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Cardiorespiratory regulation in migraine. Results in children and adolescents and review of the literature

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To investigate autonomic regulation in juvenile migraine we studied 70 children and adolescents with migraine during the headache-free period and 81 healthy controls by cardiorespiratory function tests. Heart rate variability was analysed with time and frequency domain indices during spontaneous breathing at rest and during metronomic breathing. Changes of heart rate and blood pressure were studied during tilt-table test, active standing, Valsalva manoeuvre and sustained handgrip. We found significant differences in metronomic breathing, tilt-table test and Valsalva manoeuvre. We interpret our findings and results reported in the literature as pointing to a restricted ability of the system to rest, which supports therapies intending to further this ability. In autonomic tests, hyperreactivity in juvenile migraineurs changes to hyporeactivity and passive coping in adults. This might be explained by disturbances of raphe nuclei and the periaqueductal grey. It corresponds to psychological findings in juvenile migraineurs reporting hypersensitivity and repressed aggression and claiming learned helplessness. ☐*Autonomic nervous system, cardiorespiratory regulation, child, heart rate variability, migraine*

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Introduction

The past two decades have brought about decisive advances in our understanding of the pathophysiology of migraine (1). Investigations of cerebrovascular reactivity and cortical excitability as well as studies of cognitive processes have demonstrated cerebral hyperreagibility in subjects suffering from migraine (2), raising the question whether comparable changes might also be seen in other cerebral systems. Examination of autonomic processes seems reasonable in this regard, because of the well-known autonomic symptoms that occur during a migraine attack (3) and because of the various structural and functional connections between the central autonomic network and pain-processing systems (4, 5). Thus, the possible significance of autonomic processes in migraine is a matter of discussion in the literature (6–8).

In laboratory evaluation of the autonomic nervous system (ANS), tests of cardiovascular and cardiorespiratory regulation are well developed. Because of the different aspects of this regulation, elaborate testing programmes have been established (9–11). The best established programme includes the study of heart rate variability (HRV) during spontaneous and metronomic breathing using time-domain and frequency-domain measures, study of heart rate changes induced by Valsalva manoeuvre as well as the study of heart rate and blood pressure changes upon standing, at upright tilt and at isometric handgrip or with the cold pressor test (9–11).

In adult migraineurs, studies investigating cardiorespiratory regulation (see Table 1) have most

Table 1 Cardiovascular and cardiorespiratory regulation tests in migraineurs in the headache-free interval (children and adolescents in bold type)

	Subjects	Rest	6/min	Tilting	Standing	Valsalva	SHG	Others
Gotoh et al. (23)	21 M, 30 C, ~30 years				ΔSBP↓	VR↓		A: HR↓
Havanka-Kanniainen et al. (32)	**49 M, 25 C, 11–22 years**	**E/I ratio→**	**E/I ratio→**	**ER→** **ΔSBP→** **ΔDBP→**		**VR→**	**ΔSBP→** **ΔDBP→**	
Havanka-Kanniainen et al. (12)	60 M, 35 C, 23–50 years	E/I ratio↓	E/I ratio↓	ER↓ ΔSBP(↓) ΔDBP↓		VR↓	ΔSBP↓ ΔDBP↓	
Havanka-Kanniainen et al. (13)	21 M, 19 C, 21–54 years	E/I ratio↓	E/I ratio↓	ER↓ ΔSBP(↓) ΔDBP↓		VR↓	ΔSBP(↓) ΔDBP↓	
Havanka-Kanniainen et al. (14)	188 M, 85 C, 11–69 years	E/I ratio↓	E/I ratio↓	ER↓ ΔSBP(↓) ΔDBP↓		VR↓	ΔSBP(↓) ΔDBP↓	
Boiardi et al. (15)	44 M, 34 C		ΔEI↓		ER→ ΔSBP↓	VR→	ΔDBP↓	
Mikamo et al. (16)	15 M, 15 C, 14–70 years	HR→			ΔSBP↓ ΔDBP↓		ΔHR→ ΔSBP↓ ΔDBP↓	
Cortelli et al. (20)	(females) 13 M, 18 C, 17–56 years	HR↑	E/I ratio→	ΔSBP→ ΔDBP→		VR→	ΔHR→ ΔSBP(↑) ΔDBP↑	CPT: ΔHR→ ΔSBP↑ ΔDBP(↑)
Appel et al. (26)	10 M, 10 C, ~30 years	(24 h) LF↑, HF→						
Martin et al. (21)	75 M, 78 C, ~30 years		ΔEI↓		ER↑ ΔSBP↓	VR→	ΔDBP→	
Osipova (17)	40 M, 15 C, adults	ΔEI→	ΔEI→		ER↓ ΔSBP(↑)	VR↓	ΔDBP↓	
Zigelman et al. (27)	10 M, 9 C, ~30 years	(24 h) LF↑, HF→						
Pogačnik et al. (18)	62 M, 45 C, 21–50 years	LF/HF(↓)	E/I ratio(↓)	ΔSBP→ ΔDBP→	ER→	VR→	HR ratio↓ ΔDBP(↓)	
Zigelman et al. (22)	5 M, 9 C, ~30 years	(24 h) LF↑, HF→			LF↑ HF→			

Thomsen et al. (25)	50 M, 30 C, 38–55 years	MSD(↓)	ΔEI→			VR↓		
		SDRR→						
				ΔSBP→				CPT: ΔSBP→
				ΔDBP→				ΔDBP→
Pierangeli et al. (57)	56 M, 31 C	HR→		ΔHR→		VR→		
		LF/HF→		LF/HF→				
				ΔSBP→				
				ΔDBP→				
Ostertag et al. (19)	10 M, 12 C, adults		ΔEI→		ER→	VR→		
					ΔSBP→		ΔDBP↓	
Yakinci et al. (33)	**25 M, 30 C, 8–12 years**		**ΔEI→**		**ER↑**	**VR↑**		
					ΔSBP↑		**ΔSBP↑**	
					ΔDBP(↑)		**ΔDBP→**	
Mosek et al. (24)	(females) 17 M, 16 C, 20–45 years	HR→		ΔHR→		VR→		
		SPHR→		SPHR↓				
				NRF/RF↑				
		SBP→		ΔSBP→		ΔDBP↓	ΔDBP→	
		DBP→		ΔDBP→				
		SPBD→		SPBD→/↓				
Tabata et al. (28)*	27 M, 24 C, adults	HR→						
		HRV→/↓						
Shechter et al. (61)	80 M, 85 C, 20–50 years	E/I ratio→	E/I ratio→			VR→		
Sanya et al. (62)†	30 M, 30 C, ~35 years	LF→, HF→						

Rest, Spontaneous breathing at resting in supine; 6/min, metronomic breathing with 6 breaths/min; SHG, sustained hand grip test; A, Aschner test; CPT, cold pressor test; M, number of migraineurs; C, number of controls; years, age of subjects; HR, heart rate; RR interval, interval between two neighbouring R waves; E/I ratio, ratio of RR intervals at expiration divided by RR intervals at inspiration; ΔEI, absolute value of the difference of RR intervals or of HR between expiration and inspiration; MSD, mean successive difference of the numeric values of the RR intervals; RMSSD, root-mean-square of successive differences of RR intervals; SDRR, standard deviation of the mean RR intervals; LF, power in the low-frequency band in power spectral density analysis (PSD) of heart rate; HF, power in the high-frequency band in PSD of heart rate; SPHR, total spectral power of heart rate; SPBP, total spectral power of blood pressure; NRF/RF, ratio of spectral power of non-respiratory frequency variations in blood pressure to that at respiratory frequency variations in the RR interval; ΔSBP, systolic blood pressure during the test less systolic blood pressure before the test; ΔDBP, diastolic blood pressure during the test less diastolic blood pressure before the test; ΔHR, heart rate during the test less heart rate before the test; ER, Ewing ratio; VR, Valsalva ratio; ↓, significantly reduced in migraineurs; (↓), tending to be reduced in migraineurs; ↑, significantly elevated in migraineurs; →, no significant difference.

*24-h mean of RR interval, standard deviation of mean RR interval, RMSSD, HF and LF/HF unchanged; 24-h mean of LF reduced; circadian changes of LF, HF, LF/HF unchanged; circadian changes of mean RR interval, standard deviation of mean RR interval, and root-mean-square of successive differences reduced.

†Reduced RR interval oscillatory response to 0.2 Hz neck suction in migraineurs.

frequently shown reduced reaction in the so-called handgrip test (12–20). In orthostatic manoeuvres, reduced (12–14) or enhanced (21, 22) heart rate changes and reduced blood pressure stabilization (12–17, 21, 23, 24) have been found. In Valsalva manoeuvre, heart rate changes were found dampened (12–14, 23, 25). During spontaneous (12–14, 22, 26–28) or metronomic breathing (12–15, 21, 28) altered HRV has been reported. Several older psychophysiological studies in migraineurs found higher heart rate reactivity at stressful mental tasks (29–31). However, for each test reported to be altered in migraineurs there are also reports of normal results.

Disturbances of cardiorespiratory regulation in migraineurs may be more pronounced in patients with more frequent attacks and they may develop gradually with age (14). Studying children and adolescents suffering from migraine allows minimizing the confounding influence of pain chronicity and of medication. To our knowledge, only two studies have dealt explicitly with autonomic regulation processes of juvenile migraineurs (see Table 1). Havanka-Kanniainen et al. (32) investigated 49 migraineurs aged 11–22 years. During spontaneous breathing, metronomic breathing with 6 breaths/min, tilt-table test, Valsalva manoeuvre and sustained handgrip test, they found no significant differences from controls. However, Yakinci et al. (33) studied 25 migraineurs aged 8–12 years and during active standing observed exaggerated heart rate changes and a larger increase in blood pressure, during Valsalva manoeuvre exaggerated heart rate changes, and in sustained handgrip a larger increase in systolic blood pressure, while no significant differences were found during metronomic breathing.

Thus, the only study in children proposed hyperactivity of the ANS, the study in adolescent migraineurs found no differences from controls, while the studies in adults where mostly interpreted as pointing to hypoactivity of the ANS.

The aim of the present study was to re-examine if changes in the autonomic regulation of migraine patients may be detected in childhood and adolescence and, if so, what changes may be found.

Subjects and methods

Patients suffering from migraine and healthy controls were recruited from our paediatric out-patient clinics after the study had been reported in the local print media. Eligible for inclusion were patients 6–18 years of age who had suffered from migraine for at least 1 year and who had had at least three attacks during the last 3 months. Migraine was diagnosed in a structured diagnostic interview (34) with the subject and one of his or her parents in accordance with the International Headache Society criteria (35). After publication of the revised classification, the diagnoses were checked according to the revised diagnostic criteria without any changes being necessary (36). The interview was supplemented by an age-adapted, prospective headache diary, which the patients were asked to keep over an 8-week period. Exclusion criteria were any prophylactic headache treatment or any other regular medication during the last half-year, the presence of a headache subtype different from migraine or the presence of other diseases possibly affecting autonomic testing (e.g. any chronic pain disorder, or endocrinological, cardiovascular or other neurological diseases). Patients underwent electroencephalography, the results of which were normal in all cases. Headache-free controls were classmates of the patients or had read about the study in the local newspaper. Controls were subject to the same exclusion criteria as were patients. The evaluation of subjects' medical condition was based on full medical history and complete physical and neurological examination.

Included in the study were 33 females and 37 males, aged 6–18 years, suffering from migraine. The control group consisted of 38 females and 43 males, aged 6–18 years. The study group and controls were comparable in terms of age and sex (Table 2). Age groups used for subtests were also comparable in terms of age and sex (Table 3). This was demonstrated by Pearson's χ^2 test, the Kolmogorov–Smirnov test and the Mann–Whitney *U*-test. The mean time since first episode of migraine was 4.6 ± 2.9 years. In 51.4% of the migraine patients, the current frequency of migraine attack was at least one per week. Twenty migraine patients suffered from migraine with aura. We disregarded the presence of aura in this study.

Autonomic tests were performed in the headache-free period. None of the subjects reported headache for at least 72 h before and after testing. Subjects were instructed to abstain from caffeine-containing

Table 2 Baseline characteristics of subjects

		Migraine	Controls
Group size		*n* = 70	*n* = 81
Sex,	male : female (*n*)	37 : 33	43 : 38
	(%)	53 : 47	53 : 47
Age,	mean ± SD (years)	10.73 ± 3.07	11.21 ± 3.32
	range (years)	6–18	6–18

Table 3 Baseline characteristics of subjects in dependency on age of life

		6–9 years		10–13 years		14–18 years	
Migraine		Migraine	Controls	Migraine	Controls	Migraine	Controls
Group size		*n* = 28	*n* = 30	*n* = 28	*n* = 31	*n* = 14	*n* = 20
Sex	male : female (*n*)	14 : 14	19 : 11	16 : 12	16 : 15	7 : 7	8 : 12
	(%)	50 : 50	63 : 37	57 : 43	52 : 48	50 : 50	40 : 60
Age,	mean ± SD (years)	7.79 ± 1.07	7.63 ± 1.10	11.32 ± 1.12	11.90 ± 1.14	15.43 ± 1.40	15.50 ± 1.43
	range (years)	6–9	6–9	10–13	10–13	14–18	14–18

beverages and, in the adolescents, from nicotine and alcohol for at least 24 h before the test. The examinations took place between 14.00 h and 17.00 h to avoid diurnal variation and were performed in a calm, pleasantly lit and agreeably warm room. The subjects were asked to lie down and to speak and move as little as possible.

The following autonomic tests were performed. After an initial adaptation phase, HRV was registered during a 4-min resting period of spontaneous breathing and during separated 2-min periods of metronomic breathing at frequencies of 6 and 8.5 breaths/min. For metronomic breathing the subjects were instructed to follow a rising and falling column depicted on a computer screen, the respective inspiration and expiration periods being equal. The respective registrations were started after a 1-min period of adapting to the actual breathing frequency.

Tilt-table test

After 1 min of lying supine quietly, the subjects were tilted to a head-up position of 60°, which was retained for 5 min.

Active standing

After 1 min of lying supine quietly, the subjects were asked to rise to their feet within 5 s, and to remain standing quietly for 5 min.

Valsalva manoeuvre

Subjects were instructed to blow into a mouthpiece that was connected with a manometer and to maintain a pressure of 40 mmHg for 15 s.

Sustained handgrip

After the maximal power of the subjects' left hand had been determined by means of a manometer connected to a rubber ball, the subject was asked to squeeze this ball with 30% of established maximum power for 3 min. We chose the subjects' left hand for technical reasons, independently of their handedness.

The different tests were explained immediately before the respective manoeuvres. Before starting a new test, there was an interval to allow the subject to come to rest again. Thus the whole investigation took about 50 min.

For registration and evaluation of HRV we used a commercially available polygraph (Vagus 2000/2100®; Sigma Medizintechnik, Thum, Germany). Electrocardiogram was registered by limb leads. After analogue–digital conversion, R waves were automatically detected. The R-wave marks were controlled on the screen and, if necessary, moved to the correct place. The resulting series of R waves were reflected as a tachogram showing the series of intervals between two neighbouring R waves (RR intervals) as a function of the number of the interval. This was the basis for the calculation of measures in the time domain.

The established measure for the evaluation of orthostatic manoeuvres is the Ewing ratio or 30/15 ratio (37). It is calculated from the longest RR interval around the 30th heartbeat after taking in the vertical position divided by the shortest RR interval around the 15th heartbeat. The evaluation program of the polygraph defined the 7th to 24th heartbeat as the 'region around the 15th heartbeat' and the 22nd to 43rd heartbeat as the 'region around the 30th heartbeat'.

During the Valsalva manoeuvre, the heart rate, after a short initial slowing, is elevated continually. After the manoeuvre, a very short heart rate maximum is followed by heart rate slowing. The Valsalva ratio calculates the quotient between the longest RR interval after the test and the shortest interval during the test (38).

Heart rate changes during the sustained handgrip were analysed as changes of the heart rate in the third minute of contraction in relation to the starting heart rate.

To calculate time domain measures of HRV at spontaneous or metronomic breathing, we used 120-s periods of the respective subtests: for spontaneous breathing, the middle 2 min of the 4-min test period were used; for metronomic breathing, the whole 2-min test period. For these periods we determined the mean heart rate and the expiration/inspiration (E/I) ratio. To calculate the E/I ratio, the test periods were divided into periods of 20 s, in which the longest RR interval during expiration (E) and the shortest RR interval during inspiration (I) were determined; the mean of the resulting 20-s E/I ratios was used as the E/I ratio of the respective test. For the metronomic breathing periods, by means of the triggered cross-correlation (39) between breathing movement and the cardiotachogram the frequency deviation (FD) was calculated (40). It corresponds to the difference between the highest instantaneous heart frequency during inspiration and the lowest instantaneous heart frequency during expiration and is expressed in beats/min. FD divided by the mean heart rate results in the relative FD.

At power spectral density (PSD) analysis, a time series may be analysed with regard to the frequencies of underlying oscillations or rhythms. PSD analysis of heart rate fluctuation yields measures in the frequency domain (41, 42). As is customary, a fast-Fourier transformation algorithm was applied to calculate the PSD of the instantaneous heart rate series for the relevant frequencies from 0.01–0.5 Hz. We used the three established frequency bands: very-low frequency (VLF) band (0.01–0.05 Hz), low-frequency (LF) band (0.05–0.15 Hz) and high-frequency (HF) band (0.15–0.4 Hz). The significance of the VLF band is unclear. Because of its wide use in the literature, we present the LF/HF ratio. LF/HF ratio is held to be a measure of sympathovagal balance by some authors (43, 44), which is strongly opposed by others (45–47).

Arterial blood pressure was measured discontinuously by means of an automatic device (Dinamap pro 100®; Critikon Ltd, Norderstedt, Germany). Measurements took place before standing, before tilting and before the handgrip test. These starting values were compared with measures at the third minute of the respective test.

Statistical evaluation of the data was performed using SPSS® (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL, USA). Data were summarized as mean and SD. All values were checked by the Kolmogorov–Smirnov test for normal distribution. Autonomic test results of migraine patients and controls were compared for all subjects as well as within three age groups (6–9 years, 10–13 years, 14–18 years). If normal distribution of the data could be accepted and group size was larger than 20 subjects, Student's *t*-test was used. Otherwise we employed the Mann–Whitney *U*-test. All the tests were two-sided. A *P*-value of <0.05 was considered significant. Bonferroni-like adjustment for multiple comparisons (48) was not applied (see Discussion).

The study protocol was designed in accordance with the principles of the Helsinki Declaration and was approved by the ethics commission of the University of Heidelberg. Children and parents were instructed about the study and signed informed consent was obtained from children and parents.

Results

Test results are given in Tables 4 and 5. For the majority of tests we found no significant group differences. Here, we present the significant test results.

Resting period (spontaneous breathing)

In patients aged 14–18 years the mean heart frequency was diminished.

Metronomic breathing

At a breathing frequency of 8.5 breaths/min, FD was lower in migraine patients, and at a breathing frequency of 6 breaths/min they showed a lower LF/HF ratio. This result was found also in the age group between 14 and 18 years.

Tilt-table test

In migraine patients Ewing ratio was higher than in controls.

Valsalva manoeuvre

In the group aged 6–9 years the Valsalva ratio was significantly higher in migraine patients than in controls.

In active standing and in the sustained handgrip test no significant differences were found.

Discussion

Comparing children and adolescents suffering from migraine with controls, we found significant differences in cardiorespiratory control during

Table 4 Autonomic test results in migraine patients and controls

	Migraine patients	Control subjects	*P*
Resting study (spontaneous breathing)			
Mean RR interval (ms)	782.25 ± 126.59	782.99 ± 111.53	0.970
E/I ratio	1.32 ± 0.14	1.29 ± 0.13	0.188†
LF/HF ratio	0.86 ± 0.49	0.93 ± 0.91	0.576†
Metronomic breathing with 6 breaths/min			
E/I ratio	1.51 ± 0.16	1.48 ± 0.17	0.332
FD abs (BpM)	19.38 ± 16.28	19.76 ± 11.17	0.873
FD rel (%)	25.14 ± 20.44	26.44 ± 15.95	0.669†
LF/HF ratio	5.21 ± 3.57	7.06 ± 5.21	**0.041**†*
Metronomic breathing with 8.5 breaths/min			
E/I ratio	1.50 ± 0.18	1.50 ± 0.20	0.805
FD abs (BpM)	20.83 ± 13.14	25.24 ± 13.84	**0.047***
FD rel (%)	29.03 ± 19.49	35.08 ± 19.23	0.058†
LF/HF ratio	5.64 ± 4.63	6.62 ± 5.04	0.326†
Orthostatic test—tilting			
ΔSBP (%)	1.28 ± 5.94	0.60 ± 6.22	0.914†
ΔDBP (%)	13.35 ± 15.52	9.32 ± 13.17	0.091
Ewing ratio	1.28 ± 0.14	1.23 ± 0.13	**0.047**†*
Orthostatic test—standing up			
ΔSBP (%)	2.19 ± 9.52	1.23 ± 7.76	0.511
ΔDBP (%)	13.85 ± 16.25	10.93 ± 14.46	0.259
Ewing ratio	1.46 ± 0.19	1.44 ± 0.24	0.611
Valsalva manoeuvre			
Valsalva-ratio	2.04 ± 0.43	1.95 ± 0.42	0.184
Handgrip test			
ΔSBP (%)	11.75 ± 10.62	12.33 ± 9.02	0.716
ΔDBP (%)	25.68 ± 19.76	25.02 ± 18.33	0.832
ΔHR (%)	20.96 ± 11.79	24.28 ± 16.75	0.172

*$P < 0.05$; †P-values are computed by two-sided Mann–Whitney U-test, all other P-values are computed by two-sided Student's t-test.

RR interval, interval between two neighbouring R waves; E/I ratio, expiration–inspiration ratio; LF, power in the low-frequency band in power spectral density analysis (PSD) of heart rate; HF, power in the high-frequency band in PSD of heart rate; FD abs, absolute frequency deviation; FD rel, relative frequency deviation; ΔSBP (%), systolic blood pressure during the test less systolic blood pressure before the test in per cent of the blood pressure before the test; ΔDBP (%), diastolic blood pressure during the test less diastolic blood pressure before the test in per cent of the blood pressure before the test; ΔHR (%), heart rate during the test less heart rate before the test in per cent of the heart rate before the test.

metronomic breathing, tilt-table test and Valsalva manoeuvre.

To investigate different aspects of cardiovascular and cardiorespiratory regulation, we studied changes of heart rate and of blood pressure in several function tests and by several approaches including time domain and frequency domain indices. The different tests represent different functions of the ANS and their interpretation is still a matter of discussion (9–11, 43–47). Thus for several measurements group differences were tested. It may be argued that a Bonferroni-type adjustment (48) should have been performed to correct for multiple tests and to reduce type I error. If this correction were carried out, none of the group differences would have been significant. However, the appropriateness of Bonferroni and other corrections for multiple comparisons has been questioned. A number of reasons have been reviewed why such corrections are unnecessary and deleterious to statistical inference in many cases (49–55): while the interest in this study was to examine different aspects of the ANS, with the application of Bonferroni-like adjustment we would have tested the universal null hypothesis, i.e. the hypothesis that all null hypotheses were true simultaneously. Furthermore, with Bonferroni-like

Table 5 Autonomic test results within different age groups

	Age group 6–9 years			Age group 10–13 years			Age group 14–18 years		
	Migraine	Controls	*P*	Migraine	Controls	*P*	Migraine	Controls	*P*
Resting study (spontaneous breathing)									
Mean RR interval (ms)	716.22 ± 97.25	732.50 ± 103.74	0.551	784.50 ± 108.68	807.48 ± 105.84	0.422	905.07 ± 122.75	818.15 ± 109.43	**0.039**†*
E/I ratio	1.39 ± 0.16	1.32 ± 0.13	0.081†	1.28 ± 0.12	1.31 ± 0.15	0.774†	1.25 ± 0.09	1.22 ± 0.10	0.359†
LF/HF ratio	0.82 ± 0.56	0.76 ± 0.59	0.590†	0.86 ± 0.42	0.95 ± 0.69	0.975†	0.92 ± 0.49	1. ± 1.42	0.743†
Metronomic breathing with 6 breaths/min									
E/I ratio	1.52 ± 0.18	1.55 ± 0.18	0.575	1.53 ± 0.15	1.48 ± 0.15	0.271	1.47 ± 0.17	1.40 ± 0.16	0.274†
FD abs (BpM)	17.37 ± 18.63	17.68 ± 11.77	0.946	19.91 ± 15.70	20.81 ± 12.16	0.809	22.35 ± 13.27	21.12 ± 8.64	0.849†
FD rel (%)	19.61 ± 17.83	21.51 ± 13.98	0.658†	26.05 ± 20.26	29.43 ± 18.41	0.513†	34.36 ± 23.36	29.01 ± 13.54	0.641†
LF/HF ratio	4.27 ± 2.61	4.39 ± 3.15	0.768†	5.40 ± 3.28	6.70 ± 3.87	0.207†	6.72 ± 5.18	11.31 ± 6.53	**0.025**†*
Metronomic breathing with 8.5 breaths/min									
E/I ratio	1.52 ± 0.17	1.53 ± 0.20	0.854	1.51 ± 0.19	1.50 ± 0.20	0.840	1.41 ± 0.15	1.47 ± 0.21	0.592†
FD abs (BpM)	19.17 ± 12.81	24.97 ± 16.65	0.147	20.21 ± 13.48	24.68 ± 12.48	0.191	25.37 ± 13.01	26.50 ± 11.85	0.769†
FD rel (%)	22.69 ± 14.10	30.43 ± 18.23	0.079†	29.27 ± 20.33	36.34 ± 18.80	0.171†	41.24 ± 22.32	39.88 ± 20.73	0.849†
LF/HF ratio	4.53 ± 2.31	5.18 ± 4.13	0.886†	6.22 ± 6.22	6.24 ± 4.83	0.671†	6.71 ± 4.22	9.28 ± 5.74	0.245†
Orthostatic test—tilting									
ΔSBP (%)	2.12 ± 7.23	2.21 ± 4.72	0.986†	0.85 ± 4.85	0.51 ± 6.15	0.731†	0.45 ± 5.26	–1.52 ± 7.66	0.632†
ΔDBP (%)	10.23 ± 15.76	4.36 ± 9.29	0.097	14.58 ± 15.17	12.91 ± 12.10	0.642	17.75 ± 15.62	10.69 ± 17.29	0.346†
Ewing ratio	1.30 ± 0.15	1.28 ± 0.14	0.896†	1.28 ± 0.14	1.23 ± 0.13	0.153†	1.23 ± 0.11	1.17 ± 0.10	0.120†
Orthostatic test—standing up									
ΔSBP (%)	4.05 ± 8.28	2.95 ± 7.02	0.601	1.24 ± 11.07	2.49 ± 7.96	0.628	0.24 ± 8.08	–3.06 ± 7.18	0.389†
ΔDBP (%)	11.61 ± 15.34	9.54 ± 14.21	0.606	18.54 ± 18.49	12.16 ± 16.81	0.178	7.78 ± 8.86	11.20 ± 10.91	0.602†
Ewing ratio	1.48 ± 0.23	1.45 ± 0.21	0.712	1.43 ± 0.15	1.47 ± 0.29	0.580	1.46 ± 0.19	1.37 ± 0.21	0.169†
Valsalva manoeuvre									
Valsalva ratio	2.23 ± 0.44	2.01 ± 0.39	**0.049***	1.98 ± 0.40	1.91 ± 0.44	0.546	1.80 ± 0.28	1.93 ± 0.44	0.416†
Handgrip test									
ΔSBP (%)	13.32 ± 12.87	13.71 ± 11.17	0.902	11.22 ± 8.89	13.64 ± 7.38	0.258	9.62 ± 9.02	8.03 ± 6.29	0.705†
ΔDBP (%)	22.86 ± 16.53	28.57 ± 20.08	0.244	27.55 ± 21.39	26.74 ± 18.05	0.875	27.74 ± 23.16	16.12 ± 12.92	0.196†
ΔHR (%)	22.92 ± 12.63	27.19 ± 17.18	0.299	19.94 ± 10.40	25.71 ± 16.86	0.125	18.40 ± 12.83	17.65 ± 14.89	0.767†

*$P < 0.05$; †P-values are computed by two-sided Mann–Whitney *U*-test, all other *P*-values are computed by two-sided Student's *t*-test.

RR interval, interval between two neighbouring R waves; E/I ratio, expiration–inspiration ratio; LF, power in the low-frequency band in power spectral density analysis (PSD) of heart rate; HF, power in the high-frequency band in PSD of heart rate; FD abs, absolute frequency deviation; FD rel, relative frequency deviation; ΔSBP (%), systolic blood pressure during test less systolic blood pressure before the test in per cent of the blood pressure before the test; ΔDBP (%), diastolic blood pressure during the test less diastolic blood pressure before the test in per cent of the blood pressure before the test; ΔHR (%), heart rate during the test less heart rate before the test in per cent of the heart rate before test.

adjustment the likelihood of type II error would be inflated, and the interpretation of a finding would depend on the number of other tests performed (and reported). While adjustment for multiple tests may make sense if the same comparison is conducted in multiple subgroups, this does not hold good if different tests are performed in one group. Finally, our measurements are not independent, which would make the correction even more conservative. Aware of these criticisms of Bonferroni-like corrections, and with the view that our analysis is largely exploratory, we maintained significance at $P = 0.05$. We share the opinion that, in addition to bearing in mind the increased likelihood of type I error, the best way to deal with multiple comparisons is to describe what tests have be be performed and to discuss the possible interpretation of the results in the light of prior data and of biological plausibility (49–51, 53, 56).

Prior data on autonomic regulation in migraine (see Table 1)

In the few papers that study the ANS in migraineurs and report resting heart rate, heart rate was normal (16, 24, 28, 57) or elevated (20). Also in psychophysiological studies, resting heart rate was normal (58, 59) or elevated (30, 31) in adult migraineurs and normal in juvenile migraineurs (60). We found resting heart rate reduced in adolescent migraineurs.

In adult migraineurs, during spontaneous breathing HRV was reduced (12–14) or normal (24, 25, 28, 57, 61, 62); by PSD of heart rate elevated fluctuations in the LF band were found which during spontaneous breathing does not include the breathing frequency (22, 26, 27). In children with migraine, Yakinci et al. (33) did not study spontaneous breathing. In adolescent migraineurs, Havana-Kanniainen et al. (32) found no changes of HRV during spontaneous breathing, which concurs with our results.

The reduced HRV that we found during metronomic breathing at 8.5 breaths/min corresponds to findings of reduced HRV in adults during breathing at 6 breaths/min (12–15, 18, 21); however, there are also divergent results (19, 20, 25, 61). While in healthy adults HRV is maximal at 6 breaths/min, in children this is the case at 8.5 breaths/min (personal observation, submitted for publication). Thus at the breathing frequency with the highest HRV we found HRV to be reduced in migraineurs. Yakinci et al. (33) and Havanka-Kaniainen et al. (32) studied HRV only at 6 breaths/min, which may in part explain their normal results.

We are not aware of any study on frequency domain indices of HRV at metronomic breathing in migraineurs. We found the LF/HF ratio to be decreased during metronomic breathing at 6 breaths/min. In contrast to spontaneous breathing, at 6 breaths/min the LF band includes the breathing frequency.

Concerning Valsalva manoeuvre, our findings confirm the results of Yakinci et al. (33). We found increased Valsalva ratio in our youngest patients, who are in an age group comparable to the patients of Yakinci's study. This effect was lost in adolescents, which corresponds to the normal results of Havanka-Kanniainen et al. (32). In adult migraineurs, Valsalva ratio was not significantly different from controls (15, 18–21, 24, 57, 61) or lower (12–14, 25).

During active standing, Yakinci et al. (33) found elevated Ewing ratio in children with migraine. In contrast, we found no significant group differences regarding heart rate changes during active standing. At tilting, however, which reduces the influence of the muscle pump and of motor activity in general (63–65), we found Ewing ratio increased in migraine patients. Tilting was not studied by Yakinci et al. (33). In adult migraineurs, during active standing Ewing ratio was reduced (17), normal (15, 18, 19) or elevated (21), while heart rate changes during tilting were lower than in controls (12–14). Blood pressure during tilting or standing was lower (12–16, 21) or unchanged (18–21, 24, 25, 57) in adult patients. In children with migraine, Yakinci et al. (33) found higher systolic blood pressure during active standing. We found no significant group differences in blood pressure changes in either orthostatic manoeuvre.

During sustained handgrip, also, we did not find significant group differences. For this test, Yakinci et al. (33) had found a higher systolic blood pressure in their young patients, whereas Havanka-Kanniainen et al. (32) reported normal results in adolescent migraineurs. In adult migraineurs, most (12–19) though not all (20, 21, 24) studies demonstrated a reduced blood pressure increase during sustained handgrip, while the increase in heart rate was not altered (16, 20).

During mental stress, however, adult migraineurs show mostly normal (58, 61, 66) or occasionally even greater heart rate (29–31) and blood pressure (59) responsiveness. In juvenile migraineurs heart rate reactivity to mental stress was found normal (60).

Not all studies fit into a unified picture of cardiorespiratory regulation in migraineurs. Nevertheless, our results and the main results in the literature may be summarized as follows. Resting heart rate is reduced or normal in young patients, but may be elevated in adults. Reduced HRV during spontaneous breathing seems to develop with age. However, during metronomic breathing at the breathing frequency with maximal HRV, migraineurs show reduced HRV already in their youth. Moreover, in juvenile and adult migraineurs, power spectral analysis of heart rate discloses elevation of the frequency band that does not correspond to the actual breathing frequency. While the reactions to volume shifts (Valsalva manoeuvre, orthostatic tests) may be intensified in young migraineurs, they are mostly reduced in adults. Also, the reduced autonomic activation during sustained handgrip develops with age. In contrast, adult migraineurs may show heart rate hyperreactivity during mental stress, which has not been seen in young patients.

Interpretation of study results

Changes in cardiorespiratory regulation in migraineurs were mostly interpreted in light of the question whether there are disturbances of the sympathetic and/or of the parasympathetic ANS. Short-term blood pressure changes are generated by sympathetic activation or deactivation, heart rate is determined by sympathetic and by parasympathetic activity. HRV during spontaneous and metronomic breathing is often interpreted as reflecting parasympathetic activity. To follow this interpretation, the results of cardiorespiratory regulation studies in adults are interpreted as pointing to sympathetic hypofunction (12–19, 21, 22), sympathetic hyperfunction (24, 30, 31, 59), sympathetic instability (22, 26, 27), parasympathetic hyperfunction (23) or parasympathetic hypofunction (12–14, 17, 21, 25, 28, 62). Yakinci et al. interpreted their results in children with migraine as pointing to sympathetic and parasympathetic hyperactivity (33).

We are not convinced that an interpretation in terms of sympathetic or parasympathetic activity is productive. First, though breathing-related HRV is conveyed mainly by changes of vagus nerve activity, it depends not on 'parasympathetic tone' (45–47, 67, 68). Moreover, the differentiation of the sympathetic and the parasympathetic nervous system is valid for the peripheral nervous system and its diseases; however, both systems are not mere antagonists, but may act reciprocally or non-reciprocally (69, 70). Sympathetic (71) as well as parasympathetic activity show changing differentiated activity patterns regarding different organ systems (72). Both systems are subject to a task-adapted common central regulation (69, 70, 72) with the objective of homeostasis at work and at rest (73). This task-adapted autonomic regulation includes the control of respiration (73–75). It is the prerequisite for motor or mental activity; different demands result in different patterns of autonomic activity (69, 70, 73–76).

Autonomic regulation takes place at different levels of the central nervous system. One decisive structure is the reticular formation of the lower brainstem which constitutes an adaptive common system for cardiorespiratory (77–79) and somatomotor integration (80–82). This common brainstem system (CBS) may be characterized by oscillating neuronal networks. They are dynamically organized in changing patterns depending on the actual needs of the subject which are reflected in the actual composition of inputs to the CBS. In the state of relaxed wakefulness the CBS is rhythmically organized as a whole (47, 81–83). It is beyond the scope of this paper to review the discussion on the genesis of HRV (46, 47, 83–86), but there is good evidence for the concept that rhythmic changes of heart rate are primarily caused centrally by the 'relative coordination' (87) of the respiratory and cardiovascular oscillators in the lower brainstem (47, 81–83, 85–92). Pronounced HRV at slow metronomic breathing reflects the resonance of these oscillators (47, 81–83, 87, 88). While exaggerated HRV is considered to be an essential salutogenetic mechanism of meditative techniques (93, 94), HRV in children is reduced during problem solving compared with day-dreaming or playing (95). Reduced HRV was seen in adult migraineurs during spontaneous breathing. At the metronomic breathing frequency which is typically connected with maximal HRV, juvenile migraineurs already show reduced HRV. Moreover, in juvenile and adult migraineurs, power spectral analysis of heart rate discloses elevation of the frequency band that does not correspond to the actual breathing frequency. This reduction of respiration-related HRV in migraineurs may be interpreted as reduced rhythmical coupling of breathing oscillators and cardiovascular oscillators, probably corresponding to a restricted ability of the system to rest in a state of relaxed wakefulness (47, 81–83, 93, 94). To further the ability to rest is an essential goal of biobehavioural migraine therapy (96).

Beside the ability to rest, in migraineurs the adaptation to external and internal demands is also altered. The principle physiological processes during the autonomic function tests are well known. During orthostatic tests venous return and cardiac output are reduced, which induces vasoconstriction and increased heart rate maintaining arterial pressure (63, 64). In addition to the gravitational volume shifts at tilting, standing induces direct changes of muscle vessels and autonomic changes connected with muscular activity (63–65). Static exercise is accompanied by an increase in blood pressure and heart rate caused by central command and above all by the activation of muscular 'labour' receptors (63, 97). During Valsalva manoeuvre shifts of blood volume result in changes in blood pressure and heart rate (98).

The changes in heart rate and vascular resistance due to volume shifts during orthostatic tests or Valsalva manoeuvre are primarily induced by activity changes of baroreceptors in the carotid sinus and the aortic arch which are processed in the nucleus of the solitary tract (72). Reduced baroreceptor activity, for example, induces tachycardia and vasoconstriction, but the effect of baroreceptor activity on heart rate and blood pressure is essentially determined by influences from the forebrain, from the CBS and from other brainstem structures (5, 72, 99–102). Brainstem structures involved in tuning of cardiorespiratory responses are also of essential importance in endogenous antinociception (103). Moreover, there is growing evidence that these brainstem structures, especially the ventrolateral (vl) column of the midbrain periaqueductal grey (PAG), play a pivotal role in migraine pathogenesis (1, 2, 104–108). Besides, in the task-specific steering of cardiorespiratory functions activation of the dorsolateral (dl) or lateral (l) PAG evokes active coping consisting of 'fight-or-flight' responses with tachycardia and increase in blood pressure, whereas activation of the vlPAG evokes passive coping consisting of 'no-go' behaviour with bradycardia and arterial hypotension (76, 109). While the lPAG is activated by superficial pain, which often can be controlled to some extent, the vlPAG is activated by inescapable deep and visceral pain (110). lPAG and vlPAG are influenced also by forebrain afferents; they are, however, the main input to the dlPAG, suggesting that dlPAG activity is driven essentially by mental stressors (76, 110). Furthermore, there is evidence that the PAG is involved in blood pressure increase during static exercise, the pressor response being mediated by lPAG and dlPAG while the vlPAG dampens it (111).

The vasoconstricting and heart-accelerating influences of dlPAG and lPAG seem to be exerted at least partly via serotonergic medullary raphe nuclei (102). Reduced serotonergic activity of raphe nuclei may be the cause of evoked cortical potential alterations found in migraineurs (112).

Valsalva ratio and Ewing ratio, being combined measures of heart rate acceleration and slowing, are difficult to interpret. Nevertheless, elevated ratios in juvenile migraineurs point to autonomic hyperreactivity which may be influenced by the fact that especially in children the autonomic tests also constitute mental stress. Reduction of Valsalva ratio and Ewing ratio in adult migraineurs may correspond to developing passive coping. This interpretation is corroborated by the findings that, in children with migraine, blood pressure increase during sustained handgrip may be exaggerated (33), while in adult migraineurs blood pressure increase during sustained handgrip and during orthostatic tests is dampened. This may be explained by a changing balance of different parts of the PAG destined to development of preponderant vlPAG activity accompanied by development of reduced raphe serotonergic activity. As mentioned above, vlPAG activity is intensified by inescapable pain (110) and corresponds to passive coping (76, 109). Thus, results of autonomic tests confirm the assumption of disturbances of the function of the PAG and of raphe nuclei.

Active coping strategies correspond to intrinsically determined behaviour, whereas passive coping corresponds to extrinsically determined behaviour with reduced aggression (113). In consequence, the autonomic hyperreactivity in juvenile migraineurs leading to passive coping in adult migraineurs matches psychological studies reporting juvenile migraineurs to show hypersensitivity (114, 115) and a tendency to repress aggression (116); it calls to mind psychodynamic concepts interpreting migraine as consequence of blocked aggression (117) or as learned helplessness (115).

Interictal changes of trigeminofacial reflexes (118), of evoked cortical potentials (112) and of contingent negative variation (119) normalize during and close to an attack. While the above-cited studies on autonomic regulation in migraineurs as well as our investigation were conducted in the headache-free interval, few studies in adults investigated autonomic regulation also during a migraine attack. They found either no differences between attack and interval (25), or aggravation of the interictal changes during an attack (120) or, mostly, reversal of them (121–123). It would be worthwhile to conduct further studies concerning changes of autonomic regulation in migraineurs, especially in childhood and adolescence, with regard to the temporal relation to a migraine attack.

Summary

Studying different aspects of cardiovascular and cardiorespiratory regulation in children and adolescents suffering from migraine, we found significant differences from controls during metronomic breathing, tilt-table test and Valsalva manoeuvre. Our results and the results in literature yield the following picture.

While reduced HRV during spontaneous breathing develops with age, during metronomic breathing juvenile migraineurs already show reduced rhythmical coupling of breathing oscillators and cardiovascular oscillators, corresponding to a restricted ability of the system to rest. This result supports therapies which intend to further this ability.

In young migraineurs, we found autonomic hyperreactivity during the Valsalva manoeuvre and orthostatic tests; reduced blood pressure increase during isometric muscle contraction was found by others. In adults these reactions are reduced. We interpret this as developing passive coping which might be explained by reduced raphe serotonergic activity and by a changing imbalance of different parts of the PAG. We consider this development to correspond to findings of hypersensitivity in juvenile migraineurs and interpretations of migraine as a consequence of blocked aggression or as learned helplessness.

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References

1 Pietrobon D, Striessnig J. Neurobiology of migraine. Nat Rev Neurosci 2003; 4:386–98.

2 Aurora SK. Exciting excitable brains: an update on migraine pathophysiology. J Headache Pain 2003; 4:7–12.

3 Lance JW, Anthony M. Some clinical aspects of migraine. A prospective survey of 500 patients. Arch Neurol 1966; 15:356–61.

4 Lovick TA. Integrated activity of cardiovascular and pain regulatory systems: role in adaptive behavioural responses. Progr Neurobiol 1993; 40:631–44.

5 Benarroch EE. Pain–autonomic interactions: a selective review. Clin Auton Res 2001; 11:343–9.

6 Kruszewski P, Salvesen R, White LR, Sjaastad O. Headache and the autonomic nervous system. In: Appenzeller O, editor. Handbook of clinical neurology, Vol. 75 (Revised Series 31). The autonomic nervous system. Part II. Dysfunctions. Amsterdam: Elsevier Science BV 2001:281–307.

7 Jänig W. Relationship between pain and autonomic phenomena in headache and other pain conditions. Cephalalgia 2003; 23 (Suppl. 1):43–8.

8 Peroutka SJ. Migraine: a chronic sympathetic nervous system disorder. Headache 2004; 44:53–64.

9 Low PA. Laboratory evaluation of autonomic function. In: Low PA, editor. Clinical autonomic disorders, 2nd edn. Philadelphia: Lippincott-Raven Publishers 1997:179–208.

10 Ravits JM. AAEM minimonograph #48: autonomic nervous system testing. Muscle Nerve 1997; 20:919–37.

11 Mathias CJ, Bannister R. Investigation of autonomic disorders. In: Mathias CJ, Bannister R, editors. Autonomic failure, 4th edn. Oxford, New York: Oxford University Press 1999:169–95.

12 Havanka-Kanniainen H, Tolonen U, Myllylä VV. Autonomic dysfunction in adult migraineurs. Headache 1986; 26:425–30.

13 Havanka-Kanniainen H, Juujärvi K, Tolonen U, Myllylä VV. Cardiovascular reflexes and plasma noradrenaline levels in migraine patients before and during nimodipine medication. Headache 1987; 27:39–44.

14 Havanka-Kanniainen H, Tolonen U, Myllylä VV. Autonomic dysfunction in migraine: a survey of 188 patients. Headache 1988; 28:465–70.

15 Boiardi A, Munari L, Milanesi I, Paggetta C, Lamperti E, Bussone G. Impaired cardiovascular reflexes in cluster headache and migraine patients: evidence for an autonomic dysfunction. Headache 1988; 28:417–22.

16 Mikamo K, Takeshima T, Takahashi K. Cardiovascular sympathetic hypofunction in muscle contraction headache and migraine. Headache 1989; 29:86–9.

17 Osipova V. Psychoautonomic approaches to migraine. Funct Neurol 1992; 7:263–73.

18 Pogačnik T, Sega S, Pečnik B, Kiauta T. Autonomic function testing in patients with migraine. Headache 1993; 33:545–50.

19 Ostertag D, Strittmatter M, Schimrigk K. Autonomic dysfunction in migraine and tension-type headache—a pilot study. Schmerz 1998; 12:25–9.

20 Cortelli P, Pierangeli G, Parchi P, Contin M, Baruzzi A, Lugaresi E. Autonomic nervous system function in migraine without aura. Headache 1991; 31:457–62.

21 Martin R, Ribera C, Molto JM, Ruiz C, Galiano L, Matias-Guiu J. Cardiovascular reflexes in patients with vascular headache. Cephalalgia 1992; 12:360–4.

22 Zigelman M, Appel S, Davidovitch S, Kuritzky A, Zahavi I, Akselrod S. The effect of verapamil calcium antagonist on autonomic imbalance in migraine: evaluation by spectral analysis of beat-to-beat heart rate fluctuations. Headache 1994; 34:569–77.

23 Gotoh F, Komatsumoto S, Araki N, Gomi S. Noradrenergic nervous activity in migraine. Arch Neurol 1984; 41:951–5.

24 Mosek A, Novak V, Opfer-Gehrking TL, Swanson JW, Low PA. Autonomic dysfunction in migraineurs. Headache 1999; 39:108–17.

25 Thomsen LL, Iversen HK, Boesen F, Olesen J. Transcranial Doppler and cardiovascular responses during cardiovascular autonomic tests in migraineurs during and outside attacks. Brain 1995; 118:1319–27.

26 Appel S, Kuritzky A, Zahavi I, Zigelman M, Akselrod S. Evidence for instability of the autonomic nervous system in patients with migraine headache. Headache 1992; 32:10–7.

27 Zigelman M, Kuritzky A, Appel S, Davidovitch S, Zahavi I, Hering R, Akselrod S. Propranolol in the

prophylaxis of migraine—evaluation by spectral analysis of beat-to-beat heart rate fluctuations. Headache 1992; 32:169–74.
28 Tabata M, Takeshima T, Burioka N, Nomura T, Ishizaki K, Mori N et al. Cosinor analysis of heart rate variability in ambulatory migraineurs. Headache 2000; 40:457–63.
29 Gannon LR, Haynes SN, Safranek R, Hamilton J. Psychophysiological investigation of muscle-contraction and migraine headache. J Psychosom Res 1981; 25:271–80.
30 Cohen RA, Williamson DA, Monguillot JE, Hutchinson PC, Gottlieb J, Waters WF. Psychophysiological response patterns in vascular and muscle-contraction headaches. J Behav Med 1983; 6:93–107.
31 Drummond PD. Vascular responses in headache-prone subjects during stress. Biol Psychol 1985; 21:11–25.
32 Havanka-Kanniainen H, Tolonen U, Myllylä VV. Cardiovascular reflexes in young migraine patients. Headache 1986; 26:420–4.
33 Yakinci C, Mungen B, Er H, Durmaz Y, Karabiber H. Autonomic nervous system function in childhood migraine. Pediatr Int 1999; 41:529–33.
34 Just U, Oelkers R, Benders S, Parzer P, Ebinger F, Weisbrod M, Resch F. Emotional and behavioural problems in children and adolescents with primary headache. Cephalalgia 2003; 23:206–13.
35 Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 1988; 8 (Suppl. 7):1–96.
36 Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders, 2nd edition. Cephalalgia 2004; 24 (Suppl. 1):1–160.
37 Ewing DJ, Campbell IW, Clarke BF. Heart-rate response to standing as a test for automatic neuropathy. BMJ 1978; 1:1700.
38 Levin AB. A simple test of cardiac function based upon the heart rate changes induced by the Valsalva maneuver. Am J Cardiol 1966; 18:90–9.
39 de Boer R, Kuyper P. Triggered correlation. IEEE Trans Biomed Eng 1968; 15:169–79.
40 Rabending G, Reichel G, Klöckner H, Grimmberger E. Quantitative determination of respiratory cardiac arrhythmia in neurological diagnosis. In: Lechner H, Araniba A, editors. EEG and clinical neurophysiology (International Congress Series No. 526). Amsterdam, Oxford, Princeton: Excerpta Medica 1980:565–9.
41 Peňáz J, Roukens J, van der Waal HJ. Spectral analysis of some spontaneous rhythms in the circulation. Biokybernetik 1968; 1:233–6.
42 Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 1981; 213:220–2.
43 Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho–vagal interaction in man and conscious dog. Circ Res 1986; 59:178–93.
44 Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. Circulation 1991; 84:482–92.
45 Koepchen HP. Physiology of rhythms and control systems: an integrative approach. In: Haken H, Koepchen HP, editors. Rhythms in physiological systems (Springer series in synergetics, Vol. 55). Berlin, Heidelberg: Springer-Verlag 1991:3–20.
46 Eckberg DL. Sympathovagal balance: a critical appraisal. Circulation 1997; 96:3224–32.
47 Lambertz M, Langhorst P. Simultaneous changes of rhythmic organization in brainstem neurons, respiration, cardiovascular system and EEG between 0.05 Hz and 0.5 Hz. J Auton Nerv Syst 1998; 68:58–77.
48 Bonferroni CE. Teoria statistica delle classi e calcolo delle probabilità. Pubblicazioni del Regio Istituto Superiore di Scienze Economiche e Commerciali di Firenze 1936; 8:3–62.
49 Rothman KJ. No adjustments are needed for multiple comparisons. Epidemiology 1990; 1:43–6.
50 Perneger TV. What's wrong with Bonferroni adjustments? BMJ 1998; 316:1236–8.
51 Perneger TV. Adjusting for multiple testing in studies is less important than other concerns. BMJ 1999; 318:1288.
52 Chinn S. Statistics for the European Respiratory Journal. Eur Respir J 2001; 18:393–401.
53 Feise RJ. Do multiple outcome measures require *P*-value adjustment? BMC Med Res Methodol 2002; 2:8.
54 Nakagawa S. A farewell to Bonferroni: the problems of low statistical power and publication bias. Behav Ecol 2004; 15:1044–5.
55 Schulz KF, Grimes DA. Multiplicity in randomised trials I: endpoints and treatment. Lancet 2005; 365:1591–5.
56 Goodman SN, Royall R. Evidence and scientific research. Am J Public Health 1988; 78:1568–74.
57 Pierangeli G, Parchi P, Barletta G, Chiogna M, Lugaresi E, Cortelli P. Power spectral analysis of heart rate and diastolic blood pressure variability in migraine with and without aura. Cephalalgia 1997; 17:756–60.
58 Stronks DL, Tulen JHM, Verheij R, Boomsma F, Fekkes D, Pepplinkhuizen L et al. Serotonergic, catecholaminergic, and cardiovascular reactions to mental stress in female migraine patients. A controlled study. Headache 1998; 38:270–80.
59 Hassinger HJ, Semenchuk EM, O'Brien WH. Cardiovascular responses to pain and stress in migraine. Headache 1999; 39:606–15.
60 Hermann C, Blanchard EB. Psychophysiological reactivity in pediatric migraine patients and healthy controls. J Psychosom Res 1998; 44:229–40.
61 Shechter A, Stewart WF, Silberstein SD, Lipton RB. Migraine and autonomic nervous system function: a population-based, case–control study. Neurology 2002; 58:422–7.
62 Sanya EO, Brown CM, von Wilmowsky C, Neundörfer B, Hilz MJ. Impairment of parasympathetic baroreflex responses in migraine patients. Acta Neurol Scand 2005; 111:102–7.
63 Joyner MJ, Shepherd JT. Autonomic regulation of circulation. In: Low PA, editor. Clinical autonomic disorders, 2nd edn. Philadelphia: Lippincott-Raven Publishers 1997:61–71.

64 Wieling W, van Lieshout JJ. Maintenance of postural normotension in humans. In: Low PA, editor. Clinical autonomic disorders, 2nd edn. Philadelphia: Lippincott-Raven Publishers 1997:73–82.

65 Morillo CA, Dillenburg R, Guzmán JC. To tilt or not to tilt: what is the question? Clin Auton Res 2004; 14:360–2.

66 Williams DE, Raczynski JM, Domino J, Davig JP. Psychophysiological and MMPI personality assessment of headaches. An integrative approach. Headache 1993; 33:149–54.

67 Kollai M, Mizsei G. Respiratory sinus arrhythmia is a limited measure of cardiac parasympathetic control in man. J Physiol 1990; 424:329–42.

68 Goldberger JJ, Ahmed MW, Parker MA, Kadish AH. Dissociation of heart rate variability from parasympathetic tone. Am J Physiol (Heart Circ Physiol) 1994; 266:H2152–7.

69 Langhorst P, Lambertz M, Schulz G. Central control and interactions affecting sympathetic and parasympathetic activity. J Auton Nerv Syst 1981; 4:149–63.

70 Koizumi K, Kollai M. Multiple modes of operation of cardiac autonomic control: development of the ideas from Cannon and Brooks to the present. J Auton Nerv Syst 1992; 41:19–29.

71 Folkow B. Perspectives on the integrative functions of the 'sympatho-adrenomedullary system'. Auton Neurosci 2000; 83:101–15.

72 Benarroch EE. Central autonomic network: functional organization and clinical correlations. Armonk, NY: Futura Publishing Co. 1997.

73 Cannon WB. Organization for physiological homeostasis. Physiol Rev 1929; 9:399–431.

74 Hess WR. Über die Wechselbeziehungen zwischen psychischen und vegetativen Funktionen. Schweiz Arch Neurol Neurochir Psychiatr 1924; 15:260–77.

75 Koizumi K, Brooks CM. The integration of autonomic system reactions: a discussion of autonomic reflexes, their control and their association with somatic reactions. Ergeb Physiol 1972; 67:1–68.

76 Keay KA, Bandler R. Parallel circuits mediating distinct emotional coping reactions to different types of stress. Neurosci Biobehav Rev 2001; 25:669–78.

77 Koepchen HP. Respiratory and cardiovascular 'centres': functional entirety or separate structures? In: Schläfke ME, Koepchen HP, See WR, editors. Central neurone environment. Berlin, Heidelberg: Springer-Verlag 1983:221–37.

78 Richter DW, Spyer KM, Gilbey MP, Lawson EE, Bainton CR, Wilhelm Z. On the existence of a common cardiorespiratory network. In: Koepchen HP, Huopaniemi T, editors. Cardiorespiratory and motor coordination. Berlin, Heidelberg, New York: Springer-Verlag 1989:118–30.

79 Heidel KM, Benarroch EE, Gené R, Klein F, Meli F, Saadia D, Nogués MA. Cardiovascular and respiratory consequences of bilateral involvement of the medullary intermediate reticular formation in syringobulbia. Clin Auton Res 2002; 12:450–6.

80 Langhorst P, Schulz B, Schulz G, Lambertz M. Reticular formation of the lower brainstem. A common system for cardio-respiratory and somatomotor functions: discharge patterns of neighboring neurons influenced by cardiovascular and respiratory afferents. J Auton Nerv Syst 1983; 9:411–32.

81 Ebinger F, Lambertz M, Langhorst P. Functional organization of the common brainstem system to different states at different times. In: Koepchen HP, Huopaniemi T, editors. Cardiorespiratory and motor coordination. Berlin, Heidelberg, New York: Springer-Verlag 1989:158–74.

82 Langhorst P, Kluge W, Ebinger F, Lambertz M. Dynamic functional organization: a principle realized during cardiovascular and respiratory regulation. In: Yoshikawa M, Uono M, Tanabe H, Ishikawa S, editors. New trends in autonomic nervous system research. Amsterdam, New York: Elsevier 1991:311–5.

83 Langhorst P, Schulz G, Lambertz M. Oscillating neuronal network of the 'common brainstem system'. In: Miyakawa K, Koepchen HP, Polosa C, editors. Mechanisms of blood pressure waves. Tokyo: Japan Scientific Society Press; Berlin, Heidelberg, New York, Tokyo: Springer-Verlag 1984:257–75.

84 Bernardi L, Porta C, Gabutti A, Spicuzza L, Sleight P. Modulatory effects of respiration. Auton Neurosci 2001; 90:47–56.

85 Montano N, Porta A, Malliani A. Evidence for central organization of cardiovascular rhythms. Ann NY Acad Sci 2001; 940:299–306.

86 Baselli G, Caiani E, Porta A, Montano N, Signorini MG, Cerutti S. Biomedical signal processing and modeling in cardiovascular systems. Crit Rev Biomed Eng 2002; 30: 55–84.

87 Von Holst E. Die relative Koordination als Phänomen und als Methode zentralnervöser Funktionsanalyse. Ergebn Physiol 1939; 42:228–306.

88 Golenhofen K, Hildebrandt G. Die Beziehungen des Blutdruckrhythmus zu Atmung und peripherer Durchblutung. Pflügers Arch 1958; 267:27–45.

89 Preiss G, Polosa C. Patterns of sympathetic neuron activity associated with Mayer waves. Am J Physiol 1974; 226:724–30.

90 Barman SM, Gebber GL. Basis for synchronization of sympathetic and phrenic nerve discharges. Am J Physiol 1976; 231:1601–7.

91 Taylor JA, Eckberg DL. Fundamental relations between short-term RR interval and arterial pressure oscillations in humans. Circulation 1996; 93:1527–32.

92 Spyer KM. Central nervous control of the cardiovascular system. In: Mathias CJ, Bannister R, editors. Autonomic failure, 4th edn. Oxford, New York: Oxford University Press 1999:45–55.

93 Peng CK, Mietus JE, Liu Y, Khalsa G, Douglas PS, Benson H, Goldberger AL. Exaggerated heart rate oscillations during two meditation techniques. Int J Cardiol 1999; 70:101–7.

94 Bernardi L, Sleight P, Bandinelli G, Cencetti S, Fattorini L, Wdowczyc-Szulc J, Lagi A. Effect of rosary prayer and yoga mantras on autonomic cardiovascular rhythms: comparative study. BMJ 2001; 323:1446–9.

95 Hughes M, Hutt C. Heart-rate correlates of childhood activities: play, exploration, problem-solving and day-dreaming. Biol Psychol 1979; 8:253–63.

96 Baumann RJ. Behavioral treatment of migraine in

children and adolescents. Pediatr Drugs 2002; 4:555–61.

97 Goodwin GM, McCloskey DI, Mitchell JH. Cardiovascular and respiratory responses to changes in central command during isometric exercise at constant muscle tension. J Physiol 1972; 226:173–90.

98 Nishimura RA, Tajik AJ. The Valsalva maneuver and response revisited. Mayo Clin Proc 1986; 61:211–7.

99 Langhorst P, Schulz G, Lambertz M, Stroh-Werz M, Krienke B, Graf von Keyserlingk D. Is there an influence of discharge patterns of neurones of the common brain stem system on neuronal activity in the dorsomedial part of the NTS. In: Koepchen HP, Hilton SM, Trzebski A, editors. Central interaction between respiratory and cardiovascular systems. Berlin, Heidelberg, New York: Springer-Verlag 1980:116–24.

100 Spyer KM. Central nervous mechanisms contributing to cardiovascular control. J Physiol 1994; 474:1–19.

101 Nosaka S. Modification of the arterial baroreflexes: obligatory roles in cardiovascular regulation in stress and poststress recovery. Jpn J Physiol 1996; 46:271–88.

102 Sévoz-Couche C, Comet MA, Hamon M, Laguzzi R. Role of nucleus tractus solitarius 5-HT3 receptors in the defense reaction-induced inhibition of the aortic baroreflex in rats. J Neurophysiol 2003; 90:2521–30.

103 Basbaum AI, Fields H. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. Annu Rev Neurosci 1984; 7:309–38.

104 Bahra A, Matharu MS, Buchel C, Frackowiak RSJ, Goadsby PJ. Brainstem activation specific to migraine headache. Lancet 2001; 357:1016–7.

105 Knight YE, Goadsby PJ. The periaqueductal grey matter modulates trigeminovascular input: a role in migraine? Neuroscience 2001; 106:793–800.

106 Welch KMA, Nagesh V, Aurora SK, Gelman N. Periaqueductal gray matter dysfunction in migraine: cause or the burden of illness. Headache 2001; 41:629–37.

107 Goadsby PJ. Neurovascular headache and a midbrain vascular malformation: evidence for a role of the brainstem in chronic migraine. Cephalalgia 2002; 22:107–11.

108 Welch KMA. Contemporary concepts of migraine pathogenesis. Neurology 2003; 61 (Suppl. 4):S2–S8.

109 Johnson PJ, Lightman SL, Lowry CA. A functional subset of serotonergic neurons in the rat ventrolateral periaqueductal gray implicated in the inhibition of sympathoexcitation and panic. Ann NY Acad Sci 2004; 1018:58–64.

110 Bandler R, Shipley MT. Columnar organization in the midbrain periaqueductal gray: modules for emotional expression? Trends Neurosci 1994; 17:379–89.

111 Li J, Mitchell JH. c-Fos expression in the midbrain periaqueductal gray during static muscle contraction. Am J Physiol Heart Circ Physiol 2000; 279:H2986–93.

112 Judit Á, Sándor PS, Schoenen J. Habituation of visual and intensity dependence of auditory evoked cortical potentials tends to normalize just before and during the migraine attack. Cephalalgia 2000; 20:714–9.

113 Benus RF, Bohus B, Koolhaas JM, van Oortmerssen GA. Heritable variation for aggression as a reflection of individual coping strategies. Experientia 1991; 47:1008–19.

114 Kowal A, Pritchard D. Psychological characteristics of children who suffer from headache: a research note. J Child Psychol Psychiat 1990; 31:637–49.

115 Gerber WD, Schoenen J. Biobehavioral correlates in migraine: the role of hypersensitivity and information-processing dysfunction. Cephalalgia 1998; 18 (Suppl. 21):5–11.

116 Lanzi G, Zambrino CA, Ferrari-Ginevra O, Termine C, D'Arrigo S, Vercelli P et al. Personality traits in childhood and adolescent headache. Cephalalgia 2001; 21:53–60.

117 Alexander F. Psychosomatic medicine. New York: Norton 1950.

118 Katsarava Z, Giffin N, Diener HC, Kaube H. Abnormal habituation of 'nociceptive' blink reflex in migraine—evidence for increased excitability of trigeminal nociception. Cephalalgia 2003; 23:814–9.

119 Siniatchkin M, Kropp P, Gerber WD, Stephani U. Migraine in childhood—are periodically occurring migraine attacks related to dynamic changes of cortical information processing? Neurosci Lett 2000; 279:1–4.

120 Havanka-Kanniainen H. Cardiovascular reflex responses during migraine attack. Headache 1986; 26:442–6.

121 Anthony M. Biochemical indices of sympathetic activity in migraine. Cephalalgia 1981; 1:83–9.

122 Cortelli P, Lugaresi A, Contin E, Agati R, Tinuper P, Sacquegna T. Cardiovascular reflex in migraine patients during and out of migraine attack. Cephalalgia 1987; 7 (Suppl. 6):289–90.

123 Vein AM, Danilov AB, Kolosova OA, Voznesenskaja TG, Levin JaI, Tabeeva GR et al. Migren': dinamika psichofiziologičeskogo patterna. ZH Nevrol Psikhiatr Im S S Korsakova 2000; 100:13–20.