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Response of the autonomic activity to stress provocation in females with cervicogenic headache compared to asymptomatic controls: a cross-sectional study

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Abstract

Background. Because abnormal activity of the autonomic nervous system is associated with chronification of pain, early detection of such dysfunction is important.

Aim. Although several studies highlight autonomic dysfunction in the chronification of headache, no study discussed its role in episodic cervicogenic headache.

Design. Case-controlled cross-sectional single-blind comparative study between women with episodic cervicogenic headache and matched controls.

Setting. Outpatient setting, Hasselt University.

Population. Autonomic activity of 17 females with episodic cervicogenic headache (26.6 ± 11.6 years) was compared with 17 age, gender and socio-economic matched asymptomatic controls (26.8 ± 11.9 years).

Methods. Autonomic activity was compared via repeated measures of the activity of the dermal sweat glands (μmho), peripheral circulation (%), electrical activity of the bilateral upper trapezius (μV) before, during and after cognitive stress provocation.

Results. Whereas the autonomic parameters of the Control-group behaved as expected, participants in the Headache-group showed: (1) to stress provocation a significant lower dermal sweat gland activity (3.03 (.44) vs. 4.19 (.91) μmho) ($p < .0001$), higher vasodilatation (-5.56 (1.45) vs. (-5.61 (1.85) %) (p .03), lower activity of the left upper trapezius (.21 (.44) vs. .89 (.59) μV) (p .03), significant less recuperation of the dermal sweat gland activity (-2.57 (.40) vs. -3.29 (.84) μmho) ($p < .0001$), (2) no recuperation of the activity (μV) of the left (p .83) and right (.99) upper trapezius, (3) and from stress provocation to recuperation a significant negative correlation (ρ .69) (p .04) between dermal sweat gland and right upper trapezius activity.

Conclusion. Females with episodic cervicogenic headache reacted less to cognitive stress provocation. Recuperation after such provocation was absent. More research is needed to associate autonomous responses ~~its responses~~ with a possible chronification process.

Clinical research implication. A dysfunctional reaction to cognitive stress could be a threat to allostasis.

Key words. post-traumatic headache, autonomic nervous system, stress (physiological)

Introduction

Headache ranks in the global top-ten of the most disabling conditions. The prevalence of current headache in adults is estimated to amount 50%. Among those individuals, 1.7 to 4% evolve into a chronic state.[1,2] Long-term coping with chronic headache (i.e. headache occurring on 15 or more days per month for at least 3 months) is a predisposition to develop other illnesses, and thereby imposes a substantial burden on personal and social life.[2] Therefore, factors contributing to the chronification process should be early recognized.

Chronic pain is a multidimensional interaction between physiological, psychological, and social factors.[3] Identifying those factors in an acute phase contributes to the prevention of chronification. Autonomic dysregulation for instance can be such a chronification-promoting factor.[4-6] Lack of physiological recuperation after stress, a typical feature of autonomic dysregulation, might be a risk factor that reduces the capacity to respond to new stressors.[4,5] In addition, an increased sympathetic activity facilitates the sensitization of headache by feeding the nociceptive circuits at the primary nociceptive source and corresponding dorsal horn neurons.[7,8] The development of cervicogenic headache (CeH), i.e. headache caused by a disorder of the cervical spine and its bony, disc and/or soft tissue elements, usually but not invariably accompanied by neck pain, is suggested to be associated with a spread of rostral neuraxial sensitization of the caudal trigemino-cervical nucleus.[9-12]

Since a dysfunction in the activity of the ANS might be a catalyst for the progression from episodic to chronic headache by sensitizing the caudal trigemino-cervical nucleus, its role should be further analysed in patients with CeH.[13] Although multiple pathways induce (central) sensitization, the specific objective of the current study is to explore if differences in autonomic responses can be detected between participants with episodic CeH and asymptomatic controls during cognitive stress provocation.

It is expected that a normal autonomic response is characterized by decreased sympathetic activity during relaxation, which increases during stress provocation and recovers after the omission of stress.[5,10,15-17] Participants with episodic CeH are hypothesized to show a maladaptive autonomic response.[4,15,17]

Materials and methods

The study is registered as an 'Observational Study' at 'ClinicalTrials.gov (NCT02887638)' on 01/09/2016. The Medical Ethical Committee of the 'Ziekenhuis Oost-Limburg' (Chairperson dr. P Noyens) granted approval on 21/05/2015 (B371201423025). All participants signed the written informed consent in which information was given concerning confidentiality of the data.

The protection of personal data is legally determined by the Belgian law of December 8th 1992 on the protection of privacy.

Design

A case-controlled cross-sectional single-blind design was used to compare autonomic responses before (relaxation phase), during (cognitive stress phase) and after (recuperation phase) ~~a~~ cognitive stress provocation between women with episodic CeH and matched asymptomatic controls (Control group).

Participants

Sixty-one potential candidates for the episodic CeH group responded to a general call launched at the Hasselt University campus between October 2015 and January 2016. Inclusion criteria for the episodic CeH group were: females, Dutch-speaking, between 18 and 45 years, diagnosed with episodic CeH based on the 'International Classification of Headache Disorders 3, 2018' (Table 1)' by a neurologist.

Inclusion criteria for the Control group were: asymptomatic females, Dutch-speaking, between 18 and 45 years. Exclusion criteria for the episodic CeH and Control group were: smoking, pregnancy, physiotherapy for head-or neck-related disorders, comorbid pathology (neurological, cardiovascular, endocrine, musculoskeletal, auto-immune, psychiatric), medication use (neuroleptics, anti-epileptic's, Ca^{2+}-blockers, beta-blockers, anti-depressants, hormonal supplements), medication overuse (ergotamine, NSAID, opioid, acetylsalicylic acid, triptans, simple analgesics > 10 days a month during > 3 months), substance abuse, history of neck/head trauma, headaches with autonomic features (photo- or phonophobia, nausea).

Forty-four participants were excluded from the episodic CeH group due to: no CeH diagnosis (n = 27), male gender (n = 7), trauma (n = 2), neurological comorbidity (n = 3), cardiovascular comorbidity (n = 3), metabolic comorbidity (n = 1), and pregnancy (n = 1). Eventually, 17 participants met the criteria for the episodic CeH group. Seventeen asymptomatic female participants were selected after a general call (Hasselt University campus) to compose the Control group. Purposive sampling was applied to match the Control group for age and socio-economic status (level of education, job).

[Table 1]

Outcomes, measurements and instruments

Primary outcome was the activity of the ANS. Autonomic activity was estimated by following the psychophysiological profile of the 1) activity of the dermal sweat glands (skin conductance (SC) (µmho)), 2) peripheral circulation, characterized by vasoconstriction and -dilatation (blood volume pulse (BVP) (%)), and 3) surface electrical activity of the left and right upper trapezius (surface electromyography (sEMG) (µV)) evaluated with the Procomp+ and Biograph 2.1 software (Thought Technology LTd, 2016; 5250 rue Ferrier, Suite 812 Montreal, Canada).[18] sEMG-sensors (pre-amplified MyoScan-Pro™ Sensor, filter 0-400 µV) with AgCl-electrodes (Triode™, reference electrode included) were used. The Muscular Activity Index (MAI) was calculated to estimate muscular activity (µV) during samples of the last 10 seconds in each phase (except in the stress phase data of 10 seconds peak stress were used). Electromyographically signals were automatically converted into root mean squares (RMS) (Table 2). An asymmetry index was calculated to estimate a possible asymmetry between the left and right upper trapezius using the following formula: Asymmetry index $= (RMS_{right} - RMS_{left})/(RMS_{right} + RMS_{left}) \times 100$.[19]

Secondary outcomes, namely headache intensity (100 mm Visual Analogue Scale for pain intensity (VAS (mm) per attack)[20], duration (hours per attack) and frequency (days per month), were extracted from the 'Belgian Headache Society' diary which was completed by the episodic CeH group four weeks before the start of the study.[21]

Test Procedure

A VAS for headache intensity and stress of < 30 mm on the test day were prerequisites to be tested. The intake of painkillers, alcohol, and caffeine (coffee, energy drinks, …) was prohibited 24 hours before testing. The experiment was carried out by a blinded physiotherapist in a quiet, temperature-controlled and dimly lit room at the Hasselt University (Belgium). The non-invasive psychophysiological testing consisted of four consecutive phases: baseline (1 min), relaxation phase (3 min), cognitive stress test phase (3 min) and recuperation phase (= relax after omission of the stressor) (3 min). To relax and recuperate abdominal breathing was taught by a physiotherapist before the start of the measurements (Appendix 1). Sensors for the measurement of SC, BVP and sEMG were applied (Table 2) while the participant was seated on an ergonomic chair (Gymna). The chair could be individually adjusted for comfort.[22] Autonomic activity was evaluated via a baseline measurement in which no instructions were given, followed by a relaxation where abdominal breathing was performed. Next, stress was provoked using a cognitive stress test: the participant was instructed to count down from 500 to 0 in steps of 7 during 3 minutes.[23] Hesitations or incorrect answers were penalized by

restarting the test.[24] To recuperate 3 minutes of abdominal breathing was performed. In the episodic CeH group a 100 mm VAS for headache intensity was questioned before and after testing.

[Table 2]

Statistical analysis

Analysis was done by using SAS JMP Pro 13 (Wittington House, Henley Road, Marlow, Buckinghamshire). Descriptive statistics were provided by presenting the absolute mean group values of every phase (Figure 1) and the group characteristics (Table 3).

Two-or one-tailed p-values were reported with a 95% confidence level ($p < .05$). Equality of groups was tested by an unpaired t-test. For the primary outcome, activity of the ANS, measures of the SC, BVP and sEMG were averaged from the different phases. Results were independent of the baseline (linear regression model). Mixed models with random and fixed effects were used to analyse the repeated measures of the mean SC, BVP and sEMG from baseline to recuperation within and between groups (Tukey-Kramer test). Fixed effects were the phases: baseline, relaxation, cognitive stress and recuperation. The group or the participants were random effects. Dependent variables were the mean SC, BVP and sEMG. Conditions to apply linear models were met [i.e. normal distribution (Shapiro-Wilk $p > .05$, linearity, homoscedasticity (Levene's tests $p > .05$) of the residuals].

Conditions to apply parametric statistics to assess correlations were violated. Therefore, Spearman's rho was used to estimate associations between 1) autonomic parameters (SC, BVP, sEMG) and headache-characteristics (intensity, duration, frequency), and, 2) autonomic parameters mutually.

The Minimal Detectable Change (MDC), which is the minimal amount of change a measurement must show to be larger than the within-subject variability and measurement error, was calculated based on the formula: $1.96 * \sqrt{2} *SEM$. Effect sizes (ES) (Cohen's d) were calculated in case of statistical significance ($p < .05$) (0.2 = small, 0.5 = medium, 0.8 = large ES). The sample size (n = 17) (power of 80%; .05 probability of a type-I error) was estimated a priori.[12]

Results

Group characteristics

Autonomic activity at baseline did not differ between the episodic CeH group and Control group (Table 3).

[Table 3]

Descriptive statistics

Figure 1 visualizes the mean profiles of the autonomic parameters during the different phases for both groups. Deviating patterns were observed for the sEMG of the upper trapezius in the episodic CeH group: sEMG right did not respond to relaxation and sEMG left did not recover during the recuperation phase after stress provocation.

[Figure 1]

Primary outcomes

Responses from baseline to relaxation

SC within the episodic CeH group decreased significantly (p .02). This drop was larger than the MDC (.38) (Table 4). The SC within the Control group did not change significantly. In addition, changes in BVP and sEMG, observed within both groups, were not significant (Table 4). Changes in SC, BVP and sEMG differed not significantly between groups (Table 5).

Responses from relaxation to stress provocation

Within both the episodic CeH group and Control group SC increased significantly ($p < .0001$) and BVP decreased significantly ($p < .01$) (Table 4). Changes for the SC and BVP were larger than the MDCs (CeH: 1.22 respectively 4.02; Control 2.52 respectively 5.13) (Table 4). Response of the sEMG right increased significantly (p .03) within the episodic CeH group, whereas sEMG left increased significantly (p .002) within the Control group (Table 4).

The episodic CeH group differed from the Control group by showing a significantly lower SC ($p < .0001$), higher BVP (p .02) and lower sEMG left (p .03) (Table 5).

Responses from stress provocation to recuperation

The episodic CeH and Control group responded with a significant drop in SC ($p < .0001$) after stress provocation. The observed decrease of the SC in both groups was larger than the MDC (episodic CeH: -2.57 vs 1.11; Control: -3.29 vs. 2.33) (Table 4). Whereas sEMG left and right

decreased significantly (p .003 respectively p .02) in the Control group, sEMG left (p .83) and right (p .20) did not change significantly in the episodic CeH group (Table 4). The SC recuperated significantly ($p < .0001$) less in the episodic CeH group compared to the Control group. No significant between-group differences can be presented for BVP (p .77), sEMG left (p .56) and sEMG right (p .39) (Table 5).

[Table 4]

[Table 5]

Correlations

Positive correlations between sEMG left and right during relaxation (ρ .59) (p .01) and stress (ρ .69) (p .04) were seen in the episodic CeH group. Contrarily, a negative correlation between SC and sEMG right (ρ -.51) (p .03) was calculated during recuperation.

Secondary outcomes

Pain

The mean 100 mm VAS for headache intensity (26 mm) before the psychophysiological measurement did not differ significantly from the mean VAS for headache intensity (30 mm) after the measurements in the episodic CeH group.

Discussion

Although several studies highlight an involvement of autonomic dysfunction in the chronification of headache, no study discussed its role in episodic CeH.[6,25] Whereas the autonomic parameters of our Control group responded as expected, participants in the episodic CeH group showed: 1) to relaxation no response of the right upper trapezius, 2) to stress provocation a significant lower dermal sweat gland activity, higher vasodilatation, and lower activity of the left upper trapezius, 3) significant less recuperation of the dermal sweat gland activity and no recuperation of the activity of the left and right upper trapezius after stress provocation, and 4) from stress provocation to recuperation a significant negative correlation between dermal sweat gland activity and activity of the right upper trapezius.

Dermal sweat gland activity

Cutaneous sweat glands are exclusively innervated by cholinergic nerves of the sympathetic nervous system (SNS). Electrodermal activity therefore reflects the SNS's arousal.[26] Orthostatic, physical and cognitive stressors are used to assess such arousal.[27] An increased sympathetic response to cognitive stress might contribute to an increased sensitivity to painful stimuli.[28] However, such findings are in contrast with the significant lower electrodermal reactivity in our episodic CeH group during the stress response, which could indicate a lower sympathetic activity.[5,6] The dampened electrodermal reactivity might reflect a depletion of the activity of the SNS. Sympathetic hypofunction has been mooted as a trait of depression, and as a potential patho-mechanism leading to higher risks for negative health outcomes.[29]

In healthy young controls (mean 23.3 years) electrodermal activity recovers after a cognitive (arithmetic) test.[23] Similar results were found in our Control group (26.8 years). However, in the episodic CeH group, dermal sweat gland activity recovered significantly less. A delayed inhibitory process might be associated with such results.[23] In addition, a persistent augmented activity of the SNS facilitates sensitization processes by decreasing sensory and nociceptive thresholds, and increasing muscular activity.[8] The latter was observed in the episodic CeH group.

The negative correlation between the SC and sEMG right during recuperation in the episodic CeH group, opposing the normal expectation, might be an indication of a dissociated pattern of sympathetic activity.[30,31]

Peripheral vascular response

The peripheral vascular response to stress provocation, i.e. vasoconstriction, was significantly lower in the episodic CeH group compared to the Control group. Analogously, previous analysis of Mayer (vasomotor) waves in patients with chronic tension-type headache revealed a sympathetic down-regulation. Such reaction was hypothesized to be the result of an habituation process.[32] The ability to habituate to nociceptive stimuli is a trait of chronic headache.[33] Yet, in our study participants in the episodic CeH group responded to a lesser extent to stress provocation. It could be hypothesized that these participants are already evolving into a chronic headache state. However, results from the current study cannot accept nor refute such hypothesis.

Muscular activity

Participants in the episodic CeH group seem to have difficulties to relax the bilateral upper trapezius after stress provocation: sEMG of the left upper trapezius was 27%, and sEMG of the right upper trapezius 58% higher after recuperation compared to at the end of the relaxation (Figure 1). Based on the asymmetry index, activity of the right upper trapezius was 36% higher compared to the left after recuperation. Such lacking muscular recuperation might be indicative for a dysregulated ANS.[15,17] Sustained sEMG-activity is suggested to be the result of a defective central inhibition, in which low threshold motor units remain activated. This fits the concept of 'sustained arousal'.[34,35] The observed left-right difference in sEMG activity is hypothesized to be related to two mechanisms. Firstly, hand-dominance might support such difference since dominant upper trapezius muscles demonstrate higher amplitudes of activity and less muscular rest compared to non-dominant muscles.[36] Secondly, pain-related increased activation of local muscle sympathetic nerve activity might reinforce muscular activity.[37] The higher sEMG activity of the right upper trapezius might be explained by the fact that most participants in the episodic CeH group were right-handed (94%) and suffered from right-sided CeH 4(right 53% vs. left 23.5%).

However, stress provocation could not provoke headache in the episodic CeH group. Bansevicius et al. concluded that the mean level of phasic sEMG responses during stressful conditions are of little importance to develop muscular pain.[38] It can nonetheless be argued that other physiological responses, such as prolonged activity of low-threshold motor units, might be important for such development. Since chronic pain conditions are caused by multimodal interactions, muscular responses might only partially contribute to the development of chronic pain.[17,39]

Pain provocation

Cathcart et al. supported the hypothesis in which mental stress contributes to chronic headache through sensitization of nociceptive afferents.[40] The cognitive stressor in our study did not provoke instant headache. The duration of the stressor could have been too short, or a delayed headache might have developed.

Limitations and suggestions

The authors acknowledge that case-controlled studies and purposive sampling are sensitive to selection bias. The generalisation of the results is therefore limited to females with episodic CeH between 18 and 45 years.[41] More research is needed to provide normative data, and determine clinically significant changes (minimal clinically important difference, MCID). No causative statements can be made based on the current cross-sectional study. Longitudinal designs (follow-up) are needed to determine if an autonomic dysregulation can contribute to the chronification of episodic CeH. Further, a 24-hour VAS should be questioned.

This study used a cognitive stress provocation with a limited recuperation phase (3 minutes). More research is needed to assess the contribution of an incomplete recovery to the chronification of pain.[38] Based on the current study we advise to measure the time needed to recuperate completely (= baseline) since the prolonged activity of low-threshold motor units might be important for the development of pain originating from a muscle.[38] In addition, although outside the scope of the current study, we found a dependency (linear regression model) between the magnitude of the SC, BVP, sEMG left and right in the recuperation phase (dependent variable) and the stress phase (independent variable); meaning that higher responses to stress were predictive for a stronger recuperation (Appendix 2).

Future research should question psychosocial (anxiety, depression, cognition, personality) and lifestyle factors (sleep quality, physical activity) to accentuate the biopsychosocial character of stress.

Finally, no Bonferroni corrections were applied given the explorative nature of the study. The authors realize the consequence (Type I (α) error).

Conclusion

The Control group responded as was expected from previous studies. However, females with episodic CeH reacted with a lower activity of the dermal sweat glands, a more relaxed peripheral circulation and less activity of the left upper trapezius to cognitive stress provocation. Recuperation after such provocation was contrarily absent.

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Notes

Ethics approval and consent to participate

The study is registered as an 'Observational Study' at 'ClinicalTrials.gov (NCT02887638)' on 01/09/2016. The Medical Ethical Committee of the 'Ziekenhuis Oost-Limburg' (Chairperson dr. P Noyens) granted approval on 21/05/2015 (B371201423025). All participants signed the written informed consent in which information was given concerning confidentiality of the data. The protection of personal data is legally determined by the law of December 8th 1992 on the protection of privacy according to the Belgian law.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SM drafted the manuscript. MG provided essential comments on the structure, spelling and content of the manuscript. Both authors read and approved the final manuscript.

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Tables

Table 1. Diagnostic criteria of cervicogenic headache by the International Classification of Headache Disorders 3

Description	**Headache caused by a disorder of the cervical spine and its component bony, disc and/or soft tissue elements, usually but not invariably accompanied by neck pain.**
Diagnostic criteria	A. Any headache fulfilling criterion C B. Clinical and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck, known to be able to cause headache C. Evidence of causation demonstrated by at least two of the following: 1. headache has developed in temporal relation to the onset of the cervical disorder or appearance of the lesion 2. headache has significantly improved or resolved in parallel with improvement in or resolution of the cervical disorder or lesion 3. cervical range of motion is reduced and headache is made significantly worse by provocative manœuvres 4. headache is abolished following diagnostic blockade of a cervical structure or its nerve supply D. Not better accounted for by another ICHD-3 diagnosis
Provocation	Headache provoked by at least one of the following: 1. Posture (e.g. forward head posture) 2. Repetitive cervical movement
Autonomous	1. No nausea or vomiting 2. No photophobia or no phonophobia

Table 2. Summary of the sensor and electrode placement and interpretation of the psychophysiological measurements

Measurement	Sensor and electrode placement - Interpretation
SC (µmho)	**Sensor placement**
	Two sensors attached to the distal phalanges of the ring and middle finger of the non-dominant hand.
	Interpretation
	Evaluation of electrical SC depends on the dermal sweat gland activity. SNS activity increases conductance by elevating the dermal sweat gland activity.
BVP (%)	**Sensor placement**
	Sensor attached to the palmar thumb side of the non-dominant hand.
	Interpretation
	The BVP-sensor evaluates peripheral circulation through photoplethysmography. The amount of reflected light is measured and presented as a bandwidth amplitude. Stress reduces the amplitude of the bandwidth through peripheral capillary constriction. An increased bandwidth indicates a vasodilatation of the peripheral capillaries.
sEMG (µV)	**Electrode placement**
	Triodes were placed parallel with the fibres of the upper trapezius, 10 mm lateral of the centre of the line between the acromion and spinous processus of C7 [17,21].
	Interpretation
	The sEMG measures the electrical activity of the muscle. During stress the sEMG-signal increases.

SNS, Sympathetic Nervous System; SC, Skin Conductance; BVP, Blood Volume Pulse; sEMG, surface Electromyography

Table 3. Summary of the mean group characteristics

	Episodic CeH (n = 17)	**Control (n = 17)**	***p-v*alue**
Age (*SD*), y	26.6 (11.6)	26.8 (11.9)	.19†
Hand-dominance Right/Left	16/1	15/2	1‡
Headache intensity, mean 100 mm VAS per attack (*SD*)	40.2 (22)	N/A	N/A
Frequency HA (days per month) (*SD*)	13.6 (7.3)	N/A	N/A
Duration HA (hours per attack) (*SD*)	6.8. (3.2)	N/A	N/A
SC (µmho) (*SE*)	2.7 (.4)	2.5 (.4)	.64
BVP (%) (*SE*)	10.4 (1.7)	9.4 (2.4)	.85
sEMG left (µV) (*SE*)	2.3 (.6)	1.8 (.6)	.40
sEMG right (µV) (*SE*)	1.3 (.3)	1.7 (.8)	.82

CeH, Cervicogenic Headache; HA, Headache; SD, Standard Deviation; SE, Standard Error; y, years; †, unpaired t-test; ‡, Fisher exact test; significance, $p < .05$; n, number of participants; SC, Skin Conductance; BVP, Blood Volume Pulse; sEMG, surface Electromyography; VAS, 100 mm Visual Analogue Scale; N/A, not applicable. Results concerning the headache characteristics for the episodic CeH group were retrieved from the headache diary

Table 4. Comparisons of the autonomic activity from baseline to recuperation within the episodic CeH (n = 17) and the Control group (n = 17)

		Baseline	**Relaxation**	***p**-value**	**Relaxation**	**Stress provocation**	***p*‡-value**	**Stress provocation**	**Recuperation**	***p*†-value**
Skin conductance µmho (*SE*) (CI)	CeH	2.7 (.4) (1.5 – 3.2)	1.4 (.3) (0.7 – 2.1)	***.02***	1.4 (.3) (0.7 – 2.1)	4.4 (.7) (3 – 5.9)	**< *.0001***	4.4 (.7) (3 – 5.9)	1.9 (.4) (1 - 2.8)	**< *.0001***
	Control	2.5 (.4) (1.6 – 3.5)	1.6 (.4) (0.8 – 2.3)	.71	1.6 (.4) (0.8 – 2.3)	5.8 (1.1) (3.5 – 8)	**< *.0001***	5.8 (1.1) (3.5 – 8)	2.5 (1.8) (1.6 – 3.4)	**< *.0001***
Blood volume pulse (%) (*SE*) (CI)	CeH	10.4 (1.7) (6.8 – 14)	12.3 (1.8) (8.5 – 16.2)	.66	12.3 (1.8) (8.5 – 16.2)	6.8 (1.3) (4 - 9.6)	***.002***	6.8 (1.3) (4 - 9.6)	7.6 (1.3) (4.8 – 10.4)	.96
	Control	9.4 (2.4) (4.2 – 14.5)	11.8 (2.5) (6.5 – 17.2)	.41	11.8 (2.5) (6.5 – 17.2)	6.2 (1.5) (3.1 – 9.3)	***.0001***	6.2 (1.5) (3.1 – 9.3)	8.9 (1.9) (4.9 – 12.9)	.34
sEMG Left µV (*SE*) (CI)	CeH	2.3 (.6) (1.1 – 3.5)	2.2 (.4) (1.3 – 3.1)	.99	2.2 (.4) (1.3 – 3.1)	2.4 (.4) (1.5 – 3.3)	.97	2.4 (.4) (1.5 – 3.3)	2.8 (.6) (1.5 – 4.1)	.83
	Control	1.8 (.6) (.5 – 3.2)	1.7 (.6) (.5 – 2.9)	.99	1.7 (.6) (0.5 – 2.9)	2.6 (.7) (1.1 – 4.1)	***.002***	2.6 (.7) (1.1 – 4.1)	1.5 (.4) (.8 – 2.3)	***.003***
sEMG Right µV (*SE*) (CI)	CeH	1.3 (0.3) (0.5 – 2)	1.8 (0.4) (0.8 – 2.7)	.88	1.8 (0.4) (0.8 – 2.7)	3.3 (1) (1.1 – 5.4)	***.03***	3.3 (1) (1.1 – 5.4)	3.1 (1.1) (0.9 – 5.3)	.99
	Control	1.7 (.8) (0 – 3.5)	1.8 (.7) (.3 – 3.4)	.91	1.8 (.7) (.3 – 3.4)	4.1 (1) (2.1 – 6.2)	***.01***	4.1 (1) (2.1 – 6.2)	1.9 (.4) (.9 – 2.8)	***.02***

CeH, Cervicogenic Headache; *, *p*-value (mixed model with random and fixed effects) from baseline to relaxation; ‡, *p*-value (mixed model with random and fixed effects) from relaxation to stress provocation; †, *p*-value (mixed model with random and fixed effects) from stress provocation to recuperation; *p*-values in bold and italic, $p < .05$; SE, Standard Error; CI, 95% Confidence Interval; n, number of participants.

Table 5. Comparisons of the changes in autonomic activity from baseline to recuperation between the episodic CeH (n = 17) and the Control group (n = 17)

	Baseline to relaxation (Δ)			**Relaxation to stress (Δ)**			**Stress to recuperation (Δ)**		
	CeH	**Control**	***p*-value**	**CeH**	**Control**	***p*-value (ES)**	**CeH**	**Control**	***p*-value (ES)**
Skin conductance µmho (*SE*)	-.96 (.14)	-.96 (.04)	.32	3.03 (.44)	4.19 (.91)	**< *.0001* (1.56)**	-2.57 (.4)	-3.29 (.84)	**< *.0001* (1.26)**
MDC	.38	.11		1.22	2.52		1.11	2.33	
Blood volume pulse (%) (*SE*)	1.92 (1.79)	2.46 (1.24)	.63	-5.56 (1.45)	-5.61 (1.85)	***.003* (0.73)**	.84 (1.84)	2.68 (1.2)	.77
MDC	4.96	3.43		4.02	5.13		5.1	3.33	
sEMG Left µV (*SE*)	.13 (.06)	-.13 (.14)	.99	.21 (.44)	.89 (.59)	***.03* (0.54)**	.43 (.41)	-1.01 (.62)	.56
MDC	.16	.38		1.22	1.64		1.14	1.72	
sEMG Right µV (*SE*)	.49 (.05)	.11 (.17)	.98	1.5 (.61)	2.31 (.88)	.07	-.14 (.51)	-2.28 (.96)	.39
MDC	.14	.47		1.7	2.44		1.41	2.66	

CeH, Cervicogenic Headache; SE, Standard Error; MDC, Minimal Detectable Change; Δ, differences between phases; L, Left; R, Right; *p*-value, mixed model with random and fixed effects; *p*-values in bold and italic, $p < .05$; ES, Effect Size (Cohen's d); n, number of participants. Negative values are indicative for a decrease, positive values for an increase.

Figure legend

Figure 1. Visualisation of the mean (SEM) autonomic activity in the episodic CeH group and Control group from baseline to recuperation (Cg, Control group)

Appendix 1

Diaphragmatic breathing

Diaphragmatic breathing was demonstrated by a physiotherapist, and the purpose of the breathing was explained. Abdominal breathing was first performed in supine, hereafter in sitting (relax chair, Gymna). Participants were asked to inhale the air through the nose, bulge the abdomen, hold their breath for a few seconds, and then exhale slowly with the lips pursed. During the teaching, participants were instructed to watch and feel their abdomen moving outwards during inspiration and inwards during expiration. A physiotherapist guided the movement via manual feedback. The same action was taught in a sitting position. The pace of the breathing was set at 6 to 10 breaths per minute which is an 'autonomically optimised respiration'.[42] Diaphragmatic breathing was eventually independently performed by the participant.

Appendix 2

Table 6. Stress-dependency of the primary outcomes in the recuperation phase in the episodic CeH and the Control group

	Skin conductance (µmho)	**Blood volume pulse (%)**	**sEMG Left (µV)**	**sEMG Right (µV)**
	***p*-value**	***p*-value**	***p*-value**	***p*-value**
CeH	< .0001*	.212	.004*	.002*
Control	.0006*	.002*	.003*	.193

CeH, Cervicogenic headache. Logistic transformations were applied to meet the condition of normal distribution (Shapiro-Wilk $p > .05$); Levene's test for unequal variances was $p > .05$ for all outcomes; in the linear regression model: outcomes in the stress phase were independent (x), outcomes in the recuperation phase dependent (y); *, $p < .05$ indicating a stress phase-dependency