

Cardiovascular rhythms in the 0.15 Hz band: Common origin of identical phenomena in man and canine in the reticular formation of the brain stem?

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Abstract

Selected examples from man and canine experiments with time series of reticular neurons, respiration, arterial blood pressure, and cutaneous forehead blood content fluctuations were analyzed using multiscaled Time-Frequency-Distribution (TFD), Post-Event-Scan (PES), and Pointwise Transinformation (PTI), resp.. We found in both experiments a “0.15 Hz rhythm” which exhibited periods of spindle wave epochs (increasing and decreasing amplitudes) to be phase synchronized with respiration at 1:2, 1:1 and 2:1 integer number ratios. At times of these wave-epochs and n:m phase-synchronization, the “0.15 Hz rhythm” appeared also in heart rate and arterial blood pressure fluctuations. If phase synchronization of the “0.15 Hz rhythm” with respiration was established at a 1:1 integer number ratio, it was maintained throughout and resulted in consensualization of all cardio-vascular-respiratory oscillations at 0.15 Hz. Analysis of a canine experiment supplied evidence that the emergence of the “0.15 Hz rhythm” and n:m phase synchronization appears to result from a decline in the level of the general activity of the organism which was associated with a decline in the level of activity of reticular neurons in the lower brainstem network. These findings corroborate the notion of the “0.15 Hz rhythm” to be a state marker of the ‘trophotropic mode of operation’ which was introduced by W.R. Hess.

Key Words

vegetative rhythms; cardiovascular-respiratory coordination; n:m phase synchronization; autogenic training; reticular formation; lower brainstem dynamics; dynamic systems; non-linear analysis; wavelet analysis.

Abbreviations

AT: autogenic training

CBS: common brainstem system in the reticular formation of the lower brainstem

CVRS: cardio-vascular-respiratory system

IBI: inter beat intervals

mTFD: multiscaled Time frequency distribution

NTS: nucleus tractus solitarii

PES: Post event scan

PPG: photoplethysmography

PTI: Pointwise Transinformation

respR: respiratory rhythm

In all ratios of phase synchronization the first integer number denotes respiration and the second one the “0.15 Hz rhythm”

retR: reticular rhythm

ANS: autonomic nervous system

Introduction

In 1992, a rhythm in the blood oscillations of the skin of earlobe, forehead, and heart rate was described in man (1). To this day, only little scientific attention has been given to the physiological significance of this rhythm (2-4). A striking feature of the emergence of this rhythm was the simultaneous individual experience of profound relaxation. Consequently, this rhythm was investigated during controlled relaxation induced by hypnoid relaxation (AT) which caused this rhythm to abruptly emerge (5). Under both conditions, the center of activity of this rhythm was in the frequency range of 0.15 ± 0.03 Hz. Therefore, this rhythm was hereon referred to as “0.15 Hz rhythm band”. The physiological details of the mechanisms governing this phenomenon, however, remained poorly understood demanding further investigation. Yet, this phenomenon turned out to be of pragmatic use in two clinically relevant areas: firstly, it helped monitor the depth of anaesthesia in man (6), and secondly, it supplied a more precise description of resting conditions in clinical microcirculation research which helped facilitate the differentiation of physiological or pathological temporal patterns of skin microcirculation (7) Hence, there is reason to assume that registration of the “0.15 Hz rhythm band” as a pattern contained in the time series of cyclic perfusion (using LDA [Laser-Doppler-Anemometry]), or blood content (using PPG [Photoplethysmography]) contains information on the transition from arousal to psychophysical rest.

Investigations in anaesthetized dogs, however, comprehensively illustrated the relevance of the reticular formation of the lower brainstem (RF) for the generation of cardio-vascular rhythms (e.g. 8-14). Interestingly, these authors frequently described a rhythm in the range of 0.15 Hz emerging in the neurons of the RF which was therefore referred to as the “reticular rhythm (retR)”. This rhythm was not identical with the rhythm of respiration, but both were found to be coordinated with one another exhibiting temporarily phase- and frequency-coupling (9,11). Neurons which frequently exhibited the retR were referred to as “unspecific reticular neurons” since they were not associated with any specific nuclei. Owing to Langhorst and co-workers these neurons possess a functional organization of distinct dynamics (8,15-18), i.e. these neurons were only transiently connected to various functions of the brainstem system (12,13) responsible for the regulation of the cardiovascular system, respiration, muscular tone, and the “ascending reticular system” (19). This, however, was in contrast to previous held assumptions of a persisting connection of these reticular

neurons to the various regulatory systems of the brainstem. Rather, these unspecific reticular neurons are synchronously variably involved in several of the above mentioned functions depending on visceral and somatic afferents to these neurons. This is in support of the concept of a dynamical organization of a common regulatory system in the RF. Ideas of Moruzzi (19), but also those of Hess (20-22) were subsequently extended. Owing to their functional holistic concepts, but also those of others (23-25), the dynamically organized neuronal network in the RF was termed “common brainstem system (CBS)” (8,18).

In light of our findings in man and in canine, we considered it appropriate to scrutinize the hypothesis of a common origin and common functional properties underlying the “0.15 Hz rhythm”. Using non-linear time series analysis techniques, we present experimental evidence on the “0.15 Hz rhythm” in cardio-vascular subsystems in canine on the one side, and cardio-vascular and cutaneous microcirculation in man on the other side which should greatly facilitate comparison across species helping identify common properties of underlying the origin of this rhythm.

Materials and Methods

Experiments in test persons

Following, data of recordings of one subject will be presented who took part in a controlled study on the efficacy of the autogenic training (AT, the so-called hypnoid). This widely accepted and well studied relaxation technique was chosen by us since it provided a naturalistic study design to selectively reduce psychomotor drive in the absence of pharmacological interventions likely to affect autonomic nervous system (ANS) responses (for more details see e.g. 5,26-28). Prior to the study, the test person gave written consent, were medically thoroughly examined, and a sociodemographic form was completed. The study was permitted by the university's (RWTH Aachen) ethics committee. The test person (female, age 56, non-smoker, no history of mental or physical chronic or acute illness) studied had a history of 17 year experience with AT. In order to identify physiological adaptation processes, a multi levelled block design was performed combining orthostatic stress with maneuvers to modify sensory and mental drive responses. To this end, the body posture was changed from a seated to a standing, and further to a supine position. Each

position was maintained for a total of 6 minutes, consisting of a 2 minutes interval during which eyes were kept open, a 2 minutes interval during which eyes were kept shut, and a 2 minutes interval during which AT was performed, also with the eyes kept shut.

An ambient temperature at $22 \pm 2^\circ \text{C}$ was maintained throughout. The recording session was started by an initial resting period of 30 minutes used to attach all probes (see below) allowing the test person to get accustomed to the laboratory situation.

Data acquisition

Data were recorded for all probes on-line using a personal computer equipped with an analog-to-digital (AD) converter (Data Translation, DT 2812 a), employing a commercially available multi-link software package (DiaDem®, National Instruments). Data were digitized at a sampling rate of 300 Hz at 12 bit resolution and stored on digital media for further processing. Crucial for recording relaxation responses is minimal invasiveness during the recording process.

1. We employed a photoplethysmographic probe (PPG) of own design attached to the glabella forehead region.¹ At room temperature, the glabella forehead region displays little or no vasoconstrictor activity, which could possibly influence the shape of recorded signals. Albeit there are certain interpretative shortcomings of the signal amplitude obtained by these probes, sufficient accuracy in the temporal domain of this signal had been verified extensively by simultaneous recording of the PPG and LASER-Doppler signal (29).
2. In order to detect respiration-induced fluctuations contained in cardiovascular signals, a belt equipped with a strain-gauge (ADMS) was used for the registration of the frequency and amplitude of respiratory induced thoracic movements.
3. Data analysis was executed off-line using software specifically designed in our institution for the non-linear analysis of multiple time series of bio-physiological data, and now

commercially available (Dataplore®, Datan Software Analysis GmbH, Potsdamer Str. 14b, D-14513 Teltow, Germany).

Canine Experiment

The experiment chosen was performed with an adult male mongrel dog (body weight 18 kg) anesthetized with chloralose-urethane (initial dose 70 mg chloralose, 350 mg urethane/kg body weight). During the course of the experiment, 10% of the initial dose was added whenever needed, which was controlled by EEG and corneal reflex. The anesthetized animal was intubated, the body temperature measured and kept constant. During the entire experiment, the intubated animal was able to spontaneously breathe room air. Arterial PO₂, PCO₂ and pH were controlled. If necessary, pH values were corrected to 7.39 by injection of NaHCO₃. Whenever needed, PO₂ was adjusted to 90-95 mmHg by enriching the spontaneously breathed room air with oxygen. A catheter was inserted into a femoral vein.

The medulla oblongata was exposed from the dorsal side, muscles removed layer by layer and the squama occipitalis removed osteoclastically. The cerebellum remained, the exposed medulla was covered by mineral oil at body temperature.

Brainstem neurons were recorded extracellularly with glass-insulated platinum electrodes of 10 µm diameter freely riding in the tissue, which avoids artifacts due to movements of the brain (30). Recording sites were marked by electrolytic lesions and later histologically verified. Neuronal activities were recorded from an area between 4 mm rostral and 5 mm caudal to the obex. The neurons were located in the medial two thirds of the RF (characterized by large neurons with long ascending and descending axons). The recording sites in the RF, correspond to the nucleus reticularis gigantocellularis and the nucleus reticularis caudalis. The recording sites in this area of such reticular neurons are described in former papers (see: Fig. 1 in 15, and Fig. 2 in 16).

Neuronal activities were recorded together with blood pressure, intrapleural pressure, ECG, parieto-occipital EEG (recorded with two screw-electrodes on both sides of the skull), and in some experiments phrenic nerve activity and efferent renal sympathetic nerve activity.

¹ The kind help of Dr. Walter Rütten and Prof. Dr. Blazek, Department of High-Frequency-Technology, RWTH Aachen is gratefully acknowledged.

Signal preprocessing

Recorded signals were stored on polygraph and magnetic tape. By means of window discriminators, neuronal spikes and R-waves of the ECG were converted into sequences of rectangular pulses (using electronic delay circuits, shapes and amplitudes of the neuronal spikes were watched by superposition on storage oscilloscopes). This resulted in separated sequences of rectangular pulses for the different neuronal activities and ECG which were digitized and stored on computer as event trains (accuracy 0.1 ms). From these event trains equidistant time series of the instantaneous heart rate (HR) and the frequencies of the neuronal activities were computed. Before digitizing (sample rate 1 kHz), signals were filtered to avoid aliasing (stop band above 500 Hz, ≤ -60 dB). The EEGs were filtered at 0.1 - 30 Hz. For sample rate reduction to 100 Hz all data were digitally low pass filtered (FIR, stop band above 50Hz, ≤ -60 dB) to avoid aliasing. From the arterial blood pressure, the envelopes of systolic maxima and diastolic minima were computed by interpolation. For further sample rate reduction to 10 Hz all time series were digitally low pass filtered (FIR).

Non-linear and non-stationary Analysis

The following methods of nonlinear and nonstationary analysis were applied to time series of both human and animal recordings. Detailed descriptions of these methods are given in Vandenhouten (14,31) and Lambertz et al. (12).

Multiscale Time-Frequency-Distributions (mTFD) via Morlet Wavelet Analysis

If signals showed marked rhythms, instantaneous frequencies and related shifts can be displayed in TFD. Certain disadvantages of conventional TFDs (32-34) can be overcome if spectrograms are computed with the aid of Morlet Wavelets (Morlet Wavelets Spectra (MWS)), (35) thereby minimizing the common uncertainty of frequency ω and time t ($\Delta\omega\Delta t$). The computational expense of this procedure is proportional to the length of the time series and the number of sample points in the frequency domain. TFDs shown were normalized based on the time-depending maximum (relative normalization) which allowed to track defined frequency components in the presence of marked spectra variations.

Post-Event-Scan (PES)

The PES is a peak-triggered evaluation of the coupling dynamics of two signals, the trigger and the probe signal. PES extracts probe-signal sections that vary as a function of the peaks of the trigger signal. The columns of the 2-dimensional Post-Event-Scan consist of the values of x , starting at one of the trigger times t_i , respectively:

$$y(i, j) = \begin{cases} x(t_i + j + \tau) & \text{if } j < t_{i+1} - t_i \\ 0 & \text{otherwise} \end{cases}.$$

The trigger time t_i is defined as the i^{th} peak of the trigger signal, and τ being a user-defined time delay. This will result in a 2D output surface, exhibiting rhythms in the probe signal as well as the degree of synchronization (phase relation) between trigger and probe. To examine the synchronization of two rhythms the signal with the slower rhythmic activity is taken as the trigger signal, so the oscillations of the “faster” signal produces distinct structures along the ordinate. If these patterns are stable along the time axis, rhythms are phase synchronized (31).

Pointwise Transinformation (PTI)

PTI is a measure of the mutual interaction of subsystems computed in the phase space. This method takes into account linear as well as non-linear dependencies and can be applied to non-stationary time series. Phase space reconstruction was done according to Takens (36) who described how single time series (with sample points $k=0\dots N$) can be used to reconstruct adequate representations of dynamic systems in the phase space. Vectors of a single time series are built in the phase space (embedding dimension m) by taking a number of m time-delayed samples (with preset time lag τ) of the time series. Each vector represents the state of the generating system in the phase space at the respective point k . “Trajectories” can be reconstructed (with $N \rightarrow \infty$) in the substitute phase space (R^m), which are dynamically and topologically equivalent to the trajectories in the original phase space. This enables the determination of important phase space measures for the description of the system dynamics from a single observable scalar time series, which is of crucial importance for practical system analysis.

In practice, infinite time series (with $N \rightarrow \infty$) are not available. Therefore, in every experimental situation the so-called embedding parameters m and τ have to be selected carefully in order to obtain an optimal reconstruction from a finite time series. In the present publication, the

delay τ is determined as the position of the first minimum of the first derivative of the auto-correlation function of the signal and m is determined using the False Nearest Neighbors algorithm. A detailed description of the embedding process and the selection of m and τ is given by Vandenhouten (14,31), and Lambertz et al. (12).

The PTI (37) of two observable quantities ξ and χ has been derived from Shannon's information concept (38), and is calculated from the probability densities of the observables in the phase space. In practice, this is done by calculation of empirical point densities in the neighborhood of the reconstructed trajectory. Therefore, the values of the PTI depend on the selected search radius r , the range of PTI values is not normalized and negative PTI values may occur for experimental data. However, the increase or decrease of the PTI level over the time still gives information about changes in the coupling behavior of the investigated systems. The time resolution of the PTI is principally limited merely by the sampling rate, and thus one is able to pursue also very fast changes in the coupling behavior which is not possible with conventional methods (e.g. short-time cross correlation) (31).

Results

Experiments in man

The experiment chosen shows the entire recording from an AT expert. The entire recording lasted 18 min, including postural changes and variations in sensory-mental drive.

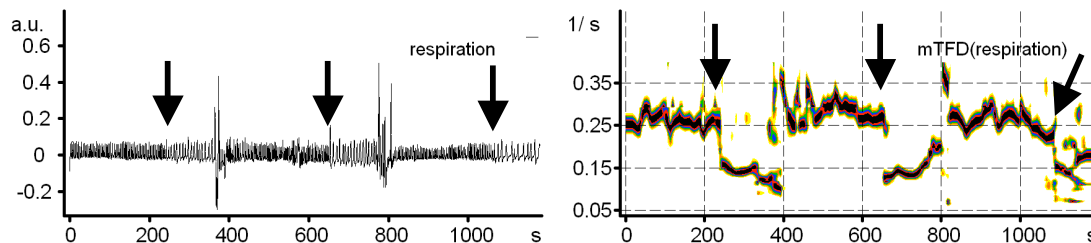


Fig. 1A+B

1A (left): Original data showing thoracic respiration movements, not paced: 0-360 s seated position (0-120 s: eyes open, 120-240 s: eyes shut, 240-360 s: arrow start of AT); 360-720 s standing position (360-480 s: eyes open, 480-600 s: eyes shut, 600-720 s: arrow start of AT); 720-1080 s supine position (720-840 s: eyes open, 840-960 s: eyes shut, 960-1080 s: arrow start of AT).

1B (right): TFD of thoracic respiration movements, showing a clear decline from the dominating frequency at ca. 0.28 Hz to ca. 0.15 Hz.

Colors in the TFD are equivalent to 10% changes in maximal amplitude: black: > 90%, red: 80%-90%, blue: 70%-80%, green: 60%-70%, orange: 50%-60%, yellow: 40%-50%.

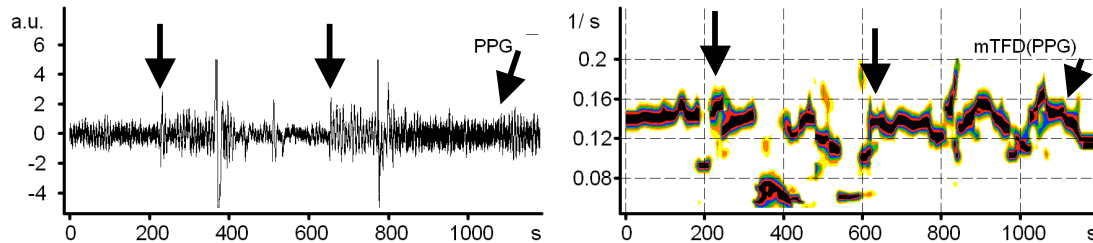


Fig. 1C+D:

1C (left): Original data showing cutaneous forehead blood oscillations (PPG): 0-360 s seated position (0-120 s: eyes open, 120-240 s: eyes shut, 240-360 s: arrow start of AT); 360-720 s standing position (360-480 s: eyes open, 480-600 s: eyes shut, 600-720 s: arrow start of AT); 720-1080 s supine position (720-840 s: eyes open, 840-960 s: eyes shut, 960-1080 s: arrow start of AT).

1D (right): TFD of cutaneous forehead blood oscillations (PPG), the dominating frequency prevails at ca. 0.15 Hz almost through the entire recording, interrupted only by a short period of ca. 0.075 Hz during postural change seated-standing.

Colors in the TFD see fig. 1B.

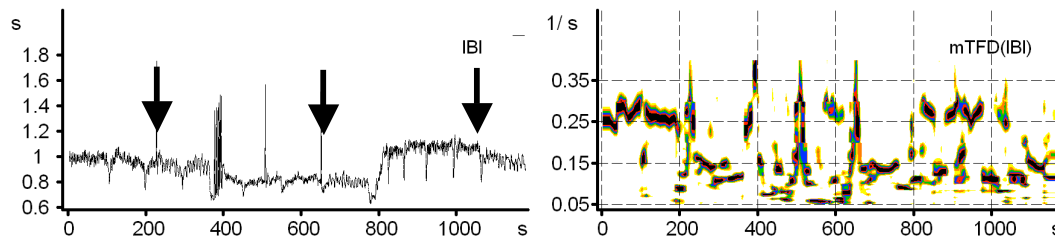


Fig. 1E+F:

1E (left): Time series of inter beat intervals (IBI) extracted from PPG-signal: 0-360 s seated position (0-120 s: eyes open, 120-240 s: eyes shut, 240-360 s: arrow start of AT); 360-720 s standing position (360-480 s: eyes open, 480-600 s: eyes shut, 600-720 s: arrow start of AT); 720-1080 s supine position (720-840 s: eyes open, 840-960 s: eyes shut, 960-1080 s: arrow start of AT).

1F (right): TFD of inter beat intervals (IBI). The TFD-analysis allows identification of frequencies in the range of that observed in the range of respiration at ca. 0.27 Hz, as well as the immediate decline to the “0.15 Hz rhythm” with the onset of AT.

Colors in the TFD see fig. 1B.

As shown in figs. 1A and B, during naïve relaxation in the seated position, the frequency of respiration remained between ca. 0.25 and ca. 0.28 Hz. With the start of AT (at the 240th s, same figs.), the respiration frequency first abruptly declined to 0.16 Hz, to further drop to 0.14

Hz. In the PPG-signal, the “0.15 Hz rhythm” was present throughout both naïve (eyes open and shut) and AT induced drive reduction (fig. 1C). Hence, during naïve relaxation the rhythm in the respiration attracted that in the IBI (fig. 1F), while during AT enhanced relaxation, the “0.15 Hz rhythm” in the PPG attracted the rhythm in the respiration, which was also observed in other experiments (data not shown). Between the 30th and the 105th s, and the 260th and the 330th s (see braces in fig. 2C), oscillations formed ‘wave epochs’: increases and decreases of amplitudes in the PPG signal. During the first wave epoch, eyes open condition, waves were smaller as during the second epoch, with AT triggered relaxation. During this wave epoch, the respiration was synchronized with the “0.15 Hz rhythm” in the PPG signal at a frequency ratio of 2:1. During the second epoch, respiration was synchronized with the “0.15 Hz rhythm” in the PPG signal at a frequency ratio of 1:1. Phase coupling during these epochs was evidenced by the post event scan (PES, fig. 2G). This analysis supplied evidence of a 2:1 phase coupling between PPG and respiration during the first wave epoch, and an extended 1:1 phase coupling between PPG and respiration during the second wave epoch (see also table 1). Throughout the entire recording, inter beat intervals (IBI) were dominated by the respiratory rhythm (rR, see e.g. fig. 2F), albeit at times interrupted by changes to the 0.1 Hz rhythm which was at times present in parallel. Almost identical courses of frequencies were observed in the standing and the supine position.

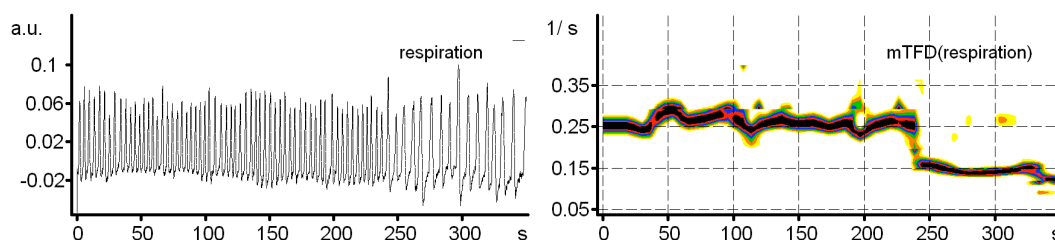


Fig. 2A-B:

2A (left): Cut from fig. 1A, showing thoracic respiration movements, not paced, seated position (0-120 s: eyes open, 120-240 s: eyes shut, 240th s start of AT).

2B (right): Abrupt decline to the “0.15 Hz rhythm” at the onset of AT, an abrupt decline first to 0.15 Hz, and further to 0.14 Hz.

Colors in the TFD see fig. 1B.

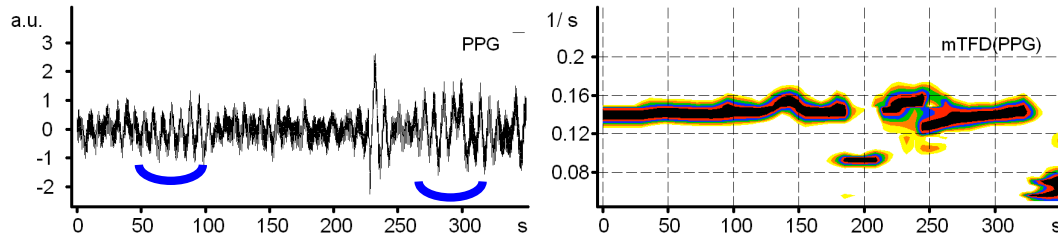


Fig. 2C-D:

2C (left): Cut from fig. 1C, cutaneous forehead blood oscillations (PPG), seated position (0-120 s: eyes open, 120-240 s: eyes shut, 240th s start of AT). Fig. 2C exhibits enhanced oscillations after the 240th s; note the ‘wave epochs’ (spindle waves) between 30th and 105th s, and 260th and 330th s (brackets);

2D (right): TFD of Fig. 2C. The “0.15 Hz rhythm” remains relative constant at a center frequency of ca. 0.14 Hz during the entire recording.

Colors in the TFD see fig. 1B.

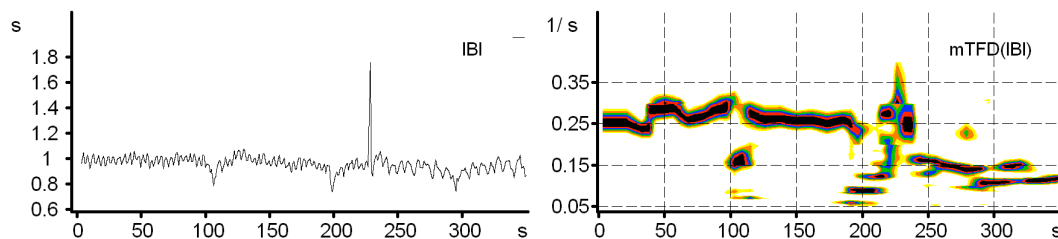


Fig. 2E-F:

2E (left): Cut from fig. 1, original recordings of inter beat intervals (IBI) extracted from PPG-signal, seated position (0-120 s: eyes open, 120-240 s: eyes shut, 240th s start of AT).

2F (right): TFD of inter beat intervals (IBI), showing dominating respiration related frequencies during eyes open and eyes shut section. At the start of AT, decline to the “0.15 Hz rhythm”, with changes to the 0.1 Hz rhythm.

Colors in the TFD see fig. 1B.

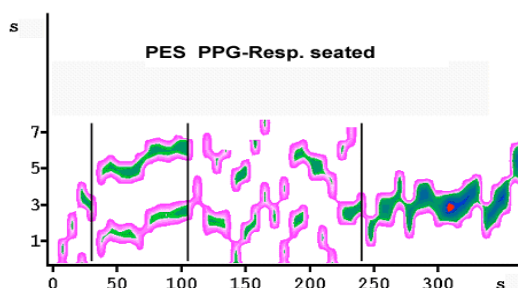


Fig. 2G: PES of PPG-0.15 Hz rhythm triggered respiration. There is a 2: 1 phase-synchronization ratio during the first wave epoch. Note the extended 1:1 phase coupling during the second wave epoch with AT triggered relaxation.

	0.15 Hz rhythm band frequency (Hz)			Respiration frequency			1:1 Coupling (s)		
	Time (s)			Time (s)			Time (s)		
	Eyes open	Eyes shut	AT	Eyes open	Eyes shut	AT	Eyes open	Eyes shut	AT
Standing	0.135 ±0.01	–	0.135 ±0.05	0.30 ±0.05	0.29 ±0.03	0.135 ±0.005	–	–	+
	120		120	–	–	–	–	–	120
Seated	0.14 ±0.003	0.147 ±0.003	0.14 ±0.004	0.26 ±0.02	0.25 ±0.01	0.14 ±0.005	–	–	+
	120	80	120	–	–	–	–	–	120
Supine	0.137 ±0.007	0.13 ±0.003	0.14 ±0.005	0.26 ±0.03	0.24 ±0.03	0.15 ±0.003	–	–	+
	120	–	120	–	–	–	–	–	120

Table 1: Appearance of the 0.15 Hz rhythm in the PPG-signal, the frequency of respiration and 1:1 coupling of the rhythms of PPG and respiration. Time [s]: duration of appearance of rhythms, 1:1 coupling of both rhythms.

Canine experiment

The experiment chosen demonstrates the appearance of the retR in response to a reduction of the overall activity of the organism due to the administration of an additional dose of anaesthetics. The phase transition which was subsequently observed was present in the activity of two RF neurons (retN1 and retN2 [only data of retN1 shown], both recorded using the same electrode at 1.15 mm caudal, 1.6 mm left lateral to the obex, depth 1.7 mm), systolic and diastolic blood pressure (systBP, diastBP), heart rate (HR), renal sympathetic activity (symp, data not shown), respiratory frequency (respF, data not shown), and intrapleural pressure (IPP).

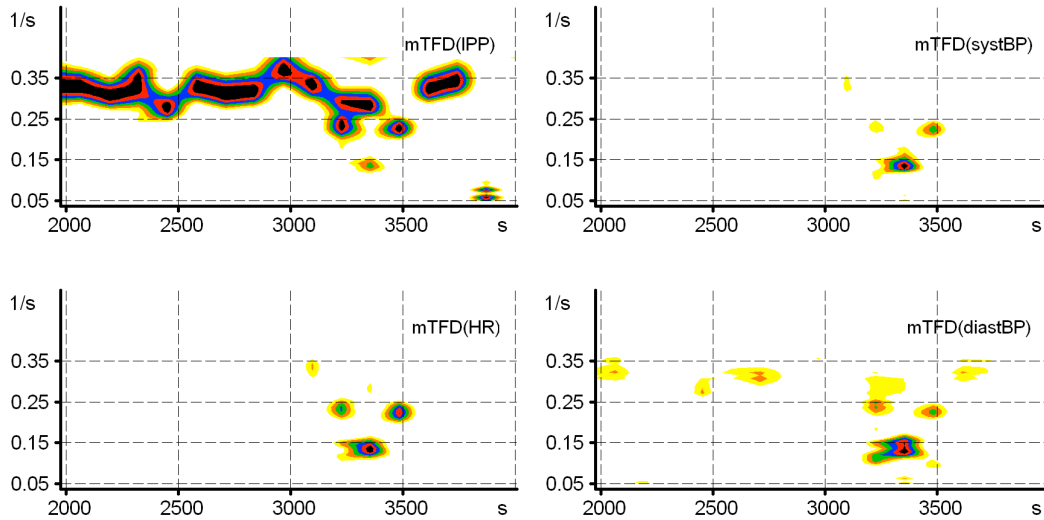
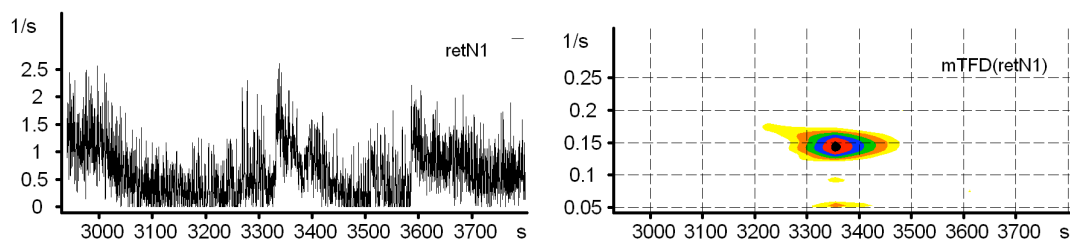


Fig. 3: The TFD analyses of respiration (intrapleural pressure, IPP), heart rate (HR) systolic and diastolic blood pressure (systBP, diastBP) of the canine experiment. The TFDs display an overview of the experimental course. The rhythm of about 0.15 Hz is clearly present between approx. the 3000th and 3500th second in systBP, diastBP, and HR and also in the IPP, at approx. half of the dominating respiratory frequency (0.28 Hz). Colors in TFDs are equivalent to 10% changes in maximal amplitude: black: > 90%, red: 80%-90%, blue: 70%-80%, green: 60%-70%, orange: 50%-60%, yellow: 40%-50%.

Signals were simultaneously recorded for a total of approx. two 2 hours (6450 s). A first overview is given using TFD-analysis (fig. 3). This exhibits a rhythm at ca. 0.15 Hz which emerged at approx. the 3300th s in the signals of systBP, diastBP, and HR. In IPP, the dominating frequency is at ca. 0.28 Hz. The emergence of the “0.15 Hz rhythm” was preceded by administration of an additional dose of anaesthetics (2970th s – 3030th s). Prior to the administration of anaesthetics, there was no “0.15 Hz rhythm” in these signals. Fig. 4 displays time series and TFD images for diastBP, systBP, HR, retN1, and IPP, immediately before, during and after administration of anaesthetics. Clear and pronounced oscillations in retN1 coincide with the emergence of the “0.15 Hz rhythm” in signals of the cardio-vascular system and the IPP.



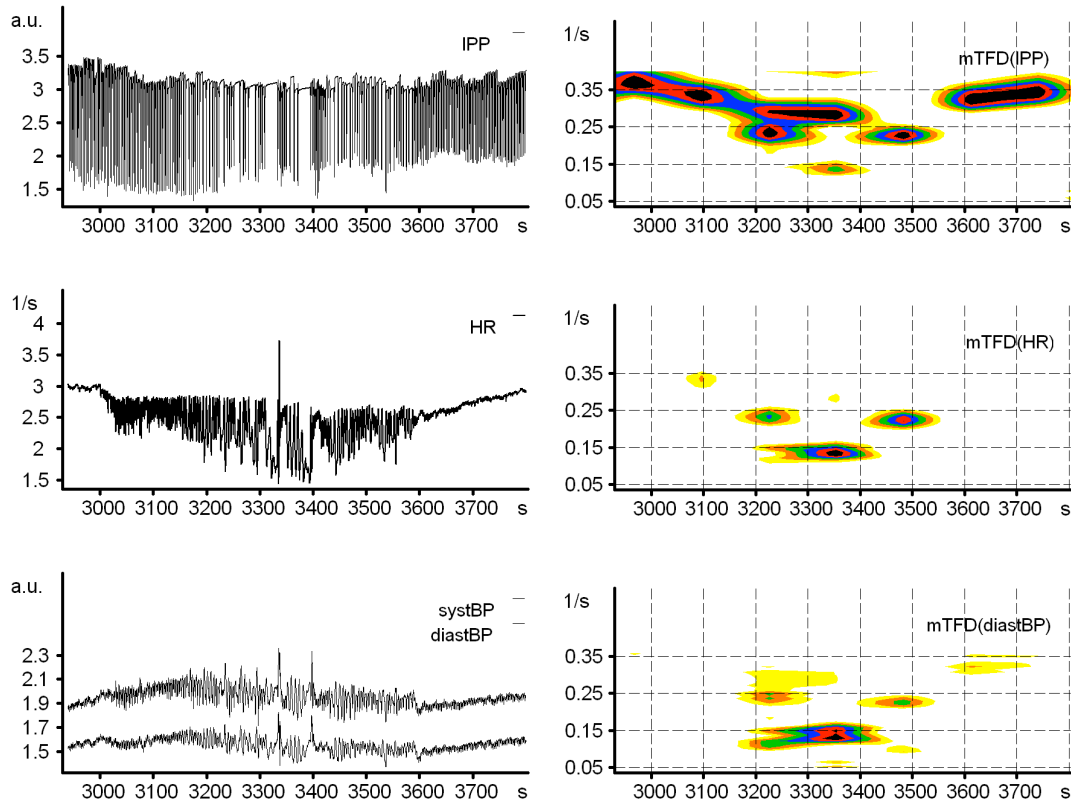


Fig. 4

Left column: Time series of intra pleural pressure (IPP), reticular neuron (retN1), heart rate (HR), and blood pressure (systBP, diastBP) immediately before, during and after administration of additional anaesthetics.

Right column: TFD analyses of time series shown in the left column. Clear emergence of the “0.15 Hz rhythm” in the TFD of retN1, the retR.

Colors in TFD’s see fig. 3.

A decline of the general basic activity (evidenced by left and right parieto-occipital EEGs, data not shown) was observed after the administration of anaesthetics. In fig. 4, a reduction of HR and retN1 is paralleled by increases in oscillations. This was also observed in retN2 and respF (data not shown). Blood pressure increased slightly after the 3000th until the 3200th s, but as HR clearly declined with a parallel increase in HRV, blood pressure waves were enhanced. As of the 3200th s, blood pressure steeply declined. Between the 3100th and the 3600th s, the respiratory frequency clearly declined, too, while there was a pronounced enhancement of oscillations. TFDs in fig. 4 give evidence that there was a solitary emergence of the “0.15 Hz rhythm” in retN1, the retR, and an emergence of this rhythm along with other components in all other signals. The emergence of the retR corresponded with enhanced rhythmic components in respiration (IPP). The interaction between retN1 and IPP was

analysed by filtering the retN1-activity (Gaussian band pass, 0.15 ± 0.03 Hz), and removing the DC-component of the IPP-signal. Signals resulting are displayed in fig 5, demonstrating an enhancement of the amplitudes of spindle shaped oscillations in retN1 between the 3150th and the 3600th s, which was paralleled by a reduction in respiratory frequency. The respiratory rhythm was clearly coupled with the retR as amplitudes in the activity of the reticular neurons were maximally enhanced (fig. not shown).

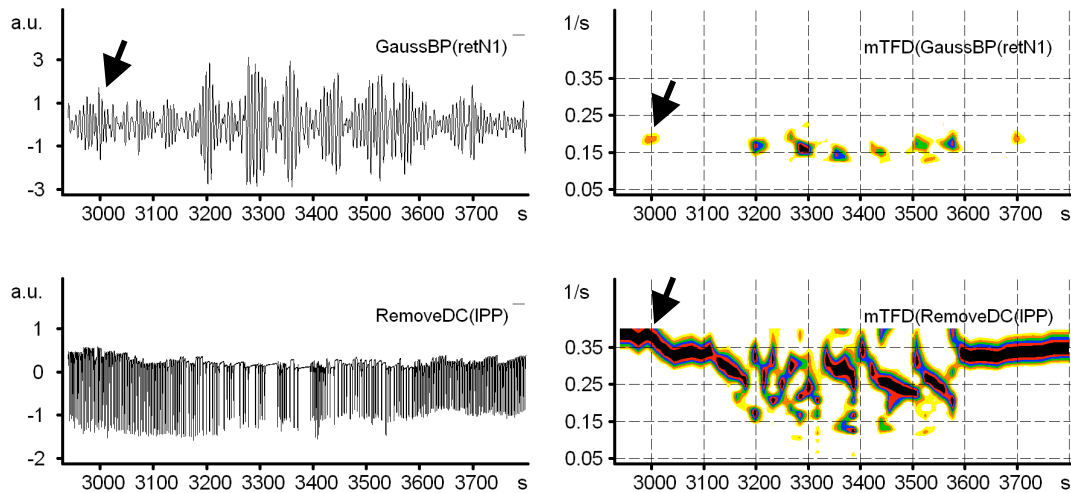


Fig. 5

Left column: Band pass filtered retN1 activity and the DC-removed IPP signal indicate coupling between both rhythms. Arrow marks time-point of first appearance of a spindle wave at the 3000th s.

Right column: TFD analyses of the signals in the left column. TFDs of both signals indicate that the respiratory rhythm tended to couple with the retR as the latter exhibited maximal amplitudes in the activity of retN1. Arrow marks time-point of first appearance of the retR in the reticular neuron at the 3000th s. This is accompanied by the decline in the frequency of respiration.

Colors in TFD's see fig. 3.

After the 3100th s, we observed enhanced oscillations in retN1 which were accompanied with phase coordination at 1:2- and 1:1-coupling ratios between retR and respiration.

High resolution TFDs (fig. 5) computed from band pass filtered reticular and IPP signals supplied evidence that the retR appeared in retN1 and retN2 (not shown) after the 3000th s due to administration of anaesthetics, accompanied by a simultaneous decline of respiratory frequency. After the 3200th s, the retR appeared more clearly in retN1, starting the coordination between the retR and respiration, the consequences of which are clearly visible

in the TFD image of the IPP-signal until the 3600th s, i.e. the TFD of IPP exhibits local amplitude maxima at ca. 0.15 Hz (fig. 5, right bottom) which precisely match with those observed in the TFD of retN1 (fig. 5, right top). Fig. 6 shows the Pointwise Transinformation (PTI) of the band pass filtered retN1 vs. IPP, HR, and diastBP. PTIs demonstrate that (linear and nonlinear) coupling between the reticular neuronal activity and respiration as well as between reticular activity and the cardiovascular system depended on the strength of the retR in the reticular activity. As amplitudes of the retR spindles in retN1 became maximal (between approx. 3200th and 3600th s), coupling (indicated by the transinformation) was clearly enhanced.

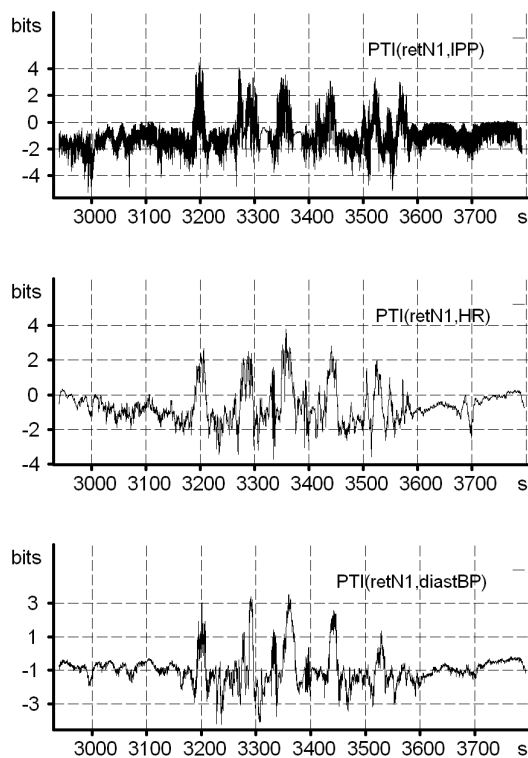


Fig. 6: Pointwise Transinformation (PTI) of band pass filtered retN1 vs. IPP, HR and diastBP, indicating that the coupling between reticular activity and respiration on the one hand and between reticular activity and the cardiovascular system on the other hand was clearly enhanced as amplitudes of the retR spindles in retN1 activity became maximal.

Parameters for computation of PTIs:

PTI(retN1, IPP): $\tau = 10$, $m = 9$ $r = 0.4$;

PTI(retN1, HR): $\tau = 12$, $m = 6$ $r = 0.3$;

PTI(retN1, systBP): $\tau = 13$, $m = 4$ $r = 0.2$. For further explanation see text.

Discussion

The results presented in this communication were obtained by non-invasively recording cardiovascular time series in man and by invasively recorded neuronal and cardiovascular time series in a canine experiment. In both experimental sets, we were able to detect a rhythm in the range of ca. 0.15 Hz. This rhythm was scrutinized and the observed phenomena were interpreted with the aid of non-linear analysis.

To the best of our knowledge, there are no previous reports on the drive dependent emergence of the “0.15 Hz rhythm” in man, as elaborated by us recently (27,39). While some influence of respiratory activity has been demonstrated (2), few investigations on the physiological nature of this phenomenon reaching beyond phenomenological description have only recently been published (3,4,40).

The findings in our test person suggest three conclusions of physiological relevance:

- psychomotor drive reduction stabilizes an easily detectable rhythm in cutaneous forehead blood content, the “0.15 Hz rhythm”;
- the “0.15 Hz rhythm” appears to varying extents in the cardio-vascular-respiratory system;
- in response to AT triggered mentally induced psychomotor relaxation the “0.15 Hz rhythm” elicits temporary phase synchronization with respiration at an integer number ratio 1:1.

The emergence of the “0.15 Hz rhythm” during psychomotor drive reduction in the present findings is in keeping with results reported by us previously. We recently demonstrated significant chronic effects of an auto-suggestive relaxation technique, the autogenic training (AT) as a naturalistic study design, on the dynamics of the emergence of the “0.15 Hz rhythm” which was clearly facilitated as AT trained individuals reduced sensomotor input by

closing their eyes, a step regularly taken when performing AT (5,27,28,39). It is noteworthy that the emergence of the “0.15 Hz rhythm” was also observed in man in response to pharmacological drive reduction, namely anesthesia (6,41). Other authors recognized the obvious difference of these regular flux waves between forehead and ear skin microcirculation with that of other skin regions, but considered this phenomenon solely being a reflection of local myogenic arteriolar vasomotion (2,42-44). Support for the notion of the “0.15 Hz rhythm” as an independent physiological process comes from findings that the “0.15 Hz rhythm” in the forehead skin emerged first during non-oscillating arterial blood flow, and, second was independent from slower oscillations at the finger at 0.07 Hz (41). Thus, recent research supplied evidence of specific parasympathetic innervation of facial skin microcirculation (45), with further evidence being supplied by psychophysiological and clinical studies demonstrating the existence of prominent parasympathetic innervation of the forehead skin vasculature (e.g. 46). This parasympathetic contribution for the emergence of the “0.15 Hz rhythm” in the forehead skin vasculature was recently shown to be facilitated by parasympathetic activation, since it was inhibited by atropine infusion (4,40).

As for the comparison canine – man, the most important similarities are:

- frequencies of these rhythms are widely similar in man and in canine;
- rhythms in the 0.15 Hz range emerge during a declining activity or a low overall activity level of the organism;
- this rhythm emerges between slow circulation rhythms and the rhythms of respiration;
- respiratory rhythms and slow circulation rhythms exhibit varying phase- and frequency coupling with the “0.15 Hz rhythm”;
- amplitudes of the “0.15 Hz rhythm” are subdued to slow modulations (spindle waves).

The obvious similarities of rhythmic phenomena, the “0.15 Hz rhythm” in man and the retR in canine suggest common, identical neurophysiological mechanisms. Many authors have observed and described such rhythms in RF neurons using animal experiments (8-11,47-50). Since the RF of the brainstem is involved in the regulation and coordination of important basic functions of the organism – e.g. respiration, cardiovascular system, sensomotor activity, and brain functions – (see e.g. 12,13,22,23,51), phenomena observed in RF neurons can be expected to also surface in these effector systems. This is apparent in the canine experiment presented, where the activity of RF neurons declined in response to the additional administration of anaesthetics, causing a reduction of the basic activity of the organism. This is evidenced by the emergence of the retR and the enhancement of rhythmic phenomena in time series of respiration and the cardiovascular system.

Properties of the retR have been thoroughly studied and published (8-14), the most important of which are:

- a decline of discharge rates regularly precedes the emergence of the retR in CBS neurons of the RF, and an increase in neuronal discharge rates follows the submergence of the retR. Decreases of the neuronal activity level occur spontaneously, i.e. in the absence of experimental manipulations, but also in response to e.g. activation of inhibitory baroreceptors, lung stretch receptors, repeated administration of anesthetics, or even upon termination of activating interventions with discharge rates of neurons declining due to the body's own counter-regulation. The latter can be observed e.g. after terminating stimulation of arterial chemoreceptors, or after terminating adequate activation of somato-sensitive receptors in skin, muscles, or joints by simple tactile inputs.
- the retR in CBS neurons exhibits prominent fluctuations of frequency and amplitude with increases and decreases of amplitudes, so-called spindle waves, waxing and waning.

- phase and frequency coupling between retR and the rhythm of respiration vary over time, following the phenomenon of “relative coordination” described by Erich von Holst (52), with complete dissociation on the one side, and a fixed 1:1 coupling of rhythms on the other side which may be later dissociating, too.
- the emergence of the retR in CBS neurons is associated with a decline of the basic activity of the organism, as evidenced by a reduction of heart rate, blood pressure, respiratory frequency, as well as a decline in cortical basic activity.
- modulations in the retR of heart rate, blood pressure, and EEG are most prominent during times of temporary phase- and frequency coordination between the retR and respiratory rhythms.

Owing to Langhorst and co-workers, the origin of the retR is likely to be the CBS. Support for this notion comes from their observation that in a variety of brainstem neurons investigated those of the reticular formation displayed this rhythm most frequently (11). Further, these authors observed the emergence of the retR in RF neurons to be constantly associated with a low activity level in these neurons. This did not depend whether the decline in general activity, as in the example chosen, was triggered by additional administration of anaesthetics, by e.g. activation of baroreceptors, or whether it occurred spontaneously in the absence of experimental interventions. Visceral, as well as somato-sensitive afferents can modify the level of activity of these reticular neurons, just as descending inputs from higher brain structures (s. also e.g. 15-17,24,25,50,53²-55). Activation of baroreceptors generally reduces (anti-ergotropic) the activation level of the organism (15,16,20,54), e.g. a process known to

² Quotation of p. 48: “... that much is known with regard to the activation of the ergotropic system that afferents from exteroceptive receptors play a crucial role. Dominating are acoustical inputs which are known to be effective of transferring those asleep from a state of passivity to an active state of wakefulness. The effect of light stimuli cannot be underestimated, also that of epicritical pain sensation. [...] In higher vertebrae, certain [...] cortically organised excitations contribute a not irrelevant ergotropic effect. ...

induce sleep (56), while activation of chemoreceptors and somato-sensitive afferents generally activates (anti-trophotropic effect, see 15,16,20). During inspiration, excitation of pulmonary stretch receptors are known to reduce the activity of these CBS-neurons (15,16,24,25), a fact which helps explain the phenomena observed during AT in our test person. The inhibitory effect of baroreceptors during expiration and respiratory pauses, however, is distinctly stronger as during inspiration (57). During these phases, muscle tone and tendon reflexes are considerably reduced (see also discussion in 58). Hence, any exercises intended to trigger relaxation will be particularly effective if extending expiration phases and respiratory pauses (respiratory feedback, e.g. 59-61). The implication these neurophysiological observations have for our results in man will be discussed below.

Depending on the level of activation of RF-neurons, Langhorst and co-workers observed several basic forms of functional organization in the CBS at different types of discharge coupling between reticular neurons (15,17,18). At a medium level of activation, dynamically organized local subpopulations³ of activated neurons with tight synchronizations of spike discharges (i.e. at maximum lags of ± 5 ms) evolve. There is reason to assume this mode of organization be caused by common input from somato-sensitive afferents to these neurons (17) due to widely overlapping dendritic areas in adjacent reticular neurons (see e.g. 23,50). Changing any given constellation of these inputs effects the discharge couplings of the neurons and thereby changes this organization. Therefore, this *dynamic adaptation* has to be considered an essential mechanism governing the functional organization of the CBS.

Lowering the medium level of activation of the CBS caused a disintegration of spike discharge synchronization. Under these conditions, neurons in general tended to exhibit lower frequency spike discharges, while discharge pauses were extended causing rhythmic

³ In the literature, such neuronal subpopulations are also designated by other authors as “transient neuronal assemblies” (see e.g. 62,63). In this publication, we prefer the term „dynamically organized neuronal subpopulations“ used in our publications as of 1980.

discharges in neurons of the entire network. As these neurons rhythmically discharged at different frequencies, they became eventually synchronised (11) which effected even spatially distanced neurons, suggesting an increasingly uniform rhythmic organization of the entire CBS (9,10 [see Fig. 3]). Under these circumstances, amplitudes of those rhythms were amplified resulting typical spindle waves in the RF neuronal activities, a characteristic which is evidenced by the dominating retR in the example shown (see also 9 [Figs 2 and 6]).

Accordingly, increasing the discharge level is of opposite effects generating conditions for a distinct differentiation of the functional CBS organization. Under these conditions, the stable synchronisation of discharge coupling in adjacent neurons increased as the rhythmic neuronal discharges started to decline. This allows to conclude that despite emerging oscillations within the reticular formation, there are no distinct oscillators in the classical (technical) sense. Rather, oscillations emerge diffusely in the entire network. This notion is corroborated by findings of Langhorst and Werz (64). These authors described that activation of baroreceptors by experimental increases of blood pressure caused discharge rates of reticular neurons to decline with a lag of a minimum of three seconds, while the increase in neuronal activities after normalisation of blood pressure occurred with a lag of a minimum of four seconds. This resulted the time span of a complete activity cycle of the retR. This assumption is plausible since all CBS-neurons are effected by baroreceptor afferents (15,16). As early as 1957, Hess mentioned that brainstem stimulation lead to “pronounced changes in the amplitude of mentioned motor effects” after 6 to 10 s, which he considered to be an expression of increasing spread of excitation at similar time courses within the reticular formation. Frequencies of oscillations in the RF at preferably approx. 0.15 Hz precisely match this temporal frame. Hence, this rhythm apparently constitutes an essential property of networks which possess only few structural differences between species, and therefore also between man and canine (23).

An increase in the amplitudes of the retR apparently increased the synchronisation of respiratory and cardiovascular rhythms, with phase- and frequency coordination according to the phenomenon of “relative coordination” (52). Also, n:m-phase synchronization between retR, respiratory rhythm, and circulation rhythms was frequently observed under these conditions. Synchronisation effects, e.g. in blood pressure and heart rate, caused an enhancement of amplitudes either in the various basic frequencies and/or in their lower and upper harmonics. There were clear synchronisation effects of the retR at various upper harmonic frequencies with variations of the faster rhythm, that of respiration. Simultaneously, there was also an evident synchronization at its lower harmonic waves with the slower circulation rhythms in the 0.1 Hz band (see also e.g. Fig 5 in 9). When interacting with the rhythms of respiration and circulation, the retR dominated all other rhythms entraining the harmonics in all three rhythms, a phenomenon suggestive of a coordination process located within the reticular formation. This notion is in keeping with that put forward by Golenhofen and Hildebrandt (65) and Koepchen (66) regarding the coupling between the respiration rhythm and the 0.1 Hz rhythm in blood pressure (or rhythms of perfusion). Their experimental results produced evidence of this coupling following mechanisms of “relative coordination” (52) to be clearly attributed to central nervous interactions. In summary, during the state of declined level of activity, with clearly reduced demands by regulation and coordination processes, the network increasingly tends to oscillate at similar frequencies which are being increasingly synchronised as they spread in the entire network (11).

With respect to these considerations on our results obtained in the canine experiment, the following explanation for the phenomena observed in the test person is suggested:

Based on the mentally induced mediation, the effects of baroreceptor afferents, i.e. a reduction of general activity, is increased in situations, such as during calm breathing, one imagery typical of AT. Though this respiration related imagery used with AT does not specify for the

phases of respiration, evidence for a general drive reduction at the onset of AT comes from our result that the respiration frequency declined abruptly to the “0.15 Hz rhythm” without externally triggering this frequency. The decrease of the activity level in the CBS causes a reduction of the basic activation of cortical structures, of muscle tone, further reducing the frequency of respiration. Also, by taking a restful position excitatory effects of somato-sensitive receptors are being additionally reduced, thereby amplifying the activity reduction within the CBS. Due to this reduced activation mediated by somato-sensitive afferents, the number of synchronous discharges in adjacent neurons in the CBS will also decline, leading to a reduction in the formation of CBS-subpopulations. Therefore, internal CBS effects, i.e. influences of CBS-neurons upon other CBS-neurons, may dominate the activity in this network. These internal coupling effects on neuronal activities are comparably weak when compared to the stronger coupling effects exerted by activated somato-sensitive afferents. But as strictly synchronised couplings of discharges are being reduced, weaker couplings become increasingly effective over a wide range within the network as a growing number of neurons of the CBS are triggered to rhythmically coupled discharge patterns.

Spindle waves were also readily apparent in PPG-signals of our test person (see fig. 2C), under conditions of triggered, as well as naïve relaxation (see also 5,27,39). Spindle waves in man may be governed by identical mechanisms mentioned above for the amplitude modulations in CBS neurons. The contribution of parasympathetic activation for the generation of spindle waves or wave-epochs as significant markers of the “0.15 Hz rhythm” in the forehead skin vasculature were recently shown to be inhibited by atropine infusion (4,44). In the time series of IBI, as well as in the time series of arterial blood pressure fluctuations (data not shown), spindle waves emerged at the onset of AT, causing an amplification of the “0.15 Hz rhythm”. Amplification of the “0.15 Hz rhythm” during such wave-epochs,

however, resulted in an extension of the duration of phase synchronization (see figs. 2C, 2E, resp., and other unpublished experiments).

Investigations on test persons using controlled different respiration frequencies demonstrated that within the typical frequency range of the retR (as observed in animal experiments) relaxed test persons also exhibited amplified modulations of heart rate, blood pressure (9), and electrodermal activity (67,68). The same rhythmical effects were described for slow eye movements during sleep onset (69,70). Thus, also in man the influence on effector systems (e.g. circulation) is maximised if oscillations of respiration and the retR are synchronised. Under spontaneous conditions, in naively relaxing test persons in a supine position, the modulation effect in heart rate and blood pressure was also almost maximal. The spontaneously occurring respiratory frequency was then established at the frequency of the retR in the “0.15 Hz rhythm” which resulted in the phenomenon quoted above by Schmid-Schönbein and co-workers (71).

The results presented in the discussions in relation to the results of many other authors are in support and of the notion that both rhythms – the retR as investigated in animal experiments and the “0.15 Hz rhythm” described in man – both apparently originate in the network of the RF of the brainstem. Rhythmic phenomena result under identical conditions of low basic activity as the organism is taking a trophotropic functional direction. Complex dimensions like ergotropy and trophotropy, or sympathetic and parasympathetic arousal, however, need to be comprehended in order to gain insight into such complex functions as the coordination processes within the autonomic nervous system, as has been discussed by Moser et al. (72). In terms of synergetics (73), phenomena such as the “0.15 Hz rhythm” are known as “phase transition” or “order-order transition”. They have been scrutinized in a wide array of scientific

disciplines (e.g. 74,75). Here, a “phase transition” or “order-order transition” sets in with the activity level of CBS-neurons taking the role of an “order parameter”. Transitions of this kind are suggested to be displaced far from thermodynamic equilibrium as a manifestation of “drive dependent coordination” (71).

These transitions to rhythmic CBS-activity can be observed after administration of anaesthetics (see 6) as well as spontaneously. There are no obvious differences between the rhythmic phenomena in both species as far as the patterns of spindle activity and their coordination with respiration and circulation rhythms are concerned.

From the point of view of these authors it therefore stands to reason to assume that the rhythmic activity in the “0.15 Hz rhythm” enhances the function of a somato-visceral coordination if a trophotropic functional direction is taken allowing the organism to rest and relax.

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