

The Treatment of Cardiovascular Disease with Acupuncture

by

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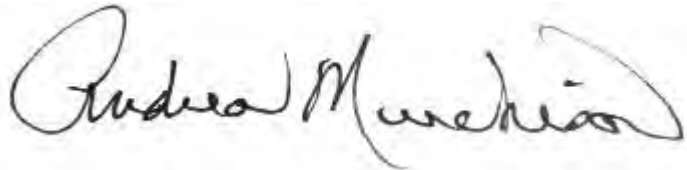
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Abstract

The purpose of this project is to identify factors that are present in scientific studies related to the use of acupuncture as a treatment for cardiovascular disease, with specific focus on the pericardium needling point (PC6). One in every four deaths in the United States is from heart disease. Coronary heart disease alone in the (US) costs \$108.9 billion each year including both direct and indirect costs. Utilizing acupuncture as a preventative measure and treatment of heart disease, Western and Eastern practitioners can collaborate to achieve more efficient and effective care of patients experiencing cardiovascular dysfunction. This movement toward the expanded use of Traditional Chinese Medicine can save lives, money, and medical resources. Such a shift would be beneficial to both Western and Eastern medical practitioners. An educational tool is needed to link Traditional Chinese Medicine practitioners with cardiovascular patients. This study draws from the research of acupuncture treatment and Western treatments to identify the most salient factors under consideration in the development of an education tool that will detail how acupuncture can prevent and treat cardiovascular disease.

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Table of Contents

Signature Approval Page.....	2
Abstract.....	3
Acknowledgements.....	4
Chapter One: Introduction.....	6
Chapter Two: Review of Literature.....	13
Overview.....	13
Cardiovascular Disease—The Heart and Its Structures.....	14
Chapter Three: Method.....	44
Chapter Four: Results.....	48
Chapter Five: Discussion.....	54
References.....	60
Appendix A:.....	71
Appendix B:.....	73
Appendix C:.....	75
Appendix D:.....	79

List of Figures and Tables

Table 1: Open coded themes and study numbers pertaining to each theme.....	49
Table 2: Axial coded themes and study numbers pertaining to each theme	50

Chapter One: Introduction

One in every four deaths in the United States is from heart disease (Kocharek, XU, Murphy & Kung, 2011). Coronary heart disease alone in the US costs \$108.9 billion each year, including both direct and indirect costs (Heidenreich, Trogon & Khavjou, 2011). There is a need, therefore, to explore alternatives for the treatment of heart disease that are effective and perhaps less-expensive to the patient. This project will outline the significance of Traditional Chinese Medicine (TCM) as related to lifestyles, diet, and treatments of heart disease and related areas of human health. It will also outline a bit of the history of some present-day cardiovascular pharmaceutical products and suggest an alternative treatment option for cardiovascular disease.

Utilizing acupuncture as prevention and treatment of heart disease with the collaboration of Western and Eastern modalities including TCM, physicians can be more efficient and effective in treating patients. This movement toward the expanded use of TCM can save money and medical resources. Such a shift would be beneficial to both Western and Eastern medical practitioners. The American lifestyle, in contrast to the Chinese, has been proven to play a contributory role on the prevalence of heart disease. Of the many elements of the Chinese lifestyle that have been investigated,

one particular point of interest has been the similarity of the Chinese diet with that of the typical American diet, such as meats, seafood, fruits, vegetables, and starches. The striking contrast, however, is that the Chinese population has a lower percentage of heart disease than the American counterpart.

The exploration of findings and lessons learned from Chinese culture, daily practices, and diet have become essential for researchers committed to understanding the biological mechanisms involved in the ultimate prevention of heart disease. The "China Study" revealed that, even in a culture with similar amounts of the same food groups (proteins, starches, and fats) as the American diet, there is a stark contrast in the ratio of heart-disease-afflicted individuals to the general population (Campbell, & Campbell, 2005). Researchers have concluded that specific elements within the Chinese diet help regulate blood plasma levels of cholesterol, especially low-density cholesterol, which has been implicated in high blood pressure, atherosclerosis, and heart disease (Campbell & Campbell, 2005). Findings from this study opened up curiosity for further investigation into the mystery of the Chinese diet and lifestyles, for the purpose of uncovering the reasons of the lower rate of heart disease in the Chinese Culture.

One of the components in the Chinese diet and lifestyle that sparked interest for further evaluation is the consumption of red yeast rice (RYR). This type of rice comes from the strain of yeast known as *Monascus Purpureus* that grows on the rice, and is considered a dietary staple in several Asian countries. RYR is traditionally used to color foods that are common in the Asian culture such as Peking duck, pickled tofu, and rice vinegar. RYR dates back as far as the Chinese Tang Dynasty in the 800 A.D., and its

medicinal value is used in TCM today for improving blood circulation and digestive disorders (Heber, Yip, Ashley, Elashoff, Elashoff, & Go, 1999). Research into this ancient Chinese secret revealed that the components of this type of rice disclosed a fungal metabolite named mevinolin, which interrupts the "mevinolate pathway," which is part of the cholesterol production pathway (Ma, Gil, Südhof, Bilheimer, Goldstein, & Brown, 1986). This research led to the creation of the pharmaceutical companies' so-called statin drugs from the first one "Simvastatin" (Tobert, 2003).

Further research discovered that there are various biomarkers, such as angiotensin, involved in "tensing" the arterial walls, causing overall vasoconstriction and a subsequent increase in blood pressure, thereby putting strain and pain on the heart. The pharmaceutical response has been "angiotensin blockers." (Venes, Thomas, & Taber, 2001).

Continued studies led to the discovery of Angiotensin-Converting Enzyme (ACE), a component of the blood pressure-regulating renin-angiotensin system that catalyses the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor, and degrades bradykinin, a potent vasodilator. This discovery led to the synthesis and marketing of the pharmaceutical "ACE inhibitor," which inhibits ACE, thereby decreasing the tension of blood vessels and blood volume, thereby lowering blood pressure, thereby easing burden on the heart (Venes, Thomas, & Taber, 2001).

With greater understanding of the mechanisms of ion channels on cell receptor sites, the pharmaceutical response has been, thus, "calcium channel blockers" and "sodium channel blockers." It is the intent of this research, therefore, to strive to eliminate the routine response by our society of relying on drugs as the prescription for

our ailments, by analyzing and developing further the Chinese practices of health and well-being and determine what more can be done to lower the incidence of cardiovascular disease in the American population.

Nonetheless, part of the Chinese regimen is not only diet and exercise but also the administration of acupuncture, which extends to the treatment of ailments that produce not only pain but also long-term dysfunctions, such as cardiovascular disease and heart disease. Research found that acupuncture on specific points such as Pericardium 6 (PC6) is effective for eliminating pain on the heart. Studies show that administration of acupuncture stimulation at PC6 increases the production of various biochemical agents, for example nitric oxide (NO), a small molecule that exhibits dilation of the arterial walls. It is this understanding that latter-day Western treatments of cardiovascular disease through pharmaceuticals were developed, in particular nitroglycerin tablets.

Although nitroglycerin tablets have been used to treat angina pectoris (chest pain produced by obstruction of a coronary artery) for over a century, recent studies of nitroglycerin have shown that it is, in actuality, the NO molecule - liberated from the nitroglycerin molecule by the liver enzyme aldehyde dehydrogenase - that performs the vasodilation, thereby lessening burden on the heart (Marsh, & Marsh, 2000).

The critical state of the American culture and the prevalence of heart disease is also enhanced because of the inadequacies and even harmful consequences of pharmaceuticals aimed at treating or averting heart disease. This project will assist the development, growing awareness, and acceptance of the American population to alternative methods for treating vasculature and coronary dysfunction. Its aim is also to

assist medical professionals in embracing various practices and techniques of Eastern medicine in treating ailments, such as acupuncture.

Significance of problem

Since it has been observed that one in four deaths in the United States results from heart disease, the issue of addressing cardiovascular problems is a major factor in our culture (Kocharek, Xu, Murphy & Kung, 2011). Acupuncture has been in existence for nearly 3,000 years. However, acupuncture was introduced to Western medicine only in the early 1970s, and specific attention to the use of acupuncture in the treatment of cardiovascular disease has been minimal. At the present time, acupuncture is utilized for research studies and clinical trials involving humans and animals. Because these studies and their results have attracted much attention, deeper explorations regarding how acupuncture facilitates the process of healing have been demanded (Ahn & Kaptchuk, 2005). It can be seen, then, that the combination of Western and TCM has the potential to create more options for the treatment and prevention of cardiovascular disease.

Research Objective

The objective of this research is to identify factors that are present in scientific studies related to the use of acupuncture as a treatment and preventative for cardiovascular disease, to be specific the use of pericardium PC6 stimulation. An educational tool will be developed as an outline based on studies and data collected. Data will be compiled to validate the uses of acupuncture for cardiovascular-related prevention and treatments. This is an important step to continuing growth in both Western and Eastern medical practices for the purpose of developing more options for

both practitioners and patients.

This chapter will conclude with a listing of terms that are used repeatedly throughout this research study. Chapter Two will engage the literature review that will provide the scholarly foundation for this study. Chapter Three will detail the method used for the current study. Chapter Four will summarize the findings. And Chapter Five will discuss those findings.

Definition of terms

The following terms provide a common basis for the understanding of a number of factors that appear repeatedly throughout this study:

- Angiotensin: Peptide hormone involved in “tensing” the arterial walls, causing overall vasoconstriction and a subsequent increase in blood pressure, thereby putting strain and pain on the heart (Taber, 2001).
- ACE = Angiotensin-Converting Enzyme: A pharmaceutical that reduces the peripheral resistance of the heart (Stedman, 1995).
- Calcium Channel blocker: Channel-blocking agent that holds back movement of calcium ions across cell membrane and into the intracellular space (Stedman, 1995).
- CNS = Central Nervous System: Part of the vertebrate nervous system, residing in both the brain and spinal cord (Stedman, 1995).
- Hypertension: High blood pressure greater than 120 mm Hg. (Taber, 2001).
- Hypotension: Low blood pressure lower than 120 mm Hg. (Taber, 2001).
- Meridian pathway: Channels running along the human body, distributing life energy, which is referred to as “Qi” (Cheng & Deng, 1999).

- Myocardial Ischaemia: A short-term condition of a lack of bloodflow to an organ (Taber, 2001).
- PC6 = Pericardium 6: An acupuncture point found on the bodies meridian pathway that is used to treat the heart and relieve pain in the chest (Deadman, Al-Khafaji & Baker,2007).
- Palpitations: Irregular heartbeat that be intermittent and have no apparent symptoms (Stedman, 1995).
- PNS = Peripheral Nervous System (Stedman,1995).
- Statin Medications: Drugs to lower cholesterol levels (Taber, 2001).
- TCM = Traditional Chinese Medicine: A medical system, commonly used to diagnosis, treat, and prevent illness. This system dates back over 2,000 years (Lao, Xu & Xu, 2012).

Chapter Two: Review of Literature

The search for articles to support this study was engaged primarily through the online research services of the Yo San University Library as well as through the resources of other medical libraries in the Southern California area (e.g., the UCLA, USC, and Loma Linda University Medical Libraries). The information in this chapter is organized to lead the reader through the history and major milestones for Western and Eastern medical practices related to cardiovascular disease. This review will begin with an overview of cardiovascular disease and Western treatment approaches. Those sections will be followed by consideration of TCM Treatment approaches with sections devoted to placebos, neuro-cardiovascular interactions, TCM and blood pressure, nitric oxide, opioids, pain, heart performance, cardiomyocytes, TCM meridians, and TCM Pericardium 6 effects on the heart.

Overview of the Heart

The heart is the largest, hardest-working muscle in the human body. Working non-stop, the blood vessels, which are considered the circulatory system, serve to deliver blood that transports oxygen, carbon dioxide, nourishing substances, antibodies, enzymes, and waste materials. Both the cardiovascular system and the

circulatory system are essential for life. The heart is positioned almost in the middle of the chest, slightly left of center. A healthy heart is the size of one clenched fist, weighing around one pound (The American Medical Association, 2003). The matrix of the heart consists of four chambers and highly functional tissue on the outer lining of the heart called the myocardium. The innermost lining is smooth membrane referred to as the endocardium (The American Medical Association, 2003).

Cardiovascular disease: The heart and the pericardium

The heart is the only organ with a protector, a strong sac called the pericardium. It is referred to in Chinese medicine as “the protector of heart” (Deadman, Al-Khafaji, & Baker 2007). The heart being in the center of the cardiovascular system (CVS) encompasses four chambers—two upper chambers called atriums, and two lower chambers called ventricles. The heart chambers function as pumps, which are adjacent to and independent of each other. The left-side pump is responsible for feeding the entire body, and exchanges carbon dioxide for nutrient-rich oxygen. The right-side pump is for circulation in the lungs.

The left side pumps oxygenate blood, from the atrium to the ventricles, then forcefully to the aorta, (the main artery of the body) to be carried systemically. The blood is then transported by smaller arteries called arterioles that then feed every organ in the body. The depleted blood travels back to the right side of the heart through the vena cava to the right atrium to the right ventricle, where the pulmonary artery takes it back to the lungs, to become rich in oxygenated blood once again. From here, the cycle continually repeats itself (The American Medical Association, 2003).

Cardiovascular disease--Biomarkers

Biomarkers are defined as biochemical, genetic, or molecular indicators that can be used to screen diseases, such as cardiovascular disease (Donald, & Clayton eds. 2001). The heart-health biomarkers commonly viewed in assessing the health of the heart are: blood pressure (BP), heart rate, cholesterol levels (the high-density and the low-density lipids [HDL/LDL]), C- reactive protein (CRP), and nitric oxide. The discovery of the role of nitric oxide in cardiovascular function is relatively new. Yet, due to the ethical and methodological limitations of research on humans, much of the research was based on animal studies. In 1990, studies were becoming increasingly popular, as scientists were able to delineate nitric oxide, which is spread throughout the cardiovascular centers, as a very important molecule involved in communication with the central nervous system (Li, 2012; Zanzinger, 1999).

While many factors have influence on the heart-health biomarkers, genetics can play a major role in the rise of these specific markers. For example, hypertension, blood pressure, and cholesterol have all been shown to have higher genetic influence. Stress has also been shown to cause significant changes in the fluctuations of heart-health biomarkers. Blood pressure is affected by both genetics and stress, but can be controlled and maintained through healthy lifestyle and education (Downey, 2012).

Western Treatment Approaches: Pharmaceuticals and Heart Disease

A significant issue with the isolating and synthesis of one element of a food and expecting that the one isolated element be a miracle-drug is that, more often than not, it is not this one element but a combination of elements that contribute in a

symbiotic manner to overall well-being. And such is the case with mevinolin, which while lowering the production of cholesterol interrupts the various pathways involved in not only the production of vitamin D but also the production of a component of the very fuel that powers every cell in the body, ubiquinone (coenzyme-Q10) (Ma, Gil, S dhof, Bilheimer, Goldstein & Brown, 1986). It has been observed that a greater incidence of vision impairment, osteopenia, osteoporosis, liver damage, and even heart disease itself has occurred for patients taking the “statin” drugs (Fokker, Langsjoen, Willis, Richardson, Xia, Ye & Tamagawa, 1990). So it can be seen very readily that a critical component in these biosynthetic pathways has been missed in the synthesis of these so-called heart-healthy pharmaceuticals, which is why it has become common practice that, along with the statin prescription, the adjunct supplement coenzyme-Q10 be administered.

TCM Treatment Approaches

Traditional Chinese Medicine (TCM), theory, and history span over 3,000 years, and has become an evidenced-based medical modality today (Ulett, JiSheng & Han, 1998). The word acupuncture is derived from the Latin acus “with a needle,” and puncture, “through the skin” (Kaptchuk, 2000). There is a record of sharp stones or bones used as treatment on bodies dating from 6000 BCE (Huang, 1996). Historians now believe that this is the first recorded acupuncture treatment.

In Traditional Chinese Medicine (TCM), the meridian of the heart is where energy moves and circulates along the surface of the skin. Its superficial flow can be easily manipulated. As energy pushes through the uppermost surface of the skin, it is not alone; the energy is the motive or force for the bloodstream to circulate. The

energy and the blood are interdependent of one another. The more the energy moves or circulates the more it becomes endogenous. The deeper energy then spreads throughout the entire body, nourishing all other vital organs (Ahn & Kaptchuk, 2005). This observation is believed to provide the cardiovascular system vital energy and is considered the life force to move blood.

The circulatory system, or the cardiovascular system, is viewed similarly in Western medicine, with one of the differences being the assignment of a meridian to the organ in Traditional Chinese Medicine, known as the Meridian System. “Meridians,” therefore, are considered the body’s energy, or the pathway of nourishment to the vital organs. The meridian we will be referring to regarding the heart and its protector in TCM is the Pericardium meridian (Eden, 2008).

The treatment in prevention of cardiovascular disease using the method of acupuncture for this proposal involves both the heart and pericardium meridians. It is noteworthy to mention again that many studies that show the effectiveness of acupuncture in the treatment of cardiovascular diseases such as arrhythmias, palpitations, low and high blood pressure, angina pains, and ischemic heart disease have been completed (Li, 2012). To be specific, the PC 6 is the area on which acupuncture has shown to be a good treatment.

Evidence-based acupuncture is a simple method for no-drug pain and prevention control. PC6 is only one of the 365 points on the human body; however, it is the PC6 meridian that controls the blood and pathway and pulses, which may give rise to diseases such as angina pectoris (Deadman, Al-Khafaji & Baker, 2007). Therefore, further study into the power of acupuncture as a way to prevent

cardiovascular disease at the PC6 is very important.

TCM: Pericardium 6 Effects on Heart

A growing amount of evidence supports the positive influence that PC6 has on the heart (Li, 2012). Studies are showing that there is a longloop pathway leading to specific brain regions including the hypothalamic rostral ventrolateral medulla (rVLM), arcuate nucleus (ARC), and the ventrolateral periaqueductal gray (vIPAG) that can be influenced by acupuncture. This modulation is accomplished through the long-loop pathway of the rostral ventrolateral medulla (rVLM). Vital for cardiovascular function, rVLM is where neurons accept information from the midbrain and hypothalamic defense areas as well as other cardiovascular centers. It is important to note other areas under current research and study, such as baroreceptors, chemoreceptors, cardiopulmonary receptors, somatic and splanchnic nerves, and the specific related acupuncture points. The rVLM sends information to the preganglionic sympathetic neurons to the intermediolateral column of the spinal cord. This is the place of activity for afferent information, which is where cardiovascular activity comes together. Current research illustrates an important link between acupuncture stimulation of PC6 and its effects on the heart, as well as showing that the heart ages more quickly as result of increased levels of stress hormones including adrenaline, low levels of endorphins and opioids, and reduced levels of nitric oxide (Li, 2012).

These important cardiovascular neurons located in the rVLM are suggested as being vital in the regulation of peripheral sympathetic tone and, thus, cardiovascular function. These pathways have been shown to have impact with treatment by acupuncture via the reducing of the sympathoexcitatory response. The specified

treatment has been shown to treat cardiovascular disorders through the modulation of CV mechanisms, the influence of neurotransmitters in the cardiovascular-related regions of the medulla, and the upregulation of nitric oxide (Li, 2012). Other studies show the role of nitric oxide in the neural control of cardiovascular function (Zanzinger, 1999).

Studies continue the work of Li (2012), Holaday (1983) Moazzami (2010), with researchers studying nitric oxide and its role in aiding cardiovascular function (Tjen-A-Looi, 2001; Guo Zi, 2003; Zanzinger, J., 1999). This research is building evidence that suggests that PC6 can modulate cardiovascular activity.

An animal study using the pericardium (PC) meridian acupuncture point with low electrical stimulation and manual stimulation was recently completed. This low-frequency manipulation with the acupuncture point on the PC channel was found to reduce myocardial ischaemia and short-term condition of a lack of blood flow to an organ (Venes, Thomas & Taber, 2001). It was noted to reduce myocardia oxygen demand and lessen the sympathoexcitatory cardiovascular automatic response, at best because of the reaction on the rVLM (Li, 2012).

Stimulation of PC6 with electro-acupuncture has been studied, using cats, isolating only the neurons that input convergent somatic and visceral information that are responsive to baroreceptor afferent stimulation, and could be analyzed as cardiovascular excitatory cells. In this particular study, the group of neurons showed increase in nitroglycderin activity in the rVLM, further supporting the activity of modulation of sympathoexcitatory cardiovascular reflex (Tjen-A-Looi, Phan & Longhurst,2001).

Ma (2003) supported findings of higher concentration of nitric oxide and nitric oxide synthase on the skin after stimulation of acupuncture points. The Ma studies focus on the circulation of Qi in the body, and further propose that the circulation of Qi throughout the meridians is a neurovascular blood-flow modulation as a means of acupuncture-induced nitric oxide upregulation (Ma, 2003).

The influence of PC6 on the neurotransmitters, in relation to the nervous system, and roles associated to the cardiovascular related areas of the medulla were viewed in Li's studies (Li, 2012). Findings suggest that both during and after acupuncture stimulation, neurotransmitters and neuromodulators affecting nociception, such as GABA and opioids, are found in the central nervous system and the peripheral nervous system. These substances include endorphins and enkephalins, which act upon the rVLM to restrict sympathetic outflow, and the usual sympathoexcitatory comeback. Continued studies regarding the stimulation of acupuncture on PC6 are showing positive effects on the up-regulation of nitric oxide and nitric oxide synthase on the myocardial tissues of the heart (Li, 2012).

Current research suggests an important link between PC6 and its effects on the heart. The heart ages more quickly as result of increased levels of stress hormones and adrenaline, and low levels of endorphins and opioids. It has been shown also that heart aging is a result of reduced levels of nitric oxide.

Meridians

Dating back to the second century BC, the theory of acupuncture developed from traditional Chinese medicine techniques and has become an integral part of Chinese healthcare practices. Based on the premise that the body possesses an

internal electrical circuitry, acupuncture stimulation is administered at various points at skin level to activate and correct imbalances of the energy flow (Qi [pronounced "chee"]) through the body. It is, as the theory suggests, the impedance of this energy flow that contributes to dysfunction and disease (Rezaei, Khorsand & Jamali, 2012).

Various recent tests aimed at determining the physiological mechanisms underlying acupuncture stimulation at PC6 and its ability to reduce myocardial ischemia, arrhythmias, and hypertension have been implemented. A recent set of tests in particular involved chloralose-anesthetized laboratory animals instrumented to measure arterial blood pressure, left ventricular pressure, left ventricular dP/dt, heart rate, left anterior descending (LAD) coronary blood velocity, and regional wall motion. Upon occluding the LAD artery and the subsequent application of bradykinin to the gallbladder, the cardiovascular system was activated, causing significant increase in myocardial oxygen demand (double) and ischemia-induced regional dysfunction (Li, Pitsillides, Rendig, Pan & Longhurst, 1998). After low-frequency (5-Hz) electrical stimulation was applied to the median nerves to mimic electroacupuncture, there was observed to be a dramatic reduction in arterial wall thickness. Also, arterial and coronary blood-flow were no longer impaired and there was a dramatic reduction in oxygen demand and diastolic blood pressure (Li, Pitsillides, Rendig, Pan & Longhurst, 1998).

The Pericardium 6 meridian

It has been shown through MRI and blood-test samples that patients experiencing heart failure also consistently elevated sympathetic activity. Moreover, it is noted that those patients presenting with the greatest sympathetic activation

have the lowest survival probability (Middlekauff, 2004). Studies focusing on the acupoint Neiguan (PC6) in patients experiencing heart failure have shown that acupuncture stimulation at, in particular, the Pericardium 6 (PC6), or Neiguan point, inhibits sympathoexcitatory cardiovascular in the neurons of specific brain regions neurons, thereby inhibiting reflex responses, and is sympatholytic in heart failure (Moazzami, Tjen-A-Looi, Guo & Longhurst, 2010). And acupuncture stimulation at this specific acupoint has been shown to affect cardiovascular physiology by various mechanisms via myelinated and unmyelinated fibers along the meridian nerve, effectively improving the symptoms of and treating chronic ailments including cardiovascular disease (Wu, Lin, Chu, Chang, Chang, Hsieh & Huang, 2004).

Acupuncture has been proven through numerous studies to improve and even normalize contractile function and diastolic values, decrease energy loss, and reverse myocardial hypertrophy. In addition, other indicators underlying the manifestation of cardiovascular disease such as palpitations, dyspnoea, vertigo, syncope, hypertension, hypotension, angina pectoris, and even myocardial infarction itself are attenuated, contributing to the greater performance of the heart and overall health of cardiovascular system (Li, Li, Chen, Liang, Wu & Wang, 2012). In recognition of the science and successful practice of acupuncture at PC6 relative to heart health, this paper discusses the correlation between PC6 acupuncture and cardiac function on the basis of central neural mechanisms, with supportive data and evidence as compiled by a wide range of studies. Although the usefulness of acupuncture as a complementary and even alternative therapy in TCM is well-established, evaluation of the effects of acupuncture at PC6 on cardiac function will

be determined by carefully combining modern scientific research methods with classic theory and clinical methods, with focus on the development of clinical efficacy.

In a recent study involving alpha-chloralose-anesthetized laboratory animals, electroacupuncture stimulation of the median nerves to mimic the effect of stimulation of the PC6 acupoint mitigated myocardial ischemia, and was found to be secondary in significance only to the inhibitory effect of electroacupuncture on reflex pressor effects evoked by bradykinin. Blood pressure, heart rate, systolic wall thickening with bilateral acupuncture stimulation of the Neiguan acupoints were not only improved but even reversed (Chao, Shen, Tjen-A-Looi, Pitsillides, Li & Longhurst, 1999).

In another study involving 15 human subjects with essential hypertension in a randomized, double-blind, placebo-controlled crossover trial, subjects were randomly assigned to a sequence of four acupuncture treatment phases, each for 15 minutes with a 7-day washout period in between. Acupuncture needles were inserted at bilateral ST 36, PC 6, ST 36 plus PC 6, and placebo points. Before and after each acupuncture treatment, flow-mediated dilation and blood pressure were measured. The conclusions drawn from the study suggest that, because endothelial bloodflow improved by attenuation of endothelial dysfunction through acupuncture stimulation at PC6, hypertensive patients are the beneficiaries of the beneficial effect of acupuncture and its significant role in preventing the progression of cardiovascular diseases (Park, Shin, Park, Sohn, Jung & Moon, 2010).

Furthermore, the great amount of attention and study on extracellular signal-regulated kinase (ERK), and the effects of acupuncture at PC6 on ERK, is due to the observation that ERK activation is a key factor in regulating cardiac hypertrophy

including gene expression and protein synthesis, and mediating extensive biological effects involving cell proliferation, cell apoptosis, inflammatory responses, oxidative stress, and even influences of the form and evolution of tumors. Extensive clinical research shows the triggering of hypertrophic myocardial cell changes that occur on the cellular and molecular levels, the pathogenesis of which related to extracellular hypertrophic stimulation, intracellular signal transduction, and intranuclear gene transcriptional activation.

A recent study exploring the influence of electroacupuncture at PC6 on myocardial hypertrophy shows the Neiguan acupoint to have a close relation with ERK signaling pathway. It has been observed that its role is through the regulation of the neuroendocrine cytokines angiotensin II and endothelin. Because they cause strong constriction of the coronary arteries and display positive chronotropic and inotropic action with long-lasting and wide-ranging effect, they are recognized as significant upstream factors of the ERK signaling pathways and, therefore, myocardial infarction. In order to provide comparison to the effects of stimulation at PC6, acupoint LI4 was chosen for stimulation and observation in the study. The study concludes the success in electroacupuncture at PC6 in mediating ERK signaling pathway through regulation of at least angiotensin II and endothelin. The data demonstrated the positive results in acupuncture at PC6 in improving cardiac function in myocardial hypertrophy (Li, Li, Liang, Hong, Wu, Tang & Wang, 2011). The results of this study are consistent with another study regarding the positive effects of acupuncture at PC6 on the mechanical cardiac function of laboratory animals presenting with acute myocardial ischemia (Cai, Hu, Wang, Wu, Chen, Long & Liu,

2010).

Placebos

In order to evaluate the benefit of acupuncture and, to be specific, acupuncture stimulation at PC6 acupoint, all studies referenced in this paper take into consideration the "placebo effect." In recognition of human subjects' perceptions and expectations of the procedures administered on them, "sham acupuncture" was employed, either with sham needles or on fake acupuncture points, that is the insertion of needles in a point within the same spinal segments as the active acupuncture but outside the Chinese meridian system. For example, in a recent study of patients in pain, positron emission tomography readings of the brain have clearly identified areas of activation in response to touch with a needle, the expectation of acupuncture, and real acupuncture. These findings suggest that real acupuncture not only activates areas associated with expectation and placebo response but also activates brain regions that represent a specific response to acupuncture in patients presenting with pain (Lewith, White & Pariente, 2005).

In one particular study involving 26 human subjects, the effect was evaluated from anginal attack rate, nitroglycerin consumption, and exercise tests. Compared to patients receiving sham acupuncture, the patients receiving active acupuncture increased cardiac work capacity significantly, expressed as difference in pressure-rate-product between rest and maximum exercise (Ballegaard, Jensen, Pedersen & Nissen, 1986).

Neuro-cardiovascular Interactions

In order to monitor the effects of acupuncture on the cardiovascular system and

to visualize the heart non-invasively with high-spatial and temporal resolution, cardiac MRIs have been used extensively through the process of acupuncture at PC6, with collected data through measurement of stroke volume, ejection fraction, cardiac output, ventricular volumes, and ventricular function (Li, Li, Chen, Liang, Wu & Wang, 2012). Cardiovascular sympathoexcitatory activity is seen to be inhibited by the vIPAG, which receives excitatory projections from the ARC, modulating rVLM premotor sympathetic neurons activated during visceral afferent stimulation and autonomic excitatory reflexes (Tjen-A-Looi, Li & Longhurst, 2006). It is evident, in fact, that excitation of the neurons of ARC inhibits rVLM neuronal activity in a disproportionate fashion (Li, Tjen-A-Looi, Guo, Fu & Longhurst, 2009).

Furthermore, it is extracellular concentration of GABA in the vIPAG that is decreased by acupuncture stimulation at PC6, suggesting that disinhibition of GABA in this area promotes the inhibition of rVLM activity mediated by acupuncture stimulation, as the projections from the vIPAG to the rVLM are mainly inhibitory (Tjen-A-Looi, Li, & Longhurst, 2009). (Fu, & Longhurst, 2009). From vIPAG as well as from baroreceptors, chemoreceptors, cardiopulmonary receptors, somatic and splanchnic nerves, and acupoints, the rVLM transmits efferent signals to the nucleus raphe obscurus, which are then transmitted to preganglionic sympathetic neurons in the intermediolateral column of the spinal cord, where afferent information that ultimately leads to cardiovascular regulation is integrated (Wu, Lin, Chu, Chang, Chang, Hsieh & Huang, 2004).

In order to determine just what the underlying mechanisms of acupuncture are, and to evaluate the role of neurobiology in the inhibition of sympathetic outflow and

the resulting cardiovascular sympathoexcitatory along this long-loop pathway, two major observation methods have been employed: (1) magnetic resonance imaging (MRI), whose response with physiological parameters provides insight into connections between acupuncture modulation of the autonomic nervous system and neuroprocessing; (Napadow, Dhond, Purdon, Kettner, Makris, Kwong, & Hui, 2005), and (2) data collection of blood samples of various biomarkers, in particular several neurotransmitters in the cardiovascular-related regions of the brain, including the ARC, which contains neurons that synthesize and release a variety of neurotransmitters and modulatory neuropeptides (Li, Li, Chen, Liang, Wu & Wang, 2012). Multiple studies illustrate the inhibitory activity on sympathetic outflow and the resultant cardiovascular sympathoexcitatory response by neuromodulators nociceptin, GABA, and opioids including endorphins and enkephalins acting through μ - and δ -opioid receptors in the rVLM through acupuncture stimulation at PC6 (Wu, Lin, Chu, Chang, Chang, Hsieh, Huang, 2004). And it is through the active contribution of the neurotransmitters acetylcholine, endocannabinoids, and glutamate that facilitates the transmission of the signals along this long-loop pathway, (Li, Tjen-A-Looi, Guo, Fu & Longhurst, 2009), where direct projections from the ARC to the rVLM serve as an important source of the opioids beta-endorphin and enkephalin (Li, Tjen-A-Looi, Guo, Fu & Longhurst, 2009).

It is no chance happening that, in the various cardiovascular centers of the brain including the rVLM, nitric oxide (NO) is widely distributed, as the NO molecule not only inhibits sympathetic efflux but also reduces cardiac oxygen consumption. Furthermore, decrease in the myocardial intracellular calcium levels in myocardial

ischemic reperfusion-injured subjects occurs upon stimulation of PC6, as well as the upregulation of myocardial nitric oxide synthase (NOS) and NO, further strengthening arguments supporting the essential role in signal transmission that NO plays in the entire cardiovascular system (Li, Li, Chen, Liang, Wu, & Wang, 2012). As well as the upregulation of NOS and NO, acupuncture stimulation at PC6 exhibits a more positive effect in increasing the glucose metabolic level in a stroke-injured area in the brain than nonacupoint stimulus and blank controls (Li, Li, Liang, Hong, Wu, Tang & Wang, 2011). Furthermore, hypertension, cardiac ischemia, and arrhythmias are all reduced by sympathetic outflow mediated by the excitation of the nucleus raphe obscurus, inhibiting cardiovascular neurons in the rVLM that then activate opioid, GABA, and 5-hydroxytryptamine receptors, important neurotransmitters that process pain signals in this region (Takeshige, Oka, Mizuno, Hisamitsu, Luo, Kobori, & Fang, 1993). Numerous studies support the observation that serotonergic neurons mediate the input from the nucleus raphe pallidus to the rVLM to inhibit the sympathetic outflow (Li, Tjen-A-Looi, Guo, Fu & Longhurst, 2009).

Therefore, it has been illustrated clearly that acupuncture at PC6 stimulates the long-loop pathway to activate the ARC, vIPAG, and nucleus raphe pallidus, inhibiting the rVLM with resultant reduction in the cardiovascular sympathoexcitatory reflex response through the upregulation of GABA, opioids, 5-HT, NO, and NOS (Wu, Lin, Chu, Chang, Chang, Hsieh & Huang, 2004). Moreover, improvement of ischemic dysfunction is actually dependent on the activation of opioid receptors, to be specific receptors located in the rVLM (Chao, Shen, Tjen-A-Looi, Pitsillides, Li, & Longhurst, 1999). Numerous recent studies substantiate that, through acupuncture stimulation

at PC6, the opioid neurons of the rVLM receiving convergent visceral and somatic input exhibit long-lasting inhibition, even by excitation induced by the splanchnic nerve (Tjen-A-Looi, Li & Longhurst, 2003). Electrophysiological findings support the ARC as being a point of origin of upregulation of multiple opioids and neurotransmitters that complement autonomic nerve activity along the long-loop pathway, modulating analgesia and the cardiovascular response through acupuncture stimulation at PC6 (Guo, & Longhurst, 2007).

TCM and Blood Pressure

Multiple studies on several types of animals as well as human subjects, with focus on the effective benefits of acupuncture stimulation at Neiguan PC6, support the observation that various neurogenic mechanisms elicit not only a neural response but also endocrine and immune responses (Wu, Lin, Chu, Chang, Chang, Hsieh, & Huang, 2004). Acupuncture stimulation at this point also shows that, as blood pressure falls, the associated changes of heart rate variability have also occurred, including marked stabilization of cardiovascular parameters disturbed by asphyxia, stabilization of left ventricular pressure, and stabilization of cardiovascular reflex pressor responses (Chang, Chao, Chiang, Li, Lu, Ma & Hsieh, 2008).

Significant studies illustrate that femoral arterial pressure, left ventricular weight, whole-heart weight, body weight, and even the size of the cardiomyocytes themselves are all reduced dramatically due to acupuncture stimulation at PC6. For the 6-day duration of acupuncture treatment on subjects in the studies, marked decreases in the femoral arterial pressure occurred, with concomitant drop in blood pressure, emphasizing acupuncture stimulation to be a beneficial treatment modality

for hypertension and hypertrophy of the heart (Wu, Lin, Chu, Chang, Chang, Hsieh & Huang, 2003). Specific cardiac enzymes have also been shown to be reduced, for example creatine phosphokinase and muscle- and brain-type creatine kinase-MB, suggesting the effectiveness of acupuncture stimulation at PC6 to possess preventative abilities against myocardial injury (Wu, Lin, Chu, Chang, Chang, Hsieh & Huang, 2004).

Even in studies involving a medicine group treated with oral administration of compound Danshen dripping pill, acupuncture stimulation at PC6 was shown to be superior. Decrease in heart rate and both systolic blood pressure and diastolic blood pressure of the studies illustrate the therapeutic effects of acupuncture at PC6 on silent myocardial ischemia (Diao, Yang, Zhou, Chen, Fan, Zhang & Liu, 2011).

Recent studies on anesthetized laboratory animals also show that, after nitro-L-arginine (L-NNA), an inhibitor of NOS, was microinjected into the rVLM, the curative effect of acupuncture at PC6 on myocardial ischemia was reduced significantly or blocked altogether. In contrast, however, saline solution of the same amount microinjected into the rVLM showed no inhibition on the curative effect of acupuncture stimulation at PC6 (Diao, Yang, Zhou, Chen, Fan, Zhang & Liu, 2011). This study, along with others, illustrates not only the role of the rVLM in modulating cardiac function but also the key function that NO has on facilitating the modulation of the cardiac flexor response (Togashi, Sakuma, Yoshioka, Kobayashi, Yasuda, Kitabatake & Levi, 1992).

Furthermore, not only the pressor effect but also vasomotor tone and muscle pump have shown improvement through acupuncture stimulation at Neiguan. And, in

spite of inhibition of hemorrhage-increased catecholamines in blood plasma, acupuncture stimulation at PC6 achieved the antihypotension effect by improving left ventricular filling of the hemorrhage-depressed left ventricular performance (Syuu, Matsubara, Hosogi, & Suga, 2003). Moreover, multiple studies of not just the cardiac muscle but also the vasculature in general illustrate that it is the very small molecule nitric oxide that is the basis for not only the near-immediate response but also the long-term effects of acupuncture stimulation at PC6.

Nitric Oxide

Nitric Oxide (NO) - synthesized from L-arginine from nitric oxide synthase (NOS) - is a member of the family of biochemicals known as endothelium-derived relaxing factor and is also a fundamental component in larger molecules, for example peptides and amino acids (Bloch, Addicks, Hescheler & Fleischmann, 2001). As an odd-electron molecule with 11 valence electrons, that is, having one unpaired electron, it is a powerful free radical, making it highly chemically reactive toward other substances. Therefore, it has strong propensity to effectuate autonomic signaling capabilities at both the presynaptic and postsynaptic junctions, which is why, it is now presumed, acetylcholine, a major neurotransmitter of the central nervous system, plays a major part.

Data from recent studies reveal that in vivo endothelial function is a direct result of NO bioavailability offered by subcutaneous arterioles, which themselves are NO synthase-dependent, showing that the acetylcholine responses were almost completely NO-dependent (Dharmashankar, Welsh, Wang, Kizhakekuttu, Ying, Gutterman & Widlansky, 2012). And, because NO is easily diffusible through the cell

membrane of vertebrates without the need of a carrier molecule, it is, therefore, an important biological regulator, from interaction with and stimulation of other biochemicals to modulation of mitochondrial respiration (Kelly, Balligand & Smith, 1996). We see dramatic activity involving NO-dependent vasodilation in vascular beds, including reactive hyperemia of the skin and muscle, exercise hyperemia of the muscle, mental stress in the muscle tissue, and even whole-body heating of the skin, inferring the major role that NO plays in the vasodilation of myocytes in response to various stresses (Joyner & Dietz, 1997).

Relative to the evident cardioprotective characteristics of NO, this prototypical endothelium-derived relaxing factor has also been shown to be a vital component in the human immune response system, as it is generated by specialized phagocytes (monocytes, macrophages, and neutrophils) (MacMicking, Xie & Nathan, 1997). These specialized T-cells activate their artillery of inducible Nitric Oxide Synthase (iNOS) and tumor necrosis factor (TNF) by the liver cytokines interferon-gamma (IFN- γ) as a single signal or by tumor necrosis factor (TNF), as well as attenuating hypoxia-induced cardiomyocyte injury by blocking several apoptotic proteins, in particular caspase-3, -7, and -9 (Yuan, Yan, Wang, Hua & Hu, 2012).

The great expanse of targets of NO throughout the vast and varied tissues throughout the body strongly suggests its wide-ranging regulatory role throughout the many systems of the body. For apparent reasons, therefore, there is accelerated interest in the application of practices that focus on regulating the production of NO and an explosion of studies as supporting evidence. Only some of the known targets of reactivity include Sulfhydryl groups (-SH), amino acids, zinc clusters, and iron

clusters, the latter of which containing a pyrole ring (N atoms centered around iron atoms, the core element of the heme molecule) (Bloch, Addicks, Hescheler & Fleischmann, 2001).

Even more specific to the subject of cardiophysiology: The ubiquitous nature and production of NO by virtually all cell types of the myocardium, too, have shown it to regulate cardiac physiology and function through means that are both vascular-dependent and vasculature-independent. NO displays numerous roles ranging from the tonicity of the coronary arteries themselves to the production of new vasculature supported by angiogenic processes, that is through vasculature endothelium growth factor (VEGF) (Kuwabara, Kakinuma, Ando, Katare, Yamasaki, Doi & Sato, 2006). In its modulating of a retinue of interacting proteins, NO is shown to exact near-immediate effects on myofibrillar contractility via the excitation-contraction coupling and cross-bridging of the myosin-actin cycle of cardiomyocytes (Bloch, Addicks, Hescheler & Fleischmann, 2001).

Further, it has been shown that NO not only modulates cardiac function and output at the cellular level but also plays a role in neurotransmission in regulating sympathoexcitatory reflexes at the very source, that is, in the brain (Guo & Longhurst, 2003), to be specific the ARC, VIPAG, and rVLM, which are activated in response to stimulation of cardiac sympathetic afferents (Chan, Chan & Chang, 2004). With studies involving the administration of bradykinin in these brainstem regions to stimulate cardiac sympathetic afferents, activity was evident by NO-producing neurons, and NO functions as a neurotransmitter and modulator in these areas to regulate the cardiac sympathoexcitatory reflexes (Guo & Longhurst, 2003).

Therefore, it has been illustrated by many studies the expansive role of NO, that is, in regulating peripheral autonomic function, acting centrally to affect autonomic responses, and modulating physiological functions specifically related to the control of sympathetic output through distribution of NO-producing neurons in central autonomic areas of the brain (Krukoff, 1999). In recent studies, bradykinin was applied to the anterior surface of the left ventricle six times every 20 minutes in anesthetized laboratory animals with bilateral barodenervation and cervical vagotomy. Nicotinamide adenine dinucleotide phosphate-diaphorase (NADPH-d) was used to histochemical-label NO-producing neurons in order to identify and observe the activity, if any, of these specialized cells. While blood pressure was consistently increased with continued application of bradykinin, the vehicle for the bradykinin resulted in no activity, the latter being a test for any effects of the saline itself. It was shown that as many as 27% of neurons positive for NADPH-d displayed immunoreactivity in several brainstem regions, including the nucleus solitarius, the locus coeruleus, and in particular the rVLM. As the results have shown that selective inhibition of nitric oxide in the brain reduces pressor responses to activation of cardiac sympathetic afferents. The resultant conclusions are that NO plays a significant role in regulating cardiac-cardiovascular sympathoexcitatory reflexes (Guo & Longhurst, 2003).

Even more specific at the cardiomyocyte level, endothelial NOS actually modulates the excitatory cardiovascular reflex elicited by stimulation of sympathetic cardiac afferents, and neuronal NOS facilitates this same activity (Tjen-A-Looi, Phan & Longhurst, 2001). In order to evaluate this specialized activity of NO, anesthetized,

sinoaortic-denervated and vagotomized laboratory animals were injected at the epicardial surface of the heart with bradykinin in order to induce transient reflex increases in arterial blood pressure. Inhibition of the production of NO at the site was accomplished through direct administration of the nonspecific NOS inhibitor NG-monomethyl-L-arginine (L-NMMA, 10 mg/kg iv). Stimulation was repeated.

Given the relationship between cardiophysiology and NO, recent tests have gone a step further to show a direct relationship between Neiguan PC 6 and cardiac function, and to evaluate the role that acupuncture on PC6 would have on NO or NOS, if any. Administration of electroacupuncture on PC6 has been shown to downregulate myocardial intracellular Ca²⁺ levels in myocytes of laboratory animals through the direct upregulation of NOS and, hence, increase in intracellular NO, thereby directly averting myocardial injury. The results provide direct evidence supporting the positive effects of acupuncture on PC6 in increasing myocardial NO, NOS, and intracellular Ca²⁺ levels in experimental myocardial ischemia-reperfusion injury (Wang, Tian, Zhou, Yang, Lin, Chang & Yan, 2010). The study entailed inducing myocardial ischemia-reperfusion injury by occluding the descending anterior branch of left coronary artery for 40 minutes and then reperfusion for 60 minutes on laboratory animals randomly divided into Neiguan (PC6) and sham-operation. After acupuncture stimulation was applied to the bilateral PC6, the myocardial tissue of the ischemic area was analyzed for assaying NO and NOS activity and Ca²⁺ concentration, and another part of the myocardium tissue was also processed in the same manner for contrast. Compared with sham group, myocardial NO and NOS contents of model group decreased mildly and significantly ($P < 0.05$), while

myocardial fluorescence intensity; that is, content of intracellular Ca²⁺ increased evidently ($P < 0.01$). In comparison with model group, the content of myocardial NO and NOS were upregulated considerably in PC6 group ($P < 0.05$), and intracellular Ca²⁺ content in PC6 group reduced significantly ($P < 0.01$) (Wang, Tian, Zhou, Yang, Lin, Chang & Yan, 2010).

Opioids

Numerous studies involving acupuncture illustrate through blood samples before and after administration the presence of more than just NO. While the two major contributors to systemic hypertension are the renin-angiotensin-aldosterone system and chronic activation of the sympathetic nervous system, it has become increasingly more evident that it is through the production and release of endogenous opioids, for example δ - and μ -opioids, enkephalins, and endogenous endorphins, in the central nervous system that central sympathetic outflow is regulated (Middlekauff, 2004). As renin and angiotensin are released in response to increased sympathetic activity, increased release of aldosterone promotes renal tubular sodium resorption via activation of angiotensin II, thereby increasing hypertension-associated intravascular fluid volume, myocardial contractility, and vascular tone. Acupuncture stimulation at PC6 produces the effect of lowering blood pressure via modulation of the endocrine system, entailing decreasing plasma renin, aldosterone, and angiotensin II activity, and increased excretion of sodium (Esler, Rumantir, Kaye & Lambert, 2001). The sympathetic neurobiology of essential hypertension: disparate influences of obesity, stress, and noradrenaline transporter dysfunction (Esler,

Rumantir, Kaye & Lambert, 2001).

Studies on anaesthetized, ventilated laboratory animals illustrate that it is the long-loop pathway involving the ARC, the vIPAG, and the rVLM that plays a key role in inhibiting overactivity of the angiotensin system and, therefore, mitigating hypertension through opioid and GABA receptor activation. Furthermore, it has been found that the effect of acupuncture stimulation is nullified by administration of naloxone (nonspecific opioid receptor antagonist) or gabazine (γ -aminobutyric acid or GABA type A receptor blocker) in the rVLM (Tjen-A-Looi, Li, & Longhurst, 2007).

The powerful evidence is accumulated by alternating unilateral microinjections of δ - and μ -opioid receptor agonists with receptor antagonists on the vIPAG and rVLM during and after acupuncture stimulation at PC6. These tests on the vIPAG and rVLM substantiate the significant role not only of opioids on the long-loop pathway but also of acupuncture stimulation at PC6 in modulating the levels of opioids along the long-loop pathway (Guo, Moazzami & Longhurst, 2004). This observation underscores the role of acupuncture stimulation at PC6 in boosting the efficacy of opioids in regulating the cardiovascular response and inhibiting the cardiovascular excitatory reflex (Yao, Andersson, & Thoren, 1982). Furthermore, highlighting the role of opioids along the long-loop pathway even further are the numerous studies that point out the inhibitory effect of acupuncture stimulation on the pressor reflex induced by bradykinin on the gallbladder and the resultant activation of opioid receptors located in the rVLM (Tjen-A-Looi, Li & Longhurst, 2007).

Thus, it is seen that the antihypertensive response to acupuncture at PC6 involves direct neuroendocrine mechanisms involving opioids along with the

neurotransmitters glutamate, acetylcholine, GABA, nociceptin, serotonin, NO, and endocannabinoids along the long-loop pathway (Fu, & Longhurst, 2009). Also, as the ARC, VIPAG, and rVLM have been shown to be activated by acupuncture stimulation at PC6, decreased levels of plasma renin, aldosterone, angiotensin II, norepinephrine, and serotonin have also been shown, illustrating the wider-ranging effects of acupuncture stimulation at PC6 to include not only the central nervous system but also the endocrine system (Zhou, Fu, Guo & Longhurst, 2007).

Pain

It is through the release of opioids and endogenous endorphins that acupuncture has been used for centuries to invoke anesthesia, with the greater understanding in more-recent times of the biomechanics involved in the body's endogenous analgesic system. Administration of acupuncture is more widely accepted and administered for use in treating chronic pain such as that related to surgical operations, post-operative pain, neuropathic pain, and even pain associated with teeth extractions and impacted wisdom teeth (Taguchi, 2008). Various experiments show that the traumatic pain impulse following traumatic event such as amputation activates pain-sensitive neurons in the spinal cord. The impulse of electro-stimulation acts to suppress activities of these pain-sensitive neurons, producing the effect of analgesia (Sun, 1995).

In a recent study employing two imaging technologies - functional magnetic resonance imaging and positron emission tomography - to investigate how specific areas of the brain are involved in acupuncture analgesia, researchers exposed 12 human subjects to heat pain, and then administered either actual or sham

acupuncture on the subjects. Then, using positron emission tomography with a radioactive tracing substance for measuring changes in opioid receptor binding during acupuncture, pain responses of the brain before and after acupuncture using functional magnetic resonance imaging were observed and evaluated. The imaging results showed acupuncture-related changes in both of the brain's pain networks: the lateral network, which is associated with sensory aspects of pain perception, and the medial network, which is associated with affective aspects, with marked activity in the vIPAG of the long-loop pathway (Wang, Mao & Han, 1990). Further investigation by independent studies into brain activity respective to analgesia elicited by acupuncture stimulation have shown there to be dramatically increased acupuncture-induced activation of the vIPAG. And, corroborated by functional magnetic resonance imaging evaluating the effects of electroacupuncture, mock electroacupuncture, and sham electroacupuncture on either real acupuncture points or non-acupuncture points on healthy human volunteers, it has been shown that analgesia involves the pain-related neuromatrix of the long-loop pathway (Lewith, White & Pariente, 2005).

To be specific, analgesia is achieved through acupuncture stimulation by activating large myelinated nerve fibers that conduct the pain stimulus to the spinal cord and specific pain centers of the brain. Various neurotransmitters and neurohormones such as serotonin, endorphins, enkephalins, norepinephrine, and substance P modulate the transmission of pain signals along the pathway (Janssens, Rogers & Schoen, 1988). Various studies have investigated the analgesic effect of needle acupuncture stimulation in patients with chronic or acute pain. Those studies have also examined the factors that determine success or failure of acupuncture

stimulation. In chronic pain conditions, acupuncture was found to be very effective in producing transient analgesia (Levine, Gormley & Fields, 1976). Also, studies have been performed to examine the change of immunoreactivity proteins in the lumbar spinal cord by traumatic pain following hind limb amputation and the effect of acupuncture stimulation. It has been shown that acupuncture stimulation not only delayed the onset of pain and facilitated the recovery of inflammatory hyperalgesia but also repressed expression of inflammation-induced immunoreactivity proteins in neurons involved in receiving noxious stimulation (Lao, Zhang, Wei, Berman & Ren, 2001).

Heart Performance

It has been demonstrated that acupuncture stimulation at Neiguan acupoint overlying the median nerve reduces premotor sympathetic cardiovascular neuronal activity in the rVLM and visceral reflex pressor responses. Various studies set out to relate this long-loop pathway to angina pectoris and cardiovascular output. In a recent study involving acupuncture stimulation at PC6 acupoint on 21 patients suffering from angina pectoris, incidents of anginal attacks decreased by almost 50%, with the same drop in percentage of intensity of pain at maximal workload (Richter, Herlitz, & Hjalmarson, 1991).

A comprehensive review of studies on acupuncture therapy has shown effectiveness between 80% and 96.2%, comparable to conventional drug regimen, with the advantage of not eliciting adverse side-effects commonly associated with Western anti-anginal drugs: 1) Nitroglycerine (headache - 63% with nitroglycerine patch and 50% with spray; syncope - 4%; and dizziness - 8% with patch; hypotension

- 4% with patch; and increased angina 2% with patch); 2) Isosorbide mononitrate (dizziness - 3 to 5%; nausea/vomiting - 2 to 4% and other reactions including hypotension, and syncope even with small doses); 3) Propranolol (bradycardia, chest pain, hypotension, worsening of AV conduction disturbance, Raynaud's syndrome, mental depression, hyperglycemia) (Xu, Xu, Gao, Wang, Zhang & Lu, 2012).

In another study of 25 human subjects with angina pectoris, it was shown that, after just one administration of acupuncture stimulation at PC6 acupoint, angina pectoris was attenuated, and that, after only 7 sessions of acupuncture stimulation, angina pectoris was alleviated not only in extent and area but also in frequency and duration of attack (Zhou, X. Q. & Liu, J. X., 1993).

Furthermore, cardioprotective effects against ischemia-reperfusion injury was shown by acupuncture stimulation of the median nerve at PC6, as validated through evaluation of myocardial protein expression profiles through Western blot analysis as well as biological responses (Tsou, Ho, Lin & Chiu, J.2004).

Cardiomyocytes

It is not just the attenuation of heart rate and pain that is the major immediate effect of acupuncture stimulation but the overall health and even strengthening of the myocytes themselves that occurs in the process. As it has been illustrated in an independent study on anesthetized laboratory animals with myocardial ischemia-reperfusion injury, acupuncture stimulation at PC6 is protective of cardiomyocytes (Weeke-Klimp, Bax, Bellu, Winter, Vrolijk, Plantinga & Lie-Venema, 2010).

It has been found that, in myocardial tissue that undergoes ischemia and hypoxia, there is a stimulation of various apoptosis (cell suicide) proteins, as well as

an increase in free radicals with a simultaneous decrease in free-radical scavengers (Sun, Wang, Halkos, Kerendi, Kin, Guyton & Zhao, 2006). As a result, oxidation by these active oxygen-derived free radicals occurs on the unsaturated fatty acids comprising cell-membranes. The end-product of this lipid peroxidation process is malondialdehyde, which has been shown to damage membranes and cause protein denaturation and enzyme deactivation, resulting in the breakage of DNA chains, which leads to apoptosis. And, as these free radicals are transferred through the vessel wall, the myocardium becomes damaged by free radicals produced by endothelial cells. However, in the presence of glutathione peroxidase, a primary endogenous antioxidant enzyme that catalytically reduces glutathione and hydrogen peroxide, membrane structure and functional integrity is preserved by the conversion of the biomembranous lipid peroxides into harmless alcohols. The conclusion is that, after acupuncture stimulation at Neiguan acupoint, not only are apoptosis and even apoptosis-controlling genes reduced but also the production of malondialdehyde is reduced and the production of glutathione peroxidase is stimulated. Furthermore, it was noted that lesser effects were elicited by acupuncture stimulation at other acupoints, for example the Lieque point Lu 7 (Zhang, Liu, Huang, Zhou, Zhang & Huang, 2009).

In another significant study, it was found that another important protein in myocardiocyte performance is affected during ischemia and hypoxia states, that is Ca^{2+} -ATPase, a carrier protein of calcium ions whose primary role is to transfer intracellular calcium to the extracellular space (Weeke-Klump, Bax, Bellu, Winter, Vrolijk, Plantinga & Lie-Venema, 2010). Through acupuncture stimulation at PC6, it

has been noted that both the activities of Ca²⁺-ATPase and the correlative gene expressions increased significantly as compared with the non-acupuncture group. The conclusions evinced the reduction of the degree of myocardial ischemia and reperfusion injury as well as the strengthening of myocardial functions (Tian, Wang, Li, Wang, Jin & Hao, 2007).

Literature Review Integration

A great deal has been accomplished in prior research linking the use of Traditional Chinese Medicine in the prevention and treatment of cardiovascular disease. There is ample evidence that acupuncture and Traditional Chinese Medicine, especially through the stimulation of the pericardium, can have a positive impact in the treatment of cardiovascular diseases (Ahn & Kaptchuk, 2005; Eden, 2008; Li, 2012; Zanzinger, 1999; Tjen-A-Looi, Phan & Longhurst, 2001; Ma, 3003; Middlekauff, 2004; Wu, In, Chu, Chang, Chang, Hsieh & Huang, 2004). To date, there has been no attempt to synthesize the abundance of existing data in the literature into a short list of factors that should be considered for incorporation into an educational tool, accessible and useful to both practitioners and patients, that will provide salient information regarding the utilization of Traditional Chinese Medicine and acupuncture in the prevention and treatment of cardiovascular disease. This project will focus on the synthesis of prior literature to generate a short list of factors to be included in such an educational tool.

Chapter Three: Method

This objective of the current study is to identify factors that are present in current scientific studies related to the use of acupuncture in the treatment and prevention of cardiovascular disease (CVD) with specific focus on the use of pericardium PC6 stimulation. These factors will be used to create an outline for a manual on the topic of the treatment and prevention of cardiovascular disease.

Research Design

The study utilized the qualitative research method of systematic literature review synthesis (Walsh & Downe, 2005; Barnet-Page & Thomas, 2009) and employed grounded theory method (Glaser & Strauss, 1967; Glaser, 2002) to identify themes that emerge from analyses across the many articles reviewed. The proposal for this research study was reviewed by the Yo San University Institutional Review Board (IRB). A copy of the letter that resulted from the review and indicating exemption from the full IRB process is included in Appendix A.

The specific focus of this study was on current Western and TCM applications utilized in the treatment and prevention of cardiovascular disease. Grounded theory method (Glaser & Strauss, 1967; Glaser, 2002) was used to gather data for the study and to analyze that data. As per grounded theory, journal and monograph literature

articles and sections were systematically reviewed and coded according to criteria pre-established by the researcher. For each literature entity, data were entered onto an Article Abstraction Form constructed by the researcher.

Grounded theory method is an appropriate choice for achieving the objectives of the current study: It enables the synthesis of data and information from various studies that will ultimately be evaluated and assessed for inclusion in the proposed educational outline that will identify the factors salient for the engagement of TCM in the treatment of cardiovascular disease. Grounded theory is most often used in what are considered groundbreaking studies. The method is used most often in preliminary research where salient factors have yet to be identified (Glaser & Strauss, 1967; Glaser, 2002).

Grounded theory method provides a systematic means for sifting through large amounts of narrative data, and collating the data and information from many different sources to contribute to the generation of new knowledge, new programs, or new theories. The systems employed in grounded theory method involve the application of two levels of coding procedures, which lead to the identification of significant factors, components, or issues that are salient to the research objective (Glaser, 2002). Grounded theory, therefore, is appropriate for the current study, since it allows for the consideration of data from a wide variety of sources including journals, texts, and observations of programs and processes, as well as personal communications, interviews, and other atypical non written sources (Glaser & Strauss, 1967; Glaser, 2002).

Article population and sampling

The population of the current study includes all published articles pertaining to cardiovascular health, relating in particular to PC6. In this study, the researcher

abstracted information from articles and monographs published in the past fifteen years from peer-refereed journals. By using already-completed research studies to identify factors from both Eastern and Western medicine articles pertaining to cardiovascular and related diseases, salient factors can be identified to enhance patient treatment and prevention options for cardiovascular disease (Glaser, 2002). Articles that pertain to other diseases unrelated to cardiovascular disease and articles that are more than ten years old (unless they are “on target” in terms of relating to the objective of this research) were excluded from consideration or inclusion in the study.

Instrumentation

The current study utilized an Article Abstraction Form. The form was designed to capture the essence of each source engaged, and data from each article reviewed were entered on a separate data abstraction form. The form includes spaces for the title, author, publication date, the population represented in the study, and space for notes regarding each source, as well as the researcher's name at the top with the major categories listed along the left-hand margin. Each category has ample space for entering data to the right. At the bottom of each form, there is a space for entering other “notes” that may be needed to provide further explication of the data derived from each article. The copy of the Article Abstraction Form is included in Appendix B.

Data Collection Procedures

All articles were reviewed and data were collected from them using coding procedures as prescribed by grounded theory method (Glaser & Strauss, 1967; Glaser, 2002). The goal was to identify salient factors for inclusion in an outline that will provide the basis for an educational tool focusing on the use of TCM and acupuncture in the

prevention and treatment of cardiovascular illnesses. Each data source was systematically summarized on the data abstraction form by inserting the appropriate information in the spaces on the form. The data forms include spaces for the indication of the appropriate open or axial coding category as per grounded theory method.

Data Analysis

The data from the Article Abstraction Forms were synthesized by searching for patterns and themes within and across the forms. The most salient patterns and themes were identified and were considered for inclusion in the educational outline resulting from this study. As indicated above, both open and axial-coded data were collected.

The first step involved open coding for a wide range of factors that were discerned across the many articles reviewed. After thorough review and analysis of sources that have been entered into open coding, two or more factors that are identified as having potential intersection or overlap were identified with axial coding (Pandit, 1996).

A schematic form was designed to assist the researcher in identifying all relevant variables and to organize those variables so that potential connections can be more easily discerned. Those completed forms are called “table shells.” As a result of the analysis of the open and axial-coded data, patterns and themes were identified relevant to the creation of an outline that will guide the creation of an educational tool for Western professionals regarding the use of acupuncture in the treatment of cardiovascular disease.

The following chapter, Results, provides a summary of the findings of the current study.

Chapter Four: Results

This Chapter discusses the data that emerged from the systematic grounded theory analysis of studies reviewed for this project. The focus of the studies reviewed was the use of acupuncture in treating cardiovascular disease. Utilizing the data abstraction form (see Appendix B), patterns and themes were identified both within and across the articles reviewed for this study. By applying the techniques pertinent to grounded theory method, especially open and axial coding, the researcher identified a number of salient factors pertaining to the use of acupuncture in the treatment of cardiovascular disease. This chapter will summarize the factors that were identified.

Table 1 below includes an summary of the themes (left-hand column) and articles (right-hand column) that emerged as a result of the application of open coding. Each article is indicated by a number. See Appendix D for the list of the consecutively numbered articles. In Appendix D, each article is listed by author and year of publication. All of the numbered articles can also be found in alphabetical order (as per the last name of the primary author) in the References list of this document.

Table 1: Open coded themes, and study numbers pertaining to each theme:

Themes pertaining to Cardiovascular Function	Codes for Articles that included designated themes
Meridian system	98, 27, 21
Pericardium 6	90, 24, 62, 1, 29, 92
Placebo	28, 49
Brain	90, 45, 68, 32, 2, 53, 54, 55, 1
Blood Pressure	1, 57, 23, 100, 74, 101, 99, 94
Nitric Oxide	85, 88, 86, 87, 89, 84, 85, 83, 66, 64, 65,67
Opioids	30, 24, 96, 47, 63, 59, 97, 77, 81, 28,105, 80, 78
Pain	104, 77, 81, 28,105, 80,78
Heart Performance	25, 103, 102, 48,
Cardiomyocytes	107, 41, 109, 108

After the completion of the open-coding process as summarized in Table 1, the researcher proceeded to identify a number of themes that had potential intersection.

Several examples of the potentially interactive themes include: "Meridian" and "PC6,"

"Placebo" and "PC 6," and "Brain" and "Nitric Oxide." Table 2 summarizes the results of the axial-coding process. In Table 2, the intersecting themes are indicated in the left-hand column with the corresponding article numbers indicated in the right-hand column.

Table 2 Axial coded themes and study numbers pertaining to each theme:

"Meridian systems" and "PC 6"	92, 27, 97, 98, 90, 24, 62, 21
"Brain" "Pain" and "Opioids"	90, 45, 68, 32, 2, 53, 54, 55, 1, 30, 31, 24, 96, 47, 63, 59, 97, 77, 81, 28, 105, 80, 78, 104, 77, 81, 28, 105, 80, 78, 29
"Nitric Oxide" and "Heart Performance" and "Cardiomyocytes"	85, 88, 86, 87, 89, 84, 85, 83, 66, 64, 65, 67, 25, 103, 102, 48, 107, 41, 109, 108

Each of the themes identified in the axial coding process will be addressed in relation to its importance in the application of acupuncture/TCM in the treatment of cardiovascular disease.

Meridian systems and "PC 6"

The data summarized in Table 2 demonstrate the importance of meridians and the PC 6 needling point in relation to the treatment of cardiovascular disease. As indicated in Table 2, eight articles manifested the "meridian"- "P6" intersection. TCM theorists and practitioners are aware that the entire human body has been mapped for meridians and energy flow, and a specific meridian called the pericardium meridian which connects directly to the heart and vasculature (Zhou, W., Fu, L. W., Guo, Z. L., & Longhurst, J. C. 2007). Also known as "PC6," this acupoint has been shown via multiple human and animal studies to stimulate the activity of a vast network of neurons

that then elicit production of neurotransmitters and biochemicals sent through the bloodstream and to the tissues (Tsuchiya, M. 2013), resulting in the calming of the muscle-cells of smooth muscle tissue including the arteries and heart (Li, P., Pitsillides, K. F., Rendig, S. V., Pan, H. L., & Longhurst, J. C. 1998) (Wu, H. C., Lin, J. G., Chu, C. H., Chang, Y. H., Chang, C. G., Hsieh, C. L., ... & Huang, C. Y. 2004).

Brain, pain and opioids

As indicated in Table 2, a total of 31 articles manifest intersection with regard to the factors of brain/pain and opioids. These factors represent the highest level of interaction across the variety of studies reviewed. It has been found that individuals experiencing heart failure exhibit elevated sympathetic activity, and those with the greatest activity have the lowest level of survival (Middlekauff, 2004). As evidenced by the articles indicated in Table 2, the administration of acupuncture stimulation at PC6 has been shown to attenuate and even eliminate myocardial ischemia, arrhythmias, and hypertension by intercepting the signals of the sympathetic pathway (Chao, Shen, Tjen-A-Looi, Pitsillides, Li & Longhurst, 1999) (Li, Li, Chen, Liang, Wu, & Wang, 2012). Magnetic resonance imaging shows that the ventrolateral periaqueductal gray (vlPAG), the rostral ventrolateral medulla (rVLM), and the arcuate nucleus (ARC) are three brain regions identified as the "long-loop pathway" responsible for the stimulation of various pain-modulating neurochemicals such as gamma-aminobutyric acid (GABA), serotonin (5-HT), opioids, enkephalins, and endocannabinoids (Tjen-A-Looi, Li, & Longhurst, 2009) (Taguchi, R. 2008). Through acupuncture stimulation at PC6, analgesia and the cardiovascular response are modulated, with the ARC as the point of origin of upregulation of multiple opioids and neurotransmitters that complement autonomic

nerve activity along the long-loop pathway (Fischer, Ludwig, Flory, Gambaryan, Singh, Finn, & Pfeffer, 2001). Acupuncture stimulation at PC6 activates neurons of the ARC, with the end-result being the reduction of cardiovascular sympathoexcitatory reflex response of the rVLM through upregulation of GABA, opioids, 5-HT, NO, and NOS (Tjen-A-Looi, Li, & Longhurst, 2009) (Fu, & Longhurst, 2009). The resultant stimulation of baroreceptors, chemoreceptors, cardiopulmonary receptors, and somatic and splanchnic nerves transmits afferent information that ultimately leads to inhibition of the neuromodulator substance P, thereby eliciting analgesia (Janssens, Rogers, & Schoen, 1988; Levine, J. D., Gormley, J., & Fields, H. L. 1976).

Nitric oxide, heart performance and cardiomyocytes

The third and final analysis of cross-referencing factors emerged regarding nitric oxide, heart performance, and cardiomyocytes. For these factors, a total of 20 articles manifested intersection. In brief, these overlapping studies indicate the strong possibility that acupuncture stimulation results in attenuation of myofibrillar contractility and metabolic homeostasis in cardiomyocytes (Bloch, W., Addicks, K., Hescheler, J., & Fleischmann, B. K. 2001). The impact of acupuncture is likely mediated, through the regulation of calcium ions in the intracellular space, upregulation of the molecule nitric oxide (Weeke-Klimp, A., Bax, N. A., Bellu, A. R., Winter, E. M., Vrolijk, J., Plantinga, J., ... & Lie-Venema, H. 2010) (Tian, Y. F., Wang, R., Li, L. Y., Wang, J., Jin, C. N., & Hao, C. Y. 2007). The end-result is acupuncture's stimulation of neurotransmitters to moderate sympathoexcitatory reflexes (Guo, Z. L., & Longhurst, J. C. 2003). At the same time, nitric oxide exerts its wide-ranging power to regulate coronary vessel tone, thrombogenicity, and inflammatory properties, as well as angiogenesis, through the

modulation of neurochemicals, angiotensin, bradykinin, and vascular endothelial growth factor (Tjen-A-Looi, S. C., Phan, N. T., & Longhurst, J. C. 2001) (Wang, C., Tian, Y. F., Zhou, D., Yang, X. F., Lin, Y. P., Chang, X. R., & Yan, J. 2010).

In summary, the following factors emerged from the current study and should form the basis for an outline for an educational tool that addresses the potential benefits of acupuncture in the prevention and treatment of cardiovascular disease:

- Meridian systems
- The “PC 6” needling point
- Brain
- Pain
- Opioids
- Nitric oxide
- Heart performance
- Cardiomyocytes

In the current study, it was the researcher’s objective to share the outline indicated above with the end-goal of creating an educational program that will inform TCM practitioners, Western medical physicians, other medical professionals, as well as patients on the benefits of administration of acupuncture in preventing and treating cardiovascular disease. The educational program to be generated later in this researcher’s career will have specific focus on the mechanisms that acupuncture stimulation engages, and will facilitate for both practitioners and consumers an enhanced appreciation for the application of acupuncture in the prevention and treatment of cardiovascular disease. An expanded and “fleshed out” version of the

educational outline is included in Appendix C. Consistent with the objective of this research study the document included in Appendix C provides a more detailed foundation for the educational tool that will be created to facilitate greater understanding of the use of acupuncture in the treatment and prevention of cardiovascular disease.

Chapter Five: Discussion

The intention of this project is to provide a means of both sharing findings regarding the science of acupuncture and inciting further study on the neurobiology of acupuncture stimulation, with the hope that acupuncture stimulation will be integrated into Western medical practices as a standard in American healthcare. Conclusions drawn on the multitude of studies on acupuncture stimulation elucidate some of the profound mechanisms involving the tapping into the body's "electrical circuitry," from the very point of acupuncture stimulation to the stimulation of specific regions of the brain to, in the end, stimulation of the targeted tissues of the body.

Implications for Theory and Practice

A wide body of literature now exists to support the findings of a multitude of studies indicating that pharmaceuticals aimed at relieving angina pectoris, myocardial ischemia, and reperfusion injury could be eliminated with the administration of acupuncture at PC6 (Chao, Shen, Tjen-A-Looi, Pitsillides, Li & Longhurst, 1999; Li, Li, Chen, Liang, Wu, & Wang, 2012; Tjen-A-Looi, Li, & Longhurst, 2009).

It has been found that the activation of the body's natural neural pathways through acupuncture stimulation renders the very same responses that pharmaceuticals such as ion channel blockers, angiotensin blockers, angiotensin-converting enzyme inhibitors, and thrombolytics, with their deleterious side-effects and far-reaching

complications, attempt to do. Moreover, because the small yet powerful molecule NO is present in all tissues of the body from brain regions to the heart muscle itself, great excitement is now generated over the practice of not only acupuncture stimulation but also acupressure at various acupoints for the purpose of the body's endogenous synthesis of NO. (Ma studies "Elucidate Therapeutic Effects and Mechanisms of Biomolecule-Mediated Meridian Practices and Therapies" - to develop a new methodological procedure to monitor and assay NO, ANP, and cGMP generated on human skin acupoints/meridians are currently (Ma, 2003). Therefore, further research will be aimed at stimulating the activity of the body's vast network of neurons along the meridians that then elicit production of neurotransmitters and biochemicals sent through the bloodstream and to the tissues, with focus on, in particular, NO, resulting in the calming of the cells of smooth muscle tissue including the arteries and heart.

Limitations of the Current Study

Validity and reliability of data:

Validity: As much as possible, all data for this study were drawn from professional peer-review journals and books published by edited publishing houses. Self-published sources were avoided. This factor contributed considerably to the validity of the data. Nonetheless, there remains the possibility of researcher bias that may skew the data in the direction of the researcher's hypotheses and objectives. That factor was minimized by the fact that a wide range of resources were engaged, and those resources resulted from systematic searchers. The researcher's biases did not influence the search terms used or the search process.

Reliability: The consistency of data engaged in the current study was enhanced

by the use of standard data collection forms, which mandated that the researcher engage each article on the same basis, searching for similar factors in each article. For each source reviewed, standard procedures were followed, and standard categories of data were collected. Both reliability and validity were also enhanced by the fact that the researcher worked closely with the Capstone Advisor and several consultants, who had the opportunity to discern any inconsistencies in the data collection and data analysis processes.

Other Limitations:

The current study was limited only by the resources engaged in the search process. Over 100 articles were reviewed for the current study. While the number of articles reviewed is substantive, it does not constitute every possible article pertaining to the topic. The researcher was the only person reviewing each article, as there was no plan for providing a backup reader for the articles. As a result, the current study does have the limitation of the current researcher's perspective. It was the researcher's intent to obtain and review articles primarily from peer-reviewed journals. Not more than 30% of the articles came from journals that are non-peer reviewed. Literary resources were accessed approximately the last 15 years. While the search included libraries in only Southern California, with access to electronic databases, the search actually extended well beyond the boundaries of Southern California,, and in essence included all literature currently available.

Recommendations for further study

Because acupuncture stimulation is developing an ever-greater presence as alternative treatment in Western medical practice, there is a greater amount of data

available for empirical analysis, from which conclusions on the efficacy of acupuncture can be drawn. The primary attention of further study for this researcher, hence, will be on the data from studies and practitioners around the world as the data are made available. The collection of the data will enable this researcher not only to better understand the biomechanics of acupuncture stimulation, in particular at the PC6 acupoint, but also to be equipped to educate others, all for the purpose of attaining a more-integrative approach to the treatment of disease in Western medical practices. As multiple studies conclude, some of the effective biomechanics of acupuncture stimulation involve activating specific neurotransmitters in specialized brain regions whose targets - through release of various neurohormones and chemicals, in particular NO - are tissues that regulate cardiovascular function, from modulating the vasculature to management of the heart-muscle itself; (Li, P., Tjen-A-Looi, S. C., Guo, Z. L., Fu, L. W., & Longhurst, J. C. 2009; Li, J., Li, J., Chen, Z., Liang, F., Wu, S., & Wang, H. 2012). It has been shown that the ubiquitous molecule NO is small enough to permeate the cell membrane of every cell type in the body, and is a synthesized molecule whose complete role and functions are not entirely understood. However, what is known about NO - and what is most pertinent to this researcher at the immediate time - is that NO is a major contributor to dilation of the arterial walls of the vasculature and relaxation of cardiomyocytes, and, hence, a major contributor to easing burden on, pain of, and damage to the heart (Wu, Lin, Chu, Chang, Chang, Hsieh, & Huang, 2004; Li, J., Li, J., Liang, F., Hong, Y., Wu, S., Tang, H., & Wang, H. 2011).

It is, therefore, the intention of this researcher to delve more deeply into the study of and research into the greater range of activity of NO and to work on a personal level

with medical researchers - for example, Dr. Ma - whose specialty is on the subject of NO. In light of the fact that, at the moment in Western medical practices, those afflicted with heart disease as well as those having undergone heart procedures are served a routine cocktail of pharmaceuticals in order to manage the activity of cardiovascular functions, it is, moreover, the ultimate goal of this researcher to encourage a lessening of reliance on pharmaceuticals in the treatment of cardiovascular disease, in particular, and all disease, in general.

As is already underway by this researcher, the educating of others will be in the form of written and online publications of the findings of the various research studies as well as through seminars and webinars whose themes will be based on alternative means for prevention of cardiovascular disease.

Summary

The current study had the objective to identify factors that are present in prior scientific studies related to the use of acupuncture in the prevention and treatment of cardiovascular disease. The study employed research synthesis and grounded theory methods that included systematic collection and analysis of data. The study focused specifically on the use of PC6 stimulation and its impact on cardiovascular disease. As the intent of this study was to facilitate the further growth of both Western and Eastern medical practices that pertain to the treatment of cardiovascular disease, an outline forming the basis for the creation of an educational tool that links PC6 with cardiovascular health was generated based on the data collected.

Conclusion

Since the researcher of this study will always consider herself to be a student,

she will continue to undertake research in her field for the enrichment of both the practice and the knowledge with which she desires to educate other medical professionals. In the broader scope, it is all for the purpose of a greater understanding of the relationship between the practices of her field with the other elements of our lifestyle, and in the end achieving for the individual - and for the society as a whole - physical, mental, and spiritual health.

References

- Ahn, A. & Kaptchuk, T. (2005). Advancing acupuncture research. *Alternative Therapies*, 11(3), 40.
- American Medical Association. (2003). *American Medical Association complete medical encyclopedia*. New York: Random House Reference.
- Ballegaard, S., Jensen, G., Pedersen, F. & Nissen, V.H.,(1986). Acupuncture in severe, stable angina pectoris: a randomized trial. *Acta Medica Scandinavica*, 220(4), 307-313.
- Barnett-Page, E. & Thomas, J. (2009). *Methods for the synthesis of qualitative research: A critical review (NCRM Working Paper Series)*. London, ESRC National Centre for Research Methods.
- Bloch, W., Addicks, K., Hescheler, J. & Fleischmann, B. K. (2001). Nitric oxide synthase expression and function in embryonic and adult cardiomyocytes. *Microscopy research and technique*, 55(4), 259-269.
- Campbell, T. C. & Campbell, T. M. (2005). The China study: the Most Comprehensive Study of Nutrition ever conducted and the starting implications for diet, weight loss and long-term health.

- Chao, D. M., Shen, L. L., Tjen-A-Looi, S., Pitsillides, K. F., Li, P. & Longhurst, J. C. (1999). Naloxone reverses inhibitory effect of electroacupuncture on sympathetic cardiovascular reflex responses. *American Journal of Physiology-Heart and Circulatory Physiology*, 276(6),
- Chang, S., Chao, W. L., Chiang, M. J., Li, S. J., Lu, Y. T., Ma, C. M., ... & Hsieh, S. H. (2008). Effects of acupuncture at Neiguan (PC 6) of the pericardial meridian on blood pressure and heart rate variability. *Chin J Physiol*, 51(3), 167-177.
- Cheng, X. & Deng, L. (1999). Chinese acupuncture and moxibustion. Beijing: ForeignLanguage Press.
- Chiu, Y. J., Chi, A. & Reid, I. A. (1997). Cardiovascular and endocrine effects of acupuncture in hypertensive patients. *Clinical and experimental hypertension*, 19(7), 1047-1063.
- Deadman, P., Al-Khafaji, M. & Baker, K. (2007). A manual of acupuncture. Hove, East Sussex, England: Journal of Chinese Medicine Publications.
- Dharmashankar, K., Welsh, A., Wang, J., Kizhakekuttu, T. J., Ying, R., Gutterman, D. D. & Widlansky, M. E. (2012). Nitric Oxide Synthase-Dependent Vasodilation of Human Subcutaneous Arterioles Correlates With Noninvasive Measurements of Endothelial Function. *American journal of hypertension*, 25(5), 528-534.
- Diao, L. H., Yang, Z. B., Zhou, G. X., Chen, Y., Fan, L. Y., Zhang, Y. Y. & Liu, S. T., (2011). Observation on therapeutic effects of electroacupuncture at Neiguan (PC 6) on silent myocardial ischemia]. *Zhongguo zhen jiu= Chinese acupuncture & moxibustion*, 31(7), 591.
- Dougherty, D. D., Kong, J., Webb, M., Bonab, A. A., Fischman, A. J., & Gollub, R. L.

- (2008). A combined [11C] diprenorphine PET study and fMRI study of acupuncture analgesia. *Behavioural brain research*, 193(1), 63-68.
- Esler, M., Rumantir, M., Kaye, D. & Lambert, G. (2001). The sympathetic neurobiology of essential hypertension: disparate influences of obesity, stress, and noradrenaline transporter dysfunction?*. *American journal of hypertension*, 14(S3), 139S-146S. The sympathetic neurobiology of essential hypertension: disparate influences of obesity, stress, and noradrenaline transporter dysfunction?*. *American journal of hypertension*, 14(S3), 139S-146S.
- Fischer, T. A., Ludwig, S., Flory, E., Gambaryan, S., Singh, K., Finn, P. & Pfeffer, J. M. (2001). Activation of Cardiac c-Jun NH2-Terminal Kinases and p38-Mitogen-Activated Protein Kinases With Abrupt Changes in Hemodynamic Load. *Hypertension*, 37(5), 1222-1228.
- Fokker's, K., Langsjoen, P., Willis, R., Richardson, P., Xia, L. J., Ye, C. Q. & Tamagawa, H. (1990). Lovastatin decreases coenzyme Q levels in humans. *Proceedings of the National Academy of Sciences*, 87(22), 8931-8934
- Fu, L. W., & Longhurst, J. C. (2009). Electroacupuncture modulates vIPAG release of GABA through presynaptic cannabinoid CB1 receptors. *Journal of Applied Physiology*, 106(6), 1800-1809.
- Gillinov, M. & Steven, N. (2012, february 02). Do negative emotions, stress, and anxiety lead to heart disease. Retrieved from <http://theatlantic.com/health/archive/2012/02/do-negative-emotions-stress-and-anxiety-lead-to-heart-disease/251540/>.
- Glaser, B. & Strauss, A. (1967). The discovery of grounded theory. In B. Glaser & A.

- Strauss (Eds.), Glaser & Strauss 1967. Sociology Press. Retrieved from (<http://groundedtheory.com/index1.html>), 1967
- Glaser, B. G., (2002, September). Constructivist grounded theory?. In *Forum Qualitative Sozialforschung/Forum: Qualitative Social Research* (Vol. 3, No. 3).
- Guo, Z. L. & Longhurst, J. C., (2003). Activation of nitric oxide-producing neurons in the brain stem during cardiac sympathoexcitatory reflexes in the cat. *Neuroscience*, 116(1), 167-178.
- Guo, Z. L., & Longhurst, J. C. (2007). Expression of c-Fos in arcuate nucleus induced by electroacupuncture: relations to neurons containing opioids and glutamate. *Brain research*, 1166, 65-76.
- Guo, Z. L., Moazzami, A. R. & Longhurst, J. C. (2004). Electroacupuncture induces c-Fos expression in the rostral ventrolateral medulla and periaqueductal gray in cats: relation to opioid containing neurons. *Brain research*, 1030(1), 103-115.
- Heber, D., Yip, I., Ashley, J. M., Elashoff, D. A., Elashoff, R. M. & Go, V. L. W. (1999). Cholesterol-lowering effects of a proprietary Chinese redyeast- rice dietary supplement. *The American journal of clinical nutrition*, 69(2), 231-236.
- Heidenreich, P. A., Trogon, J. G., Khavjou, O. A., Butler, J., Dracup, K., Ezekowitz, M. D. & Woo, Y. J. (2011). Forecasting the Future of Cardiovascular Disease in the United States A Policy Statement From the American Heart Association. *Circulation*, 123(8), 933-944.
- Holaday, J. W. (1983). Cardiovascular effects of endogenous opiate systems. *Annual review of pharmacology and toxicology*, 23(1), 541-541.
- Huang KC. (1996) *Acupuncture: the past and the present*. New York: Vantage.

- Kochanek, K. D., Xu, J., Murphy, S. L., Miniño, A. M. & Kung, H. C. (2011). National vital statistics reports. *National Vital Statistics Reports*, 59(4), 1.
- Janssens, L. A., Rogers, P. A. & Schoen, A. M. (1988). Acupuncture analgesia: a review. *Veterinary Record*, 122(15), 355-358.
- Joyner, M. J. & Dietz, N. M. (1997). Nitric oxide and vasodilation in human limbs. *Journal of Applied Physiology*, 83(6), 1785-1796.
- Kelly, R. A., Balligand, J. L. & Smith, T. W. (1996). Nitric oxide and cardiac function. *Circulation Research*, 79(3), 363-380.
- Krukoff, T. L. (1999). Central actions of nitric oxide in regulation of autonomic functions. *Brain research reviews*, 30(1), 52-65.
- Kuwabara, M., Kakinuma, Y., Ando, M., Katare, R. G., Yamasaki, F., Doi, Y. & Sato, T. (2006). Nitric oxide stimulates vascular endothelial growth factor production in cardiomyocytes involved in angiogenesis. *The Journal of Physiological Sciences*, 56(1), 95-101.
- Lao, L., Zhang, G., Wei, F., Berman, B. M. & Ren, K. (2001). Electro-acupuncture attenuates behavioral hyperalgesia and selectively reduces spinal Fos protein expression in rats with persistent inflammation. *The Journal of Pain*, 2(2), 111-117.
- Levine, J. D., Gormley, J. & Fields, H. L. (1976). Observations on the analgesic effects of needle puncture (acupuncture). *Pain*, 2(2), 149-159.
- Lewith, G. T., White, P. J. & Pariente, J. (2005). Investigating acupuncture using brain imaging techniques: the current state of play. *Evidence-Based Complementary and Alternative Medicine*, 2(3), 315-319.

- Li, J., Li, J., Liang, F., Hong, Y., Wu, S., Tang, H., & Wang, H. (2011). Electroacupuncture at PC6 (Neiguan) Improves Extracellular Signal-Regulated Kinase Signaling Pathways Through the Regulation of Neuroendocrine Cytokines in Myocardial Hypertrophic Rats. *Evidence-Based Complementary and Alternative Medicine*, 2012.
- Li, J., Li, J., Chen, Z., Liang, F., Wu, S. & Wang, H. (2012). The influence of PC6 on cardiovascular disorders: a review of central neural mechanisms. *Acupuncture in*
- Li, P., Pitsillides, K. F., Rendig, S. V., Pan, H. L. & Longhurst, J. C. (1998). Reversal of Reflex-Induced Myocardial Ischemia by Median Nerve Stimulation A Feline Model of Electroacupuncture. *Circulation*, 97(12), 1186-1194.
- Li, P., Tjen-A-Looi, S. C., Guo, Z. L., Fu, L. W. & Longhurst, J. C. (2009). Long-loop pathways in cardiovascular electroacupuncture responses. *Journal of Applied Physiology*, 106(2), 620-630.
- Lao, L., Xu, L. & Xu, S. (2012). Traditional Chinese Medicine. In *Integrative Pediatric Oncology* (pp. 125-135). Springer Berlin Heidelberg.
- Ma, P. T., il , ., S dhof, T. C., Bilheimer, D. W., Goldstein, J. L. & Brown, M. S. (1986). Mevinolin, an inhibitor of cholesterol synthesis, induces mRNA for low density lipoprotein receptor in livers of hamsters and rabbits. *Proceedings of the National Academy of Sciences*, 83(21), 8370-8374.
- Ma, S. X. (2003). Enhanced nitric oxide concentrations and expression of nitric oxide synthase in acupuncture points/meridians. *The Journal of Alternative & Complementary Medicine*, 9(2), 207-215.
- MacMicking, J., Xie, Q. W. & Nathan, C. (1997). Nitric oxide and macrophage function. *Annual review of immunology*, 15(1), 323-350.

- Marsh, N. & Marsh, A., (2000). A short history of nitroglycerine and nitric oxide in pharmacology and physiology. *Clinical and Experimental Pharmacology and Physiology*, 27(4), 313-319.
- Middlekauff, H. R., (2004). Acupuncture in the treatment of heart failure. *Cardiology in review*, 12(3), 171-173.
- Moazzami, A., Tjen-A-Looi, S. C., Guo, Z. L. & Longhurst, J. C. (2010). Serotonergic projection from nucleus raphe pallidus to rostral ventrolateral medulla modulates cardiovascular reflex responses during acupuncture. *Journal of Applied Physiology*, 108(5), 1336-1346.
- Pandit, N. R. (1996). The creation of theory: A recent application of the grounded theory method. *The Qualitative Report*, 2(4), 1-14.
- Rezaei, S., Khorsand, A., & Jamali, J. (2012). Characterisation of human skin impedance at acupuncture point PC4 Ximen and pericardium meridian using the four-electrode method. *Acupuncture in Medicine*, 30(2), 127-131.
- Richter, A., Herlitz, J. & Hjalmarson, A. A. (1991). Effect of acupuncture in patients with angina pectoris. *European heart journal*, 12(2), 175-178.
- Stedman, T. L. (1995). *Stedman's medical dictionary*. Baltimore: Williams & Wilkins.
- Venes, D., Thomas, C. L. & Taber, C. W. (2001). *Taber's cyclopedic medical dictionary*. (19 ed.). Philadelphia: F A Davis Co.
- Sun, H. Y., Wang, N. P., Halkos, M., Kerendi, F., Kin, H., Guyton, R. A. & Zhao, Z. Q. (2006). Postconditioning attenuates cardiomyocyte apoptosis via inhibition of JNK and p38 mitogen-activated protein kinase signaling pathways. *Apoptosis*, 11(9), 1583-1593.

- Sun, W. (1995). [Electroacupuncture at " huatuo jiaji point" inhibits the expression of Fos protein in rat spinal cord induced by traumatic pain]. *Zhen ci yan jiu= Acupuncture research/[Zhongguo yi xue ke xue yuan Yi xue qing bao yan jiu suo bian ji]*, 21(1), 60-64.
- Syuu, Y., Matsubara, H., Hosogi, S. & Suga, H. (2003). Pressor effect of electroacupuncture on hemorrhagic hypotension. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 285(6), R1446-R1452.
- Taguchi, R. (2008). Acupuncture anesthesia and analgesia for clinical acute pain in Japan. *Evidence-based complementary and alternative medicine*, 5(2), 153-158.
- Tjen-A-Looi, S. C., Li, P. & Longhurst, J. C. (2009). Processing cardiovascular information in the vIPAG during electroacupuncture in rats: roles of endocannabinoids and GABA. *Journal of Applied Physiology*, 106(6), 1793-1799.
- Tjen-A-Looi, S. C., Li, P. & Longhurst, J. C. (2006). Midbrain vIPAG inhibits rVLM cardiovascular sympathoexcitatory responses during electroacupuncture. *American Journal of Physiology-Heart and Circulatory Physiology*, 290(6), H2543-H2553.
- Tjen-A-Looi, S. C., Li, P. & Longhurst, J. C. (2007). Role of medullary GABA, opioids, and nociceptin in prolonged inhibition of cardiovascular sympathoexcitatory reflexes during electroacupuncture in cats. *American Journal of Physiology-Heart and Circulatory Physiology*, 293(6), H3627-H3635.
- Tjen-A-Looi, S. C., Phan, N. T. & Longhurst, J. C. (2001). Nitric oxide modulates sympathoexcitatory cardiac-cardiovascular reflexes elicited by bradykinin.

American Journal of Physiology-Heart and Circulatory Physiology, 281(5), H2010-H2017.

Tian, Y. F., Wang, R., Li, L. Y., Wang, J., Jin, C. N. & Hao, C. Y. (2007). Effects of acupuncture at the points of the Pericardium Meridian on the activity of myocardial Ca²⁺-ATPase and gene expression in the rat of myocardial ischemia and reperfusion injury]. *Zhongguo zhen jiu= Chinese acupuncture & moxibustion*, 27(3), 205.

Tobert, J. A. (2003). Lovastatin and beyond: the history of the HMG-CoA reductase inhibitors. *Nature Reviews Drug Discovery*, 2(7), 517-526.

Togashi, H., Sakuma, I., Yoshioka, M., Kobayashi, T., Yasuda, H., Kitabatake, A. & Levi, R. (1992). A central nervous system action of nitric oxide in blood pressure regulation. *Journal of Pharmacology and Experimental Therapeutics*, 262(1), 343-347.

Tsou, M. T., Ho, J. Y., Lin, C. H. & Chiu, J. H. (2004). Proteomic analysis finds different myocardial protective mechanisms for median nerve stimulation by electroacupuncture and by local somatothermal stimulation. *International journal of molecular medicine*, 14(4), 553-616.

Tsuchiya,, M. (2013). *Nitric oxide in acupuncture mechanism*. Retrieved from <http://www.intechopen.com/books/acupuncture-in-modern-medicine/nitric-oxide-in-acupuncture-mechanism>.

Tsuchiya, M., Sato, E. F., Inoue, M., & Asada, A. (2007). Acupuncture enhances generation of nitric oxide and increases local circulation. Ulett, G. A., JiSheng, H. A. N. & Han, S. (1998). Traditional and evidence-based acupuncture: history, mechanisms,

and present status. *Southern Medical Journal*, 91(12), 1115-1120.

Walsh, D. & Downe, S. (2005). Meta-synthesis method for qualitative research; a literature review. *Journal of Advanced Nursing*. 50 (2) 204-211.

Wang, Q., Mao, L. M. & Han, J. S. (1990). The role of periaqueductal gray in mediation of analgesia produced by different frequencies electroacupuncture stimulation in rats. *International Journal of Neuroscience*, 53(2-4), 167-172.

Wang, C., Tian, Y. F., Zhou, D., Yang, X. F., Lin, Y. P., Chang, X. R. & Yan, J. (2010). Influence of electroacupuncture on myocardial NO and NOS and intracellular Ca²⁺ contents in myocardial ischemia-reperfusion injury rats]. *Zhen ci yan jiu= Acupuncture research/[Zhongguo yi xue ke xue yuan Yi xue qing bao yan jiu suo bian ji]*, 35(2), 113.

Weeke-Klimp, A., Bax, N. A., Bellu, A. R., Winter, E. M., Vrolijk, J., Plantinga, J. & Lie-Venema, H. (2010). Epicardium-derived cells enhance proliferation, cellular maturation and alignment of cardiomyocytes. *Journal of molecular and cellular cardiology*, 49(4), 606-616

Wu, H. C., Lin, J. G., Chu, C. H., Chang, Y. H., Chang, C. G., Hsieh, C. L. & Huang, C. Y. (2003). The effects of acupuncture on cardiac muscle cells and blood pressure in spontaneous hypertensive rats. *Acupuncture & electro-therapeutics research*, 29(1-2), 83-95.

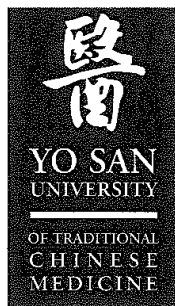
Wu, H. C., Lin, J. G., Chu, C. H., Chang, Y. H., Chang, C. G., Hsieh, C. L. & Huang, C. Y. (2004). The effects of acupuncture on cardiac muscle cells and blood pressure in spontaneous hypertensive rats. *Acupuncture & electro-therapeutics research*, 29(1-2), 83.

- Xu, L., Xu, H., Gao, W., Wang, W., Zhang, H. & Lu, D. P. (2012). Treating angina pectoris by acupuncture therapy. *Acupuncture & electro-therapeutics research*, 38(1-2), 17-35.
- Yao, T., Andersson, S. & Thoren, P. (1982). Long-lasting cardiovascular depressor response following sciatic stimulation in spontaneously hypertensive rats. Evidence for the involvement of central endorphin and serotonin systems. *Brain research*, 244(2), 295-303.
- Yuan, H., Yan, B., Wang, H. H., Hua, S. & Hu, A. (2012). Nitric oxide preserves XIAP and reduces hypoxia/reoxygenation-induced cardiomyocytes apoptosis via ERK1/2 activation. *Biochemical and Biophysical Research Communications*, 421(1), 134-139.
- Zanzinger, J. (1999). Role of nitric oxide in the neural control of cardiovascular function. *Cardiovascular research*, 43(3), 639-649.
- Zhang, H., Liu, L., Huang, G., Zhou, L., Wu, W., Zhang, T. & Huang, H. (2009). Protective effect of electroacupuncture at the Neiguan point in a rabbit model of myocardial ischemia-reperfusion injury. *Canadian Journal of Cardiology*, 25(6), 359-363.
- Zhong, H. & Li, G. Z. (2009). Study on the mechanism of electroacupuncture of "Neiguan"(PC 6) in inhibiting ventricular arrhythmia induced by hypothalamic electrostimulation in the rabbit]. *Zhen ci yan jiu= Acupuncture research/[Zhongguo yi xue ke xue yuan Yi xue qing bao yan jiu suo bian ji]*, 34(1), 43.
- Zhou, W., Fu, L. W., Guo, Z. L. & Longhurst, J. C. (2007). Role of glutamate in the

rostral ventrolateral medulla in acupuncture-related modulation of visceral reflex sympathoexcitation. *American Journal of Physiology-Heart and Circulatory Physiology*, 292(4), H1868-H1875.

Zhou, X. Q. & Liu, J. X. (1993). [Metrological analysis for efficacy of acupuncture on angina pectoris]. *Zhongguo Zhong xi yi jie he za zhi Zhongguo Zhongxiyi jiehe zazhi= Chinese journal of integrated traditional and Western medicine/Zhongguo Zhong xi yi jie he xue hui, Zhongguo Zhong yi yan jiu yuan zhu ban*, 13(4), 212-4.

Appendix A: IRB exemption letter



April 4, 2013

Lisa C. Nelson, L.Ac
14104 Panaway #188
Marina Del Rey, CA 90292

Dear Lisa,

Your Claim for Exemption from the Institutional Review Board (IRB) has been reviewed. Your research proposal has been approved, with no recommendations effective April 1, 2013 through March 31, 2014.

Should there be any significant changes that need to be made which would alter the research procedures that you have explained in your proposal, please consult with the IRB coordinator prior to making those changes.

Respectfully,

Shelley Cerny, L.Ac
IRB Coordinator

Appendix B: Article abstraction form

Descriptive only– to identify the article and source.	
Code#	
Reference information:	
Author:	
Journal Title:	
Publication date:	
Comments: Triangulation, the emergence of data pointing to salient factor theme.	
Year of study:	Country of study:
Human or animal:	
Data source:	Duration of study:
Data collected:	
Notes:	

Appendix C: List of Articles indicated in Table #1 Table #2**Indicated by study number**

Appendix C: List of Articles indicated in Table #1 Table #2

indicated by study number

- 1 Wu, Lin, Chu, Chang, Chang, Hsieh, & Huang, (2004)
- 2 Li, P., Tjen-A-Looi, Guo, Fu, & Longhurst, (2009)
- 23 Wu, Lin, Chu, Chang, Chang, Hsieh, & Huang, (2003)
- 24 Middlekauff, (2004)
- 25 Richter, Herlitz, & Hjalmarson, (1991).
- 27 Li, Pitsillides, Rendig, Pan, & Longhurst, (1998)
- 28 Lewith, White, & Pariente, (2005).
- 29 Chao, Shen, Tjen-A-Looi, Pitsillides, Li & Longhurst, (1999)
- 30 Guo, Moazzami, & Longhurst, (2004)
31. Guo, Z. L., & Longhurst, J. C. (2007)
- 32 Tjen-A-Looi, Li, & Longhurst, (2006)
- 41 Sun, Wang, Halkos, Kerendi, Kin, Guyton, & Zhao, (2006)
- 45 Fischer, Ludwig, Flory, Gambaryan, Singh, Finn, & Pfeffer, (2001)
- 47 Tjen-A-Looi, Li, & Longhurst, (2007)
- 48 Tsou, Ho, Lin, & Chiu, (2004).
- 49 BALLEGAARD, JENSEN, PEDERSEN, & NISSEN, (1986)
- 53 Li, P., Tjen-A-Looi, S. C., Guo, Z. L., Fu, L. W., & Longhurst, J. C. (2009)
- 54 Tjen-A-Looi, Li, & Longhurst, (2009)
- 55 Fu, & Longhurst, (2009)
- 57 Chang, Chao, Chiang, Li, Lu, Ma & Hsieh, (2008)
- 59 Tjen-A-Looi, Li, & Longhurst, (2007)

- 62 Moazzami, Tjen-A-Looi, Guo, & Longhurst, (2010)
- 63 Yao, Andersson, & Thoren, (1982)
- 64 Krukoff, (1999)
- 65 Tjen-A-Looi, S. C., Phan, N. T., & Longhurst, J. C. (2001)
- 66 Guo, & Longhurst, (2003)
- 67 Wang, Tian, Zhou, Yang, Lin, Chang, & Yan, (2010)
- 68 Zhong, & Li, (2009)
- 74 Togashi, Sakuma, Yoshioka, Kobayashi, Yasuda, Kitabatake, & Levi, (1992)
- 77 Sun, W. (1995).
- 78 Lao, Zhang, Wei, Berman, & Ren, (2001).
- 80 Levine, Gormley, & Fields, (1976).
- 81 Wang, Mao & Han, (1990)
- 83 Kuwabara, Kakinuma, Ando, Katare, Yamasaki, Doi, & Sato, (2006)
- 84 Yuan, Yan, Wang, Hua, & Hu, (2012)
- 85 Bloch, Addicks, Hescheler, & Fleischmann, (2001)
- 86 Kelly, Balligand, & Smith, (1996)
- 87 MacMicking, Xie, & Nathan, (1997)
- 88 Dharmashankar, Welsh, Wang, Kizhakekuttu, Ying, Gutterman, & Widlansky, (2012)
- 89 Joyner, & Dietz, (1997)
- 90 Li, Li, Chen, Liang, Wu, & Wang, (2012)
- 94 Chiu, Chi, & Reid, (1997)
- 96 Esler, Rumantir, Kaye, & Lambert, (2001)
- 97 Zhou Fu, Guo, & Longhurst, (2007)
- 98 Rezaei, Khorsand, & Jamali, (2012)

- 99 Diao, Yang, Zhou, Chen, Fan, Zhang, & Liu, (2011)
- 100 Diao, Yang, Zhou, Chen, Fan, Zhang, & Liu, (2011)
- 101 Syuu, Matsubara, Hosogi, & Suga, (2003
- 102 Zhou, & Liu, (1993).
- 103 Xu, Xu, Gao, Wang, Zhang, & Lu, (2012).
- 104 Taguchi, R. (2008).
- 105 Janssens, Rogers, & Schoen, (1988).
- 106 Dougherty, D. D., Kong, J., Webb, M., Bonab, A. A., Fischman, A. J., & Gollub, R. L. (2008).
- 107 Weeke-Klimp, Bax, Bellu, Winter, Vrolijk, Plantinga, & Lie-Venema, (2010)
- 108 Tian, Wang, Li, Wang, Jin, & Hao, (2007)
- 109 Zhang, Liu, Huang, Zhou, Wu, Zhang, & Huang, (2009).

Appendix D: Outline for the educational program

Lisa Nelson, L.Ac

Educational program outline:

- Educational Materials Including:

- o Physician Reference Kit: Laminated pocket and office forms with information such as: How acupuncture has a direct relationship over the regulation of neurotransmitters and neurohormones, (dopamine, inulin, serotonin, substance P, opiates, GABA, enkaphalins)

- o Customized Power Point educational presentations: to educate physicians, medical staff, and the community on the treatment of cardiovascular disease with acupuncture.

Table of content:

I.

A. History of acupuncture.

B. What is acupuncture?

II.

A. Uses of acupuncture:

- Pain
- Ease burden of heart and prevention of cardiovascular disease.
- Anxiety
- Addiction

III.

A. Acupuncture modulation of nitric oxide:

- PC6 acupuncture point.
- Long –loop- pathway (RVLM)

VI.

A. Four major pharmaceutical drugs given to heart patients:

- Ace inhibitors
 - Calcium channel blockers
 - Sodium channel blockers
 - Angiotensin blockers
-
- Present and discuss the most commonly occurring questions and concerns presented by referring physicians and self-insured employers related to the prevention of cardiovascular disease through acupuncture.

On site presentation for cardiologists, M.D. and primary care physicians by Lisa C. Nelson, L.Ac.