No Effect Of Chinese Acupuncture On Isocapnic Hyperventilation With Cold Air In Asthmatics, Measured With Impulse Oscillometry

Monica Malmström, Johan Ahlner, Christer Carlsson, Birgitta Schmekel

Introduction
Asthma is characterised by inflammation of the airway mucosa, reversible airway obstruction and increased responsiveness of the bronchial tree to a variety of specific and non-specific stimuli. Bronchial hyperresponsiveness (BHR) is thought to be related to inflammation in asthmatic airways. Isocapnic hyperventilation of cold air (IHCA) is an indirect bronchial challenge technique to influence bronchial smooth muscle. The technique is established, reproducible and is considered to be able to distinguish asthmatic patients from a general population. Bronchial obstruction and BHR is commonly treated with bronchodilators and anti-inflammatory drugs, i.e. beta-2 agonists and corticosteroids. Asthma imposes a significant and increasing economic burden on society due to sick leave, costs of asthma care and, for individuals affected by the disease, restricted physical activity. In an attempt to limit the pharmaceutical costs of asthma treatment, a number of complementary treatments have been practised. Several studies of the effect of acupuncture on the condition have been evaluated and a positive effect on the disease has been suggested after a single or a few treatments. It has been claimed, however, that the design of some of the studies does not allow firm conclusions regarding the efficacy of acupuncture. This has also been suggested for the few published long-term studies. Meta-analyses and reviews of the literature have concluded that more rigorous studies on the efficacy of acupuncture in asthma are urgently needed.

The aim of this study was to evaluate the effect of 15 weeks treatment with traditional Chinese acupuncture on bronchial provocation with IHCA in stable asthmatic patients. A parallel group randomised placebo controlled trial with evaluator blinding was conducted on patients with mild and moderate asthma.

Summary
The cost to society and the individual of treating asthma has been increasing in developed countries. This has given rise to studies of the efficacy of complementary treatments. The aim of this study was to evaluate the efficacy of traditional Chinese Acupuncture in patients with mild asthma. The method used for evaluation of efficacy was total airway resistance at 5Hz (R5) as measured by impulse oscillometry (IOS) – a forced oscillation technique, at baseline and after a bronchial challenge with voluntary isocapnic hyperventilation of cold air (IHCA). The study was a parallel group randomised placebo controlled trial with evaluator blinding. Twenty-seven asthmatics were recruited and 24 completed the study, 10 of them received acupuncture and 14 received a placebo treatment (mock-TENS). Treatment continued for 15 weeks, and efficacy was tested two weeks following the last treatment. Randomisation resulted in female over representation in the acupuncture group, but lung-function and bronchial responsiveness to IHCA were comparable in the two populations before the start of treatment (p>0.05 vs p>0.05). There were no statistically significant effects of the treatment before (p>0.05) or after IHCA (p>0.05) in either of the groups. The statistical power of the study to show a clinically relevant difference in bronchial responsiveness to IHCA after treatment was near 80%. We conclude that there were no significant effects of traditional Chinese Acupuncture on airway status in our patients with asthma.

Keywords
Acupuncture, asthma, cold air challenge, bronchial hyperresponsiveness.
Methods

Patients

Fifty-eight patients were randomly selected from a pool of 200 patients monitored and treated for dyspnoea in two general practitioners’ offices. Inclusion criterion for this study were a clinical diagnosis of asthma, as defined by a history of recurrent attacks of wheezing and variable airway constriction, and a significant bronchial response to IHCA, as measured by impulse oscillometry (IOS). IOS after IHCA has previously been shown to have a high discriminative capacity to correctly diagnose asthma.13 To ensure stable conditions, patients on regular inhaled corticosteroids (ICS) were recruited only if the individually titrated dose, based on clinical grounds, was 800 £g/day or less. Oral treatment with corticosteroids was not allowed, and treatment by means of acupuncture or other complementary methods, or participation in any other clinical study, was not allowed for three months prior to the study. Significant upper airway infection in the three weeks preceding any test day resulted in exclusion from evaluation.

Twenty-seven patients met the inclusion criteria. The mean age of these patients was 41±11 years, and their mean forced expiratory volume in one second (FEV1) was 93±11% of the predicted normal value.14;15 Nine of the patients had a known allergy to aeroallergens, such as animal dander or house dust mites, and nine patients had a seasonal allergy to birch or grass pollen. All tests performed on atopic patients were performed out of season. All but three asthmatics used short acting $\beta_2$ receptor agonists on rare occasions, but $\beta_2$ receptor agonists were not allowed eight hours prior to any lung function test. Thirteen of the patients were randomly allocated to acupuncture and fourteen to a placebo intervention (see table 1). Twenty-one of the patients had regular treatment with an ICS (Budesonid, Astra, Södertälje, Sweden, range 400-800 mcg/day). There was a slight, but not statistically significant, tendency to inhale higher doses of ICS in the acupuncture group than in the placebo group (average dose was 600 vs. 400 mcg/day, p>0.05, Mann Whitney U-test). None of the patients changed their doses of ICS during the course of the study.

The Research Ethics Committee at the Faculty of Health Sciences, University of Linköping, Sweden approved the trial. All subjects gave informed consent prior to participation.

Study Design and Procedure

Eligible patients completed diary cards of peak expiratory flow rate (PEFR) measured twice a day, and the number of actuations of rescue medication (i.e. short-acting $\beta_2$ receptor agonists) during three separate weeks in a run-in period of up to twelve weeks. After run-in and stratification for the presence or absence of allergy, patients were randomly allocated to receive either a series of treatments with traditional Chinese acupuncture or a series of placebo treatments, which were sham transcutaneous electrical nerve stimulation (mock-TENS). Randomisation was performed according to a predefined random number list, which was kept secret for the technician (evaluator) who performed all lung function tests. Acupuncture or placebo treatments were given over a 15 week period, and were performed by one experienced nurse. Efficacy of treatment was measured approximately 2 weeks after completion of the treatments. Total airway resistance at 5Hz ($R_5$) was measured by means of an impulse oscillation technique at baseline and after a challenge with IHCA. FEV1 and subjective scoring of chest tightness or discomfort (10-grade Borg scale16) were recorded at baseline and after IHCA.

Functional Tests

Lung Function Test

Tests were performed by means of an MS-IOS Digital instrument (Erich Jaeger AG, Würzburg, Germany) attached to an ALR 486 computer (Evolution IV, Irvine, CA, USA). The equipment was calibrated daily to room temperature and

<table>
<thead>
<tr>
<th>Table 1 Baseline data.</th>
<th>Acupuncture (n=13)</th>
<th>Placebo (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (F/M)</td>
<td>10/3</td>
<td>5/9</td>
</tr>
<tr>
<td>Age (years)</td>
<td>42 [36-48]</td>
<td>39 [33-46]</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160 [156-173]</td>
<td>171 [166-176]</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74 [67-82]</td>
<td>80 [71-80]</td>
</tr>
<tr>
<td>FEV1 (% pred.)</td>
<td>91 [83-98]</td>
<td>95 [88-101]</td>
</tr>
<tr>
<td>$R_5$ (kPa/l/s)</td>
<td>0.50 [0.39-0.60]</td>
<td>0.47 [0.39-0.55]</td>
</tr>
</tbody>
</table>

Figures given are means with confidence intervals [95% CI].
pressure, and calibrated regarding flow and volume. Total airway resistance (R5) was selected to indicate airway status. Measurements at baseline were performed in duplicates and variability in values was not allowed to exceed 10%. Repeatability index (Ri) as calculated by the formula (variance between individuals / variance between individuals + variance within individuals) was 0.96 for R5. The same equipment was used for measurements of FEV1. The highest volume recorded in three successful FEV1 manoeuvres was documented at baseline and a single recording was performed at seven minutes after bronchial challenge.

**Bronchial Challenge**

Provocation was performed as previously described by a four-minute isocapnic hyper-ventilation test (dry cold air at approximately -15°C and 70% of predicted maximal voluntary ventilation).13 R5 was documented prior to, and at four and six minutes after, challenge with IHCA. A significant bronchial response to IHCA was defined by an increase in R5 of at least 30% after challenge.13 A therapy-induced change in airway responsiveness of at least 25% was defined to be a clinically relevant difference. Subjective perception of chest tightness or discomfort was rated on a 10-grade Borg scale before and at five minutes after completion of IHCA.

**PEF Variability**

PEFR was recorded by patients in their diary cards during the run-in period, and these data formed the basis for calculations of mean PEFR variability expressed as a percentage (mean morning PEFR value minus mean evening PEFR value / mean value of morning and evening values).

**Treatments**

A nurse (MM) who had practised traditional Chinese acupuncture for more than five years administered the acupuncture and the mock-TENS. Both groups of patients received an identical number of treatments. They were performed twice a week for the initial five weeks and once a week for the following 10 weeks, thus each patient had a total of 20 treatments. The nurse who was giving the treatments spent 30 minutes with each patient at each session, and she was instructed not to discuss the study or the design of the study. The patients were informed that the study was designed to compare traditional Chinese acupuncture with a new form of weak electrical stimulation over the upper back. This was said to be a new method that could be equally effective as acupuncture.

**Acupuncture**

The acupuncture points were chosen according to standard textbooks.17 Acupuncture needles were inserted into points at an angle of 90 degrees, and stimulation was applied using a manual method. The nurse was instructed not to discuss the study or the design of the study. The patients were informed that the study was designed to compare traditional Chinese acupuncture with a new form of weak electrical stimulation over the upper back. This was said to be a new method that could be equally effective as acupuncture.

**Placebo**

TENS electrodes were applied in a paravertebral and bilateral position on the upper part of the dorsal thorax, at the level of T3 to T5. The stimulators were used in the usual way, except that no current actually passed between the electrodes. During stimulation flashing lamps were displayed, visible to the patients, as on common TENS-stimulators.

**Statistical Methods**

Mean and 95% confidence interval [95%CI] were used to describe normally distributed data, and median value (lower to upper quartile) was used to describe non-normally distributed data unless otherwise stated. T-test for dependent or independent samples or Mann-Whitney U-test.
sign test or Fisher's exact test were used for calculating differences. A p-value of 0.05 or less was set to indicate statistical significance. A two group t-test with a 0.05 two-sided significance level would have more than 85% power to detect a 25% difference in group mean responsiveness, assuming that the common standard deviation was 20%, when the sample sizes in the two groups are 13. Commercially available programs were used for statistical or power calculations (Statistica 6.0, Statsoft, Tulsa, Oklahoma, USA and nQuery Advisor 4.0, Statistical solutions, Saugus, MA, USA, respectively).

Results

Twenty-four of the 27 patients completed the study. One patient was withdrawn from the final evaluation due to an upper airway infection. Two female patients discontinued treatment and did not participate in the final evaluation of effect, and these subjects were considered as dropouts. Reported reasons to discontinue the study were not related to subjective discomfort of the treatment. All three patients had been allocated to acupuncture. Randomisation, withdrawal and dropouts thus created a group containing ten eligible patients who had been treated with acupuncture, while all 14 patients who completed placebo treatment were eligible.

Patient characteristics of both groups are presented in table 1. There tended to be a higher proportion of females in the acupuncture group as compared to the placebo group. Baseline status was similar in the two groups of patients, as recorded by PEFR variability or number of actuations of rescue medication recorded by patients during a run-in period, or as recorded by pulmonary function tests or bronchial challenge of IHCA at entry into the study (see table 2). There was a significant inverse association between R5 at baseline and body height (r=-0.41, p<0.04). The skewed sex-distribution in the groups and significantly shorter females (p<0.01) may have influenced values of airway resistance, giving higher relative values of R5 at baseline in the group with more females. However, there was no significant difference in total airway resistance at baseline between the treatment groups after correction for body height (84 [67-101] kPa/l/s x cm vs. 80 [68-92] kPa/l/s x cm, p>0.05). Peak responses to IHCA as recorded by IOS, occurred at 4 or 6 minutes after challenge in all patients. There were no differences between the magnitudes of airway responses recorded in the two groups, whether responses were recorded by IOS at 4 or 6 minutes after IHCA (p>0.05. See table 2) or by FEV1 at 7 minutes after IHCA (data not shown, p>0.05).

Subjective perception of chest discomfort or tightness after IHCA at entry into the study tended to be less pronounced in the acupuncture group than in the placebo group (3 [2-3] vs. 4 [3-4], p=0.02, Mann Whitney U-test) despite similar ratings at baseline before challenge (p>0.05). There was no obvious association between perception of discomfort and dose of regularly taken ICS or gender.

<table>
<thead>
<tr>
<th>Table 2 Results.</th>
<th>Acupuncture (n=10)</th>
<th>Placebo (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Run in period</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEFR variability (%)</td>
<td>1.5 (0.7-5.0)</td>
<td>0.7 (0.1-7.0)</td>
</tr>
<tr>
<td>Actuation of rescue medication (no.)</td>
<td>0 (0-1.1)</td>
<td>0 (0-1.7)</td>
</tr>
<tr>
<td><strong>Before treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R5 baseline value (kPa/l/s)</td>
<td>0.50 [0.38-0.61]</td>
<td>0.47 [0.39-0.55]</td>
</tr>
<tr>
<td>R5 peak value after IHCA (kPa/l/s)</td>
<td>0.76 [0.62-0.89]</td>
<td>0.89 [0.71-1.06]</td>
</tr>
<tr>
<td><strong>After treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R5 baseline value (kPa/l/s)</td>
<td>0.53 [0.40-0.65]</td>
<td>0.47 [0.39-0.56]</td>
</tr>
<tr>
<td>Change in baseline R5 (%)</td>
<td>8 [-10 to +26]</td>
<td>1 [-10 to +11]</td>
</tr>
<tr>
<td>R5 peak value after IHCA (kPa/l/s)</td>
<td>0.74 [0.54-0.93]</td>
<td>0.93 [0.70-1.16]</td>
</tr>
<tr>
<td>Change in response to IHCA (%)</td>
<td>-7 [-23 to +9]</td>
<td>4 [-8 to +16]</td>
</tr>
</tbody>
</table>

Figures given are means with confidence intervals [95% CI].
There were no statistically significant changes in baseline values of R₅ or bronchial responses to IHCA in either treatment groups after completion of treatments (p>0.05, both comparisons, see table 2). On an individual basis, airway responsiveness deteriorated at least 25% in one of the acupuncture patients and four of the control patients and improved in one from each group. Collectively, there was no significant impact on bronchial responsiveness to IHCA as a result of acupuncture (p>0.05, Fishers exact test). Simulating data as ‘best case’ or ‘worst case’ responses in the two dropouts resulted in a statistically significant improvement in the former (p=0.02) but not the latter case (p>0.05). Taking all data together, there were no obvious or statistically significant effects on airway status following 15 weeks treatment with acupuncture.

Power calculation performed after completion of the study disclosed a 78% power to detect a 25% difference in group mean responsiveness to IHCA of 10 and 14 evaluated patients respectively, using a two group t-test with a 0.05 two-sided significance level.

Patients, who had received acupuncture, tended to rate chest discomfort or tightness elicited by IHCA lower than the placebo patients did (2.5 (2-3) vs. 4 (3-4), p=0.02, Mann Whitney U-test) despite similar ratings before the challenge. The subjective perception of chest discomfort or tightness elicited by bronchial challenge was generally low, and did not change after treatments by means of either acupuncture or placebo (p>0.05, sign test).

Discussion

This study showed no significant improvement in bronchial status after 20 sessions of acupuncture over 15 weeks. Twenty-four patients with mild to moderate asthma completed the study during a stable phase of their disease, as reflected by stable airway condition, bronchial responsiveness to IHCA and subjective perception of chest discomfort or tightness. The primary outcome was responsiveness to bronchial challenge, which is frequently used in pharmaceutical trials. We chose an indirect bronchoconstrictor stimulus, since challenge with exercise or cold air was felt to have better clinical relevance than direct methods such as inhaled stimuli, such as methacholine or histamine aerosol. IHCA was judged to be an adequate test model since alternative comparative treatments – anti-inflammatory or bronchodilator drugs, are known to lessen bronchial hyperresponsiveness (BHR) to IHCA. Baseline values of resistance at 5Hz were 30% higher in our asthmatics than in healthy volunteers, and almost 50% higher than baseline values of resistance at 8Hz recorded in a group of stable asthmatics who experienced an on average 26% decrease of responsiveness to IHCA after treatment with an inhaled corticosteroid for six weeks. Based on these data we postulated that a 25% improvement in BHR would be a realistic possible effect of treatment in our study. Measurements of bronchial status using IOS was considered to be a more sensitive method of detecting changes in bronchial tone than forced expirations. The difference relative to forced expirations may rely on the fact that performance of the FEV₁ manoeuvre includes a preceding deep inhalation that may induce changes in bronchial dynamics in susceptible patients. Furthermore, neither the technician nor the test subject is able to influence results recorded by impulse oscillometry in contrast to forced expiratory manoeuvres.

A cross over design would have reduced the number of participants required and increased power of the study. Such a design would, on the other hand, have introduced a possible risk of error due to carry over effects. Furthermore, by increasing the study-time for each patient, there may have been increased variability in asthma symptoms. In order to avoid the risk of these effects, we used a parallel group study design.

Before interventions, the two groups of patients were similar regarding activity of disease as mirrored by BHR and baseline lung function tests. Since asthma is associated with predictable as well as unpredictable variability in status, our patients were randomised and stratified with respect to presence of known allergy. To minimise the risk of increased BHR due to exposure to allergens, all subjects with seasonal allergy were studied off-season. Randomisation, withdrawal and dropouts created a group with merely ten patients treated with acupuncture while all fourteen remained for evaluation in the placebo group, leaving us with a power of near 80% to...
detect a relevant difference in efficacy. Simulation of data as ‘worst case’ or ‘best case’ did not result in a significant alteration of our conclusions. To reach a power of 90% in this study, an additional eight patients with similar characteristics would have been needed. However, considering the lack of any trend in the results, it is unlikely that there would have been any significant difference had we been able to include eight more asthmatics.

A double blind efficacy test is normally required in studies of efficacy of asthma treatments. Blinding of studies on the efficacy of acupuncture has been much disputed. We allowed for an evaluator blind study, since it is probably not possible to find an adequate double-blinded control intervention, due to the fact that acupuncture is invasive and recognisable. Using needles in the ‘wrong’ places on the body (according to traditional ideas) is not a physiological inert intervention, and therefore not an ideal placebo control either. Many suggestions of placebo treatments have been made of which there are two main methods, mock-TENS and minimal acupuncture. Minimal acupuncture involves minimal surface stimulation, and needles are positioned at, or away from, traditional acupuncture points or trigger points, inserted 1-2 mm and stimulated very lightly. Clinical effects have, however, been reported after such minimal acupuncture. Mock-TENS was first used in a trial of acupuncture in the treatment of low back pain. Recently, a placebo acupuncture needle has been developed, but this device also produces a sensation and is therefore not completely inert. We chose mock-TENS as a placebo treatment since the stimulus was judged to be insignificant.

We asked the patients to score their subjective perception of chest tightness or discomfort at baseline as well as after the bronchial challenge. Randomisation had created female over-representation in the acupuncture treatment group. This group of patients tended to rate subjective scoring of chest tightness after IHCA lower than the placebo group, and this was true before as well as after the treatment period. We do not know if the low scoring was associated to any possible effect of ICS, gender or chance. However, it is notable that this study was solely evaluator blinded, and patients may well have been aware of what kind of treatment they were given, which might introduce a risk of bias in the patient’s own evaluation of symptoms. It is also noted that there was no significant treatment-related effect in scoring of subjective symptoms.

An alternative tool to monitor asthma in long-term comparative studies would be to compare the number of exacerbations experienced. Our patients had a mild form of asthma and none of them reported any exacerbation of asthma during the course of this study, which lasted approximately 17 weeks. Another possible way to evaluate efficacy of any treatment given over several weeks, might be questionnaires and tests of quality of life, or requirements of rescue medication. The number of inhaled doses of rescue medication was negligible in our patients with mild asthma, presumably due to the fact that most of our patients took ICS on a regular basis. Questionnaires and tests of quality of life normally require a larger number of patients in each study group to allow firm conclusions on the efficacy of treatments. PEFR variability has also been used as an index of disease activity in asthma, but the use of this index as a proxy for changes in bronchial responsiveness has been questioned. An additional way of studying effectiveness from the community perspective might be to compare cost-effectiveness between acupuncture and conventional anti-inflammatory treatment. In this first step, we limited the study to evaluate only primarily physiological effects.

We conclude that traditional Chinese acupuncture is no more effective than placebo (mock-TENS) in controlling asthma symptoms, airway contraction and bronchial responsiveness to cold air hyperventilation in patients with mild to moderate asthma. We found no objective beneficial physiological effect related to treatment with acupuncture or mock-TENS in our patients.

Acknowledgement
The assistance of Mrs Elisabeth Forsström is greatly appreciated. This study was supported by The Swedish Medical Research Council no. 11553, The Heart and Lung Foundation, The Asthma and Allergy Foundation and Östergötlands County Council, The Health Research Council in the south-east of Sweden no. F97-112.
Figure 1  Total airways resistance following acupuncture as a percentage of baseline.

Figure 2  Total airways resistance following placebo as a percentage of baseline.

Figure 3  Response to IHCA following acupuncture as a percentage of baseline.

Figure 4  Response to IHCA following placebo as a percentage of baseline.
### Reference List


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*Acupunct Med* 2002 20: 66-73
doi: 10.1136/aim.20.2-3.66

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