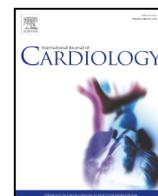




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A randomized controlled trial of acupuncture in stable ischemic heart disease patients^{☆,☆☆}

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ABSTRACT

Background: Heart rate variability (HRV) is reduced in stable ischemic heart disease (SIHD) patients and is associated with sudden cardiac death (SCD). We evaluated the impact of traditional acupuncture (TA) on cardiac autonomic function measured by HRV in SIHD patients.

Methods: We conducted a randomized controlled study of TA, sham acupuncture (SA), and waiting control (WC) in 151 SIHD subjects. The TA group received needle insertion at acupuncture sites, the SA group received a sham at non-acupuncture sites, while the WC group received nothing. The TA and SA groups received 3 treatments/week for 12 weeks. 24-Hour, mental arithmetic stress, and cold pressor (COP) HRV was collected at entry and exit, along with BP, lipids, insulin resistance, hs-CRP, salivary cortisol, peripheral endothelial function by tonometry (PAT), and psychosocial variables.

Results: Mean age was 63 ± 10 ; 50% had prior myocardial infarction. Comparison of WC and SA groups demonstrated differences consistent with the unblinded WC status; therefore by design, the control groups were not merged. Exit mental stress HRV was higher in TA vs. SA for markers of parasympathetic tone ($p \leq 0.025$), including a 17% higher vagal activity ($p = 0.008$). There were no differences in exit 24-hour or COP HRV, BP, lipids, insulin resistance, hs-CRP, salivary cortisol, PAT, or psychosocial variables.

Conclusions: TA results in intermediate effects on autonomic function in SIHD patients. TA effect on HRV may be clinically relevant and should be explored further. These data document feasibility and provide sample size estimation for a clinical trial of TA in SIHD patients for the prevention of SCD.

Condensed abstract: We conducted a randomized, single-blind trial of traditional acupuncture (TA) vs. sham acupuncture (SA) vs waiting control (WC) in stable ischemic heart disease (SIHD) patients to evaluate cardiac autonomic function measured by heart rate variability (HRV). Exit mental stress HRV was higher in the TA compared to SA group for time and frequency domain markers of parasympathetic tone (all $p \leq 0.025$), including a 17% higher vagal activity ($p = 0.008$). These data document feasibility and provide sample size estimation for an outcome-based clinical trial of TA in SIHD patients for the prevention of sudden cardiac death.

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Abbreviations: CES-D, Center for Epidemiologic Study Depression Scale; COP, cold pressor testing; DASI, Duke Activity Status Index; HOMA, homeostasis model assessment; HRV, heart rate variability; PAT, peripheral arterial tonometry; SA, sham acupuncture; SAQ, Seattle Angina Questionnaire; SIHD, stable ischemic heart disease; TA, traditional acupuncture; WC, waiting control.

HRV abbreviations: TP, total power; HF, high frequency; LF, low frequency; SDNN, standard deviation of normal RR (NN) intervals; SDANN, standard deviation of 5-minute mean RR intervals; aSDNN, average of standard deviations of normal RR intervals in 24 h; rMSSD, root-mean square of difference of successive RR intervals; pNN50, proportion of adjacent RR intervals more than 50 ms different.

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1. Introduction

Sudden cardiac death (SCD) is a significant problem in patients with stable ischemic heart disease (SIHD), and accounts for 30 to 50% of deaths in this group (~150,000 deaths annually) despite the identification and treatment of their disease [1–3]. Risk factors for SCD are similar to those for SIHD, and include cigarette smoking, hypertension, physical inactivity, hyperlipidemia, and diabetes [4,5]. The mechanism of SCD in SIHD patients is predominantly arrhythmic, and involves the cardiac autonomic nervous system (ANS) [6]. Heart rate variability (HRV), a measure of cardiac ANS function, is reduced in patients with SIHD and predictive of arrhythmic SCD [7]. Cardiac arrhythmias have been implicated both as a risk factor and an etiology for SCD, suggesting that alteration of cardiac ANS tone may provide an opportunity for reducing acute cardiac events and SCD.

Traditional acupuncture (TA) is a complementary and alternative medicine (CAM) practice with documented beneficial effects on the cardiovascular system. For example, the TA technique has been shown to significantly reduce arrhythmias [8], hypertension in an animal model [9], mental stress in humans [10], and angina pectoris in SIHD patients [11]. These effects are consistent with the hypothesis that the TA technique causes autonomic remodeling, likely by reducing sympathetic and increasing parasympathetic activity.

We undertook a randomized, controlled trial of 12 weeks of TA compared to sham acupuncture (SA) and waiting control (WC) in 151 SIHD patients with the primary outcome of cardiac autonomic function measured by HRV. We also measured the secondary outcomes of blood pressure, lipoprotein profile, and insulin resistance, salivary cortisol, vascular inflammation, endothelial function measured by peripheral arterial tonometry (PAT), and psychosocial variables.

2. Methods

2.1. Patient population

Inclusion criteria: women and men aged >18 years, with SIHD documented by prior myocardial infarction, coronary angiography, angioplasty, or coronary bypass surgery. **Exclusion criteria:** 1. unstable acute coronary syndrome; 2. congestive heart failure > New York Heart Association class III; 3. renal failure; 4. acute myocardial infarction in the preceding 3 months; 5. atrial fibrillation or a predominantly paced rhythm, significant conduction system disease, or automatic internal defibrillator; 6. prior TA; 7. HIV infection, chronic or active hepatitis or other blood-borne illness that precluded the safe use of needles; 8. renal or liver failure as clinically assessed; 9. cognitive, psychological or substance-related impairment, as clinically assessed; and 10. participation in a formal psychosocial stress management program or participation in another trial. The Institutional Review Board at Cedars-Sinai Medical Center (CSMC) approved the study; all participants gave written informed consent prior to participation.

2.2. Study design

Patients were recruited from a supervised cardiac exercise and rehabilitation program at CSMC and the surrounding community. The study design was a randomized, single-blind, attention-controlled trial. Randomization to TA, SA or WC for 12 weeks was performed via a computerized program with blocking, whereby eligible patients were grouped according to age ≥ 65 and sex (male vs female), then assigned to a treatment group accordingly. The outcome data were collected and analyzed by personnel blinded to patient treatment status. At study entry and exit, following an overnight fast, patients underwent a medical history review including cardiac risk factors, physical activity level, psychosocial assessment, and medication assessment along with PAT (Endo-PAT, Itamar, Israel) and blood sampling. HRV was collected for 24-hour Holter monitoring, 2-minute mental arithmetic and 2-min cold pressor (COP) at study entry and exit. Compliance to the TA and SA sessions was assessed by attendance. Participation in the cardiac rehabilitation exercise program was assessed by enrollment. The blood pressure protocol included 5 min of sitting quietly followed by three blood pressure measurements at one-minute intervals using a mercury sphygmomanometer, and then averaged for screening, entry and exit visits [12,13]. Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, and body mass index (BMI) calculated (kg/m^2).

2.2.1. TA, SA and WC interventions

The eight TA point protocol (Table 1, Fig. 1) was selected based upon the expertise of our team members, literature review, and the time-honored TA practice that uses multiple points. The SA points were selected by our acupuncturist team to be proximate to the TA site (to enhance the treatment blind), but not in the TA meridian, and not known to be

Table 1
TA points.

Acupoint	Anticipated effect
PC 6	HRV, PAT, ST depression, arrhythmia
PC 4	HRV, PAT, ST depression, arrhythmia
HT 7	HRV, ST depression, arrhythmia
Ren 17	HRV, ST depression, arrhythmia
LI 4	Psychosocial stress, ST depression
LIV 3	Psychosocial stress, ST depression
ST 36	HRV
SP 6	Vessel dilation

PC 6 – location: 2 cun above of the transverse crease of the wrist, between the tendons of m. palmaris longus and m. flexor carpi radialis. Method: puncture perpendicularly 0.5–0.8 in., even method.

PC 4 – location: 5 cun above of the transverse crease of the wrist, between the tendons of m. palmaris longus and m. flexor carpi radialis. Method: puncture perpendicularly 0.5–1 in., even method.

HT 7 – location: at the ulnar end of the transverse crease of the wrist, in the depression on the radial side of the tendon of m. flexor carpi ulnaris. Method: puncture perpendicularly 0.3–0.5 in., even method.

Ren 17 – location: on the anterior midline, at the level with the fourth intercostal space, midway between the nipples.

Method: puncture subcutaneously 0.3–0.5 in., even method.

LI 4 – location: on the dorsum of the hand, between the 1st and 2nd metacarpal bones, approximately in the middle of the 2nd metacarpal bone on the radial side. Method: puncture perpendicularly 0.5–1 in., reducing method.

LIV 3 – location: on the dorsum of the foot, in the depression distal to the junction of the first and second metatarsal bones. Method: puncture perpendicularly 0.3–0.5 in., reducing method.

ST 36 – location: 3 cun below St35 (it is at the lower board of the patella, in the depression lateral to the patellar ligament), one index finger-breadth from the anterior crest of the tibia, in m. tibialis anterior. Method: puncture perpendicularly 0.5–1.2 in., reinforcing method.

SP 6 – location: 3 cun directly above the tip of the medial malleolus, on the posterior border of the medial aspect of the tibia. Method: puncture perpendicularly 0.5–1 in., reinforcing method.

relevant for SIHD outcomes. Fig. 1 depicts both the active TA and sham sites. The TA and SA groups underwent three 30-minute sessions weekly while the WC received nothing for 12 weeks. All TA and SA subjects had their eyes covered with eye shades from the beginning of each session, so that they will not be able to view the treatment procedure. Following skin site cleansing with alcohol, disposable acupuncture needles (1–1.5 in. sterilized stainless steel) were inserted up to 1 in. deep through a plastic needle tube. The tube was then secured with adhesive tape to mimic SA protocol. For the SA group, pressure was initially applied with a plastic needle tube to produce a discernible sensation at non-acupuncture sites near TA acupoints but no needle was inserted, and plastic tubes were secured with adhesive tape.

TA and SA were delivered in a standardized fashion using our Acupuncture Delivery Protocol, which provided guidelines about communications between the acupuncturist and the subject. We validated our SA technique using an Acupuncture Delivery Subject Assessment questionnaire, evaluating subjective feelings and the strength of the perceived benefit of the procedure, in a pilot study among 17 SIHD patients randomized to TA vs SA which demonstrated no differences in ratings between TA and SA in this subject population.

2.2.2. Autonomic nervous system provocative testing

Patients fasted overnight and withdrew from caffeine, tobacco, and vasoactive medications for 48 h prior to provocative testing. HRV was obtained during a 24-hour period and during two provocative tests following 15 min of rest in a quiet, temperature-controlled room: (1) mental arithmetic stress test, where subjects were instructed to subtract serial 7s from a four-digit number for 2 min. Subjects were mildly harassed during this procedure; (2) COP, where subjects had a 1.5 l bag filled with 800 ml crushed ice and 200 ml of water (Temp 4 °C) placed on their forehead for 2 min. The two provocative tests were administered in a counterbalanced order, with a 10-minute recovery period between tasks.

2.2.3. Holter monitor HRV

Holter monitoring was recorded and analyzed during a 24-hour period and during provocative testing using our previously validated and published methods [13]. A 24-hour recording was considered eligible for this study if it had more than 12 h of analyzable data, had half of the nighttime and daytime periods analyzable, and if more than 50% of the recording revealed sinus rhythm. The HRV was analyzed using the Marquette® software (Marquette electronics, Milwaukee, WI). To analyze the effect of provocative stimulation on HRV, a 5-minute period of baseline HRV was compared to the 2-minute period during provocative testing, at study entry and exit.

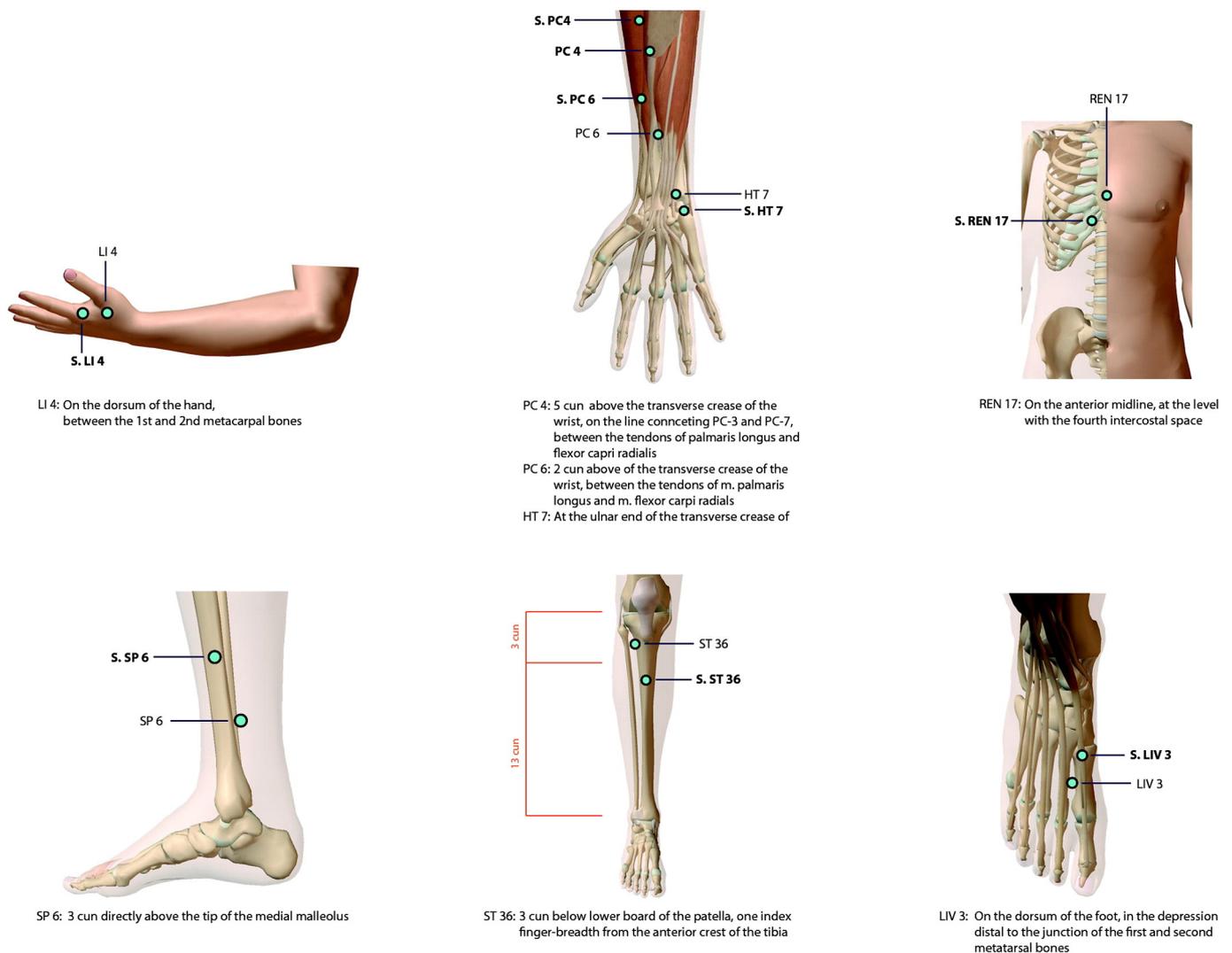


Fig. 1. TA and SA sites. Sham acupuncture sites are depicted by S prior to the TA site.

2.2.4. Blood, saliva and homeostasis model assessment (HOMA) testing

Total plasma cholesterol, triglyceride, LDL, and HDL were determined as previously published [14]. Serum glucose concentrations and plasma insulin were measured using an Elan Glucose reagent [15], and an automated immunoassay instrument and ultrasensitive insulin kit from Beckman-Coulter [16], respectively. Assays were performed in batches, and in duplicate. The degree of insulin resistance in each subject was estimated by the homeostasis model assessment (HOMA) using the formula: fasting plasma glucose level (mmol/L) times fasting plasma insulin (mU/l) divided by 22.5 according to the method by Matthews [17], where high values indicate high insulin resistance. Prior study has documented the reliability of HOMA by comparison to a euglycemic-hyperinsulinemic clamp technique [18,19]. Salivary cortisol was collected and measured at baseline, at study entry and exit.

2.2.5. Peripheral arterial tonometry (PAT)

To specifically test the effect of TA modulation on peripheral endothelial function, we performed PAT 30 min after the sympathetic stimulus of mental stress testing at study entry and exit, following an overnight fast and withdrawal of vasoactive medications for 48 h prior to testing [12,20]. Subjects were lying down supine comfortably with legs uncrossed, in a quiet, temperature-controlled room. A fitted blood pressure cuff was placed on one arm, and the PAT was performed as previously published and validated [21–24].

2.2.6. Psychosocial, angina, and functional status measures

Psychosocial variables obtained at study entry and exit included: 1) perceived environmental stress – assessed by a questionnaire previously demonstrated to be predictive of future adverse cardiac events in patients with SIHD [25]; 2) hostility – assessed by Cook–Medley Hostility Inventory [26,27]; 3) anxiety – assessed by Spielberger trait anxiety scale [28]; 4) social support – assessed by Duke Support Index [29]; and 5) quality of life – assessed by Short-Form Health Survey (SF-36) [30]. The Duke Activity Status Inventory (DASI) [31] and the Seattle Angina Questionnaire (SAQ) [32] to assess physical functioning and angina were obtained at study entry and exit. The Center for Epidemiological Studies–Depression Scale (CES-D), a self-reported, validated, reliable measure for

detecting depressive symptoms during the previous week [33,34], was also obtained at study entry and exit.

2.3. Statistical analysis

Data are presented in tables as means \pm standard deviations for continuous variables and frequencies and percentages for categorical variables. Comparison of treatment groups at entry and exit was performed using ANOVA for normally-distributed continuous data, Kruskal–Wallis test for non-normal continuous variables, and Chi-square or Fisher's exact test for categorical data. HRV outcomes are classified into two spectral domains (the time and frequency domains). A MANOVA model was fitted to test overall between-group difference in both domains. Post-hoc analysis used Bonferroni adjustment to adjust the significance level for the two spectral domain HRV outcomes hypothesized to be effected by the intervention. Since data are correlated within each domain, p-values ≤ 0.025 were regarded statistically significant for comparisons of individual HRV variables across the treatment groups. In all other comparisons, a p-value < 0.05 was required for statistical significance. Analyses were performed using SAS 9.2 (Cary, NC).

We also conduct repeated measure analysis using SAS procedure Proc Genmod for measures from the time domain (LF, HF, LF/HF, TP) and frequency domain (MeanNN, SDNN, rMSSD, pNN50). For each measurement, we used the values of the difference between exit and entry. We also conducted pairwise comparisons among three groups for the baseline, arithmetic, COP, and 24-hour tests, respectively.

3. Results

Among the 151 patients enrolled, 131 (87%) subjects completed the study. The primary reason for subject withdrawal was time commitment and inability to take time off from work or unrelated, non-cardiac illness. The Acupuncture Delivery Protocol TA and SA were well-tolerated and

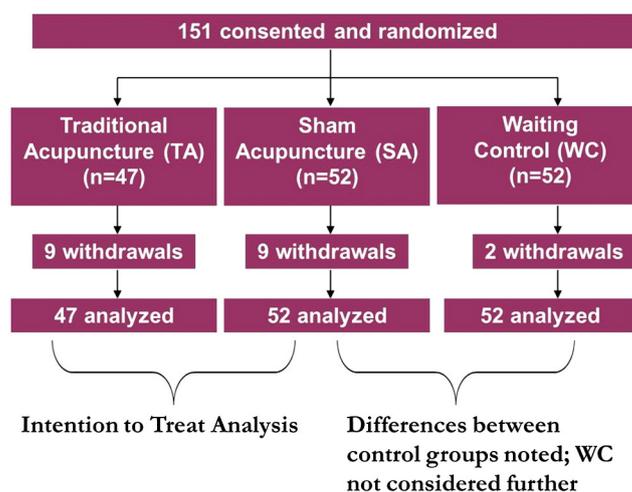


Fig. 2. Study flow diagram.

there were no adverse side effects. The subject study flow is depicted in Fig. 2.

By design, the WC group served as a second control group for the purpose of detecting a potential placebo effect in the SA group. Accordingly, initial analyses of entry and exit variables compared the two control groups (SA and WC), in order to merge the two control groups if no significant differences were found. At baseline, more people in the WC group had prior MI ($p = 0.05$), and total cholesterol was higher in the WC group compared to SA ($p = 0.05$), however no differences in LDL, HDL, or triglycerides. The WC group demonstrated important exit differences in better endothelial function (PAT: WC 2.43 ± 0.61 vs SA 2.08 ± 0.54 vs TA 2.19 ± 0.61 , $p = 0.03$) and a trend toward a greater average number of cardiac rehabilitation exercise sessions (WC 5.9 vs SA 4.3 vs TA 3.9 , $p = 0.06$) compared to the SA and TA groups, most consistent with higher health-seeking behavior related to their unblinded, waiting status. By pre-specified study design due to our experience

with improved exit behavioral health variables in a prior open label CAM trial [35], we therefore did not merge the control groups.

The entry demographic and clinical characteristics of the three groups are shown in Table 2, and demonstrate a predominantly male, older SIHD population with high rates of hypertension, dyslipidemia and obesity. A minority of patients had diabetes. Medical management of SIHD was near optimal, with high rates of statin, aspirin and anti-hypertensive medication use. The WC group had lower statin use compared to the TA group ($p = 0.03$) although total and LDL cholesterol were not different (Table 2). Over the intervention period, the number of patients who had changes in their cardiac medications (discontinued, started or dosing changes directed by their treating physician) was similar between the groups (TA = 6.4%, SA = 2%, WC = 6%, $p = 0.63$). More subjects in the SA compared to TA group were actively participating in cardiac rehabilitation during the study ($p = 0.05$) (Table 2).

Table 2
Entry baseline clinical characteristics by intervention group.

	TA (n = 47)	SA (n = 52)	WC (n = 52)	p-Value (TA vs. SA)	p-Value (TA vs. WC)	p-Value (SA vs. WC)
Age (years) (mean \pm SD)	64.9 \pm 11	63.0 \pm 11	62.5 \pm 11	0.41	0.27	0.79
Male (N, %)	32 (68%)	37 (71%)	35 (67%)	0.74	0.93	0.67
BMI (kg/m ²) (mean \pm SD)	28.7 \pm 5.3	30.5 \pm 5.7	28.5 \pm 6.5	0.13	0.63	0.35
History of hypertension (N, %)	32 (68%)	31 (59.6%)	34 (65.4%)	0.30	0.66	0.54
History of diabetes (N, %)	9 (19%)	11 (21.2%)	7 (13.5%)	0.50	0.41	0.30
Prior myocardial infarction (N, %)	24 (51%)	20 (38.5%)	30 (57.7%)	0.17	0.58	0.05
Prior angioplasty or stenting (N, %)	35 (74.5%)	38 (73.1%)	33 (63.5%)	0.73	0.22	0.36
Current smoking (N, %)	2 (4.3%)	3 (5.8%)	2 (3.8%)	0.83	0.80	0.63
Statin use (N, %)	32 (68.1%)	30 (57.7%)	23 (44.2%)	0.31	0.03	0.18
ACE-inhibitor use (N, %)	9 (19.1%)	15 (28.8%)	15 (28.8%)	0.16	0.09	0.75
Calcium channel blocker use (N, %)	13 (27.7%)	8 (15.4%)	6 (11.5%)	0.17	0.08	0.68
Beta-blocker use (N, %)	24 (51.1%)	24 (46.2%)	22 (42.3%)	0.86	0.87	1.00
DASI entry (mean \pm SD)	33.7 \pm 18.5	36.5 \pm 17.6	36.4 \pm 18.6	0.45	0.47	0.99
Resting heart rate (mean \pm SD)	65 \pm 12	65 \pm 10	62 \pm 7	0.97	0.25	0.19
Resting systolic blood pressure (mm Hg) (mean \pm SD)	130 \pm 19	128 \pm 18	125 \pm 26	0.63	0.28	0.47
Resting diastolic blood pressure (mm Hg) (mean \pm SD)	74 \pm 10	73 \pm 9	70 \pm 10	0.51	0.06	0.20
Blood sugar (mean \pm SD) ^a	103 \pm 33	106 \pm 32	101 \pm 20	0.37	0.65	0.58
HOMA (mean \pm SD)	1.82 \pm 1.70	2.12 \pm 1.45	1.93 \pm 1.39	0.14	0.53	0.42
hs-CRP (mg/L) (mean \pm SD) ^a	1.98 \pm 2.96	3.40 \pm 4.96	2.13 \pm 3.2	0.13	0.83	0.26
Total cholesterol (mean \pm SD)	168 \pm 39	158 \pm 36	179 \pm 55	0.20	0.31	0.05
LDL (mean \pm SD)	100 \pm 35	91 \pm 34	108 \pm 51	0.24	0.41	0.07
HDL (mean \pm SD)	49 \pm 17	47 \pm 16	53 \pm 16	0.70	0.28	0.12
Triglycerides (mean \pm SD)	98 \pm 49	97 \pm 55	96 \pm 65	0.79	0.48	0.55
RH-peripheral arterial tonometry (mean \pm SD)	2.37 \pm 0.47	2.36 \pm 0.62	2.39 \pm 0.54	0.92	0.87	0.38
Salivary cortisol (mean \pm SD) ^a	0.19 \pm 0.11	0.26 \pm 0.35	0.23 \pm 0.41	0.48	0.44	0.09
Actively participating in cardiac rehabilitation (N, %)	11 (23%)	18 (35%)	17 (33%)	0.22	0.31	0.84

Values expressed as either (mean \pm standard deviation) or [frequency (%)].

ACE = angiotensin converting enzyme, BMI = body mass index, DASI = Duke Activity Status Inventory, TA = traditional acupuncture, SA = sham acupuncture.

^a Wilcoxon *t*-test for determining differences between the two treatment groups.

Table 3
Exit mental stress heart rate variability.

	TA (n = 38) Mean ± SD	SA (n = 43) Mean ± SD	WC (n = 50) Mean ± SD	p-Value (TA vs. SA)	p-Value (TA vs. WC)	p-Value (SA vs. WC)
Mental stress						
<i>Frequency domain ln (ms²)</i>						
LF	6.09 ± 1.44	5.63 ± 0.97	5.97 ± 0.92	0.100	0.65	0.09
HF	5.25 ± 1.41	4.50 ± 1.00	5.08 ± 1.06	0.008	0.54	0.009
LF/HF	1.18 ± 0.16	1.28 ± 0.24	1.2 ± 0.16	0.015	0.38	0.08
TP	7.44 ± 1.24	7.00 ± 0.93	7.5 ± 0.75	0.070	0.80	0.006
<i>Time domain</i>						
Mean NN (ms)	1028 ± 166	953 ± 115	993 ± 127	0.021	0.27	0.13
SDNN (ms)	77.54 ± 43.8	59.33 ± 29.7	74.1 ± 33.6	0.033	0.85	0.02
rMSSD (ms)	38.30 ± 26.6	24.21 ± 11.7	32.5 ± 15.0	0.019	0.43	0.02
pNN50 (%)	15.26 ± 18.9	5.66 ± 8.5	9.2 ± 10.3	0.025	0.37	0.05
COP						
<i>Frequency domain ln (ms²)</i>						
LF	6.04 ± 1.59	5.81 ± 0.94	6.10 ± 1.00	0.43	0.81	0.15
HF	5.44 ± 1.57	5.01 ± 1.01	5.36 ± 0.92	0.14	0.76	0.09
LF/HF	1.14 ± 0.24	1.19 ± 0.21	1.15 ± 0.16	0.14	0.42	0.37
TP	7.70 ± 1.16	7.33 ± 0.90	7.82 ± 0.81	0.12	0.58	0.008
<i>Time domain</i>						
Mean NN (ms)	1038.55 ± 169.82	968.19 ± 121.37	1016.94 ± 124.56	0.03	0.49	0.06
SDNN (ms)	74.79 ± 39.19	63.67 ± 27.15	77.84 ± 27.29	0.23	0.23	0.010
rMSSD (ms)	38.76 ± 26.28	26.86 ± 12.23	32.54 ± 14.99	0.05	0.64	0.06
pNN50 (%)	16.01 ± 18.90	7.51 ± 9.15	10.43 ± 10.97	0.04	0.40	0.11

Abbreviations as in the text.

3.1. Primary outcome HRV results

3.1.1. 24-hour HRV

There were no differences in the time or frequency domain 24-hour HRV variables at study entry or exit among the three groups. There were no group differences in entry to exit (delta) HRV. When stratified by prior myocardial infarction, diabetes, or gender there were no significant group differences in entry or exit 24-hour HRV. There was also no difference between daytime (6 AM to 11 PM) and nighttime (11 PM to 6 AM) HRV in both men and women.

3.1.2. Provocative testing HRV

3.1.2.a. *Mental arithmetic stress HRV.* There were no differences at entry mental stress HRV between groups, however exit mental arithmetic stress HRV was significantly higher in the TA compared to the SA group, evidenced by differences in high frequency (HF), low frequency (LF)/(HF) ratio, mean NN, rMSSD, and pNN50 (Table 3). Compared to

SA, the TA HF (determined by efferent vagal activity) was 17% higher (p = 0.008, Table 3). Both rMSSD and pNN50, measures of rapid change from one heart beat to the next [36], were higher in the TA compared to the SA group (Table 3). In contrast, parasympathetic tone was lower in the SA vs. the WC group, with 11% lower vagal activity (p = 0.009). The LF/HF ratio, a measure of sympathovagal balance, was better in the TA group [8% lower compared to the SA (p = 0.015) and 2% lower compared to the WC group (p = 0.38)]. Interestingly, SDNN was lower in the SA vs. the WC group (p = 0.02) consistent with WC group improvement (Table 3). Multivariate analysis for time and frequency domain HRV during mental stress showed no significant treatment effects among the groups (Supplemental Table A).

When stratified by three frequency domain HRV thresholds previously reported to be associated with adverse cardiac prognosis (SDNN < 50 ms [37], rMSSD < 17 ms [38], and pNN50 < 4% [39]), lower risk was evident in the TA vs. SA groups at exit for two variables (Fig. 3).

3.1.2.b. *COP HRV.* Similar to arithmetic mental stress HRV, exit markers of parasympathetic tone with COP were higher with the TA compared to the SA and WC groups, although they failed to reach statistical significance (rMSSD: p = 0.05; pNN50: p = 0.04) (Table 3). Interestingly,

Frequency Domain HRV at Study Exit during Mental Arithmetic Stress Test

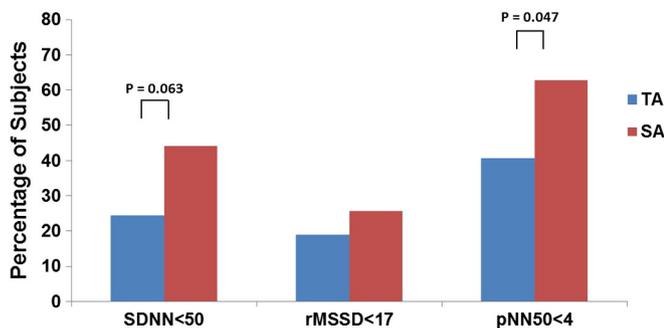


Fig. 3. Frequency domain heart rate variability at study exit during mental arithmetic stress test. When stratified by time domain HRV measures associated with adverse CV prognosis (SDNN < 50 ms [37], rMSSD < 17 ms [38], and pNN50 < 4% [39]), the percentage of subjects with an improved SDNN and pNN50 was higher with TA vs. SA at exit compared to baseline.

Table 4
Multivariate analysis of time domain HRV for baseline and exit mental arithmetic and COP testing.

Time domain HRV variable	Pairwise group comparison	Treatment differences	Standard error	p-value
Mean NN	TA vs. SA	-2.363	18.15	0.90
	TA vs. WC	-13.093	18.81	0.49
	SA vs. WC	-10.730	16.89	0.53
SDNN	TA vs. SA	9.578	4.34	0.027
	TA vs. WC	6.626	4.36	0.129
	SA vs. WC	-2.952	3.70	0.425
rMSSD	TA vs. SA	3.109	2.13	0.14
	TA vs. WC	1.887	1.97	0.34
	SA vs. WC	-1.221	2.12	0.57
pNN50	TA vs. SA	2.375	1.65	0.15
	TA vs. WC	1.692	1.51	0.26
	SA vs. WC	-0.683	1.76	0.70

Abbreviations as in the text.

COP SDNN was also lower in the SA compared to the WC group ($p = 0.01$), again consistent with WC group improvement. Comparison of the 5-minute period of baseline HRV to the 2-minute period of COP HRV at study entry and exit, demonstrated no significant differences detected between the TA vs. SA groups. Unlike mental arithmetic stress, multivariate analysis for HRV domains for COP did not demonstrate any significant treatment effects in the TA group (Supplemental Table A).

In a multivariate analysis, combined baseline, mental stress, and COP showed a strong trend to improvement in SDNN from entry to exit with TA vs. SA ($p = 0.027$) (Table 4). Again, stratification by prior myocardial infarction, diabetes, gender, or daytime vs. nighttime 24-hour HRV variables did not demonstrate any group differences in the provocative HRV outcome.

3.2. Secondary outcome results

There were no group differences between TA vs. SA for exit resting heart rate, blood pressure, lipid profile, HOMA, hs-CRP, salivary cortisol, PAT, or psychosocial variables.

4. Discussion

The current study results demonstrate that 12 weeks of TA resulted in significantly higher HRV compared to SA. The physiological effects were accomplished without changes in traditional risk factors or medication changes. Both time and frequency domain components of HRV indicative of parasympathetic activity were significantly higher at exit with TA vs. SA, suggesting that the observed effect was reasonably robust. The magnitude of exit SDNN difference between TA vs. SA may be clinically relevant, as prior work has shown that $SDNN < 70$ ms predicts arrhythmias in patients with low ejection fraction post-myocardial infarction [40]. HRV is a practical, validated approach to study cardiac autonomic function, and an intermediate outcome which predicts an adverse prognosis, including sudden cardiac death [37,41–43]. To our knowledge, our study is the first sham controlled study to show the beneficial impact of TA in an optimally-treated, stable SIHD population.

We did not find significant group differences between TA vs. SA vs. WC at entry and exit 24-hour HRV or cold pressor HRV. Long term 24-hour HRV recordings can be difficult to interpret because HRV is influenced by many internal as well as external factors, such as temperature changes, activity, sleep patterns and habits, mid-day naps, environmental stimuli, etc., and we did not normalize external environmental conditions for 24 h in this study. Parasympathetic tone was significantly lower in the SA group compared to the WC group at exit for mental arithmetic and COP. We are cautious to draw any conclusions about the negative impact of SA because the WC group engaged in higher health-seeking behavior in this trial, similar to our prior experience with an unblinded WC CAM trial [35].

Acupuncture has been used for thousands of years to treat many cardiovascular illnesses, including angina, arrhythmias, and hypertension [11,44]. It is known that cardiovascular-specific acupuncture points stimulate group III and IV afferent autonomic nervous system pathways that transmit to regions in the hypothalamus, midbrain, and medulla that regulate the cardiovascular system [8]. Our acupuncture team chose the points based primarily on Chinese literature that had demonstrated reductions in cardiac dysfunction and arrhythmia burden in non-randomized, uncontrolled and unblinded studies [11,45–52]. Accordingly, using a more rigorous design, our current results suggest that TA causes autonomic remodeling by improving parasympathetic tone.

A recent systematic review by Lee et al. [53] of 12 randomized trials conducted in non-SIHD subjects examined the effect of acupuncture vs. sham treatment on HRV, and concluded that the results were inconsistent regarding the impact of acupuncture on HRV and more rigorous research is warranted [53]. The impact of TA on HRV in the setting of mental stress has also been previously studied in two randomized trials

in normal healthy subjects [54,55], and a meta-analysis of these two trials showed no favorable effects of acupuncture on HF, LF, or LF/HF ratio [53]. Our findings expand these prior findings and indicate that TA may be beneficial in diseased SIHD subjects. Consistent with our findings, a recent trial on acupuncture in patients with atrial fibrillation demonstrated that acupuncture treatment prevents arrhythmic recurrences and is as effective as amiodarone after cardioversion in patients with persistent atrial fibrillation [56].

We did not find significant TA vs SA group differences in our secondary outcome measures of exit blood pressure, fasting lipid panel, insulin resistance, hs-CRP, or salivary cortisol. We also did not find a group difference in endothelial function measured by PAT despite the established role of the autonomic nervous system in the regulation of arterial vasomotor function [57–60]. Because episodes of mental stress cause transient autonomic nervous system imbalance [61] and endothelial dysfunction [62], we measured PAT following stress testing to improve sensitivity to detect beneficial effects, yet were unable to detect group differences. Our overall resting blood pressures at exit did not differ between TA and SA, which could be due to well controlled hypertension with medications, or a lack of a TA effect in SIHD subjects. While some work on smaller trials in medically treated hypertensive patients has suggested a beneficial impact of TA on blood pressure [63,64], a randomized, sham controlled clinical trial of acupuncture in 141 untreated patients with moderate hypertension [65] failed to show a benefit of active acupuncture over sham acupuncture on blood pressure, hyperlipidemia, glucose, or quality of life, consistent with our results. Finally, we did not observe group differences in the various psychosocial parameters. There are a variety of explanations for not seeing a beneficial effect of TA on the secondary outcomes in our study. Our population was optimally treated with anti-anginal, anti-atherosclerotic medications such that the additive impact of TA on blood pressure, lipid profile, hs-CRP, and angina may not have been present or too small to be detectable.

5. Limitations

Our population may not be representative of the general SIHD population, as it is well documented that rates of optimal medical management achievement in non-selected SIHD populations [66–69] are below that observed in our study subjects. We used a predictor of sudden cardiac death risk (HRV) that is used as an outcome in clinical trials [37,70]; and while a significant beneficial effect was observed in HRV as hypothesized, this may have been minimized by the involvement in a proportion of our subjects in cardiac rehabilitation and the role exercise conditioning plays in cardiac autonomic nervous system tone [61]. A major limitation of our study is that we did not collect sleep characteristics (sleep habits and sleep quality) which can impact HRV. While our finding of a 17% difference in HF HRV is noteworthy, we acknowledge that HRV measurements can have a range of intra-individual variability that can make it difficult to determine the significance of changes noted with intervention [71]. Our results may also have been minimized by the use of SA, as prior work has shown that SA can have a therapeutic effect over non-sham placebos [72–74]. Due to the improved health behavior in our unblinded WC group, we were unable to test this hypothesis. While we hypothesize that the WC group had increased “health seeking behavior”, it is also possible that the TA and SA groups had worse parameters due to the “liberalization” of medication or lifestyle efforts due to a belief in the benefits of acupuncture. We cannot fully exclude that our findings are due to chance, despite the Bonferroni correction, although our consistent findings to mental stress in a similar direction argue against this. Our subgroup analyses were underpowered to test specific hypotheses in diabetic subjects, post-CABG, women and the elderly.

6. Implications

We studied TA in a blinded, randomized fashion, with a practical sham technique. Trials to study alternative and complimentary techniques are

difficult due to various problems inherent in the nature of this type of study, however, given the rise in the use of alternative and complementary techniques such as acupuncture in United States, our work sheds light into the practical and possibly beneficial use of acupuncture in optimally-treated, SIHD patients. Given acupuncture's beneficial impact on HRV, it should be studied with regard to its ability to reduce sudden cardiac death. Our current results suggest that the next most appropriate outcome for this line of investigation should be actual sudden cardiac death/defibrillator cardioversions in patients with implantable cardiac defibrillators (ICDs). In the landmark Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) [75] of 2521 patients with congestive heart failure and a left ventricular ejection fraction of 35% or less, those in the NYHA Class II had a 32% mortality rate in the placebo arm vs. 20% in the ICD arm over 5 years. Based on these prior data and applying the effect size in our current study to test the impact of TA vs. SA in a stable heart failure population, a sample size of 229 subjects per group (total 458) would provide 80% power at the 0.05 significance level to detect a 12% group difference in mortality/ICD shocks at 5 years. Given the magnitude of the problem of sudden cardiac death, further clinical trials evaluating TA as an adjunct or temporary replacement of ICDs in subjects at risk for SCD are warranted and should be conducted.

7. Conclusions

Our current trial results demonstrate that 12 weeks of TA compared to SA has intermediate effects in cardiac autonomic modulation measured by HRV in SIHD patients. The TA magnitude of benefit on HRV may be clinically relevant and should be explored further. These data document feasibility and provide sample size estimation for a sudden cardiac death outcome clinical trial of sympatho-vagal modulation using TA in subjects at high risk for sudden cardiac death.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ijcard.2014.07.011>.

8. Conflict of interest

Full disclosures: **Mehta:** Research support – Gilead, General Electric, NIH, CTSI. Lectures (paid to CSMC) – Medical Education Speakers Network; **Minissian:** Research support – Gilead; **Shufelt:** Research support – Gilead; Bairey Merz: CME Lectures (paid to CSMC) – Mayo Foundation, Bryn Mawr, Practice Point Communications, Allegheny General Hospital, Gilead (grant review committee), Duke, Japanese Circ Society, UCSF, Vox Media, Emory, PCNA, Kaiser Permanente, Garden State, AHA. Honorarium and consulting (paid to NBM) – Victor Chang Cardiac Research Institute, University of New Mexico, NIH-SEP (grant review study section), Research Triangle Institute International. Research support – NIH, Gilead, CTSI, FAMRI; **Others:** none.

References

- [1] Lopshire JC, Zipes DP. Sudden cardiac death: better understanding of risks, mechanisms, and treatment. *Circulation* 2006;114:1134–6.
- [2] Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics—2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2008;117:e25–146.
- [3] Maestri R, Raczak G, Torunski A, et al. Day-by-day variability of spontaneous baroreflex sensitivity measurements: implications for their reliability in clinical and research applications. *J Hypertens* 2009;27:806–12.
- [4] Estes III NA. Predicting and preventing sudden cardiac death. *Circulation* 2011;124:651–6.
- [5] Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic impact goal through 2020 and beyond. *Circulation* 2010;121:586–613.
- [6] Williams JK, Vita JA, Manuck SB, Selwyn AP, Kaplan JR. Psychosocial factors impair vascular responses of coronary arteries. *Circulation* 1991;84:2146–53.
- [7] Vaseghi M, Shivkumar K. The role of the autonomic nervous system in sudden cardiac death. *Prog Cardiovasc Dis* 2008;50:404–19.
- [8] Longhurst J. Electroacupuncture treatment of arrhythmias in myocardial ischemia. *Am J Physiol Heart Circ Physiol* 2007;292:H2032–4.
- [9] 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;97:1186–94.
- [10] Middlekauff HR, Yu JL, Hui K. Acupuncture effects on reflex responses to mental stress in humans. *Am J Physiol Regul Integr Comp Physiol* 2001;280:R1462–8.
- [11] Richter A, Herlitz J, Hjalmarson A. Effect of acupuncture in patients with angina pectoris. *Eur Heart J* 1991;12:175–8.
- [12] Shechter M, Sharir M, Labrador MJ, Forrester J, Merz CN. Improvement in endothelium-dependent brachial artery flow-mediated vasodilation with low-density lipoprotein cholesterol levels <100 mg/dl. *Am J Cardiol* 2000;86:1256–9 [A6].
- [13] Pardo Y, Merz CN, Paul-Labrador M, et al. Heart rate variability reproducibility and stability using commercially available equipment in coronary artery disease with daily life myocardial ischemia. *Am J Cardiol* 1996;78:866–70.
- [14] Program LRC. The manual of laboratory operations: lipid and lipoprotein analysis. DHEW publication No. 75-628. Bethesda, MD: National Institutes of Health; 1974.
- [15] Pesce A, Kaplan L. Methods in clinical chemistry. St. Louis: The CV Mosby Company; 1987.
- [16] Allauzen S, Mani JC, Granier C, Pau B, Bouanani M. Epitope mapping and binding analysis of insulin-specific monoclonal antibodies using a biosensor approach. *J Immunol Methods* 1995;183:27–32.
- [17] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412–9.
- [18] Bonora E, Formentini G, Calcaterra F, et al. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. *Diabetes Care* 2002;25:1135–41.
- [19] Bonora E, Targher G, Alberiche M, et al. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care* 2000;23:57–63.
- [20] Shechter M, Sharir M, Labrador MJ, Forrester J, Silver B, Bairey Merz CN. Oral magnesium therapy improves endothelial function in patients with coronary artery disease. *Circulation* 2000;102:2353–8.
- [21] Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. *Arterioscler Thromb Vasc Biol* 2003;23:168–75.
- [22] Bonetti PO, Pumper GM, Higano ST, Holmes Jr DR, Kuvin JT, Lerman A. Noninvasive identification of patients with early coronary atherosclerosis by assessment of digital reactive hyperemia. *J Am Coll Cardiol* 2004;44:2137–41.
- [23] Bonetti PO, Barsness GW, Keelan PC, et al. Enhanced external counterpulsation improves endothelial function in patients with symptomatic coronary artery disease. *J Am Coll Cardiol* 2003;41:1761–8.
- [24] Goor DA, Sheffy J, Schnall RP, et al. Peripheral arterial tonometry: a diagnostic method for detection of myocardial ischemia induced during mental stress tests: a pilot study. *Clin Cardiol* 2004;27:137–41.
- [25] Rosengren A, Tibblin G, Wilhelmsen L. Self-perceived psychological stress and incidence of coronary artery disease in middle-aged men. *Am J Cardiol* 1991;68:1171–5.
- [26] Barefoot JC, Dahlstrom WG, Williams Jr RB. Hostility, CHD incidence, and total mortality: a 25-year follow-up study of 255 physicians. *Psychosom Med* 1983;45:59–63.
- [27] Barefoot JC, Dodge KA, Peterson BL, Dahlstrom WG, Williams Jr RB. The Cook–Medley hostility scale: item content and ability to predict survival. *Psychosom Med* 1989;51:46–57.
- [28] Spielberger C, Gorsuch R, Lushene R. Manual for the state–trait anxiety inventory. Palo Alto, CA: Consulting Psychologists Press; 1970.
- [29] Goodger B, Byles J, Higginbotham N, Mishra G. Assessment of a short scale to measure social support among older people. *Aust N Z J Public Health* 1999;23:260–5.
- [30] Ware Jr JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473–83.
- [31] Hlatky MA, Boineau RE, Higginbotham MB, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). *Am J Cardiol* 1989;64:651–4.
- [32] Spertus JA, Winder JA, Dewhurst TA, et al. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. *J Am Coll Cardiol* 1995;25:333–41.
- [33] Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). *Am J Prev Med* 1994;10:77–84.
- [34] Sui X, Laditka JN, Church TS, et al. Prospective study of cardiorespiratory fitness and depressive symptoms in women and men. *J Psychiatr Res* 2009;43:546–52.
- [35] Paul-Labrador M, Polk D, Dwyer JH, et al. Effects of a randomized controlled trial of transcendental meditation on components of the metabolic syndrome in subjects with coronary heart disease. *Arch Intern Med* 2006;166:1218–24.
- [36] Stein PK, Bosner MS, Kleiger RE, Conger BM. Heart rate variability: a measure of cardiac autonomic tone. *Am Heart J* 1994;127:1376–81.
- [37] Kleiger RE, Miller JP, Bigger Jr JT, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987;59:256–62.
- [38] Bruggemann T, Andresen D, Voller H, Schroder R. Heart rate variability from Holter monitoring in a normal population. *Trans Biomed Eng* 1991;17.
- [39] Bigger Jr JT, Albrecht P, Steinman RC, Rolnitzky LM, Fleiss JL, Cohen RJ. Comparison of time- and frequency domain-based measures of cardiac parasympathetic activity in Holter recordings after myocardial infarction. *Am J Cardiol* 1989;64:536–8.
- [40] Huikuri HV, Raatikainen MJ, Moerch-Joergensen R, et al. Prediction of fatal or near-fatal cardiac arrhythmia events in patients with depressed left ventricular function after an acute myocardial infarction. *Eur Heart J* 2009;30:689–98.

- [41] Bigger Jr JT, Hoover CA, Steinman RC, Rolnitzky LM, Fleiss JL. Autonomic nervous system activity during myocardial ischemia in man estimated by power spectral analysis of heart period variability. The Multicenter Study of Silent Myocardial Ischemia Investigators. *Am J Cardiol* 1990;66:497–8.
- [42] Cripps TR, Malik M, Farrell TG, Camm AJ. Prognostic value of reduced heart rate variability after myocardial infarction: clinical evaluation of a new analysis method. *Br Heart J* 1991;65:14–9.
- [43] Farrell TG, Bashir Y, Cripps T, et al. Risk stratification for arrhythmic events in postinfarction patients based on heart rate variability, ambulatory electrocardiographic variables and the signal-averaged electrocardiogram. *J Am Coll Cardiol* 1991;18:687–97.
- [44] Tam KC, Yiu HH. The effect of acupuncture on essential hypertension. *Am J Chin Med (Gard City N Y)* 1975;3:369–75.
- [45] Ballegaard S, Karpatschoff B, Holck JA, Meyer CN, Trojaborg W. Acupuncture in angina pectoris: do psycho-social and neurophysiological factors relate to the effect? *Acupunct Electrother Res* 1995;20:101–16.
- [46] Fan A. Acupuncture combined with oxygenation for myocardial infarction patients. *Chin Acupunct Moxabustion* 1999;4:213–4.
- [47] Ho FM, Huang PJ, Lo HM, et al. Effect of acupuncture at nei-kuan on left ventricular function in patients with coronary artery disease. *Am J Chin Med* 1999;27:149–56.
- [48] Lao L, Bergman S, Langenberg P, Wong RH, Berman B. Efficacy of Chinese acupuncture on postoperative oral surgery pain. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995;79:423–8.
- [49] Lin JG, Ho SJ, Lin JC. Effect of acupuncture on cardiopulmonary function. *Chin Med J (Engl)* 1996;109:482–5.
- [50] Ma Y, Sui S, Liu A. Acupuncture LI20 to treat fast heart rate arrhythmia. *Acupuncture and Moxabustion*; 1996 5.
- [51] Shi X, Wang ZP, Liu KX. Effect of acupuncture on heart rate variability in coronary heart disease patients. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 1995;15:536–8.
- [52] Syuu Y, Matsubara H, Kiyooka T, et al. Cardiovascular beneficial effects of electroacupuncture at Neiguan (PC-6) acupoint in anesthetized open-chest dog. *Jpn J Physiol* 2001;51:231–8.
- [53] 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.
- [54] Kang MS, Kim LH. The effect of mental stress stimulation and acupuncture at Shinnum (HT7) on heart rate variability. *J Orient Neuropsychiatry* 2009;20:165–76.
- [55] Park SU, Jung WS, Moon SK, et al. Effects of acupuncture on autonomic nervous system in normal subjects under mental stress. *J Korean Orient Med* 2008;29:107–15.
- [56] Lomuscio A, Belletti S, Battezzati PM, Lombardi F. Efficacy of acupuncture in preventing atrial fibrillation recurrences after electrical cardioversion. *J Cardiovasc Electrother* 2011;22:241–7.
- [57] Cardillo C, Kilcoyne CM, Quyyumi AA, Cannon 3rd RO, Panza JA. Role of nitric oxide in the vasodilator response to mental stress in normal subjects. *Am J Cardiol* 1997;80:1070–4.
- [58] Dakak N, Quyyumi AA, Eisenhofer G, Goldstein DS, Cannon III RO. Sympathetically mediated effects of mental stress on the cardiac microcirculation of patients with coronary artery disease. *Am J Cardiol* 1995;76:125–30.
- [59] Skantze HB, Kaplan J, Pettersson K, et al. Psychosocial stress causes endothelial injury in cynomolgus monkeys via beta1-adrenoceptor activation. *Atherosclerosis* 1998;136:153–61.
- [60] Yeung AC, Vekshtein VI, Krantz DS, et al. The effect of atherosclerosis on the vasomotor response of coronary arteries to mental stress. *N Engl J Med* 1991;325:1551–6.
- [61] Pardo Y, Merz CN, Velasquez I, Paul-Labrador M, Agarwala A, Peter CT. Exercise conditioning and heart rate variability: evidence of a threshold effect. *Clin Cardiol* 2000;23:615–20.
- [62] Ghiadoni L, Donald AE, Cropley M, et al. Mental stress induces transient endothelial dysfunction in humans. *Circulation* 2000;102:2473–8.
- [63] Flachskampf FA, Gallasch J, Gefeller O, et al. Randomized trial of acupuncture to lower blood pressure. *Circulation* 2007;115:3121–9.
- [64] Yin C, Seo B, Park HJ, et al. Acupuncture, a promising adjunctive therapy for essential hypertension: a double-blind, randomized, controlled trial. *Neurol Res* 2007;29(Suppl. 1):S98–S103.
- [65] Macklin EA, Wayne PM, Kalish LA, et al. Stop Hypertension with the Acupuncture Research Program (SHARP): results of a randomized, controlled clinical trial. *Hypertension* 2006;48:838–45.
- [66] Blackburn DF, Dobson RT, Blackburn JL, Wilson TW, Stang MR, Semchuk WM. Adherence to statins, beta-blockers and angiotensin-converting enzyme inhibitors following a first cardiovascular event: a retrospective cohort study. *Can J Cardiol* 2005;21:485–8.
- [67] Gislason GH, Rasmussen JN, Abildstrom SZ, et al. Long-term compliance with beta-blockers, angiotensin-converting enzyme inhibitors, and statins after acute myocardial infarction. *Eur Heart J* 2006;27:1153–8.
- [68] Ho PM, Spertus JA, Masoudi FA, et al. Impact of medication therapy discontinuation on mortality after myocardial infarction. *Arch Intern Med* 2006;166:1842–7.
- [69] Tricoci P, Peterson ED, Roe MT, Initiative CQI. Patterns of guideline adherence and care delivery for patients with unstable angina and non-ST-segment elevation myocardial infarction (from the CRUSADE Quality Improvement Initiative). *Am J Cardiol* 2006;98:30Q–5Q.
- [70] Lombardi F, Sandrone G, Pernpruner S, et al. Heart rate variability as an index of sympathovagal interaction after acute myocardial infarction. *Am J Cardiol* 1987;60:1239–45.
- [71] Maestri R, Raczak G, Danilowicz-Szymanowicz L, et al. Reliability of heart rate variability measurements in patients with a history of myocardial infarction. *Clin Sci (Lond)* 2010;118:195–201.
- [72] Kaptchuk TJ. The placebo effect in alternative medicine: can the performance of a healing ritual have clinical significance? *Ann Intern Med* 2002;136:817–25.
- [73] Kaptchuk TJ, Stason WB, Davis RB, et al. Sham device v inert pill: randomised controlled trial of two placebo treatments. *BMJ* 2006;332:391–7.
- [74] Liu T. Acupuncture: what underlies needle administration? *Evid Based Complement Altern Med* 2009;6:185–93.
- [75] Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225–37.