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Spontaneous Heart Rate Turbulence in Patients with Dilated Cardiomyopathy

A. Voss, R. Schroeder, S. Truebner, M. Goernig, A. Schirdewan, H.R. Figulla

Abstract— **Parameters of heart rate turbulence (HRT) and blood pressure turbulence (BPT) reflect the baroreflex mediated transient acceleration-deceleration response of the sinus node triggered by a premature ventricular complex (PVC) and are known to be useful risk markers in different cardiac diseases. However, the analyses of HRT and BPT are based on the prevalence of PVC. In this study the spontaneous HRT and BPT after most premature normal beats (MPNB) was investigated in comparison to HRT and BPT after PVC. ECG and blood pressure were recorded from 91 patients with dilated cardiomyopathy (DCM) and 45 healthy subjects (REF). In 69% of DCM and 33% of REF data sets PVCs were present. HRT and BPT were determined for all patients with PVC as well as in all patients triggered by MPNB. Univariate statistical analysis of the comparison between DCM and REF revealed similar results for HRT/BPT after PVC and MPNB. In conclusion, HRT and BPT triggered by PVC might be substituted by spontaneous HRT and BPT after MPNB. In contrast to the HRT and BPT after PVC, an increased number of data sets can be included in the analysis and may lead to an enhancement in risk stratification in different cardiac diseases.**

I. Introduction

Autonomic and central nervous regulations as well as complex interactions of haemodynamic, electrophysiological and humoral systems and their variables cause linear and non-linear phenomena in sinus rhythm generation. Cardiovascular variability characterized by different measures from heart rate variability (HRV), blood pressure variability (BPV) as well as heart rate and blood pressure turbulence (HRT, BPT) are known to be useful markers for risk stratification in different cardiac diseases [1],[2],[3],[4].

HRT and BPT reflect the transient acceleration-deceleration response of a sinus node triggered by a premature ventricular contraction (PVC). Several studies proved the usefulness of the HRT analysis for risk stratification after acute myocardial infarction [3],[5],[6],[7],[8] as well as in patients suffered from DCM [4],[9] and heart failure [10]. According to the World Health Organization, cardiomyopathy were defined as "disease of the myocardium associated with cardiac dysfunction" [11]. The sudden cardiac death (SCD) is a leading cause of mortality with an incidence of 3 million cases per year worldwide, e.g. SCD accounts for at least 30% of all deaths in DCM and may occur at any stage [12]. However, the problem of risk stratification in patients suffering from SCD is still not finally solved [9], and therefore, of great importance.

The analyses of HRT and BPT are based on the prevalence of PVC. Consequently, parameters of HRT and BPT are only suitable measures for risk stratification in patients with occurring PVC. Due to this fact, in this study the HRT and BPT after most premature normal beats (MPNB) was investigated in comparison to HRT and BPT after PVC.

II. Materials and Methods

A. Patients and Data Recording

From 91 DCM patients with sinus rhythm as well as 45 healthy subjects (REF) high resolution short term ECG (3 channels, 1600Hz sampling frequency, 32 bit) and synchronized continuously recorded noninvasive blood pressure (NIBP, 500 Hz sampling frequency) were recorded over 30 minutes. All measurements were performed under resting conditions using the Portapres non-invasive blood pressure monitor (TNO-TPD Biomedical Instrumentation, Netherlands). Based on the volume clamp method [13] and the calibration criteria [14] the peripheral arterial blood pressure was measured via finger cuff.

DCM was diagnosed in all DCM subjects by coronary angiography and echocardiography. The clinical measures ejection fraction (EF) and end-diastolic diameter of the left ventricle (LVEDD) were registered from every patient by an experienced cardiologist. Additionally, the functional and therapeutic classification (NYHA: range I – IV) of the New York Heart Association quantifying the status of heart failure was implemented (see Table I).

Patients with chronic renal failure, diabetes mellitus or a permanent pacemaker were excluded from this study. In 69% of DCM and 33% of REF data sets single PVCs were registered.

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A. Voss is with the University of Applied Sciences Jena, Department of Medical Engineering, Carl-Zeiss-Promenade 2, 07745 Jena, Germany (corresponding author to provide phone: 49-3641-205-625; fax: 49-3641-205-626; e-mail: voss@ fh-jena.de).

R. Schroeder is with the University of Applied Sciences Jena, Department of Medical Engineering, Jena, Germany (e-mail: rico.schroeder@ fh-jena.de).

S. Truebner is with the University of Applied Sciences Jena, Department of Medical Engineering, Jena, Germany (e-mail: sandra.truebner@ fh-jena.de).

M. Goernig is with the Clinic of Internal Medicine I, Friedrich Schiller University Jena, Jena, Germany (e-mail: matthias.goernig@med.uni-jena.de).

A. Schirdewan is with the Franz-Volhard-Clinic, Charité, Humboldt University Berlin, Berlin, Germany (e-mail: schirdewan@fvk-berlin.de).

H.R. Figulla is with the Clinic of Internal Medicine I, Friedrich Schiller University Jena, Jena, Germany (e-mail: hans.figulla@med.uni-jena.de).

TABLE I
PATIENTS CHARACTERISTICS : N – NUMBER OF SUBJECTS, EF – EJECTION FRACTION [%], LVEDD – LEFT VENTRICULAR ENDDIASTOLIC DIAMETER [MM], MEAN – MEAN VALUE, SD – STANDARD DEVIATION, PVC – PREMATURE VENTRICULAR COMPLEX

CLINICAL	DCM	REF
N (MALE/FEMALE)	91 (70/21)	45 (29/16)
AGE (MEAN ± SD)	55 ± 10	53 ± 10
EF (MEAN ± SD)	36 ± 12	-
NYHA (MEAN ± SD)	2.3 ± 0.8	-
LVEDD (MEAN ± SD)	63 ± 8	-
N WITH PVC	63	15

B. Data Preprocessing

Data preprocessing was performed by calculating tachograms (series of successive beat to beat intervals – BBI), systograms (systolic blood pressure values S_n over time) and diastograms (diastolic blood pressure values D_n over time) of the given time series (see Figure I; II).

For the estimation of standard HRV parameters and both HRT and BPT after MPNB artefacts were rejected and interpolated in the tachograms, systo- as well as diastograms to obtain normal-to-normal (NN) time series. This filtering was performed applying an adaptive variance estimation algorithm, considering the variance within the time series just before and directly after an artefact.

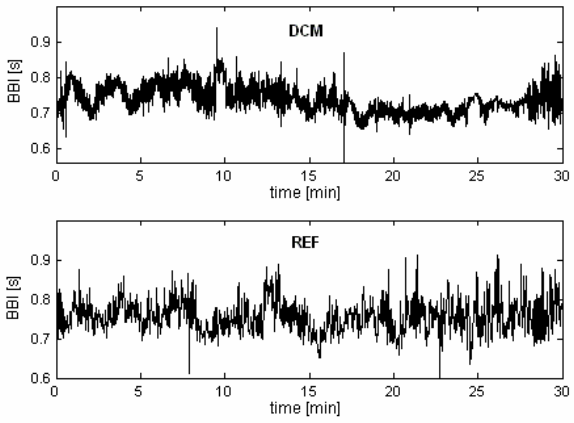

FIGURE I
TACHOGRAM OF A PATIENT WITH DILATED CARDIOMYOPATHY (DCM) IN COMPARISON TO A HEALTHY SUBJECT (REF); BBI – BEAT TO BEAT INTERVAL

C. Methods

Standard parameters [15] of short term HRV from linear time and frequency domain were calculated. Time domain measures were: meanNN - the mean value of the NN-intervals; sdNN - standard deviation of the NN-intervals; rmssd - square root of the mean squared differences of successive NN intervals; sdNN5 - standard deviation of mean values of successive 5 minutes NN-intervals.

To determine the frequency domain measures tachograms were resampled (10Hz) and linear interpolated to get equidistant time series. The spectra were estimated using the Fast Fourier transform. To avoid any leakage effect, a Blackman Harris window function was applied. The following frequency domain parameters were calculated: LFn – normalized low frequency power (0.04 – 0.15Hz) and HFn - normalized high frequency power (0.15 – 0.4Hz). Additionally the ratio between the low and high frequency power (LF/HF) of the estimated spectrum was computed.

HRT is characterized by a short initial acceleration (1 or 2 beats) followed by a deceleration of the heart rate. The short initial acceleration can be quantified by the HRT parameter Turbulence Onset (HR_TO) whereas the Turbulence Slope (HR_TS) reflects the deceleration phase [3].

HR_TO [%] was calculated as the percentage difference between the first two BBIs (BBI_{+1}, BBI_{+2}) following a PVC and the two BBIs preceding the PVC (BBI_{-2}, BBI_{-1}) (see Equation 1) and represents the averaged HR_TO for each PVC. A positive HR_TO indicates a deceleration whereas negative values suggest an acceleration of the sinus rhythm [3],[16].

$$HR\_TO\ [\%] = \frac{\left(\left(BBI_{+1} + BBI_{+2}\right) - \left(BBI_{-2} + BBI_{-1}\right)\right)}{\left(BBI_{-2} + BBI_{-1}\right)} * 100 \qquad (1)$$

HR_TS [ms/beat] was defined as the maximum positive slope of the linear regression line through five subsequent BBI intervals within the first 20 sinus rhythm intervals after a PVC. CI/COMPP is the ratio between the length of the coupling interval (CI) and the compensatory pause (COMPP). Furthermore, parameters of BPT were determined [4],[10]:

- MBP_TS [mmHg/beat] (mean blood pressure turbulence slope): slope of the regression line over five subsequent mean blood pressure values within the first 15 sinus rhythm intervals followed a PVC,
- MBP_TSn [mmHg/beat]: mean blood pressure turbulence slope normalized to blood pressure variance,
- SBP_5 [mmHg]: mean systolic blood pressure of five consecutive systolic amplitudes before PVC,
- DBP_5 [mmHg]: mean diastolic blood pressure of five consecutive diastolic amplitudes before PVC,
- PEAP [%] (postextrasystolic potentiation): relative deviation of the first normal BP amplitude (difference between systolic and diastolic blood pressure) after a PVC (AMP_{+1}) in comparison to the last normal BP amplitude before the PVC (AMP_{-1}) (see Equation 2).

$$PEAP\ [\%] = \frac{\left(AMP_{+1} - AMP_{-1}\right)}{AMP_{-1}} * 100 \qquad (2)$$

The calculation of the HRT as well as BPT required the correct detection and classification of PVCs (see Figure II) as well as artefact- and arrhythmic-free BBIs before and after a PVC. Further on, filters were applied to exclude BBI from the HRT analysis with a duration of <300ms and >2000ms, a difference to the preceding BBI >200ms and a difference of >20% to the reference interval (mean of the five last sinus BBI) [3].

Corresponding to HRT and BPT after PVC we introduced

parameters to describe transient fluctuations of the heart rate after MPNB. The definition of these parameters characterized by the suffix "$_{MPNB}$" were comparable to standard HRT and BPT after PVC, e.g. HR_TS_{MPNB} [ms/beat] was defined as the maximum positive slope of the linear regression line through five subsequent BBI intervals within the first 20 sinus rhythm intervals after a MPNB.

The detection of MPNB (see Figure II) was a precondition for the calculation of HRT/BPT_{MPNB} and based on the application of thresholds for coupling interval (a_{CI}) and compensatory pause (a_{COMPP}). Similar to ectopic beats MPNB were characterized by a shortened coupling interval ($CI_{MPNB}<a_{CI}\times BBI_{REF}$) and an elongated compensatory pause ($COMMP_{MPNB}>a_{COMPP}\times BBI_{REF}$), whereas BBI_{REF} is defined as the mean value of all NN intervals. Usable values for a_{CI} and a_{COMPP} were 0.8 (a_{CI}) and 1.2 (a_{COMPP}) and had to be adapted according to the basic variability of data sets.

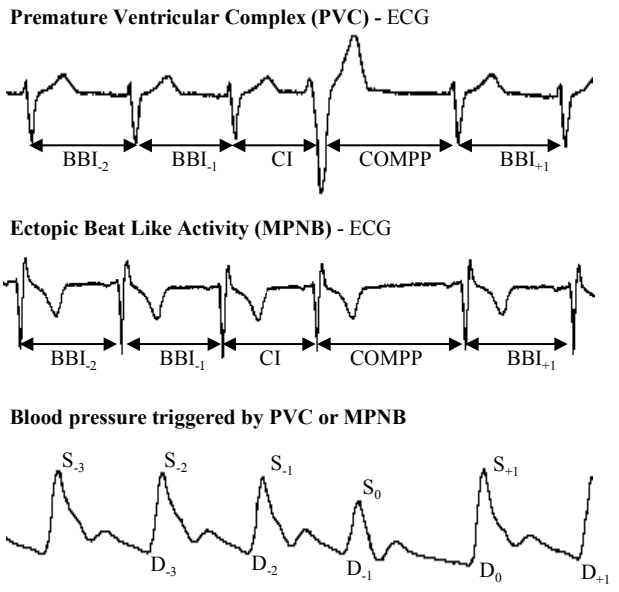

FIGURE II
SCHEMATIC ILLUSTRIATION OF PVC, MPNB (ECG) AND THE RELATED BLOOD PRESSURE: BBI – BEAT TO BEAT INTERVAL, CI – COUPLING INTERVAL, COMPP – COMPENSATORY PAUSE, S – SYSTOLIC MAXIMA, D – DIASTOLIC MINIMA

D. Statistics

Statistical analyses for comparison of HRT and BPT after PVC as well as after MPNB in DCM patients and healthy subjects were performed using the Mann-Whitney U test to get the univariate significances (significance level $p<0.5$). Descriptive statistics were used to describe the basic features of the data sets e.g. mean value as well as standard deviation.

III. RESULTS

A. HRV

Both groups, DCM and REF were age-matched (p=0.1670) and gender-matched (p=0.1526). Neither short term HRV parameters from time domain nor from frequency domain revealed significant differences ($p<0.5$) between DCM and REF (see Table II). Mean Value and standard deviation of the NN intervals, square root of the mean squared differences of successive NN intervals (rmssd) as well as the spectral power of the LF and HF frequency components were comparable in both groups.

TABLE II
HRV - SIGNIFICANCES (P) FOR DISCRIMINATION BETWEEN DCM AND REF (MEAN – MEAN VALUE, SD – STANDARD DEVIATION)

	P	DCM MEAN±SD	REF MEAN±SD
meanNN	0.2448	895±143	860±126
sdNN	0.3327	38±22	40±18
sdNN5	0.4197	16±12	17±9
rmssd	0.9229	23±14	23±16
LF/HF	0.2643	3.2±3.5	3.3±2.5
LFn	0.2641	0.66±0.18	0.69±0.16
HFn	0.2641	0.34±0.18	0.31±0.16

B. HRT and BPT after PVC

Whereas parameters of BPT show significant differences between DCM and REF the ratio between coupling interval and compensatory pause (CI/COMPP) as well as HR_TO and HR_TS are not suitable for a differentiation of DCM patients (see Table III). The mean systolic and diastolic blood pressure before a PVC (SBP_5, DBP_5) are significant decreased in patients with DCM. Furthermore, the mean blood pressure turbulence slope (MBP_TS, MBP_TSn) as well as the postextrasystolic potentiation (PEAP) were significantly increased in patients suffering from DCM.

TABLE III
HRT/BPT AFTER PVC - SIGNIFICANCES (P) FOR DISCRIMINATION BETWEEN DCM AND REF (* - P<0.05, MEAN – MEAN VALUE, SD – STANDARD DEVIATION)

	P	DCM MEAN±SD	REF MEAN±SD
CI/COMPP	0.1024	0.5±0.1	0.5±0.1
HR_TO	0.2462	-0.4±3.7	-3.1±6.7
HR_TS	0.3924	14.1±11.0	21.0±20.3
SBP	0.0006 *	83±23	104±19
DBP	0.0263 *	50±12	57±13
PEAP	0.0000 *	30±18	10±7
MBP_TS	0.0051 *	1.3±0.7	0.8±0.4
MBP_TSn	0.0000 *	71.6±46.4	2.3±7.4

C. HRT and BPT after MPNB

The investigation of HRT and BPT after MPNB showed similar results in comparison to the analysis of HRT and BPT after PVC. The quotient between coupling interval and compensatory pause CI/COMPP as well as HR_TO_{MPNB} and HR_TS_{MPNB} revealed no significant differences. In contrast, mean systolic and diastolic blood pressure (SBP_5_{MPNB}, DBP_5_{MPNB}) before occurring MPNB were reduced and the normalized mean blood pressure turbulence slope (MBP_TSn_{MPNB}) was increased in patients with DCM.

TABLE IV
HRT/BPT AFTER ECTOPIC BEAT LIKE ACTIVITIES (MPNB) - SIGNIFICANCES (P) FOR DISCRIMINATION BETWEEN DCM AND REF (* - P<0.05, MEAN – MEAN VALUE, SD – STANDARD DEVIATION)

	P	DCM MEAN±SD	REF MEAN±SD
$CI/COMPP_{MPNB}$	0.6764	0.97±0.04	0.98±0.01
HR_TO_{MPNB}	0.2647	0.5±2.5	0.4±1.0
HR_TS_{MPNB}	0.7492	11.8±9.1	12.3±8.9
SBP_5_{MPNB}	0.0030 *	112±21	123±21
DBP_5_{MPNB}	0.0000 *	57±13	67±11
$PEAP_{MPNB}$	0.2452	2.2±3.9	1.5±2.1
MBP_TS_{MPNB}	0.7794	0.7±0.3	0.7±0.2
MBP_TSn_{MPNB}	0.0000 *	60.0±33.3	3.5±13.7

IV. DISCUSSION AND CONCLUSION

In this study we investigated HRT and BPT after MPNB in comparison to HRT and BPT after PVC as well as standard HRV in patients with DCM and healthy subjects.

The analysis of HRV of short term ECG did not contribute to classify DCM patients. The results were in accordance to the MACAS study [9]. Like-wise, the application of heart rate turbulence after PVC and MPNB revealed no significant differences between DCM and REF. In contrast, the regulation of blood pressure after the occurrence of PVC or MPNB measured by parameters of BPT and BPT_{MPNB} was significantly changed in DCM patients [4]. Both BPT after PVC and BPT after MPNB revealed similar results. Mean systolic (SBP_5) and diastolic (DBP_5) blood pressure before PVC and MPNB were significantly reduced in DCM patients, the normalized mean blood pressure turbulence slope was notable increased in DCM after PVC as well as MPNB.

With the standard methods of HRT and BPT only a limited number of patients i.e. patients with PVC can be analyzed. In contrast, using this new method of analyzing HRT and BPT after MPNB all patients could be included in this study which results in an enlarged study population. The accuracy of both methods (HRT/BPT) after PVC and MPNB, was comparable. After validation of both MPNB triggered methods and verification of the study results by means of an increased number of patients, HRT and BPT after MPNB should be implemented in the standard analysis. Further studies should be performed to determine the differences between HRT/BPT triggered by a PVC and HRT/BPT_{MPNB} in other cardiac diseases. Finally, the suitability of especially BPT after MPNB for the enhancement in risk stratification of sudden cardiac death should be investigated.

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