Rapid Response of Autonomic Nervous System to Acupuncture in Subjects Under Stress

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ABSTRACT

Introduction: During functional magnetic resonance imaging (fMRI) investigating effects of acupuncture, numerous subjects reported immediate reduction in anxiety upon needle insertion. We hypothesised that the autonomic nervous system (ANS) reacted more rapidly to acupoint stimulation than previously reported. We investigated whether valid results could be obtained from 220 seconds of pulse recording. Furthermore, we looked for evidence that ANS responses differed depending on acupoints stimulated. Methods: 40 subjects participated in each of two sessions of acupuncture using LI4 *Hegu*, SP6 *Sanyinjiao*, PC6 *Neiguan* or ST36 *Zusanli*. A sterile hypodermic needle (Terumo, Ø0.50 × 16 mm) was inserted into the selected point. After a 10-minute washout period, 0.5 mL of normal saline was injected into the point at 30-second intervals for 5 doses, a total dose of 2.5 mL in 150 seconds. Continuous pulse recording was commenced 70 seconds before the first injection and continued for 220 seconds until the end of the injections. Calculated spectral power of the recordings was compared between the pre-stimulation and stimulation phases. Results: Paired-samples t-tests showed significant increases in low frequency (LF) power band for *Sanyinjiao* and *Neiguan* and in LF/HF (high frequency) ratio for *Hegu*, but not for *Zusanli*. A significant decrease in heart rate (HR) from baseline was demonstrated for all points by the end of the experiment, 10 minutes after cessation of stimulation. Conclusion: The significant decrease in HR between baseline and end-point implies effectiveness of point injection (PI) for acupoint stimulation. The initially elevated ANS response to an alien experimental environment was not reduced by acupoint stimulation, discounting ANS modulation as a cause for the self-reported reduction in anxiety. Despite the severe experimental environment, it was possible to show changes in HRV produced by stimulation of different acupoints, these changes being different between points.

KEYWORDS acupuncture, autonomic nervous system, heart rate variability, point injection, power spectral analysis.

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Aust J Acupunct Chin Med 2007;2(1):9–15.

Introduction

During the course of a number of functional magnetic resonance imaging (fMRI) experiments conducted to determine the effects of acupoint stimulation on the central nervous system (CNS), a number of subjects reported immediate reduction of anxiety upon stimulation. This relaxation seemed to continue after the end of the experiments. Acupuncture is reported to modulate activities of the autonomic nervous system (ANS),[1-4] but this effect has only been measured 30 minutes after stimulation. We hypothesised that the ANS reacted more rapidly to acupoint stimulation than previously reported. Since we were testing point injection (PI) as a method of acupoint stimulation, we also hypothesised that PI would cause a similar ANS response to that reported with manual needling or electroacupuncture (EA). To demonstrate these hypotheses, we needed to determine whether valid power spectral analysis (PSA) results could be obtained from 220 seconds of pulse recording. Published data indicate that 7.2-second recordings or recordings of 100 heartbeats could provide adequate spectral samples of heart rate variability (HRV) if results are cautiously interpreted.[5,6]

Photoplethysmography (PPG) gives the summary information reflecting both cardiac and blood vessel components of heart rate variability (HRV), and could be used to assess the response of the ANS. There is a significant correlation between inter-beat interval data measured by both electrocardiography (ECG) and PPG in short-term steady-state recordings.[7,8]

Sayers[9] first demonstrated changes in HRV associated with mental activity; later Malliani and Montano[10] concluded that autonomic changes induced by mental/physical activity could be investigated easily with spectral analysis of HRV to reveal aspects of interaction between sympathetic and vagal outflow. The low frequency (LF) spectral components of HRV are considered a measure of sympathetic tonus while high frequency (HF) reflects parasympathetic tonus and fluctuations caused by spontaneous respiration. The LF/HF ratio is indicative of sympathetic/parasympathetic balance,[11] a decrease in score being a possible indication of either an increased parasympathetic or decreased sympathetic tonus.

A number of studies have reported that acupuncture changes LF and HF components of HRV. Shi, Wang and Liu[12] reported a significant reduction in the LF component of HRV after needling PC6 *Neiguan* in patients suffering coronary heart disease. They also noted a significant change in LF/HF ratio when electroacupuncture was applied. In a study of acupuncture treatment for minor depression, Agelink et al.[13] showed a combined trend towards an increase in HF, decrease in LF and an overall significant decrease in LF/HF ratio when needling classical points. Haker, Egekvist and Bjerring[14] noted a statistically significant decrease in heart rate (HR) after stimulation of LI4 *Hegu* and demonstrated an increase in sympathetic and parasympathetic activity during stimulation and a prolonged sympathetic decrease after stimulation. Only single acupoint stimulation was studied in the above-mentioned trials, and no study to date has compared the effects of different acupoints in the same subject. Clinically, a number of acupoints may be used in combination as treatment; it would be advantageous to understand the effects of each point on the ANS before the combined effects are studied.

Manual acupuncture, although widely used in research and clinical applications, is difficult to accurately control and hard to quantify, making reproducibility a research issue.[15] PI is an attractive exploratory method. Precise doses of fluid (usually normal saline) can be delivered into an acupoint at set intervals giving a reproducible stimulation session to session, although individually specific tissue distensibility and fluid resorption are seen as confounding variables.

AIMS

As part of a neuroimaging study into the effects of acupuncture on the CNS, we determined to investigate whether:

1. The ANS reacts more rapidly to acupoint stimulation than previously reported;
2. There are differing ANS responses from stimulation of different acupoints; and
3. PSA results obtained from 220 seconds of pulse recording could give interpretable data.

Methods

VOLUNTEERS

With approval from the University of Queensland (UQ) Medical Ethics Research Committee and the Uniting Health Care Human Research Ethics Committee, subjects were recruited from a pool of normal healthy volunteers comprised of UQ students and staff who had participated in previous neuroimaging trials.

Forty right-handed subjects (21 males) ranging in age from 18 to 52 (mean = 27) participated in each of two sessions of acupuncture stimulation. Of these, 13 (32.5%) were naive to acupuncture. No subject had a history of psychiatric or neurological disorder or head trauma with loss of consciousness, and pregnant or possibly pregnant females were excluded. Informed consent in writing was obtained prior to investigation. Subjects were instructed not to eat, drink caffeine-containing beverages, or smoke two hours prior to testing.

SELECTION OF ACUPOINTS

LI4 *Hegu* on the left hand and SP6 *Sanyinjiao* on the right leg were chosen for study in male subjects, and PC6 *Neiguan* on the right and ST36 *Zusanli* on the left were studied in female subjects. The order of acupoint stimulation and the possible effects of the stimulation were not explained and all subjects considered this 'just another fMRI experiment' for which they had volunteered. A period of one week between acupoint stimulations allowed time for washout of any possible ongoing acupuncture effects.

No clinical importance was placed on the acupoints selected. The four acupoints were chosen because of their frequent clinical use, previous use in a research setting, and accessibility from within an MRI scanner. *Hegu* is a commonly adopted research acupoint as it is easy to identify.[17] *Sanyinjiao* is another common acupoint for research. *Neiguan* has been used in HRV studies[13] and *Zusanli* has been investigated previously with fMRI.[18]

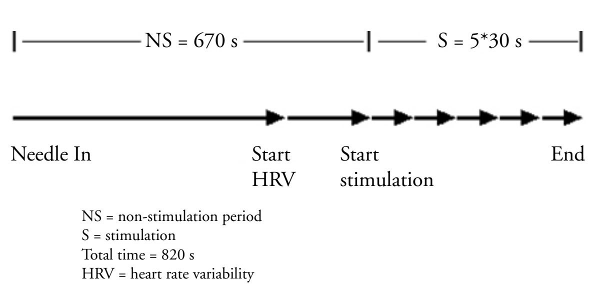

FIGURE 1 Design for acupoint stimulation

STIMULATION

An acupuncturist with 30 years experience in traditional needling techniques and four years experience in PI (MWS) performed all stimulations. Under normal conditions for skin penetration, a hollow Terumo Neolous (Terumo Corp., Elkton, MD, USA) Ø0.50 × 16 mm sterile, single use needle was inserted to a depth of 13 mm into the selected point 10 minutes prior to commencement of the experiment. The full effect of needle insertion was reported to occur within the first three seconds after needle placement,[15] and we considered a 10-minute washout period to be adequate, with any effects demonstrated after this a result of stimulation due to saline infusion.

A 10 mL Luerlok syringe containing sterile normal physiologic saline (0.9% NaCl) was mounted in a purpose-built computer-controlled syringe driver and connected remotely to the needle by minimal volume tubing. Commencing 70 seconds after starting the imaging experiment and PPG acquisition, 0.5 mL saline was delivered at a rate of 1.0 mL/s into the acupoint every 30 seconds for five doses, giving a total stimulation time of 150 seconds and a total experimental time of 220 seconds (Fig. 1). Figure 2 outlines the basic saline delivery layout.

PRESSURE RECORDING

Tissue resistance was measured with a conventional piezo bridge sensor (Baxter, Kobe, Japan) connected in-line. Intrapoint pressure recordings, later used as a covariant for data analysis, were made at 2.5-second intervals in parallel with PPG and neuroimaging recordings.

PULSE RECORDING

The beat-to-beat pulse interval was recorded from a pulse probe (K2203 4752866; Siemens, Erlangen, Germany) attached to the right middle finger. Recording commenced at the beginning of the neuroimaging experiment and continued for 220 seconds until completion of fMRI image acquisition.

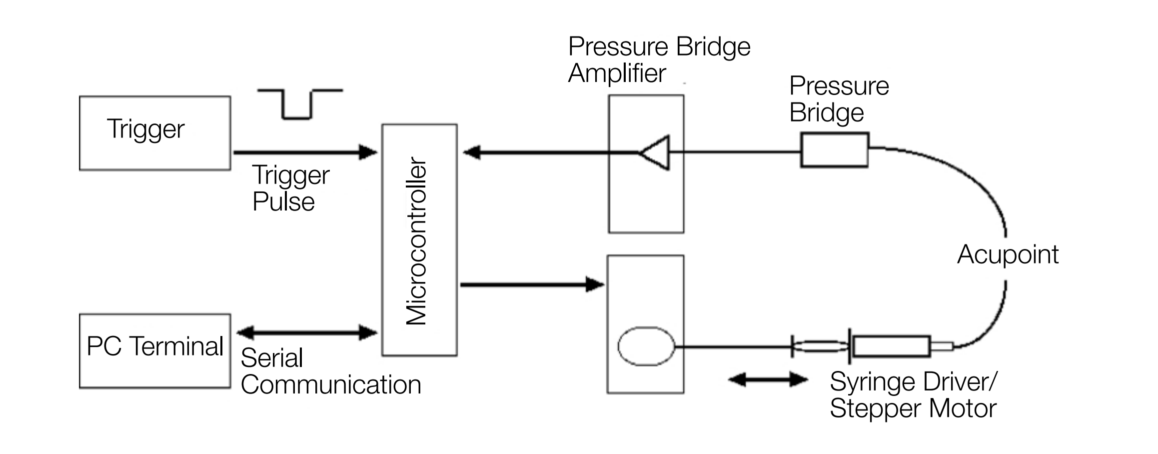

FIGURE 2 Basic layout of saline delivery

1 Volt peak-to-peak trigger pulse can be provided from any source. This system is configured for 2 sources; 1. Manual push button operation for use in the PI validation study; 2. Automatically from a square wave pulse delivered from a Siemens Magnetom (Siemens, Erlangen, Germany) MR scan system.

11 000 samples of beat-to-beat interval were acquired, in total, at a sampling rate of 50 Hz. These samples were subdivided into two components: the first 3500 samples acquired before onset of saline infusion ('rest'), and the remaining 7500 samples acquired during the 150 seconds of acupoint stimulation ('task'). Each of the two components was analysed separately using HRV Analysis Software 1.1 for Windows.[19] Data were detrended using a smoothness priors algorithm to remove LF baseline trends.[20] Power spectral analysis of R-R interval variability was performed using a 1024-point fast Fourier transformation (FFT) with interpolation rate of 2 Hz and a parametric 16-order autoregression model. Results were returned in normalised units of LF and HF, as well as an LF/HF ratio.

HEART RATE RECORDING

During both stimulation experiments, baseline HR was recorded before entering the MR suite and an end-point measurement was recorded after leaving the MR suite, 10 minutes after the end of acupoint stimulation and needle removal.

STATISTICAL ANALYSIS

Data were analysed in SPSS 11.0 (Macintosh Version 11.0.4, SPSS Inc.) to determine any significant modulation of the ANS resulting from the stimulation paradigm. Spectral components of HRV, and HR, across the four acupoints were analysed with paired t-tests to determine any significant differences between baseline and end-point of the experiment. One-way ANOVAs were used to examine any overall difference in acupoint pressure between baseline and stimulations, and amongst stimulations themselves. A multivariate ANOVA (MANOVA) model was used to test whether HR at the four time points was different across the two stimulations.

Results

Since raw pulse-recording data were affected by noise, only selected data were included in this section. Results are presented as mean and standard deviation in Table 1. Measured in normalised units, resting LF ranged from 73.9 to 83.7 (mean = 78.8), resting HF from 21.5 to 25.3 (mean = 23.4), and resting LF/HF from 3.5 to 4.2 (mean = 3.9) across all acupoints. Corresponding ranges during acupoint stimulation were 75.7–83.7 (mean = 81.2) for LF, 20.1–22.2 (mean = 21.2) for HF, and 4.0–4.7 (mean = 4.4) for LF/HF ratio. Paired t-tests of the mean values at rest compared with stimulation showed statistically significant increases in the LF component of HRV for *Sanyinjiao* and *Neiguan* and a significant increase in the LF/HF ratio for *Hegu*. Stimulating *Zusanli* produced no significant changes in any aspect of HRV.

Figure 3 graphs pressure recording at baseline through the five injections from each point. Repeated-measures ANOVA of peak acupoint pressures at the baseline and the five doses measured for the four individual acupoints demonstrated a significant difference (P <0.001) while a similar repeated-measures ANOVA at the five doses only showed no significant difference (P = 0.80). To evaluate the possibility of an 'all or nothing' response to the first injection alone, paired-samples t-tests were conducted to compare baseline intrapoint pressure (prior to injection) with pressure measured after the first injection. There was a statistically significant increase in pressure from rest to first injection at all four acupoint sites as shown in Table 2, as would be expected.

Paired t-test of the HR change from baseline to end-point (10 minutes after end of experiment) showed a statistically significant decrease in HR (summarised in Table 3).

TABLE 1 Mean (and standard deviation) of the spectral analysis of heart rate variability measured at rest and during point injection at four acupoints

	LI4 *Hegu* (n = 20)		SP6 *Sanyinjiao* (n = 21)		PC6 *Neiguan* (n = 18)		ST36 *Zusanli* (n = 17)	
	Rest	Task	Rest	Task	Rest	Task	Rest	Task
LF	83.69 (21.40)	82.93 (18.38)	77.69 (7.22)	83.69** (10.51)	73.88 (11.70)	82.37* (12.63)	74.71 (7.82)	76.82 (6.6)
HF	25.26 (7.89)	20.65 (10.41)	21.49 (7.45)	20.05 (7.19)	24.66 (9.69)	20.52 (6.86)	23.95 (8.88)	22.19 (7.48)
LF/HF	3.48 (0.91)	4.54* (1.58)	4.23 (2.16)	4.73 (1.74)	4.21 (4.17)	4.49 (1.77)	3.73 (1.93)	3.96 (1.64)

Notes: Rest denotes a period of 70 seconds before onset of point injection. Task denotes a period of 150 seconds of PI stimulation.
LF = Low Frequency component in normalised units; HF = High Frequency component in normalised units; LF/HF = calculation ratio LF/HF.
* P < 0.05 ** P < 0.01 (Paired-sample t-test).

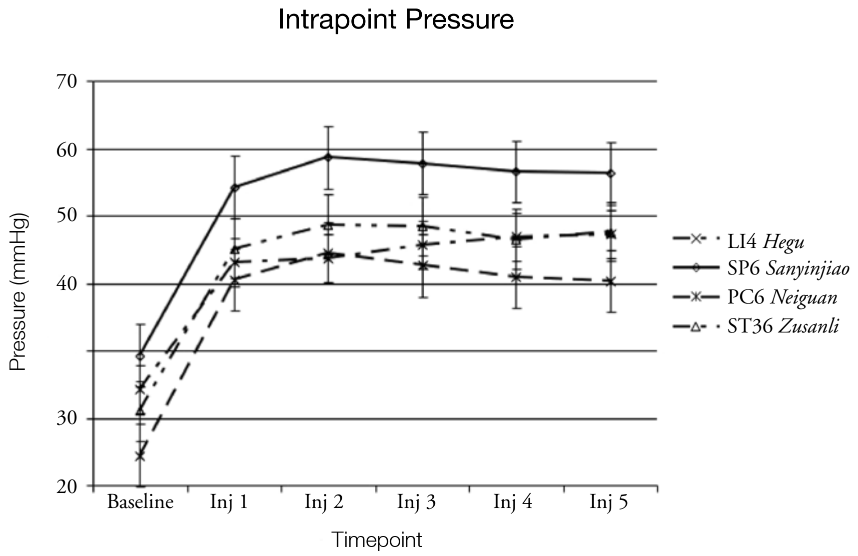

FIGURE 3 Intrapoint pressure measured at five timepoints (mean, SEM)

Timepoint 0 is the baseline pressure recorded after needle insertion and 10 min before first saline injection. Timepoints 1 to 5 are the times of each 0.5 mL injection. (Inj = injection)

MANOVA showed there was no difference in HR resulting from the different acupoint stimulations (Wilks's Lambda = 0.94, $F(4, 75) = 1.224$, $P = 0.308$).

Discussion

This is the first study to compare the effects of acupuncture at different acupoints in the same subject with a novel, reproducible stimulation method, namely PI.

Normal values for the LF and HF spectral components of HRV (in normalised units) are given as: LF 54 ±4 ms^2 and HF 29 ±3 ms^2; LF being seen as a measure of sympathetic tonus while HF reflects parasympathetic tonus and fluctuations caused by spontaneous respiration. The LF/HF ratio (normal range = 1.5–2.0) is used to indicate balance between sympathetic and parasympathetic tone[11] with a decrease in the score being a possible indication of either an increase in parasympathetic or decrease in sympathetic tone.

In this study, LF was elevated whereas HF was reduced beyond the normal range, even in the pre-stimulation phase of the experiment, indicating the subjects were anxious. The reasons for this relate to the specific experimental design. Data were collected during an fMRI experiment designed to study the effects of acupoint stimulation on the CNS. The stimulation was delivered in a novel manner – by point injection. These conditions presented an alien environment that included high noise, confinement to a narrow tunnel and intentionally reduced visual stimulation (all related to the fMRI experiment), and also the needle insertion with expectation of later saline infusion. Understandably these conditions provoked an anxiety response in the subjects as evidenced by the initially elevated LF components and LF/HF ratios. During the stimulatory (task) phase of the experiment there was a significant increase in LF components related to the sympathetic ANS instead of a decrease as we hypothesised, discounting ANS modulation as a cause for the reduction in anxiety reported by subjects.

Changes in HRV varied depending on the acupoints stimulated. *Sanyinjiao* and *Neiguan* both produced elevation of the LF component; *Hegu* caused an increase in the LF/HF ratio without significant changes in LF or HF; *Zusanli* produced no significant modulation of the ANS. Our results are consistent with those reported by Haker, Egekvist and Bjerring,[14] who demonstrated an increase in the LF and HF power spectra during stimulation of *Hegu* with a prolonged sympathetic decrease and an increased LF/HF ratio after stimulation (LF/HF: pre-stimulation = 1.467, stimulation = 1.365, post-stimulation = 1.562). The significant decrease in HR recorded 10 minutes after stimulation of each acupoint, indicating an ultimate increase in parasympathetic activity, is also consistent with the observations made by Haker, Egekvist and Bjerring.[14] The distinct ANS responses at different points need further

TABLE 2 Mean (and standard deviation) with results of paired-sample t-tests of initial intrapoint pressure (mmHg) and pressure after first injection

Acupoint	Baseline	First injection	Paired difference	|t|	df	*P* (2-tailed)
LI4 *Hegu*	34.19 (8.30)	53.00 (11.19)	18.18 (7.41)	11.63	20	< 0.001
SP6 *Sanyinjiao*	39.29 (15.85)	64.24 (24.39)	24.95 (14.26)	8.02	20	< 0.001
PC6 *Neiguan*	24.42 (4.30)	50.47 (20.49)	26.05 (18.45)	6.16	18	< 0.001
ST36 *Zusanli*	31.00 (5.68)	55.11 (7.26)	24.11 (6.77)	15.53	18	< 0.001

TABLE 3 Mean (and standard deviation) with results of paired-sample t-tests of heart rate (min^{-1}) measured at baseline and end of experiment

Stimulation	Baseline	End-point	Paired difference	|t|	df	*P* (2-tailed)
1	66.5 (1.9)	62.2 (1.5)	4.7 (1.3)	3.57	39	< 0.001
2	68.6 (1.7)	64.8 (1.7)	3.7 (1.1)	3.44	39	< 0.001

investigation in healthy and diseased human subjects, and this may shed light on the interpretation of the clinical response or outcome.

The evidence from HRV and HR appear contradictory as HRV indicates increased stress and HR decreased sympathetic response. Evidence from acupuncture analgesia studies suggests that a delayed response to acupuncture exists.[21] Yao[22] demonstrated that acupuncture stimulation produces a temporary increase in sympathetic tone, followed by a more prolonged depression. Our HRV data were collected during the experimental stimulation period and the HR data 10 min after. This time differential might explain the contradictory results.

One of the limitations of this study is the short pulse recording time. The preferred time is five minutes. However, the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology[11] states that a minimum of two minutes is required to address the LF component. The experimental design constrains recording time to a maximum of 220 seconds. HRV analysis standards formalised by the Task Force prefer frequency domain methods for the investigation of short-term recordings as these usually provide results more easily interpretable in terms of physiological regulation. The document states, 'Unless special investigations are performed that use the 24-hour HRV signal . . . the results of the frequency-domain analysis are equivalent to those of the time domain analysis.' Data from the engineering literature indicated that an adequate spectral sample of HRV could be made with a 7.2-second record[5] or with 100 heartbeats.[6] Although we were unable to perform the five-minute recordings usually required for confident interpretation of HRV spectral analysis, our comparison with published data provides preliminary validation for this study and the methods employed. It proved possible to determine short-term modulation of the ANS in response to PI at acupoints.

Since decreased HR is a response to parasympathetic modulation and is a known response to effective acupuncture,[3] it could be inferred that acupoint stimulation by PI is effective as a method of stimulating acupoints. Whether this is a result of the needle insertion alone, as suggested by Marcus,[15] who considers the acupuncture effect to have occurred within the first three seconds of needle placement with no further effect produced over time, or in combination with fluid injection and tissue distension, needs further investigation.

Analysis of intrapoint pressure data demonstrated an apparent 'all-or-nothing' response. The pressure recorded after needle insertion but before any saline injection was significantly different from that recorded immediately after the first injection – an expected result. Further injections produced no significant difference in intrapoint pressure from dose to dose. This may be explained by a dynamic system involving tissue distensibility and saline resorption factors. PI could be used as a research tactic to overcome some of the perceived problems of controls in acupuncture trials. If PI does produce similar effects to traditional methods, and the measured results are a result of tissue distension or minor trauma, an acupoint may be used as its own control.

Conclusion

We have demonstrated the possibility of investigating an immediate response of the ANS to acupoint stimulation. Changes in PSA of HRV indicative of ANS modulation could be demonstrated in a period as short as 220 seconds, much faster than previously reported. Point injection produces responses in HR and HRV that agree with previously published data, a possible indication of the similarity of effect between PI and traditional needling. Despite the anxiety induced by the experimental environment, it was possible to show differing ANS modulation at different points, these changes differing between acupoints. However, the immediate relaxation upon needling insertion is not related to the moderation of the ANS.

Acknowledgments

We thank Dr Greig de Zubicaray (Centre for Magnetic Resonance, UQ) for expert technical assistance and advice on data collection and analysis, and Dr S Wilson (School of Information Technology & Electrical Engineering, UQ) for expert technical assistance with the syringe driver and software.

This work was partially funded by the University of Queensland (External Enabling Grant), the Australian College of Natural Medicine (Project Grant), and the Australian Acupuncture and Chinese Medicine Association (Project Grant 05/02).

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