 2000). Validity in this case is the degree to which an instrument measures what it is intended to measure, and reliability is defined as the consistency with which an instrument or rater measures a variable (Portney & Watkins, 2000).

Many instruments were used to measure the biophysical parameters, anthropometric parameters, and independent and dependent variables. The reliability and validity of all of these instruments were tested, and calibration was performed before the data collection to minimize the measurement error.

5.6.1 Automatic blood pressure monitoring device

An automatic blood pressure monitoring device (Dinamap Pro-400 v2) was used to measure blood pressure. It was calibrated annually by the company to ensure its validity. Before data collection, local calibration was performed by comparing the blood pressure of the researcher as measured by the automatic blood pressure monitoring device and a sphygmomanometer, which is the gold standard for blood pressure measurement, to ensure that the monitoring device was valid and reliable (O'Brien, Beevers, & Lip, 2001).

5.6.2 Measuring tape

A measuring tape was used to measure body height in centimeters (cm). The subjects were instructed to take off their shoes, place their ankles against a wall, and keep their eyes horizontal during measurement.

5.6.3 Weighing scale

A weighing scale was used to measure body weight in kilograms (Kg). The subjects were instructed to take off their shoes and set down any belongings that they were carrying. The weighting scale was calibrated before the data collection. The scale needle was tuned to zero by depressing a button at the back of the scale, and a known weight was then put on the scale. If the reading did not corresponded with the known weight, then the needle was tuned to the correct reading.

5.6.4 TCM pulse assessment form

A VAS is a method used to assess subjective experience, which in this study was the intensity of the eight elements (Portney & Watkins, 2000). A VAS consists of a 10cm line with both ends marked with anchors. The method is simple to use and its validity and reliability have been established (Grossman, 1994). It is congruent with the usual practice of pulse assessment in TCM, and provides various ratings for a TCM doctor to choose that do not mask the actual sensation felt by the doctor. A numerical or ordinal scale would compress the information collected, because the choice would be restricted and the descriptors and numerals anchored to the numerical or ordinal scale could potentially introduce subjective judgment.

As a VAS is administered in paper and pen format and requires the researcher to measure a mark made on the line with a ruler, measurement error can occur. However, it has been showed that the VAS has good construct validity in clinical and research use (Paice & Cohen, 1997; Vallerand, 1997) and fits the concept of TCM pulse diagnosis. It was thus used to measure the intensity of the eight elements.

5.6.4.1 Construction of the TCM pulse assessment form

A TCM pulse assessment form was developed, based on the conceptual framework, for recording the intensity of the eight elements at the six locations. The form is attached in Appendix I.

The form comprised six sections, each of which related to one of the six locations. In each section, the depth, rate, width, length, smoothness, stiffness, and strength of the pulse were rated using a VAS. For depth, the opposite ends of the scale were labeled “deepest” and “most floating”. Rate was scaled from “slowest” to “fastest,” width from “smallest” to “largest,” length from “shortest” to “longest,” smoothness from “roughest” to “smoothest,” stiffness from “least stiff” to “stiffest,” and strength from “least forceful” to “most forceful.” As length was measured across cun, guan, and chi, it contained only two items – length at the left side and length at the right side. Regularity was a categorical variable that was either regular (0) or irregular (1).

5.6.4.2 Content validation

After constructing the pulse assessment form, content validation was performed to see whether the items on the assessment form were relevant to the domains of TCM pulse diagnosis. Content validity is the degree to which the items in an instrument adequately reflect the content domain being measured (Portney & Watkins, 2000). The content domain in this study was the eight elements at the six locations.

The content validation was performed by inviting a panel of TCM experts to determine the relevancy of the items on the assessment form. A Content Validation Index (CVI) was calculated as the percentage of agreement over the list of items among the expert panel. The panel of experts comprised five TCM doctors working at the School of Nursing and Beijing-Hong Kong Chinese Medical Clinic of The Hong Kong Polytechnic University. They were asked to comment on the relevancy of the items and the use of the anchoring words at the ends of the VAS. They were informed of the purpose of the content validity and the purpose of the TCM pulse assessment form, and were asked to rate the relevancy of the items on a four-point scale and to give additional comments where necessary. The four-point scale comprised “irrelevant,” “somewhat relevant," "relevant," and "very relevant." The content validity assessment rating form is attached in Appendix II.

Thirty two items were agreed upon by all five experts, but two experts disagreed on items 3, 7, 10, 14, 17, 21, 25, 29, 32, 36, 39, and 43. "Agreed" refers to a rating of "relevant" or "very relevant" and "Disagreed" to a rating of "irrelevant" or "somewhat relevant." The two experts that disagreed on the twelve items explained that although there is no standard for assessing pulse condition in TCM, they did not think that the twelve items were good enough to represent TCM pulse diagnosis. However, as the majority of the experts on the panel agreed on these items, the researcher retained these items on the TCM pulse assessment form.

To compute the percentage of agreement, the number of "agreed" items was first calculated and then divided by the total number of items retained in the content validity assessment rating form.

% of agreement (CVI) = number of agreed items/total number of items retained

= 32/44

= 0.73.

The content validity index was thus 0.73, which is acceptable.

5.6.5 Pulse acquisition system

A pulse acquisition system was developed to acquire the arterial pressure waveform. The system was made up of three components: a tonometer, a forearm holder, and a tonometer holder. The tonometer was used to acquire the arterial pressure waveform, and the two holders were designed to minimize the measurement error.

5.6.5.1 Tonometer

A tonometer (SPT-301 tonometer, Millar Instruments Inc.) was used to acquire the arterial pressure waveform. The validity of this instrument has been demonstrated by Kelly et al. (1989). Figure 5-1 shows the tonometer.

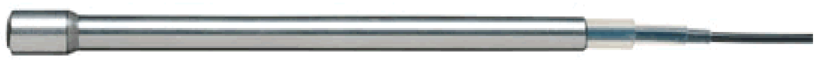

Figure 5-1 SPT-301 tonometer

Its maximum output value was 4.00 volts, which is equivalent to 400 mmHg. It was connected to a pressure control unit (model PCU-2000; Millar Instruments Inc.) and then to an A/D converter. Labview was used as the pulse acquisition interface, and the sampling frequency was set at 400 Hz in accordance with the Nyquist Theorem, as the frequency of the arterial pulse is less than 40 Hz (Lee, Jeong, Hwang, Lee, & Lee, 2001; Wang & Xiang, 1998). Figure 5-2 illustrates the configuration of the pulse acquisition unit.

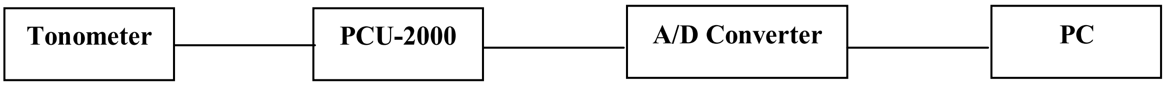

Figure 5-2 Pulse acquisition unit

The pressure signal of a tonometer is not readily recognized by computers, and thus the pressure control unit and the A/D converter were used to convert the pressure signal into a recognizable digital signal.

To ensure the reliability of the pulse acquisition unit, it was calibrated just before the data collection according to the manufacturer's recommendations, as follows.

1. Set the PCU-2000 mode switch to "standby" and the power switch to "on."
2. Adjust the monitor to a zero baseline. Ensure that the 25 mmHg and 100 mmHg calibration buttons are in the "off" position.
3. Press the 25mmHg calibration button, the 100mmHg calibration button, or both buttons to obtain a 125mmHg calibration signal, according to the desired range, and then adjust the monitor baseline to the corresponding value.
4. Turn the PCU-2000 function switch to "transducer".

5.6.5.2 Forearm holder

Motion artifacts, such as the involuntary movement of the subjects, are a challenge for researchers aiming to acquire high-quality arterial pressure waveforms. Due to the small diameter (about 4 mm) of the radial artery (Mohrman & Heller, 1997), even a slight movement of the forearm or fingers greatly affects the quality of the arterial pressure waveform obtained. As in this study the duration of the pulse acquisition procedure was about 40 minutes, it was impossible to ask the subjects to hold the arm in one position for so long without feeling tired. To reduce the motion artifacts, a forearm holder was designed to hold the forearm of the subjects in a comfortable and natural position. Figure 5-3 shows the forearm holder.

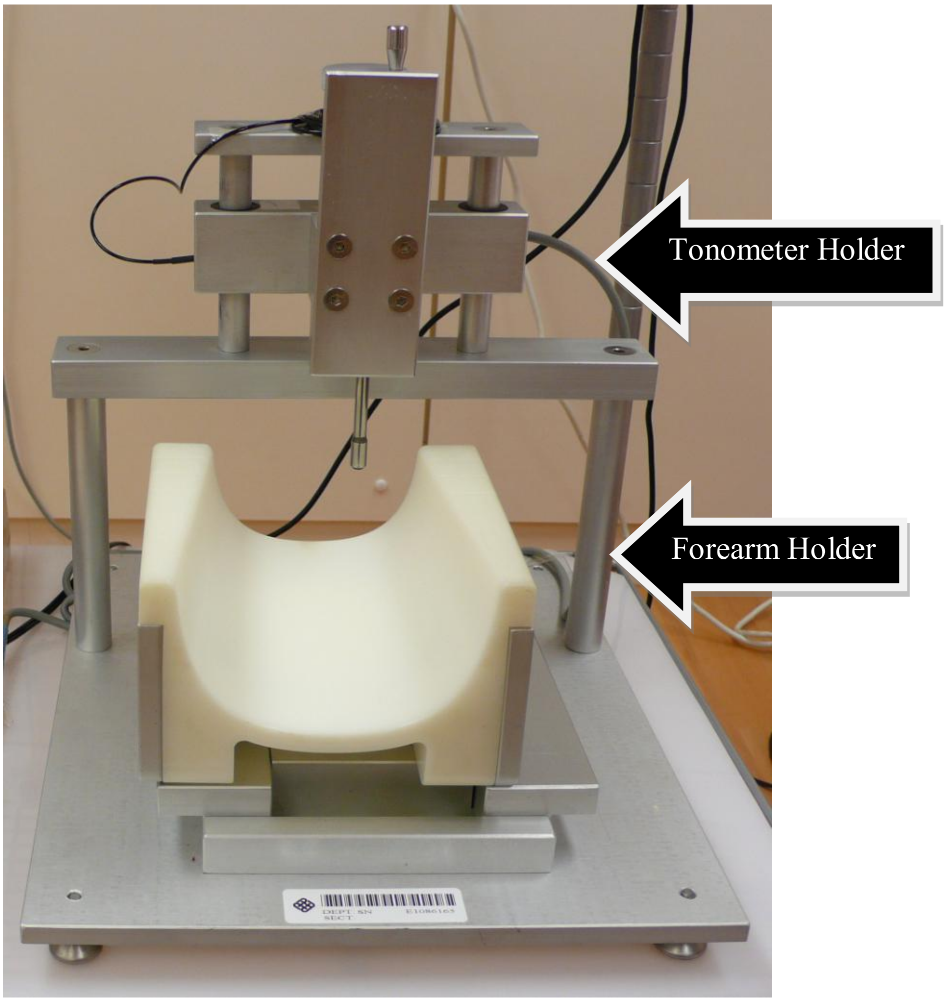

Figure 5-3 Forearm holder and tonometer holder

During pulse acquisition, the forearm of the subject rested naturally on the white plastic holder at the level of the heart. The forearm holder moved in two dimensions –to and fro and left and right –to adjust the position of the forearm for pulse acquisition. The holder helped the subjects to feel more relaxed during the pulse acquisition procedure, as the forearm was well supported in a natural way. When held in this position, the blood flow to the forearm was not affected and the movements of the subject due to fatigue were reduced. Figure 5-4 shows the position of the forearm in the forearm holder.

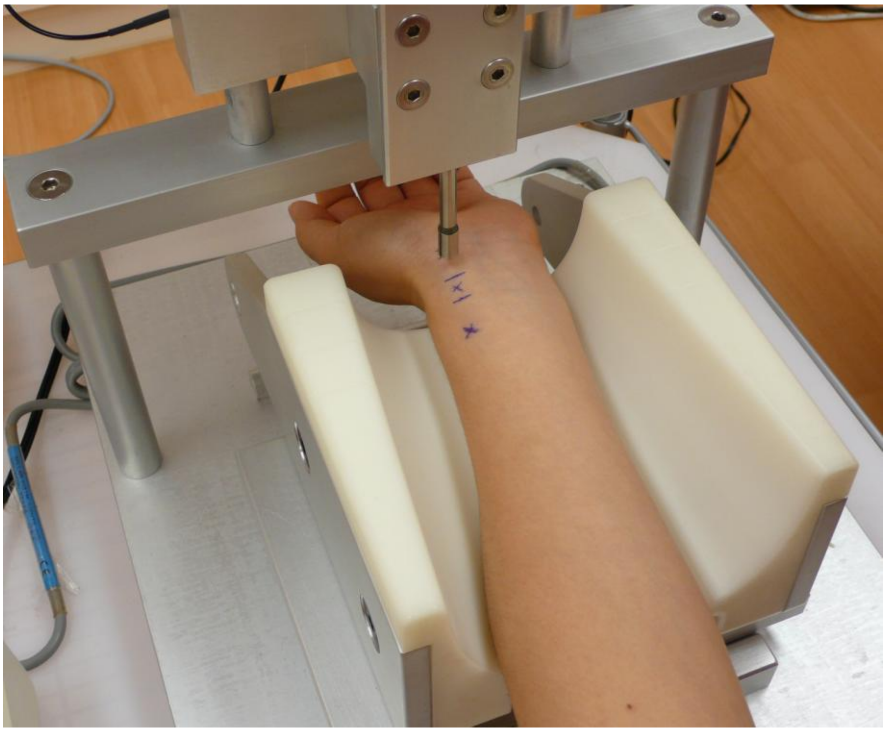

Figure 5-4 Forearm resting on the forearm holder

5.6.5.3 Tonometer holder

The SPT-301 tonometer is a hand-held pencil probe. As the duration of each individual pulse acquisition was about 15 seconds for each hold-down pressure, it was difficult for the researcher to maintain the appropriate constant pressure for the required duration. A tonometer holder was thus developed to mount the tonometer and avoid this problem.

Figure 5-3 shows the tonometer holder. The tonometer holder was designed with a lever at the top that could be rotated clockwise or anticlockwise to increase or decrease the hold-down pressure.

5.6.6 Feature extraction program

O'Rourke and Hill (1993) have patented a technique for extracting the features from an arterial pressure waveform, but the program could not be used in this study because the copyright has been sold to a company for commercial development. A feature extraction program developed by the Centre for Integrative Digital Health was used instead to extract and generate the physical parameters from the arterial pressure waveforms.

The program was developed using C++ and targets the features amppeak, h_1, h_3, h_4, h_5, t, t_1, t_4, t_5, A_T, A_S, A_D, W, and PPI for extraction. The extraction program was tested against manual extraction by the researcher.

5.6.6.1 Testing of the extraction program

Ten normotensive and hypertensive subjects were recruited by convenience. The purpose of the study and the potential harm that could be caused by the pulse acquisition were explained to them, and their written consent was obtained before the pulse acquisition.

The subjects were asked to rest on a bed with their forearm resting on the forearm holder. Arterial pressure waveforms were extracted from left guan with the pulse acquisition system. Hold-down pressures ranging from 0 mmHg to 400 mmHg with a 20mmHg interval were applied. At each hold-down pressure, a 15-second tracing of the arterial pressure waveform was recorded and stored in the computer.

After the pulse acquisition, the features were extracted using the aforementioned program. For the manual extraction, the researcher saved the tracing in Excel format and regenerated the arterial pressure waveform in the Excel program by pointing to the features with the curser and then recording them. A paired sample t-test was used to compare the agreement between the two sets of data.

Seventy percent of the tracings had all of the features extracted and were regarded as "valid" tracings. The remaining 30% of "invalid" tracings failed to have all of the features extracted, which was due to two reasons. The first was that the tracings were too noisy for the program to correctly identify, in which case the tracings were discarded. The second was that h_3 and h_5 were not recognized by the program. This was especially that case with the hypertensive group, as in the hypertensive subjects h_3 was very close to h_1, overlapped with h_1, or superimposed h_1, and the program was not sufficiently intelligent to differentiate h_3 under these three conditions. Similarly, h_5 readings that were flattened or below the incisura could not be identified.

The valid tracings were compared with the manual extractions. There was no significant difference in the fourteen features between the program and manual extraction ($p > 0.05$) procedures, which implies that the program was able to locate the features accurately in 70% of the tracings.

5.7 Rater reliability

The consistency of the rater in measuring the variables is as important as the validity of the instrument. In this study, there were two kinds of raters – a TCM doctor and the researcher. The TCM doctor assessed the intensity of the eight elements at the six locations, and the researcher acquired the radial arterial pressure waveforms at the six locations with the pulse acquisition device. The reliability of both the TCM doctor and the researcher was examined.

5.7.1 Rater reliability of the TCM doctor

A TCM doctor with over 10 years of clinical experience was invited to perform the pulse assessments. The doctor, who currently works in the Beijing-Hong Kong Chinese Medical Clinic of The Hong Kong Polytechnic University, assessed the pulse condition at the six locations in each eligible subject and rated the eight elements using VAS.

As only one TCM doctor was involved in the data collection in the main study, his consistency in relation to other TCM doctors was of concern because this could affect the external validity of the results. Furthermore, his own consistency was also an issue, because inconsistency could lead to invalid data. To this end, the consistency of this doctor both alone and in relation to other TCM doctors was tested according to the following two objectives.

1. To examine the inter-rater reliability among three TCM doctors.
2. To examine the intra-rater reliability of the TCM doctor participating in the main study.

The intraclass correlation coefficient (ICC) was used to examine the rater reliability, as it is an index that covers both the agreement and the strength of association among two sets of data. ICC (Model 2) was used to examine the inter-rater reliability, in which the three doctors were treated as the independent variables and the result was generalized to other TCM doctors. ICC (Model 3) was used to examine the intra-rater reliability of the TCM doctor participating in the study.

5.7.1.1 "TCM doctor" reliability testing

Eleven subjects were recruited by convenience sampling to undergo pulse assessment, and had the purpose of the study explained to them. Written consent was obtained before the data collection, and the subjects were asked not to communicate with the doctor during the pulse assessment.

Three TCM doctors – the doctor participating in the main study and two others who worked in the school clinic – performed a pulse assessment on the 11 subjects in their offices. They were blinded to the purpose of the study to avoid the Hawthorne effect, which is an effect on the dependent variables that results from subjects' awareness that they are participants in a study (Polit et al., 2001).

The TCM doctors assessed the pulse at the six locations and recorded the intensity of the eight elements on the TCM pulse assessment form. They were not allowed to communicate with the subjects during the assessment. The completed TCM pulse assessment forms were collected by the researcher, and none of the doctors were told of the ratings given by the other doctors. The TCM doctor who participated in the main study repeated the pulse assessment for the 11 subjects 15 minutes after the assessment by the other doctors.

Table 5-2 shows the result of inter-rater reliability of the TCM doctor participating in the main study. The correlation coefficient ranges from 0.39 to 0.63, which indicates a poor to average consistency. As the ICC reflects both the reliability and the agreement among the TCM doctors, this result suggests that he was inconsistent with the other TCM doctors.

Table 5-2 Inter-rater reliability of the three TCM doctors (N=11)

Eight Elements at the Six ***Element***	***Location***	***Intraclass Correlation Coefficient (Single Measure)***	***Significance****
Depth	Left cun	0.47	0.02
Rate	Left cun	0.53	0.01
Regularity	Left cun	0.53	0.02
Width	Left cun	0.56	0.02
Length	Left cun, guan, chi	0.59	0.01
Smoothness	Left cun	0.41	0.03
Stiffness	Left cun	0.39	0.03
Strength	Left cun	0.63	0.01
Depth	Left guan	0.57	0.01
Rate	Left guan	0.52	0.02
Regularity	Left guan	0.53	0.01
Width	Left guan	0.55	0.01
Smoothness	Left guan	0.39	0.04
Stiffness	Left guan	0.40	0.01
Strength	Left chi	0.51	0.01
Depth	Left chi	0.46	0.02
Rate	Left chi	0.52	0.01
Regularity	Left chi	0.53	0.01
Width	Left chi	0.60	0.01
Smoothness	Left chi	0.40	0.01
Stiffness	Left chi	0.50	0.01
Strength	Left chi	0.53	0.01
Depth	Right cun	0.39	0.03
Rate	Right cun	0.43	0.02
Regularity	Right cun	0.53	0.01
Width	Right cun	0.42	0.03
Length	Right cun, guan, chi	0.56	0.01
Smoothness	Right cun	0.53	0.01
Stiffness	Right cun	0.41	0.02
Strength	Right cun	0.60	0.02
Depth	Right guan	0.43	0.03
Rate	Right guan	0.43	0.03
Regularity	Right guan	0.53	0.01
Width	Right guan	0.63	0.01
Smoothness	Right guan	0.40	0.02
Stiffness	Right guan	0.44	0.03
Strength	Right chi	0.42	0.03
Depth	Right chi	0.41	0.04
Rate	Right chi	0.43	0.03
Regularity	Right chi	0.53	0.02
Width	Right chi	0.51	0.03
Smoothness	Right chi	0.53	0.02
Stiffness	Right chi	0.43	0.02
Strength	Right chi	0.59	0.01

*$p < 0.05$ denotes statistical significance.

The correlation coefficient for the intra-rater reliability was high at mostly over 0.80 (Table 5-3). This demonstrates that although the doctor was not in agreement with the other TCM doctors, which is always an issue in TCM pulse diagnosis, the TCM doctor himself was reliable and consistent in his assessments.

Table 5-3 Intra-rater reliability of the TCM doctor (N=11)

Eight Elements at the Six		*Intraclass Correlation Coefficient*	*Significance**
Element	***Location***		
Depth	Left cun	0.83	0.01
Rate	Left cun	0.86	0.01
Regularity	Left cun	1.00	0.01
Width	Left cun	0.84	0.01
Length	Left cun, guan, chi	0.85	0.01
Smoothness	Left cun	0.84	0.01
Stiffness	Left cun	0.82	0.01
Strength	Left cun	0.89	0.01
Depth	Left guan	0.80	0.01
Rate	Left guan	0.85	0.01
Regularity	Left guan	1.00	0.01
Width	Left guan	0.82	0.01
Smoothness	Left guan	0.83	0.01
Stiffness	Left guan	0.86	0.01
Strength	Left chi	0.85	0.01
Depth	Left chi	0.86	0.01
Rate	Left chi	1.00	0.01
Regularity	Left chi	0.84	0.01
Width	Left chi	0.78	0.01
Smoothness	Left chi	0.74	0.01
Stiffness	Left chi	0.83	0.01
Strength	Left chi	0.81	0.01
Depth	Right cun	0.83	0.01
Rate	Right cun	0.82	0.01
Regularity	Right cun	1.00	0.01
Width	Right cun	0.86	0.01
Length	Right cun, guan, chi	0.87	0.01
Smoothness	Right cun	0.84	0.01
Stiffness	Right cun	0.79	0.01
Strength	Right cun	0.83	0.01
Depth	Right guan	0.85	0.01
Rate	Right guan	0.82	0.01
Regularity	Right guan	1.00	0.01
Width	Right guan	0.84	0.01
Smoothness	Right guan	0.81	0.01
Stiffness	Right guan	0.85	0.01
Strength	Right chi	0.87	0.01
Depth	Right chi	0.83	0.01
Rate	Right chi	1.00	0.01
Regularity	Right chi	0.86	0.01
Width	Right chi	0.81	0.01
Smoothness	Right chi	0.73	0.01
Stiffness	Right chi	0.82	0.01
Strength	Right chi	0.79	0.01

*$p < 0.05$ denotes statistical significance.

5.7.1.2 Justification for assessing pulse using a single TCM doctor

The reliability tests demonstrate a low inter-rater reliability among TCM doctors, which could introduce measurement error if more than one doctor were used in the study. As there is no standard to determine which TCM doctor had the best pulse assessment skill, only one TCM doctor was used to assess pulse in the main study. The intra-rater reliability tests show that the selected TCM doctor was consistent, and would give consistent results for the assessment of the eight elements.

In terms of validity, as no standard is available to determine which doctor performed best, the only way to assess the validity of the doctor participating in the main study is to examine the criterion validity. Criterion validity is the degree to which scores on an instrument are correlated with an external criterion (Polit et al., 2001). The external criterion in this study was hypertension. The criterion validity of the participating TCM doctor was examined in a pilot study (see Chapter 6).

5.7.2 Rater reliability of the researcher

The researcher was responsible for acquiring the arterial pressure waveform using the pulse acquisition system. As the accuracy of pulse acquisition greatly depends on the positioning of the tonometer (Mattys & Verdonck, 2002; Sato et al., 1993; Vlachopoulos & O'Rourke, 2000), it was necessary to examine the intra-rater reliability of the researcher to determine the researcher's competence in acquiring the arterial pressure waveform.

5.7.2.1 Researcher reliability test

Eleven subjects were again recruited by convenience sampling to undergo a tonometric pulse assessment. They were told the purpose of the study and that they could leave at any time during the data collection if they feel uncomfortable without any penalty. The process of the data collection was described and the potential harm that might arise from the process, such as the pain caused by the hold-down pressure, were explained. Written consent was obtained before the data collection.

The subjects were asked to lie on the bed with their forearm resting on the forearm holder. The height of the bed was adjusted until the forearm was level with the heart. The arterial pressure waveform was acquired twice at left guan at a hold-down pressure of 80 mmHg. The researcher used the following procedure to acquire the arterial pressure waveform.

1. Locate left guan.
2. Adjust the forearm in the forearm holder until the tonometer is at the center of the radial artery at left guan.
3. Adjust the hold-down pressure to 80 mmHg with the tonometer holder.
4. Acquire the arterial pressure waveform for 15 seconds.

Amppeak, h_1, h_3, h_4, h_5, t, t_1, t_4, t_5, A_T, A_S, A_D, and W were extracted from the arterial pressure waveform using the feature extraction program. The Pearson product moment correlation coefficient was used to examine the correlation between the features from the first and second acquisition.

The correlation coefficients of the features of the arterial pressure waveform are shown in Table 5-4. The r value was over 0.80, which indicates that the researcher was competent to control the pulse acquisition system.

Table 5-4 Correlations of the features extracted from the first and second pulse acquisition (N=11)

Feature	***r***	***Significance****
Amppeak	0.83	0.02
h_1	0.83	0.02
h_3	0.88	0.01
h_4	0.89	0.01
h_5	0.90	0.01
t_1	0.89	0.01
t_4	0.93	0.01
t_5	0.98	0.01
T	0.98	0.01
A_T	0.87	0.01
A_S	0.84	0.01
A_D	0.91	0.01
W	0.97	0.01

*$p < 0.05$ denotes statistical significance.

5.8 Data collection for the main study

5.8.1 Setting

The data collection for the main study was conducted in the TCM laboratory of the School of Nursing at The Hong Kong Polytechnic University. The temperature in the laboratory was kept at 22 degrees Celsius throughout the data collection, as fluctuations in the environmental temperature are known to affect a pulse (Fei, 2003). The aim of using a consistent setting was to avoid systematic bias.

5.8.2 Data collection

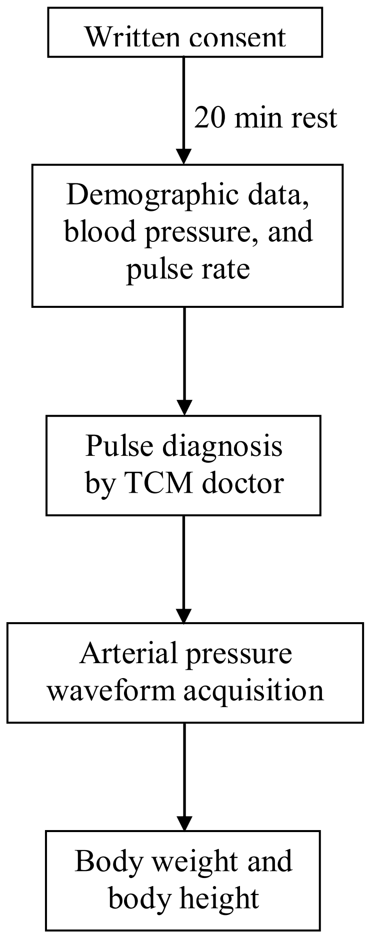

Figure 5-5 Data collection flow chart

Figure 5-5 shows the flow of the data collection. The purpose, procedure, and potential harm of the study were described and explained to the subjects, who were told that they could withdraw from the study at any time without penalty. Written consent was obtained before the data collection. The subjects were also informed that told they could consult a TCM doctor about their health condition only after completing the whole procedure. A $50 Park'n coupon was issued as a transportation subsidy.

The subjects were asked to lie on a bed for 20 minutes before data collection, as it has been demonstrated that hemodynamic modification stabilizes after 20 minutes in a new posture (Jacob et al., 2005). Demographic data were solicited during this interval. After the 20 minutes of rest, the systolic and diastolic blood pressure of the patients was measured at the left and right brachial artery.

The TCM doctor was blinded to the health status of the subjects, and was not allowed to communicate with the subjects during the pulse assessment to minimize the potential of observation bias from knowing the health state of the subjects. He assessed the pulse at the six locations and marked the intensity of the eight elements on the VAS line with a pen.

After the pulse assessment by the TCM doctor, the researcher acquired the arterial pressure waveform at the six locations according to the following procedure.

1. Ask the subject to put his or her forearm into the forearm holder.

2. Start the pulse acquisition in a sequence from cun to chi on the left and right sides.
3. Apply hold-down pressures from 0 mmHg to 400 mmHg with 20mmHg intervals by rotating the lever of the tonometer holder.
4. For each hold-down pressure, acquire and record on the computer a 15-second tracing of the arterial pressure waveform.
5. Repeat steps 4 and 5 at the six locations.

As the hold-down pressure temporarily affected the blood flow to the radial artery, the arterial pressure waveform was acquired in the sequence given in step 2 to minimize the effect of the hold-down pressure on the arterial pressure waveform. The 50g interval suggested by Fei (2003) is too wide because it does not allow changes in the arterial pressure waveform within this 50g to be examined. However, as technological limitations mean that it is impossible to acquire the arterial pressure waveform continuously, an interval of 20 mmHg was chosen as an alternative. Body weight and body height were measured after the pulse acquisition.

5.8.3 Justification for choosing a 20mmHg interval to acquire the arterial pressure waveform

To determine an appropriate pressure interval, the duration of pulse acquisition and the pulse information preserved were considered. The quality of an acquired waveform is affected by the duration of the pulse acquisition, because prolonged acquisition induces motion artifacts and arm numbness in the subjects. In addition, applying the hold-down pressure on the artery for a long time affects the blood flow. As it is technically impossible to acquire the waveform continuously, there must be a trade-off between the interval and the duration of pulse acquisition.

No studies have reported an optimal pressure interval for pulse acquisition, so the researcher compared the duration of pulse acquisition and the average amppeak change in the arterial pressure waveform between hold-down pressures in three subjects. Five pressure intervals were examined: 10 mmHg, 20 mmHg, 30 mmHg, 40 mmHg, and 50 mmHg. Pulse acquisition was performed at left guan and the duration of acquisition recorded. The average amppeak change between two successive hold-down pressures was then calculated. Table 5-5 compares the results.

Table 5-5 Comparison of the duration and average amppeak change for the five pressure intervals (N=3)

Pressure Interval (mmHg)	***Average Amppeak Change (mm)***	***Duration of Pulse Acquisition (min)***
10	0	15
20	5.6	10
30	12.3	8
40	15.7	7
50	16.3	7

It was found that the average amppeak change increased at 20 mmHg, which indicates that 20 mmHg was the minimum interval for which the average amppeak change under different hold-down pressures can be preserved. As shown in Table 5-5, it took about 10 minutes to acquire an arterial pressure waveform at one location with a 20mmHg interval, which means that approximately 1 hour would be required to perform pulse acquisition at the six locations. With a 30 mmHg interval, it took about 50 minutes to complete the pulse acquisition. As the duration of pulse acquisition was only 10 minutes less with a 30 mmHg interval than with a 20 mmHg interval, 20 mmHg was chosen as the pressure interval for the main study.

5.8.4 Data management

5.8.4.1 Ratings of the TCM doctor

After data collection, the researcher measured the ratings of the eight elements on the VAS with the same ruler to ensure consistency. The ratings were taken as the distance between the mark made by the doctor and the left-hand anchor on the VAS line in centimeters (cm).

5.8.4.2 Feature selection

Fourteen features were extracted by the feature extraction program after pulse acquisition. The physical parameters were derived from the mean of seven to ten arterial pressure waveforms, with only arterial pressure waveforms that were free from noise or minimally affected by noise being eligible for selection.

5.8.4.2.1 Feature selection within the tracings

There are no studies that report the normal ranges of the features, and thus a statistical method of a 95% confidence interval was adopted as a selection criterion. A 95% confidence interval is the interval of the mean ± 1.96 standard error of mean (SEM). Standard deviation is the average deviation from the mean, and is commonly used in statistics to indicate the dispersion of the sample. A 95% confidence interval means that when 100 samples are randomly selected, there is a 95% confidence that the samples fall within the range of ± 1.96 SEM.

To calculate the 95% confidence interval for each feature, arterial pressure waveforms in the same tracing were averaged and the standard error of mean calculated, from which the 95% confidence interval was then deduced. Arterial pressure waveforms with all features that fell within the 95% confidence interval were selected for the subsequent physical parameter generation.

5.8.4.2.2 Selection of the best tracing for a location

In the physical parameter generation, only one tracing was selected for each location. The criteria for selecting this tracing were as follows.

1. Compare t, t_1, t_4, and t_5 among the tracings from the same location.
2. If the tracing has a very diverse t, t_1, t_4 and t_5, then it is regarded as "invalid" and discarded because the time interval of a subject should be stable.

3. The best of the “valid” tracings is regarded as the one with the largest amppeak and with most of the other features preserved.

After selecting the best tracing for a location, the sixteen physical parameters were generated and used for subsequent data analysis.

5.9 Data analysis procedure

Descriptive statistics were computed to determine the distribution of the data. Linear statistical tests were performed using Statistical Package for Social Sciences (SPSS) version 15. An artificial neural network (ANN) was used to compute the nonlinear relationship with MatLab 8.0.

5.9.1 Conventional statistical tests

Univariate analysis was used to examine the effect of group and location on the physical parameters and the elements at the six locations. The Pearson product moment correlation coefficient and the Spearman’s rank-order correlation coefficient were utilized to investigate the association among the physical parameters at the six locations and among the eight elements at the six locations. Principal component analysis was used to reduce the dimensions of the dataset. The relationships among the physical parameters and the eight elements at the six locations were investigated by regression analysis, and logistic regression was used to reveal the relationship between the eight elements at the six locations and hypertension. A p–value of less than 0.05 denoted statistical significance.

5.9.2 Artificial neural network

ANN was used to develop nonlinear models of the relationship among the physical parameters and the eight elements at the six locations and the relationship between the eight elements at the six locations and hypertension. A backpropagation algorithm and a radial basis network were used to establish the models separately. Linear regression was used to evaluate the performance of the former model, and predictive accuracy, sensitivity, and specificity were used to evaluate the performance of the latter model.

5.10 Ethical considerations

Ethical approval was obtained from the Ethical Committee of the School Research Committee of the Hong Kong Polytechnic University (HSEAR20061102004). Before the commencement of the study, an information sheet was given to eligible subjects to inform them of the purpose and procedure of the study, and written consent was obtained from each subject before data collection. A $50 Park'n coupon was issued to each subject as a transportation subsidy.

5.11 Conclusion

The research protocol described in this chapter was developed to guide the data collection. The reliability and validity of the instruments, the TCM doctor, and the researcher were established to ensure the internal validity of the study. The statistical methods utilized in the data analysis are described.

As no similar studies are reported in the literature, a pilot study was conducted before the main study to estimate the sample size, examine the feasibility of the research protocol, and test the validity of the TCM doctor. The results of the pilot study, a discussion of the results, and the subsequent amendments made to the main study are presented in the next chapter.

CHAPTER SIX

PILOT STUDY

6.1 Introduction

A pilot study was conducted before the main study between June and July 2007. The objectives of the pilot study were to test the feasibility of the proposed study design, estimate the sample size for the main study, and revise the protocol, if necessary.

This chapter presents the results of the pilot study. It reports the determination of the sample size from the calculation of the effect size of each result, and the examination of the validity of the TCM doctor. The feasibility of the study design and amendments made to the design are discussed.

The following research questions were posed based on the study objectives.

i. Is it possible to conduct the main study with the proposed study design?

ii. Do any amendments need to be made to the study design?

iii. Does the TCM doctor's rating differentiate hypertension from normotension through TCM pulse assessment?

iv. What is the effect size of the pilot study?

v. How many subjects are required for each group in the main study?

The pilot study followed the protocol described in Chapter Five.

6.2 Background information of the pilot study subjects

Fourteen subjects were recruited for the normotensive and hypertensive groups respectively. A Mann Whitney U-test was used to examine the differences in the gender, age, and body mass index between the groups. An independent t-test was used to examine the differences in the left-side blood pressure, right-side blood pressure, and pulse rate between the groups. The results are shown in Table 6-1.

Table 6-1 Background information of the subjects (N=28)

		Normotensive Group$^{\psi}$ *(n=14)*	*Hypertensive Group*$^{\psi}$ *(n=14)*	*Significance**
Gender	Male	6	11	---
	Female	8	3	
Age (yrs)	18-34	6	5	---
	35-64	6	5	
	≥ 65	2	4	
BMI (kg/m^2)	<18.5	2	0	---
	18.50-22.99	8	8	
	≥ 23.00	4	6	
LBP (mmHg)		109(12)/67(5)	149(15)/87(13)	0.01
RBP (mmHg)		108(14)/67(6)	150(13)/87(12)	0.01
Pulse Rate (bpm)		63(11)	79(10)	0.01

BMI = Body mass index; LBP = Left-side blood pressure; RBP = Right-side blood pressure.
$^{\psi}$The mean (SEM) is reported for the continuous variables and the median for the categorical variables.
*p <0.05 denotes statistical significance.

There was a statistically significant difference ($p < 0.01$) in pulse rate and blood pressure between the groups. The subjects in the normotensive group had a blood pressure within the normal range (≤ 120/80 mmHg), whereas the subjects in the hypertensive group had a blood pressure either above 140 mmHg for systolic blood pressure or above 90 mmHg for diastolic blood pressure, or both. There were no significant differences in gender, age, and body mass index between the groups ($p > 0.05$).

6.3 Effect of group and location on the eight elements

Univariate analysis was used to investigate the effect of group and location on the eight elements. No interaction effect was discerned ($p > 0.05$). Table 6-2 tabulates the mean and standard errors of the group and location factors.

Table 6-2 Effect of group and location on the eight elements (N=28)

Element	*Location*	*Normotension*$^{\psi}$ *(n=14)*	*Hypertension*$^{\psi}$ *(n=14)*	*Significance** *Group*	*Location*
Depth	Left chi	4.16(0.35)	6.88(0.44)	0.01	0.01
	Left cun	5.36(0.35)	7.94(0.44)	0.01	
	Left guan	5.51(0.36)	7.84(0.34)	0.01	
	Right chi	5.39(0.34)	7.54(0.38)	0.01	
	Right cun	5.91(0.34)	7.99(0.38)	0.01	
	Right guan	5.96(0.34)	8.01(0.32)	0.01	
Rate	Left chi	4.41(0.15)	4.54(0.19)	---	---
	Left cun	4.55 (0.17)	4.73(0.13)	---	
	Left guan	4.56(0.12)	4.66(0.16)	---	
	Right chi	4.97(0.18)	4.65(0.19)	---	
	Right cun	4.85(0.14)	4.66(0.16)	---	
	Right guan	4.9(0.17)	4.54(0.18)	---	
Regularity	Left chi	0	1	0.01	---
	Left cun	0	1	0.01	
	Left guan	0	1	0.01	
	Right chi	0	1	0.01	
	Right cun	0	1	0.01	
	Right guan	0	1	0.01	
Width	Left chi	4.27(0.23)	5.66(0.31)	0.01	0.01
	Left cun	4.74(0.24)	7.01(0.35)	0.01	
	Left guan	4.96(0.25)	6.24(0.39)	0.01	
	Right chi	4.81(0.26)	6.49(0.29)	0.01	
	Right cun	5.69(0.28)	7.24(0.34)	0.01	
	Right guan	5.27(0.31)	6.75(0.40)	0.01	
Length	Left cun, guan, chi	4.87(0.23)	7.76(0.40)	0.01	---
	Right cun, guan, chi	5.65(0.27)	8.08(0.32)	0.01	
Smoothness	Left chi	5.29(0.24)	5.37(0.19)	---	0.01
	Left cun	5.56(0.21)	5.64(0.19)	---	
	Left guan	5.86(0.15)	5.7(0.17)	---	
	Right chi	5.76(0.18)	5.43(0.21)	---	
	Right cun	5.86(0.22)	6.39(0.20)	---	
	Right guan	5.88(0.22)	6.02(0.19)	---	
Stiffness	Left chi	3.64(0.29)	3.69(0.30)	---	0.01
	Left cun	3.74(0.18)	4.51(0.26)	0.02	
	Left guan	3.77(0.21)	3.81(0.29)	---	
	Right chi	5.01(0.15)	5.17(0.16)	---	
	Right cun	4.18(0.18)	4.20(0.29)	---	
	Right guan	4.69(0.26)	4.71(0.22)	---	
Strength	Left chi	4.14(0.36)	3.88(0.31)	---	0.01
	Left cun	5.03(0.24)	5.29(0.32)	---	
	Left guan	5.04(0.29)	4.37(0.29)	---	
	Right chi	5.46(0.31)	5.26(0.21)	---	
	Right cun	5.76(0.27)	5.5(0.34)	---	
	Right guan	5.62(0.33)	5.5(0.26)	---	

$^{\psi}$ The mean (SEM) is reported for the continuous variables and the median for the categorical variables.
*p <0.05 denotes statistical significance.

The pulse of the hypertensive subjects tended to be irregular ($p < 0.01$), shallower ($p < 0.01$), larger ($p < 0.01$), and longer ($p < 0.01$) than that of the normotensive subjects at all six locations. The pulse at the left cun was stiffer in the hypertensive group ($p < 0.02$).

There was a statistically significant difference in depth ($p < 0.01$), width ($p < 0.01$), smoothness ($p < 0.01$), stiffness ($p < 0.01$), and strength ($p < 0.01$) among the six locations, and thus the interaction of the six locations for these elements was further investigated using a Bonferroni test.

For depth, the pulse at left cun was more floating than at left chi ($p < 0.04$), right cun ($p < 0.03$), and right guan ($p < 0.01$). Width at left chi was smaller than at left cun ($p < 0.04$), right cun ($p < 0.01$), and right guan ($p < 0.01$). The pulse at left chi was less smooth than at right cun ($p < 0.01$) and right guan ($p < 0.02$), and the pulse at right chi was stiffer than at left cun ($p < 0.01$), left guan ($p < 0.01$), left chi ($p < 0.01$), and right cun ($p < 0.04$). The pulse at right guan was stiffer than at left guan ($p < 0.01$) and left chi ($p < 0.01$). Strength at left chi was weaker than at left cun ($p < 0.01$), right cun ($p < 0.01$), right guan ($p < 0.01$), and right chi ($p < 0.01$), and weaker at left guan than at right cun ($p < 0.03$).

In summary, the pulse at left cun was more floating, smaller, and stronger than at left chi. The pulse at right cun was deeper than at left cun; stronger than at left guan; smaller, smoother, and stronger than at left chi; rougher and weaker than at right guan; and more elastic than at right chi. The pulse at right guan was deeper than at left cun, stiffer than at left guan, and stiffer and smaller than at left chi. The pulse at right chi was stiffer than at left cun, left guan, and left chi, and weaker than at left chi.

6.4 Effect of group and location on the sixteen physical parameters

One hundred and sixty-eight tracings of arterial pressure waveforms (28 x 6) were selected. All of the physical parameters except for SD-PPI and Δ80%pamax were generated from the tracings. SD-PPI could not be calculated because the noise in the tracings and the fluctuating baseline of the arterial pressure waveform resulted in a large variation in the PPI. As PPI is the interval between two successive arterial pressure waveforms, the noise in the tracing made it difficult to obtain enough values for averaging. By the same token, Δ80%pamax could not be calculated because the features of the arterial pressure waveform became imprecise and “invalid” when the hold-down pressure increased. Thus, only fourteen of the physical parameters were successfully generated.

Univariate analysis was used to reveal the effect of group and location on the physical parameters. There was a significant difference in most of the physical parameters between the groups. However, location had no direct effect on the physical parameters and no significant interaction effect with group on the physical parameters. Table 6-3 summarizes the results.

Table 6-3 Effect of group and location on the fourteen physical parameters (N=28)

Physical Parameter	*Location*	*Normotension* $^{\psi}$ *(n = 14)*	*Hypertension* $^{\psi}$ *(n = 14)*	*Significance** *Group*	*Location*
h_3/h_1	Left chi	0.49(0.03)	0.77(0.03)	0.01	---
	Left cun	0.50(0.02)	0.76(0.03)	0.01	
	Left guan	0.49(0.03)	0.75(0.03)	0.01	
	Right chi	0.47(0.03)	0.73(0.04)	0.01	
	Right cun	0.49(0.03)	0.75(0.03)	0.01	
	Right guan	0.47(0.02)	0.73(0.04)	0.01	
h_4/h_1	Left chi	0.31(0.02)	0.43(0.02)	0.01	---
	Left cun	0.32(0.01)	0.44(0.02)	0.01	
	Left guan	0.32(0.02)	0.42(0.02)	0.01	
	Right chi	0.30(0.02)	0.38(0.02)	0.01	
	Right cun	0.32(0.02)	0.42(0.02)	0.01	
	Right guan	0.32(0.02)	0.38(0.02)	0.01	
h_5/h_1	Left chi	0.10(0.01)	0.05(0.01)	0.01	---
	Left cun	0.10(0.01)	0.03(0.01)	0.01	
	Left guan	0.11(0.02)	0.04(0.01)	0.01	
	Right chi	0.12(0.01)	0.06(0.01)	0.01	
	Right cun	0.11(0.01)	0.05(0.01)	0.01	
	Right guan	0.11(0.01)	0.06(0.01)	0.03	
W/t	Left chi	0.12(0.01)	0.22(0.01)	0.01	---
	Left cun	0.12(0.01)	0.23(0.01)	0.01	
	Left guan	0.11(0.01)	0.21(0.02)	0.01	
	Right chi	0.11(0.01)	0.20(0.01)	0.01	
	Right cun	0.12(0.01)	0.22(0.01)	0.01	
	Right guan	0.11(0.01)	0.21(0.01)	0.01	
t	Left chi	0.99(0.04)	0.89(0.04)	---	---
	Left cun	0.95(0.04)	0.86(0.03)	---	
	Left guan	1.01(0.04)	0.88(0.03)	0.02	
	Right chi	0.98(0.04)	0.87(0.03)	0.03	
	Right cun	0.97(0.04)	0.85(0.03)	0.02	
	Right guan	0.99(0.04)	0.85(0.03)	0.01	

$^{\psi}$ The mean (SEM) is reported.
*p <0.05 denotes statistical significance.

Table 6-3 Effect of group and location on the fourteen physical parameters (N=28) (Con't)

Physical Parameter	***Location***	***Normotension***$^{\psi}$ ***(n = 14)***	***Hypertension***$^{\psi}$ ***(n = 14)***	***Significance**** ***Group***	***Location***
t_1/t	Left chi	0.12(0.01)	0.14(0.01)	0.02	---
	Left cun	0.13(0.01)	0.16(0.01)	0.02	
	Left guan	0.11(0.01)	0.15(0.01)	0.01	
	Right chi	0.12(0.00)	0.14(0.00)	0.01	
	Right cun	0.12(0.01)	0.15(0.01)	0.01	
	Right guan	0.12(0.00)	0.14(0.01)	0.01	
t_4/t	Left chi	0.37(0.01)	0.39(0.01)	---	---
	Left cun	0.39(0.01)	0.41(0.01)	---	
	Left guan	0.36(0.01)	0.40(0.01)	0.03	
	Right chi	0.37(0.01)	0.41(0.01)	0.02	
	Right cun	0.37(0.01)	0.41(0.01)	0.02	
	Right guan	0.37(0.01)	0.41(0.01)	0.01	
t_5/t	Left chi	0.63(0.01)	0.61(0.01)	---	---
	Left cun	0.61(0.01)	0.59(0.01)	---	
	Left guan	0.64(0.01)	0.60(0.01)	0.03	
	Right chi	0.63(0.01)	0.59(0.01)	0.02	
	Right cun	0.63(0.01)	0.59(0.01)	0.02	
	Right guan	0.63(0.01)	0.59(0.01)	0.02	
A_T	Left chi	15947(968)	24383(2168)	0.01	---
	Left cun	18234(1429)	26334(2703	0.01	
	Left guan	17535(764)	24329(2004)	0.01	
	Right chi	16573(1311)	21782(1887)	0.03	
	Right cun	18103(1748)	24615(1884)	0.01	
	Right guan	17983(1326)	26630(2363)	0.01	
A_S	Left chi	9882(605)	15890(1373)	0.01	---
	Left cun	11379 (749)	17398(1708)	0.01	
	Left guan	10626(515)	15971(1200)	0.01	
	Right chi	10352(842)	14664(1223)	0.01	
	Right cun	11049(1027)	16441(1149)	---	
	Right guan	11033(882)	17845(1465)	0.01	

$^{\psi}$ The mean (SEM) is reported

*p <0.05 denotes statistical significance.

Table 6-3 Effect of group and location on the fourteen physical parameters (N=28) (Con't)

Physical Parameter	*Location*	*Normotension*$^{\psi}$ *(n = 14)*	*Hypertension*$^{\psi}$ *(n = 14)*	*Significance** *Group*	*Location*
	Left chi	6066(581)	8493(864)	0.03	
	Left cun	6855(772)	8936(1062)	---	
	Left guan	6909(479)	8358(843)	---	
A_D	Right chi	6221(567)	7118(717)	---	---
	Right cun	7055(812)	8175(835)	---	
	Right guan	6950(577)	8785(965)	---	
	Left chi	159(16)	251(24)	0.01	
	Left cun	154(17)	271(24)	0.01	
Pamax	Left guan	123(15)	211(23)	0.01	---
	Right chi	148(15)	227(22)	0.01	
	Right cun	159(20)	283(27)	0.01	
	Right guan	139(20)	194(19)	---	
	Left chi	44.38(3.60)	59.35(5.86)	0.04	
	Left cun	48.82(3.03)	65.75(7.02)	---	
Amppeak	Left guan	46.80(2.60)	61.38(5.78)	0.03	---
	Right chi	46.84(4.27)	57.04(5.34)	---	
	Right cun	48.28(4.26)	62.16(4.19)	0.03	
	Right guan	49.92(4.55)	68.74(5.57)	0.02	
	Left chi	400(41)	502(67)	---	
	Left cun	402(29)	524(69)	---	
h_1/t_1	Left guan	425(32)	513(70)	---	---
	Right chi	418(49)	483(55)	---	
	Right cun	419(37)	502(45)	---	
	Right guan	445(51)	595(69)	---	

$^{\psi}$ The mean (SEM) is reported.
*$p < 0.05$ denotes statistical significance.

Pamax, h_3/h_1, h_4/h_1, W/t, t_1/t, and A_T at the six locations were larger in the hypertensive group than in the normotensive group ($p < 0.05$). h_5/h_1, at the six locations was smaller in the hypertensive group than in the normotensive group ($p < 0.01$). t and t_5/t at left guan, right cun, right guan, and right chi were significantly smaller in the hypertensive group than in the normotensive group, whereas the opposite was the case for t_4/t ($p < 0.05$). Although the differences at left cun and left chi were statistically insignificant for these three physical parameters, t and t_5/t were smaller and t_4/t was larger in the hypertensive group than in the normotensive group.

6.5 Relationship among the eight elements and the physical parameters at the six locations

Each element at each location was taken as a dependent variable, and the physical parameters at the six locations were the independent variables.

6.5.1 Correlations of the physical parameters

The Pearson product moment correlation coefficient and Spearman's rank correlation coefficient were used to examine the correlations of the fourteen physical parameters at the six locations. The results demonstrate that they were highly correlated with each other. As the multicollinearity demonstrated by the correlation would affect a regression analysis, principal component analysis was conducted to determine whether it was possible and clinically meaningful to group the physical parameters into several components.

Principal component analysis with varimax rotation was conducted to examine the underlying structure of the physical parameters at the six locations. Nine components were identified with an eigenvalue of greater than 1, and the percentage of variance accounted for was 22.47, 16.53, 5.98, 5.74, 5.67, 5.42, 5.40, 4.98, and 4.45. The total variance explained by these 10 components was 76.66%. Table 6-4 shows the physical parameters and component loadings for the 9 components. Component scores were calculated for each subject and treated as 9 new variables.

Table 6-4 Nine components identified by principal component analysis with an eigenvalue of greater than 1 (N=28)

		Component Loadings								
Physical Parameter	***Location***	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***
t	Right cun	0.92								
t_4/t	Right cun	-0.91								
t_5/t	Right cun	0.91								
t	Right guan	0.90								
t	Right chi	0.80								
t_4/t	Right guan	-0.89								
t_5/t	Right guan	0.89								
t_4/t	Right chi	-0.88								
t_5/t	Right chi	0.88								
t	Left guan	0.87								
t	Left cun	0.86								
t	Left chi	0.85								
t_4/t	Left cun	-0.81								
t_5/t	Left cun	0.81								
t_4/t	Left chi	-0.80								
t_5/t	Left chi	0.80								
t_5/t	Left guan	0.78								
t_4/t	Left guan	-0.78								
t_1/t	Right chi	-0.72								
t_1/t	Right guan	-0.71								
t_1/t	Right cun	-0.67								
t_1/t	Left chi	-0.64								
t_1/t	Left cun	-0.60								
t_1/t	Left guan	-0.58								
h_3/h_1	Left chi		0.92							
h_3/h_1	Left guan		0.90							
h_3/h_1	Left cun		0.89							
h_3/h_1	Right guan		0.89							
h_3/h_1	Right cun		0.88							
h_3/h_1	Right chi		0.88							
W/t	Left chi		0.85							
W/t	Left cun		0.85							
W/t	Left chi		0.82							
W/t	Right cun		0.81							
W/t	Left guan		0.81							
h_4/h_1	Left guan		0.80							
W/t	Right guan		0.78							
W/t	Right chi		0.77							
h_4/h_1	Right chi		0.77							
h_4/h_1	Left cun		0.77							
h_4/h_1	Right cun		0.71							
h_4/h_1	Right guan		0.68							
h_5/h_1	Left cun		-0.65							
h_5/h_1	Left guan		-0.61							
h_5/h_1	Right cun		-0.58							
h_5/h_1	Right guan		-0.51							
h_5/h_1	Left chi		-0.60							
h_5/h_1	Right chi		-0.52							

Table 6-4 Nine components identified by principal component analysis with an eigenvalue of greater than 1 (N=28) (Con't)

		Component Loadings								
Physical Parameter	***Location***	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***
Amppeak	Right cun			0.92						
A_T	Right cun			0.91						
A_S	Right cun			0.90						
h_1/t_1	Right cun			0.87						
A_D	Right cun			0.82						
A_T	Left cun				0.90					
Amppeak	Left cun				0.89					
A_S	Left cun				0.86					
h_1/t_1	Left cun				0.86					
A_D	Left cun				0.83					
A_T	Right chi					0.90				
Amppeak	Right chi					0.89				
A_S	Right chi					0.87				
A_D	Right chi					0.82				
h_1/t_1	Right chi					0.82				
Amppeak	Left guan						0.89			
A_T	Left guan						0.87			
A_S	Left guan						0.83			
h_1/t_1	Left guan						0.80			
A_D	Left guan						0.77			
Amppeak	Left chi							0.87		
A_T	Left chi							0.86		
A_S	Left chi							0.83		
A_D	Left chi							0.79		
h_1/t_1	Left chi							0.78		
Amppeak	Right guan								0.82	
h_1/t_1	Right guan								0.81	
A_T	Right guan								0.80	
A_D	Right guan								0.80	
A_S	Right guan								0.75	
Pamax	Left guan									0.66
Pamax	Right chi									0.65
Pamax	Right guan									0.62
Pamax	Left chi									0.33
Pamax	Left cun									0.46
Pamax	Right cun									0.51

As shown in Table 6-4, the largest component was composed of the physical parameters related to time. t_1/t and t_4/t were negatively related to this component. The second component was made up of the physical parameters related to wave reflection, to which h_5/h_1 was negatively correlated. Components 3 to 9 comprised physical parameters related to the area of the arterial pressure waveform. Unlike the first two components, the physical parameters presented in these 6 components were the same but at different locations. The last component was related to the hold-down pressure with the largest average amppeak.

6.5.2 Regression analysis

Multiple regression was used to study the relationship among group, the 9 components, and depth, rate, width, length, smoothness, stiffness, and strength. Logistic regression was used to examine the relationship among group and the 9 components. The R-squared ranged from 0.33 to 0.84, with smoothness at left guan obtaining the smallest value and width at left chi and right cun the largest. Table 6-5 shows the models and their significant components.

Table 6-5 Regression models for the eight elements and physical parameters at the six locations (N=28)

Dependent Variable Element	Location	*Components with p < 0.05*	R^2	*Model Significance* ψ
Depth	Left chi	5, 7, 9, group	0.82	0.01
	Left cun	---	0.73	0.01
	Left guan	7, 9	0.72	0.01
	Right chi	7	0.69	0.02
	Right cun	3, group	0.83	0.01
	Right guan	5, 7, 9	0.77	0.01
Rate	Left chi	1	0.68	0.02
	Left cun	1	0.56	---
	Left guan	1	0.71	0.01
	Right chi	1	0.68	0.02
	Right cun	---	0.55	---
	Right guan	1	0.73	0.01
Regularity	Left chi	group	0.69	0.03
	Left cun	group	0.69	0.03
	Left guan	group	0.69	0.03
	Right chi	group	0.69	0.03
	Right cun	group	0.69	0.03
	Right guan	group	0.69	0.03
Width	Left chi	1, 7, 8, 9, group	0.84	0.01
	Left cun	1, 3, 7, group	0.83	0.01
	Left guan	7	0.57	---
	Right chi	group	0.79	0.01
	Right cun	3, 4, group	0.84	0.01
	Right guan	1, 4, 7, 9, group	0.78	0.01
Length	Left cun, guan, chi	5, 7	0.82	0.01
	Right cun, guan, chi	3, group	0.83	0.01
Smoothness	Left chi	8	0.49	---
	Left cun	---	0.36	---
	Left guan	7, 9	0.68	0.02
	Right chi	7, 8, 9	0.69	0.01
	Right cun	7	0.67	0.03
	Right guan	---	0.33	---
Stiffness	Left chi	3	0.47	---
	Left cun	---	0.41	---
	Left guan	7, 9	0.66	0.03
	Right chi	1, 5, 7	0.67	0.02
	Right cun	1, 7, 9	0.73	0.01
	Right guan	---	0.40	---
Strength	Left chi	3, 9	0.71	0.01
	Left cun	7, 9	0.67	0.02
	Left guan	5, 7	0.82	0.01
	Right chi	3, group	0.83	0.01
	Right cun	---	0.45	---
	Right guan	8	0.50	---

ψ The model is statistically significant at $p < 0.05$.

6.5.3 ANN

In the pilot study, a three-layer ANN was constructed using a backpropagation algorithm. The input layer had 10 input neurons, which comprised group and the nine components, the hidden layer had 10 hidden neurons and was estimated empirically, and the output layer had 44 output neurons, which were the eight elements at the six locations. The learning rate was set at 0.8 s.

The independent and dependent variables were first normalized. The dataset was randomly divided into 7 subsets. The 7 subsets were randomly assigned into training set, validation set, and testing set at a ratio of 3:3:1. The training set and validation set had 12 subjects each and the testing set had 4 subjects.

The network was trained with the training set, and overfitting was prevented by a validation set. The models established by the ANN were then evaluated with the testing set. The predicted outcome of the ANN was compared with the target outcome using linear regression. The r-squared of the models ranged from 0.10 to 0.60. As the purpose of the pilot study was only to test whether it was possible to establish a model using the ANN, not all of the training algorithms were used. The low r-squared may have been due to the small sample size. Table 6-6 summarizes the results. The reported r-squared is the average of ten training results.

Table 6-6 r-squared of the ANNs of the eight elements at the six locations (N=28)

Dependent Variable		r^2
Element	***Location***	
Depth	Left chi	0.56
	Left cun	0.53
	Left guan	0.58
	Right chi	0.53
	Right cun	0.50
	Right guan	0.56
Rate	Left chi	0.43
	Left cun	0.38
	Left guan	0.40
	Right chi	0.45
	Right cun	0.32
	Right guan	0.33
Regularity	Left chi	0.10
	Left cun	0.10
	Left guan	0.10
	Right chi	0.10
	Right cun	0.10
	Right guan	0.10
Width	Left chi	0.54
	Left cun	0.53
	Left guan	0.56
	Right chi	0.60
	Right cun	0.54
	Right guan	0.56
Length	Left cun, guan, chi	0.50
	Right cun, guan, chi	0.53
Smoothness	Left chi	0.42
	Left cun	0.48
	Left guan	0.46
	Right chi	0.39
	Right cun	0.47
	Right guan	0.46
Stiffness	Left chi	0.50
	Left cun	0.51
	Left guan	0.52
	Right chi	0.56
	Right cun	0.50
	Right guan	0.54
Strength	Left chi	0.59
	Left cun	0.54
	Left guan	0.57
	Right chi	0.59
	Right cun	0.57
	Right guan	0.57

6.6 Relationship of the eight elements at the six locations and hypertension

In this analysis, hypertension was the dependent variable and the eight elements at the six locations were the dependent variables.

6.6.1 Correlations of the eight elements at the six locations

The Pearson product moment correlation coefficient was used to examine the correlations of the continuous variables and the Spearman's rank correlation coefficient was used to examine the correlations of the categorical variables. The majority of the variables were highly correlated with one another and their correlations were statistically significant ($p < 0.05$).

As the variables were highly correlated, it was likely that multicollinearity would affect the regression modeling and placing a large number of covariates into a regression model would decrease the power of the result. Thus, principal component analysis was used rather than regression to reduce the risk of redundancy.

Principal component analysis with varimax rotation was conducted to assess the underlying structure for the eight elements at the six locations, and 8 components were identified. Table 6-7 shows the 8 components and their corresponding elements and component loadings. The percentage of variance accounted for by each component was 18.07, 13.98, 12.21, 10.24, 9.51, 7.59, 5.27, and 3.79. The component scores for each subject were calculated and used as 8 new variables in the logistic regression to distinguish the normotensive and hypertensive groups.

Table 6-7 Eight components identified by principal component analysis with an eigenvalue of greater than 1 (N=28)

		Component Loadings							
Element	***Location***	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***
Length	Left cun, guan, chi	0.95							
Length	Right cun, guan, chi	0.93							
Depth	Left cun	0.90							
Depth	Right cun	0.89							
Depth	Left guan	0.81							
Depth	Right guan	0.78							
Depth	Left chi	0.76							
Depth	Right chi	0.72							
Regularity	Right guan		0.98						
Regularity	Right cun		0.98						
Regularity	Right chi		0.98						
Regularity	Left guan		0.98						
Regularity	Left cun		0.98						
Regularity	Left chi		0.98						
Rate	Right guan			0.93					
Rate	Right chi			0.90					
Rate	Right cun			0.88					
Rate	Left guan			0.85					
Rate	Left chi			0.85					
Rate	Left cun			0.77					
Smoothness	Right chi				0.83				
Smoothness	Right cun				0.81				
Smoothness	Left chi				0.80				
Smoothness	Left guan				0.76				
Smoothness	Right guan				0.76				
Smoothness	Left cun				0.74				
Width	Right guan					0.81			
Width	Right chi					0.74			
Width	Left guan					0.70			
Width	Left chi					0.67			
Width	Left cun					0.60			
Width	Right cun					0.58			
Stiffness	Left cun						0.73		
Stiffness	Right cun						0.66		
Stiffness	Left guan						0.65		
Strength	Left cun						0.61		
Strength	Left guan						0.45		
Strength	Right cun						0.43		
Stiffness	Right chi							0.78	
Strength	Right chi							0.66	
Stiffness	Right guan							0.61	
Strength	Right guan							0.46	
Strength	Left chi								0.61
Stiffness	Left chi								0.54

The results of the principal component analysis demonstrate that the same elements, despite being from different locations, grouped together in the same component. Some separate elements were consistently grouped in the same component, such as depth and length and stiffness and strength, which suggests that in some cases the intensity of a particular element was based on the intensity of another element. Component scores for each subject were calculated and then used as 8 new variables in the logistic regression to distinguish the normotensive and hypertensive groups.

6.6.2 Regression analysis

The component scores for the 8 components were treated as independent variables to differentiate hypertension from normotension. The r-squared was 0.75 ($p < 0.01$), and the accuracy of the model was 89%. Component 2, component 4, and component 5 significantly contributed to the model. Component 2 was composed of regularity at the six locations and its odds ratio reflects that the hypertensive subjects tended to have an irregular pulse. Component 4 was composed of smoothness at the six locations, and indicates that subjects with a low intensity of smoothness tended to have hypertension. Component 5 was width at the six locations, and demonstrates that a large pulse was more prevalent in the subjects with hypertension. Table 6-8 shows the results of the regression analysis.

Table 6-8 Predictive model of hypertension using logistic regression (N=28)

Component	***β***	***Odds Ratio***	***Significance****
1	-0.53	0.59	---
2	0.47	1.59	0.01
3	-0.30	0.74	---
4	-1.28	0.28	0.01
5	0.94	2.56	0.03
6	0.46	1.58	---
7	0.12	1.18	---
8	0.17	1.18	---

*$p < 0.05$ denotes statistical significance.

6.6.3 ANN

A three-layer ANN and the backpropagation algorithm were again used for the modeling. The input layer had eight input neurons, which were the 8 components, the hidden layer contained 10 hidden neurons, and the output layer had one output neuron, which was group. The established model had an overall accuracy of 60%.

In terms of differentiating hypertension from the perspective of TCM pulse diagnosis, the predictive accuracy of the logistic regression was about 30% higher than the model established by the ANN, which indicates that logistic regression is a better choice than the ANN.

6.7 Estimation of sample size for the main study

As no similar studies have been conducted before, the sample size for the main study was based on the effect size in the pilot results. The estimation of the sample size was carried out using two-way ANOVAs and multiple regression based on the procedure set out in Portney and Watkins (2000).

For the two-way ANOVA of main effect, the effect size f was calculated with the equation $f = (SS_b/SS_e)^{1/2}$, where SS_b is the between-groups sum of squares and SS_e is the error in the sum of squares. For the effect of group, the smallest $SS_b = 2.28$, $SS_e = 57.09$, so $f = (2.28/57.09)^{1/2} = 0.20$. To achieve an 80% power with one degree of freedom, the sample size would thus need to be 99. For the effect of location, the smallest $SS_b = 2.12$, $SS_e = 57.09$, so $f = (2.12/57.09)^{1/2} = 0.19$. To achieve an 80% power with five degrees of freedom, the sample size would need to be 54.

For the two-way ANOVA of interaction effect, the effect size was estimated using $f_{AB} = (SS_{AB}/SS_e)^{1/2}$, where A and B are group and location, respectively, and SS_{AB} is the interaction of the sum of squares of group and location. For the interaction effect of group and location, the smallest SS_{AB}= 18.40, SS_e= 460.52, so $f_{AB} = (18.40/460.52)^{1/2}$=0.20, giving an estimated sample size of 54.

The effect size of multiple regression was calculated with the equation N= [λ (1-R^2)/R^2], where is R^2 is the coefficient of the determinant of the established model and λ is a value that is used to determine the sample size of an F-test for regression analysis. The lowest insignificant r-squared was 0.33, k=10, df_{res} = 28-10-1=17, λ = 24.4, and N = [24.4 (1-0.33)/0.33]= 49.54, and it was thus calculated that to achieve an 80% power in the main study, a sample size of 50 would be needed.

Table 6-9 shows the effect sizes and corresponding sample sizes estimated for the statistical tests. According to conventional statistical sample size estimation, the minimum sample size required for the main study was 99 per group.

Table 6-9 Effect size and estimated sample size

Statistical Test	*Effect Size*[Ψ]	*Power*	*Sample Size Estimated*
Two-way ANOVA (main effect) of group	f = 0.20	0.80	99
Two-way ANOVA (main effect) of location	f=0.19	0.80	54
Two-way ANOVA (interaction effect)	f = 0.20	0.80	54
Multiple regression	λ = 24.40	0.80	50

[Ψ] The effect size reported is the smallest among all of the variables.

6.7.1 Justification of the estimated sample size using an ANN

According to Lisboa (2002), sample sizes for exploratory studies should be five to ten times the number of independent variables. By this token, the number of samples required for modeling the relationship of the eight elements and the physical parameters at the six locations is 10 x 10 = 100 samples, and for modeling the relationship among hypertension and the eight elements at the six locations is 8 x 10 = 80 samples.

As the dataset for the ANN was split into a training set and testing set, there was an issue with the sample size of the testing set (Hart & Wyatt, 1990). Wasson, Sox, Neff and Goldman (1985) proposed that an ANN testing set should contain at least five examples per item of the input data per class. Based on this suggestion, the sample size of the testing set required for modeling the relationship of the elements and the physical parameters at the six locations would be 5 examples x 10 x 100 (the unit of rating was 0.1) = 5000 samples, and for modeling the relationship among hypertension and the elements at the six locations would be 5 x 8 x 2 = 80 samples.

As it is impossible to have 5,000 samples in the testing set, it was not considered in sample size estimation. Thus, based only on the conventional statistical sample size calculation and the suggestion of Lisboa (2002), it was determined that at least 100 subjects per group were required. Considering the shortcomings of the feature extraction program, it was decided to recruit an extra 20% per group. Thus, 120 subjects per group were recruited in the main study.

6.8 Criterion validity for the TCM doctor

The results for the criterion validity test of the TCM doctor selected to perform the pulse assessment in the main study indicate that his pulse assessment was accurate and could differentiate hypertension from normotension. As his intra-rater reliability was also high, he was thus deemed competent to differentiate hypertension based on TCM pulse assessment.

6.9 Revisiting and amending the study design

The pilot study showed that the procedure and data analysis were feasible, and that the TCM doctor understood the rating scale in the TCM pulse assessment form and could rate the elements without difficulty. Thus, no major revision to these factors was required for the main study.

In terms of the subjects, the pilot study demonstrated that as they were in a supine position for the whole process and the environment in the TCM laboratory was sufficiently quiet to allow them to relax, the incidence of motion artifacts due to fatigue was greatly reduced. The forearm holder held their arms in a natural position such that they did not feel numb or uncomfortable. However, the time required for pulse acquisition was longer than expected, with the average time taken to acquire the arterial pressure waveform at the six locations of one hour and fifteen minutes. The prolonged duration was caused by the need for repeated pulse acquisition at the same location caused by the movement of the subjects. It was found that the longer the duration of the pulse acquisition, the poorer the quality of the arterial pressure waveform. Thus, to confine the duration of pulse acquisition to less than an hour, the pressure interval of pulse acquisition was increased to 30 mmHg for the main study.

As the pilot study revealed that the feature extraction program could only accurately extract waveforms with a stable baseline, manual screening was deemed necessary to check the accuracy of the extracted physical parameters. Further, the pilot study also showed that the peak-to-peak interval could not be extracted because the program was not able to differentiate whether the interval was between two consecutive arterial pressure waveforms or more. Also, Δ80%pamax was not calculated because the feature extraction program was not ready to calculate this parameter. It was thus determined that further enhancement of the feature extraction program was required.

6.10 Conclusion

The pilot study proved the proposed study design to be feasible, but suggested that the pressure interval of the hold-down pressure should be changed to 30 mmHg to shorten the time required to acquire the arterial pulse waveforms. The results of the pilot study were used to calculate the sample size for the main study, and the value of 120 per group was obtained. The TCM doctor was found to be competent in assessing pulse using the TCM pulse assessment form, but because of deficits in the feature extraction program, it was identified that manual screening would be required in the main study to ensure the quality of the features extracted.

Following the pilot study, data collection for the main study was carried out from June to October 2008. The next chapter describes the results of the main study.

CHAPTER SEVEN

RESULTS OF THE MAIN STUDY

7.1 Introduction

The main study was conducted from June to October 2008. This chapter presents the results of the main study in terms of the research objectives, research questions, and hypotheses.

Differences in the demographic information on the subjects and the hemodynamic and anthropometric parameters were examined to identify any confounding effects that might influence the results. Univariate analysis was used to examine the differences among the eight elements and the physical parameters at the six locations between the normotensive and hypertensive groups.

Regression analysis and an ANN were used to model the relationships among the eight elements and the physical parameters at the six locations and the relationships among the eight elements at the six locations with hypertension.

7.2 Background information on the subjects

Two hundred and sixty subjects were recruited, of which 139 were in the normotensive group and 121 were in the hypertensive group. A Mann Whitney U-test was used to examine the differences in gender, age, and body mass index between the groups. The differences in pulse rate, left-side blood pressure, and right-side blood pressure were tested by using an independent t-test. The demographic information, blood pressure, body mass index, and pulse rate of the subjects is presented in Table 7-1. There was no statistically significant difference in gender, age, and body mass index between the groups ($p > 0.05$), but a statistically significant difference in pulse rate, left-side blood pressure, and right-side blood pressure was identified ($p < 0.01$).

Table 7-1 Background information on the subjects (N=260)

		Normotensive Group$^{\psi}$ *(n=139)*	*Hypertensive Group*$^{\psi}$ *(n=121)*	*Significance* (p < 0.05)*
Gender	Male	55	53	---
	Female	84	68	
Age (yrs)	18-34	43	9	---
	35-64	86	93	
	≥ 65	10	19	
BMI (kg/m^2)	<18.50	12	5	---
	18.50-22.99	103	96	
	≥ 23.00	24	20	
LBP (mmHg)		112(13)/68(7)	150(16)/95(11)	0.01
RBP (mmHg)		113(13)/68(7)	150(15)/95(11)	0.01
Pulse Rate (bpm)		65(10)	70(11)	0.01

BMI = Body mass index; LBP = Left-side blood pressure; RBP = Right-side blood pressure.
$^{\psi}$The mean (SD) is reported for the continuous variables and the frequency for the categorical variables.
*p < 0.05 denotes statistical significance.

7.3 Effect of group and location on the eight elements

Univariate analysis was conducted to examine the effect of group and location on the eight elements. No interaction effect between group and location on the eight elements was identified ($p > 0.05$), but there was a statistically significant difference in the eight elements between the groups ($p < 0.04$) and at the six locations ($p < 0.02$). The null hypothesis is thus rejected and the alternate hypothesis supported. Table 7-2 summarizes the results.

Table 7-2 Means, medians, and standard deviations for the eight elements at the six locations between the groups (N=260)

Element	*Location*	*Normotension*[Ψ] *(n = 139)*	*Hypertension*[Ψ] *(n = 121)*	*Significance** *Group*	*Location*
Depth	Left chi	6.8(1.2)	7.2(1.3)	0.04	0.01
	Left cun	8.2(1.3)	8.2(0.9)	---	
	Left guan	7.9(1.4)	8.1(0.9)	---	
	Right chi	7.2(1.6)	7.4(1.1)	---	
	Right cun	8.3(1.1)	8.3(0.8)	---	
	Right guan	8.0(1.2)	8.1(0.8)	---	
Rate	Left chi	4.7(0.5)	4.6(0.5)	---	---
	Left cun	4.7(0.6)	4.7(0.5)	---	
	Left guan	4.7(0.5)	4.7(0.5)	---	
	Right chi	4.7(0.6)	4.6(0.5)	---	
	Right cun	4.7(0.5)	4.6(0.5)	---	
	Right guan	4.6(0.6)	4.6(0.5)	---	
Regularity	Left chi	0	1	0.01	---
	Left cun	0	1	0.01	
	Left guan	0	1	0.01	
	Right chi	0	1	0.01	
	Right cun	0	1	0.01	
	Right guan	0	1	0.01	
Width	Left chi	5.7(1.2)	6.7(1.2)	0.01	0.01
	Left cun	6.6(1.3)	7.5(1.1)	0.01	
	Left guan	6.0(1.2)	7.2(1.1)	0.01	
	Right chi	5.7(1.1)	6.9(1.1)	0.01	
	Right cun	6.9(1.1)	7.7(1.0)	0.01	
	Right guan	6.1(1.1)	7.2(1.2)	0.01	
Length	Left cun, guan, chi	8.0(1.4)	8.4(1.0)	0.03	0.02
	Right cun, guan, chi	8.3(1.2)	8.6(0.7)	0.01	
Smoothness	Left chi	5.7(0.7)	5.1(0.8)	0.01	0.01
	Left cun	6.0(0.8)	5.2(0.9)	0.01	
	Left guan	6.0(0.7)	5.3(0.8)	0.01	
	Right chi	5.7(0.7)	5.1(0.7)	0.01	
	Right cun	6.2(0.7)	5.6(0.9)	0.01	
	Right guan	6.0(0.7)	5.5(0.7)	0.01	
Stiffness	Left chi	4.4(1.2)	4.7(1.2)	0.01	0.01
	Left cun	5.2(1.1)	5.5(1.2)	0.01	
	Left guan	3.8(1.0)	4.4(1.2)	0.01	
	Right chi	4.9(1.0)	5.2(1.1)	0.01	
	Right cun	4.3(0.9)	4.7(1.1)	0.01	
	Right guan	4.3(1.0)	4.9(1.1)	0.01	
Strength	Left chi	4.9(1.2)	4.8(1.4)	---	0.01
	Left cun	5.5(1.1)	5.2(1.2)	---	
	Left guan	5.0(0.9)	5.0(1.1)	---	
	Right chi	5.2(1.1)	5.3(1.2)	---	
	Right cun	5.8(0.9)	5.6(1.0)	---	
	Right guan	5.3(1.0)	5.4(1.0)	---	

[Ψ]The mean (SD) is reported for the continuous variables and the median for the categorical variables.

*$p < 0.05$ denotes statistical significance.

Group had a significant effect on regularity, width, length, smoothness, and stiffness at the six locations ($p < 0.05$), with the pulse of the subjects in the hypertensive group being irregular, larger, longer, rougher, and stiffer. The pulse of the hypertensive subjects was also more floating at left chi than that of the normotensive subjects ($p < 0.04$).

Location had a statistically significant effect on depth, width, length, smoothness, stiffness, and strength, and thus a Bonferroni test was performed to investigate the mean differences in these elements at the six locations. Length at right side was larger than that at left side ($p < 0.02$). Depth at left chi and right chi were statistically significantly deeper than at cun and guan on both sides ($p < 0.01$). Width decreased from cun to chi. On both sides, width at cun was larger than at guan and chi ($p < 0.01$), and width at guan was larger than at chi ($p < 0.01$).

The pulse at left and right chi was rougher than at cun and guan on both sides ($p < 0.01$), and was smoother at right cun than at left cun ($p < 0.01$). Pulse at left guan was statistically significantly less stiff than at the other five locations ($p < 0.01$), whereas pulse at left cun was significantly stiffer than at the other five locations (p

< 0.01). In terms of strength, pulse at right cun was strongest among the six locations ($p < 0.01$), and was weaker at left guan and chi than at left cun, right cun, and right guan ($p < 0.01$).

7.4 Effect of group and location on the sixteen physical parameters

Features of the arterial pressure waveform could only be correctly extracted from 229 subjects, 135 in the normotensive group and 94 in the hypertensive group. The peak-to-peak interval (PPI) could not be extracted from the tracings by the feature extraction program. The Δ80%pamax parameter was successfully extracted and calculated for all of the normotensive subjects and 70 of the hypertensive subjects, but could not be extracted for 24 of the hypertensive subjects because the amplitude of their arterial pressure waveforms did not level off or decrease when the maximum hold-down pressure was reached. Table 7-3 compares the means and standard deviations of the physical parameters of the normotensive and hypertensive groups.

Table 7-3 Means and standard deviations of the physical parameters at the six locations between the groups (N=229)

Physical Parameter	***Location***	***Normotension (n = 135)***	***Hypertension (n = 94)***	***Significance* Group***	***Significance* Location***
h_3/h_1	Left chi	0.64(0.17)	0.81(0.15)	0.01	---
	Left cun	0.63(0.16)	0.82(0.13)	0.01	
	Left guan	0.63(0.17)	0.81(0.15)	0.01	
	Right chi	0.61(0.18)	0.80(0.14)	0.01	
	Right cun	0.62(0.18)	0.80(0.15)	0.01	
	Right guan	0.63(0.17)	0.79(0.16)	0.01	
h_4/h_1	Left chi	0.37(0.11)	0.43(0.10)	0.01	---
	Left cun	0.36(0.07)	0.41(0.09)	0.01	
	Left guan	0.37(0.09)	0.43(0.09)	0.01	
	Right chi	0.35(0.09)	0.42(0.09)	0.01	
	Right cun	0.35(0.10)	0.41(0.11)	0.01	
	Right guan	0.37(0.09)	0.41(0.09)	0.01	
h_5/h_1	Left chi	0.06(0.06)	0.03(0.03)	0.01	0.01
	Left cun	0.05(0.05)	0.03(0.03)	0.01	
	Left guan	0.06(0.05)	0.03(0.03)	0.01	
	Right chi	0.08(0.08)	0.04(0.04)	0.01	
	Right cun	0.07(0.07)	0.06(0.04)	0.01	
	Right guan	0.06(0.05)	0.04(0.03)	0.01	
W/t	Left chi	0.18(0.06)	0.24(0.05)	0.01	---
	Left cun	0.18(0.06)	0.24(0.04)	0.01	
	Left guan	0.18(0.07)	0.23(0.04)	0.01	
	Right chi	0.17(0.06)	0.23(0.05)	0.01	
	Right cun	0.17(0.06)	0.23(0.05)	0.01	
	Right guan	0.18(0.07)	0.23(0.05)	0.01	
t	Left chi	0.95(0.17)	0.92(0.15)	---	---
	Left cun	0.93(0.13)	0.91(0.13)	---	
	Left guan	0.94(0.13)	0.92(0.15)	---	
	Right chi	0.95(0.14)	0.92(0.16)	---	
	Right cun	0.94(0.13)	0.91(0.15)	---	
	Right guan	0.94(0.14)	0.92(0.16)	---	

*$p < 0.05$ denotes statistical significance.

Table 7-3 Means and standard deviations of the physical parameters at the six locations between the groups (N=229) (Con't)

Physical Parameter	*Location*	*Normotension (n =135)*	*Hypertension (n = 94)*	*Significance* Group*	*Significance* Location*
t_1/t	Left chi	0.14(0.03)	0.15(0.03)	0.02	0.01
	Left cun	0.15(0.03)	0.16(0.03)	0.01	
	Left guan	0.14(0.03)	0.15(0.03)	0.01	
	Right chi	0.13(0.03)	0.14(0.14)	0.03	
	Right cun	0.13(0.03)	0.15(0.03)	0.01	
	Right guan	0.14(0.03)	0.15(0.03)	0.01	
t_4/t	Left chi	0.40(0.06)	0.40(0.05)	---	---
	Left cun	0.41(0.06)	0.42(0.05)	---	
	Left guan	0.40(0.05)	0.41(0.05)	---	
	Right chi	0.39(0.05)	0.40(0.05)	---	
	Right cun	0.39(0.05)	0.41(0.05)	---	
	Right guan	0.40(0.05)	0.41(0.05)	---	
t_5/t	Left chi	0.60(0.06)	0.60(0.05)	---	---
	Left cun	0.60(0.06)	0.58(0.05)	---	
	Left guan	0.61(0.05)	0.59(0.05)	---	
	Right chi	0.61(0.05)	0.60(0.05)	---	
	Right cun	0.61(0.05)	0.59(0.05)	---	
	Right guan	0.60(0.05)	0.59(0.05)	---	
A_T	Left chi	17898(6833)	22721(8830)	0.01	---
	Left cun	18489(5760)	23510(10333)	0.01	
	Left guan	18021(5513)	25842(9873)	0.01	
	Right chi	17852(6018)	24459(9749)	0.01	
	Right cun	17526(7181)	22219(11752)	0.01	
	Right guan	17430(5838)	26928(11274)	0.01	
A_S	Left chi	12009(5117)	15233(5782)	0.01	---
	Left cun	12445(4011)	15892(6788)	0.01	
	Left guan	11928(3777)	17525(6340)	0.01	
	Right chi	11723(4129)	16325(5940)	0.01	
	Right cun	11676(5031)	15078(7348)	0.01	
	Right guan	11455(3789)	18200(7203)	0.01	

*$p < 0.05$ denotes statistical significance.

Table 7-3 Means and standard deviations of the physical parameters at the six locations between the groups (N=229) (Con't)

Physical Parameter	Location	Normotension (n = 135)	Hypertension (n = 94)	Significance* Group	Significance* Location
A_D	Left chi	5889(2675)	7489(3494)	0.01	---
	Left cun	6044(2386)	7618(3841)	0.01	
	Left guan	6093(2331)	8317(4017)	0.01	
	Right chi	6129(2492)	8133(4268)	0.01	
	Right cun	5850(2711)	7141(4733)	0.01	
	Right guan	5975(2537)	8728(4503)	0.01	
Pamax	Left chi	173(79)	230(81)	0.01	0.01
	Left cun	167(70)	246(85)	0.01	
	Left guan	149(71)	202(76)	0.01	
	Right chi	175(71)	225(78)	0.01	
	Right cun	173(80)	248(93)	0.01	
	Right guan	150(62)	207(70)	0.01	
Amppeak	Left chi	44(15)	51(20)	0.01	---
	Left cun	47(15)	54(24)	0.01	
	Left guan	46(14)	61(22)	0.01	
	Right chi	46(15)	56(20)	0.01	
	Right cun	45(18)	53(25)	0.01	
	Right guan	44(15)	64(24)	0.01	
h_1/t_1	Left chi	351(138)	397(195)	---	0.01
	Left cun	374(141)	412(213)	---	
	Left guan	378(150)	475(221)	0.01	
	Right chi	384(157)	450(189)	0.01	
	Right cun	379(153)	417(224)	---	
	Right guan	370(160)	509(227)	0.01	
Δ80%pamax	Left chi	69(49)	57(57) 24miss	---	0.01
	Left cun	71(44)	96(53) 24miss	0.01	
	Left guan	71(49)	72(52) 24miss	---	
	Right chi	80(51)	79(56) 24miss	---	
	Right cun	66(48)	93(47) 24miss	0.01	
	Right guan	69(49)	75(52) 24miss	---	

*p < 0.05 denotes statistical significance.

The results reject the null hypothesis that there would be no difference in the physical parameters at the six locations between the normotensive and hypertensive groups. h_3/h_1, h_4/h_1, W/t, t_1/t, A_T, A_S, A_D, pamax, and amppeak at the six locations in the hypertensive group had significantly greater values than in the normotensive group ($p < 0.03$), and h_5/h_1 at the six locations was significantly smaller in the hypertensive group than in the normotensive group ($p < 0.01$). Further, h_1/t_1 at left guan, right guan, and right chi was significantly larger in the hypertensive group than in the normotensive group ($p < 0.01$), and Δ80%pamax at left cun and right cun was significantly larger in the hypertensive group than in the normotensive group ($p < 0.01$).

For both groups, h_5/h_1, t_1/t, and pamax were significantly affected by location. h_5/h_1 at left cun, guan, and chi were smaller than at right chi ($p < 0.01$), t_1/t at left cun was larger than at right chi ($p < 0.01$), and pamax at cun and chi on both sides had larger values than at guan on both sides ($p < 0.05$).

A_T, A_S, A_D, amppeak, h_1/t_1, and Δ80%pamax were subject to an interaction effect between group and location ($p < 0.02$). Among the subjects with hypertension, A_T, A_S, A_D, amppeak, and h_1/t_1 were significantly larger at left and right guan than among the normotensive subjects ($p < 0.02$), and Δ80%pamax was significantly larger at left and right cun ($p < 0.01$).

7.5 Relationship of the eight elements and the physical parameters at the six locations

7.5.1 Correlations of the physical parameters at the six locations

The correlations among the 15 physical parameters that could be extracted were examined, and it was found that the majority was significantly correlated with each other and had moderate to high correlations with one or more of the other physical parameters ($p < 0.05$). As they were used as independent variables for modeling the eight elements at the six locations, such multicollineairy could affect the results of a regression analysis, and thus principal component analysis was performed to reduce the redundancy of the variables.

Ten components with an eigenvalue of greater than 1 were identified using principal component analysis with varimax rotation. The total variance explained by the ten components was 84.00%, and the variance explained by the individual components was 19.53%, 18.17%, 12.36%, 6.19%, 5.45%, 5.17%, 5.06%, 4.82%, 4.05%, and 3.20%. Table 7-4 shows the 10 components, the corresponding physical parameters, and their component loadings.

Table 7-4 Ten components of the physical parameters at the six locations (N=229)

		Component Loadings									
Physical Parameter	***Location***	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***
t_4/t	Right cun	-0.90									
t_5/t	Right cun	0.90									
t	Right cun	0.89									
t	Right chi	0.89									
t	Left guan	0.88									
t	Right guan	0.88									
t	Left chi	0.87									
t	Left cun	0.86									
t_5/t	Right guan	0.87									
t_4/t	Right guan	-0.87									
t_5/t	Right chi	0.87									
t_4/t	Right chi	-0.87									
t_5/t	Left guan	0.87									
t_4/t	Left guan	-0.87									
t_5/t	Left cun	0.84									
t_4/t	Left cun	-0.84									
t_4/t	Left chi	-0.84									
t_5/t	Left chi	0.84									
t_1/t	Right guan	-0.73									
t_1/t	Right chi	-0.73									
t_1/t	Left chi	-0.70									
t_1/t	Left guan	-0.68									
t_1/t	Right cun	-0.67									
t_1/t	Right chi	-0.66									
h_3/h_1	Right guan		0.89								
h_3/h_1	Left guan		0.87								
h_3/h_1	Right cun		0.86								
h_3/h_1	Right chi		0.85								
h_3/h_1	Left chi		0.85								
h_3/h_1	Left cun		0.84								
h_4/h_1	Right chi		0.81								
h_4/h_1	Left guan		0.80								
W/t	Left chi		0.79								
h_4/h_1	Left chi		0.78								
W/t	Left guan		0.77								
W/t	Left cun		0.77								
h_4/h_1	Right guan		0.77								
W/t	Right cun		0.75								
W/t	Right guan		0.75								
h_4h_1	Left cun		0.74								
W/t	Right chi		0.73								
h_5/h_1	Left guan		-0.73								
h_5/h_1	Left chi		-0.73								
h_5/h_1	Left cun		-0.73								
h_4/h_1	Right cun		0.72								
h_5/h_1	Right cun		-0.68								
h_5/h_1	Right guan		-0.65								
h_5/h_1	Right chi		-0.64								

Table 7-4 Ten components of the physical parameters at the six locations (N=229) (Con't)

Physical Parameter	*Location*	*Component Loadings* 1	2	3	4	5	6	7	8	9	10
Amppeak	Right cun			0.93							
A_T	Right cun			0.92							
A_S	Right cun			0.90							
A_D	Right cun			0.84							
h_1/t_1	Right cun			0.82							
Amppeak	Left cun				0.91						
A_T	Left cun				0.87						
A_D	Left cun				0.85						
A_S	Left cun				0.84						
h_1/t_1	Left cun				0.79						
Amppeak	Right chi					0.90					
A_T	Right chi					0.89					
A_S	Right chi					0.84					
A_D	Right chi					0.84					
h_1/t_1	Right chi					0.79					
Amppeak	Left guan						0.91				
h_1/t_1	Left guan						0.86				
A_T	Left guan						0.75				
A_S	Left guan						0.74				
A_D	Left guan						0.63				
Amppeak	Left chi							0.86			
A_T	Left chi							0.80			
A_D	Left chi							0.78			
A_S	Left chi							0.75			
h_1/t_1	Left chi							0.59			
Amppeak	Right guan								0.89		
h_1/t_1	Right guan								0.81		
A_T	Right guan								0.68		
A_S	Right guan								0.65		
A_D	Right guan								0.63		
Pamax	Left cun									0.73	
Pamax	Right cun									0.70	
Pamax	Right guan									0.69	
Pamax	Left guan									0.69	
Pamax	Right chi									0.64	
Pamax	Left chi									0.64	
Δ80%pamax	Right chi										0.78
Δ80%pamax	Left chi										0.78
Δ80%pamax	Right guan										0.67
Δ80%pamax	Left guan										0.65
Δ80%pamax	Right cun										0.45
Δ80%pamax	Left cun										0.43

The first component was composed of the physical parameters related to time. t_1/t and t_4/t were negatively correlated and t and t_5/t were positively correlated with this component. The second component comprised the physical parameters related to wave reflection. h_5/h_1 was negatively associated and all of the other parameters were positively associated with the component. Components 3 to 8 contained the parameters related to the area of the arterial pressure waveform, classified into 6 components according to the six locations, respectively. The ninth component comprised the hold-down pressure with the largest average local maxima among the tracings of the arterial pressure waveforms at the same location. The last component was the difference in hold-down pressures at 80% amppeak.

7.5.2 Regression analysis: The physical parameters and the eight elements at the six locations

After reducing the dimensions of the physical parameters, multiple regression was used to explore the relationship among the 10 components and depth, rate, width, length, smoothness, stiffness, and strength (the eight elements) between the groups. The relationship of the 10 components and group with regularity was investigated using logistic regression. Forty-four regression models were established, which refer to the relationship of the 15 physical parameters at the six locations with each element at each location. Table 7-5 presents the significant components and the R-squared values of the regression models.

Table 7-5 Regression models of the relationships among the eight elements and the physical parameters at the six locations (N=229)

Dependent Variable Element	Location	Components with $p < 0.05$	R^2	Model Significance[ψ]
Depth	Left chi	2,9,10,group	0.21	0.01
	Left cun	2,9,10	0.15	0.01
	Left guan	9,10	0.17	0.01
	Right chi	9,10,group	0.15	0.01
	Right cun	2,9,10	0.19	0.01
	Right guan	7,10	0.10	0.04
Rate	Left chi	1,2,9	0.25	0.01
	Left cun	1,10	0.20	0.01
	Left guan	1,2,9	0.29	0.01
	Right chi	1,2,9	0.25	0.01
	Right cun	1,2,9	0.24	0.01
	Right guan	1,2,9	0.26	0.01
Regularity	Left chi	1,2,9	0.19	0.01
	Left cun	1,2,9	0.19	0.01
	Left guan	1,2,9	0.19	0.01
	Right chi	1,2,9	0.19	0.01
	Right cun	1,2,9	0.19	0.01
	Right guan	1,2,9	0.19	0.01
Width	Left chi	3,9,10,group	0.24	0.01
	Left cun	3,10, group	0.23	0.01
	Left guan	3,10,group	0.23	0.01
	Right chi	9,10,group	0.33	0.01
	Right cun	5,9,10,group	0.24	0.01
	Right guan	10,group	0.27	0.01
Length	Left cun, guan, chi	2,9,10	0.16	0.01
	Right cun, guan, chi	1,2,10	0.17	0.01
Smoothness	Left chi	2,7,9,group	0.27	0.01
	Left cun	1,2,9,group	0.31	0.01
	Left guan	2,9,group	0.28	0.01
	Right chi	9,group	0.22	0.01
	Right cun	3,9,group	0.19	0.01
	Right guan	9,group	0.17	0.01
Stiffness	Left chi	7,9,10,group	0.18	0.01
	Left cun	4	0.15	0.01
	Left guan	group	0.15	0.01
	Right chi	3,6,9,10,group	0.28	0.01
	Right cun	5,9,group	0.13	0.01
	Right guan	2,5,group	0.20	0.01
Strength	Left chi	7,9,10	0.20	0.01
	Left cun	4,9	0.13	0.01
	Left guan	2,9,10,group	0.17	0.01
	Right chi	2,9,10,group	0.20	0.01
	Right cun	9,10	0.21	0.01
	Right guan	2,5,9,group	0.13	0.01

[ψ] Statistically significant at $p < 0.05$.

All of the models were statistically significant ($p < 0.05$), but their R-squared was low, which means that the 10 components did not explain the eight elements at the six locations and were not related in a linear way. ANN was thus used to test for nonlinear relationships.

7.5.3 ANN: The physical parameters and the eight elements at the six locations

An ANN was applied to determine whether a mathematical model could be developed for the relationships among the physical parameters and the eight elements at the six locations.

7.5.3.1 Design of the ANN

Three factors could be manipulated in the modeling: the number of hidden layers, the number of hidden neurons, and the training algorithms used. As there is no protocol in ANN studies to guide the training process, the three factors were systematically adjusted during the modeling to generate the best results.

To increase the efficiency of the training, the input data and target data were pre-processed before training commenced. The input and target data were first normalized to a zero mean and a unity standard deviation, and the numbers of neurons in the input and output layers were fixed. The 11 input neurons were the group and the 10 components. The eight elements at the six locations were the output neurons, meaning that there were 44 in total. A backpropagation and radial basis networks were the two training approaches used. The performance of the modeling process was then determined by calculating the r-squared of the predicted value from the models and the target value using linear regression.

7.5.3.1.1 Backpropagation

Initially one hidden layer was used, and the number of hidden neurons was set at 20 and then increased in five-neuron intervals until the performance leveled off or decreased. If the three-layer network failed to train the models, then a four-layer network was attempted using the same number of hidden neurons in successive trainings and criteria for stopping the training as for the three-layer network.

Log-sigmoid function was used as the transfer function to connect the input layer to the first hidden layer and between subsequent hidden layers, if any. A pure linear function was used as the transfer function connecting the nth hidden layer to the output layer. The learning rate, or speed at which the ANN reached the optimum solution, was arbitrarily set at 0.02s, and the momentum used to prevent the training from converging to the local minimum was arbitrarily set at 0.8. The number of training epochs was set at 500. The Levenberg-Marquardt algorithm (LM), resilient backpropagation (RB), and Bayesian regularization (BR) were used separately to train the backpropagation model.

The LM, RB, and BR differ in the way that they handle the problem of overfitting, which is the excessive fitting of the trained model to the predetermined relationship in the dataset that decreases the generalizability of the trained model (Demuth & Beale, 1998). With the LM and RB, early stopping is used to prevent overfitting. Early stopping prevents overfitting by monitoring the error in the training set during training. The level of error in the training set and validation set decreases initially, but after a certain number of training epochs the validation set error rises and the network stops training the models. This is the point at which the weight and bias among the neurons within the model are determined.

As a validation set is required for the LM and RB approaches, the dataset was randomly divided into a training set, a validation set, and a testing set. At the beginning of the training, the dataset was subdivided randomly into seven subsets, and each subset was randomly assigned to the training set, validation set, or testing set at a ratio of 3:3:1. A total of 10 trainings were performed to determine the average performance.

The BR does not use early stopping to avoid overfitting, but uses regularization instead. Regularization modifies the performance function, which is the sum of the squares of the errors, by the addition of a mathematical term (Demuth & Beale, 1998). Thus, only a training set and a testing set are required. Before training, the dataset was randomly subdivided into seven subsets, each of which was then randomly assigned into the training set or the testing set. A total of 10 trainings were performed to average the performance.

7.5.3.1.2 Radial basis networks

Unlike backpropagation, radial basis networks have only one hidden layer, which is called the radial basis layer (Demuth & Beale, 1998). A radial basis function is used in the hidden layer as a transfer function, and a pure linear function is used to connect the hidden layer and the output layer. The generalized regression neural network (GRNN), which is one of the training algorithms used in radial basis networks to perform function approximation, was used to model the relationships among the physical parameters and the eight elements at the six locations. The data division and assignment processes were the same as those used for the BR.

7.5.3.2 Results

The initial attempt using a three-layer network failed to establish the models for the four training algorithms. In successive trainings, 20, 25, 30, 35, 40, and 45 hidden neurons were tried. The r-squared values for the three training algorithms in the backpropagation were low, ranging from 0.20 to 0.30. The r-squared for GRNN ranged from 0.40 to 0.50, which was somewhat better. As the structure of the GRNN cannot be manipulated, a second attempt at backpropagation was made using a four-layer network.

In the second attempt, the LM and BR showed a similar pattern of performance, with their r-squared increasing with an increasing number of hidden neurons until reaching an optimum at 45, at which point the r-squared decreased. The r-squared of the RB also increased until the level of 45 hidden neurons was reached, but its performance was poorer than that of the LM algorithm and the BR. The r-squared at the optimum for the LM algorithm and the BR was about 0.70, and whereas that of the RB was only 0.45 at most.

The best algorithm for modeling the relationships was the LM, the r-squared of which improved until it reached the optimum at 45 hidden neurons for depth, rate, regularity, width, smoothness, stiffness, and strength and decreased with further increases in hidden neurons. For length, it achieved optimal performance at 25 hidden neurons. Table 7-6 summaries the r-squared of the models.

Table 7-6 Summary of the performance of the best models for the eight elements at the six locations using the Levenberg-Marquardt algorithm (N=229)

Dependent Variable ***Element***	***Location***	***Training Algorithm***	***Number of Hidden Neuron***	r^2
Depth	Left chi	LM	45	0.71
	Left cun	LM	45	0.70
	Left guan	LM	45	0.70
	Right chi	LM	45	0.72
	Right cun	LM	45	0.70
	Right guan	LM	45	0.72
Rate	Left chi	LM	45	0.64
	Left cun	LM	45	0.68
	Left guan	LM	45	0.62
	Right chi	LM	45	0.64
	Right cun	LM	45	0.63
	Right guan	LM	45	0.63
Regularity	Left chi	LM	45	0.66
	Left cun	LM	45	0.65
	Left guan	LM	45	0.66
	Right chi	LM	45	0.66
	Right cun	LM	45	0.65
	Right guan	LM	45	0.65
Width	Left chi	LM	45	0.70
	Left cun	LM	45	0.69
	Left guan	LM	45	0.70
	Right chi	LM	45	0.70
	Right cun	LM	45	0.72
	Right guan	LM	45	0.71
Length	Left cun, guan, chi	LM	25	0.86
	Right cun, guan, chi	LM	25	0.86
Smoothness	Left chi	LM	45	0.70
	Left cun	LM	45	0.72
	Left guan	LM	45	0.71
	Right chi	LM	45	0.73
	Right cun	LM	45	0.72
	Right guan	LM	45	0.72
Stiffness	Left chi	LM	45	0.75
	Left cun	LM	45	0.74
	Left guan	LM	45	0.75
	Right chi	LM	45	0.73
	Right cun	LM	45	0.73
	Right guan	LM	45	0.75
Strength	Left chi	LM	45	0.81
	Left cun	LM	45	0.80
	Left guan	LM	45	0.82
	Right chi	LM	45	0.81
	Right cun	LM	45	0.80
	Right guan	LM	45	0.80

The model performed similarly for the same elements across the locations. The best performance was achieved for the model of length, with a r-squared of 0.86.

The second best was the model of strength, with a r-squared of 0.80. These results demonstrate that the models established for length and strength accounted for most of the variance in these elements. The models for the other six elements showed a moderate performance, with r-squared ranging from 0.60 to 0.70, meaning that about 30-40% of the variance could not be explained.

In sum, the best models were trained by the Levenberg-Marquardt algorithm with 45 hidden neurons in two hidden layers. The moderate r-squared of this model indicates the presence of nonlinear relationships among the physical parameters and the eight elements at the six locations.

7.6 Differentiation of hypertension from normotension using the eight elements at the six locations

7.6.1 Correlations of the eight elements at the six locations

The Pearson product moment correlation coefficient and the Spearman rank coefficient were used to reveal the correlations among the eight elements at the six locations. The resulting moderate to high significant correlations ($p < 0.05$) indicated a need to reduce their redundancy, and thus principal component analysis was used to reduce their dimensions.

The principal component analysis identified 7 components. The total variance explained by this model was 78.06%, and the corresponding variance accounted for by each component was 14.24%, 13.97%, 11.47%, 11.32%, 11.14%, 9.54%, and 6.38%. Table 7-7 shows the identified components and their corresponding elements at the six locations. The component scores were calculated and saved for each subject for later modeling.

Table 7-7 Seven components identified by the principal component analysis with an eigenvalue of greater than 1 (N=260)

Element	***Location***	***Component Loadings*** 1	2	3	4	5	6	7
Depth	Right cun	0.91						
Depth	Left cun	0.90						
Length	Right cun, guan, chi	0.88						
Length	Left cun, guan, chi	0.88						
Depth	Left guan	0.74						
Depth	Right guan	0.72						
Depth	Left chi	0.62						
Depth	Right chi	0.62						
Regularity	Right cun		0.99					
Regularity	Left guan		0.99					
Regularity	Left chi		0.99					
Regularity	Left cun		0.99					
Regularity	Right chi		0.98					
Regularity	Right guan		0.98					
Rate	Right guan			0.91				
Rate	Right chi			0.89				
Rate	Right cun			0.88				
Rate	Left chi			0.86				
Rate	Left guan			0.86				
Rate	Left cun			0.73				
Width	Right guan				0.86			
Width	Right chi				0.85			
Width	Left guan				0.83			
Width	Left chi				0.83			
Width	Right cun				0.72			
Width	Left cun				0.72			
Smoothness	Left guan					0.83		
Smoothness	Left chi					0.81		
Smoothness	Right cun					0.81		
Smoothness	Left cun					0.81		
Smoothness	Right guan					0.79		
Smoothness	Right chi					0.73		
Stiffness	Left chi						0.73	
Stiffness	Left cun						0.71	
Strength	Left chi						0.70	
Stiffness	Left guan						0.68	
Strength	Left cun						0.67	
Strength	Left guan						0.64	
Stiffness	Right chi							0.75
Strength	Right chi							0.69
Stiffness	Right guan							0.64
Strength	Right guan							0.60
Stiffness	Right cun							0.59
Strength	Right cun							0.57

Rate, regularity, width, and smoothness formed their own components in which the results for all six locations were grouped together. The high correlation of the elements across the six locations implies that these elements were assessed under the same standard by the TCM doctor across the locations. Length and depth formed a component together, which may be due to the fact that the intensity of length depended on the depth of pulse at cun, guan, and chi.

The last 2 components were composed of stiffness and strength on each side, again suggesting that their intensity as rated by the TCM doctor may be mutually dependent, and that the clinical implication of stiffness and strength of pulse on the left and right sides may be different.

7.6.2 Regression analysis: Differentiation of hypertension with the eight elements at the six locations

In this analysis, group was the dependent variable, and was labeled 0 for normotension and 1 for hypertension. The 7 components from the principal component analysis were treated as the independent variables, and logistic regression was used to compute the model to differentiate hypertension from normotension using the seven components. Table 7-8 presents the weights and odds ratios of the seven components.

Table 7-8 Predictive model of hypertension using logistic regression (N=260)

Component	***β***	***Odds Ratio***	***Significance****
1	-0.04	0.96	---
2	0.47	1.59	0.01
3	-0.20	0.82	---
4	1.16	3.18	0.01
5	-1.22	0.30	0.01
6	0.17	1.18	---
7	0.31	1.36	---

*$p < 0.05$ denotes statistical significance.

Components 2, 4, and 5 were the only statistically significant components in the model ($p < 0.01$). Component 2 was composed of regularity at the six locations, component 4 was composed of width at the six locations, and component 5 was composed of smoothness at the six locations. The three components had an odds ratio of 1.59, 3.18, and 0.30, respectively, demonstrating that the hypertensive subjects were 1.59, 3.18, and 0.30 times more likely to have an irregular, large, and smooth pulse. By extension, people with irregular, large, and rough pulses are more likely to have hypertension.

The model successfully classified subjects with hypertension and normotension ($p < 0.01$) at an overall accuracy of 82.30% with a sensitivity of 0.88 and specificity of 0.75, where sensitivity is the percentage of true positive cases that are accurately identified as positive by the model and specificity is the percentage of true negative cases are correctly identified as negative by the model (Altman & Bland, 1994). However, although the model attained an over 80% accuracy, it could only account for a moderate amount of the variance ($R^2 = 0.51$, $p < 0.01$). A better model was thus sought using an ANN in place of regression for the model development.

7.6.3 ANN: Hypertension and the eight elements at the six locations

In this analysis, the dependent variable was group, which was assigned a value of 0 for normotension and 1 for hypertension. The 7 components of the eight elements at the six locations were the independent variables, the input neurons were the seven components, and the output neuron was group.

7.6.3.1 Design of the ANN

A three-layer neural network was initially used and the number of hidden neurons was set at 10, and increased at five-neuron intervals until the performance of the model leveled off or decreased. Both backpropagation and the radial basis network were tried in the modeling. The LM, RB, and BR algorithms were used for the backpropagation, and the log-sigmoid function and pure linear function were used as the transfer functions to connect the input layer to the first hidden layer and the hidden layer to the output layer, respectively. If the performance was not satisfactory, then a four-layer neural network was tried.

A probabilistic neural network was used to differentiate hypertension in the model generated by radial basis networks. A probabilistic neural network is a radial basis network that uses a Bayesian classifier to estimate the probability. There is only one hidden layer in the network, and the radial basis function is used as the transfer function. The transfer function connecting the hidden layer to the output layer is a compete function that chooses the class with the largest probability (Demuth & Beale, 1998).

The performance of the models was evaluated according to their sensitivity, specificity, and predictive accuracy.

7.6.3.2 Results

Table 7-9 compares the result of the BR, LM, and RB generated ANNs with 10, 15, 20, and 25 hidden neurons. The value reported is the average of 10 trainings. The accuracy of the three algorithms increased slightly with an increasing number of hidden neurons, and ranged between 0.74 and 0.79. Their specificity, however, dropped with an increasing number of hidden neurons, and their sensitivity stopped increasing at 15 hidden neurons.

Table 7-9 Comparison of the specificity, sensitivity, and accuracy of the three training algorithms for backpropagation with different numbers of hidden neurons (N=260)

Algorithm	*Number of Hidden Neurons*	*Specificity (%)*	*Sensitivity (%)*	*Accuracy (%)*
Bayesian Regularization	10	69.96	76.57	73.50
	15	73.46	84.49	79.27
	20	73.20	84.80	79.30
	25	69.33	84.80	77.51
Levenberg-Marquardt Algorithm	10	68.29	86.75	78.06
	15	63.17	90.88	77.83
	20	63.67	88.04	76.56
	25	62.93	87.40	75.87
Resilient Backpropagation	10	72.19	83.91	78.41
	15	63.67	91.33	78.28
	20	66.61	91.30	79.67
	25	65.85	90.22	78.74

The corresponding specificity, sensitivity, and accuracy of the ANN generated with the probabilistic neural network was 0.68, 0.78, 0.74 (Table 7-10). Table 7-10 compares the best model for each ANN algorithm and the model developed by logistic regression.

Table 7-10 Comparison of the specificity, sensitivity, and accuracy of the best results of the models using different ANN training algorithms and the logistic regression

Algorithm	***Specificity (%)***	***Sensitivity (%)***	***Accuracy (%)***	***Remarks***
Bayesian Regularization	73.46	84.49	79.27	15 hidden neurons
Levenberg-Marquardt	68.29	86.75	78.06	10 hidden neurons
Resilient Backpropagation	72.19	83.91	78.41	10 hidden neurons
Probabilistic Neural Network	68.49	78.32	73.76	---
Logistic Regression	88.49	75.21	82.31	---

A model with a high true positive rate is preferable, which means that the sensitivity should be sufficiently high while the specificity is preserved. The models developed by Bayesian regularization and resilient backpropagation achieved a similar specificity and sensitivity, which establishes that either Bayesian regularization or resilient backpropagation is the best training algorithm for formulating the ANN classification model for hypertension.

The ANN results suggest that the eight elements at the six locations can differentiate hypertension from normotension. The null hypothesis that the eight elements at the six locations cannot differentiate hypertension from normotension is thus rejected.

7.7 Conclusion

Analyses were performed using conventional statistical methods and an ANN to verify the hypotheses and answer the research questions. The null hypothesis that the eight elements and the physical parameters at the six locations would not differ between the hypertensive and normotensive groups is rejected. The elements and the physical parameters showed a statistically significant difference at the six locations and between the groups, and an interaction effect of group and location was found on A_T, A_S, A_D, h_l/t_1, Δ80%pamax, and amppeak.

Principal component analysis demonstrated the physical parameters to be highly correlated with each other, as were the eight elements. This multicollineairty may be due to the fact that several of the variables refer to the same domain.

The physical parameters and the eight elements at the six locations were not linearly related. Regression analysis failed to establish models for the elements at the six locations using the physical parameters, and thus an ANN was developed that performed better than the multiple regression, although the r-squared of the model was still only moderate for most of the elements. This suggests that the physical parameters explain the eight elements at the six locations in a nonlinear way. In the classification model for hypertension, the eight elements at the six locations successfully differentiated hypertension from normotension when either regression analysis or ANN was used, and the two models showed a similar performance.

Possible explanations for the results reported in this chapter are given in the next chapter.

CHAPTER EIGHT

DISCUSSION

8.1 Introduction

The results of the main study demonstrate that pulse condition at the six locations can be quantified by the arterial pulse in the time domain, and that hypertension can be classified by TCM pulse diagnosis. This chapter provides possible explanations for the findings and discusses the limitations of the study. Recommendations for further studies are also suggested.

8.2 Pulses in normotensive subjects

It is assumed that when the eight elements fall in the middle of the Yin-Yang continuum, the person is healthy. The results of this study demonstrate that pulse in the normotensive group was floating, large, long, smooth, and soggy. Pulse is affected by numerous external factors, including time of year, age, gender, height, and weight (Fei, 2003; Xu & Hu, 2000; Yang & Chen, 1999; Zhao, 2001), and any variation in these factors may have had a bearing on the pulse characteristics in the normotensive group. At the time of data collection, it was summer, which is a season in which pulse may be larger and more floating (Huang, 2007; Huang & Sun, 1995). Soggy, especially at left guan, implies that there is insufficient blood supply to nourish the body (Deng & Guo, 1983; Zhao). The overall sogginess of the pulse in the normotensive group indicate qi and blood deficiency or spleen deficiency and dampness (Fei), which may be caused by the unbalanced diet commonly seen in people living in urban environments. A smoother pulse with a regular and moderate beat is indicative of a healthy status, and healthy people are more likely to have long pulse, as this indicates the smooth flow of qi and blood (Fei; Xu & Hu).

As this is the first study to use a VAS to measure the intensity of the eight elements, no comparisons could be made regarding the normal range of their intensity in normotensive people. However, the normal range presented in this study may provide a reference for future studies.

8.3 Variation in the elements at the six locations

Pulse condition at the six locations should be similar in healthy people, as it indicates a Yin-Yang balance (Fei, 2003; Zhao, 2001). However, depth, width, length, smoothness, stiffness, and strength varied across the six locations in the normotensive group. A few studies have reported similar variation in the elements at the six locations. The findings in this study nevertheless substantiate the descriptions of pulse condition given in traditional Chinese medical texts.

It was found that depth was deepest at chi and most floating at cun. Pulse at chi was significantly deeper than at cun and guan. Zhao (1985) stated that the pulse at chi is commonly deeper than that at cun and guan because cun is Yang and chi is Yin (Xu, 1994). Traditional Chinese medical texts mention some variation in the rate and regularity of pulse at the six locations in the same individual, yet the findings of this study show that rate and regularity were the same at the six locations. Previous studies have reported that pulse condition related to rate and regularity, such as the slow, the rapid, the intermittent, the skipping, and the bounding, is associated with cardiac function (Huang & Sun, 1995; Ping, Ping, & Zhang, 2002; Zhao, 2001), and if rate and regularity are indeed initiated by the heart, then it is reasonable to assume that they would be the same throughout the arterial system.

The significant differences in the elements across the locations can also be explained by modern scientific theories, including the anatomy of the vascular system, the palmar arches by-pass effect and pulse-feeling piezoresistive effect (Chen & Luo, 1984), and the physiological response to the autonomous nervous system at the six locations (Huang, 2007).

8.3.1 Anatomy of the vascular system

You (2003) and Yu (2006) explained the variation in the depth of pulse at the six locations in terms of the anatomical position of the radial artery. The radial artery is near the skin in cun, deep inside the muscle and tendons in chi, and supported by the styloid process at guan. The ascending vertical distance from the radial artery to the skin from cun to guan to chi contributes to this phenomenon.

However, other researchers have found pulse at the six locations to occur at different depths, and comment that the anatomical position of the radial artery cannot explain differences in depth of pulse. Yang (1994) observed that the radial artery at guan was nearest to the skin and chi was furthest away from the skin. Luo (2008) claimed that most of the time the pulse at cun is absent in a clinical setting, and found that pulse was strongest at guan, which contradicts the notion that from the anatomical point of view pulse at cun should be the most floating. It is also assumed that pulse at cun, guan, and chi emanates from the radial artery, but Luo discovered that the artery palpated at cun during pulse assessment was the superficial palmar artery. The superficial palmar artery is a small branch of the radial artery with a diameter about half that of the radial artery, and its blood supply comes from both the radial artery and the ulnar artery (Yang). The smaller diameter and greater blood supply may have contributed to the more floating pulse at cun found in this study. Further, although the result was insignificant, the results of this study show that the depth of pulse at the right side was more floating than at the left side. The larger diameter of the radial artery on the right (Yang) and the asymmetry of the left and right vascular systems (Lewis, 2000) may account for this variation.

Width may be related to the intrinsic asymmetry of the vascular system, and the difference in the length, direction, and connection with the surrounding tissues of the left and right vasculatures (Li, 2004) may have contributed to the variation in depth and width at the left and right sides found. For instance, the diameter of the right radial artery is larger than that on the left (Yang, 1994). After the ejection of blood from the left ventricle, the blood on the right side directly flows to the innominate artery before branching into the right carotid artery and the right subclavian artery, whereas at the left side it flows separately into two arteries – the left carotid artery and the left subclavian artery – at the aortic arch. Furthermore, the right subclavian artery is situated at a higher position than the left subclavian artery (Lewis, 2000). The greater width at the right side than at the left side, although insignificant, may be related to right-hand dominance in the majority of people, with stronger arm muscle at the right side leading to a larger pulse (Luo, 2008; You, 2003).

The significantly smoother pulse at right cun than at left cun may be related to the anatomy of the superficial palmar arteries. The diameter of the right superficial palmar arteries is larger than that of the left arteries (Yang, 1994). As a larger artery has a smaller blood flow, it explains why the blood flow at right cun was smoother than that at left cun.

8.3.2 Palmar arches by-pass effect and pulse-feeling piezoresistive effect

The significant decrease in the width of pulse across cun, guan, and chi can be explained by the palmar arches by-pass effect proposed by Chen and Luo (1984). This states that the distal side of the radial artery reflects the peripheral circulation whereas the proximal side reflects the central circulation. As blood flow to the superficial palmar artery comes from both the radial artery and the ulnar artery, when vasodilatation occurs, such as during fever or in hot weather, the pulse at cun is much wider because the blood flow to the superficial palmar artery is doubled.

Pulse at chi was significantly rougher than at cun and guan. This can be explained by the pulse-feeling piezoresistive effect proposed by Chen and Luo (1984), who state that when pressure is applied to the radial artery, the pulse at the distal site, or cun, is smoother and the pulse at the proximal site, or chi, is steeper. The palmar arches by-pass effect may also explain the finding, because peripheral vasodilatation in hot weather, such as occurs during the summer, leads to better blood supply and a lower peripheral resistance to the blood flow at cun, making the pulse at this location smoother.

8.3.3 Physiological responses to the autonomous nervous system at the six locations

The anatomy of the vascular system and the two effects proposed by Chen and Luo (1984) can only explain some of the results of the study, but not the difference in length, stiffness, and strength at the six locations. The results reveal that length at the right side was significantly longer than that at the left, stiffness at left guan was significantly less stiff than at the other five locations, with the pulse at left cun the stiffest, and strength on the right was significantly stronger than that on the left. The theory proposed by Huang (2007) may give a more comprehensive explanation of these variations in elements across the locations. According to this theory, the resonance of different segments of the radial artery and surrounding tissues result in different intensities of the eight elements and the physical parameters at the six locations. Huang postulated that the number of neuroreceptors at different segments of the radial artery and the surrounding tissue vary, and thus the responses to the neurotransmitters emitted from the autonomous nervous system also vary under different physiological conditions. The difference in the contours of the arterial pressure waveforms at cun, guan, and chi in this study may thus explain by this theory.

8.4 Variation in the physical parameters at the six locations

Few studies discuss the effect of location on the physical parameters, and the handful that do investigate the effect focus on only selected physical parameters, such as h_1, h_4/h_1, and pamax. The normal range of the physical parameters in healthy people has not been reported. The results in this study may thus provide a reference for future studies.

h_1 is commonly discussed in the literature, but here amppeak is discussed instead because the maximum amplitude of an arterial pressure waveform may not be h_1. In the majority of the hypertensive subjects, the early return of the reflected wave augmented or was superimposed on h_1. Moreover, due to the deficits of the feature extraction program, the majority of the features in the hypertensive cases with an augmented with or superimposed h_1 could not be extracted, and thus amppeak in the dataset is taken as being the same as h_1. There was no significant difference in amppeak at the six locations in the normotensive group, which is incongruent with the results reported by Zheng et al. (1994), who found that h_1 at guan was significantly larger than at cun and chi. The difference in the mean h_1 reported at the six locations varies in other studies (Chen, 2008; Fei, 2003; Huang, 2007; Huang & Sun, 1995; Zheng et al.), which may be due to the different pulse acquisition devices used.

The h_4/h_1 ratio indicates the peripheral resistance and arterial stiffness. In this study, there was no significant difference in h_4/h_1 across the locations and its mean was about 0.35, which is consistent with the value reported by Zheng et al. (1994).

h_5/h_1 indicates arterial stiffness. In general, h_5/h_1 at the right side was larger than at the left side, and h_5/h_1 at right chi was significantly larger than at left cun, guan, and chi ($p < 0.01$). The larger h_5/h_1 at the right side implies that the pulse wave velocity at the right side was lower than that at the left side. The results for h_3/h_1 echo this finding, with h_3/h_1 at the right side being generally smaller than at the left side. The difference in the pulse wave velocity on the left and right sides may be explained by the asymmetry of the vascular system. The tidal wave and dicrotic wave are formed by wave reflections from the peripheral circulatory system. In normal circumstances, the dicrotic wave is mainly made up of wave reflections from the lower part of the body, whereas the tidal wave consists of wave reflections from the upper part of the body (O'Rourke, 1971). The velocity of the wave reflection is thus largely attributed to arterial stiffness, especially in hypertensive subjects (Nichols & O'Rourke, 1998), and this intrinsic non-uniformity of arterial stiffness in the vascular system may lead to variation in the pulse wave velocity (Li, 2004). Furthermore, the geometric non-uniformity of the vascular system and the variation in the wave reflection sites in the body also alter the nature of the wave reflection. The geometric non-uniformity is manifested as differences in the diameter, length, and direction of the branching at the arterial terminations. However, there is no consensus among researchers on the exact number of wave reflection sites in the body, and so far only the arterioles have been recognized as major wave-reflecting site (Li).

The results show that pamax at cun and chi was significantly larger than pamax at guan. This implies that a larger hold-down pressure was required to achieve the maximum amplitude of the arterial pressure waveform. This is consistent with the results of Zheng et al. (1994). Pamax is affected by many factors, including the anatomical position of the radial artery, and the thickness of subcutaneous fat and of the tissue around the radial artery. The further the artery from the skin, the larger the hold-down pressure that is required to achieve the maximum amplitude. As the artery at guan is well supported by the styloid process underneath, the arterial pressure pulse at guan is relatively easier to acquire, which may explain why pamax at guan was the smallest among the locations (Yang, 1994).

8.5 Hypertension and the physical parameters

h_3/h_1, h_4/h_1, W/t, t_1/t, A_T, A_S, A_D, amppeak, and pamax were significantly larger and h_5/h_1 significantly smaller at the six locations in the hypertensive group. There was no significant difference in t, t_4/t, t_5/t between the normotensive and hypertensive groups. A_T, A_S, A_D, amppeak, h_1/t_1, and Δ80%pamax were subject to the interaction effect of group and location.

In the principal component analysis, h_3/h_1, h_4/h_1, h_5/h_1, W/t were grouped into the same component, as they were all related to arterial stiffness. It is widely believed that hypertension is related to arterial stiffness, and that the increased arterial stiffness in hypertensive people increases the pulse wave velocity. This is because the reflected waves travel back to the central artery faster when the arterial walls are stiffer, resulting in the early arrival of reflected waves in the early systole instead of the late systole or the diastole, as occurs in normotensive people. The augmentation of the percussion wave and reflected waves results in a larger h_3/h_1 and W/t and a smaller h_5/h_1. The larger h_4/h_1 in the hypertensive group is indicative of an increase in peripheral resistance.

Chen (2008) found that people with ischemic heart disease had a significantly larger t_1/t at left cun than healthy people, which implies poorer left ventricular function in people with ischemic heart disease. The larger t_1/t in the hypertensive group indicates that hypertensive people also have poorer left ventricular function. Studies of hypertension mostly focus on arterial stiffness, but a larger t_1/t may also be an indicator of weaker ventricular function, whether congenital or caused by persistent high blood pressure.

Pamax was the hold-down pressure with the largest amplitude of arterial pressure waveform among the tracings taken at the same location. According to the principle of applanation tonometry, the intra-arterial pressure can be measured accurately if the radial artery is fully flattened. However, practically it is impossible to fully flatten the artery due to the anatomical position of the radial artery and the surrounding tissues, and thus the intra-arterial pressure can only be approximated (Nichols & O'Rourke, 1998). Given this assumption, the larger pamax implies a larger intra-arterial pressure in the hypertensive group, probably caused by the increase in peripheral resistance and the increase in arterial stiffness (Safar & Laurent, 1997), as reflected by the increase in $h_4/h_1$and h_3/h_1 and the decrease in h_5/h_1 in the hypertensive group.

The sample size for Δ80%pamax at left and right cun was only 70, as some of the Δ80%pamax could not be calculated because the amplitude of the arterial pressure waveform did not level off or decrease when the maximum hold-down pressure was reached. However, the continuous increase of the arterial pressure waveform indicates that it has a strong resistance to external pressure, possibly due to the high intra-arterial pressure because of increased arterial stiffness and high peripheral resistance. Left cun and right cun reflect the health status of the heart and the lungs, and it is thus postulated that the heart and the lungs may contribute to hypertension. However, as the relationship of the physical parameters and the eight elements at the six locations is not readily known, this postulation cannot be verified.

The increase in A_T, A_S, A_D, amppeak, and h_1/t_1 in the hypertensive group reflects the role of cardiac function in hypertension, with the five physical parameters being grouped into one component in the principal component analysis with respect to the six locations. h_1/t_1 indicates the systolic ejection velocity. A_T, A_S and A_D are related to the cardiac output, and amppeak reflects the systolic function of the left ventricle. The significant increase in these five physical parameters in the hypertensive group may be related to the increase in peripheral resistance and arterial stiffness, which causes systolic blood pressure or diastolic blood pressure to rise (Safar & Laurent, 1997). Stronger ejection of the left ventricle might be the regulatory response to high peripheral resistance.

It was found that A_T, A_S, A_D, amppeak, and h_1/t_1 were significantly larger at left and right guan in the hypertensive group than in the normotensive group. In TCM, the left and right guan reflect the health status of the liver and the spleen, respectively. The significant increase in these five physical parameters at guan may thus indicate the altered health status of the spleen and the liver. Modern medicine seldom studies hypertension in relation to the function of the spleen and the liver, but it is postulated here that the function of the liver and the spleen may be a possible cause of hypertension.

8.6 Correlations of the eight elements at the six locations

Principal component analysis regrouped the eight elements at the six locations into seven components. Rate, regularity, width, and smoothness were grouped at the six locations to each form a new component. This grouping implies that these four elements represent four unique dimensions in TCM pulse diagnosis. However, this was not the case for depth, length, stiffness, and strength.

Depth, length, stiffness, and strength at the six locations were grouped into three components – depth and length at all six locations, stiffness and strength at left cun, guan, and chi, and stiffness and strength at right cun, guan, and chi. The new groupings of these elements indicate that length and strength are not unique dimensions in TCM pulse diagnosis, and can be replaced with other elements.

The new component formed by depth and length suggests a strong correlation between these two elements. The relationship between depth and length of pulse is seldom discussed in the literature, which mainly concentrates on the relationship between length and width. Huang and Sun (1995) investigated the short with arterial pressure waveforms acquired at cun, guan and chi, and found that the amplitude of the waveforms at cun, guan, and chi was smaller. Fei (2003) proposed quantifying length by width, and suggested that pulse is long when pulse width across cun, guan, and chi is moderate to large. In this study, depth, width, and length were highly correlated ($p < 0.01$), thus confirming the association between width and length but also highlighting the strong correlation between depth and length. Although this does not support the finding of a weak correlation between depth and width in Yoon et al. (2000), other evidence that points to the fact that both depth and width are subject to anatomical and physiological effects supports the result of this study. Huang and Sun, for example, stated that vasodilatation leads to a more floating pulse, and Zhu et al. (2007) found that width was related to the spatial movement of the artery and the pressure applied to the artery.

Strength and stiffness were grouped into two new components – left stiffness and strength and right stiffness and strength. The strong correlation between stiffness and strength indicates that the intensity of strength relies on stiffness. Other studies have shown that strength is affected both by stiffness and by other elements. Zhao (2001) proposed quantifying strength by depth and width, and Zhu et al. (2007) showed that the spatial movement of the radial artery is related to width, smoothness, stiffness, and strength. The moderate correlation between strength and width and between strength and depth similarly suggests that both width and depth are correlated with strength. These findings support the proposition that strength is not a unique element in TCM pulse diagnosis, but consists of a combination of other elements. The separation of stiffness and strength at left and right side into two components further reinforces this proposition. In TCM pulse diagnosis, the left side is Yin, which represents the blood and the right side is Yang, which represents qi, with deficiency or excess in either side indicating Yin-Yang imbalance. The palpation of pulse at the left and right sides thus assesses two different aspects of health.

According to the Eight Principles, strength and length of pulse are indicative of deficiency or excess. As length and strength refer to the same category in the Eight Principles and their intensity is found to be dependent on other elements, it is proposed that the dice model formulated based on the eight elements could possibly be replaced by one with only six elements, namely, depth, rate, regularity, width, smoothness, and stiffness.

8.7 Relationship among the eight elements and the physical parameters

The regression analysis showed that the relationship of the eight elements and the physical parameters could not be established in a linear way, as the r-squared of the models were too low to account for the variance. The models established by the ANN further indicated that the relationships are nonlinear. Although explanatory power is important in medical research (Hart & Wyatt, 1990; Lisboa, 2002; Silver & Hurwiz, 1996), the failure of the regression analysis to model the relationships among the eight elements and the physical parameters but the successful modeling using the ANN suggests that the ANN approach is applicable to the quantification of pulse condition at the six locations. It is true that the relationships established by the ANN are still somewhat obscure, but with more resources and further study they could be more thoroughly elucidated.

Despite the successful establishment of the models using ANN, the moderate r-squared attained indicates that the physical parameters only moderately explain the eight elements at the six locations. There are several possible reasons for the moderate r-squared values. First, TCM doctors usually assess pulse at the six locations both individually and simultaneously. However, in this study the pulse acquisition device used was a single-probe type, as no validated three-sensor pulse acquisition device is available, and the arterial pressure waveforms could only be acquired one at a time. Thus, the simultaneous manipulation of pulse at the six locations carried out in a typical TCM pulse assessment could not be examined. Second, the pulse acquisition process was fairly long at about one hour, which may have provoked motion artifacts in the subjects that affected the quality of the arterial pressure waveforms acquired. Third, the baseline of the arterial pressure waveform fluctuated due to the movement and breathing pattern of the subjects, and the feature extraction program was insufficiently developed to remove this noise from the waveforms. The rescaling of the fluctuating baseline into a horizon would have distorted the arterial pressure waveform and introduced errors into the features extracted. Further, the peak-to-peak interval (PPI) could not be extracted by the program and thus could not be used in the modeling. Fourth, the pulse acquisition device limited the hold-down pressure to a maximum of 400 mmHg, but the amplitude of the arterial pressure waveform did not decrease in some of the hypertensive subjects, and thus Δ80%pamax could not be calculated. Fifth, the sample size required by the ANN was too large to be recruited in a clinical study, and the smaller sample size used may have lowered the effect size of the models. Finally, the hypertensive subjects recruited had a stable prognosis and the intensity of the eight elements was confined to a narrow range, and such homogeneity in the samples may have lowered the r-squared.

8.8 Hypertension and the eight elements at the six locations

The relationships among the eight elements at the six locations and hypertension were established by both logistic regression, which is the most common statistical method for predicting outcomes in medical studies (Sargent, 2001; Zhang, 2000), and the ANN method. The results show that the etiology of hypertension may be related to the accumulation of phlegm and stagnated blood.

TCM does not diagnose hypertension, it explains hypertension in terms of "wind-dizziness" ("風眩"). Wind-dizziness is the consequence of Yang excess and Yin deficiency of the liver and the kidneys（肝腎陰虛陽亢）. Wind (風邪) is one of the six excess (六淫) causing diseases. Its nature is Yang which is manifested as exterior and superior. In hypertension, the invasion of wind moves the liver fire (肝火) upward, resulting in the ascending hyperactivity of liver Yang (肝陽上亢) and causing the hypertensive symptoms: headache, dizziness and high blood pressure (Lin, 2002). As the disease progresses, it will lead to Yang excess and Yin deficiency of the liver and the kidneys.

8.8.1 Pulse condition in hypertensive subjects

Depending on the stage of hypertension, different syndromes can appear singly or simultaneously (Wang & Zhang, 1997). Currently, there is no explicit guideline for the diagnosis of syndromes, and no consensus about which syndromes occur in the presence of hypertension (Ao, 2002; Dong & Ko, 1998; Fan, Zou, Zhang, & Huang, 2007; Hu, 2004; Wang & Zhang, 1997). As the eight elements are rooted in the Eight Principles, investigating hypertension with the eight elements at the six locations may be a means of simplifying and standardizing the syndromes associated with hypertension.

The results of this study show that regularity, width, length, smoothness, and stiffness at all six locations had significantly higher values in the hypertensive group than in the normotensive group. Hence, pulse in the hypertensive group tended to be irregular, larger, longer, rougher, and stiffer. Pulse depth at left chi was more floating in the hypertensive group. These findings suggest that stiffness is only one of the dimensions of pulse conditions related to hypertension, and that its interaction with other elements also plays a crucial role.

The current findings are consistent with the pulse conditions commonly diagnosed in hypertension (Lin, Hu, & Qiao, 2007), which include stiff and forceful, large and replete, and irregular and rough. The string-like is a typical pulse condition found in hypertensive cases (Deng & Guo, 1984; Fan et al., 2007; Wang et al., 2000; Xia, 2004; Xu & Hu, 2000; Yang & Chen, 1999; Zhao, 1985; Zhao, 2001), with one study reporting over 90% of hypertensive subjects manifesting the string-like (Wang et al.; Xia; Zhao). A stiff and forceful pulse is caused by the weakness of the spleen and the stomach, which leads to the accumulation of phlegm and retained fluid. This means that qi movement is inhibited and the liver is not well nourished, which results in an excess of liver Yang that is reflected in the pulse as string-like (Rong, 1982; Xu & Hu; Yang & Chen; Yuan, 1993).

A large pulse indicates strong pathogenic qi or weak healthy qi (Yang & Chen, 1999). The replete is a compound pulse condition that is composed of four elements –forceful, long, large, and stiff (Fei, 2003). The replete indicates excess heat and fire (Lin et al., 2007), and may reflect excessive liver Yang, excessive overall Yang, or hot interior syndrome (Yang & Chen). A stiff and long pulse signifies the presence of static blood (Zhao, 2001). Both the stiff and large pulse can be caused by overexertion and fatigue, which are common health issues in urban dwellers (Zhao) such as the subjects in this study.

An irregular pulse originates from the accumulation of stagnated qi, stagnated blood, and phlegm, which affect the function of the heart (Lin et al., 2007). Depending on the type, irregularity can indicate an excess in Yin and deficiency in Yang, wind syndrome, or visceral deficiency. If the irregularity is accompanied by a rapid pulse, then Yang syndrome is likely to be the cause (Xu & Hu, 2000; Yang & Chen, 1999).

The rough indicates a deficiency in nutrient qi and qi blood stagnation (Yang & Chen, 1999; Zhao, 2001). If it is manifested with the replete, then this may indicate the accumulation of stagnated blood that affects the blood flow in the vessels, meaning that qi cannot flow smoothly and nutrients cannot be delivered to the liver. As a consequence, the liver is unable to control Yang qi, which results in the ascendant hyperactivity of liver Yang (Lin et al., 2007).

In addition to these four categories of pulse condition identified in hypertensive patients, a greater intensity of depth at left chi has been associated with hypertension, which indicates a deficiency in kidney Yin (Fei, 2003; Zhao, 2001). Chi is the location that reflects the health status of the kidneys. According to Yin Yang theory, the left side represents Yin and the right side Yang, and thus a more floating pulse at left chi indicates kidney Yin deficiency, which leads to uncontrollable blood flow and hypertension (Lin et al., 2007).

To summarize, a long, large, stiff, and forceful pulse condition at the six locations may signify excessive Yang, whereas irregular and rough at the six locations and floating at the left chi may indicate healthy Yin deficiency. These results consolidate the proposition of the pathogenesis of essential hypertension recently put forward, which is explained in the next sub-section.

8.8.2 A new perspective in TCM on the pathogenesis of hypertension

Li, Shi, Yan, and Pan (2003), Han, Zhu, and Li (2007), and Wang (2008) proposed that hypertension is caused by the accumulation of phlegm and stagnated blood. In TCM, phlegm is composed of body fluid and stagnated blood is composed of blood. Blood and body fluids are closely related, and thus the formation of phlegm leads to the formation of stagnated blood and vice versa. The accumulation of phlegm and stagnated blood is induced by the abnormal functioning of the spleen, the kidneys, and the liver. Deficiency in kidney Yin is caused by the abnormal functioning of the spleen, because the spleen is responsible for acquiring nutrients to nourish the body. Phlegm and stagnated blood is also directly affected by the liver Yin (blood). A deficiency in liver Yin means that liver Yang is not controlled, leading to an increase in liver Yang. Clearly, many of the syndromes diagnosed in hypertension are related to the liver and the kidneys.

The excess and deficiency syndromes reflected by the eight elements in hypertensive patients are indicative of an excessive Yang and a deficiency in healthy Yin. Yang excess is the excessive liver Yang or the liver fire. The presence of excessive liver Yang might be due to either the liver Yin deficiency or the invasion of pathogenic Yang (陽邪) or both. Liver Yin deficiency is caused by the insufficient nourishment or the overconsumption of the liver. For the former cause, it might be due to the imbalanced diet. For the latter one, it might be due to the overexertion in urban dwellers. The weak liver Yin cannot exert its control over the liver Yang and thus leads to the ascendant hyperactivity of the liver Yang. The invasion of pathogenic Yang might be due to the overconsumption of food which is heat in nature and the wind, the invasion of the wind moves the accumulated heat in the liver (liver fire) upward and leads to the symptoms in hypertension. As a consequence, the abnormal qi flow contributes to the production of phlegm and stagnated blood which further strengthens the pathogenic Yang.

Healthy Yin deficiency is the deficient Kidney Yin. It is influenced by the function of the spleen. In TCM, the spleen is responsible for assimilating and conveying nutrients from the stomach to all over the body, the spleen dysfunction consequences in the insufficient nourishment of other organs, e.g. the liver and the kidneys. The acquired essence (後天之精) in the kidneys relies on the function of the spleen. Thus, the dysfunction of the spleen will lead to the Kidney Yin deficiency and further affects the function of the liver.

Healthy Yin is determined by kidney Yin and liver Yin, whereas pathogenic Yang refers to the accumulation of phlegm and stagnated blood and invasion of wind. The simultaneous appearance of deficiency and excess in the pulse conditions suggests that the subjects in the hypertensive group in this study were in the middle stage of hypertension (Wang, 2008). This finding is reasonable, as the majority had had hypertension for more than five years and was currently taking anti-hypertensive medication.

As many pulse conditions can appear in hypertension, the weight of the eight elements at the six locations in hypertension is unlikely to be identical. No studies have reported how the eight elements at the six locations are related to hypertension, and this doctoral work is the first to explore and model hypertension with the eight elements at the six locations. The model generated by logistic regression established the three components of regularity, width, and smoothness to be significant, indicating that pulse in hypertensive patients tends to be irregular, large, and rough. However, although the predictive accuracy of the model was as high as 80%, its moderate r-squared indicates that it may not be a good model to explain the variance in the results. The model established by the ANN showed a better specificity and sensitivity than the model established by logistic regression, but its low explanatory power downgrades its favorability as a predictive model for hypertension. Nevertheless, the pathogenesis of hypertension might be unfolded if more advanced technology were available to extract the weights of the neurons in the ANN model.

8.9 Limitations of the study

This study has several limitations. First, the subjects recruited were in a stable condition, and thus the model developed is confined to stable hypertensive cases and cannot be extrapolated to other conditions such as severe hypertension and hypotension.

Second, the feature extraction program could not extract the peak-to-peak interval, because fluctuations in the baseline of the arterial pressure waveform led to a large variation in the peak-to-peak interval in the same tracing. The program also could not extract arterial pressure waveforms in which h_3 augmented or superimposed h_1. This may have affected the accuracy of the results because of biased samples in the hypertensive group.

Third, the maximum pressure that could be tolerated by the tonometer was 400 mmHg, which limited the hold-down pressure to the range of 0 mmHg to 400 mmHg. For arterial pressure waveforms that did not level off or decrease at 400 mmHg, the Δ80%pamax could not be calculated.

8.10 Recommendations for teaching, research, and clinical practice

8.10.1 Teaching recommendations

The results support the interrelationship of the arterial pulse and the eight elements at the six locations, and show that the eight elements at the six locations can differentiate hypertension from normotension. It is thus recommended that the dice model be used as a new paradigm of TCM pulse diagnosis. The model presents pulse condition in a precise way that should make learning the concept of TCM pulse diagnosis simpler for students.

The study also suggests that hypertension, which is currently diagnosed by brachial blood pressure, can also be predicted by other information in the arterial pressure waveform. Clearly, blood pressure is not the only parameter that can screen for hypertension, and other features of the arterial pressure waveform should also be considered.

8.10.2 Research recommendations

In view of the limitations of the study, five recommendations are made for further studies in this area. First, the feature extraction program requires further enhancement to extract all of the necessary features from the arterial pressure waveform. The development of the feature extraction program is a major part of the study because the physical parameters are calculated based on the features extracted by the program. Second, it is suggested that a validated three-sensor pulse acquisition device be developed so that the effect of simultaneous hold-down pressure on the arterial pressure waveforms at cun, guan, and chi can be examined. Third, a program should be generated that can extract the underlying relationships among the physical parameters and the eight elements at the six locations and the relationships among the eight elements at the six locations and hypertension. Increasing the explanatory power of the models in this way would provide modern scientific theoretical backing for TCM pulse diagnosis and more evidence to support TCM theories. Fourth, more subjects should be recruited to verify the models. The models established are preliminary models that demonstrate the nonlinearity of the physical parameters and the eight elements, but a larger sample is required to validate them fully. Fifth, as only subjects with a stable prognosis were recruited into the hypertensive group, the models cannot be extrapolated to patients with severe hypertension or hypotension. It is thus recommended to recruit subjects with severe hypertension or hypotension in future studies to increase the generalizability of the models. In addition, patients with other diseases should also be recruited to examine its ability to differentiate hypertension from other diseases.

8.10.3 Clinical recommendations

In view of the increasing popularity of TCM therapies in clinical practice, the aim of the model developed in this thesis was to quantify TCM pulse diagnosis. The established model thus serves as an objective and reliable guideline for assessing pulse condition and the prognosis of patients with hypertension from the TCM perspective.

The developed model could be used as an early screening tool for hypertension. As elevated blood pressure may already be indicative of hypertension, the intensity of the eight elements at the six locations may be applicable to the prospective prediction of hypertension. Relevant health advice on preventing hypertension could then be provided to patients in accordance with the pulse condition identified at the six locations.

Also, with further verification of the present model, it is hoped that the model can be applied to telehealth clinic. By then, patients in remote area can receive pulse diagnosis and TCM consultation through internet.

8.11 Conclusion

This is the first study to investigate the relationships among the eight elements of pulse condition at the six locations and the physical parameters of the arterial pressure waveform. The results show a significant difference among the eight elements and the physical parameters at the six locations, and indicate that they differ under different physiological conditions, in this case hypertension and normotension. The significantly larger A_T, A_S, A_D, amppeak, and h_l/t_l parameters at left and right guan, the larger Δ80%pamax at left and right cun, and the larger t_l/t in the hypertensive group lead to the postulation that essential hypertension, which is idiopathic in origin, may be related to the function of the heart, the lungs, the spleen, and the liver.

The results of the principal component analysis demonstrate that length and strength are not unique elements in the TCM pulse diagnostic framework, and it is hence proposed that the eight elements in the framework be reduced to six, namely, depth, rate, regularity, width, smoothness, and stiffness.

The failure of the regression analysis to model the relationships among the eight elements and the physical parameters at the six locations rejects the possibility that those relationships are linear. ANN was thus used as an alternative statistical method to establish the models, and its higher sensitivity and specificity in predicting hypertension favors its applicability for developing a predictive model for hypertension.

The models provide a biomedical basis for TCM pulse diagnosis and establish an objective standard for diagnosing hypertension using TCM pulse diagnosis. They also suggest that the pathogenesis of hypertension could be revealed by integrating TCM and modern medicine to study the disorder.

A summary of the whole study and the conclusions drawn are presented in Chapter Nine.

CHAPTER NINE

CONCLUSION

9.1 Introduction

This is the first study to quantify TCM pulse diagnosis and differentiate hypertension using the eight elements at the six locations. The models established are the first to demonstrate the nonlinear relationship of the arterial pressure waveform in the time domain and the eight elements at the six locations. Models developed using an ANN quantify the qualitative TCM descriptions of pulse condition and translate these terms into data that is potentially useful in modern medicine. This chapter reviews the research questions posed at the beginning of the thesis and summarizes the methodology, results, and conclusions.

9.2 Recapitulation of the research objectives

Four objectives were posed at the beginning of this doctoral work.

i. To examine the difference in magnitude of the eight elements (depth, rate, regularity, width, length, smoothness, stiffness, and strength) at the six locations (left and right cun, guan, and chi) in hypertensive and normotensive patients.

ii. To examine the difference in magnitude of the arterial pressure waveform in the time domain at the six locations in hypertensive and normotensive patients.

iii. To investigate the relationship of the eight elements and the arterial pressure waveform in the time domain at the six locations.

iv. To differentiate hypertension from normotension using the eight elements at the six locations.

Four research questions were posed based on these research objectives.

i. Are there any differences in the eight elements at the six locations between normotensive and hypertensive patients?

ii. Are there any differences in the arterial pressure waveform in the time domain at the six locations between normotensive and hypertensive patients?

iii. What are the relationships among the eight elements and the arterial pressure waveform in the time domain at the six locations?

iv. Is it possible to differentiate hypertension from normotension using the eight elements at the six locations?

9.3 Summary of the study strategies

To answer these research objectives and research questions, a conceptual framework for TCM pulse diagnosis in the form of a dice model was formulated to guide the study. The dice model integrates the concepts of pulse in TCM and modern medicine, and describes the dynamic interrelationship of the arterial pulse, the eight elements, the six locations, and health status.

The findings from previous studies show that there is a relationship between pulse condition and the arterial pressure waveform. However, few studies have reported the relationship among the eight elements and the physical parameters of the time domain at the six locations, and to the best of the researcher's knowledge, no studies have attempted to differentiate hypertension from normotension using the eight elements at the six locations. Of the existing studies on pulse condition and the eight elements, none report the reliability and validity of the instruments, and the procedures vary significantly and are in some cases not justified. There are no studies that report the applicability of regression analysis for modeling the relationships among the arterial pressure waveform in the time domain and the eight elements at the six locations. To overcome the weaknesses of previous studies and the gaps in the literature, a structured study design was used in this doctoral work.

9.3.1 Methodology

The thesis reports a correlational study with two groups of subjects – hypertensive and normotensive patients. The arterial pulse was the independent variable and hypertension was the dependent variable. The arterial pulse was operationalized as the arterial pressure waveform in the time domain. In the data collection, the six locations (left and right cun, guan, and chi) were first located by the researcher, and then the pulse at each location was assessed by a TCM doctor in each of the subjects. The pulse at each location was assessed on the basis of the eight elements. The elements were operationalized as ratings on a 10-cm visual analogue scale. A TCM pulse assessment form was developed to record the doctor's assessment of the eight elements at the six locations.

A pulse acquisition device was designed to acquire the arterial pressure waveforms at the six locations, and a feature extraction program was developed to extract the features of the arterial pressure waveform in the time domain to generate the physical parameters. The use of only one TCM doctor to carry out the assessment and the procedure of arterial pressure waveform acquisition have been fully justified and explained.

Before proceeding to the data collection, the validity and reliability of the instruments and personnel involved were tested. Content validation was performed to ensure that the content of the TCM pulse assessment form was relevant to TCM pulse diagnosis, and the intra-rater and inter-rater reliability of the TCM doctor involved in the study were calculated. His validity in being able to differentiate hypertension with TCM pulse diagnosis was also demonstrated. A validated tonometer was used for the acquisition of the arterial pressure waveforms at the six locations, and all of the instruments were calibrated before the data collection to ensure their accuracy. The inter-rater reliability of the researcher in acquiring the arterial pressure waveform was established, and the feature extraction program was tested for its accuracy in extracting the physical parameters from the arterial pressure waveform in the time domain.

A pilot study was conducted to test the feasibility of the research protocol and estimate the sample size for the main study. The research protocol was modified and the sample size was calculated based on the results of the pilot study. The sample size for the ANN was also justified.

Descriptive statistics were computed to obtain a general picture of the distribution of the data. Univariate analysis was performed to examine the difference in magnitude of the eight elements at the six locations and the physical parameters at the six locations between the normotensive and hypertensive groups. To examine the relationships among the eight elements at the six locations and the physical parameters at the six locations, both regression analysis and an ANN were used, and the performance of the models established by each method were compared by using the r-squared. To establish a differentiation model of hypertension and normotension, regression analysis and ANN were used and their performance compared in terms of their overall predictive accuracy, sensitivity, and specificity.

9.3.2 Results

Two hundred and sixty subjects were recruited into the study, 139 in the normotensive group and 121 in the hypertensive group. There was no mean difference in gender, age, and body mass index between the normotensive and hypertensive groups.

9.3.2.1 Significant location difference in the eight elements and the physical parameters

The findings from the main study support the alternate hypothesis that the eight elements and the physical parameters at the six locations differ significantly. Depth, width, length, smoothness, stiffness, and strength all differed significantly at the six locations. Pulse at chi was significantly deeper than at cun and guan ($p < 0.01$); width decreased significantly from cun to guan and then chi ($p < 0.01$); and length of pulse on the right side was longer than on the left ($p < 0.01$). Pulse at chi was rougher than at cun and guan, and was smoother at right cun than at left cun ($p < 0.01$). Pulse at left guan was the least stiff among the six locations ($p < 0.01$). Strength at right cun was the strongest among the six locations, and pulse at guan and chi was weaker than at left cun, right cun, and right guan ($p <0.01$).

In terms of the physical parameters, only h_5/h_1, t_1/t, and pamax differed significantly across the six locations. h_5/h_1 at left cun, guan, and chi were significantly smaller than on the right ($p < 0.01$); t_1/t at left cun was larger than that at right chi ($p < 0.01$); and pamax at cun and chi had a higher value than at guan ($p < 0.05$).

9.3.2.2 Significant group difference in the eight elements and the physical parameters at the six locations

Compared with the normotensive group, pulse in the hypertensive group was more irregular, larger, longer, rougher, and stiffer at the six locations ($p < 0.01$) and more floating at left chi ($p < 0.05$).

In terms of the physical parameters at the six locations, A_T, A_S, A_D, amppeak, and h_1/t_1 in the hypertensive group were found to be significantly larger at left and right guan than in the normotensive group ($p < 0.02$), and Δ80%pamax at left and right cun was significantly larger in hypertensive group ($p < 0.01$).

9.3.2.3 Nonlinear relationships among the eight elements and the physical parameters at the six locations according to ANN

Both multiple regression and ANN were used to establish models of the relationships among the eight elements and the physical parameters at the six locations. As each location reflects the health state of a particular organ and the eight elements are the core components of pulse condition at each location, 44 models (each corresponding to each element at each location) were established.

The results show that multiple regression failed to establish their relationship, giving a model with a very low R-squared of less than 0.30.

As there are currently no explicit principles for training ANNs, the ANNs generated in this study was obtained by trial and error, with several training algorithms, different numbers of hidden layers, and different numbers of hidden neurons being tried to obtain the optimal result. Levenberg-Marquardt algorithm, resilient backpropagation, and Bayesian regularization were used in backpropagation because they overcome overfitting in different ways. In addition to backpropagation, a generalized regression neural network was used with a radial basis network for the modeling. The predicted outcomes of the models so generated were compared with the target output, and the model with the highest r-squared was regarded as the best model for each element at each location. The results demonstrate that the Levenberg-Marquardt algorithm was the best training algorithm overall for modeling the relationships of interest. The best model for depth, rate, regularity, width, smoothness, stiffness, and strength was trained by a four-layer neural network with 45 hidden neurons, and the best model for length was trained by a four-layer neural network with 25 hidden neurons. The r-squared of the best models ranged from 0.60 to 0.80.

9.3.2.4 Differentiation of hypertension from normotension using the eight elements at the six locations

The results for the differentiation of hypertension support the alternate hypothesis that the eight elements at the six locations can differentiate hypertension from normotension. These findings are consistent with what has been described in the literature. Both logistic regression and ANN were used to establish the differentiation model for hypertension, and both models attained an 80% predictive accuracy, while a three-layer neural network model trained by either Bayesian regularization with 15 hidden neurons or resilient backpropagation with 10 hidden neurons had the best sensitivity (72-74%) and specificity (83-85%). It is thus proposed that the ANN approach is better for modeling the relationships among the eight elements at the six locations and hypertension than logistic regression.

9.3.3 Discussion

The significant differences among the eight elements and the physical parameters at the six locations can be explained by the anatomical position of the radial artery, the inherent asymmetric property of the vascular system, the palmar arches by-pass effect, the pulse-feeling piezoresistive effect, and the physiological response of different segments of the radial artery to the autonomous nervous system.

Due to the black box quality of ANN, the interconnections within the ANN model are not readily known. However, the results confirm the proposed relationship of the arterial pulse and the eight elements at the six locations represented by the dice model, and give insight into the physiological basis of the eight elements. This finding points to clear future directions for further study.

The successful modeling of hypertension using the eight elements at the six locations substantiates the recent proposition that the etiology of hypertension in TCM is the accumulation of phlegm and stagnated blood. It is thus proposed that integrating TCM and modern medicine in studying hypertension would help to elucidate the pathogenesis of hypertension.

9.4 Limitations

There are several limitations. First, the feature extraction program is not sufficiently sophisticated, and physical parameters including the peak-to-peak interval, h_3/h_1 and h_5/h_1, could not be recognized and accurately extracted. Second, the maximum hold-down pressure that could be applied was limited by the pulse acquisition device. As some of the arterial pressure waveforms did not level off at 400 mmHg, which was the upper limit of the pulse acquisition device, Δ80%pamax could not be calculated for these waveforms. Third, the subjects recruited into the hypertensive group had a stable prognosis, and thus the models developed in this study cannot be extrapolated to patients with extremely high or extremely low blood pressure. Fourth, the interconnections among the independent variables and between the independent and dependent variables could not be visualized due to the black box quality of ANNs.

9.5 Implications and significance

The findings of this work infer that there is a physiological basis for the eight elements at the six locations, and further demonstrate the applicability of TCM pulse diagnosis in clinical practice. With further development, an objective, reliable, and TCM specific pulse diagnostic standard could be established by which the efficacy of TCM therapies and the prognosis of hypertensive patients could be evaluated objectively.

Appendix I

THE HONG KONG POLYTECHNIC UNIVERSITY
香港理工大學

School of Nursing 護理學院

參加者編號：________________
日期：________________

中醫脈診評估記錄

左手腕之寸部

1. 深度　最深 ________________ 最淺
2. 速率　最慢 ________________ 最快
3. 節律　□規律　□不規律
4. 寬度　最小 ________________ 最大
5. 流利度　最不滑 ________________ 最滑
6. 柔軟度　最不弦 ________________ 最弦
7. 強度　最虛 ________________ 最實

左手腕之關部

8. 深度　最深 ________________ 最淺
9. 速率　最慢 ________________ 最快
10. 節律　□規律　□不規律
11. 寬度　最小 ________________ 最大
12. 流利度　最不滑 ________________ 最滑
13. 柔軟度　最不弦 ________________ 最弦
14. 強度　最虛 ________________ 最實

左手腕之尺部

15. 深度　　最深 |________________| 最淺

16. 速率　　最慢 |________________| 最快

17. 節律　　☐規律　☐不規律

18. 寬度　　最小 |________________| 最大

19. 流利度　　最不滑 |________________| 最滑

20. 柔軟度　　最不弦 |________________| 最弦

21. 強度　　最虛 |________________| 最實

左手脈之長度

22. 長度　　最短 |________________| 最長

右手腕之寸部

23. 深度　最深 |________________| 最淺
24. 速率　最慢 |________________| 最快
25. 節律　□規律　□不規律
26. 寬度　最小 |________________| 最大
27. 流利度　最不滑 |________________| 最滑
28. 柔軟度　最不弦 |________________| 最弦
29. 強度　最虛 |________________| 最實

右手腕之關部

30. 深度　最深 |________________| 最淺
31. 速率　最慢 |________________| 最快
32. 節律　□規律　□不規律
33. 寬度　最小 |________________| 最大
34. 流利度　最不滑 |________________| 最滑
35. 柔軟度　最不弦 |________________| 最弦
36. 強度　最虛 |________________| 最實

右手腕之尺部

37. 深度	最深		最淺
38. 速率	最慢		最快
39. 節律	□規律 □不規律		
40. 寬度	最小		最大
41. 流利度	最不滑		最滑
42. 柔軟度	最不弦		最弦
43. 強度	最虛		最實

右手脈之長度

44. 長度	最短		最長

Appendix II

中醫脈診量化評估表之評核表

醫師編號：______

請細閱中醫脈診量化評估表內的項目，然後在適當空格內加 ‘√’ 以表明閣下認爲該項目在中醫脈診中的相關程度：

項目	絕不相關	不相關	相關	絕對相關	其他意見(如有)
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
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