Improvement of menopausal symptoms with acupuncture not reflected in changes to heart rate variability

Cheryl L Wright,1 Mikel Aickin2

ABSTRACT

Hypothesis Studies indicate that menopausal symptoms are relieved by acupuncture. Additional studies have suggested that acupuncture may affect heart rate variability (HRV). This paper reports a pilot study that investigated whether menopausal symptoms responded to acupuncture, and if changes in the spectral analysis of HRV, either suppression of low frequency or augmentation of high frequency bands, corresponded with symptom report.

Methods/interventions 12 healthy menopausal subjects were enrolled in this feasibility study. At baseline, subjects were experiencing moderately distressing menopausal symptoms, scoring at least 22 of a possible 44 points on the Menopausal Rating Scale. 10 traditional Chinese medicine-based, protocol acupuncture treatments were administered over a 4 week period, three times a week for 2 weeks, followed by twice a week for 2 weeks.

Outcome measures Menopausal Rating Scale questionnaire, 11 menopausal symptoms were evaluated on a zero to four severity scale via self-administered daily checklist for 4 weeks. Dynamic measures of HRV (autoregressive model) were captured before, during and after acupuncture at each session. Spectral analysis of the heart rate was used to compute power in the low frequency and high frequency bands, and their ratio.

Results All subjects complied fully with the protocol without any reported adverse events. While all 11 symptoms showed significant improvement, and one HRV measure changed, on average over the study period, there was essentially no support for a relationship between HRV, menopausal symptom report and acupuncture intervention.

INTRODUCTION AND BACKGROUND

Menopause is a normal physiological event that most women will eventually experience, and about 15–30% will have symptoms significant enough to visit a healthcare provider for relief at some point.1 However, while overall quality of life for many women transitioning through menopause may not dramatically decrease,2 a smaller subset of women may have quite severe symptoms.3 For those who experience them, the most prevalent menopausal symptoms include vasomotor symptoms (hot flashes) (50–80%), vaginal dryness (17–30%), mood (8–38%) and sleep (35–60%) disturbances.4

The Women’s Health Initiative in 20025 marked a new era for menopausal symptom management as many women reconsidered the use of hormone replacement therapy in light of possible increased risks of breast cancer and thromboembolic events. Currently, many women choose to find safer, preferably non-pharmaceutical alternatives for symptom management.6

In multiple studies, acupuncture has reduced vasomotor symptoms, irrespective of needle placement, depth or type of stimulation.7-13 This non-specificity of the acupuncture intervention has led critics to state that acupuncture effectiveness does not have a specific physiological basis beyond that of a placebo, expectation or non-specific response.14 15 This argument needs to be taken seriously, as the placebo effect is varied and potent,16 and could conceivably be the mechanism by which acupuncture ameliorates menopausal symptoms. However, other researchers have hypothesized that there are specific effects of acupuncture, which occur in the peripheral and central nervous system as a direct response of the needle stimulating tissue around major nerves, and this alternative mechanism, to some degree has been demonstrated in an animal model,17 with fMRI imaging data to bolster the model.18 19 Accepting the peripheral and central nervous system theory, that the acupuncture needle does affect potent central neurotransmitters that could be reflected in HRV, the goal of this study was to begin to understand what physiological response, if any, may be occurring during acupuncture, especially when women report improved menopausal symptoms. The ECG can be used to measure some degree of autonomic modulation on the heart through calculations of the inter-beat-interval (heart beat-to-heart beat), or the time (in fractions of seconds) that elapses from the peak of one R wave to the peak of the next R wave in the QRS complex, as seen on an oscilloscope.20 Although there are intrinsic cardiac pacing
tissues, such as the sinoatrial and atrioventricular nodes, heart rate and beat-to-beat variability are also determined by the autonomic nervous system (ANS) influence on the sinoatrial node. Sympathetic influences associated with the ‘fight or flight’ response result in a rapid heart rate with decreased beat-to-beat variability, while parasympathetic influences, vagally mediated through release of acetylcholine, result in a slower heart rate with more beat-to-beat variability. Respirations also impart a significant influence on the inter-beat-interval through the parasympathetic nervous system, and can be seen on an ECG tracing as a respiratory sinus arrhythmia, which also affects the overall HRV. Spectral analysis, one of several methods used to assess HRV, uses cyclic fluctuations of R-R intervals. Accepted measurement standards for high frequency (HF) spectral analysis are in the frequency range of 0.15–0.4 hertz, low frequency (LF) ranges from 0.04–0.15 hertz, and ultralow frequency, not generally analysed in short-term measures, occurs in the ranges of 0.008–0.04 Hz.

**HRV, MENOPAUSE AND ACUPUNCTURE**

HRV declines with age, but has also been shown to decline after surgical menopause as well as natural menopause. Since ageing and menopause are related, the association between declining HRV cannot yet be strongly linked to menopause, however the data suggests that there may be a relationship.

In other biomedical disorders, various acupuncture researchers have attempted to establish a biomarker to explain a physiological mechanism for acupuncture effectiveness, and have turned to HRV as a possibility. To date, however, no significant effect on HRV has been reported. However, studies revealed decreased LF band to HF band ratio in subjects with mild anxiety and depression who received nine standard protocol, therapeutic acupuncture treatments. A second finding, LF bands increased and were sustained for 10 min after needle removal in patients with migraines who received a series of 12 therapeutic protocol acupuncture treatments. Finally, in normal subjects, a decrease in LF with an increase in HF was reported. However, no study to date has looked at HRV in a manner consistent with how acupuncture services are delivered in a community setting, how HRV differs before and during treatments or throughout a series of acupuncture treatments, to assess variability at different stages in the treatments, as well as through time.

In summary, our informal hypotheses were that menopausal symptoms, specifically vasomotor symptoms—hot flashes and sweats, anxiety and heart palpitations—would improve after 10 protocol acupuncture treatments. Concurrent with symptom changes, heart rate variability would increase as measured by decreased LF bands and increased HF bands, ultimately seen as an increased ratio of HF/(LF+HF), providing a potential relationship between HRV, acupuncture and symptom changes.

**METHODS**

Human subjects’ approval was obtained through the University of Arizona Institutional Review Board. This was an early-phase, exploratory study to assess the feasibility for a larger randomised controlled trial. A convenience sample was recruited through radio and newspaper advertisements between 1 September 2008 and 15 December 2008. Seventy-five potential subjects were screened by telephone for inclusion/exclusion criteria, which included assessment for symptom severity using the Menopause Rating Scale (MRS). Twelve subjects met inclusion/exclusion criteria, and subsequently provided written informed consent. There was no separate control group; each woman served as her own control to assess for symptom and HRV changes from baseline through time. Demographics are presented in table 1.

Inclusion criteria consisted of women between 48 and 65 years of age, non-surgical menopause, without a menstrual period for at least 12 months, but no more than 45 months, experiencing moderately severe symptoms (as determined by a minimal MRS score of 22 of a possible 44), that significantly affected quality of life. Exclusion criteria: surgical menopause, major infection in the past 3 months, autoimmune disease, diabetes, herbal or hormone replacement therapy to control menopausal symptoms in the past 6 months, history of, or demonstrated, cardiac rhythm disturbance, prior use of acupuncture for menopausal symptom relief in the past 12 months or in the past 6 months for any reason, or needle phobia. All subjects who were taking medications had been on stable doses for at least 5 months, and no medication changes occurred during the study. Two subjects were on stable doses of a selective serotonin reuptake inhibitor, two different subjects were taking antihypertensives (an ACE inhibitor and a calcium channel blocker), and one subject was on levothyroxine.

**Outcome measures**

The MRS questionnaire, designed to be self-administered, is a sensitive and specific questionnaire that measures 11 menopausal symptoms for frequency and severity, before and after an intervention, and has been validated in 1400 US women. Each symptom has a possible score that ranged from zero (no symptoms) to a maximum score of four (very severe symptoms). Symptoms captured include hot flashes, heart palpitations, quality of sleep, depressed mood, irritability, anxiety, fatigue, sexual dysfunction, bladder dysfunction, vaginal dryness and musculoskeletal

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Sample demographics</th>
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<tbody>
<tr>
<td>Age range (years)</td>
<td>48–62 (53.2)</td>
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<tr>
<td>Education range (mean)</td>
<td>13–18 years (15.4)</td>
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<tr>
<td>Body mass index range (mean)</td>
<td>19.9–32.9 (25.9)</td>
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<td>Baseline MRS (0–44) scores range (mean)</td>
<td>22–28 (25)</td>
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pain. One additional question was added to capture the global distress experienced due to all symptoms. As each subject underwent 10 standard protocol acupuncture treatments over 4 weeks, the MRS questionnaires were completed daily.

The ECGs were digitally recorded using a Cadwell Easy Ambulatory 2 System (Cadwell Laboratories, Kennewick, Washington, USA). Sampling rate was 2400 samples per second. A software program written by one of the authors (MA) and based on a Physionet program,35 was used to convert the ECG file into an inter-beat-interval file using Stata V.10.56

Heart rate variability (HRV) analysis was performed by the authors using software developed at the University of Kuopio (downloaded from the Department of Physics at the University of Kuopio, in Kuopio, Finland at http://it.uku.fi/biosignal/software.shtml). For the analysis, the primary outcome was the ratio (in percent) of the HF spectral power to the sum of the HF and LF spectral power, HF/(HF+LF). This was computed before, during and after acupuncture at each session. Each subject was seen at the same time of day, plus or minus 2h to avoid confounding circadian rhythms,30 and the treatment room was kept at an ambient temperature between 68°F (20°C) and 72°F (22.2°C).

Each subject was placed in a comfortable, supine position on a massage table, and three skin sensor electrode leads were placed on the chest wall. Placement was consistent for all subjects to capture a standard lead II QRS configuration. No postural changes or movement occurred during 30 min of ECG collection.

Before HRV analysis, ECG data were screened for ectopic beats, artifact and correct placement of the R wave marker on the QRS complex. The fiducial point was verified on the QRS complex, and was consistent and stable for each segment. Three 10-min segments were isolated from each of the 10 sessions, and the final 5 min of each segment was used for HRV analysis.70 These segments included: (1) baseline, before acupuncture began; (2) after 10 min of acupuncture; (3) after mid-session needle stimulation, the final 10 min of acupuncture, which represented a total of 20 min of acupuncture.

**Acupuncture protocol**

A standard traditional Chinese medicine (TCM) acupuncture point protocol was used. The author (CW), an experienced licensed acupuncturist with 4 years experience administered all acupuncture. Stainless steel, single-use, sterile Seirin needles (Seirin-America, Weymouth, MA, USA) were used for all acupuncture treatments. Size ranged in length from 15 mm to 75 mm and in gauge from 0.16 mm to 0.30 mm. Body habitus and point location determined size and gauge per standardised protocol.38 39 The protocol and point selection was determined based on the most common TCM patterns seen with the biomedical condition, menopause and symptoms congruent with subjects’ symptom report.40–42

Acupuncture point protocol: HT7, P6, ST36, LV3, K6, SP6, Du20.38 In addition, using the Chinese ear model, two ear points were included: Shenmen and Uterus.42 Acupuncture was administered three times a week for 2 weeks, then twice a week for 2 weeks, for a total of 10 treatments over 4 weeks. Each point was needled bilaterally, except Du20 and the ear points. Ear points were placed on the alternate ear at each treatment. All needles were inserted perpendicularly to the channel/skin (even method), and all needles were stimulated upon insertion until the subject reported a dull ache, commonly associated with the arrival of de qi.42 Midway through each treatment, all needles were re-stimulated until sensation was reported. The ear points were inserted, but not manipulated.

**Statistical analyses**

All menopausal symptoms and the HF/(HF+LF) measurements were regressed on time (in units of weeks) within each subject separately. This provided a baseline value (the intercept, at time 0) and a slope, representing the average rate of change, for each outcome variable, for each participant. T-tests were used to test for zero slopes, with conventional two-sided p values. Since the main intent of the study was to examine the HRV outcome as a mechanistic variable,43 we regressed the slope of each menopausal symptom on the slopes of the three HF/(HF+LF) measures. A non-zero coefficient in such a regression would indicate that within participants, a change in the HRV measure was associated with a change in a menopausal symptom. We did not adopt formal rules of hypothesis testing, since the purpose of this pilot study was to assess the advisability and direction of potential further research. Due to concern about an inherent mathematically-induced artifact44 in the a priori normalised HF power (HF/LF+HF), a post hoc analysis was performed to evaluate only the non-normalised HF data, from the autoregressive model, measured in ms², to see if results tracked the a priori results.

The post hoc analysis was performed with SPSS V.14.0.45 The HF data was not normally distributed and was transformed using the natural logarithm. Following confirmation of normality and sphericity of the transformed HF data with Mauchly’s test ($X^2(2)=1.22; p=0.544$),29 a two-way repeated measures analysis of variance was performed using longitudinal changes over time (10 visits), and the three phases of acupuncture (before, during and after). Pulse data was normally distributed and a one-way repeated measures analysis of variance was performed. Bonferroni correction was used for each analysis, and $\alpha$ was set at 0.05.

**RESULTS**

Subject retention rate was 100%, and there were no adverse events or missing data values. All 11 symptoms on the MRS showed significant decreases, at rates varying from −0.17 to −0.53 per week (see table 2). The HF/(HF+LF) slopes were not significant for either the pre-acupuncture or postacupuncture within-session time point, but they significantly decreased for the during acupuncture point. In the tests of the mechanistic hypotheses (11 symptom slopes each regressed on 3 HRV slopes)
none of the coefficients were nominally significant, and most p values were quite high. Due to the finding of a trend only in the during-acupuncture HF/(HF+LF), as a secondary analysis we regressed each symptom slope on this specific HRV slope alone. Only one of the 11 p values was significant (0.047).

**Post hoc analyses**

There was no significant main effect on the HF bands, F (2, 22)=3.37, p=0.053, nor was there a significant interaction between time (from first to tenth treatment) and HF bands, F (18, 198)=0.972, p=0.493.

Pulse data demonstrated a statistically significant decrease from baseline within subjects from time 1 (before acupuncture) to time 2 (during) of −1.83 beats per minute (bpm) (95% CI −2.9 to −0.75), p=0.002 and from time 1 to time 3 (after acupuncture), −2.67 bpm (95% CI −4.28 to −1.06), p=0.002. While these findings were statistically significant they were not clinically significant, and could not be attributed solely to acupuncture, but more probably to the relaxing environment and reclining posture.

**DISCUSSION**

From our analysis, even with the very small sample size we conclude that we have been able to confirm results in the literature that menopausal symptoms improve during acupuncture treatment, however, a non-specific or placebo effect cannot be ruled out. We did not find evidence of similar changes in the HF/(HF+LF) measured either before or after acupuncture at each session. We do find a downward trend in the during-acupuncture HF/(HF + LF), which indicates less variability that may be consistent with the uncomfortable stimulus during the acupuncture treatment. Additionally, even after using a method that may more reliably reflect changes in vagal activity, we found no significant trends in the non-normalised HF bands in response to the intervention, though pulse rates did significantly decrease, it was not a clinically significant one. Thus we conclude, after an exhaustive analysis of the relationships between HRV slopes and symptom slopes and post hoc analyses of HF bands alone, there is essentially no evidence favouring a mechanistic interpretation between HRV and decreased menopausal symptoms.

This pilot study confirmed the safety, feasibility and acceptability of an intensive acupuncture intervention for menopausal symptoms. It replicates findings that acupuncture may successfully alleviate vasomotor symptoms as well as other menopausal symptoms. We found it interesting that subjects reported improvement of vaginal dryness, which has not been commonly reported in prior studies, and this finding may be an indication of an expectation or possible Hawthorne effect.

Novel findings included the degree and amount of interpersonal as well as intra-individual variability seen in the HRV before, during and after each acupuncture treatment, which was consistent across time. See figures 1 and 2 for a typical HF band data set. This variability suggests several things. First, when using HRV as an outcome measure, sampling bias may be problematic if measurements are...
only taken at baseline and at the final treatment, or if only two measurements are taken close together. This high degree of variability suggests that if HRV is to be used as an outcome measure in response to acupuncture or other intervention, more frequent measurements may be needed before actual trends or effects can be identified. This finding is supported by a report from a recent intervention in 10 healthy subjects that examined the effects of postural change and intravenous cardioselective β-adrenergic blockade and muscarinic cholinergic blockade on HRV, which suggested that HRV as an outcome measure was neither reliable or predictable in a healthy sample. While HRV seems to be a reliable prognostic marker for some types of disordered physiology, it should not be assumed to be a reliable outcome measure of change in a sample with a healthy cardiac status. Thus, researchers should carefully consider the complex physiology that drives HRV, as well as the variable physiological events that produce the data before choosing it as a measure that represents any single physiological response to an intervention.

Secondly, particular to this small sample, if the subjects’ baseline HRV does not demonstrate a predominance of LF or HF bands, there may be no changes seen because there was nothing to change. In fact, postmenopausal women may not consistently have a predominance of increased or decreased HRV, which was suggested by findings in a prior study. In our small sample, however, there were two exceptions to this. One subject began with very severe vasomotor symptoms, and an accompanying HRV that had a high percentage of LF bands with almost no HF bands. By the final acupuncture treatment her symptoms had dramatically improved, and her HRV demonstrated a more balanced distribution of low and HF bands, which can be seen in figures 3–5. Conversely, another subject demonstrated almost no LF bands with a prominent HF peak, and post acupuncture intervention, showed decreased HF peak with a greater predominance of LF bands, which can be seen in figures 6–8.

If HRV could be considered a reliable marker for change, one hypothesis put forward by Li and colleagues suggested that acupuncture may not consistently change HRV in any particular direction, but may modulate or balance physiology rather than driving it in a particular direction. When the physiology is disordered, the acupuncture may

restore homeostasis. This could explain the two subjects in our study who each began with prominent LF or HF bands which ‘corrected’ to a more balanced distribution of LF/HF bands. Thus, a response in HRV to acupuncture may rely on the functional status of the subject at times of measurement.

STUDY LIMITATIONS
This pilot feasibility study was not designed or powered for statistical significance, rather, to assess feasibility for measuring change in HRV in a symptomatic population. Thus, in addition to bias, both type I and type II errors could be present in the analysis. Additionally, this was a very early phase study, and the goals were to evaluate changes in symptoms and HRV in a setting that would most closely resemble that of a community acupuncture setting. For these reasons, we did not have our subjects pace their respirations to control for the sinus arrhythmia effect on HF bands, as paced respiration has been used as an effective intervention for managing menopausal symptoms.51 Additionally, five of the 12 subjects were on medications that can influence HRV, however, this was not a washout trial, but a pragmatic trial, and women who seek acupuncture for menopausal symptom management are not likely to stop taking their medications. We were interested in symptom changes and HRV in the presence of a stable medication regime, and the goal was to identify changes in HRV as would occur if any woman sought menopausal symptom management in a community acupuncture setting. Importantly, on a very small scale, we chose to replicate studies that examined HRV and symptom response to various iterations of acupuncture interventions, with the addition of more frequent measures precisely to assess for the possibility of measurement biases in acupuncture studies that used HRV as an outcome measure.

The larger and more important question that should be addressed is the significance of using HRV as a biomarker for change in acupuncture research. Can we or should we use HRV as a quantitative proxy for a systemic autonomic ‘balance’ in the absence of direct measurement, for example, sympathetic recording via microneurography? HRV alone

Figure 5 Raw high frequency data from subject ‘A’.

Figure 6 Kuopio Software HRV output: baseline subject ‘B’.

Figure 7 Kuopio Software HRV output: subject ‘B’ after 10 acupuncture treatments.
**CONCLUSION**

In summary, our data suggest that an intensive acupuncture protocol may relieve an array of menopausal symptoms; however, symptom relief may be the result of expectation or non-specific effect commonly associated with the placebo response. In light of recent work in the use of HRV as a reliable outcome measure in response to an intervention, caution is advised. The HRV data suggests that there are high degrees of variability in HRV, and frequent sampling may be needed before definitive conclusions can be reached that acupuncture has a directional effect on HRV. Finally, HRV alone should not be considered a proxy for changes in the influence of the ANS activity.

**Summary points**

- Acupuncture treatment reduces menopausal hot flushes.
- The mechanism involves the autonomic nervous system.
- We found no change in heart rate variability (HRV) in women given acupuncture for hot flushes.

**Acknowledgements** CW is grateful to Alex Holland, LAc president of the Asian Institute of Medical Studies and Leslie Romero, LAc of Ancient Ways Acupuncture Clinic for their thoughtful and detailed comments.

**Funding** This work was supported by NIH T32 grant numbers T32 AT001287 and 5 T32 NR0007061.

**Competing interests** None.

**Ethics approval** This study was conducted with the approval of the University of Arizona institutional review board.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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doi: 10.1136/aim.2010.003053

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