Autonomic Function in Seasonal Allergic Rhinitis and Acupuncture – an Experimental Pilot Study within a Randomized Trial

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Keywords
Acupuncture · Complementary and alternative medicine · Seasonal allergic rhinitis · Autonomic nervous system · Heart rate variability

Summary
Background: Acupuncture was shown to reduce symptoms of seasonal allergic rhinitis (SAR). The present study investigated (a) whether autonomic function would differ in SAR patients and healthy controls, and (b) whether acupuncture treatment would evoke changes in autonomic function compared to sham acupuncture. Patients and Methods: SAR patients (n = 30) were recruited from a larger randomized controlled trial investigating the efficacy of acupuncture in SAR. 21 patients received acupuncture, and 9 patients received sham acupuncture. Among other we measured resting heart rate variability and cardiovascular reactivity to a cold pressure test prior to and after 12 sessions of acupuncture or sham acupuncture. In addition, 30 age- and sex-matched healthy controls were tested once. Results: SAR patients showed higher resting heart rate and lower heart rate variability as well as blunted cardiovascular responses compared to controls. After treatment, resting heart rate had decreased, and systolic blood pressure response to the cold pressure test had increased in SAR patients. We found no significant differences in autonomic function changes between patients receiving acupuncture or sham acupuncture. Conclusion: SAR patients showed alterations in autonomic function, which had partially normalized after treatment. However, in this sample we found no specific effect of acupuncture compared to sham acupuncture.

Zusammenfassung

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Introduction

Population-based studies from USA and elsewhere suggest that between 10 and 20% of the population experience allergic rhinitis (AR) symptoms [1, 2]. Approximately USD 1.2 billion is spent annually on therapies for AR in the USA [3]. Despite advances in pharmacotherapy for treatment of grass pollen allergy including allergen immunotherapy, and the development of clearly defined guidelines the lifetime prevalence for the use of CAM in patients with AR ranges from 27 to 46% [4]. In particular, acupuncture is used by 17–19% of AR patients [5, 6]. However, previous systematic reviews of acupuncture for the treatment of AR have yielded inconclusive results [7, 8].

We thus conducted the Acupuncture in Seasonal Allergic Rhinitis (ACUSAR) trial, which was designed to investigate the efficacy of acupuncture plus rescue medication (RM, cetirizine) compared to sham acupuncture plus RM and to RM alone in patients suffering from seasonal allergic rhinitis (SAR) [9]. With 422 participants, ACUSAR is the largest randomized controlled trial (RCT) including a sham acupuncture group on acupuncture for SAR to date. We found that acupuncture treatment was significantly superior to sham acupuncture and RM alone regarding the rhinitis-specific quality of life measured with the Rhinitis Quality of Life Questionnaire (RQLQ). Moreover, the same effect was observed for a RM score, which documented the cetirizine use [10].

Despite intensive investigation, the mode of action of acupuncture in SAR is only poorly understood. Acupuncture-specific changes of autonomic functions were shown for the treatment of migraine and irritable bowel syndrome [11, 12]. Furthermore, neuroimaging studies have found that acupuncture induced specific changes in brain regions involved in autonomic regulation [13, 14].

It has been proposed that autonomic dysfunction is an important pathophysiological aspect of SAR. Previous studies demonstrated sympathetic hypofunction and enhanced parasympathetic activity at the local nasal mucosa as well as systemic changes by measures of heart rate variability (HRV) [15–18]. A hypofunction of the hypothalamic-pituitary-adrenal (HPA) axis has also been reported in SAR patients [19–21]. McDonald et al. [22] recently proposed a model, by which acupuncture may affect inflammatory activity in AR. Among other factors, acupuncture effects on vagal mediated cholinergic anti-inflammatory activity, HPA axis function, and proinflammatory cytokine regulation are hypothesized to play an important role.

The AUTO-ACUSAR (Autonomic and Neuroendocrine Function- ACUSAR) study as an experimental sub-study of the ACUSAR trial was initiated to investigate the role of the autonomic nervous system for both the pathophysiology of SAR and the possible target of acupuncture action. Therefore, the aim of the study was to investigate (a) whether SAR patients differ from healthy controls in terms of autonomic and neuroendocrine function, and (b) whether acupuncture or sham acupuncture treatment evokes specific changes of the autonomic nervous system (ANS).

Methods

AUTO-ACUSAR consisted of 2 parts: Firstly, we compared autonomic function between a sample of randomized SAR patients from ACUSAR, and age- and gender-matched healthy controls in a cross-sectional analysis. Secondly, in this sample of ACUSAR we compared changes in autonomic function between SAR patients receiving acupuncture and SAR patients receiving sham acupuncture.

ACUSAR was a three-armed, multicenter RCT investigating the efficacy of acupuncture plus RM versus penetrating sham acupuncture plus RM, versus RM alone in patients with SAR on birch and grass pollen. Details of the study protocol have been described previously [9]. ACUSAR was conducted according to the common guidelines for clinical trials (Declaration of Helsinki, ICH-GCP) and was registered at ClinicalTrials.gov (NCT00615584). AUTO-ACUSAR was registered at ClinicalTrials.gov registration number NCT01271595. AUTO-ACUSAR was declared as an amendment of the ACUSAR study in February 2009, and was approved by the Charité ethics committee.

Patients and Participants

ACUSAR patients were primarily recruited at the start of the birch pollen season by newspaper articles and information flyers in outpatient clinics and study centers. Main inclusion criteria comprised IgE positivity to grass and birch pollen assessed by either a skin-prick test or specific IgE level; age 16–45 years; and moderate to severe SAR for at least 2 years. Mean exclusion criteria were perennial allergic rhinitis, allergic asthma, other moderate to severe atopic diseases, previous acupuncture treatment for SAR, and any CAM use. After inclusion, patients were centrally randomized (ratio 2:1:1) in blocks of 8–1 of the 3 treatment groups. Details are described elsewhere [10].

Recruitment for AUTO-ACUSAR was conducted during the birch and grass pollen season from March to May 2009 in 8 ACUSAR study centers in Berlin. Patients who were randomized to either the acupuncture or sham acupuncture group were informed about the AUTO-ACUSAR sub-study and were asked for participation. We did not include patients with beta-adrenergic antagonist medication or pacemakers. Patients on other cardiovascular medication remained on stable medication during the study period. AUTO-ACUSAR patients were followed up for 8 weeks. Additionally, 30 healthy age- and sex-matched control subjects were recruited by advertisements at university notice boards between June and October 2009. Subjects were reimbursed with EUR 20 for participation. Written informed consent was obtained from all participants.

Study Intervention

Acupuncture was administered by specially trained and qualified physicians. For AUTO-ACUSAR, only practitioners from Berlin outpatient clinics were included. All practitioners received extensive information about the aims and methods of AUTO-ACUSAR in addition to the study training sessions for ACUSAR. The treatment included 12 sessions of semi-standardized acupuncture according to Chinese medicine or penetrating sham acupuncture within 8 weeks. Only second-generation oral antihistamines (cetirizine) were offered as anti-allergic RM. Details are described elsewhere [23].

Experimental Setting

All participants in the AUTO-ACUSAR sub-study underwent standardized measurements of ANS parameters by trained study staff over 30 min. In the SAR patients, measurements were conducted in the study center immediately before the first and the last acupuncture or sham acupuncture treatment session. Healthy controls were measured only once.

Subjects were seated in a quiet room during physiological recordings. The session started with a 5-min resting period to get accustomed to the environment. This was followed by a 5-min period of paced breathing. Subjects were instructed to breathe with a given frequency of 12 per min following an acoustic signal. After that, subjects again rested for 5 min. Next, a cold pressure test was applied [24]. The subjects’ right hand was immersed into a basin of ice-cold water (0–1°C) for 30 s. The procedure was repeated every min for 20 s for a total duration of 5 min. Finally, subjects rested again for 10 min (fig. 1).
Study Outcome Measurements

Heart rate and heart rate variability: Heart rate (HR) was continuously recorded using a Polar® heart frequency monitor (Polar RS800CX, Polar Electro GmbH, Büttenborn, Germany). Raw data were transferred online by a Polar Advantage Interface Receiver to a computer. Analysis of HRV was performed according to standard methods using Kubios HRV version 2.0 software (BioSignal Analysis and Medical Imaging Group, Kuopio, Finland) [25]. The Root Mean Square of the Successive Differences (RMSSD) between adjacent normal RR-intervals was calculated as a time-domain measure of HRV. Frequency-domain parameters of HRV were obtained by power spectral analysis of beat-to-beat values of the RR-interval, using a Fast Fourier Transformation model. High-frequency (HF) power (0.15–0.40 Hz) was computed as a measure of parasympathetic activity, and low-frequency (LF) power (0.04–0.15 Hz) was computed as a measure of both sympathetic and parasympathetic activity. The LF/HF power ratio as a measure of sympathovagal balance was also calculated. To control for inter-individual differences in breathing frequency, only the HRV values during paced breathing were analyzed. All HRV values except for the LF/HF ratio were logarithmically transformed before the analysis to achieve normal distribution.

Blood pressure: Blood pressure was determined at the end of every period using an automatic oscillometric device (OMRON® M5 Professional HEM-7001-D, OMRON Medizintechnik Handelsgesellschaft mbH, Mannheim, Germany) according to standard methods.

Cortisol awakening response: Cortisol awakening response (CAR) was evaluated in the morning before the day of ANS function assessment. Subjects received salivettes along with verbal and written instructions from the study personnel at the inclusion day. Subjects were instructed to collect saliva 0, 30, 45 and 60 min after awakening. Samples were stored deep-frozen (−20°C) until they were analyzed in the laboratory of the department of psychosomatic medicine of the Charité – University Medical Center, Berlin. Laboratory analyses were based on a radioimmunoassay (DPC Biermann, Bad Nauheim, Germany). For the cortisol awakening response, the areas under the curve with respect to the increase (AUCi) and with respect to the ground (AUCg) were calculated using trapezoid formulas [26]. To calculate AUCi and AUCg, samples of at least 3 time points had to be available.

For interpreting the results, we considered responder rates of the RQLQ, one of the primary trial outcomes of the ACUSAR trial. A response was defined as a decrease in RQLQ score of at least 0.5 points [27].

Statistical Analysis

Since AUTO-ACUSAR was an experimental pilot study, we did neither perform a sample size calculation nor defined primary and secondary outcomes. After the documentation had been completed, pseudonymous data from the psycho-physiological laboratory of the Department of Psychosomatic Medicine, Charité – University Medical Center, Berlin were entered into the MS Access database (version 2003) at the Institute of Social Medicine, Epidemiology and Health Economics at the Charité – University Medical Center, Berlin. After automated checks for plausibility, correctness, and completeness, the clean files were transposed to a SPSS file (version 10.07) for statistical analysis. Group differences between SAR patients and healthy controls were analyzed using univariate analyses of variance (ANOVA) and chi-square tests. Reactivity to the cold pressure test (CPT) was compared using ANOVA for repeated measures with 3 measurement points (after 5, 20, and 30 min of recording; fig. 1) as within-subjects factor, and group (SAR patients versus controls) as between-subjects factor. Greenhouse-Geisser corrections were made when appropriate.

We hypothesized that SAR patients would be characterized by (a) decreased HRV, (b) reduced sympathetic activation to the CPT, and (c) a reduced CAR.

For the longitudinal part of the study, possible demographic baseline differences between SAR patients receiving acupuncture and SAR patients receiving sham acupuncture were explored by univariate ANOVA and chi-square tests. The effects of acupuncture versus sham acupuncture were analyzed by ANOVA for repeated measurements with pre-treatment and post-treatment measures of autonomic and neuroendocrine function as within-subjects factor, and group (acupuncture and sham acupuncture) as between-subjects factor.

Results

Recruitment and Populations for Analyses

Between March and May in 2009, a total of 42 SAR patients from acupuncture and 18 patients from sham acupuncture group were consecutively contacted in the participating study centers, and a total of 30 patients was included. Following the 2:1:1 randomization scheme of ACUSAR we included 9 patients in the sham acupuncture group and 21 in the acupuncture group. At the same time, 30 healthy controls were recruited.

Three patients from the acupuncture group dropped out due to personal reasons (n = 2) or circulation problems during the CPT (n = 1; fig. 2).

Cross-sectional Study: Differences between SAR Patients and Healthy Controls

Demographic characteristics: Demographic characteristics of the SAR patients and the matched controls are shown in table 1. The 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SAR patients, n = 30</th>
<th>Controls, n = 30</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>34.3 ± 7.96</td>
<td>34.10 ± 7.88</td>
<td>0.38</td>
</tr>
<tr>
<td>Sex (female), %</td>
<td>50.00</td>
<td>50.00</td>
<td>1.00</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.83 ± 3.86</td>
<td>23.68 ± 2.71</td>
<td>0.80</td>
</tr>
<tr>
<td>Smoking status (smokers), %</td>
<td>10.34</td>
<td>40.00</td>
<td>0.009</td>
</tr>
<tr>
<td>Physical activity (low active), %</td>
<td>4.55</td>
<td>3.70</td>
<td>0.32</td>
</tr>
</tbody>
</table>

SAR = seasonal allergic rhinitis; BMI = body mass index.
groups were not significantly different with respect to age, sex, body mass index, and physical activity. SAR patients were more likely to be non-smokers. Thus, we adjusted for smoking status in all subsequent group comparisons.

**HRV during paced breathing**: Compared to the controls, SAR patients showed a significantly higher HR (F(2.57) = 12.73; p = 0.001, ηp² = 0.183), a lower RMSSD (F(2.57) = 5.55; p = 0.02, ηp² = 0.09), and a lower HF power of HRV (F(2.57) = 3.96; p = 0.05, ηp² = 0.065, table 2). LF power of HRV and LF/HF ratio were not significantly different between SAR patients and controls (table 2).

**Reactivity measures during CPT**: CPT induced significant changes of systolic blood pressure (SBP) (main effect of time: F(2.58) = 5.35; p = 0.01, ηp² = 0.084), diastolic blood pressure (DBP) (main effect of time: F(2.58) = 5.60; p = 0.008, ηp² = 0.088), and HR (main effect of time: F(2.58) = 10.19; p = 0.001, ηp² = 0.149) in all participants. SAR patients showed a blunted SBP response to CPT compared to healthy controls (interaction effect of group × time: F(2.58) = 5.22; p = 0.01, ηp² = 0.084). We found no significant differences between SAR patients and controls with respect to the DBP re-

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SAR patients, n = 30</th>
<th>Controls, n=30</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>80.63 ± 11.80</td>
<td>71.54 ± 11.42</td>
<td>0.001</td>
</tr>
<tr>
<td>RMSSD, ln ms</td>
<td>3.07 ± 0.71</td>
<td>3.45 ± 0.66</td>
<td>0.02</td>
</tr>
<tr>
<td>Low frequency power, ln ms²</td>
<td>5.77 ± 0.85</td>
<td>6.09 ± 0.10</td>
<td>0.16</td>
</tr>
<tr>
<td>High frequency power, ln ms²</td>
<td>5.48 ± 1.42</td>
<td>6.07 ± 1.28</td>
<td>0.05</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>2.43 ± 4.14</td>
<td>1.41 ± 1.35</td>
<td>0.26</td>
</tr>
<tr>
<td>Cortisol awakening response</td>
<td>807.06 ± 321.27</td>
<td>744.87 ± 259.28</td>
<td>0.38</td>
</tr>
<tr>
<td>AUCg</td>
<td>199.99 ± 298.84</td>
<td>280.07 ± 271.91</td>
<td>0.28</td>
</tr>
</tbody>
</table>

SAR = seasonal allergic rhinitis; HR = heart rate; HRV = heart rate variability; RMSSD = Root Mean Square Successive of Differences between adjacent normal RR-intervals; LF/HF = low-frequency / high-frequency ratio/power of HRV; AUCg = area under the curve with respect to the ground; AUCi = area under the curve with respect to the increase. 

*p values adjusted for smoking status.
response (interaction effect of group × time: F(2.57) = 1.93; p = 0.16, \( \eta_p^2 = 0.033 \)), and the HR response (interaction effect of group × time: F(2.57) = 0.48; p = 0.51, \( \eta_p^2 = 0.008 \)) (fig. 3).

Cortisol awakening response: We found no significant differences between SAR patients and controls with respect to AUCg (F(2.51) = 0.62; p = 0.44, \( \eta_p^2 = 0.012 \)) and AUCi (F(2.51) = 0.80; p = 0.38, \( \eta_p^2 = 0.015 \)) (table 2).

**Table 3.** Demographic characteristics of seasonal allergic rhinitis patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Acupuncture, n = 18</th>
<th>Sham acupuncture, n = 9</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
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</tr>
<tr>
<td>Age, years</td>
<td>35.12 ± 7.80</td>
<td>32.33 ± 8.43</td>
<td>0.38</td>
</tr>
<tr>
<td>Sex (female), %</td>
<td>47.6</td>
<td>55.6</td>
<td>0.70</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.71 ± 3.50</td>
<td>25.12 ± 4.83</td>
<td>0.80</td>
</tr>
<tr>
<td>Smoking status (smokers), %</td>
<td>29.60</td>
<td>11.10</td>
<td>0.89</td>
</tr>
<tr>
<td>Physical activity (low active), %</td>
<td>0.00</td>
<td>7.14</td>
<td>0.41</td>
</tr>
</tbody>
</table>

BMI = body mass index.

**Table 4.** Autonomic and neuroendocrine characteristics of seasonal allergic rhinitis patients at baseline and after acupuncture or sham acupuncture treatment; Rhinitis Quality of Life Questionnaire responder

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Acupuncture, n = 18</th>
<th>Sham acupuncture, n = 9</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>HR and HRV during paced breathing at baseline</td>
<td></td>
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<td></td>
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<tr>
<td>HR, beats/min</td>
<td>76.77 ± 10.37</td>
<td>81.00 ± 15.11</td>
<td>0.53</td>
</tr>
<tr>
<td>RMSSD, ms</td>
<td>3.12 ± 0.60</td>
<td>3.14 ± 0.88</td>
<td>0.76</td>
</tr>
<tr>
<td>LF, ms²</td>
<td>5.82 ± 0.75</td>
<td>5.70 ± 1.13</td>
<td>0.76</td>
</tr>
<tr>
<td>HF, ms²</td>
<td>5.57 ± 1.16</td>
<td>5.68 ± 1.60</td>
<td>0.61</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>2.82 ± 4.84</td>
<td>1.51 ± 1.42</td>
<td>0.34</td>
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</table>

Heart rate and heart rate variability during paced breathing after intervention

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<thead>
<tr>
<th>Heart rate and heart rate variability during paced breathing after intervention</th>
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<tbody>
<tr>
<td>HR, beats/min</td>
<td>71.43 ± 10.84</td>
<td>74.60 ± 7.96</td>
<td>0.82</td>
</tr>
<tr>
<td>RMSSD, ms</td>
<td>3.32 ± 0.79</td>
<td>3.43 ± 0.72</td>
<td>0.76</td>
</tr>
<tr>
<td>LF, ms²</td>
<td>5.93 ± 0.96</td>
<td>6.10 ± 1.04</td>
<td>0.45</td>
</tr>
<tr>
<td>HF, ms²</td>
<td>5.94 ± 1.44</td>
<td>6.26 ± 1.37</td>
<td>0.73</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>1.01 ± 1.28</td>
<td>1.05 ± 0.90</td>
<td>0.46</td>
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Cortisol awakening response

<table>
<thead>
<tr>
<th>Cortisol awakening response at baseline</th>
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</thead>
<tbody>
<tr>
<td>AUCg</td>
<td>829.08±358.77</td>
<td>839.89±203.72</td>
<td>0.76</td>
</tr>
<tr>
<td>AUCi</td>
<td>221.92±320.28</td>
<td>249.52±232.43</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Rhinitis Quality of Life Questionnaire Responder, n (%)

14 (76) 7 (77)

HR = heart rate; HRV = heart rate variability; RMSSD = Root Mean Square Successive of Differences between adjacent normal RR-intervals; LF/HF = low-frequency / high-frequency ratio/power of HRV; AUCg = area under the curve with respect to the ground; AUCi = area under the curve with respect to the increase. *p values given for time × intervention interaction effects.
Longitudinal Study: Effects of Acupuncture versus Sham Acupuncture

Demographic characteristics: Patients in the acupuncture and sham acupuncture group were not significantly different with respect to age, sex, BMI, smoking status, and exercise habits (table 3).

HRV during paced breathing: There was a main effect of time for HR ($F(1.25) = 6.69; p = 0.02, \eta^2_p = 0.21$), which was lower after acupuncture or sham acupuncture treatment ($78.18 \pm 12.01$ beats/min vs. $72.49 \pm 9.93$ beats/min). No significant effects of time were found for RMSSD, HF, and LF power of HRV, or LF/HF ratio. There were no significant interactions of time × type of intervention (acupuncture vs. sham acupuncture) for all HRV measures under investigation (table 4).

Reactivity Measures (CPT)

SBP and DBP responses to CPT increased significantly after the intervention (interaction effect of SBP course during CPT by time (pre- vs. post-intervention): $F(1.25) = 4.65; p = 0.02, \eta^2_p = 0.157$; interaction effect of DBP course during CPT by time (pre- vs. post-intervention): $F(1.25) = 3.24; p = 0.05, \eta^2_p = 0.115$). HR responses to the CPT did not significantly change over time. The type of intervention (acupuncture or sham acupuncture) had no significant impact on the changes of any reactivity measure (fig. 4).

Cortisol Awakening Response

There were no significant main effects over time with respect to CARg and CARI. Also, no significant time × type of intervention interaction effects could be observed.

There was no significant difference in RQLQ responder rates (table 4).

Discussion

The main findings of our study were that (1) SAR patients showed marked alterations in autonomic function compared to healthy controls; (2) autonomic function changed significantly over the course of treatment; and (3) no specific superior effect of acupuncture over sham acupuncture could be observed.
Autonomic dysfunction in AR patients was described previously. Ishman et al. [17] evaluated ANS function in patients with perennial AR measuring HRV and blood pressure responses to a broad battery of autonomic function. They found a sympathetic hypofunction but no parasympathetic dysfunction. Lan et al. [28] compared the HRV responses to postural change between AR patients and healthy controls. They found a poor sympathetic modulation in the sitting position of AR patients. One study group reported increased 24-h HRV in children [29] and adults [18] with AR. However, differences in HRV measures more specifically reflecting vagal activity, such as HF power of HRV, were only found in children [29].

SAR patients in our study showed reduced vagal activity, as indexed by decreased resting HR and, more specifically, reduced HF power of HRV. Vagal activity was previously shown to be closely related to innate immune activity [30]. Within this cholinergic anti-inflammatory pathway, vagal efferences tonically inhibit the release of pro-inflammatory cytokines, such as interleukin 1, interleukin 6, and tumor necrosis factor from monocytes, macrophages, and other cytokine-releasing cells [31]. Weber et al. [32] have previously shown an impaired post-stress recovery of tumor necrosis factor α in healthy subjects with low HRV. All these cytokines were also shown to be involved in the pathogenesis of AR [33, 34]. Further, measures of HRV were found to be associated with inflammatory activity in autoimmune diseases, such as rheumatoid arthritis [35, 36]. Thus, it is possible that reduced vagal activity might predispose an individual to develop allergic diseases, such as SAR, via dysfunction of the cholinergic anti-inflammatory pathway. SAR patients were also characterized by a sympathetic hyporeactivity, as indicated by blunted SBP responses to the CPT. Activation of α1-adrenoceptors leads to vasoconstriction, and α1-adrenoceptor agonists are used as nasal decongestants to alleviate SAR symptoms. Interestingly, it was shown that the α1-adrenoceptor agonist oxymetazoline reduced the release of pro-inflammatory cytokines from immune cells in vitro [37]. Sympathetic hyporeactivity may hence promote allergy-related symptoms, such as nasal obstruction and local inflammation.

SAR patients did not differ from controls with respect to CAR. Hypofunction of the HPA axis was hypothesized to be a common feature of atopic diseases [20]. However, Buske-Kirschbaum et al. [21] found a blunted cortisol response to social stress only during active inflammation in SAR patients. At the same time, no differences with respect to CAR were found. Fidan et al. [19] reported an altered circadian rhythm of salivary cortisol with overall lower levels, but the most pronounced differences were observed during nighttime. Hence, possible alterations in HPA function in SAR patients may not be captured by CAR assessment.

Because our data are cross-sectional, no definite conclusion with respect to causality can be drawn. Low vagal activity may also be a consequence of the disease itself, or the psychological distress associated with it. Studies investigating SAR patients during active and inactive disease states may be helpful to disentangle cause and effect of autonomic function and allergic inflammation.

After acupuncture and sham acupuncture treatment series, resting HR was significantly decreased, while the blood pressure response to CPT, especially SBP, had increased. However, we found no evidence for a specific effect of acupuncture versus sham acupuncture with respect to changes of autonomic and neuroendocrine parameters. The lack of group difference is consistent with the RQLQ responder rates: 76% of the patients in the acupuncture and 75% in the sham acupuncture group had clinically relevant reduced RQLQ scores after the treatment series. Larger samples may be needed to detect possible, more subtle differences in autonomic parameters after acupuncture or sham acupuncture treatment.

The enhanced SBP response together with a reduced HR after treatment could be carefully read as a normalization of sympathetic activity, and could reflect an unspecific, maybe relaxing effect of the acupuncture / sham acupuncture treatment. Relaxing effects are also described for other techniques from Chinese medicine, such as acupressure and Qigong [38–40]. However, we cannot rule out that the observed changes occurred due to habituation to the experimental setting or the natural course of the disease.

Acupuncture effects on ANS function in healthy individuals have been described previously [41]. Although there seem to be no short-term effects on ANS response to CPT induced by acupuncture [42], various effects on HRV were, depending on the localization and category of acupuncture points, needling technique or the needle manipulation [43, 44]. In patients with disturbed ANS function, such as in migraine, a serial acupuncture treatment led to a decrease of LF power of HRV in those patients who responded to 12 sessions of acupuncture or sham acupuncture treatment. The authors interpreted the results as a possible reduction of sympathetic activity [11].

The strength of AUTO-ACUSAR is the ACUSAR trial in which it is embedded as a sub-study. To date, the ACUSAR trial is the largest and most rigorous trial investigating the efficacy of acupuncture including a sham control group in SAR. Its strengths include a pre-published protocol [9], strictly concealed central randomization, interventions provided by qualified medical acupuncturists, and well-accepted outcome measurements [45].

On the other hand, a sub-study of a large RCT comprises clearly some limitations: The study sample for AUTO-ACUSAR was small and not powered to detect differences between the intervention groups. In addition, the setting of the experimental measurements was not as standardized as recommended for the measurements of autonomic parameters due to feasibility aspects in the study centers.

Conclusion

In conclusion, SAR patients showed altered autonomic function, which were partially normalized after treatment. However, we found no evidence for a specific superior effect of acupuncture over sham acupuncture with respect to changes in autonomic or neuroendocrine function.

Acknowledgments

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Disclosure Statement

The authors declare that they have no conflict of interests concerning this study.