Advanced analysis of spontaneous baroreflex sensitivity, blood pressure and heart rate variability in patients with dilated cardiomyopathy

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ABSTRACT

Baroreflex sensitivity (BRS) is an important parameter in the classification of patients with reduced left ventricular function. This study aimed at investigating BRS in patients with dilated cardiomyopathy (DCM) and in healthy subjects (controls), as well as comparing the values of BRS parameters with parameters of heart rate variability (HRV) and blood pressure variability (BPV). ECG, continuous blood pressure and respiration curves were recorded for 30 min in 27 DCM patients and 27 control subjects. The Dual Sequence Method (DSM) includes the analysis of spontaneous fluctuations in systolic blood pressure and the corresponding beat-to-beat intervals of heart rate to estimate bradycardic, opposite tachycardic and delayed baroreflex fluctuations. The number of systolic blood pressure/beat-to-beat interval fluctuations in DCM patients was reduced in comparison with controls (DCM patients: male, 154.4 ± 93.9 ms/mmHg; female, 93.7 ± 40.5 ms/mmHg; controls: male, 245.5 ± 112.9 ms/mmHg; female, 150.6 ± 55.8 ms/mmHg, P < 0.05). The average slope in DCM patients was lower than in controls (DCM, 5.3 ± 1.9 ms/mmHg; controls, 8.0 ± 5.4 ms/mmHg; P < 0.05). Discriminant function analysis showed that, in the synchronous range of the standard sequence method, the DCM and control groups could be discriminated to only 76% accuracy, whereas the DSM gave an improved accuracy of 84%. The combination of six parameters of HRV, BPV and DSM gives an accuracy of classification of 96%, whereas six parameters of HRV and BPV could separate the two groups to only 88% accuracy. Thus the DSM leads to an improved characterization of autonomous regulation in order to differentiate between DCM patients and healthy subjects. BRS in DCM patients is significantly reduced and apparently less effective.

INTRODUCTION

Spontaneous baroreflex sensitivity (BRS) is a very important marker for risk stratification, particularly in patients who have suffered from myocardial infarction [1–7]. A low BRS in patients with coronary heart disease and reduced left ventricular function is an important prognostic parameter [8,9]. In this pilot study, we tested...
the hypothesis that vegetative regulation in patients with dilated cardiomyopathy (DCM) can be better characterized by analysis of spontaneous BRS using the Dual Sequence Method (DSM). Furthermore, we analysed the classification value of BRS, heart rate variability (HRV) and blood pressure variability (BPV) parameters in order to differentiate between DCM patients and controls.

Compared with the standard sequence method, the DSM also includes different delay times of baroreflex regulation. The characteristic behaviour of baroreflex regulation is determined by the reflexory change in heart frequency (beat-to-beat interval; BBI) to induced fluctuations in systolic blood pressure (SBP). In patients, BRS can be determined after pharmacologically (phenylephrine, nitroprusside) [4,6,8,10–13,15] or mechanically [14,15] induced changes in SBP.

Heart rate responses (BBI) to induced changes in SBP have been analysed by different methods [15–19]. Furthermore, the spontaneous behaviour of the baroreflex was analysed in subjects at rest without stimulation [15,19]. Analysis of the BBI response has been performed by spectral estimation, ARMA (autoregressive moving average) models and various sequence methods [18–23].

In most of the sequence methods, BRS is calculated as the regression slope of SBP and BBI. An increased SBP activates parasympathetic tone, resulting in bradycardia. After a delay the cardiac sympathetic tone decreases. The reflected tachycardia is initiated by parasympathetic withdrawal, and later by sympathetic activation.

In the present investigation, the DSM was applied to gain new information about spontaneous BRS. The DSM considers different types of bradycardic and tachycardic fluctuations, in either synchronous or shifted mode. It is based on different splitting methods for analysing the sectors of slopes. In addition, the variable shifting operation between BBI and SBP curves allows (1) analysis of the time shift between the BBI response to identical SBP fluctuations, and (2) assessment of the influence of respiration on BRS.

**METHODS**

**Data analysis**

Using the DSM, the most relevant parameters for estimating the spontaneous baroreflex are the slopes as a measure of sensitivity [16]. The DSM is based on standard sequence methods, and its innovations are as follows. Two kinds of BBI responses were analysed: bradycardic (an increase in SBP that causes an increase in BBI) and tachycardic (a decrease in SBP that causes a decrease in BBI) fluctuations. Both types of fluctuation were analysed both in a synchronous and in a shifted mode. However, only the bradycardic fluctuations primarily represent the vagal spontaneous baroreflex [17,20]. Analysis of the tachycardic fluctuations allows for the acquisition of enhanced information about autonomous regulation, especially investigation of the relationship between vagally (bradycardic) and sympathetically (tachycardic) mediated fluctuations in BBI (Figure 1).

The BRS slopes contain three consecutive SBP and BBI values. Sequences of more than three values were proved to not be useful in our study, because the duration of these sequences is caused by spontaneous changes in SBP, in contrast with pharmacologically induced changes [19], and thus we did not obtain sufficient numbers of sequences for statistical analyses. The calculated slopes were analysed by splitting them into different sectors. The occurrence of the slopes within the slope sectors is described by the number in that sector, and as a percentage of the total number of all slopes.

The analysis showed that the BBI does not respond to the fluctuation in SBP in the same time window. Obviously, the BBI response depends on the different velocities of vagal and sympathetic regulation [12,20]. In contrast with other sequence methods [24,25], the time series were shifted to register the synchronous and the delayed BBI responses. The response of the third heartbeat after the synchronous beat to the SBP fluctuation is demonstrated in Figure 2. Tachycardic time-
delayed responses of heart rate (shift 3) we assign to the slower sympathetic regulation [26]; however, we also expect superimposed vagally mediated regulation using delayed BBI responses. As one can see in Figure 2, the next six BBI values after SBP changes are analysed.

The following parameter groups are calculated by DSM: (1) the total numbers of slopes in the different sectors within 30 min; (2) the percentage of the slopes in relation to the total number of slopes in the different sectors; (3) the numbers of bradycardic and tachycardic slopes; (4) the shift operation from the first (sync mode) to the third (shift 3 mode) heartbeat triple (see Figure 2); and (5) the average slopes of all fluctuations.

Definitions of the DSM parameters are given in Appendix 1. The parameters were calculated for bradycardic as well as for tachycardic fluctuations up to a shift of 40 values, to analyse the maximal and long-term responses of the BBI to the same SBP oscillation. This shifting operation up to 40 was done to register all possible sympathetically and vagally mediated influences.

We investigated the HRV and BPV of DCM patients and healthy subjects in order to evaluate the prognostic value of the DSM method. The stepwise discriminant analysis was applied to estimate the classification ratios of each method. The HRV and BPV parameters were calculated by applying time- and frequency-domain as well as non-linear-domain measures.

We applied the stepwise discriminant function analysis to objectively find combinations of HRV, BPV and BRS parameters that could differentiate between DCM patients and controls, while being aware of the multiplicity effect of statistical tests (too many parameters will lead to a higher probability of overestimating classification rates). The different parameter sets are demonstrated in Appendix 2. These parameter sets were tested to compare the clinical relevance of the different methods. In the statistical evaluation, all calculated parameter sets were analysed using the $t$ test (Kolmogorov–Smirnov test, Levene test). Furthermore, the parameters were analysed using correlation techniques in order to investigate the linear relationships between BRS, HRV and BPV.

**Patients**

Altogether, 21 male and six female DCM patients (age 50.8 ± 12.3 years) and 27 gender- and age-matched healthy control subjects (age 50.1 ± 10.5 years) were included in the study. The DCM patients showed a significant left ventricular dilation related to a reduced left ventricular ejection fraction of 29.5 ± 11.2% (NYHA class II–III).

For all patients and controls, a high-resolution ECG (2000 Hz sampling frequency, 16 bit resolution, 30 min) was recorded under standard resting conditions (time of day and location). Simultaneously, a continuous blood pressure signal was recorded applying the volume-clamp photopletysmographical blood pressure device Port-apres Mod 2 (BMI-TNO, Amsterdam, The Netherlands). The respiration curve was registered by the piezocrystal sensor technique. The sensor was fixed on a respiration belt on the thorax.

All 27 patients were treated with angiotensin-converting enzyme (ACE) inhibitors, and 11 patients were treated with β-blockers. The recorded data were filtered to exclude ventricular premature beats, artifacts and noise [31]. Furthermore, for smoothing and amplifying the dominant signal components, the time series were filtered using a moving average filter (second order) before calculating BRS.

The study was performed in accordance with the guidelines of the Ethical Committee of the Charité Berlin. Consent was obtained from all participants.

**RESULTS**

**Maximal BRS**

Periodic oscillations of the total number of bradycardic and tachycardic fluctuations were found in 70% of all DCM patients and controls (both genders) by shifting the SBP and BBI time series up to 40 values. An example of these baroreflex oscillations is shown in Figure 3.

We compared the registered baroreflex oscillations with the respiration frequencies, detected by the respiration belt and determined by the respiration peaks in HRV spectra. It could be shown that the respiration frequencies differ by only 12.5% from these baroreflex oscillations. The respiration process, as expected, superimposes the bradycardic and tachycardic baroreflex fluctuations, among other processes. Therefore only those baroreflex parameters should be used for the analysis of spontaneous BRS, which was calculated in synchronous or in three-value-shifted time series. The number of positive and negative changes in SBP as the cause of the baroreflex is demonstrated in Table 1. The results show significant decreases in both total numbers
Table 1  Total numbers and percentages of increases and decreases in blood pressure as a cause of baroreflex regulation

Values are expressed as means ± S.D. Significance of differences: **P < 0.01 for DCM patients compared with controls of the same gender.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DCM patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Positive SBP slopes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number</td>
<td>316.7 ± 101.9**</td>
<td>267.5 ± 81.8**</td>
</tr>
<tr>
<td>Percentage</td>
<td>14.5 ± 4.7**</td>
<td>12.3 ± 4.5**</td>
</tr>
<tr>
<td>Negative SBP slopes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number</td>
<td>336.7 ± 130.3**</td>
<td>261.3 ± 91.7**</td>
</tr>
<tr>
<td>Percentage</td>
<td>15.4 ± 5.9**</td>
<td>12.0 ± 4.6**</td>
</tr>
</tbody>
</table>

Table 2  Total numbers of fluctuations and average slopes for male and female DCM patients and for control subjects

For definitions of parameters, see the Methods section and Appendix 1. Values are expressed as means ± S.D. Significance of differences: *P < 0.05, **P < 0.01 for DCM patients compared with controls of the same gender; †P < 0.05 for females compared with males in the same group.

<table>
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<th>Parameter</th>
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<th>Controls</th>
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<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>All brady...sync...n</td>
<td>130.4 ± 75.0**</td>
<td>91.3 ± 34.0</td>
</tr>
<tr>
<td>Brady...sync...s</td>
<td>5.4 ± 2.1*</td>
<td>5.0 ± 1.5</td>
</tr>
<tr>
<td>All tachy...sync...n</td>
<td>154.5 ± 93.9**</td>
<td>93.7 ± 40.5†</td>
</tr>
<tr>
<td>Tachy...sync...s</td>
<td>5.2 ± 2.8*</td>
<td>5.1 ± 2.0</td>
</tr>
<tr>
<td>All brady...3...n</td>
<td>69.1 ± 39.8**</td>
<td>66.8 ± 25.9*</td>
</tr>
<tr>
<td>Brady...3...s</td>
<td>6.5 ± 2.6</td>
<td>6.1 ± 2.3</td>
</tr>
<tr>
<td>All tachy...3...n</td>
<td>73.0 ± 48.7**</td>
<td>64.2 ± 26.4</td>
</tr>
<tr>
<td>Tachy...3...s</td>
<td>5.6 ± 2.4</td>
<td>6.0 ± 2.5</td>
</tr>
</tbody>
</table>

Table 3  Number of synchronous (sync) bradycardic fluctuations in different slope sectors

For definitions of parameters, see the Methods section and Appendix 1. Values are expressed as means ± S.D. Significance of differences: *P < 0.05, **P < 0.01 for DCM patients compared with controls of the same gender; †P < 0.05 for females compared with males in the same group.

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<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Brady...sync...n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–7.5</td>
<td>26.6 ± 18.7*</td>
<td>18.5 ± 9.7</td>
</tr>
<tr>
<td>7.5–10</td>
<td>15.2 ± 13.9*</td>
<td>11.7 ± 10.8</td>
</tr>
<tr>
<td>5–10</td>
<td>41.9 ± 30.0*</td>
<td>30.2 ± 19.5</td>
</tr>
<tr>
<td>All</td>
<td>130.4 ± 75.0**</td>
<td>91.5 ± 34.0</td>
</tr>
</tbody>
</table>

and percentages of positive and negative slopes in SBP in DCM patients compared with controls.

On comparison of the synchronous and the three-value-shifted time series, it was deduced that, in shift 3-calculated parameters, fewer bradycardic and tachycardic slopes were calculated. The decreased number of slopes was more significant in males than in females (Table 2). The parameters 'brady_sync_s' and 'tachy_sync_s' (see Appendix 1) represent the average slopes of the standard sequence method.

On comparing healthy males with healthy females, the total numbers of bradycardic and tachycardic fluctuations differed significantly in the synchronous regulation. In males in particular, we found highly significant
differences between DCM patients and controls with regard to the total numbers of bradycardic and tachycardic fluctuations.

Furthermore, we analysed the relationship between spontaneous changes in SBP (Table 1) and total numbers of baroreflexes (Table 2). The synchronous baroreflex reacts to 41–50% of SBP fluctuations in male DCM patients and controls, whereas in females only 35% of SBP changes lead to baroreflex regulation. With delayed baroreflex fluctuations (shift 3), the DCM patients show reduced baroreflex regulation (DCM patients: male, 21%; female, 25%; controls: male, 31%; female, 30%).

Distribution of BRS

For the different slope sectors of synchronous bradycardic fluctuations, four parameters were calculated, describing the slope ranges of 5–7.5, 7.5–10, 5–10 and all slopes (Table 3).

Male DCM patients and controls differed significantly, especially in the sector of high slopes. This means that male DCM patients showed only 60% of baroreflex fluctuations compared with healthy subjects. In the slope sector containing the highest slope values (7.5–10), we calculated a less proportional slope number. Therefore we assume that the autonomous regulation of the greatest changes in heart rate in response to possible fluctuations in SBP is ineffective.

The average slopes were normally distributed (Kolmogorov–Smirnov test) and had different variances in the two groups (Levene test; \( P < 0.05 \)). Using the \( t \)-test, the average slope of DCM patients differed significantly from that of healthy subjects (DCM, 5.34 ± 1.94 ms/mmHg; controls, 7.98 ± 5.37 ms/mmHg; \( P < 0.05 \)).

Correlation and discriminant function analysis

Correlation analysis was performed to check the different HRV, BPV and BRS parameters for linear dependence [27,32]. In general, the average correlation was low between the different parameter sets (\( r = 0.22 \)). However, several high correlations were observed between BRS and HRV parameters (time domain, frequency domain and non-linear dynamic), and between BRS and BPV parameters (frequency domain only).

We calculated a high correlation (\( r = 0.85 \)) between the HRV time domain parameter ‘r’msssd’, ‘pNN50’ and the average slope of the synchronous bradycardic baroreflex fluctuation ‘brady_sync_s’ (rmsssd, root of square NN-interval differences; pNN50, percentage of NN-interval differences greater than 50 ms). This demonstrates the relationship between the calculated vagal component of the heart frequency in a short time window and the baroreflex slope as the degree of vagal activity [25]. A high value of ‘r’msssd’ and ‘pNN50’ yields a high average slope and vice versa.

The increase in HRV with values < 20 ms (parameter pNN120: percentage of NN-interval differences lower than 20 ms) is correlated (\( r = 0.73 \)) with the percentage of fluctuations in the lowest slope sector. These sectors are represented by the parameters ‘0–5_brady_sync_p’ and ‘0–5_tachy_sync_p’. The average correlation coefficient between BRS and HRV parameters is \( r = 0.35 \).

A high correlation (\( r = 0.75 \)) between the frequency-domain HRV parameter ‘HF’ (see Appendix 2) and the average slope (brady_sync_s) of the baroreflex characterizes the relationship between the high-frequency component of HRV and the increased slopes of BRS. Both increases represent the vagal component of BRS. The average correlation between all frequency-domain HRV and BRS parameters was \( r = 0.2 \).

The HRV parameter ‘FWSHANNON’ from non-linear dynamics is correlated (\( r = 0.82 \)) with the lowest slope sectors characterizing BRS parameters ‘0–5_brady_sync_p’ and ‘0–5_tachy_sync_p’. The analysis of the Shannon entropy of BBI showed that a lower number of generated words is correlated with a decrease in HRV and with the lowest slopes of BRS. This fact correlates with the lowest slopes of BRS. The non-linear parameter ‘PLVAR20’ of the symbolic dynamics of HRV determines the increase in the range 0–20 ms, which is related (\( r = 0.82 \)) to the increased average slope ‘brady_sync_s’. The average correlation of all non-linear HRV and BRS parameters was \( r = 0.33 \).

A correlation of \( r = 0.72 \) was calculated between the frequency-domain parameters of BPV ‘LF’ and the lowest BRS slopes, ‘0–2.5_brady_sync_n’. The increase in the low-frequency component of BBI determines the increase in the lowest BBI fluctuations. This fact is related to that BRS parameter which describes the number of the lowest slopes of BRS. The average correlation value between BPV and BRS parameters was \( r = 0.15 \).

Stepwise discriminant function analysis was used to find the optimal combinations of HRV, BPV and BRS parameters to differentiate between DCM patients and healthy subjects. We limited the maximal number of included parameters to six, to avoid statistical overfitting and the multiple testing problem. These included combinations of parameters are presented in Figure 4.

A correct classification of 74–86% was obtained with sets of six parameters of HRV, BPV and BRS. The following parameter sets of mainly three items distinguish between DCM patients and healthy subjects: (1) the high frequency in HRV; (2) the mean values and low frequency of BPV; and (3) the highest slopes and the number of baroreflex fluctuations.

The set of six parameters of HRV and BPV increased the accuracy of classification up to 88%. Furthermore, the accuracy of classification could be improved using additional BRS parameters. Using a set of six parameters of BPV and BRS, a correct classification of 94% was
DISCUSSION

The analysis of BRS is an established method for improved characterization of different cardiac diseases. In contrast with most BRS methods, the introduced DSM records the biosignals of patients at rest and without any additional stimulation (e.g. intake of drugs or other stimuli). The DSM contains the analysis of both synchronous and shifted time series.

By analysis of the BBI response to SBP fluctuations, we could demonstrate a visible superposition of the respiratory process on the baroreflex oscillations. The analysis showed that there are significant differences between DCM patients and healthy subjects with respect to the calculated parameters. Mean values of BBI and SBP were calculated in DCM patients and healthy subjects to determine the difference in the active range of the baroreflex. This regulatory behaviour of BRS function in DCM patients and healthy subjects is represented schematically in Figure 5. The average BBI value in DCM patients was calculated to be 795.9 ± 107.7 ms. This value is considerably lower than that in the control group (862.4 ± 130.5 ms; *P* < 0.05). The average SBP values in DCM patients and healthy subjects behave inversely to the BBI values (DCM, 101.5 ± 19.6 mmHg; controls, 112.9 ± 25.7 mmHg; *P* < 0.05).

This behaviour of BBI and SBP in DCM patients shows that the reduced BBI regulation that occurs in these patients, despite the adaptation of the baroreflex to the altered average SBP [1], is due to the disease. This decrease in BBI regulation is characterized by a smaller number of baroreflex fluctuations and by lower slope values in patients compared with healthy subjects.

A limitation of the present study is the rather low number of subjects and the gender distribution within the patient and control groups. The calculated parameters should be confirmed in a major study. Additionally, we did not separate the patient group according to their treatment. We assume that the observed inhibition of vagally mediated regulation is not influenced by the *β*-blocker therapy taken by a subgroup of the DCM patients. Moreover, the effects of reduced vagal activation should be increased without any *β*-blocker treatment [33]. Furthermore, we assume a small influence of ACE inhibitor treatment on vagal regulation.

We recorded 35–40% more spontaneous baroreflex slopes in healthy men than in healthy women. This could be due to different respiratory physiology or to differences in vagal or sympathetic regulation in men and women [5]. These differences could also be detected in DCM patients, but they were not significant for bradycardic fluctuations. We assume that the gender differences are reduced after the occurrence of the disease [34,35].

Synchronous fluctuations differed by almost 40% and shifted time series by approx. 50% between DCM patients and control subjects. In female patients these differences were less pronounced, which could be due to...
the low number of females included in the study and the high standard deviation. Thus autonomous regulation seems to be less effective in DCM patients than in healthy subjects. This is characterized by the lower number of baroreflex fluctuations and by the lower average slope of BRS.

The discriminant function analysis of BRS parameters showed that the following three features are the most important for discriminating between DCM patients and healthy subjects: (1) the DSM parameters determining the highest slopes (percentage and number), (2) the total number of all baroreflex fluctuations, and (3) the average BRS slope [36]. Furthermore, the total number of fluctuations, the shifting operation and the subdivision into bradycardic and tachycardic fluctuations can be used as additional criteria for improved discrimination. On the other hand, the lowest slopes of BRS seem to have no value for discrimination between DCM patients and controls.

In comparison with synchronous baroreflex analysis (based on the standard sequence method), use of the DSM resulted in improved accuracy of classification (84% compared with 76%). Apparently, analysis of delayed regulation leads to registration of additional regulatory effects. Consideration of DSM parameters in combination with HRV and BPV parameters results in a significant increase in discriminatory power. The combination of six parameters of HRV, BPV and BRS gives an accuracy of classification of 96%. For the independent analysis of HRV, BPV or BRS, an accuracy of only 74–84% was achieved, whereas the combination of HRV and BPV parameters gave a classification of 88%.

To estimate the usefulness of the DSM in obtaining prognostic information about DCM disease, we analysed a subgroup of four male DCM patients who died during a 2-year follow-up. In these patients, the number of tachycardic synchronous slopes was lower than in the DCM group as a whole (all_tach_sync.n: subgroup of four patients, 120.0 ± 27.4; DCM patients, 173.9 ± 69.7; \( P < 0.05 \)). We conclude that a lower number of slopes and a lower mean slope are indicative of a poor prognosis.

In conclusion, we have found that DSM parameters increase the amount of information that can be obtained about the cardiovascular system. The use of the DSM for analysis of BRS improves diagnostic accuracy in discriminating between DCM patients and healthy subjects. In particular, the combination of HRV and BPV with DSM parameters reveals the importance of multiparametric analyses.

**APPENDIX I**

The DSM contains the following definitions. The / symbols denote that the introduced fields are incomplete parts of a DSM parameter; only a set of /dual type/, /sectors of slopes/, /shift operation/ and /mode/ defines a complete parameter.

**Dual types of slopes**

Bradycardic fluctuation: /brady/
Tachycardic fluctuation: /tachy/

This code describes the classification into bradycardic and tachycardic fluctuations. The bradycardic fluctuations correspond to the vagal BRS (an increase in SBP causes an increase in BBI), and the tachycardic parameters correspond to the reverse fluctuation (a decrease in SBP causes a decrease in BBI).

**Sectors of slopes**

Slope range 0–2.5 ms/mmHg: /0–2.5/
Slope range 2.5–5 ms/mmHg: /2.5–5/

Similarly for /0–5/; /5–7.5/; /7.5–10/; /5–10/; /10–12.5/; /12.5–15/ and /10–15/

All occurring slopes: /all/

The ranges of the slope sectors correspond to the threshold values of the slope sectors. Based on the knowledge of the mean slopes, these threshold values of the sectors have been defined [19]. The definition of the sectors was determined by the expected distribution of the slopes.

**Shift operation between BBI and SBP curves**

Synchronous: /sync/
Shift 3: /3/

The shifting operation is divided into synchronous (sync) and three-beat-shifted (shift 3) time series, in order to analyse the time-variable response of the BBI. The shift 3 operation contains a shift of three values after the synchronous heartbeat.

**Mode**

Number: /n/
Percentage: /p/
Average slope: /s/

All calculated different slope values were classified into the above slope sectors. Within these slope sectors the absolute number (n) of occurring slopes, the percentage of these numbers (p) with respect to the total number of slopes, and the average slope (s) were determined. The threshold charge was set to 1 mmHg for SBP and to 1 ms for BBI. For changes of < 5 ms for BBI and < 1 mmHg for SBP, we suppose noise.

**Examples**

Given below are three examples of calculated DSM parameters:

1. 5–7.5.brady_sync.p = percentage of bradycardic slopes in the range 5–7.5 using sync;
2. tachy.3.s = the average slope of all tachycardic slopes using shift 3;
(3) all.brady..sync..n = number of all bradycardic slopes using sync.

**APPENDIX 2**

The following parameter sets were applied in order to compare the discriminatory value of BRS parameters with HRV and BPV parameters.

**Set 1 (HRV):** XF, HF, WPSUM13, HFn, FWShannon, Shannon

**Set 2 (BPV):** HFn, meanNN, PLVAR10, (ULF+VLF)/P, ULF/P, XF

**Set 3 (BRS):** all.brady..3..n, all.brady..sync..p, 5–12.5.brady..3..p, 10–12.5.tachy..sync..p, 5–7.5.brady..sync..p

**Set 4:** PHVAR20, LF, XF, FWShannon (HRV); all.brady..3..n, 10–12.5.brady..3..p (BRS)

**Set 5:** rmssd (BPV); all.brady..3..n, 5–7.5.brady..sync..p, 10–12.5.brady..3..p, 0–5.tachy..sync..n, 12.5–15.tachy..sync..n (BRS)

**Set 6:** PNN50, XF (HRV); HFn, LF/P, PLVAR10, meanNN (BPV)

**Set 7:** WPSUM13 (HRV); rmssd (BPV); all.brady..3..n, 5–7.5.brady..sync..p, 10–12.5.brady..3..p, 12.5–15.tachy..sync..n (BRS)

The following HRV and BPV parameters have already been described and published in detail [27–30].

**REFERENCES**


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