*Acta Physiologica Sinica*, February 25, 2015, 67(1): 19–31
DOI: 10.13294/j.aps.2015.0002 http://www.actaps.com.cn


**Invited Review**

# Integrating acupuncture into the cardiology clinic: can it play a role?

Jeannette Painovich, John Longhurst*
*Department of Medicine, University of California, Irvine, Irvine, CA 92697, USA*

**Abstract:** Despite continued improvement in risk factor recognition and aggressive medical management, heart disease remains the number one killer in the world. Medications for primary or secondary prevention of heart disease can cause unpleasant side effects leading to non-compliance. Novel therapies are needed to serve as a complement to or alternative for current medical management. Acupuncture and more specifically electroacupuncture may serve as a safe and viable option in the cardiology clinic. This review article focuses on both mechanistic and clinical studies evaluating acupuncture's effectiveness with symptomatic heart disease. Although continued research is needed, currently evidence warrants consideration of acupuncture's use with myocardial ischemia, hypertension, arrhythmias, heart failure as well as autonomic dysfunction.

**Key words:** acupuncture; electroacupuncture; mechanisms; cardiology

# 针刺在临床上用作心脏病综合治疗的手段之一：是否有效？

Jeannette Painovich, John Longhurst*
加州大学欧文分校医学院，欧文 CA 92697，美国

**摘 要**：尽管人们对心脏病危险因素的认识和医疗手段在不断进步，但该病仍是世界头号杀手。对心脏病的一级和二级药物治疗可引起多种副作用，结果导致病人不能坚持用药。当前需要新的治疗手段，或用于补充或用于替代传统的药物治疗。在心脏病临床中观察到，针刺，特别是电针不失为一种安全和切实可行的选择。本综述旨在通过对针刺防治心脏病的基础理论和临床研究来评估针刺的有效性。根据已有的证据，可认为针刺在治疗心肌缺血、高血压、心律失常、心衰和自主神经功能紊乱中有效，但仍需进一步的研究。

**关键词**：针刺；电针；机制；心脏学
**中图分类号**：R246

## 1 Introduction

Heart disease remains the number one killer of men and women in the United States [1, 2]. Despite aggressive management of traditional risk factors (e.g., hyperlipidemia, tobacco use and hypertension) and ever-evolving pharmaceutical options, the majority of patients with established coronary heart disease (CHD) will have recurrent cardiovascular events [3, 4]. Thus there is continued need for safe, viable treatment options for patients with heart disease. Acupuncture and more specifically, electroacupuncture (EA) modalities within traditional Chinese medicine (TCM) may provide a viable therapy for integration into current biomedical treatment protocols.

As one of the oldest healing practices in the world, acupuncture has been used for several thousand years to treat many illnesses. In 2003, the World Health Organization published a list of evidence-based conditions for which acupuncture could be used [5]. Specific to

Received 2014-06-30 Accepted 2014-08-21
This review was funded by Adolph Coors Foundation, DANA Foundation, Susan Samueli Center for Integrative Medicine at the University of California, Irvine and National Center for Advancing Translational Sciences, NIH Grant UL1TR000153.
*Corresponding author. Tel: +1-949-824-5602. E-mail: jcl@uci.edu

cardiology, angina pectoris, hypotension and hypertension were listed. Within the past few decades, however, acupuncture's effectiveness in the treatment of these and other manifestations of cardiovascular disease such as ischemia, arrhythmias, heart failure as well as its effect on heart rate variability (HRV) have been studied. Likewise, acupuncture's mechanistic actions and point specificity responsible for these cardiovascular benefits also have been explored. Dissemination of this information to physicians and other health care practitioners has the potential to influence attitudes and incorporation of this therapeutic strategy into their clinical practice.

## 2 Mechanisms of acupuncture actions in cardiovascular regulation

Recently, experimental studies have identified regulatory mechanisms responsible for EA's cardiovascular effects through inhibition of sympathetic outflow. Many acupuncture points overlie nerve bundles containing both motor and sensory nerves. These include, for example, the median nerve underlying pericardium meridian (P)5-P6 and the deep peroneal nerve underlying stomach meridian (ST)36-ST37[6–8]. The sensory components, including both Group III and IV finely myelinated and unmyelinated afferents, provide the critical pathway since local anesthesia rather than motor paralysis blocks acupuncture's cardiovascular effects[6]. These sensory nerves project to cardiovascular regions in the hypothalamus, midbrain and brainstem where neurotransmitters lead to EA-associated neural processing [6]. One of the more important regions where EA exerts its actions is the rostral ventrolateral medulla (rVLM), an important region in the brainstem that regulates sympathetic outflow[9–11]. Several studies suggest that EA causes release of opioids, gamma-aminobutyric acid (GABA), nociception and serotonin (5-hydroxytryptamine) in this region[10, 12, 13]. Endorphin, enkephalins and perhaps endomorphin, but not dynorphin, contribute to the EA modulatory response in the rVLM[14–16]. Immunohistochemical staining studies have demonstrated that EA activates enkephalinergic neurons in the rVLM and endorphinergic neurons in the arcuate nucleus (ARC), which project directly to the rVLM[17]. EA modulates sympathoexcitatory reflexes through opioid-mediated inhibition of glutamate in the rVLM [18].

As diagrammed in Fig. 1, 20–30 min of EA modulates sympathoexcitatory reflex responses through activation of a long-loop pathway extending from the hypothalamus to the midbrain and ultimately to the medulla [19]. Specifically, the hypothalamic ARC, ventrolateral periaqueductal gray (vlPAG) and medullary raphé (nucleus raphé obscurus), as well as the rVLM each play a role during EA[9, 10, 17, 20, 21]. These actions are mediated by the EA-induced release of both excitatory and inhibitory neurotransmitters including glutamate in the ARC and vlPAG [22, 23], acetylcholine in the ARC[22], endocannabinoids in the vlPAG[19, 24], serotonin[25], opioids, GABA and nociceptin in the rVLM [12, 26], ultimately modulate autonomic outflow.

Experimental studies also have shown that EA can modulate parasympathetic outflow in two models of reflex induced bradycardia and hypotension, one involving gastric distension in rats ventilated with a hypercapnic gas mixture that leads to a respiratory acidosis and a second using phenylbiguanide to stimulate cardiopulmonary receptors to evoke a vasovagal reflex [21, 27]. Through both opioid and GABA mechanisms in the nucleus ambiguus and the caudal ventrolateral medulla, EA inhibits parasympathetic and sympathetic outflow. These studies indicate that acupuncture has the potential to regulate both branches of the autonomic nervous system.

## 3 Point specificity

The lack of a consistent method of determining the ideal acupuncture point prescription remains an inherent limitation of acupuncture research. Recent studies employing objective measures have afforded more precise methods to evaluate point specificity. Cardiovascular studies have found that during exercise EA at points P5-P6 and large intestine meridian (LI)4-lung meridian (LU)7 increase maximum workload, reduce systolic and mean blood pressure (BP) and rate pressure (or double) product (RPP), an index of myocardial oxygen demand[28], as well as reduce sympathoexcitatory reflex responses, while EA applied to gallbladder meridian (GB)37-GB39 did not alter cardiovascular function [29]. In another study, manual stimulation of acupoint P6 led to decreases in heart rate and increases in the high-frequency HRV, an index of cardiac vagal modulation, while stimulation of a sham acupoint (1 cm to the ulnar side of P6) decreased heart rate without changing vagal outflow[30]. A comprehensive laboratory study of point specificity evaluated changes induced by stimulating several sets of acupuncture points with respect to reflex increases in BP [31]. It was discovered that EA at P5-P6,

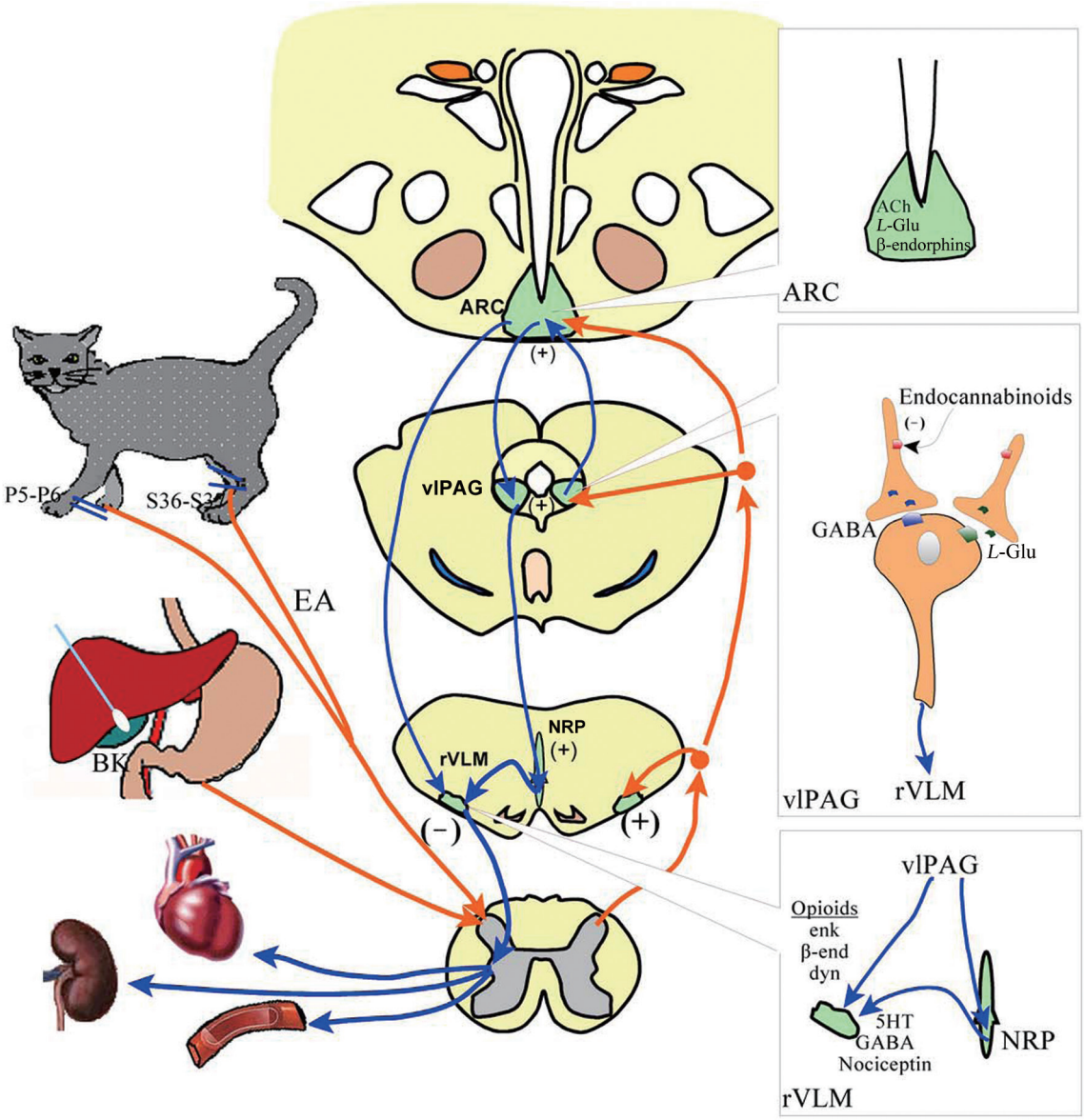


Fig. 1. Neuroendocrine modulation of the cardiovascular centers by electroacupuncture (EA). Slices from top to bottom are hypothalamus, midbrain, medulla and spinal cord. The orange arrows are ascending neuronal pathways and the descending pathways are indicated in blue. GABA, γ-aminobutyric acid; 5HT, 5-hydroxytryptamine or serotonin; ACh, acetylcholine; *L*-Glu, glutamate; ARC, arcuate nucleus; vlPAG, ventrolateral periaqueductal gray; rVLM, rostral ventrolateral medulla; NRP, nucleus raphé obscurus; enk, enkephalins; β-end, β-endorphins; dyn, dynorphins. Reproduced and modified from Li *et al*. 2010[23].

ST36-ST37, LI4-LU7 and LI10-LI11 reduced the pressor response while LI6-LI7 and kidney meridian (K)1-UB67 did not [31]. The authors then looked at the neural activity in the rVLM evoked by stimulating these points and found that EA at P5-P6, ST36-ST37 and LI10-LI11 induced a significantly higher evoked activity in the rVLM than the other points. In a study examining the specific effects of manual acupuncture and different EA intensities at P5-P6, Zhou *et al*. found that thirty minutes of low-current, low-frequency (0.3–0.5 mA, 2 Hz) EA at these points significantly decreased reflex pressor responses as did two minutes of manual acupuncture at P5-P6 every 10 min for 30 min, while needle insertion without stimulation or higher frequencies of stimulation (40 Hz, 100 Hz) did not influence the sympathoexcitatory reflexes [32]. Thus, it appears that P6 is an important acupoint that can be used to treat cardiovascular disease and often times is paired with P5 using 2 Hz electrostimulation. It also appears that combining these points with EA at ST36-ST37 may be ben-

eficial[31, 32].

## 4 Myocardial ischemia

Myocardial ischemia, cell starvation resulting from a lack of blood flow to the heart muscle, can lead to cell death or infarction[33]. The severity and duration of post-ischemic changes depend on the length and intensity of the ischemia and can ultimately lead to heart failure[34]. Norepinephrine, a neurotransmitter released by the sympathetic nervous system, can increase the extent of ischemia by increasing myocardial oxygen demand and causing coronary vasoconstriction[35]. Increases in sympathetic activation during myocardial ischemia can also lead to arrhythmias and increase infarct size[36]. Preventing ischemic events, therefore, is an important goal in the management of patients with coronary artery disease.

A recent laboratory trial by Zhou and coworkers examined the response to EA in a model of myocardial ischemia-reperfusion (MIR) injury[37]. To induce ischemia, six different groups of rabbits had the left anterior descending (LAD) artery occluded for 30 min followed by 90 min of reperfusion. One group had no EA, one had EA at P5-P6 (2 Hz for 30 min) immediately after onset of LAD occlusion, and one group (for control) had needles inserted at P5-P6 after occlusion with no stimulation. The other three groups had EA at P5-P6 after the onset of occlusion and were pretreated with either naloxone (non-selective opioid inhibitor), chelerythrine [a non-selective protein kinase C (PKC) inhibitor], or naloxone and chelerythrine together. EA significantly improved MIR-induced systolic and diastolic left ventricular dysfunction, lowered heart rate and the RPP, attenuated ST segment elevation during ischemia, reversed ST elevation to baseline after 90 min of reperfusion and reduced infarct size and arrhythmia scores. Control acupuncture had no effect. Administration of either naloxone or chelerythrine separately as a pretreatment to EA, blocked the infarct reduction and the anti-arrhythmic effect was partially reversed. Both drugs given together completely eliminated the anti-arrhythmic effect of EA. The increase in interstitial norepinephrine associated with MIR was suppressed by 40% in the EA group while no suppression was observed in the controls. Once again, this reduction was partially blocked by either naloxone or chelerythrine given separately as a pretreatment and completely eliminated when they were administered together. The authors concluded that EA reduces ischemia-reperfusion injury through both opioid and PKC-dependent mechanisms and has the potential to play an important role in the clinical treatment of cardiac ischemia.

In contrast, another animal study using rats did not find EA at P5-P6 to be cardioprotective[38]. In this study, similar EA protocols were used, although EA was started 5 min prior to LAD occlusion rather than immediately after onset of occlusion as in Zhou's study[37]. EA did not alter heart rate, arrhythmias or infarct size. Unlike studies showing cardioprotective effects[37, 39], there was no change in heart rate, BP or RPP in the EA group compared to the control group after the onset of occlusion thus eliminating the potential for EA to reduce myocardial oxygen demand and ameliorate ischemia, which EA is capable of doing in ischemia exacerbated by sympathoexcitatory reflex stimulation[6].

In human trials, early work by Ballegard demonstrated that three weeks of manual acupuncture (seven treatments) at P6, ST36, and urinary bladder meridian (BL)14 in normotensive patients with >50% coronary stenosis, positive stress tests and severe refractory angina, significantly increased cardiac work capacity, expressed as difference in RPP comparing rest to maximal exercise as well as maximal RPP during exercise compared to sham (outside meridians, same dermatome) [40]. In this same study they observed no decrease in angina attacks or nitroglycerin consumption. A subsequent study using the same active acupuncture and sham protocol in patients with moderate angina revealed an increase in exercise tolerance and delayed onset of chest pain only in the acupuncture group[41]. Both the acupuncture and sham groups, however, reduced angina and nitroglycerin consumption by 50%. Ballegaard *et al*. also conducted a two-year prospective, non-randomized trial to explore the cost savings potential of acupuncture followed by acupressure as part of a lifestyle program incorporating stress reduction, Shiatsu massage and healthy eating for patients with severe angina[42]. Of the 69 patients followed in this study, 49 were candidates for coronary bypass grafting (CABG) while the other 20 had been rejected for surgery. After following patients for two years, researchers compared their endpoint findings with those of a large prospective, randomized trial comparing CABG with percutaneous transluminal coronary angioplasty (PTCA). The incidence of death and myocardial infarction was 21% among the patients undergoing CABG, 15% among the patients undergoing PTCA and 7% among acupuncture

patients. No significant difference in pain relief was found in the three groups. Hospital stays were reduced by 90% and invasive treatment (angioplasty and bypass) by 61%. The researchers estimated that this program produced an approximate cost savings of $12 000 per patient. Another five-year study saved $32 000 per patient over the course of the project and demonstrated a 90% reduction in hospitalization and a 70% reduction in surgery[43]. An investigation by Richter *et al*. demonstrated that manual acupuncture (manipulated only once upon insertion) at P6, heart meridian (HT)5, UB15, UB20 and ST36 administered three times each week for 30 min for four weeks reduced the number of anginal attacks, intensity of pain and ST segment depression compared with a tablet placebo. They also observed an increased exercise threshold for angina but no improvement in maximal workload [44]. Antianginal medications remained constant over the duration of the study.

In conclusion, research conducted in patients with symptomatic coronary artery disease supports the possibility that acupuncture in situations associated with demand-induced ischemia can reduce both the intensity and frequency of anginal attacks, improve quality of life and is cost-effective[42–44]. Interestingly, these clinical improvements were gained using manual acupuncture with little manipulation and conducted prior to recent work demonstrating the cardiovascular benefits of using EA at P5-P6 and ST36-ST37 in non-ischemic patients, which include increasing maximal workload and reducing BP, RPP and sympathoexcitatory reflex responses[29]. We hypothesize that using these points on ischemic patients would produce even greater benefit; however, research to confirm this postulate is needed.

## 5 Hypertension

A large study examining data from 14 international trials on patients with either unstable angina/non-ST elevation myocardial infarction and/or percutaneous coronary intervention showed that 59% of females and 39% of males had hypertension[45]. There is a general agreement that overactivity of the sympathetic nervous system commonly initiates and sustains BP elevation in patients with essential hypertension[46]. Hypertension also can be caused by overactivity of the renin-angiotensin-aldosterone system (RAAS)[47, 48]. This hormonal system is responsible for regulating BP and fluid balance in the body. Regulation of one or both of these systems has been the cornerstone of hypertension pharmacological interventions for decades[49]. Unfortunately, many patients with hypertension require two or more drugs for optimal control[49] and people often become non-compliant due to adverse side-effects[50, 51]. Recently a preliminary study has suggested that acupuncture reduces elevated BP in hypertensive patients by reducing sympathetic overactivity and modulating the RAAS suggesting that this therapy may serve as a viable option for some patients[52].

A few high quality trials examining the effect of acupuncture and EA have been conducted, but their results have not been universally consistent. In studies using acupuncture as an adjunct to patients on anti-hypertensive medications, the results have been encouraging. Yin *et al*. examined the use of individualized manual acupuncture versus non-invasive sham as an add-on therapy for hypertensive patients concurrently treated with various anti-hypertensive medications [53]. Patients received three to four treatments per week for eight weeks. A significant reduction in both systolic and diastolic BP was observed in the acupuncture compared to sham group. Flachskampf *et al*. also compared individualized treatments to sham. However in this study, the sham was invasive and applied to acupuncture points believed not to influence hypertension[54]. Of the 160 subjects in this study, all but 35 were on some type of anti-hypertensive medication and each received 22 manual treatments over six weeks. A significant difference in post treatment mean systolic and diastolic BP between the active and sham acupuncture groups was observed at the end of treatment. This finding was consistent in both medicated and non-medicated groups.

Studies conducted on non-medicated patients have yielded more varied results. Kim *et al*. found that manual stimulation involving insertion only at P6, ST36 two times a week for eight weeks reduced nocturnal diastolic BP when compared to sham (1 cm lateral to verum points and superficially inserted) [55]. There were no acupuncture-associated responses in the diurnal BP. Likewise, the Stop Hypertension with the Acupuncture Research Program (SHARP) trial compared manually stimulated individualized and standard acupuncture to invasive sham at non-acupuncture points applied twice weekly for six to eight weeks (12 total treatments) [56]. No difference between groups was observed. Recently, a preliminary study examining point specific responses as the hypertension control found that applying EA at P5-P6 and ST36-ST37 once weekly for eight weeks

reduced peak and average systolic and peak diastolic BP by 5 mmHg or more in 70% of patients while EA at LI6-LI7 and GB37-GB39 did not consistently lower BP [52]. More interestingly, when patients who had no decrease in BP in the LI/GB treated group were allowed to cross-over into the P/ST group, the investigators observed an average decrease in peak systolic blood pressure (SBP) of 16 mmHg and 6 mmHg in average SBP confirming that these BP changes were point specific. This study also reported that plasma norepinephrine, renin activity and aldosterone were reduced in responders but not in non-responders, suggesting that EA may lower elevated BP by reducing sympathetic outflow and the RAAS. Baseline norepinephrine and renin activity pre-EA were higher in responders versus non-responders, suggesting that patients with elevated sympathetic and renin activities are more responsive. A small subset of patients who responded to the initial eight weeks of treatment participated in a maintenance arm of the study. EA reinforcement treatment at P5-P6 and ST36-ST37 once per month maintained the reduction in BP over the six-month period. Interestingly, when EA is used on normotensive patients, reductions in resting BPs are not seen [29].

In a recent meta-analysis examining randomized controlled trials using real versus sham acupuncture for the treatment of hypertension, four trials qualified for analysis as they were considered higher quality with Jadad scores of 4–5[57]. Jadad evaluates the general quality of research trials, including randomization procedures, blinding, description of withdrawals and drops and methods of both randomization and blinding[58]. This meta-analysis suggested that acupuncture significantly lowers SBP and diastolic blood pressure (DBP) in patients taking antihypertensive medications while only lowering DBP in unmedicated patients. The majority of these patients received individualized manual acupuncture treatment according to TCM principles to guide the selection of acupoints.

Inconsistent findings between studies are not surprising given that varied acupuncture protocols have been administered. Stimulation of a variety of points falls in line with TCM theory, which bases point prescriptions on individualized pattern diagnosis rather than an all-encompassing clinical diagnosis and selection of standardized points [59]. A single diagnosis like hypertension can have several different underlying Chinese pattern diagnoses, thus warranting different point prescriptions for optimal treatment. Although clinically relevant for individual practitioners, using this theory in clinical trials is challenging at best, since a variety of different acupoints may be stimulated from patient to patient. Likewise, studies assessing reliability of inter-practitioner pattern diagnoses have shown there is little agreement on diagnosis, diagnosis related variables and/or point prescriptions[60–63]. Although debate continues over the use of individualized versus standardized point specific protocols, the future use of standardized acupoints in clinical trials, including for example EA at 2 Hz for 30 min at P5-P6 and ST36-ST37 improves reproducibility and efficiency in research as well as practical application for practitioners in the clinical setting.

## 6 Arrhythmias

Cardiac arrhythmias have been implicated both as a risk factor and an etiology for sudden cardiac death, the most lethal manifestation of heart disease [64]. Ischemia and increases in sympathetic activity are causal factors for both supraventricular and ventricular arrhythmias [65–67]. Given that acupuncture reduces ischemia and inhibits sympathetic outflow, it could also be used as a modality in the treatment of cardiac arrhythmias that are related to augmented sympathetic outflow and sympathetic/parasympathetic imbalance [6, 19, 44, 52, 68].

In early experimental models, it was demonstrated that EA at P6 and ST36 reduced premature ventricular contractions (PVCs) and ventricular tachycardia [69]. Likewise, reperfusion-related ventricular tachycardia in rats was reduced by EA at P5-P6 in association with a decrease in myocardial oxygen demand, measured as a reduced RPP and decreased ST segment elevation [70]. A recent meta-analysis by Kim *et al*. was published examining the effectiveness of acupuncture in the treatment of cardiac arrhythmias [71]. This review evaluated the response of paroxysmal supraventricular tachycardia (PSVT), PVCs and atrial fibrillation (AFib) to acupuncture. One trial found that long-term acupuncture treatment for PSVT had similar rates of conversion to sinus rhythm as did diltiazem [72]. Three trials demonstrated that acupuncture was effective in reducing the number of PVCs [73–75]. Two studies suggested a beneficial effect of acupuncture in conversion from AFib to sinus rhythm [76, 77]. Specifically, the Lomuscio trial examined the role of acupuncture in preventing arrhythmic recurrences after cardioversion in patients with AFib [76]. Eighty patients with persistent AFib who un-

derwent electrical cardioversion were randomized to receive active acupuncture (P6), sham acupuncture (needling outside of meridian), amiodarone or no antiarrhythmic medication. Overall, AFib reoccurred in 44% of patients. In patients receiving acupuncture, AFib reoccurred in only 35% compared to 69% in sham and 54% in the no drug group. In the amiodarone group, 27% developed recurrent AFIb. The study concluded that active acupuncture was almost as good as amiodarone in reducing the reoccurrence of AFib after cardioversion. All patients were on anticoagulants and no serious side effects, like bleeding, occurred during acupuncture. Given that the majority of studies were low methodological quality and included small sample sizes, Kim *et al*. cautiously concluded that acupuncture may be an effective treatment for arrhythmias. Although it is agreed that additional high quality studies in this area are warranted, it appears that acupuncture could be used as a complement or possibly in place of antiarrhythmic drugs.

## 7 Heart failure

Left ventricular dysfunction begins with injury to, or stress on, the myocardium and is generally a progressive process, even in the absence of a new identifiable insult to the heart [78]. Increased sympathetic nerve activity is a characteristic feature of heart failure. A strong link has been demonstrated between the level of cardiac sympathetic outflow in patients with heart failure and the development of ventricular arrhythmias, progressive left ventricular deterioration, and reduced survival[79–81]. Other consequences of the increase in sympathetic tone include an increase in local and circulating concentrations of norepinephrine, which induces cardiac myocyte hypertrophy either directly or secondarily through activation of the RAAS[82, 83]. Norepinephrine also is directly toxic to myocardial cells [84, 85].

These deleterious effects are mitigated by the use of β-adrenergic blockade or combined β- and α-adrenergic blockade, i.e. drugs that block the activity of the sympathetic nervous system [86, 87]. Once thought to be contraindicated in the treatment of heart failure due to the short-term support the sympathetic nervous system provides by partly restoring cardiac output and optimizing the distribution of limited blood flow to vital organs, β blockade is now known to prolong life and improve symptoms and quality of life[88–90]. In fact, the benefits of β-blockers are greatest in patients with the highest level of sympathetic activation[91]. Given that acupuncture works by inhibiting sympathetic outflow and has been shown to reduce levels of norepinephrine, renin and aldosterone[57], it has the potential to reduce morbidity and mortality associated with increased sympathetic activity in heart failure.

Only a few small human trials examining the effect of acupuncture in heart failure are available. Middlekauff *et al.* (2002) examined the effect of 15 min of manual acupuncture at LI4, liver meridian (LV)3 and P6 versus non-acupoint stimulation and no needle stimulation on sympathetic activation during mental stress in advanced heart failure patients [92]. They demonstrated that acupuncture eliminated the increase in muscle sympathetic nerve activity seen in mental stress testing while the control did not and concluded that the immediate effect of acupuncture is to attenuate sympathoexcitation in advanced heart failure patients. Another trial employing acupuncture twice weekly found that it increased submaximal exercise tolerance, increased HRV, decreased the inflammatory cytokine tumor necrosis factor alpha (TNF-α) and improved patient satisfaction in patients with class II-IV heart failure, while the non-penetrating, telescoping placebo needle placed 2 mm outside the verum acupoint placement was ineffective[93]. Left ventricular ejection fraction and maximal exercise capacity were, however, unchanged.

A recent, interesting animal study employed EA at P5-P6 and LI6-LI7 in rats with heart failure[94]. In this experiment, heart failure was induced by coronary artery ligation, and EA intervention began four weeks later. Subjects were divided into three groups: EA at P5-P6, EA at LI6-LI7 (control) or no EA. EA was delivered once daily for seven days at 2 Hz for 30 min. For comparison of the effects of EA on heart function, metoprolol was administered for seven days in the medicated control group. One week of EA significantly improved ejection fraction, left ventricular fractional shortening, and reversed enlargement of left ventricular end-diastolic and systolic dimension as well as reduced infarct size compared to control and no EA rats. These results were similar to those observed with metoprolol although the reduction in infarct size was slightly smaller. This laboratory study is the first of its kind to directly examine EA effects on progression of heart failure and the improvement observed in cardiac function, remodeling and infarct size.

Given the lack of adequately powered, randomized, blinded clinical trials on the effectiveness of acupunc-

ture in heart failure, it is hard to draw a concrete conclusion on its use in the clinical setting. However, given that increased sympathetic activity is deleterious in heart failure and EA at P5-P6 and ST36-ST37 has been shown to modulate the autonomic nervous system, its use should be considered.

## 8 HRV

HRV is a measure of the naturally occurring beat-to-beat changes in heart rate[95]. HRV analysis can serve as a relatively reliable marker for parasympathetic (vagal) tone and to a lesser extent, sympathetic activity[96, 97]. Individuals at rest showing higher vagal tone than average tend to be more resilient to stress, adapting well across a number of different situations[98]. Specific to heart disease, low levels of vagal modulation may not adequately counteract sympathetic stimulation, leaving the heart vulnerable to ventricular arrhythmias and sudden cardiac death, especially in heart failure[99–101]. Given that EA has been shown to modulate both sympathetic and parasympathetic activity[15, 21], one would expect that it might alter HRV in heart failure patients.

A meta-analysis examining the effect of acupuncture on HRV concluded that acupuncture elicited no substantial impact[102]. In a more recent meta-analysis of 14 studies, the authors reported moderate support for acupuncture's effect on decreasing low frequency (LF, a low grade marker of sympathetic tone) and the sympathovagal balance marker LF/HF (high frequency, a marker of vagal tone) in non-healthy individuals and LF in healthy subjects[68]. One group of the non-healthy individuals included individuals with heart disease[103]. This decrease in LF activity led the authors to suggest that acupuncture may modulate parasympathetic outflow. ST36 and P6 seemed to be key points in modulating HRV although this was stated with caution because information on needling technique is lacking. In a study by Sakatani *et al.* (2010) not included in this last meta-analysis, acupuncture at LI4 but not sham acupuncture (2–3 mm outside of LI4) decreased the LF/HF ratio, and increased the HF power again indicating a shift to parasympathetic dominance [104].

Manual acupuncture applied three times per week for 12 weeks at P4, P6, HT7, ST36, spleen meridian (SP)6, Ren17, LI4 and LV3 in patients with known heart disease revealed an increased HRV during mental arithmetic stress (rapid mental math calculations) more than a sham (off channel, non-penetrating) group[105]. The high frequency component (indicative of parasympathetic activity) was 17% higher in the acupuncture group. These findings suggest that acupuncture inhibits the stress response in heart disease patients by modulating parasympathetic activity. In a cross-over study by Kim *et al*., manual acupuncture at LI4 and SP6 induced a significant decrease in LF/HF ratio and an increase in HF power compared to a non-penetrating sham at the same points[106]. Li *et al*. found similar results when using acupuncture at P6 and LI4 and a similar sham[107]. Similarly, Huang *et al*. found that acupuncture at P6 increased HF and decreased LF/HF markers compared to off-channel sham or no treatment [30].

Chinese medical theory has long touted the ability of acupuncture to balance the body and achieve homeostasis[59], a concept that appears to be supported by acupuncture's action on the autonomic nervous system. Given that the majority of these studies support the use of acupuncture to modulate HRV, its use may be beneficial in patients with suspected sympathetic overactivity or parasympathetic dysfunction. Although there is no consistency in the acupoints used, it appears that P6 may be one of the important points to use for modulating HRV. Further high quality research is warranted to confirm more point specific protocols and to relate changes in HRV with arrhythmias in susceptible patients.

## 9 Conclusion

Although the number of high quality studies evaluating the efficacy of manual acupuncture or EA to treat symptoms of heart disease is small, it appears that this ancient therapy may be beneficial in several cardiovascular disease conditions. EA appears to be useful in patients with mild to moderate hypertension, whether or not anti-hypertensive drugs are used. Certainly it can provide a treatment alternative to those individuals who elect to remain unmedicated due to unwanted side effects. Given that EA inhibits sympathetic overactivation, it might be useful to prevent or slow the progression in heart failure. In patients with myocardial ischemia, acupuncture also may reduce angina and the need for nitroglycerin and when integrated into a holistic program, may produce cost savings. EA also may help treat arrhythmias. In this regard, it may be useful as a deterrent to the recurrence of atrial fibrillation after cardioversion. As an added benefit, acupuncture may modulate the autonomic nervous system, thus reducing the

risk of sudden cardiac death. Given the array of possible benefits, lack of side effects (0.13% incidence)[108] and the relatively low cost, the use of acupuncture and more specifically EA, may be warranted.

In terms of treatment protocols, it appears that P6 is the most common point used in the treatment of cardiovascular conditions, probably because the underlying sensory neural pathways stimulated project to cardiovascular regulatory regions of the brain stem[30]. Given that the use of manual acupuncture can vary between clinicians, using EA at P5-P6 at 2 Hz for 30 min rather than just manual P6 stimulation will likely reduce interpractitioner variability and lead to more consistent clinical outcomes. Although more research is needed to determine what other points may or may not provide an added benefit, at this time it appears that employing EA at ST36-ST37 in conjunction with P5-P6 might provide optimal clinical cardiovascular responses. The frequency of treatments has not been well studied, but it appears that EA once or twice weekly for four to eight weeks should be adequate to achieve desired clinical outcomes and then once monthly treatments may be enough to sustain benefit.

* * *

**ACKNOWLEDGEMENTS:** We would like to give special thanks to Dr. Peng Li for his foundational research work in this field and to Stephanie Tjen-A-Looi, PhD for her assistance on this manuscript.

## REFERENCES

1 Piepoli MF, Corrà U, Adamopoulos S, Benzer W, Bjarnason-Wehrens B, Cupples M, Dendale P, Doherty P, Gaita D, Höfer S, McGee H, Mendes M, Niebauer J, Pogosova N, Garcia-Porrero E, Rauch B, Schmid JP, Giannuzzi P. Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery: A Policy Statement from the Cardiac Rehabilitation Section of the European Association for Cardiovascular Prevention & Rehabilitation. Endorsed by the Committee for Practice Guidelines of the European Society of Cardiology. Eur J Prev Cardiol 2012; 21: 664–681.

2 Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho PM, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, McDermott MM, Meigs JB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Rosamond WD, Sorlie PD, Stafford RS, Turan TN, Turner MB, Wong ND, Wylie-Rosett J; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2011 update: a report from the American Heart Association. Circulation 2011; 123: e18–e209.

3 Goldschmidt-Clermont PJ, Dong C, Seo DM, Velazquez OC. Atherosclerosis, inflammation, genetics, and stem cells: 2012 update. Curr Atheroscler Rep 2012; 14: 201–210.

4 Rauscher FM, Goldschmidt-Clermont PJ, Davis BH, Wang T, Gregg D, Ramaswami P, Pippen AM, Annex BH, Dong C, Taylor DA. Aging, progenitor cell exhaustion, and atherosclerosis. Circulation 2003; 108: 457–463.

5 Zhang X. Acupuncture: Review and Analysis of Reports on Controlled Clinical Trials. World Health Organization 2002.

6 Li P, Pitsillides KF, Rendig SV, Pan HL, Longhurst JC. Reversal of reflex-induced myocardial ischemia by median nerve stimulation: a feline model of electroacupuncture. Circulation 1998; 97: 1186–1194.

7 Tjen-A-Looi SC, Fu LW, Zhou W, Syuu Z, Longhurst JC. Role of unmyelinated fibers in electroacupuncture cardiovascular responses. Auton Neurosci 2005; 118: 43–50.

8 Zhou W, Fu LW, Tjen ALSC, Li P, Longhurst JC. Afferent mechanisms underlying stimulation modality-related modulation of acupuncture-related cardiovascular responses. J Appl Physiol 2005; 98: 872–880.

9 Tjen-A-Looi SC, Li P, Longhurst JC. Midbrain vlPAG inhibits rVLM cardiovascular sympathoexcitatory responses during electroacupuncture. Am J Physiol Heart Circ Physiol 2006; 290: H2543–H2553.

10 Li P, Tjen-A-Looi SC, Longhurst JC. Excitatory projections from arcuate nucleus to ventrolateral periaqueductal gray in electroacupuncture inhibition of cardiovascular reflexes. Am J Physiol Heart Circ Physiol 2006; 290: H2535–H2542.

11 Huang W, Pach D, Napadow V, Park K, Long X, Neumann J, Maeda Y, Nierhaus T, Liang F, Witt CM. Characterizing acupuncture stimuli using brain imaging with FMRI--a systematic review and meta-analysis of the literature. PLoS One 2012; 7: e32960.

12 Crisostomo MM, Li P, Tjen ALSC, Longhurst JC. Nociceptin in rVLM mediates electroacupuncture inhibition of cardiovascular reflex excitatory response in rats. J Appl Physiol 2005; 98: 2056–2063.

13 Huangfu D, Li P. The inhibitory effect if ARC-PAG-NRO system on the ventrolateral medullary neurons in the rabbit. Chin J Physiol Sci 1988; 4: 115–125.

14 Tjen-A-Looi SC, Phan NT, Longhurst JC. Nitric oxide modulates sympathoexcitatory cardiac-cardiovascular reflexes elicited by bradykinin. Am J Physiol Heart Circ Physiol 2001; 281: H2010–H2017.

15 Zhou W, Longhurst JC. Neuroendocrine mechanisms of acupuncture in the treatment of hypertension. Evid Based Complement Alternat Med 2012; 2012: 878673.

16 Li P, Tjen-A-Looi S, Longhurst JC. Rostral ventrolateral medullary opioid receptor subtypes in the inhibitory effect of electroacupuncture on reflex autonomic response in cats. Auton Neurosci 2001; 89: 38–47.

17 Guo ZL, Longhurst JC. Expression of c-Fos in arcuate nucleus induced by electroacupuncture: relations to neurons containing opioids and glutamate. Brain Res 2007; 1166: 65–76.

18 Zhou W, Fu LW, Guo ZL, Longhurst JC. Role of glutamate in the rostral ventrolateral medulla in acupuncture-related modulation of visceral reflex sympathoexcitation. Am J Physiol Heart Circ Physiol 2007; 292: H1868–H1875.

19 Tjen-A-Looi SC, Li P, Longhurst JC. Processing cardiovascular information in the vlPAG during electroacupuncture in rats: roles of endocannabinoids and GABA. J Appl Physiol 2009; 106: 1793–1799.

20 Moazzami A, Tjen-A-Looi S, Guo Z, Longhurst J. Serotonergic projections from nucleus raphe pallidue to rostral ventrolateral medulla participate in acupuncture modulation of cardiovascular excitatory relexes. Faseb J 2007; 582: 23.

21 Tjen-A-Looi SC, Li P, Li M, Longhurst JC. Modulation of cardiopulmonary depressor reflex in nucleus ambiguus by electroacupuncture: roles of opioids and gamma-aminobutyric acid. Am J Physiol Regul Integr Comp Physiol 2012; 302: R833–R844.

22 Li P, Tjen-A-Looi SC, Guo ZL, Longhurst JC. An arcuate-ventrolateral periaqueductal gray reciprocal circuit participates in electroacupuncture cardiovascular inhibition. Auton Neurosci 2010; 158: 13–23.

23 Li P, Tjen-A-Looi SC, Longhurst JC. Nucleus raphe pallidus participates in midbrain-medullary cardiovascular sympathoinhibition during electroacupuncture. Am J Physiol Regul Integr Comp Physiol 2010; 299: R1369–R1376.

24 Fu LW, Longhurst JC. Electroacupuncture modulates vlPAG release of GABA through presynaptic cannabinoid CB1 receptors. J Appl Physiol 2009; 106: 1800–1809.

25 Moazzami A, Tjen ALSC, Guo ZL, Longhurst JC. Serotonergic projection from nucleus raphe pallidus to rostral ventrolateral medulla modulates cardiovascular reflex responses during acupuncture. J Appl Physiol 2010; 108: 1336–1346.

26 Tjen-A-Looi SC, Li P, Longhurst JC. Role of medullary GABA, opioids, and nociceptin in prolonged inhibition of cardiovascular sympathoexcitatory reflexes during electroacupuncture in cats. Am J Physiol Heart Circ Physiol 2007; 293: H3627–H3635.

27 Tjen-A-Looi SC, Guo ZL, Li M, Longhurst JC. Medullary GABAergic mechanisms contribute to electroacupuncture modulation of cardiovascular depressor responses during gastric distention in rats. Am J Physiol Regul Integr Comp Physiol 2013; 304: R321–R332.

28 Gobel FL, Norstrom LA, Nelson RR, Jorgensen CR, Wang Y. The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. Circulation 1978; 57: 549–556.

29 Li P, Ayannusi O, Reid C, Longhurst JC. Inhibitory effect of electroacupuncture (EA) on the pressor response induced by exercise stress. Clin Auton Res 2004; 14: 182–188.

30 Huang ST, Chen GY, Lo HM, Lin JG, Lee YS, Kuo CD. Increase in the vagal modulation by acupuncture at neiguan point in the healthy subjects. Am J Chin Med 2005; 33: 157–164.

31 Tjen-A-Looi SC, Li P, Longhurst JC. Medullary substrate and differential cardiovascular responses during stimulation of specific acupoints. Am J Physiol Regul Integr Comp Physiol 2004; 287: R852–R862.

32 Zhou WY, Tjen ALSC, Longhurst JC. Brain stem mechanisms underlying acupuncture modality-related modulation of cardiovascular responses in rats. J Appl Physiol 2005; 99: 851–860.

33 Remme WJ. Overview of the relationship between ischemia and congestive heart failure. Clin Cardiol 2000; 23: IV4–IV8.

34 Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. Circulation 1982; 66: 1146–1149.

35 Hashimoto M, Okamoto M, Yamagata T, Yamane T, Watanabe M, Tsuchioka Y, Matsuura H, Kajiyama G. Abnormal systolic blood pressure response during exercise recovery in patients with angina pectoris. J Am Coll Cardiol 1993; 22: 659–664.

36 Harris AS OH, Bocage AJ. The induction of arrhyuthmias by sympathetic activity before and after occlusion of a coronary artery in canine heart. J Electrocardiol 1971; 4: 434–443.

37 Zhou W, Ko Y, Benharash P, Yamakawa K, Patel S, Ajijola OA, Mahajan A. Cardioprotection of electroacupuncture against myocardial ischemia-reperfusion injury by modulation of cardiac norepinephrine release. Am J Physiol Heart Circ Physiol 2012; 302: H1818–H1825.

38 Dow J, Painovich J, Hale SL, Tjen ALS, Longhurst JC, Kloner RA. Absence of actions of commonly used Chinese

herbal medicines and electroacupuncture on myocardial infarct size. J Cardiovasc Pharmacol Ther 2012; 17: 403–411.

39 Gao J, Fu W, Jin Z, Yu X. Acupuncture pretreatment protects heart from injury in rats with myocardial ischemia and reperfusion via inhibition of the beta(1)-adrenoceptor signaling pathway. Life Sci 2007; 80: 1484–1489.

40 Ballegaard S, Jensen G, Pedersen F, Nissen VH. Acupuncture in severe, stable angina pectoris: a randomized trial. Acta Med Scand 1986; 220: 307–313.

41 Ballegaard S, Pedersen F, Pietersen A, Nissen VH, Olsen NV. Effects of acupuncture in moderate, stable angina pectoris: a controlled study. J Intern Med 1990; 227: 25–30.

42 Ballegaard S, Norrelund S, Smith DF. Cost-benefit of combined use of acupuncture, Shiatsu and lifestyle adjustment for treatment of patients with severe angina pectoris. Acupunct Electrother Res 1996; 21: 187–197.

43 Ballegaard S, Johannessen A, Karpatschof B, Nyboe J. Addition of acupuncture and self-care education in the treatment of patients with severe angina pectoris may be cost beneficial: an open, prospective study. J Altern Complement Med 1999; 5: 405–413.

44 Richter A, Herlitz J, Hjalmarson A. Effect of acupuncture in patients with angina pectoris. Eur Heart J 1991; 12: 175–178.

45 Khot UN, Khot MB, Bajzer CT, Sapp SK, Ohman EM, Brener SJ, Ellis SG, Lincoff AM, Topol EJ. Prevalence of conventional risk factors in patients with coronary heart disease. JAMA 2003; 290: 898–904.

46 Oparil S, Zaman MA, Calhoun DA. Pathogenesis of hypertension. Ann Intern Med 2003; 139: 761–776.

47 Weir MR, Dzau VJ. The renin-angiotensin-aldosterone system: a specific target for hypertension management. Am J Hypertens 1999; 12: 205S–213S.

48 Gordon RD, Kuchel O, Liddle GW, Island DP. Role of the sympathetic nervous system in regulating renin and aldosterone production in man. J Clin Invest 1967; 46: 599–605.

49 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003; 42: 1206–1252.

50 Bloom BS. Continuation of initial antihypertensive medication after 1 year of therapy. Clin Ther 1998; 20: 671–681.

51 Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther 2001; 23: 1296–1310.

52 Li P, Cheng L, Liu DM, Painovich J, Vinjanury SP, Tjen-a-looi S, Longhurst JC. Long-lasting inhibitory effect of electroacupuncture in hypertensive patients - role of catecholamine, renin and angiotensin. Faseb J 2014; 28: 1140.3.

53 Yin C, Seo B, Park HJ, Cho M, Jung W, Choue R, Kim C, Park HK, Lee H, Koh H. Acupuncture, a promising adjunctive therapy for essential hypertension: a double-blind, randomized, controlled trial. Neurol Res 2007; 29 Suppl 1: S98–S103.

54 Flachskampf FA, Gallasch J, Gefeller O, Gan J, Mao J, Pfahlberg AB, Wortmann A, Klinghammer L, Pflederer W, Daniel WG. Randomized trial of acupuncture to lower blood pressure. Circulation 2007; 115: 3121–3129.

55 Kim HM, Cho SY, Park SU, Sohn IS, Jung WS, Moon SK, Park JM, Ko CN, Cho KH. Can acupuncture affect the circadian rhythm of blood pressure? A randomized, double-blind, controlled trial. J Altern Complement Med 2012; 18: 918–923.

56 Macklin EA, Wayne PM, Kalish LA, Valaskatgis P, Thompson J, Pian-Smith MC, Zhang Q, Stevens S, Goertz C, Prineas RJ, Buczynski B, Zusman RM. Stop Hypertension with the Acupuncture Research Program (SHARP): results of a randomized, controlled clinical trial. Hypertension 2006; 48: 838–845.

57 Li DZ, Zhou Y, Yang YN, Ma YT, Li XM1, Yu J, Zhao Y, Zhai H, Lao L. Acupuncture for essential hypertension: a meta-analysis of randomized sham-controlled clinical trials. Evid Based Complement Alternat Med 2014; 2014: 279478.

58 Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996; 17: 1–12.

59 Maciocia G. The Foundations of Chinese Medicine: A Comprehensive Text for Acupuncturists and Herbalists. Second Edition. Oxford: Churchill Livingston; 2005.

60 Berkeflet O, Laake P, Vollestad N. Low inter-rater reliability in traditional Chinese medicine for female infertility. Acupunct Med 2011; 29: 51–57.

61 Sung JJ, Leung WK, Ching JY, Lao L, Zhang G, Wu JC, Liang SM, Xie H, Ho YP, Chan LS, Berman B, Chan FK. Agreements among traditional Chinese medicine practitioners in the diagnosis and treatment of irritable bowel syndrome. Aliment Pharmacol Ther 2004; 20: 1205–1210.

62 Kim M, Cobbin D, Zaslawski C. Traditional Chinese medicine tongue inspection: an examination of the inter- and intrapractitioner reliability for specific tongue characteristics.

J Altern Complement Med 2008; 14: 527–536.

63 Zhang GG, Bausell B, Lao L, Handwerger B, Berman BM. Assessing the consistency of traditional Chinese medical diagnosis: an integrative approach. Altern Ther Health Med 2003; 9: 66–71.

64 Zheng ZJ, Croft JB, Giles WH, Mensah GA. Sudden cardiac death in the United States, 1989 to 1998. Circulation 2001; 104: 2158–2163.

65 Kalman JM, Munawar M, Howes LG, Louis WJ, Buxton BF, Gutteridge G, Tonkin AM. Atrial fibrillation after coronary artery bypass grafting is associated with sympathetic activation. Ann Thorac Surg 1995; 60: 1709–1715.

66 Schwartz PJ, La Rovere MT, Vanoli E. Autonomic nervous system and sudden cardiac death. Experimental basis and clinical observations for post-myocardial infarction risk stratification. Circulation 1992; 85: I77–91.

67 Wyse DG, Friedman PL, Brodsky MA, Beckman KJ, Carlson MD, Curtis AB, Hallstrom AP, Raitt MH, Wilkoff BL, Greene HL; AVID Investigators. Life-threatening ventricular arrhythmias due to transient or correctable causes: high risk for death in follow-up. J Am Coll Cardiol 2001; 38: 1718–1724.

68 Chung JW, Yan VC, Zhang H. Effect of acupuncture on heart rate variability: a systematic review. Evid Based Complement Alternat Med 2014; 2014: 819871.

69 Guo X (郭学勤), Jia R, Cao Q, Guo Z, Li P. Inhibitory effect of somatic nerve afferent impulses on the extrasystole induced by hypothalamic stimulation. Acta Physiol Sin (生理学报)1981; 33: 343–350 (Chinese, English abstract).

70 Lujan HL, Kramer VJ, DiCarlo SE. Electroacupuncture decreases the susceptibility to ventricular tachycardia in conscious rats by reducing cardiac metabolic demand. Am J Physiol Heart Circ Physiol 2007; 292: H2550–H2555.

71 Kim TH, Choi TY, Lee MS, Ernst E. Acupuncture treatment for cardiac arrhythmias: a systematic review of randomized controlled trials. Int J Cardiol 2011; 149: 263–265.

72 Wu RD (吴仁定), Lin LF. Clinical observation on weist-ankle acupuncture for treatment of paroxysmal supraventricular tachycardia. Chin Acupunct Moxibust (中国针灸) 2006; 26: 854–856 (Chinese, English abstract).

73 Liu LY (刘丽英). Clinical trial of integrated traditional and western medicine for frequent ventricular premature beat. J Emerg Tradit Chin Med (中国中医急症) 2005; 14: 619–621 (Chinese).

74 Fan ZJ (范志军), Ai BW. Clinical trail of acupuncture plus western medication for ventricular premature beat. Chin J Integr Trad West Med (中国中西医结合杂志) 2002; 22: 312–313 (Chinese).

75 Zhong C (钟晨). Observation on the effecacy of combined acupuncture and medicine in treatng verticular premature beat organic heart disease. Shanghai J Acu-Mox (上海针灸杂志) 2008; 27(5): 15–16 (Chinese, English abstract).

76 Lomuscio A, Belletti S, Battezzati PM, Lombardi F. Efficacy of acupuncture in preventing atrial fibrillation recurrences after electrical cardioversion. J Cardiovasc Electrophysiol 2011; 22: 241–247.

77 Xu HK (许宏珂), Zhang YF. Comparison between therapeutic effects of acupuncture and intravenous injection of amiodarone in the treatment of paroxymal atrial fibrillation and atrial flutter. Chin Acupunct Moxibust (中国针灸) 2007; 27: 96–98 (Chinese, English abstract).

78 Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B; American College of Cardiology; American Heart Association Task Force on Practice Guidelines; American College of Chest Physicians; International Society for Heart and Lung Transplantation; Heart Rhythm Society. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation 2005; 112: e154–e235.

79 Esler M, Kaye D. Measurement of sympathetic nervous system activity in heart failure: the role of norepinephrine kinetics. Heart Fail Rev 2000; 5: 17–25.

80 Barretto AC, Santos AC, Munhoz R, Rondon MU, Franco FG, Trombetta IC, Roveda F, de Matos LN, Braga AM, Middlekauff HR, Negrão CE. Increased muscle sympathetic nerve activity predicts mortality in heart failure patients. Int J Cardiol 2009; 135: 302–307.

81 Francis GS, Goldsmith SR, Levine TB, Olivari MT, Cohn JN. The neurohumoral axis in congestive heart failure. Ann Intern Med 1984; 101: 370–377.

82 Bristow MR, Ginsburg R, Minobe W, Cubicciotti RS, Sageman WS, Lurie K, Billingham ME, Harrison DC, Stinson EB. Decreased catecholamine sensitivity and beta-adrenergic-receptor density in failing human hearts. N Engl J Med 1982; 307: 205–211.

83 Hirsch AT, Dzau VJ, Creager MA. Baroreceptor function in congestive heart failure: effect on neurohumoral activation and regional vascular resistance. Circulation 1987; 75: IV36–48.

84 Mann DL. Inflammatory mediators and the failing heart:

past, present, and the foreseeable future. Circ Res 2002; 91: 988–98.

85 Tan LB, Jalil JE, Pick R, Janicki JS, Weber KT. Cardiac myocyte necrosis induced by angiotensin II. Circ Res 1991; 69: 1185–1195.

86 Eichhorn EJ, Heesch CM, Barnett JH, Alvarez LG, Fass SM, Grayburn PA, Hatfield BA, Marcoux LG, Malloy CR. Effect of metoprolol on myocardial function and energetics in patients with nonischemic dilated cardiomyopathy: a randomized, double-blind, placebo-controlled study. J Am Coll Cardiol 1994; 24: 1310–1320.

87 Bristow MR. Pathophysiologic and pharmacologic rationales for clinical management of chronic heart failure with beta-blocking agents. Am J Cardiol 1993; 71: 12C–22C.

88 Chadda K, Goldstein S, Byington R, Curb JD. Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. Circulation 1986; 73: 503–510.

89 Fisher ML, Gottlieb SS, Plotnick GD, Greenberg NL, Patten RD, Bennett SK, Hamilton BP. Beneficial effects of metoprolol in heart failure associated with coronary artery disease: a randomized trial. J Am Coll Cardiol 1994; 23: 943–950.

90 Olsen SL, Gilbert EM, Renlund DG, Taylor DO, Yanowitz FD, Bristow MR. Carvedilol improves left ventricular function and symptoms in chronic heart failure: a double-blind randomized study. J Am Coll Cardiol 1995; 25: 1225–1231.

91 Gilbert EM, Anderson JL, Deitchman D, Yanowitz FG, O'Connell JB, Renlund DG, Bartholomew M, Mealey PC, Larrabee P, Bristow MR. Long-term beta-blocker vasodilator therapy improves cardiac function in idiopathic dilated cardiomyopathy: a double-blind, randomized study of bucindolol versus placebo. Am J Med 1990; 88: 223–229.

92 Middlekauff HR, Hui K, Yu JL, Hamilton MA, Fonarow GC, Moriguchi J, Maclellan WR, Hage A. Acupuncture inhibits sympathetic activation during mental stress in advanced heart failure patients. J Card Fail 2002; 8: 399–406.

93 Kristen AV, Schuhmacher B, Strych K, Lossnitzer D, Friederich HC, Hilbel T, Haass M, Katus HA, Schneider A, Streitberger KM, Backs J. Acupuncture improves exercise tolerance of patients with heart failure: a placebo-controlled pilot study. Heart 2010; 96: 1396–1400.

94 Ma L, Cui BP, Shao Y, Ni B, Zhang W, Luo Y, Zhang S. Electroacupuncture improves cardiac function and remodeling by inhibition of sympathoexcitation in chronic heart failure rats. Am J Physiol Heart Circ Physiol 2014; 306: H1464–H1471.

95 Malik M, Camm AJ. Components of heart rate variability--what they really mean and what we really measure. Am J Cardiol 1993; 72: 821–822.

96 Randall DC, Brown DR, Raisch RM, Yingling JD, Randall WC. SA nodal parasympathectomy delineates autonomic control of heart rate power spectrum. Am J Physiol 1991; 260: H985–H988.

97 Gehrmann J, Hammer PE, Maguire CT, Wakimoto H, Triedman JK, Berul CI. Phenotypic screening for heart rate variability in the mouse. Am J Physiol Heart Circ Physiol 2000; 279: H733–H740.

98 Kok BE, Fredrickson BL. Upward spirals of the heart: autonomic flexibility, as indexed by vagal tone, reciprocally and prospectively predicts positive emotions and social connectedness. Biol Psychol 2010; 85: 432–436.

99 Houle MS, Billman GE. Low-frequency component of the heart rate variability spectrum: a poor marker of sympathetic activity. Am J Physiol 1999; 276: H215–H223.

100 Bonaduce D, Petretta M, Marciano F, Vicario ML, Apicella C, Rao MA, Nicolai E, Volpe M. Independent and incremental prognostic value of heart rate variability in patients with chronic heart failure. Am Heart J 1999; 138: 273–284.

101 Piccirillo G, Magri D, Naso C, di Carlo S, MoisE A, De Laurentis T, Torrini A, Matera S, Nocco M. Factors influencing heart rate variability power spectral analysis during controlled breathing in patients with chronic heart failure or hypertension and in healthy normotensive subjects. Clin Sci (Lond) 2004; 107: 183–190.

102 Lee S, Lee MS, Choi JY, Lee SW, Jeong SY, Ernst E. Acupuncture and heart rate variability: a systematic review. Auton Neurosci 2010; 155: 5–13.

103 Shi X (石现), Wang ZP, Liu KX. Effect of acupuncture on heart rate variability in coronary heart disease patients. Chin J Integr Trad West Med (中国中西医结合杂志)1995; 15: 536–538 (Chinese, English abstract).

104 Sakatani K, Kitagawa T, Aoyama N, Sasaki M. Effects of acupuncture on autonomic nervous function and prefrontal cortex activity. Adv Exp Med Biol 2010; 662: 455–460.

105 Mehta P, Polk D, Shufelt C, Kirschner-Fusaro J, Qiao Y, Ma X, Chen I, Brantman A, Kothawade K, Bairey Merz CN, Li N. A randomized controlled trial of autonomic remodeling by sympathovagal modulation in coronary heart disease. J Am Coll Cardiol 2012; 59.

106 Kim E, Cho JH, Jung WS, Lee S, Pak SC. Effect of acupuncture on heart rate variability in primary dysmenorrheic women. Am J Chin Med 2011; 39: 243–249.

107 Li Z, Wang C, Mak AF, Chow DH. Effects of acupuncture on heart rate variability in normal subjects under fatigue and non-fatigue state. Eur J Appl Physiol 2005; 94: 633–640.

108 MacPherson H, Thomas K, Walters S, Fitter M. The York acupuncture safety study: prospective survey of 34 000 treatments by traditional acupuncturists. BMJ 2001; 323: 486–487.