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Differentiation of autonomic nervous activity in different stages of coma displayed by power spectrum analysis of heart rate variability

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Abstract The analysis of heart rate (HR) variability offers a noninvasive method to investigate autonomic nervous system activity in comatose patients. We analyzed three components of the HR variability in a group of comatose patients: the low-frequency band (LF), representing mainly sympathetic influence, the mid-frequency band (MF), representing sympathetic and parasympathetic influence, and the high-frequency band (HF), representing the parasympathetic influence. A value for sympathovagal balance was defined as LF/HF and MF/HF ratio. Moreover, the skin conductance level (SCL) and the skin conductance resistance (SCR) variability were recorded. The patient group consisted of 22 patients with traumatic brain injuries. Coma depth was assessed by the Glacow Coma Scale and artifact-free HR, SCL, and SCR were measured 75 times in the patient group. The results documented a significant gain in sympathetic nervous system activity corresponding with the state of emerging from coma. This gain was most pronounced in the HF component of the HR and in the sympathovagal balance between LF/HF. The findings in SCL and SCR variability endorsed this result. It is concluded that emerging from coma is accompanied by an increasing influence of the sympathetic nervous system on HR control. This leads to a change in the sympathovagal balance, i.e., a reintegration of parasympathetic and sympathetic activity.

Key words Coma · Autonomous nervous system · Neuromonitoring · Heart rate variability · Spectral analysis

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Introduction

In neurophysiological terms, coma can be considered as a decoupling of the cortex from the brain stem or a lack of activity in the brain stem centers for cortical arousal [22, 24]. Such a decoupling of the brain stem from higher nervous system activity leaves fundamental autonomic functions per se intact, but leads to a loss of integration of different compartments of such functions. Zwiener et al. [29] documented a lack of integration of the respiratory cycle in heart rate (HR) by frequency analysis and argued that this was the result of a lesion of the nuclei dorsalis vagii. Clinical observatíons show that circadian rhythms, such as sleep-wake cycles, decay during coma because of a lacking hypothalamic control of brain stem activity. Desintegration of different compartments of nervous system activities into combined and phase-locked processes may also be the reason why different environmental stimuli lead to different forms of covert but not overt behavior [14]. The lack of a chronological integration of processes in different compartments of neuronal activity means that these responses are not enduring and do not lead to an integrated behavior as it would be a presupposition of consciousness [28].

When coma states are considered in such a way, phase-locked structures of neuronal activity gain particular importance.With regard to the autonomous nervous system, an analysis of the frequency spectrum of the HR proved to be a sensitive indicator of various aspects of neuronal control. Following the works of Akselrod et al. [1, cf. 20], three different frequency bands have been distinguished within the HR that include essential information on the autonomous nervous system activity. In the high-frequen-

cy range, a band is distinguished between 0.2 and 0.5 Hz to which, in functional regards, the respiratory activity is basic and which neuroanatomically is controlled essentially by the parasympathetic compartment of the nervous system. A pharmacological blockage [1, 2, 16] or corresponding lesions within the projection areas of the nervus vagus [10] thus lead to a complete reduction of this frequency band in the spectrum of the HR.

In the range of the mid-frequency spectrum, a band can be identified between 0.9 and 0.15 Hz. This band obviously represents the activity of baroreceptors and blood pressure control. It responds sensitively to posterial changes and is considered to be related to cognitive strain [16, 20, 25, 26]. According to current knowledge, the middle frequency band is a result of the common activity of the sympathetic and parasympathetic tonus. Thus, it is not completely reduced during a blockage of the parasympathetic activity [1, 16].

In the lowest frequency range (0.02–0.09 Hz) a band can be differentiated which covaries with the control of thermoregulation. This thermoregulatory band also reflects both parasympathetic and sympathetic activity as could be assessed by blocking the parasympathetical tonus [1]. On the other hand, due to the high significance of the sweat glands and the striate artery muscular system for thermoregulatory homeostasis, sympathetic activity plays a dominant part for this low-frequency band [13].

While the activity of the parasympathetic tonus is demonstrated directly by the level of the 0.2- to 0.5-Hz band, the sympathetic activity can be made accessible only in indirect ways. To control the parasympathetic activity, it is common to divide the values of the low- or middle-frequency band by the values of the high-frequency band. So the activity of the lower-frequency bands is standardized to the higher ones, and thus accounting for parasympathetic influence.

The three frequency bands of the HR thus enable a noninvasive examination of how far it is the parasympathetic or the sympathetic tonus that is concerned or integrated into a regular time-dependent pattern. The analysis of the HR activity offers an excellent possibility to record time-sensitive integrated autonomous activity of the nervous system. In accordance with the theory that during coma such time-locked processes break down and restart with the emerging from coma, i.e., greater closeness to consciousness, corresponding changes in the HR should be monitored and demonstrated by means of the remission process. Such a measure would mean to provide direct access to the respective psychophysiological condition of the patient and thus to gain a high significance for the assessment of interventions. To look into this question, we examined a group of patients in coma and analyzed the specific changes in HR.

Methods

Patient group

With the exception of three patients with intracerebral mass bleeeding, exclusively patients with diagnosed traumatic brain injuries and with at least 3 days of coma duration were included in the study. The exclusion criteria were primarily pupilloplegia at the accident, an age below 15 years, cardiac arrest, and death within the first 3 days after the injury. Evaluation of the coma depth was carried out by means of the Glasgow Coma Scale (GCS)

Table 1 Patient group

Patient (code number)	Age (years); gender	ID of measure and GCS value at measure													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
K002	57; m.	4													
K005	21; m.	6	7												
K006	27; m.	4	4	9	10										
K007	52; m.	7	7	8											
K008	34; m.	6	6	6	10										
K012	21; m.	6	6												
K013	17; m.	7	7												
K014	46; m.	3	3												
W001	43; f.	8	5												
W004	50; m.	3	6	6	10	10									
W006	30; f.	4	6	6	6	6	10	9							
W007	38; m.	6													
W009	16; m.	4	9	9											
W010	80; m.	5	8	7	8										
W103	63; f..	4	7	8											
W104	25; m.	3													
W105	26; f.	3	5	5	4	3	4	4	6	6	5	5	5	3	4
W106	19; m.	4	5	3	5	6	5	6	9	9					
W110	44; f.	6	6	6											
W201	27; m.	3	3	3	4	3	3	3	3						
W202	27; f.	5	3	3	3	3									
W501	42; m.	6	6	7	7	7	7								

NOTE: 22 patients, mean age 35, 16 males, 6 females
GCS 3–5: 42 recordings of 14 patients; GCS 6–7: 33 recordings of 14 patients; GCS 8–10: 16 recordings of 10 patients

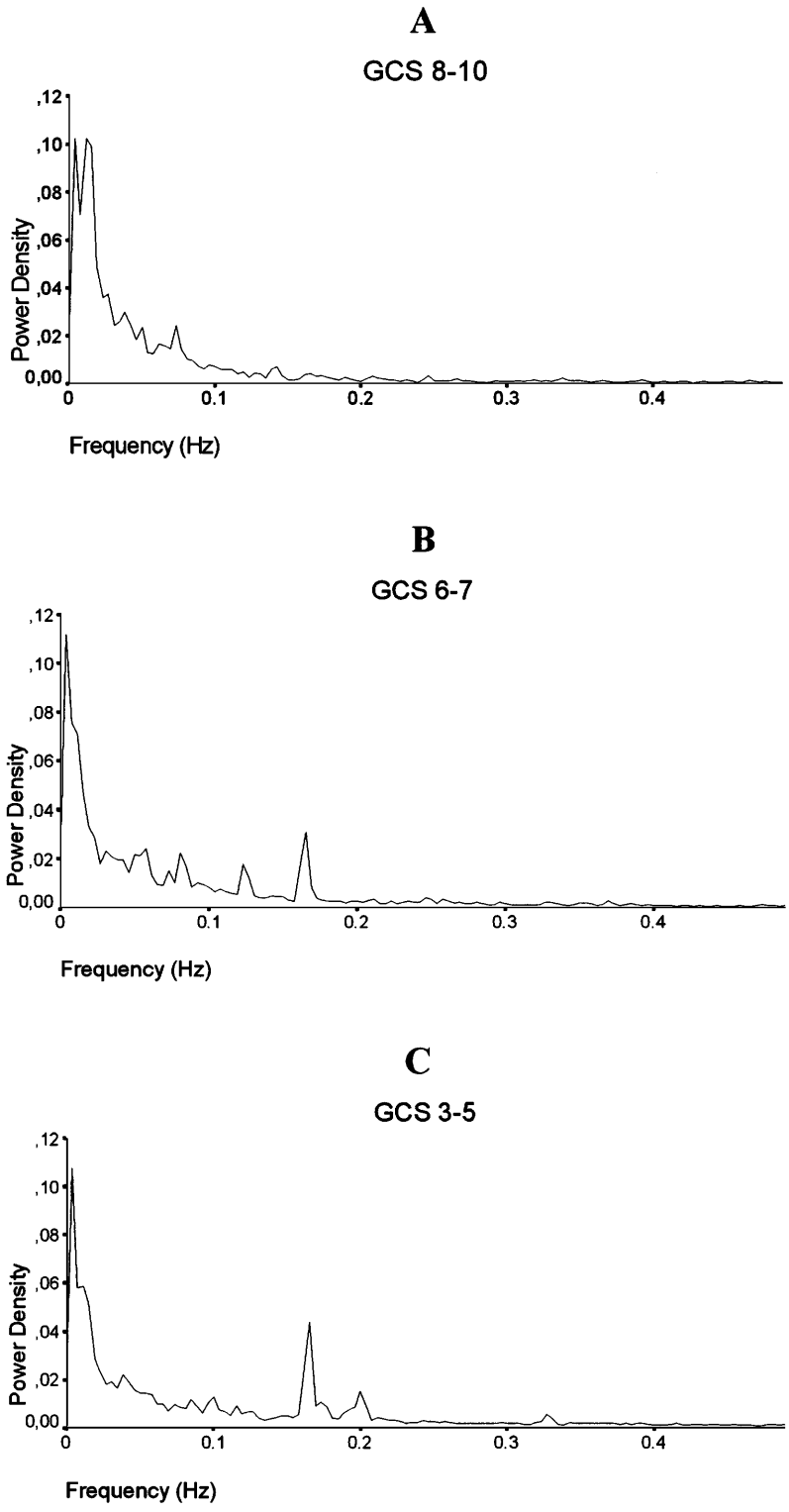

Fig. 1A–C Graphs of the power spectra taken from 256-s epochs during different coma stages. **A** Averaged power spectrum of the group GCS 8–10; **B** averaged power spectrum of the group GCS 6–7; **C** averaged power spectrum of the group 3–5. (See for this the respective paragraph in the section of methods on the standardization of single measurements)

[7, 12, 22, 23] before each measurement. Because some of the patients were given care together with other patients in the same room, an uncontrolled noise level had to be accepted during all measurements.

Measurements were taken in the afternoon between 1 and 6 p.m. Most patients were medicated for sedation, pain relief, and relaxation. The medication included Dormicum, Fentanyl, Somsanit and only for one patient each either Rohypnol or Dipidolor.

In order to enable comparisons of different coma depths, we aggregated the values reached by the patients in the GCS according to three groups: a state of deep coma with a GCS value between 3 and 5 (group 1), a state of middle coma depth with a GCS value of 6 or 7 (group 2), and a state of light coma or the transition to consciousness, respectively, with a GCS of 8–10. In total, we performed 91 measurements. Not all of these measurements were artifact free. The exclusion of measurement artifacts (see below)

led to a reduction of assessable measures to 75. Table 1 offers an overview on the residual patient group (n = 22) and the number of measurements for each patient.

Recording procedure

The physiological data were taken in the intensive care unit and recorded with a medical instrument (PARPORT R, Par-Elektronik, Berlin, Germany). This instrument allows the recording of max. 6 channels with the possibility of online monitoring. This allows adjustment of the electrodes to enable a reliable data sampling. Recordings were carried out by means of an electrocardiogram (ECG) as a basis for the determination of the HR, and, for monitoring the patients' responses, the muscular tonus (EMG) and the electrodermal activity (EDA) were recorded.

The HR was assessed by the R-spike interval. The R-spike signal can be easily detected due to the high amplitude and the high flank steelness. The amplitude maximum was determined by a Schmitt-Trigger. The signal was normed by a maximum detection which controlled a variable amplifier. The common mode rejection was performed by an initial highpass with 0.5-Hz cutoff frequency. The P- and T-waves, which have a lower frequency spectrum than the R-spike, were rejected by a bandpass with cutoff frequencies of 20 and 30 Hz. In addition, an R-spike interval lower than 240 ms was prevented by a monostable multivibrator. So the maximum HR could be 250 min^{-1}.

Before the evaluation of the data, we first visualized separately the data and tested them for possible artifacts. Additionally, we controlled the stationarity of the HR by means of the variance and standard deviations of the measured data for the selected range (256-s epochs). These procedures resulted in 75 artifact-free measurements, but none of the patients had to be excluded.

A fast Fourier transform (FFT) method of the HR was applied without smoothing on 256-s epochs of the baseline.

The FFT was carried out by a FORTRAN routine [9]. Before executing the FFT, the data of the periods were transformed to a mean value of zero by subtracting the HR mean value (of the concerning period) from each of the 256 HR values. Mean values for the power density were calculated separately for the three regions of the whole spectra: for the LF (0.02–0.09 Hz), for the MF (0.09–0.15 Hz), and for the HF (0.2–0.5 Hz). The sympathovagal balance was determined by dividing the LF and MF values by the HF values separately.

The statistical processing of the data was carried out with the Statistical Software Package SPSS 6.01 for Windows. For further statistical analysis the patients' data were mediated in addition so that patients with several measurements and with equal coma depth were only represented once in the respective coma group. Then the data were transposed into a design for independent samples (coma depth). All the statistical calculations were carried out with these data and were based, in a first step, on a univariate variance analysis and a post hoc least significant difference determination between the groups. In case of violations to the variance homogeneity we additionally calculated a non-parametric Kruskal-Wallis. We analyzed the mean values of HR, LF component, MF component, HF component, the autonomic balance LF/HF and MF/HF, and also the EDA during the baseline measurement for each coma group. For the coma group-specific visualization (Fig. 1) some further processing of the data was performed separately. First of all, the FFT was carried out with Hamming window. Since in the graphical presentation of the power spectra it is not the absolute power density which is in the foreground, but the measurements which shall equally enter into the required formation of coma group mean values, the power density of each measurement was standardized as to individual total achievement. For this, we calculated the total achievement and divided each single achievement value of the 128 Fourier frequencies by the total achievement.

Table 2 HR and HRV in different coma depths

GCS	HR		HRV	
	am	sd	am	sd
GCS 3–5 (n = 14)	85.3	21.5	27.0	35.2
GCS 6–7 (n = 14)	94.7	19.1	28.0	28.3
GCS 8–10 (n = 10)	90.4	18.0	17.3	16.9

Results

Heart rate

The mean HR increased slightly in the second coma group (from 85.3 to 94.7 beats per minute), and decreased again in the group with a GCS value between 8 and 10 (to 90.4 beats per minute; see Table 2). The increase of the HR between the individual coma groups was not significant for the univariate analysis of variance [F(2/35) = 0.7867; p = 0.5]. The variability of the HR, given in absolute values, was higher in the first than in the second and in the third group. But these differences also did not reach significance (see Table 2).

Power spectra of HR variability

The mean values of the Power Spectra of HR variability of the different coma groups are shown in Table 3.

The power of the LF component (0.02–0.09) and the MF component (0.09–0.15 Hz) showed no variance between the different coma groups [LF: F (2/35) = 0.5, p = 0.6; MF: F (2/35) = 0.7164, p = 0.495]. In absolute values, there was no consistent change in the LF component, whereas in the MF component a successive reduction took place from the first coma group down to the third coma group.

The power of the HF component (0.2–0.5 Hz) revealed highly significant differences between the coma groups in the univariate analysis of variance [F (2/35) = 3.1903, p = 0.05] (but Kruskal-Wallis: df = 2, χ^2 = 1.7758, p = 0.4). This band showed the highest values in the first group, the

Table 3 LF, MF, and HF components in different coma depths

GCS	LF		MF		HF	
	am	sd	am	sd	am	sd
GCS 3–5 (n = 14)	313 004	426 508	144 024	264 181	170 783	256 800
GCS 6–7 (n = 14)	441 114	455 310	115 247	220 248	38 751	33 959
GCS 8–10 (n = 10)	301 658	326 566	40 939	46 675	30 534	46 910

lowest in the third. Post hoc least significant differences revealed that the deeply comatous group differed from both other groups. The difference between the second and the third group, however, did not gain significance. The power spectra of different coma groups are shown in Fig. 1.

Emerging from coma resulted in a marked change in the sympathovagal balance. This is valid for the balance between the LF and the HF component. The univariate analysis of variance yielded a value of [F (2/35) = 6.1976, p = 0.005] (Kruskal–Wallis: df = 2, χ^2 = 7.1494, p = 0.028). Least significant differences documented a significant difference between deeply comatous patients and both other patient groups but not between the second and the third coma group. The MF to HF ratio was not significant [F (2/35) = 1.6716, p = 0, 2] (Kruskal–Wallis: df = 2, χ^2 = 4.494, p = 0.11), though the non-parametric Mann-Whitney U-test between the first and the second coma group was almost significant (p = 0.06). In general, for the mean values of both ratios a successive increase was observed with emerging from coma (cf. Fig. 2 and Table 4).

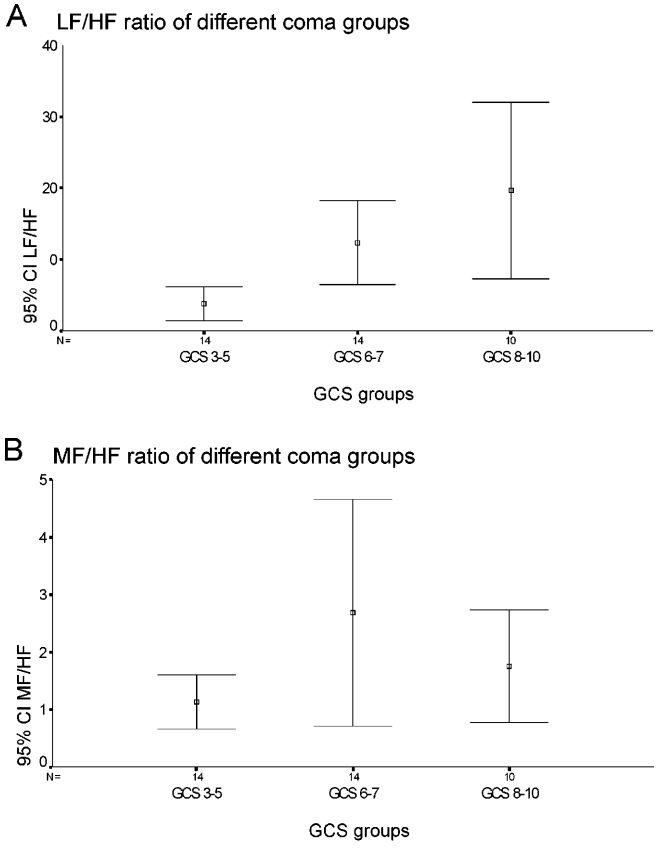

Fig. 2 A, B Autonomic balance during different coma stages. **A** Low-frequency (0.02–0.09 Hz) to high-frequency (0.2–0.5 Hz); **B** medium-frequency (0.09–0.15 Hz) to high-frequency (0.2–0.5 Hz) ratio. The impact of sympathetic activation is continuously growing during emerging from coma as shown by higher-frequency ratios. **A** Significant difference between GCS groups 3–5 and 6–7, and 3–5 and 8–10; **B** significant difference between GCS groups 3–5 and 6–7 failed to be significant at 0.06

Table 4 Sympathovagal balances in different coma depths

GCS	LF/HF		MF/HF	
	am	sd	am	sd
GCS 3–5 (n = 14)	3.79	4.12	1.13	0.82
GCS 6–7 (n = 14)	12.35	10.18	2.68	3.41
GCS 8–10 (n = 10)	19.68	17.26	1.75	1.36

Table 5 EDA in different coma depths

GCS	SCL		SCR	
	am	sd	am	sd
GCS 3–5 (n = 14)	0.0038	0.013	4.098	4.101
GCS 6–7 (n = 14)	0.2739	0.544	5.488	3.658
GCS 8–10 (n = 10)	1.161	1.948	12.656	10.579

Electrodermal activity (EDA)

Electrodermal activity was evaluated to get HR-independent information about sympathetical activation of comatous patients. We compared the mean skin conductance level (SCL) as tonic activation marker and the variability of skin conductance resistance (SCR) as marker of phasic activation changes. Table 5 shows development of EDA in correlation with coma depth.

Awaking from coma was accompanied by higher SCL values [F (2/35) = 3.5065, p = 0,04] (Kruskal–Wallis: df = 2, χ^2 = 3.9367, p = 0.14). Least significant difference documented an increased level for patients in the third coma group.

The variability of SCR increased also, revealing significant results [F (2/35) = 6.5248, p = 0,004] (Kruskal-Wallis: df = 2, χ^2 = 5.9882, p = 0.05]. Again, the third coma group documented the highest amount of SCR variability compared with both other groups. In general, SCL and SCR increased with higher GCS values.

Discussion

Our results show, as in previous studies [17, 18, 29], that emerging from coma is attended by a systematic change in the sympathetic and parasympathetic nervous activity. Such a change could be demonstrated at two levels.

Firstly, though we found no significant differences in HR variance between coma groups, there was a reduction accompanying the awaking of coma in absolute terms. Moreover, on the level of the different power spectra bands we found a significant decrease in the HF component with patients' becoming increasingly more aware, whereas the LF component and the VLF component revealed no significant changes. Baharev et al. [3] found a similar trend for different sleep phases. In their study the parasympathic 0.2–0.5 component was the almost exclusively dominant component during non-REM sleep, whereas in REM sleep and during drowsiness the LF and

MF components were also present. The dominant 0.2–0.5 component during non-REM sleep is exactly the pattern we found with emerging from coma.

On the other hand, we would suppose that the lack of influence of coma stages in the LF and MF component is a result of its dependence from both sympathetic *and* parasympathetic activity. These parallel processes may have resulted in a relatively unchanged LF and MF component. Previous studies have shown that the MF component is more influenced by the HF component than the LF component, but both react to the power of the HF component. This corresponds to our results where the MF component decreases linearly from the first coma group to the third, whereas the LF component showed no consistent alternation.

Standardized to HF, the significance of LF increases significantly during the process of coma remission. An independent evaluation of the electrodermal activity and the muscle tonus [11] with regard to different coma phases makes the increase of the LF appear to be a growing sympathetic activity that increases in the emerging from coma. There is a general consensus that the LF to HF ratio documents changes in fluctuations related to temperature regulation and tonic alertness [21].

As a second systematic change, we found an increased relative importance of the LF component in HR variability which has been demonstrated in other studies as a physiological indicator of sympathetically induced arousal. Independent analyses of SCR and SCR variability in different coma depths supported our findings of an increasing importance of the sympathetic nervous system activity during awaking from coma.

The HF component is most marked in the group with deepest coma. Together with the increase in the standardized LF band the imbalance of sympathethic and parasympathetic activity can be regarded as a loss of arousal, depending on the noradrenergic and cholinergic reticular activation systems (RAS). The RAS modulates cortical and also autonomic nervous system activity. Sleep and wake rhythms are strongly coupled to the influence of RAS modulation. Denervation of thalamic nuclei and of the cortex of RAS impulses leads to coma or coma vigile [6, 15]. Severe traumatic brain injuries with prolonged periods of coma are in general accompanied by brain swelling and increased intracranial pressure and a deafferentiation of cortical activity. An alternative interpretation [11, 28] would be that integrated time-locked reactions, supposing multi-component coordination of autonomous and motoric nervous system activity, are inhibited by diffuse axonal sharing. Because HR variability depends on the harmonious coupling or chronological integration of different phase-dependent processes of the autonomous nervous system into the heart cycle, we would interpret the assessed reduction of HR variability as a first indicator of the importance of chronological couplings of different compartments of the autonomous nervous system during awaking from coma. Such a phase-locked coupling makes the heart enervation smoother and allows for an ergotropic activation under environmental load [21]. The increased importance of sympathetic modulation follows from the raised LF/HF ratio and has been documented in the past under Clonindine and during performance of sustained attention tasks [19]. But in general, our results and different pathogenetic coma interpretations document that the sympathovagal balance may be a precise indicator of different coma steps.

There are, however, several reasons suggesting not to take our result at face value. Firstly, the pharmacological influence for the patients in deep coma is greater than it is in later stages of the emerging process. So the measured parasympathetic activity could partly be a result of the decrease in the sympathetic activity. Up to now, only few studies have analyzed the influence of medication on HRV and frequence spectra of HR. None of the studies analyzed the influence of opioid (Fentanyl and Dipidolor) and only one study the impact of benzodiazepine (Lorazepam) on HR and HRV [26]. In clinical practice, influences of opioid and benzodiazepine medication on the HR are uncommon, because these substances do modulate directly alpha and beta receptors. The one study on the influence of Lorazepam describes a combined increase of HR, HRV, and in the high-frequency band of HR, because of a stimulation of parasympathetic activity. Most of our patients received a benzodiazepine derivative (Dormicum) for sedation. Although we do not know how far the different biochemical structures of Lorazepam, on the one hand, and Dormicum or Rohypnol, on the other, leads to different changes in HR and HRV, we *did not* find an increased HR in the first coma group. This argues against a systematic influence of medication on our results. Secondly, patients in deep coma are in general ventilated. The ventilation frequency is approximately 11 per minute and – in part – higher in patients with polytrauma. So the extreme triggering of the ventilation frequency could play a significant part in our results [11].

In summary, our results make the process of the emerging from coma appear a successive increase of the sympathetic activity and a reintegration of the sympathovagal balance. Although our results clearly will have to be corroborated by further studies, their pattern of coma remission is in accordance with essential neuroanatomical and neurophysiological coma states. The sympathovagal balance then might be a promising indicator for monitoring the process of emerging from coma and for evaluating coma stimulation procedure [27] on-line. This would open a possibility for a systematic analysis of different coma rehabilitation programmes.

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