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Heart rate dynamics and cardiorespiratory coordination in diabetic and breast cancer patients

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Short title:
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Summary

Objective of this study was to evaluate cardiac autonomic function in female breast cancer patients on the basis of linear and nonlinear heart rate variability (HRV) as well as on musical heart rate rhythmicity. The latter method has been recently developed and enables particularly the quantification of cardiorespiratory coordination solely on the basis of ECG recordings. To provide a broad basis of comparability, 37 breast cancer patients were compared with 37 age-matched healthy women and 40 age-matched female diabetic patients who serve as pathological controls. During night sleep, all parameters showed a tendency towards lower variability, complexity, or rhythmicity of HRV in cancer patients. The most prominent alterations were found for the binary pattern predominance and for the ratio of heart rate and respiration. In particular, when comparing metastasized and non-metastasized cancer patients, the discriminatory power of binary heart rate rhythmicity emerges: the histograms of one-hour intervals during night sleep with a predominance of cyclically recurrent phase locking patterns unveiled a clear transition from higher to lower cardiorespiratory coordination ratios and to a loss of coordination capability in metastasized patients.

Keywords

heart rate variability, approximate entropy, musical rhythmicity, cardiorespiratory synchronization, nonlinear dynamics, vegetative function

Introduction

Analysis of heart rate variability (HRV) has been widely used to approach cardiovascular autonomic control, and to provide parameters for the quantification of vegetative function in man. Most of the HRV methods were adopted from linear time series analysis which characterize heart rate dynamics in the time and frequency domain. Moreover, as a result of extensive research, particularly in the field of linear HRV analysis, a 'standardization of measurement, physiological interpretation, and clinical use' could be achieved (Task Force, 1996). Nevertheless, it is well accepted that linear methods gain only very limited access to the complexity of autonomic control. Nonlinear methods seem to be more appropriate, and at least, they are much more intriguing. Consequently, a wide spectrum of methods has been developed to quantify the complexity, the irregularity, the dimensionality, etc. of heart rate dynamics. Unfortunately, coherence in heart rate complexity research is poor, and guidelines for the use of complexity measures in diagnostics and prognostics of diseases related to regulatory dysfunction are still lacking.

In previous studies, we had the opportunity to expand classical heart rate analysis methods by techniques which explicitly take complex musical rhythm principles into consideration (Bettermann et al., 1999, 2000). The methods used are based on ethnomusicology with a main focus on some compositional principles of African Music, on the theory of symbolic dynamics, which has its origin in nonlinear dynamical system theory, and on combinatorial theory which helps classifying symbolic heartbeat rhythms. Therefore, it is truly interdisciplinary and complementary, and it does not fit into any category like 'linear' or 'nonlinear' time series analysis.

One goal of the present study was to examine how 'musical' heart rate rhythmicity, induced by cardiorespiratory coordination, differs in various groups of patients for which differences in autonomic control *per se* should be expected. Having the lack of comparability between the different complexity measures in mind, we felt also the necessity to compare the results from our algorithms with at least one method of both linear and nonlinear time series analysis. To this end we chose the low and high frequency power (*LF* and *HF*) of the FFT based HRV spectrum as linear representative, and the approximate entropy (*ApEn*) as the best established (nonlinear) measure of heart rate complexity or irregularity (Pincus, 2000).

A second important objective of the study was to evaluate autonomic regulatory dysfunction in female breast cancer patients in comparison with two age (and gender) matched control groups. As far as we know the relationship between autonomic cardiac function and cancer using the methods of HRV analysis has not yet been reported, although already in 1954 Clemens (cited in Wenger, 1966) showed an ergotropic or sympathetic predominance of autonomic tone in cancer patients applying the methods of his time. Vegetative dysregulation in cancer had been assumed in the last decades but study data are rare and the few results are even contradictory (Zinnitz & Bergner, 1961; Trageser, 1986). This study is the second study in a series of studies investigating parameters, related to vegetative function, circadian phase position, constitution and quality of life in breast cancer patients (Kröz et al., 2000a), which have been designed to corroborate clinical experience. In addition to a healthy control group, women with diabetes mellitus were included as pathological controls to provide a broad basis of compa-

rability. For the latter a reduction of HRV, mainly as a result of autonomic neuropathy, is well described in literature (see references in Task Force, 1996).

Methods

[insert Table 1 here]

2.1 Subjects

The observational study was carried out at the Gemeinschaftskrankenhaus Havelhöhe from March 1998 to August 1999. A total of 158 women were included in the study: 52 with breast cancer (group B), 53 age-matched women with diabetes mellitus (type 1 and 2, group D), and 53 age-matched healthy women as control (group C). All subjects gave their informed written consent. Breast cancer patients with a Karnofsky-index with at least 50% were included if they had no radiation or chemotherapy for at least 3 months and no operation for at least 1 week before recording. Alcohol consumption was not allowed at least 24 h before ECG recording. As no further clinical exclusion criteria were defined, patient groups became very inhomogeneous, particularly regarding diagnosis of autonomic neuropathy, medication and time interval from major surgery (see Table 1 for detailed clinical data). Moreover, 28% of the women had to be excluded because of missing ECG data: Ten women rejected ECG recording after inclusion, 12 ECGs could not be analyzed because of technical problems during recording, 18 ECG data records got lost because of a hard disk damage, and post-operative scar pain caused 4 breast cancer patients to remove ECG electrodes during recording. Therefore, only 114 women (37 in B, 40 in D, 37 in C) finally remained in the study. Eleven of the 37 breast cancer patients had metastases (subgroup B1). Metastasized patients were 10 years older on average than non-metastasized patients (subgroup B0).

2.2 Data recording

Oxford FD3 solid state recorders with simultaneous R wave detection were used for the 24-h ECG registration which were recorded once in all subjects. Visual inspection of the automatically detected R waves was performed on an Oxford Excel ECG-Analyzer. The R times of all beats were written to a binary data file which was then exported to a Pentium PC for further analysis.

All heart rate parameters, which are described below, were calculated with C and Matlab routines for each 10-min interval of the day, resulting in maximally 144 values. To reduce information, taking the circadian variations of cardiac activity into account, the mean values between 5 a.m. and 1 a.m. (daytime values) and between 1 a.m. and 5 a.m. (night-time values) were calculated. These parameters were labeled ‘d’ and ‘n’, respectively.

2.3 Heart rate variability (linear analysis)

A Fast Fourier Transformation (FFT) based spectral analysis of HRV was performed for each 10-min interval of the day. The resulting spectral power density function was integrated in the low frequency band (0.04-0.15 Hz) and the high frequency band (0.15-0.40 Hz). Low and high frequency power (*LF*, *HF*) were computed in milliseconds such that

they correspond to the standard deviation of the LF and HF band-passed RR tachogram (times between R waves in milliseconds). *LF* and *HF* were not log-transformed. Furthermore the balance $BAL = LF / HF$ and the mean RR interval (*RR*) were calculated. The spectral analysis was performed according to the methods of Rottman et al. (1990) and is described in detail elsewhere (Bettermann et al., 1997).

2.4 Heart rate irregularity (nonlinear analysis)

The approximate entropy (*ApEn*) was introduced by Pincus (1991) to quantify serial irregularity, i.e. the 'extent of randomness' in sequences or time series (Pincus, 2000). One important feature of *ApEn* is that it is model-independent and no constraint delimits the length of the series under consideration. Although the theoretical basis of the method is broad and mathematical details complicated, the central idea of the method is straightforward and can be verbalized in only one sentence: *ApEn(m,r)* measures 'the negative logarithmic likelihood that runs of patterns that are close (within tolerance r) for $k - 1$ observations remain close on the next incremental comparison' (Pincus, 2000).

Practically, when analyzing heart period sequences, for each m-dimensional vector (or pattern) of successive RR intervals all vectors in the r-neighborhood (e.g. within an Euclidean state space distance $< r$) have to be found. Then, incremental comparison is carried out by increasing the number of vector components by one and comparing the distances of previously neighbored vectors. Finally, some trivial computations lead to the values of *ApEn* and to the associated quantification strategy of RR regularity: low values indicate serial regularity, and large values imply irregularity or randomness in RR tachograms. For further details and computing algorithms the reader is referred to the relevant literature (Bettermann & Van Leeuwen, 1998; Pincus, 2000).

2.5 Heart rate rhythmicity (musical analysis) and cardiorespiratory coordination

Binary coding or symbolization of RR differences enables a simple form of percussive musical interpretation of essential heart rate dynamics (Bettermann et al., 1999, 2000). Binary coding works as follows: RR differences < 0 are marked with 1 which corresponds to an acceleration of the heartbeat; RR differences ≥ 0 are marked with 0 which corresponds to a deceleration of the heartbeat (see also Schäfer et al., 1995). If the resulting series of 1s and 0s is interpreted as percussive pattern, e.g. as strokes and rests or as strokes on two different drums, musical impression follows instantly. Moreover, from the music point of view, the analysis of musical rhythmicity and rhythmical complexity (Essens, 1995) seems to be crucial.

In our approach, we use a classification scheme, originally developed to classify timeline rhythms in the music of Afro-American origin (Dauer, 1988). In short, this method follows two purposes: (i) to search for statistically predominant binary (percussive) pattern classes in differential heart rate dynamics, and (ii) to judge pattern classes as musically significant or predominant, if the corresponding patterns occur very often and cyclically recurrent. In this sense, rhythm or rhythmicity is regarded as what it basically is: the cyclic repetition of similar patterns in time or space (see discussion in Bettermann et al., 2000).

In our previous studies we were able to show that primarily intermittent cardiorespiratory coordination leads to the above described musical rhythmization of differential heart rate dynamics, i.e. to high predominance and cyclical stability of so-called phase locking patterns. Consequently, the analysis of musical heart rate rhythmicity has been

proposed to approach synchronization phenomena of heartbeat and respiration over a longer period of time particularly during night sleep, because this technique requires *only ECG recordings* and do not depend on costly and bothering respiratory flow measurements.

In the above mentioned context, two different aspects of musical rhythmicity are considered in this study. The first one is the evaluation of the pattern predominance (*PP*). This parameter corresponds to the contrast in the frequency distribution of pattern class occurrence, i.e. it quantifies to what extent some of the patterns disappear, whereas other patterns occur much more frequently than would be expected in equally distributed random symbol sequences (corresponding to a random walk RR tachogram). In this study *PP* has been evaluated for each 1-h interval of the day. The second aspect also considers the cyclical stability of the patterns. The algorithm identifies phase locking pattern classes that are both, twice as much frequent than pattern classes in a random walk RR tachogram, and cyclically recurrent over two heartbeats on average. The latter condition means that, when moving a window in equidistant steps of one heartbeat over the binary sequence, the classes, which appear within the window, must be the same over two steps on average. This technique results in a table that displays the number of 1-h intervals with a predominance of cyclically recurrent phase locking patterns. And it results also in the weighted phase coordination ratio (*PCR*) which weights the 'locking ratios' of the phase locking pattern classes (except the 2:1 ratios) according to the frequency of their hourly predominance; e.g. if $n(4{:}1) = 30\%$ and $n(7{:}2) = 20\%$ then $PCR = (30 \cdot 4 + 20 \cdot 3.5)/50 = 3.8$.

A third technique to detect long-term coordination processes of heartbeat and respiration is simply to evaluate their frequency ratio *PRQ* (pulse respiration quotient). This method has been extensively used in chronobiology (Heckmann et al., 1990; Moser et al., 1995). It has to be noted that, although mean frequency ratios cannot be used to reveal phase or frequency locking between different oscillators, their computation can give evidence of long-term entrainment processes caused by coupling mechanisms. The *PRQ* can reliably be computed from 24-h ECG with the help of the respiratory rate detection method (Bettermann et al., 1996, 2000) on the basis of quantitative evaluation of respiratory sinus arrhythmia (RSA). Here *PRQ* is defined as the average ratio of the momentary RSA cycle length and the mean RR interval during the respective RSA cycle. As could be shown in a previous study, *PRQ* correlates strongly with *PCR* in healthy individual subjects (Bettermann et al., 2000).

Both methods, the identification of binary phase locking pattern classes and the evaluation of *PRQ*, work under the assumption that RSA is dominant, i.e. RSA should be larger than other regular heart rate fluctuations. Most probably this condition is met during night sleep. Thus, in the following above all nighttime statistics are presented and discussed.

2.6 Statistics

The statistical methods used in this paper are descriptive. Box plots are used for visualization and p-values of the Mann-Whitney U-test are calculated for the descriptive classification of group differences. Two subgroups of breast cancer patients are also considered: the metastasized (B1) and the non-metastasized patients (B0). Because of significant age differences between these subgroups, age-adjustment for all parameters was performed when comparing B1 with B0. Age-adjusted parameters are labeled with '+'. Statistical analysis was carried out with Matlab 5.3.

Results

[insert Table 2 here]

[insert Table 3 here]

The main results for all dynamical parameters are summarized in Tables 2 and 3, respectively. Between the main groups no parameter shows a tendency towards higher variability, complexity, or rhythmicity of heart rate in diabetic and breast cancer patients, but many parameters clearly indicate the opposite. Particularly mean and median values of *PPn* differ noticeably (see Fig. 1). *PPn* is the only parameter which provides p-values below the level of statistical significance ($p < 0.05$, between C and B). Classical HRV parameters (*LF, HF, BAL*) and also the complexity analysis failed to discriminate the three main groups.

[insert Fig. 1 here]

[insert Fig. 2 here]

[insert Fig. 3 here]

The differences between the two subgroups of metastasized (B1) and non-metastasized (B0) patients are much larger. All age-adjusted parameters indicate clearly lower variability, complexity, and rhythmicity of heart rate dynamics in B1. Thus, reduced autonomic control is evident, although, because of the small B1 group size ($N = 11$), p-values are relatively high. The best group separation was found for *PRQ* during daytime and nighttime (see Fig. 2) which suggests a qualitative change of cardiorespiratory coordination from higher to lower coordination ratios particularly in metastasized patients.

Figure 3 displays the percentage histograms of 1-h intervals during night sleep (from 1 a.m. to 5 a.m.) with a predominance of cyclically recurrent phase locking patterns. The quotients identify the pattern classes that are linked with the corresponding cardiorespiratory coordination ratio (heartbeats vs. respiratory cycles). In many one-hour intervals the coordination ratio switched frequently (e.g. from 9:2 to 4:1 and vice versa), thus two or more phase locking pattern classes could be predominant simultaneously.

The diagram demonstrates the reason for lower *PRQ* values in both patient groups (see Tab. 2). Relevant phase locking pattern classes with ratios greater than 4:1 were significantly less predominant and/or cyclically stable. From C to D and from C to B a reduction of about 50% and 75%, respectively, can be observed for both the 9:2 and the 5:1 phase locking pattern class, whereas the predominance of the lower coordination ratios remained unchanged. Surprisingly, this effect was much larger for the cancer group than for the diabetic group. When comparing B and C, it is striking that in B the 9:2 and the 5:1 rhythms tended to disappear whereas the 3:1 and the 7:2 rhythms were even more pronounced, indicating a shift from higher to lower cardiorespiratory coordination ratios. The central 4:1 rhythms were affected least of all.

Also remarkably, in both patient groups the 2:1 rhythms increased considerably. These rhythms, which correspond to simply alternating 1s and 0s (101010...), do not really result from a 2:1 phase coordination process, but their existence indicates a high portion of noisy variability caused by a loss of autonomic control.

The transition from higher to lower coordination ratios and to a loss of coordination capability is even more pronounced when comparing the B0 and B1 subgroups of B. In comparison with healthy controls the non-metastasized women showed a clear reduction

of the 9:2 and 5:1 rhythms and even a slight augmentation of the 7:2 and the 4:1 rhythms (see Fig. 3). The clear reduction is also mirrored by *PPn* which is markedly lowered in B0 in comparison to C (mean 5.26 vs. 7.34, see tables). The 11 metastasized women differed noticeably. All coordination rhythms diminished drastically, and stochastic influences are rampant. In this case also the 3:1 rhythms (100100...) are probably due to stochastic fluctuations and seem to have their origin in regulatory dysfunction.

Discussion

In the past only few studies investigated the relationship between heart rate and cancer. Persky et al. (1981) and Wannamethee et al. (1993) reported that resting heart rate in men is an independent prognostic factor for cancer mortality. Mean heart rate level is linked with physical activity which may play an important role in lowering the risk to die of cancer. As far as we know, relationships between heart rate variability and cancer have only been reported analyzing the influence of paclitaxel chemotherapy (Ekholm et al., 2000) or of anthracycline treatment (Viniegra et al., 1990). On the other hand, a large number of studies can be found demonstrating that circadian physiological rhythms are altered in breast cancer: Touitou et al. (1995) showed that altered circadian variations of circulating blood cells counts, serum cortisol, CA15-3 and others are associated with poor prognosis in metastasized breast cancer. Circadian de-synchronization has been described for local breast skin temperature (Gautherie & Gros, 1977) and core temperature (von Laue & Henn, 1991). Indirect markers of autonomic function like subjective cold extremities and predominance of eveningness were used in two studies (Kröz et al., 2000a,b) and disclosed symptoms of ergotropic prevalence as well as a circadian phase shift of vegetative regulation in breast cancer patients for premorbid and morbid lifetime.

In this study a wide spectrum of methods was applied to analyze heart rate variability in breast cancer and in diabetic women as well as in age-matched healthy controls. Here, diabetic patients served as pathological controls for which well described classical HRV characteristics can be found in literature (see references in Task Force, 1996): in patients with diabetic autonomic neuropathy, besides tachycardia, low and high frequency spectral HRV power, when expressed in absolute units, were found to be significantly reduced during several experimental conditions; relative or normalized parameters are not effected. The present study did not confirm these findings: On the one hand, HRV was not determined during controlled conditions, a pre-condition which seems to be very important for an effective clinical application of HRV analysis and, on the other hand, many factors like medication, duration of illness and others (see Table 1) might have interfered with HRV parameters. Most important, 8 diabetic patients were treated with antiarrhythmic or heart rate lowering drugs which could have biased group parameters towards higher variability and complexity. The inhomogeneity of the diabetes group was also the reason for omitting diabetic subgroup statistics. However, focusing on HRV in diabetes mellitus was not a topic in the present study either.

We were not surprised to find also virtually no differences of classical HRV and HR complexity parameters between cancer patients and healthy controls, because situation of data recording and homogeneity of the patient group were similar. Surprisingly, the group differences regarding heart rate's musical rhythmicity were larger. *PP* has been

shown to discriminate the cancer and the control group with $p = 0.017$ during night sleep, and a loss of rhythmicity seems to be evident. However, the box plots in Fig. 1 demonstrate that, because of large inter-individual deviations in each group, specificity and sensitivity even of *PP* is low.

Much clearer are the results of the cardiorespiratory coordination analysis. The reduction of coordination processes with higher locking or coordination ratios during night sleep in cancer and in diabetic patients is striking and needs no further statistical confirmation. The best parameter to quantify these effects is the weighted phase coordination ratio *PCR* that corresponds to the frequency ratio of pulse and respiration only during intermittent periods of apparent cardiorespiratory coordination. Therefore *PCR* is better suited to quantify coordination behavior than *PRQ*, because *PRQ* has been defined as the average frequency ratio over the entire time period under consideration, regardless of whether phase coordination is present or not. In a recent study it could be shown that both parameters correlate strongly in individual healthy subjects during night sleep (Bettermann et al., 2000), but it remained to be proven if this correlation holds in patients too. Although the correlation was not a matter of investigation, in this study, *PCR* reflected subtle differences of intermittent cardiorespiratory coordination between the main groups, whereas *PRQ* did not. For that reason, it must be concluded that *PCR* provides a deeper and different insight into cardiorespiratory coordination processes.

As a third and new parameter to quantify the loss of autonomic control we propose the relative number of one-hour intervals with cyclically recurrent and predominant '2:1 rhythms' which correspond to an alternating acceleration and deceleration of heartbeat. The percentage of these rhythm-predominated 1-h intervals was noticeably higher in diabetic and cancer patients, indicating an increasing portion of Gaussian fluctuations in heart rate. As demonstrated in recent work (Bettermann et al., 1999, 2000) the predominance e.g. of 10101010 patterns in Gaussian-distributed random RR tachograms is per se 5.6 times higher than in random walk RR tachograms where all pattern classes appear equally frequent. Thus, if these patterns are predominantly found in physiological data, normally distributed stochastic influences can be concluded.

The analysis of heart rate rhythmicity in breast cancer patients demonstrated its power when comparing metastasized with non-metastasized patients. Before adjustment for age, all parameters of heart rate dynamics illustrated huge group differences between the two subgroups (data not presented here). Due to high correlation with age this disparity diminished after age-adjustment. Nevertheless, *PRQ* (see Fig. 2) and the group's weighted phase coordination ratio *PCR* (see Fig. 3) remained very good subgroup discriminators during night sleep. Together with the histograms of Figure 3 these parameters unveiled a loss of coordination capability and a transition from higher to lower cardiorespiratory coordination ratios particularly in metastasized cancer patients.

The well-known HRV reduction e.g. in coronary artery disease and in diabetes is commonly regarded as a result of myocardial dysfunction and arrhythmia, or autonomic neuropathy, respectively. In breast cancer cardiac dysfunction is much more seldom. In our study, only one patient had had a pericardial effusion of clinical importance before recording. In literature, symptomatic pericardial effusion is described in about 2% and asymptomatic pericardial alterations in 25% of all autopsy cases (Meuret, 1995). Therefore, asymptomatic pericardial alterations can not be excluded for these patients. Eight women had either pleural effusion or lung metastases (one with a significant clinical dyspnea). Thus, the observed alterations in cardiorespiratory interaction and heart rate rhythmicity could be because of disturbances in respiration or due to cardiac dysfunc-

tion. Surprisingly, we as well found a reduction of *PPn* and of higher coordination ratios in non-metastasized breast cancer patients, comparable with the reductions in diabetes. Therefore, also other factors must cause heart rate rhythmicity alterations in breast cancer, independently from the status of metastazation. Such factors could be: physical activity during daytime, staging and grading, operation and psychological factors like depression and anxiety. In this respect, it should also be mentioned that influences of sleep stages and quality of sleep were disregarded in this study which probably largely influence heart rate variability and rhythmicity during night sleep. Because of all these uncertainties, conclusions must be drawn very tentatively and only further extended investigations could gain insight into the pathophysiology of cardiorespiratory regulation in breast cancer patients.

In the clinical practice particularly the relationship between heart rate dynamics and cancer mortality could be important, and further studies are needed on this topic. Remembering the results of the early 'heart rate and cancer studies' (see above), and regarding the alterations found in heart rate rhythmicity between metastasized and non-metastasized breast cancer in this study, the questions arise: Do patients with higher coordination capability have a favorable prognosis? Is rhythm-coordination a sign of good physical condition and wellness? Furthermore, is it possible to improve prognosis of cancer by improving autonomic regulation? Indeed, these questions are very suggestive and speculative, but due to failing success in conventional anti-cancer therapy new questions must be asked and complementary methods are needed both in diagnosis and in therapy.

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Tables

Tab. 1 Basic group statistics; C: controls, D: diabetic patients, B: breast cancer patients; age, body mass index (BMI) and duration of illness as mean ± SD

	C	D	B
N	37	40	37
Age (yrs)	53±12	55±15	56±12
BMI	24±3	29±7	24±5
Premenopausal	12	16	13
Smokers	7	8	7
Autonomic neuropathy	–	14	–
Type 1 diabetes	–	11	–
Type 2 diabetes	–	29	–
Duration of illness (yrs)	–	15.5±9.2	2.4±4.8
Metastasized	–	–	11
1 – 4 weeks after surgery	–	–	12
≥ 4 weeks after surgery*	–	–	21
Antihormone therapy	–	–	13
Glibenclamide	–	7	–
ACE-inhibitors	–	14	–
Antiarrhythmic drugs	3	8	–
Theophylline	–	1	–
Female hormone therapy	1	1	–

*Four cancer patients had no surgery before recording

Tab. 2 Mean and standard deviation (SD) of heart rate parameters in main groups during daytime (_d) and during night sleep (_n).

	Mean			SD		
	C	D	B	C	D	B
RRd(ms)	759	764	759	94	88	73
RRn(ms)	895	893	873	111	120	119
LFd(ms)	24.8	22.3	23.3	8.9	10.4	10.2
LFn(ms)	24.1	23.0	20.7	11.5	12.0	9.2
HFd(ms)	16.7	16.4	16.8	6.9	7.9	8.7
HFn(ms)	19.2	20.0	17.1	8.8	12.6	11.4
BALd	1.73	1.59	1.69	0.41	0.50	0.45
BALn	1.37	1.35	1.47	0.39	0.49	0.51
ApEnd	0.37	0.33	0.33	0.09	0.12	0.12
ApEnn	0.41	0.39	0.38	0.11	0.15	0.14
PPd	3.85	3.62	3.28	1.85	2.10	1.30
PPn	7.34	5.48	5.02*	4.49	3.19	3.01
PRQd	4.59	4.31	4.56	0.95	0.97	0.93
PRQn	4.08	3.85	3.91	0.67	0.68	0.54

*$p < 0.05$, B vs. C

Tab. 3 Mean and standard deviation (SD) of age-adjusted (_+) heart rate parameters in metastasized (B1) and non-metastasized (B0) breast cancer patients

	Mean		SD	
	B0	B1	B0	B1
RRd+(ms)	760	755	68	85
RRn+(ms)	889	837	112	131
LFd+(ms)	24.3	20.8	10.1	9.3
LFn+(ms)	21.7	18.1	9.4	8.2
HFd+(ms)	17.3	15.7	8.7	8.8
HFn+(ms)	17.6	16.0	11.3	12.2
BALd+	1.71	1.65	0.45	0.39
BALn+	1.47	1.45	0.53	0.44
ApEnd+	0.34	0.30	0.10	0.12
ApEnn+	0.39	0.34	0.12	0.17
PPd+	3.45	2.89	1.47	0.71
PPn+	5.26	4.45	2.90	2.86
PRQd+	4.81	4.05*	0.95	0.37
PRQn+	4.04	3.67	0.57	0.39

*$p < 0.05$, B1 vs. B0

Figure legends

Fig. 1 Box and whisker plots to visualize the main group differences of the pattern predominance during daytime and during night sleep (*PPd*, *PPn*). pC-D and pC-B are the p-values from Mann-Whitney U-test between controls (C) and diabetics (D), and between controls and breast cancer patients (B) respectively (see also Table 2). The box plots display median and quartiles (horizontal lines), mean (star), maximum and minimum (whiskers), and outliers which are more than 1.5 times the interquartile range away from the top or the bottom of the box (plus signs).

Fig. 2 Box and whisker plots to visualize the subgroup differences of age-adjusted day- and nighttime pulse respiration quotient (*PRQd+*, *PRQn+*) in metastasized (B1) and non- metastasized (B0) breast cancer women (see also Table 3).

Fig. 3 Percentage histograms of one-hour intervals during night sleep (from 1 to 5 a.m.) with a predominance of cyclically recurrent phase locking patterns. The quotients on the horizontal axes identify the pattern classes which are linked with the corresponding cardiorespiratory phase coordination ratio (heartbeats vs. respiratory cycles). *PCR* is the group's weighted phase coordination ratio (see methods section for further details).

Figure 1

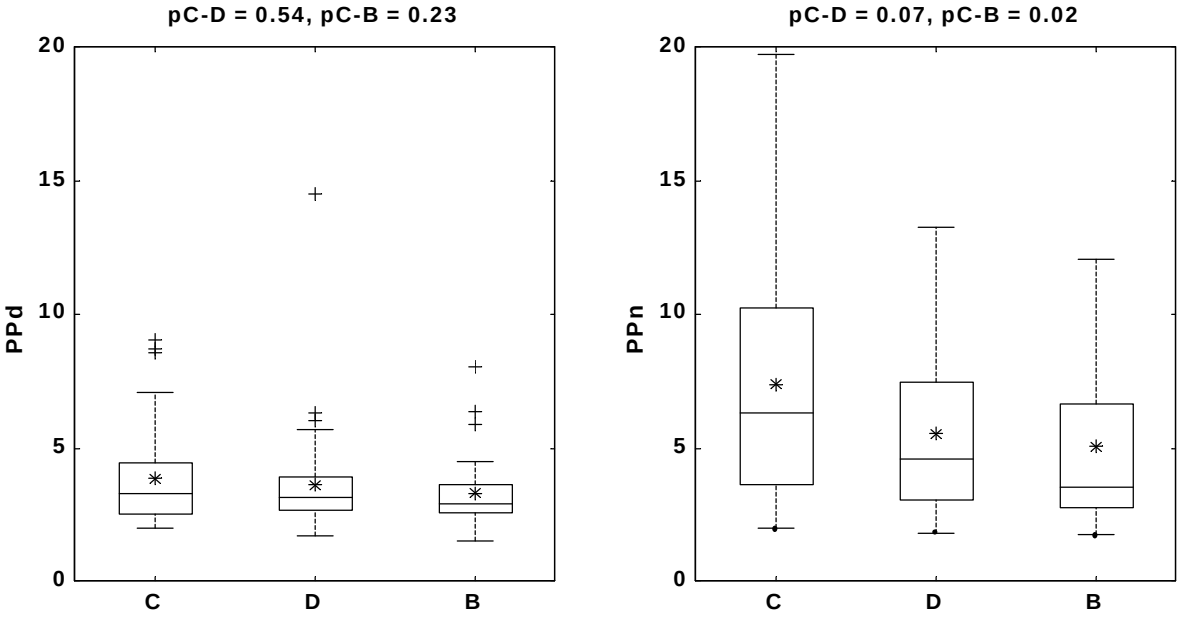


Figure 2

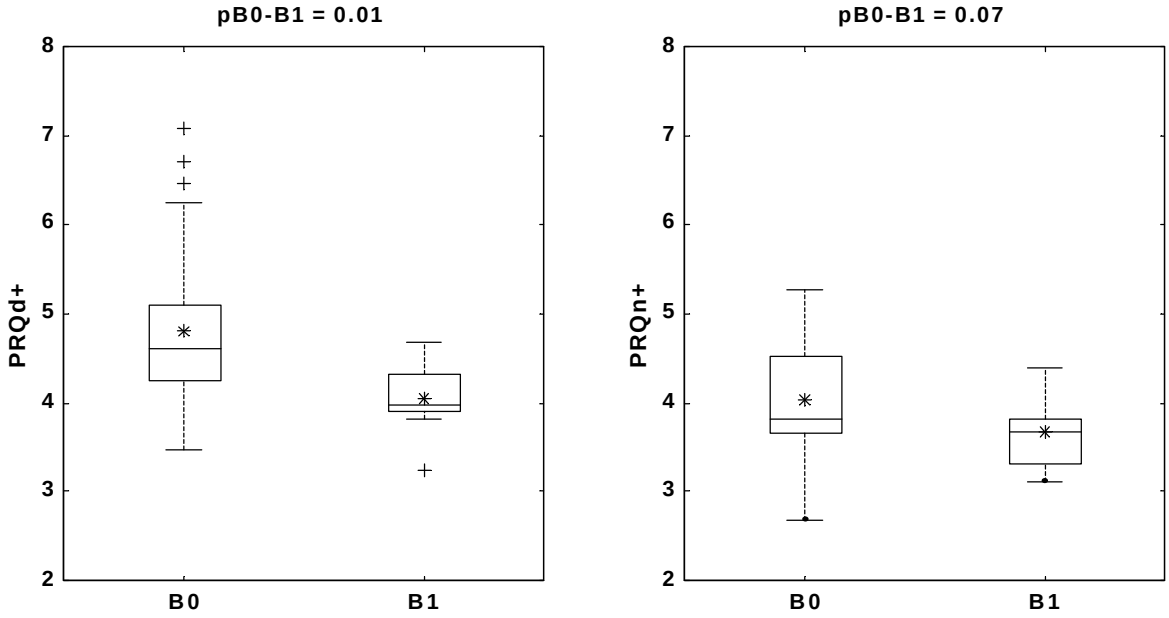
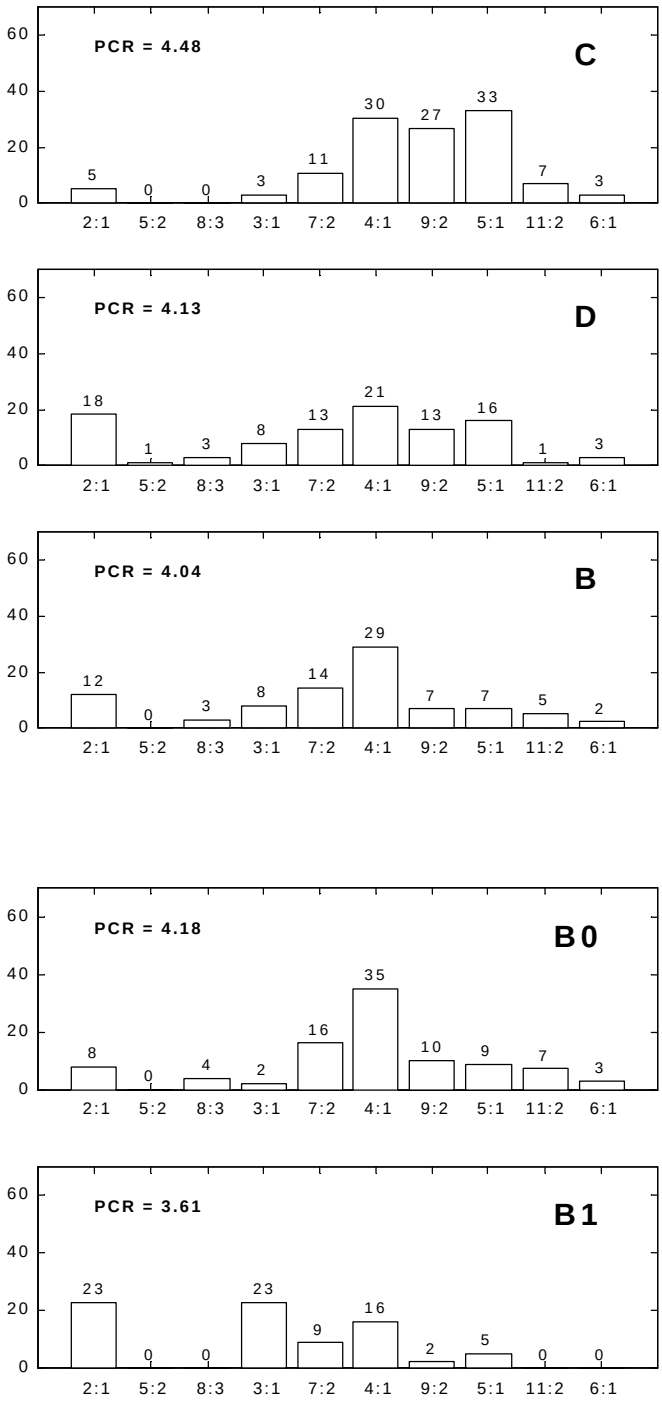


Figure 3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C
5 0 0 3 11 30 27 33 7 3
PCR = 4.13
D
18 1 3 8 13 21 13 16 1 3
PCR = 4.04
B
12 0 3 8 14 29 7 7 5 2
PCR = 4.18
B0
8 0 4 2 16 35 10 9 7 3
PCR = 3.61
B1
23 0 0 23 9 16 2 5 0 0
0 20 40 60
2:1 5:2 8:3 3:1 7:2 4:1 9:2 5:1 11:2 6:1