

# Short-Term Dynamics of Coherence between Respiratory Movements, Heart Rate, and Arterial Pressure Fluctuations in Severe Acute Brain Disorders

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## Summary

In our previous study, healthy volunteers showed considerable short-term dynamics and patterns of the coherence of high time resolution between respiratory movements (RESP), heart rate fluctuations (HRF), and arterial blood pressure fluctuations (BPF). These are physiological indicators of autonomic short-term coordination mediated mainly by the brainstem which could be impaired in severe brain disorders. We hypothesized a direct or indirect impairment of these functions by these disorders and examined these patterns in 16 patients suffering from severe brain disorders. We calculated partial and ordinary coherence sequences and found almost the same patterns of coherence sequences as in healthy volunteers, but a distinctly reduced frequency of pattern incidence in patients ( $2.8 \pm 1.5/10$  min/patient and  $9.5 \pm 2.8/10$  min/subject,  $P < 0.05$ ). Furthermore, there is a significantly smaller frequency of HRF-related patterns in patients with poor outcome, compared with those in patients with good outcome ( $1.8 \pm 0.8/10$  min/patient and  $4.5 \pm 2.7/10$  min/patient,  $P < 0.05$ ). We conclude that severe brain disorders reduce physiological short-term dynamics of autonomic coordination patterns in the mean values of patients, but not in every patient.

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## Key words

Autonomic short-term coordination • Coherence sequence • High time resolution • Heart rate fluctuations • Arterial pressure fluctuations • Severe brain disorders

## Introduction

In healthy animals and volunteers, we found considerable short-term dynamics in the relative coordination between heart rate fluctuations (HRF), arterial blood pressure fluctuations (BPF), and respiratory movements (RESP). These physiological dynamics were obtained by new methods of coherence calculation of high time resolution (Arnold *et al.* 1998, Zwiener *et al.* 2001). Here trivariate, adaptive autoregressive modeling

of the mentioned autonomic time series using Kalman filtering was performed (Arnold *et al.* 1998) to obtain coherence sequences of high time resolution. These sequences are very sensitive parameters of autonomic short-term control at intervals shorter than 1 min (Zwiener *et al.* 2001). The physiological background of these short-term dynamics was described – as far as is known – in our previous paper (Zwiener *et al.* 2001). This phenomenon of “relative coordination” (von Holst 1939), is a short-term varying one of different degrees

between complete synchronization and “dissociation” (Barman and Gebber 1976). It was also called “sliding coordination” (Langhorst *et al.* 1983) between RESP, HRF and BPF, and is above all, but not exclusively, mediated by brainstem interactions. The resulting phenomenon was demonstrated for a longer duration, firstly between pulse intervals and diastolic blood pressure fluctuations by Fišer *et al.* (1978).

Presumably, the central nervous mechanisms involve competitive interactions between rhythmically active respiratory and cardiovascular neuronal assemblies. For instance, Gebber *et al.* (1994a,b) have found that efferent sympathetic activities from the brainstem quickly change their mutual couplings, but also represent the respiratory rhythm to a temporally changing degree. Furthermore, Langhorst *et al.* (1983) and Schulz *et al.* (1985) found changes of cardiovascular and respiratory related rhythms and their couplings in simultaneously recorded brainstem neurons.

Therefore, it is obvious that severe brain disorders, especially those of the brainstem and their autonomic control functions can change the central mediation of HRF, BPF, RESP, and their coordination. Consequently, a large number of results showed a more or less impaired central autonomic mediation of HRF and of the respirocardial coordination (overviews in Winchell and Hoyt 1997, Kennedy 1998). These clinical states concern not only severely disturbed autonomic brainstem functions, but also other severe brain disorders, such as brain trauma or intracranial bleeding. This is obvious because of the known influences of supramedullar brain regions on the central autonomic regulation mediated by the brainstem.

However, these results concern mean statistical properties of the HRV and respirocardial coordination within several minutes or longer, but not the short-term dynamics. The calculation of these autonomic parameters by “classical” time series analysis (used up to now), needs recording intervals of greater than 5 min and stationary conditions of time series. This is, however, not the case because high biological dynamics was observed in our studies (Arnold *et al.* 1998, Zwiener *et al.* 2001). Moreover, these results obtained in patients (Winchell and Hoyt 1997, Kennedy 1998) did not always show sufficiently clear differences to physiological states. Therefore, they cannot serve for the development of neuromonitoring or as a part of this for vital brainstem functional analysis. This monitoring is not available, although might be very essential for clinical medicine.

In our previous study (Zwiener *et al.* 1991)

respirocardial coordination parameters were quantified by “classical” coherence between RESP and HRF in defined patients suffering from severe brain disorders with good or poor outcome. Obviously, autonomic coordinations are especially sensitive for evaluating the impairment of central autonomic functions. However, this analysis also requires time series of longer than 8 min duration and off-line data processing. This is also not suitable for monitoring. Therefore, from pathophysiological and clinical points of view it seems promising to test whether physiological short-term dynamics of autonomic coordinations, as described by Arnold *et al.* (1998), Zwiener *et al.* (2001), is significantly disturbed in severe brain disorders. This could be a contribution to the understanding of pathophysiology of central autonomic coordination.

We hypothesize that time variant dynamics of these coherence sequences between RESP, HRF, and BPF are impaired by these severe brain disorders because of direct or indirect pathological change especially of autonomic brainstem functions. Furthermore, we assume that vitally critical disorders as confirmed by poor outcome will reduce these short-term dynamics more than less severe ones. The pathophysiological effect could be that the stronger impairment of these dynamics is correlated with a worse coupling between these vital organs (Godin and Buchman 1996, Goldstein *et al.* 1998).

We calculated and compared the ordinary and partial coherences in order to separate direct couplings between pairs of RESP, HRF, and BPF from the indirect ones. The latter means those from the respective third time series influencing simultaneously the other two time series as it was found in healthy volunteers (Arnold *et al.* 1998, Zwiener *et al.* 2001). In this way, we attempted to improve the interpretation of the physiological or pathophysiological background of changes.

## Methods

The present study was conducted according to the principles established in the declaration of Helsinki and was approved by the local authorities. Fourteen patients were examined (10 patients with severe brain trauma, 2 with severe ischemic brain hypoxia, 2 with severe subarachnoid hemorrhage; no other organ disorders, GCS < 7 > 3; 14-58 years old of both sexes). Within 1-2 days after acute severe brain disorders, the breast ECG, respiratory or artificial ventilation movements (impedance respirography), and the arterial

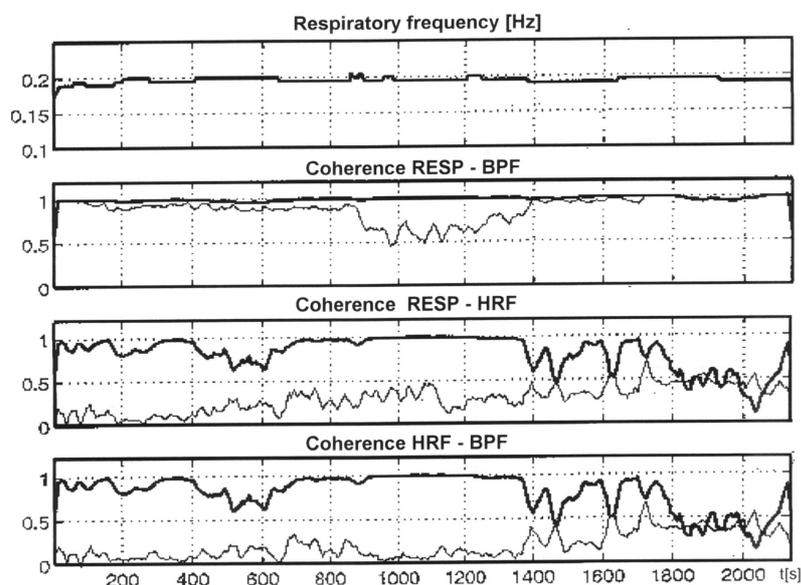
blood pressure (the brachial artery, Statham transducer) were continuously registered for at least 20 min during 2 days (intensive care conditions). All patients were ventilated under pressure or volume control. The PaO<sub>2</sub> and PaCO<sub>2</sub> were maintained at 80-100 mm Hg, and 30-45 mm Hg, respectively. The intracranial pressure was continuously measured. Medication consisted mainly of common analgesedation, i.e. a combination of Propofol 2 mg/kg/h with Midazolam 2 mg/h (12 patients) or Sufentanyl (10 µg/h, 2 patients). This was performed in 28 of 39 recordings, i.e. two recordings in every patient. In 4 patients, recordings with and without analgesedative regimes were done (2 patients with good and 2 with poor outcome, 11 recordings without analgesedation).

After registration of original signals, the instantaneous heart rate sequence was calculated from the ECG (further details see Zwiener *et al.* 2001). The traces of RESP, HRF and BPF were sampled at 128 Hz, the HRF preprocessed with a 2 Hz low pass FIR-filter system (Zwiener *et al.* 1995, 2001) and resampled with 8 Hz to avoid aliasing (Zwiener *et al.* 1996, 2001). The resulting heart rate time series were free of ectopic beats. A trivariate autoregressive model order of 22 time-varying coefficients was fitted to the simultaneously measured signal as described by Arnold *et al.* (1998) and Zwiener

*et al.* (2001). The spectral parameters of ordinary and partial coherence of high time resolution were computed for the three possible pairs of RESP, HRF, and BPF according to Arnold *et al.* (1998) and Zwiener *et al.* (2001). Their coherence maxima within the respiratory frequency were chosen to build the continuous coherence sequences (Fig. 1). Coherences < 0.4 were judged as uncertain, changing ones between 0.4-0.95 as gradual, and coherences > 0.95 as complete coordination (Zwiener *et al.* 2001). We determined the same pattern of coherence sequence as in Zwiener *et al.* (2001), i.e. short-term fluctuations (> 0.5 during 25-60 s, Fig. 1, in RESP-HRF and HRF-BP coherence), short term-changes (> 0.5 during 60-80 s in the same time series), trends (changes > 0.5, 80-200 s), and longer changes (> 0.5 during > 200 s; < 600 s; Fig. 2 in RESP-HRF/BPF and HRF-BPF/RESP).

The mean coherences were calculated by the mean of all coherences determined during 20 min.

The results were analyzed statistically with regard to significant differences by the non-parametric Mann-Whitney test (Sachs 1992). Patients who survived were considered to have a good, the others to have a poor outcome.



**Fig. 1.** Respiratory frequency, sequence of ordinary coherences (bold lines) and partial coherences (thin lines) between respiratory movements (RESP) and arterial blood pressure fluctuations (RESP-BPF and RESP-BPF/HRF), RESP and heart rate fluctuations (RESP-HRF and RESP-HRF/BPF), and HRF and BPF (HRF-BPF and HRF-BPF/RESP) in a 45-year-old pressure-controlled ventilated male patient after severe brain trauma with traumatic subarachnoid bleeding and brainstem contusion, but with good outcome.

## Results

### Mean coherences

In most patients (12 of 14), the partial coherence RESP-BPF/HRF moves mainly at the level 0.7-0.95

(Table 1). Only in 4 of these 12 subjects, this level of partial coherence is partly > 0.95 (Fig. 1). Thus, the RESP-BPF/HRF is almost always gradually, and more seldom, completely coordinated. The other partial coherences, RESP-HRF/BPF and HRF-BPF/RESP of the

patient groups have mainly coherence levels  $< 0.5$  (Figs 1 and 2, Table 1), i.e. they have mainly uncertain, but almost absent direct coordinations. However, there are periods of 200-700 s of RESP-HRF/BPF in 8 patients in which the coherences exceed 0.5. In 3 patients only, the coherences HRF-BPF/RESP exceed the 0.5 level for a shorter period ( $< 200$  s) (Fig. 1). The ordinary coherences, between RESP-BPF, RESP-HRF, and HRF-BPF mainly exceed 0.7. This means that the sum of direct and indirect parts of coordination have mainly levels

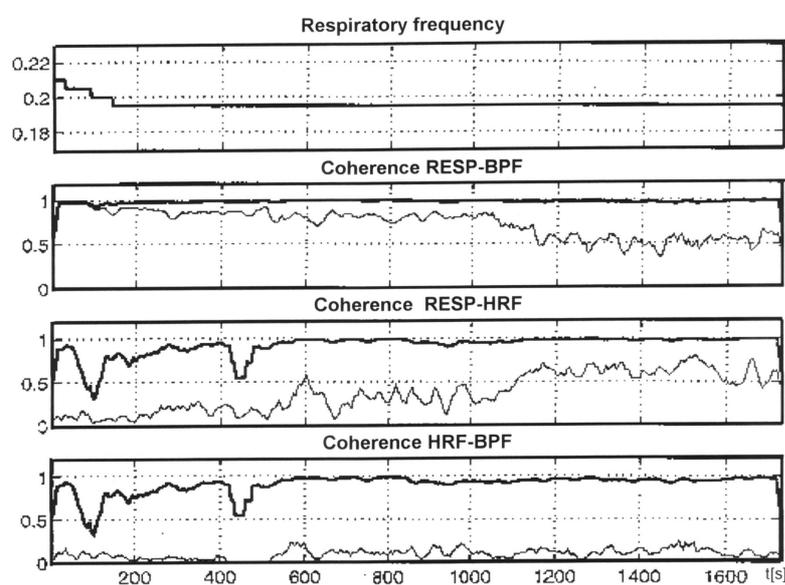
$> 0.7$  (Table 1, Figs 1 and 2). Only at intervals of  $< 300$  s lower values were also found.

In both groups of patients, there were significantly higher ordinary and partial RESP-BPF coherences, but only higher ordinary HRF-BPF coherences with no significant differences in all RESP/HRF coherences against healthy volunteers (Table 1, Zwiener *et al.* 2001). This means that the HRF-BPF coherence is mainly caused by an influence of RESP on BPF and from BPF to HRF in patients. This is almost certainly the influence of artificial ventilation.

**Table 1.** Mean levels of ordinary coherence and partial coherence between RESP, BPF, and HRF in 5 patients with poor outcome, 9 patients with good outcome and 6 healthy volunteers (from Zwiener *et al.* 2001).

Groups	RESP/BPF		RESP/HRF		HRF/BPF	
	Ordinary	Partial	Ordinary	Partial	Ordinary	Partial
Poor outcome	$0.99 \pm 0.01^*$	$0.85^* \pm 0.20$	$0.83 \pm 0.10$	$0.39 \pm 0.23$	$0.86^{**} \pm 0.06$	$0.32 \pm 0.26$
Good outcome	$0.99 \pm 0.01^*$	$0.87^* \pm 0.14$	$0.84 \pm 0.14$	$0.44 \pm 0.16$	$0.81^{**} \pm 0.14$	$0.36 \pm 0.18$
Healthy volunteers	$0.67 \pm 0.06$	$0.35 \pm 0.09$	$0.83 \pm 0.12$	$0.66 \pm 0.15$	$0.67 \pm 0.05$	$0.25 \pm 0.07$

\* Significant differences from healthy volunteers in both groups of ordinary and partial coherences RESP/BPF, but in ordinary HRF/BPF coherence only \*\*  $P < 0.01$ .



**Fig. 2.** The same parameters as in Fig. 1 of a 30-year-old male patient after strangulation, reanimation, and generalized brain edema with good outcome.

Neither the mean partial, nor the mean ordinary coherences between RESP, HRF, and BPF in the frequency range of RESP and calculated from 20 min traces were different in patients with poor or good

outcome (Table 1). There were no differences between mean coherences of different recordings in the same patient and of patients with or without analgesedation.

### Short-term dynamics within the coherence sequences

As for the dynamic patterns of these partial and ordinary coherence sequences (as described in Methods), there are mainly the same types in patients with good or poor outcome and healthy volunteers (Table 2). Figure 1 shows such patterns of coherence fluctuations in all ordinary and partial coherences with the exception of ordinary coherences of RESP-BPF.

In all patients, there was a significantly lower frequency of occurrence of all patterns ( $2.8 \pm 1.5/10$  min/patient) than in healthy volunteers ( $9.5 \pm 2.8/10$  min/subject;  $P < 0.05$ ). There were distinct, but not statistically significant differences ( $P = 0.05$ ) of the numbers of short-term and long-term patterns of ordinary RESP-BPF and partial RESP-BPF/HRF between the two patient groups together (poor and good outcome) and healthy controls (Table 2). This was found only in a part of ordinary and partial coherences of RESP-HRF and of HRF-BPF. There was a significantly lower frequency of all HRF-related patterns in patients with poor outcome ( $1.8 \pm 2.7/10$  min/patient  $P < 0.05$ ) than in those with good outcome ( $4.5 \pm 2.7/10$  min/patient).

There was no difference in the frequency of pattern occurrence of both ordinary and partial coherence RESP/BPF between both patient groups.

As for the trends and changes of levels of coherence sequences, the results were following: 11 patients show opposite changes only between the partial coherences RESP-BPF/HRF and RESP-HRF/BPF

(Fig. 2) and only three patients did not (Fig. 1). There was no significant difference between the groups of poor or good outcome. In all 14 patients, RESP-HRF and HRF-BPF coherences showed the same direction of changes (Figs 1 and 2). There were always similar and sometimes identical ordinary coherence patterns between RESP-HRF and HRF-BPF in 12 of these 14 patients (Figs 1 and 2).

There were no significant differences between two recordings in the same patient.

### Influence of analgesedative regime upon the coherence patterns

To obtain a rough evaluation of the influence of the analgesedative regime upon the frequency of these coherence patterns, we compared this frequency of occurrence of coherence pattern in recordings of 4 patients with or without an analgesedative regimen. All mean levels of ordinary and partial coherences between RESP, HRF, and BPF were not different. The frequency of coherence patterns mentioned with this medication was  $3.5/10$  min/patient, without it was  $3.0/10$  min/patient (not statistically different,  $P = 0.10$ ). Two of these patients had a good outcome and two a poor outcome. Comparing all 25 recordings during analgesedative regimes with these 11 recordings without these regimens, we found no significant difference in mean occurrence of dynamic patterns in the former ( $4.56/10$  min/patient) and in the latter ( $3.86/10$  min/patient).

**Table 2.** Frequency (number/10 min) of dynamic pattern occurrence of instantaneous ordinary coherences and partial coherences between 20 min recordings of RESP, HRF, and BPF in 5 patients with poor outcome (first number), 9 patients with good outcome (second number), and in 6 healthy volunteers (third number, Zwiener *et al.* 2001).

Patterns	RESP-BPF		RESP-HRF		HRF-BPF	
	Ordinary	Partial	Ordinary	Partial	Ordinary	Partial
<i>Short-term fluctuations</i> (changes > 0.5; 25-60 s)						
<i>short-term changes</i> (changes > 0.5; 60-80 s)						
	0.2/0/3.0	0.2/0.1/2.3	1.0/1.9/2.0	0.4/1.3/2.7	0.6/2.0/2.3	0.2/0.8/0.3
<i>Trends</i> (changes > 0.5; 80 > 200 s)						
<i>Longer changes</i> (changes > 0.5; > 200 s < 600 s)						
	0.2/0/1.0	0.2/0/1.3	0/0.9/0.7	0.2/0.2/2.3	0.2/1.0/1.0	0/0.4/1.7
<i>Total/10min/subject</i>	0.2/0/2.0	0.2/0.1/1.8	0.5/1.4/1.3	0.3/0.7/2.5	0.4/1.5/1.7	0.1/0.6/1.0

Statistically significant smaller numbers of dynamic pattern of all HRF related coherences in patients with poor outcome compared with those of good outcome ( $P < 0.05$ ).

## Discussion

### *Mean coherences*

There are significant differences of mean ordinary and partial RESP-BPF coherences and ordinary HRF-BPF coherences between both groups of patients and healthy volunteers. These differences have to be explained mainly by the effects of (i) artificial ventilation and/or (ii), the analgosedation of patients, and (iii) the brain disorder. There were no differences between patients with or without analgosedation. Examined autonomic coherences in which the influence of RESP is excluded as in the partial HRF-BPF coherence did not show any difference between patients and healthy volunteers. Therefore, a statistically significant effect of brain disorders was not found. Thus, the main reason for the differences is rather the artificial ventilation. We suggest that a possible pathophysiological effect of severe brain impairment on mean autonomic coherences (Zwiener *et al.* 1991) in ventilated patients with analgosedation is not present.

Contrary to the results in spontaneously breathing patients (Zwiener *et al.* 1991), the levels of all mean partial and ordinary coherences between ventilated patients with good and poor outcome were not statistically different. Hence critical impairment of autonomic brainstem functions of ventilated patients cannot be determined by changes of mean coherences between RESP, HRF, and BPF.

As far as the physiological mechanism is concerned, we have to take into account a masking influence of the controlled ventilation. This strengthens the direct interaction between RESP, arterial blood pressure, HRF, and BPF by additional stretch receptor activity, peripheral hemodynamic and intrathoracic pressure mediated, and reflex couplings (Richter and Spyer 1990, Richter *et al.* 1991, Shapiro and Peruzzi 2000, Malpas 2002). This explanation is supported by the following comparison with earlier results. The ordinary coherences between RESP, HRF, and BPF were always higher in ventilated patients than in spontaneously breathing healthy volunteers. Furthermore, the ordinary coherence of RESP/HRF and RESP/BPF is also higher in these ventilated patients than that of RESP/HRF in spontaneously breathing patients with the same severe brain disorders from our previous study (Zwiener *et al.* 1991).

Also the RESP-HRF coherences of ventilated patients with poor outcome were never as small (0.68-0.98) as in the spontaneously breathing patients with poor

outcome (0.11-0.13) (Zwiener *et al.* 1991). This means that the coordination between RESP and HRF is always distinctly changed by artificial ventilation. Furthermore, the higher ordinary, but not partial HRF-BPF coherence in patients only as an expression of simultaneous RESP influence of both HRF and BPF can be explained by the effects of artificial ventilation.

### *Short-term dynamics of coherence sequences*

There is a significantly lower number of pattern occurrence within the coherence sequences of high time resolution in the group of all patients compared with those in healthy volunteers reported by Zwiener *et al.* (2001). This confirms our hypothesis of impaired short-term dynamics between RESP, HRF, and BPF expressing the disturbance caused by central nervous disorders. Barman and Gebber (1976) and Gebber *et al.* (1994a,b) found changing activity patterns of vagally and sympathetically related brainstem neuron assemblies and their interactions with similar dynamics as observed for the coherence pattern in our study (Zwiener *et al.* 2001). We assume the impairment of modification of these neuronal functions by severe brain disorders. Artificial ventilation as the reason for these differences as postulated for mean coherences is unlikely because ventilation exerts a continuous and constant influence. Non-nervous mechanisms such as other organ disorders are also unlikely because these patients were excluded.

Furthermore, the frequency of patterns of HRF coherences to the other two time series of the patients with poor outcome was also significantly lower than those of patients with good outcome. This confirms our further hypothesis that vitally critical severe brain disorders, i.e. those with poor outcome, have more severely impaired dynamics of autonomic short-term coordination. It is also unlikely that reduced pattern frequency in patients is the effect of ventilation because ventilation was not different in patients with poor and good outcome.

There is no difference between the two groups of patients in ordinary and partial coherences of RESP/BPF. Because only HRF and its coordination to RESP and partly to BPF is vagally mediated, we can assume a stronger vagal impairment in these brain disorders with poor outcome.

There were also no differences between the frequency of pattern occurrence of ordinary and partial coherences. This means (i) that the direct influences between the time series investigated already showed these

coordinations, or (ii) the indirect influences from the third time series to either of the others are not essential.

Patients with and without analgesedation showed no differences between the mean coherence levels as well as the number of such patterns within the sequence of coherences of high time resolution. Therefore, we can assume that such drugs exert a rather limited influence upon these parameters of autonomic nervous coordination in patients with severe brain disorders. At least, there is a distinctly smaller influence of medication compared with that of pathological factors causing severe brain disorders.

In conclusion, the high short-term dynamics between HRF, RESP, and BPF found earlier in healthy volunteers is reduced in severe brain disorders. This can be explained by impaired central autonomic coordination. It is not the result of analgesedation because there is no difference between patients with and without analgesedation, but between patients and healthy volunteers. This explanation of the reduction of short-term coordination by severe brain damage itself is supported by the lower frequency of pattern occurrence in patients with poor outcome, i.e. with more severe impairment. However, it does not exclude that peripheral mediations or peripheral-central feedbacks (Malpas 2002) are also reasons for these changed short-term coordinations.

Although the biological meaning of these short-term dynamics and the pathophysiological effect of these reduced dynamics are not clear, some hints can be found in the literature. Langhorst *et al.* (1983) and Schulz *et al.* (1985) have found that the degree and pattern of rhythmic fluctuations in brainstem neurons related to respiratory or

cardiovascular functions and their mutual influence on the efferent activities to lung, heart, and vessels depend on actual brainstem afferent activities. This concerned those from peripheral somatic and visceral stimuli to the brainstem. Therefore, we can assume that these short-term dynamics of coordinations are for example autonomic adaptations to changed external conditions.

As far as the meaning of their pathological reduction is concerned, the concepts of “uncoupling” (Godin and Buchman 1998) or “decomplexification” (Goldstein *et al.* 1996) in severe central nervous or septic processes seem to be promising. The more these couplings decrease, the poorer the outcome was for the patients. The idea is that the uncoupling between lungs, heart, and the vascular system decreases their functional performances. However, it is not clear whether the observed continuous decrease of these couplings is the main process involved in these disorders or only an epiphenomenon. Despite this, the observed changes in short-term dynamics seem to be an appropriate pathophysiological parameter of changed autonomic short-term dynamics in many, but not all cases of severe brain disorders. Perhaps, nonlinear methods of autonomic time series analysis (Zwiener *et al.* 1996) or their coordination could be a more sensitive approach, for example, for assessing their mutual relations (Hoyer *et al.* 1998, 2002), if similar short-term procedures were developed.

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