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RESEARCH ARTICLE

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Acupuncture effects on autonomic responses to cold pressor and handgrip exercise in healthy humans

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Abstract Acupuncture at P6, Liv 3 and Li 4 attenuates the increase in blood pressure during mental stress in healthy humans. The purpose of this study was to test the hypothesis that acupuncture at these points has a generalized depressor effect seen during other stimuli to the autonomic nervous system. Thirty-eight healthy humans (mean age 33 ± 13 years) performed handgrip exercise (n = 20) or the cold pressor test (n = 18) before and after acupuncture at P6, Liv 3 and Li4. To control for repeated interventions, subjects underwent an identical protocol on a different day, during which acupuncture was replaced by quiet rest. Blood pressure and heart rate increased similarly during the first and repeat intervention (handgrip or cold pressor test). Acupuncture did not attenuate the increase in blood pressure (delta mean arterial pressure [MAP] 9.3 ± 1.8 vs 7.3 ± 3.1 mmHg) or the increase in heart rate (delta heart rate [HR] 6.7 ± 2.1 vs 6.0 ± 2.0 bpm) during handgrip exercise. Similarly, acupuncture did not attenuate the increase in blood pressure (delta mean arterial pressure [MAP] 14.8 ± 5.0 vs 14.8 ± 4.8 mmHg) or the increase in heart rate (delta heart rate [HR] 5.3 ± 2.1 vs 8.7 ± 3.6 bpm) during the cold pressor test. In summary, in normal healthy humans, acupuncture at P6, Liv 3 and Li 4 does not attenuate the blood pressure or heart rate responses during handgrip exercise or the cold pressor test.

Key words acupuncture · blood pressure · mental stress · cold pressor test · exercise

Introduction

Acupuncture has been used for thousands of years to treat a variety of diseases, including cardiovascular diseases. Although acupuncture has been shown to be effective in several clinical conditions including post-operative dental pain, and post-operative or chemotherapy-induced nausea [15], its efficacy in cardiovascular diseases, such as hypertension, has been largely untested and remains unproven. The impact of acupuncture on the autonomic nervous system is just beginning to be methodically evaluated in humans [13, 14].

Data from animal models of acupuncture have been consistent with the concept that acupuncture can modulate the autonomic nervous system, specifically the sympathetic nervous system [3–5, 11, 22]. In spontaneously hypertensive rats, in which hypertension has been attributed to sympathetic activation, acupuncture-like stimulation of the sciatic nerve has a depressor effect [22]. In a cat model of ischemia, acupuncture-like stimulation of the median nerve attenuates myocardial ischemia by attenuating hypertension and reducing cardiac demand [11].

In human studies, the effect of acupuncture on the sympathetic nervous system has been variable [10, 14,

20]. Knardahl and colleagues reported that electroacupuncture at Li 11 and Li 4 resulted in a transient increase in muscle sympathetic nerve activity [10]. Sugiyama and colleagues found that sympathetic nerve activity increased during manual needle stimulation at the Tsusanli acupoint [20], followed by a return of sympathetic activity to basal levels after removal of the needle. In our study of normal humans [14], we used mental stress testing in increase blood pressure and activate the sympathetic nervous system. We found that acupuncture at P6, Liv 3 and Li 4 attenuated the blood pressure response to mental stress. This was not mediated by modulation of the sympathetic nervous system, since the sympatho-excitation during mental stress was not attenuated by acupuncture.

In order to test the hypothesis that the depressor effect of acupuncture at P6, Liv3 and Li4 is a robust, generalizable effect seen during other stimuli to the autonomic system, we sought to determine if acupuncture decreased the pressor response during handgrip exercise and the cold pressor test. Both of these interventions elicit greater blood pressure responses than those elicited by mental stress. Further, the blood pressure increases during the cold pressor test and handgrip exercise are largely mediated by peripheral vasoconstriction, in contrast to mental stress, in which an increase in cardiac output plays the predominant role [2, 7.16, 21].

Materials and methods

Human subjects

Following written informed consent, 38 healthy volunteers participated in these protocols. Study protocols were approved by the UCLA Internal Review Board. Mean age of volunteers was (33 ±13 years). All subjects were healthy, as confirmed by medical history and physical examination, and were not taking medications. Volunteers were nonsmokers, and abstained from caffeine on the day of the study. All were acupuncture naïve.

Acupuncture

All acupuncture was performed by the same certified acupuncturist (JYL). The skin was cleaned with alcohol. Acupuncture needles (4 cm, 0.25-mm diameter; Natural, Suzhou Guso Acupuncture and Moxibustion Appliance) were inserted into the right Li4 (at the highest point of the m. adductor pollicis with the thumb and index finger adducted; Hegu, Large intestine 4), bilateral Liv3 (between first and second metatarsal bones, 2 fingerbreadths proximal to the margin of the web; Taichong, Liver 3) and right P6 (between tendons m. palmaris longus and m.flexor carpi radialis, 2 fingerbreadths proximal to the transverse crease of the wrist; Neiguan, Pericardium 6) points and manually stimulated for approximately 15 seconds to achieve the De Qi sensation of heaviness, fullness, or soreness. Needles were left in place while volunteers rested for 15 minutes, and then needles were removed.

Handgrip exercise

Before each experimental session, maximal voluntary contraction (MVC) was determined in the nondominant arm using a handgrip dynamometer (Stoelting). Subjects were reminded to breathe normally during exercise to avoid inadvertent performance of a Valsalva maneuver. Static handgrip exercise was performed for 2 minutes at 30 % of the subject's MVC.

Cold pressor test

The subject's nondominant hand was placed in an ice water slurry (0 °C) for 2 minutes.

Blood pressure and heart rate

Blood pressure and heart rate were measured continuously using an automated sphygmomanometer (Press-Mate 8800, Colin Medical Instrument, San Antonio, TX). Systolic, diastolic, and mean blood pressures were automatically measured every 20–30 s at baseline and during mental stress. The accuracy of the Colin 8800 is within the ±5 mmHg required by the Association for Advanced Medical Instruments, and it is found to be ±2.81, ±0.04, and ±0.96 mmHg for systolic, diastolic, and mean blood pressure, respectively, compared with auscultatory methods [12].

Experimental protocols

Protocol 1: handgrip exercise (Fig.1)

The purpose of this protocol was to determine if acupuncture modulates the blood pressure response during static handgrip exercise in normal healthy humans. Subjects were studied in the supine position. After placement of sphygmomanometer cuffs and determination of MVC, subjects rested in a quiet room for 10 minutes. Baseline measurements of blood pressure and heart rate were determined for 2 minutes. Then static handgrip exercise at 30 % of the subject's MVC was performed for 2 minutes. Blood pressure and heart rate were measured twice during each minute. The subject then rested for 40 minutes. Acupuncture was then performed as described above. The acupuncture needles were then removed, and the exercise paradigm was repeated immediately.

Protocol 2: cold pressor test

The purpose of this protocol was to determine if acupuncture modulates the blood pressure response during cold pressor test in normal healthy humans. The protocol was performed in the same sequence as the handgrip exercise (above), except that the cold pressor test was performed in place of handgrip exercise. Immediately following CPT, subjects were asked to rate the level of discomfort associated with hand immersion on a scale of 0–100, with "0" corresponding to no pain, and "100" corresponding to maximal pain.

Protocol 3: control studies

The control studies were performed on a different day, in random order, from the acupuncture studies. The purpose of the time control study was to determine if repetition of exercise or the cold pressor test would effect the results. Each subject enrolled in the handgrip exercise protocol or the cold pressor test also participated in a control session. During this session, 20 minutes of acupuncture was replaced by 20 minutes of quiet rest. The order of the study days (acupuncture or control) was randomized.

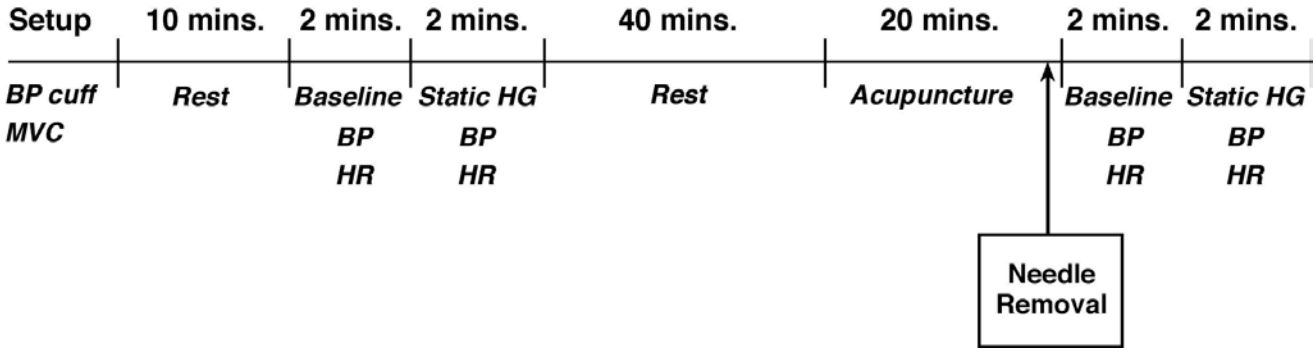

Fig. 1 Experimental protocol. After the blood pressure cuff was positioned, and maximum voluntary capacity (MVC) was determined, the subject had a 10 minute rest period. Baseline blood pressure (BP) and heart rate (HR) were then measured for 2 minutes followed by 2 minutes of static handgrip (HG) exercise at 30 % MVC. Following a 40-minute recovery period, acupuncture was performed (see Methods for details of acupuncture). Needles were removed after 20 minutes. Baseline BP and HR were again measured for 2 minutes, followed by repeat static HG exercise

Data analysis

Statistical analysis was performed using paired t-tests and repeated measure ANOVA. Data were analyzed at baseline and peak during the final minute of intervention (handgrip or cold pressor test). Probability values of < 0.05 were considered statistically significant.

Results

All subjects tolerated acupuncture and cold pressor testing well. No subjects withdrew during the study protocols.

Static handgrip exercise (n = 20)

Acupuncture day

During static handgrip exercise, before acupuncture, mean arterial pressure (MAP) increased (base vs peak: 81 ± 2 vs 91 ± 2, $p < 0.0001$) and heart rate increased (base vs peak: 69 ± 2 vs 76 ± 2, $p = 0.009$). Following acupuncture, baseline MAP (81 ± 2 vs 84 ± 2, $p = 0.12$), and baseline heart rate (69 ± 2 vs 66 ± 2, $p =$ NS) were unchanged. During static handgrip exercise following acupuncture, MAP increased (base vs peak: 84 ± 2 vs 92 ± 3, $p < 0.0001$) and heart rate increased (base vs peak: 66 ± 2 vs 73 ± 2, $p = 0.01$). The increases in MAP and heart rate during exercise were not significantly different following acupuncture compared to before acupuncture (Fig. 2).

Control day

Before the rest period, during static handgrip exercise, MAP increased (base vs peak: 84 ± 2 vs 91 ± 2, $p < 0.0001$) and heart rate increased (base vs peak: 73 ± 3 vs 77 ± 52, $p = 0.01$). Following the rest period, baseline MAP (84 ± 2 vs 81 ± 1, $p = 0.10$), and heart rate (73 ± 3 vs 70 ± 3, $p =$ NS) were unchanged. Following the rest period, during static handgrip exercise, MAP increased (base vs peak: 81 ± 1 vs 89 ± 2, $p < 0.0001$) and heart rate increased (base vs peak: 70 ± 3 vs 76 ± 2, $p = 0.01$). The increases in MAP and heart rate during exercise were not significantly different following the rest period compared to before the rest period (Fig. 2).

Cold pressor test (n = 18)

Acupuncture day

Before acupuncture during cold pressor testing, MAP increased (base vs peak: 83 ± 2 vs 99 ± 4, $p < 0.0001$) and heart rate increased (base vs peak: 70 ± 2 vs 76 ± 3, $p = 0.015$). Following acupuncture, baseline MAP (83 ± 2 vs 84 ± 2, $p =$ NS), and heart rate (70 ± 2 vs 67 ± 2, $p =$ NS) were unchanged. Following acupuncture during cold pressor testing, MAP increased (base vs peak: 84 ± 2 vs 99 ± 4, $p < 0.0001$) and heart rate increased (base vs peak: 67 ± 2 vs 76 ± 3, $p < 0.0001$). The increases in MAP and heart rate during exercise were not significantly different following acupuncture compared to before acupuncture (Fig. 2). The subjects' perception of discomfort associated with CPT was not different following acupuncture (62 ± 20 vs 62 ± 17, $p =$ NS).

Control day

Before the rest period, during cold pressor testing, MAP increased (base vs peak: 81 ± 2 vs 97 ± 3, $p < 0.0001$) and heart rate increased (base vs peak: 70 ± 2 vs 79 ± 3, $p = 0.0001$). Following the rest period, baseline MAP (81 ± 2 vs 78 ± 2, $p =$ NS), and heart rate (70 ± 2 vs 67 ± 3, $p = 0.009$) were not significantly different. Following the rest period, during cold pressor testing, MAP increased (base vs peak: 77 ± 2 vs 94 ± 3, $p < 0.0001$) and heart rate increased (base vs peak: 67 ± 3 vs 77 ± 3, $p < 0.0001$). The increases in MAP and heart rate during exercise were

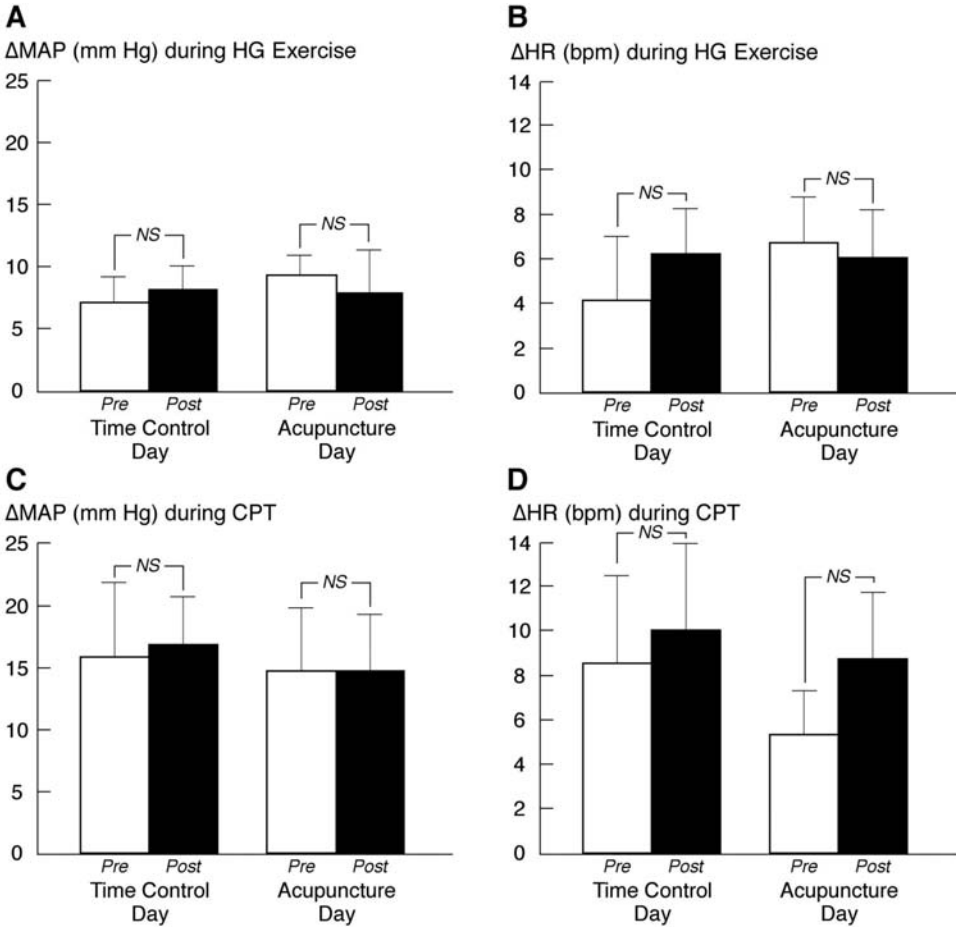

Fig. 2 Acupuncture effects on delta mean arterial pressure (MAP) and heart rate (HR) during handgrip (HG) exercise and cold pressor test (CPT). **A** On the time control day, the increase in MAP was the same during HG exercise upon repeated studies. Similarly, on the acupuncture day, the increase in MAP during HG exercise was the same pre/post acupuncture. **B** On the time control day, the increase in HR was the same during HG exercise upon repeated studies. Similarly, on the acupuncture day, the increase in HR during HG exercise was the same pre/post acupuncture. **C** On the time control day, the increase in MAP was the same during CPT upon repeated studies. Similarly, on the acupuncture day, the increase in MAP during CPT was the same pre/post acupuncture. **D** On the time control day, the increase in HR was the same during CPT upon repeated studies. Similarly, on the acupuncture day, the increase in HR during CPT was the same pre/post acupuncture

not significantly different following the rest period compared to before the rest period (Fig. 2). The subjects' perception of discomfort associated with CPT was not different upon repeat CPT (63 ± 22 vs 62 ± 16, p = NS).

Discussion

In studies of animal models of acupuncture, acupuncture in the forelimb or hindlimb has been shown to have a sympatholytic/depressor effect [3–5, 11, 22]. These studies have led to the concept that acupuncture needling activates somatosensory nerves. These nerves are integrated centrally, releasing opioids, and/or nitric oxide, which then inhibit central sympathetic neural outflow [3–5]. Studies in humans investigating the effects of acupuncture on the autonomic nervous system, and its underlying mechanisms, are just beginning [13, 14].

The main findings from these studies are: 1) acupuncture at P6, Li4 and Liv3 does not attenuate the pressor response elicited by handgrip exercise or the cold pressor test in normal healthy humans; and, 2) in control experiments, repetition of the stimulus (either handgrip or cold pressor test) elicits blood pressure and heart rate responses indistinguishable from those elicited by the first stimulus.

In our prior study [14], we followed a similar protocol as was used in these studies, substituting handgrip exercise and cold pressor testing for mental stress. Microneurographic recording of muscle sympathetic nerve recording was not performed in this study, since no effect of acupuncture at these points was seen in our previous study. In this study, in contrast to our prior study of mental stress, we found no depressor effect of acupuncture during either stimulus, handgrip exercise or cold pressor testing. Possible explanations for these findings are 1) the acupuncture points selected in these studies are specific for mental stress only; 2) the pressor responses during these stimuli in this study were more robust, and overwhelmed any potentially mitigating effects of acupuncture; or 3) the mechanisms of blood pressure elevation by the handgrip/cold pressor stimuli are sufficiently different from those underlying the pressor effect of mental stress testing, and perhaps less susceptible to modulation by acupuncture. These possibilities will be addressed separately below.

The acupuncture points used in these protocols were selected because they had been effective in lowering blood pressure responses during mental stress testing, and our purpose was to determine if this was a generalized depressor effect, or if it was confined to the setting of mental stress. These points were selected for our prior study because they are associated with stress reduction (Liv3 and Li4) [9] or may be used in the setting of cardiovascular disease, such as hypertension (P6) [6, 17, 18]. The selection of acupoints by acupuncturists in the treatment of the vast majority of diseases is not standardized, and is based on tradition and experience, not "scientific evidence" as judged by Western standards [8, 9]. The specificity of acupoints is highly controversial. We can conclude that these 3 acupoints do not result in a generalized depressor effect during all stimuli to the autonomic nervous system, but it remains unknown whether other acupoints might have a depressor effect during handgrip or the cold pressor test.

The peak increases in blood pressure during these handgrip/cold pressor stimuli were 2 to 3 times those elicited by our mental stress paradigm. The cold pressor test is a very potent pain stimulus [1]. One could argue that such potent pressor stimuli may overwhelm any depressor effect of acupuncture. However, if it were just a matter of degrees, one may expect to see at least a partial modification of the pressor response during these stimuli. No effect on the blood pressure response was detectable, but we can not exclude that a small effect may be detectable in a much larger sample size. Ashton and colleagues [1] reported that acupuncture at Daling (PC 7) increased the pain threshold during the cold pressor test, but blood pressure was not measured during their study. In contrast, in our study we did not find a reduction in perceived pain following acupuncture. The difference between this report and our study may be explained by the specific acupoints studied.

Interestingly, in contrast to the more robust increases in blood pressure during handgrip/cold pressor test compared to mental stress, the increases in heart rate were similar during handgrip/cold pressor stimuli and mental stress. This disparity between the increases in heart rate and the increases in blood pressure are consistent with the different mechanisms underlying the pressor responses during handgrip/cold pressor stimuli and mental stress. The increase in blood pressure during handgrip exercise and especially the cold pressor test are mediated largely by increases in total vascular resistance [2, 7, 16]. During cold pressor test and handgrip exercise, vascular resistance increases in the renal, splanchnic and non-working muscle circulations, and this increase in vascular resistance is mediated by activation of the sympathetic nervous system [7, 14, 16, 21]. Increases in cardiac output also contribute to the increase in blood pressure, but proportionally less than during mental stress [16]. In contrast, during mental stress, the increase in cardiac output largely underlies the increase in blood pressure, with some contribution from renal vasoconstriction [2, 13, 16]. Muscle vascular resistance does not increase, and may actually decrease during mental stress [2, 16]. Thus, although all 3 stimuli activate the autonomic nervous system, the mechanisms underlying the circulatory adjustments, and their relative contribution, differ.

Limitations

Only three acupoints were tested in this study, and these were chosen because they had been efficacious in attenuating blood pressure responses during mental stress [9]. It is possible that other acupoints or other stimulation protocols (e. g. electroacupuncture), not studied in the present study, may attenuate the blood pressure responses elicited by handgrip exercise or the cold pressor test. The optimal timing following acupuncture needling to test its effects on the autonomic nervous system is not known. In our study, the subjects performed the provocative test (handgrip or cold pressor test) 20 minutes following acupuncture needling, since this timing was effective in our study of acupuncture and mental stress. However, it is possible that the maximal acupuncture effect on the autonomic nervous system may have been missed. We studied healthy volunteers, yet acupuncture has been found to have more potent effects in animal models of hypertension or sympathetic overactivity [22]. Thus, our findings may not be extrapolated to patients with hypertension or sympathetic activation.

In summary, in normal healthy humans, acupuncture does not attenuate the blood pressure or heart rate responses during handgrip exercise or the cold pressor tests.

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