Acupuncture in Migraine
Investigation of Autonomic Effects

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Objective: A dysregulation of the autonomic nervous system is discussed as a pathogenetic factor in migraine. As acupuncture has been shown to exhibit considerable autonomic effects, we tested whether the clinical effects of acupuncture in migraine prophylaxis are mediated by changes of the autonomic regulation.

Methods: We simultaneously monitored changes of heart-rate variability (HRV) as an index of cardiac autonomic control and clinical improvement during an acupuncture treatment in 30 migraineurs. HRV was derived from spectral analysis of the electrocardiogram, which was performed before, during, and after the first and the last session of a series of 12 acupuncture sessions. Migraineurs were randomly allocated to 2 groups receiving either verum acupuncture (VA) or sham acupuncture (SA) treatment.

Results: Across the combined VA and SA groups, the clinical responders (with at least 50% reduction of migraine attacks) exhibited a decrease of the low-frequency (LF) power of HRV in the course of the treatment, which was not be observed in patients without clinical benefit. VA compared with SA induced a stronger decrease of high-frequency power. The mode of acupuncture, however, did not have an impact on the LF component of HRV or the clinical outcome.

Discussion: The data indicate, that VA and SA acupuncture might have a beneficial influence on the autonomic nervous system in migraineurs with a reduction of the LF power of HRV related to the clinical effect. This might be due to a reduction of sympathetic nerve activity. VA and SA induce different effects on the high-frequency component of HRV, which seem, however, not to be relevant for the clinical outcome in migraine.

Key Words: acupuncture, migraine, mechanism of action, heart rate variability, sympathetic nerve activity, autonomic nervous system

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Acupuncture is increasingly used as adjunctive treatment in primary headache syndromes[1] and there is growing evidence from clinical trials, that it might be beneficial in the treatment of migraine,[2–5] with an effect size comparable to pharmacologic treatment.[5] As one major aspect in the pathophysiology of migraine, a dysregulation of the autonomic nervous system (ANS) has been postulated.[6–8] As acupuncture has been shown to induce distinct autonomic effects,[9] the clinical effects in migraine might be mediated by a modulation of the ANS.

Although in the last 3 decades the physiologic mechanisms of acupuncture have been investigated extensively, its mechanisms of action still remains elusive. Neurophysiologic data from animals show that on a spinal level, acupuncture exhibits an influence on autonomic outflow to the viscerum by somatovisceral reflexes.[10] In healthy human participants, a modulation of muscle sympathetic nerve activity has been observed by microneurographic recordings.[11] Early studies applying thermography of the skin found systemic increases of the skin temperature induced by acupuncture.[12] Monitoring of heart rate and arterial blood pressure in healthy volunteers showed relevant pressor and depressor responses of the cardiovascular system evoked by acupuncture.[13,14] Employing functional magnetic resonance imaging during acupuncture in healthy participants, activation of the hypothalamus and periaqueductal gray matter has been shown, which indicates involvement of higher centers of autonomic control.[15] The impact of acupuncture on the ANS has rarely been investigated in disease. In a previous study employing measurements of heart-rate variability (HRV), acupuncture induced an increase of cardiovagal control in patients with minor depression and anxiety disorders.[16] Whether acupuncture has a relevant autonomic effect in migraineurs is

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unknown. In the present study we, therefore, addressed the following questions:
(1) Does acupuncture induce a distinct autonomic modulation in migraineurs?
(2) Is the modulation of the ANS specific for the needling of classic acupoints?
(3) Does the autonomic response vary with the clinical benefit?

To answer these questions, changes of heart-HRV were monitored as an index of autonomic cardiac control in 30 migraineurs receiving acupuncture or sham acupuncture for headache prophylaxis. The analysis of HRV has been shown to be a useful and noninvasive tool to investigate changes of cardiac autonomic tone under various conditions.[17,18] Aspects of cardiovascular autonomic control are derived from spectral analysis of the electrocardiogram (ECG) with the high-frequency (HF) power [ie, respiratory sinus arrhythmia (RSA)] reflecting parasympathetic cardiac control.[17] The origin of the low-frequency (LF) component is more uncertain, but most researchers believe that both vagal and sympathetic influences on the heart[18] importantly contribute to LF HRV. Changes of HRV were monitored before, during and after the first and the last session of a series of 12 acupuncture treatments.

METHODS

Patients

Patients represented a subpopulation of a multicenter, randomized, controlled trial for acupuncture in migraine[3] enrolled at the Study Center of the Department for Integrative Medicine, University of Duisburg-Essen, Germany. They were recruited from the Outpatient Clinic and via advertisements in regional newspapers. Inclusion criteria were the diagnosis of migraine for a duration of at least 12 months with or without aura, according to the diagnostic criteria of the International Headache Society[19] and with a minimum of 2 migraine attacks per month and an age of 18 to 65 years. Exclusion criteria included cooccurrence of a secondary headache type (eg, analgesic-induced headache), pharmacologic migraine prophylaxis within the last 4 weeks, acupuncture treatment within the last 6 months, and the existence of another severe acute disease. Thirty migraineurs participated in the study after giving informed consent. Patients were examined in the interictal phase without any headache at the day of the physiologic measurements.

Acupuncture

To test whether clinical and autonomic responses are specific for needling of classic acupoints patients were randomly allocated to 2 groups receiving either verum acupuncture (VA) or a sham acupuncture (SA) treatment. The randomization was performed by the Institute of Medical Statistics and Epidemiology at the Technical University Munich using the software Samp Size 2.0. The acupuncturists and researchers performing data acquisition and analysis were not involved in the randomization process. Patients were blinded for the treatment, but they were told that 2 different modes of acupuncture would be tested, and that we were investigating whether one type might be more effective than the other. An additional waitlist group was not employed due to logistic reasons and because we considered that an active control procedure (SA) was most relevant to our research questions. The study protocol was approved by the local ethics committee of the University of Essen. After randomization, patients received 12 treatments over a period of 8 weeks. All treatments were performed with sterile, stainless steel needles (Seirin, B type) of 40-mm length and 0.25-mm diameter by 2 experienced acupuncturists.

VA

Acupuncture was performed according to the standard literature[20] and based on an expert consensus process for acupuncture treatment of migraine.[21] During the physiologic recordings acupuncture was performed in a standardized fashion with needling the same points (basic points) in a standardized sequence during the same period of time. During the other sessions acupuncture treatment was performed in a semistandardized manner with needling the basic points with the option to needle additional points on the basis of the patient's individual symptoms and location of pain.[3]

For detailed information about the anatomic localization, see Table 1. The following points were needled bilaterally during 2 minutes of paced breathing: 3B 5, GB 41, LR 3 (for further details of the paced breathing procedure see below). To complete the treatment the points Gb 20, Taiyang, Gv 20 were needled directly after the paced breathing episode. After insertion of the needles they were manually rotated for approximately 2 seconds. At the points GB 41, LR 3, 3B 5, and Gb 20 they were manually rotated with a frequency of 2 to 4 Hz and an amplitude of approximately 90 to 120 degrees to achieve a needle sensation (DeQi sensation). Needles in 3B 23, Gv 20, and Taiyang were not further stimulated. All needles were than retained in their locations for 30 minutes.

SA

SA was performed in the same way in all sessions. Only areas of the skin that were outside a classically described acupuncture point were chosen. Additionally acupuncture needles were inserted more superficially into the subcutaneous layer. Detailed information about the anatomic localization of the points is given in Table 1. The points "deltoideus," "upper arm," and "upper leg 1" were needled bilaterally during 2 minutes of paced breathing. Finally, the points "upper leg 2" and "upper leg 3" were needled. After insertion of the needles they remained in their location for a period of 30 minutes without further stimulation.

TABLE 1. Anatomic Localization of Verum and Sham Points

	Anatomic Localization
Verum points	
Gv 20	On the vertex, 8-10 cm above the midpoint of the anterior hairline, at the midpoint of the line connecting the apexes of both ears
Gb 20	On the neck, below the occipital bone, in the depression between the upper ends of the sternocleidomastoid and trapezius muscle
Taiyang (Ex HN 5)	On the face, in the depression 2 cm posterior to the midpoint of the line joining the tip of the eyebrow and outer canthus
3B 23	On the face, in the depression at the lateral end of the eyebrow
3B5	On the dorsal side of the forearm, approximately 4 cm proximal to the dorsal crease of the wrist, between radius and ulnar
LR 3	On the instep of the foot, in the depression of the posterior end of the first interosseus metatarsal space
Gb 41	On the lateral side of the instep of the foot, posterior to the fourth metatarsophalangeal joint, in the depression lateral to the tendon of the extensor muscle of the little toe
Sham points	
"Deltoideus"	In the middle of the line insertions of Musculus deltoideus and acromion
"Upper arm"	Approximately 4 cm lateral and 6 cm below the anterior end of the axillary crease
"Upper leg 1"	Approximately 12 cm above the upper edge of the patella
"Upper leg 2"	Approximately 8 cm above the upper edge of the patella
"Upper leg 3"	Approximately 4 cm dorsally of the median line on the lateral aspect of the thigh, approximately 14 cm above the upper edge of the patella

Experimental Procedure and Acquisition of Physiologic Data

Physiologic data were recorded at the first and the 12th acupuncture session. All measurements were performed between 7.00 and 9.00 AM and patients were firmly requested to abstain from any food intake, coffee, tea, or smoking at least 8 hours before the experiment. Patients were seated comfortably on a couch in a quiet room. The ECG was continuously monitored before (baseline), during, and after the acupuncture treatment. ECG electrodes were placed bilaterally over the inner side of the wrists, proximal to the ankles and on the left costal arch. Because respiratory variation can confound HF estimation of cardiac vagal tone[17,18,22] HRV was calculated from paced-breathing periods to evaluate cardiac vagal control under standard and stable respiratory conditions (9 breaths/min at eucapnic tidal volume). Before data collection, patients were trained to pace their breathing easily and comfortably to the signal. An ascending tone signaled patients to inspire and a descending tone to expire. To control for the maintenance of eucapnic tidal volume, the end-tidal $P_{et}CO_2$ was measured by infrared analysis of the expired air (Capnogard), and abdominal and thoracical respiratory excursions were monitored via inductive plethysmography (Respitrace, Ardsley, NY). The experimental sequence is shown in Figure 1. The protocol consisted of a 20-minute calibration period, a 14-minute pretreatment period with 1 episode of 2-minute paced breathing (episode A) followed by a 30-minute acupuncture period with 3 episodes of 2-minute paced breathing (episode B: needles inserted and stimulated, episodes C and D: needles left in the body without further stimulation after respective 10 and 20 min) and finally a posttreatment period of 14 minutes after the needles were taken out with another episode of 2-minute paced breathing (episode E).

Acquisition of Clinical Data and Definition of Clinical Response

The clinical effect was monitored by a headache diary and pain questionnaires. The patients were asked to document their headaches in the diaries in a baseline

		baseline, pre-treatment resting period			Acup.	Acupunture needles in the body					post-treatment period		
		10 min.			30 min.						10 min.		
10 min.		8 min.	2 min.	2 min.	2 min.	8 min.	2 min.	8 min.	2 min.	8 min.	10 min.	2 min.	2 min.
			A		B		C		D			E	
preparation of the measurements	calibration		paced breathing (9/min.)		paced breathing (9/min.)		paced breathing (9/min.)		paced breathing (9/min.)			paced breathing (9/min.)	

FIGURE 1. Experimental Sequence: ECG and respiratory parameters were measured before A, and during acupuncture B, with the needles in the body after respective 10 and 20 mintues C, D, and after the needles were taken out E, for respective 120 seconds. In the periods of interest (A–E), in which patients were breathing to an ascending and descending auditory signal (paced breathing), data were recorded for 2 minutes, respectively.

period of 4 weeks before the treatment and for 12 weeks after randomization. The questionnaires applied were the (1) the German version of the Pain Disability Index (PDI),[23] (2) a scale for differentiating the sensory and emotional aspects of pain (Schmerzempfindungsskala SES),[24] (3) the depression scale (German Version of CES-D, Center for Epidemiological Studies Depression Scale),[25] and (4) the German version of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) to assess health-related quality of life,[26] which had to be filled in before randomization and after the treatment in week 12. According to International Headache Society recommendations for controlled trials in migraine,[27] a reduction of at least 50% of migraine attacks in the weeks 9 to 12 compared with the baseline period was taken as the primary clinical efficacy measure. The separation of responders and nonresponders for the other parameters was realized by splitting patients according to the median of the whole study population. Two patients with the same outcome beside the median were defined as nonresponders when their response was lower than the mean of the population and vice versa. The secondary clinical outcome measures were monitored to see whether the relation between changes of HRV and reduction of migraine attacks would be reproducible also for dimensions of well-being.

Data Analysis

After the measurement data were stored on a hard disk with a sampling frequency of 1000 Hz and analyzed off-line by custom tailored software written in the Matlab (Mathworks, Natick, MA) programing environment.[28] Artefacts including ectopic beats or abnormal intervals were detected manually and replaced by linearly interpolated values. Data files with greater than 10% ectopic beats, tachycardia (> 100 beats/min) or bradycardia (< 50 beats/min) were not submitted to spectral analysis. Parameters of respiratory rate and tidal volume were used as control variables to establish adherence to paced-breathing conditions. Additionally the respiratory data were employed to ensure that HF R-R interval power was coherent with respiration (> 0.7) and thus reflected vagally mediated RSA. After the editing process, a Fast-Fourier transformation was applied to the interpolated data. Power spectra were derived for each paced breathing period (A-E). A fixed bandwidth was defined for all power spectral analysis, based on optimal identification of the HF component.

Changes of the HF and LF component of HRV in the course of acupuncture were defined as respective primary and secondary physiologic outcome measures. The bandwidth was 0.070 to 0.1299 Hz for the low frequency band and 0.130 to 0.50 Hz for the high frequency, or, RSA, band. To control for variations of respiratory depth during acupuncture, RSA, or the HF component of HRV, was normalized for tidal volume and quantified in units of s/L (indicating the gain of RSA upon tidal volume, that is, ms change in RSA amplitude per liter of tidal volume at the standard frequency of 9 breaths/min). This measure, known as RSA transfer function, (trRSA) has been shown to provide a valid estimation of the cardiac vagal control accounting for task-related changes of breathing in the laboratory and during everyday life.[29,30] In this paper, we refer to this measure alternatively as the HF component or RSA.

HRV data were then analyzed by multivariate repeated-measures analysis of variance (ANOVA), with experimental episodes (A-E), day (first session, last session), acupuncture types (SA, VA), and clinical response (responder vs. nonresponder) as independent factors. The effect of the clinical response was tested first for the combined sham and verum groups and then the impact of the acupuncture type was tested. The randomization, acupuncture treatment, data acquisition, and offline analysis was performed by different researchers.

RESULTS

From 30 included patients 17 received VA and 13 were treated with SA. Data of 7 patients (5 VA, 2 SA) had to be rejected because of a high number of ectopic beats or nonadherence to paced breathing. One patient (VA) was excluded because of tachycardia, another patient (VA) was excluded because of bradycardia at baseline. Two patients (1 VA, 1 SA) did not complete their headache diary. Thus, complete data sets of 19 patients (2 males) were included into the final analysis. These patients had a mean age of 43.5 (8.5 SD) and a mean migraine duration of 21 (12 SD) years; 6 patients had migraine with aura.

VA Versus SA

Clinical Response to VA and SA

Clinical data of the SA and VA group are shown in Table 2. Across all patients there was a significant improvement in attack frequency, days with moderate or severe headache, emotional dimension of pain intensity, and SF 36 score for physical health. Changes in the sensory dimension of pain, SF 36 score for mental health, and the Allgemeine Depressionsskala (ADS) depression scale did not show significant changes as determined by t test for paired samples.

Analyzing differences between SA and VA by analysis of covariance (with the difference between baseline and weeks 9 to 12 as dependent variables, SA vs. VA as independent grouping factor and baseline values as covariates), there was no group effect for any clinical parameter for the difference between baseline and weeks 9 to 12. Additionally VA and SA group did not differ in any clinical variable at baseline as determined by ANOVA (Table 2). In summary, patients improved in both groups and the mode of acupuncture (SA vs. VA) did not have an influence on the clinical outcome. For the primary efficacy measure (50% reduction of migraine attacks) there were 6 responder in the VA group and 6 responders in the SA group, whereas 3 patients did not show a clinical benefit in the VA and 4 patients did not

TABLE 2. Clinical Effects

	All Patients Baseline/ Follow-up	VA Baseline/Follow-up	SA Baseline/Follow-up	Baseline VA vs. SA*	Treatment Effect VA vs. SA†	Responder Baseline/ Follow-up‡	Nonresponder Baseline/ Follow-up	Baseline Responder vs. Nonresponder,* P	Treatment Effect Responder vs. Nonresponder,† P
Attack frequency (SD)	3.1 (1.0)/1.5 (1.5)	3.1 (0.9)/1.0 (1.2)	3.3 (1.1)/1.8 (1.7)	NS	NS	3.2 (1.0)/0.5 (0.7)	3.3 (1.1)/3.3 (0.8)	NS	0.000
PDI (SD)	30.2 (16.7)/19.1 (13.6)	35.5 (15.2)/17.9 (12.8)	26.7 (18.4)/18.3 (15.9)	NS	NS	42.1 (20.0)/15.7 (16.9)	23.5 (8.9)/19.8 (11.9)	0.013	0.007
SES a (SD)	57.2 (8.7)/51.8 (10.4)	59.8 (7.2)/53.1 (7.2)	54.4 (9.2)/48.2 (8.7)	NS	NS	59.7 (8.7)/46.5 (9.4)	54.6 (7.7)/55.8 (10.6)	NS	0.000
SES s (SD)	52.9 (7.1)/50.7 (10.0)	54.7 (8.8)/53.3 (12.3)	50.5 (3.6)/47.2 (5.2)	NS	NS	52.7 (8.1)/47.0 (9.0)	52.8 (5.7)/54.8 (10.0)	NS	0.000
SF 36 physical health (SD)	42.0 (5.8)/47.1 (7.6)	38.5 (7.8)/47.0 (6.5)	43.7 (4.6)/48.3 (8.7)	NS	NS	38.7 (7.9)/51.0 (7.0)	43.6 (4.8)/44.1 (7.0)	NS	0.000
SF 36 mental health (SD)	49.1 (8.0)/48.2 (8.7)	51.9 (4.2)/50.7 (5.7)	46.8 (9.8)/46.7 (8.9)	NS	NS	47.6 (6.8)/50.7 (6.0)	51.0 (8.8)/46.3 (8.6)	NS	0.007
ADS (depression Scale) (SD)	46.0 (7.8)/46.6 (9.7)	46.6 (5.9)/43.5 (5.7)	46.2 (10.0)/49.6 (10.5)	NS	NS	47.7 (7.8)/41.4 (8.5)	44.7 (8.1)/50.6 (8.9)	NS	0.004

Data of 19 included patients (10 SA, 9 VA, 12 responders, 7 nonresponders).
*Statistical differences as analyzed by ANOVA (see Methods).
†Statistical differences as analyzed by analysis of covariance (see Methods).
‡Patients were considered as clinical responders when they showed a reduction of at least 50% of migraine attacks (primary outcome measure).

respond in the SA group. These results are in keeping with the results of the entire multicenter trial, which is published separately.[3]

Within-session and Between-session Autonomic Responses to VA and SA

Acupuncture induced significant changes of HRV over the course of a session with a distinct response pattern in VA versus SA. Across all patients and experimental episodes (SA and VA) both HF and LF power showed a tendency to decrease from days 1 to 12 without reaching a statistical significance (main effect of session for RSA: $P < 0.12$, for LF: $P < 0.10$). Across all patients (SA and VA) and both sessions (days 1 and 12) ANOVA revealed a significant main effect for "experimental episode" on the LF component of HRV ($P < 0.03$), indicating a distinct response pattern within the acupuncture session. Compared with baseline (experimental episode A), LF power significantly increased ($P < 0.003$) during acupuncture (episodes B, C, and D) and remained increased after removal of the needles (episode E), as determined by post hoc analysis (Fig. 2, lower panel). This was somewhat mirrored by HF changes during the needling, with a decrease of RSA during insertion of the needles, an increase with the needles in the body and a final decrease after the needles were taken out (Fig. 2, upper panel). For changes of HF power, however, the main effect of the experimental episode did not reach statistical significance [$P < 0.06$; Rao R (4.15) = 1.41; $P < 0.27$].

The mode of needling (VA vs. SA) significantly influenced changes in HF power of HRV, with a 3-way interaction effect for acupuncture type (VA, SA) × session (first, 12th acupuncture session) × experimental episode ($P < 0.008$, with correction for baseline differences), indicating that the 2 acupuncture modes evoked different response patterns during needling and induced a different modulation of the HF power from sessions 1 to 12. This is illustrated in Figure 3, which shows the response pattern of HF power during the first and 12th acupuncture session in VA and SA. A second analysis including responder/nonresponder as covariate was performed to determine whether the difference of HRV changes between the acupuncture groups was driven by the nonresponder results, which showed that the clinical response did not have an impact on this finding.

For changes of the LF power of HRV there was neither a main nor an interaction effect of acupuncture mode. HRV data of the VA and SA groups at baseline and follow up are shown in Table 2.

Responder Versus Nonresponder

A significant clinical response with a reduction of at least 50% of migraine attacks was observed in 12 of 19 patients (respective 6 in SA and VA group). Seven patients did not benefit from the treatment (4 in SA and 3 in VA group). Attack frequency decreased in the responder group from 3.2 (1.0 SD) to 0.6 (0.7 SD) whereas across nonresponders there was no considerable

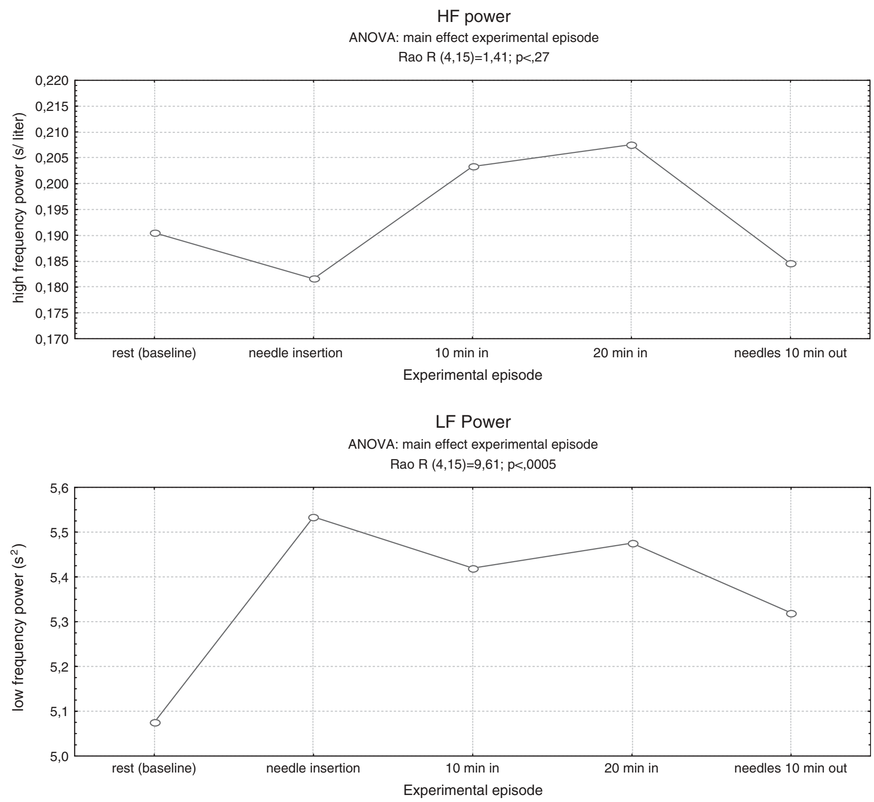

FIGURE 2. Changes of LF and HF component of HRV during acupuncture, data of all patients (N = 19) in all sessions. Data illustrate the modulation of HRV during the different experimental episodes (*x*-axis): rest (baseline), needle insertion, needles in the body for 10 and 20 minutes and rest 10 minutes after needles have been taken out. Upper graph, *y*-axis: power spectral density for the low frequency band (0.070 to 0.1299 Hz) of HRV. Lower graph, *y*-axis: the high-frequency component (0.130 to 0.50 Hz) normalized for tidal volume (RSA transfer function). The graphs contain data of all included patients (N = 19) in both sessions.

difference from baseline [3.0 (1.2 SD)] to weeks 9 to 12 [3.3 (0.8 SD)].

The responder group showed significant different changes of HRV compared with nonresponders. This however was confined to the LF component of HRV, whereas changes of the HF power did not vary with the clinical outcome. The modulation pattern of HF and LF power in responders and nonresponders is shown in Figure 4, the mean HRV data of the respective 5 experimental episodes during the first and the 12th sessions are given in Table 3. For changes of LF power, ANOVA revealed a significant 3-way interaction effect for the factors clinical response × session (first, 12th session) × experimental episode [Rao R (4.13) = 3.15; $P < 0.05$]. This indicated that responders compared with nonresponders showed a different response pattern of the LF power to acupuncture within the acupuncture session and a different change of the LF power from sessions 1 to 12. Post hoc analysis revealed, that this was mainly due to a pronounced reduction of the baseline level (experimental

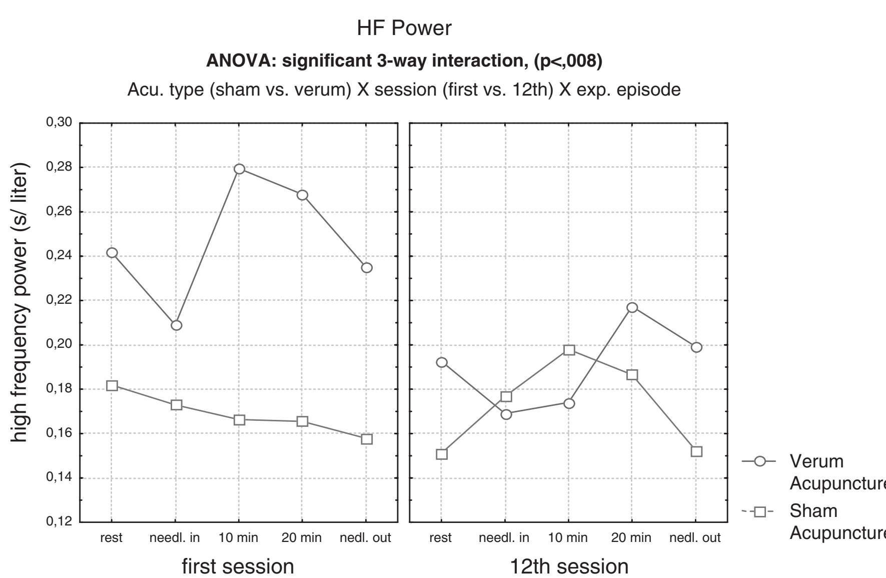

FIGURE 3. Modulation of HF component of HRV during VA and SA at first and 12th acupuncture session. The graph shows the response pattern of HF power to VA (circles) and SA (squares) during the first acupuncture session (left panel) and the 12th session (right panel). *Y*-axis: high-frequency band of HRV normalized for tidal volume (RSA transfer function). Note a significant change of response patterns from sessions 1 to 12. There was no effect of the acupuncture type on the changes of the LF component of HRV.

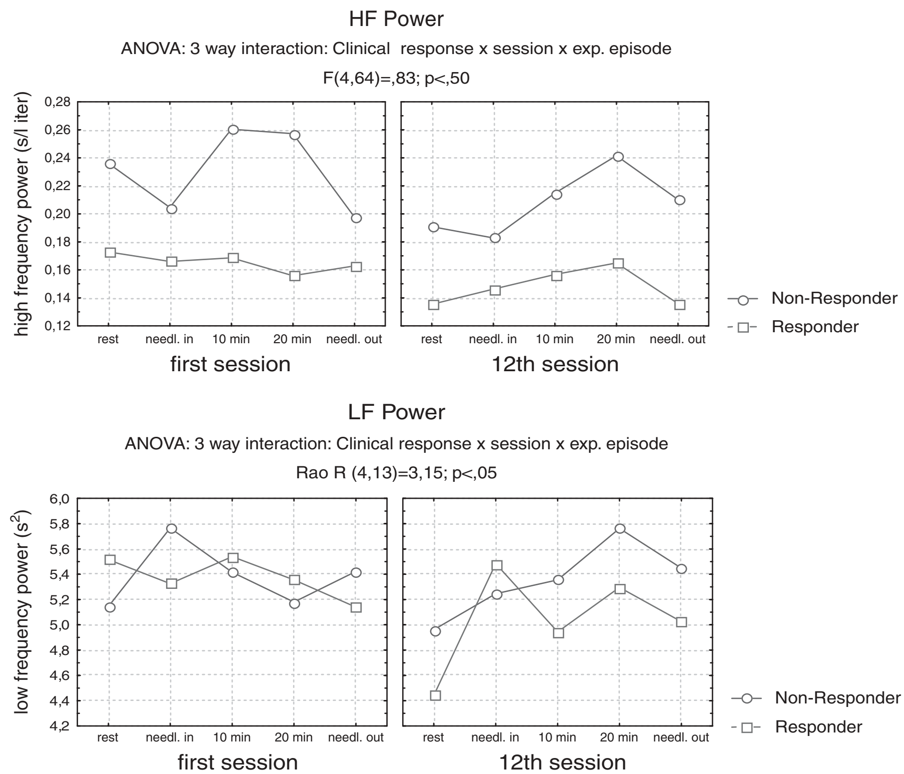

FIGURE 4. Modulation pattern of HF and LF component of HRV in responders and nonresponders (50% reduction of attack frequency) at first and 12th acupuncture session. Upper graph, *y*-axis: high-frequency band of HRV (RSA transfer function), lower graph: power spectral density for the low-frequency band of HRV before. *X*-axis: experimental episodes A-E (baseline, insertion of needles, needles 10 and 20 min in the body, 10 min after removal of the needles). Responder are reflected by squares, nonresponder by triangles. For changes of LF power there is a significant ($P<0.05$) interaction effect of clinical response × experimental episode × session (first vs. 12th acupuncture treatment), which is due to a significant ($P<0.02$) baseline decrease at LF power from sessions 1 to 12 in the responder group. There was no main nor interaction effect of the clinical response on the HF power.

episode A) of LF power from sessions 1 to 12 in the responder group ($P < 0.02$) (Fig. 4). In contrast the clinical response did not influence changes of HF power from sessions 1 to 12 [ANOVA, HF power: clinical response × session (first, 12th session) $P < 0.85$]. Both responders ($P < 0.057$) and nonresponders ($P < 0.06$) tended to decrease their baseline HF from the first to the 12th treatment session.

For the secondary efficacy measures there was also a 2-way interaction effect between the clinical response and the session (first, 12th session) on changes of the LF component of HRV (PDI $P < 0.009$, SES $P < 0.04$, ADS $P < 0.01$). Comparable to the main efficacy measure this was due to a significant decrease of LF power from sessions 1 to 12 in the responder group (PDI $P < 0.002$, SESs $P < 0.01$, ADS $P < 0.004$), which was not found in the nonresponder group. Again HF power tended to decrease in responders and nonresponders without any interaction between session × clinical response. The SF 36 score for physical and mental health and the SES for the emotional domain of pain intensity (SESa) did not show any interaction with neither changes of LF nor HF component of HRV. Finally, we noticed a significant difference at baseline level in session 1 in the LF power between responders and nonresponders with higher values in the responder group (PDI, $P < 0.05$; SESs, $P < 0.001$; ADS, $P < 0.07$).

DISCUSSION

The main finding was that patients in the combined verum and sham groups who responded clinically to the treatment, exhibited a decrease of the LF power of HRV in the course of the treatment, whereas this could not be observed in nonresponders. The mode of acupuncture did have an impact on the HF component of HRV but did neither influence changes of the LF component of HRV nor the clinical outcome.

Although the HF component of HRV is generally regarded to be mediated by changes of vagal cardiac nerve traffic and thus provides an index of vagal activity[18]

TABLE 3. Changes of HRV

	All Patients First/12th Session	VA First/12th Session	SA First/12th Session	Responder First/12th Session	Nonresponder First/12th Session
HRV, LF (s^2)	5.38/5.16	5.55/5.14	5.23/5.17	5.38/5.03	5.38/5.35
HRV, HF (s/L)	0.19/0.17	0.22/0.17	0.17/0.17	0.16/0.15	0.23/0.21

LF and HF of HRV measured during the first and the 12th acupuncture sessions of 19 included patients (10 SA, 9 VA, 12 responders, 7 nonresponders). Data are given as mean of respective 5 experimental episodes per session.

the origins of low frequency heart rate fluctuations are controversial. Some workers[31,32] argue that LF heart rate rhythms reflect mainly fluctuations of the sympathetic traffic to the sinoatrial node. Other researchers believe that LF rhythms reflect fluctuations of both autonomic branches.[18] In our data LF and HF components are modulated differentially in responders and nonresponders. We speculated that, if HF power reflects vagal and the LF power reflects both vagal and sympathetic activity, the lack of LF decrease in nonresponders might be due to a lack of sympathetic withdrawal, because the HF power and thus the vagal control tended to decrease in both groups. Thus, the therapeutic effect of VA and SA in migraine might be related to a decrease of sympathetic nerve activity.

Autonomic Mechanism of Acupuncture in Migraine

A disturbance of the sympathetic nervous system (SNS) has been postulated as a pathogenetic factor in migraine from different workers, and a recent large population-based study in migraineurs supports this assumption.[7] There are various findings which indicate an altered condition of the SNS in the interictal interval including lowered plasma norepinephrine level,[33,34] impaired orthostatic blood pressure response,[35] hypersensitivity of peripheral adrenergic receptors,[8] and a pathologic stress response to external stimuli.[36] Peroutka[8] suggests that migraine attacks are evoked when there is a critical level of sympathetic hypofunction as a result of a preceding overstimulation of the SNS in the headache-free interval. Beta blocking agents, as first line drugs in the prophylactic treatment of migraine, have been found to reduce the LF power of HRV in migraineurs to a similar extent compared with our study.[37] This raises the physiologic plausibility for acupuncture in migraine prophylaxis.

It should be considered, that the clinical improvement in the responder group might be due to the natural course of the disease. Although we cannot exclude this, a responder rate of 63% (12 of 19 patients) after 12 weeks would be an unexpected high proportion of spontaneous improvement. Migraine has a good long-term prognosis (years) as shown in several epidemiologic studies.[38] The short-term outcome (weeks), as determined in various pharmacologic placebo controlled trials, however, ranges between approximately 25% for the placebo group and 30% to 45% for the active treatment group.[39] Additionally, despite the assumption that acupuncture induced the decrease of LF power, we have to consider that sympathetic withdrawal in the responder group might be secondary to the clinical improvement. Patients with less migraine might be more relaxed and thus there may be less sympathetic activity as a consequence of the clinical improvement. This, however, would be contradicted by the observation that the HF power, and presumably the cardiovagal control tended to decrease as well in these patients.

VA and SA

The autonomic response to acupuncture differed significantly between VA and SA. Differences, however, were confined to changes of HF power, whereas the acupuncture mode did not have an impact on LF changes. Moreover in accordance with the entire multicenter trial[3] the clinical response did not differ between the SA and VA groups. These data underline the findings gained from the analysis of responder/nonresponder differences insofar as they show that changes of the HF power of HRV might not be relevant for the clinical response in migraineurs. To our knowledge changes of the autonomic tone during SA and VA in a cohort of patients with chronic pain has not been studied previously. Thus, studies are needed to further elucidate the impact of the mode of acupuncture therapy on the autonomic regulation. The present study points to a comparable clinical effect of sham and verum needling in the treatment of migraine, however, this might not be the case in other diseases, like for example, irritable bowel syndrome, where not a sympathetic but vagal disturbance can be seen.

Acupuncture is a procedure of inserting fine stainless steel needles into the tissue, mostly down to the muscular layer and connective tissue planes,[40] where they excite A-fiber and C-fiber afferents. From a neurophysiologic point of view, acupuncture can therefore be considered as a form of repetitive somatosensory stimulation. Whereas for other diseases the needling of classic acupoints seems to evoke a better clinical effect than sham acupuncture,[41] in migraine a certain part of the therapeutic effect might be induced by the fact alone that a patient receives repetitive somatosensory stimuli, independent on the location of needling. On the other hand the clinical relevance of "needling per se" has recently been questioned for the therapy of migraine. Using a "placebo-needle,"[42] which does not penetrate the skin some workers found no difference in the clinical response compared with VA when needling 15 migraineurs.[43] Acupuncture is a complex intervention, which is characterized by a close interaction between patient and therapist. Paterson and Dieppe[44] recently argued that psychologic factors which are categorized as "unspecific" (placebo) in the context of drug trials, might be considered as characteristic and thus "specific" within acupuncture therapy. These factors, equally present in SA and VA, have certainly also contributed to the observed effects and future studies should be undertaken to further investigate the role of unspecific sensory stimulation and patient-therapist interactions in acupuncture therapy.

Limitations of the Study

A relatively large number of participants (7 of 30 included patients) was rejected from analyses because of nonadherence to the paced breathing. A likely explanation for the inability of these patients to pace their breathing adequately is that they might have been distracted by the acupuncture stimulation. Acupuncture often evokes a quite unusual and strong sensation,[14] that might easily capture the attention of patients and distract them from all other sensory signals. The observation that this artifact was more prominent in the VA group might be explained by VA likely inducing a more intense (and painful) sensation because of the needle inserted more deeply down to the muscular layer compared with the superficial SA procedure. Acupuncture represents a strong sensory stimulus. This should be taken into account in further studies employing HRV measurements for acupuncture research, because task-related changes of breathing can substantially influence HRV in such a manner as to confound estimation of autonomic control.

The relatively large number of comparisons we made underline the fact that this investigation is, to a major degree, exploratory. Future research is required with a larger patient sample, a more limited number of analysis, and the addition of a no-treatment control group.

CONCLUSIONS

The data indicate, that VA and SA may have a beneficial influence on the ANS in migraineurs with a reduction of the LF power of HRV related to the clinical effect. We suggest that this might be due to a reduction of sympathetic nerve activity. These findings are tentative, pending further research. Because both sympathetic and vagal influences are believed to influence the LF component of HRV, a next step would be to employ more direct measures of sympathetic tone like for example, changes of electrodermal activity to study changes of the SNS during acupuncture in migraine.

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