# ANALYSIS OF CARDIOVASCULAR VARIABILITIES FOR ENHANCED RISK STRATIFICATION IN PATIENTS WITH DCM

A. Voss*, S. Truebner*, R. Schroeder*, D. Selbig**, M. Meesmann***, M. Goernig#, G. Schmidt##, A.Schirdewan** and H.R. Figulla#

*Department of Medical Engineering, University of Applied Sciences Jena, Germany
**Franz-Volhard-Clinic, Charité, Humboldt University Berlin, Germany
*** Stiftung Juliusspital Wuerzburg, Germany
# Clinic of Internal Medicine I, Friedrich Schiller University Jena, Germany
## German Heart Centre of the Technical University Munich, Germany

voss@fh-jena.de

**Abstract: Dilated cardiomyopathy (DCM) is characterised by dilation and impaired contraction of the left ventricle or both ventricles. It was shown that standard heart rate variability (HRV) analysis did not contribute to an enhanced risk stratification. Therefore, we studied the ability of a more complex variability analysis for an improved risk prediction in DCM. Continuous non-invasive blood pressure and high resolution ECG were recorded from 91 male and female DCM patients. During follow-up of 24 months, 14 patients died due to a cardiac event or needed resuscitation because of a life threatening arrhythmia. Analysing the HRV and blood pressure variability (BPV) measures from time domain, frequency domain and nonlinear dynamics as well as baroreflex sensitivity were calculated. Additionally parameters from heart rate and blood pressure turbulence were estimated. Using Mann-Whitney u test and Bonferroni criterion univariate differences between the patient groups – high risk and low risk – were evaluated. Six parameters of BPV show high univariate significant differences between high risk and low risk groups. Mainly non-linear measures from diastolic blood pressure variability contribute to an enhanced risk stratification in patients suffering from dilated cardiomyopathy.**

## Introduction

Heart failure is recognised as a major and escalating public health problem in industrialised countries with ageing populations. The overall prevalence of clinically identified heart failure is estimated up to 20 cases/ 1000 population, but rises to >100 cases/ 1000 population in those aged >65 years. The prevalence of confirmed left ventricular systolic dysfunction also increases with age and is more common in men [1].

According to the classification of the World Health Organization dilated cardiomyopathy (DCM) is characterised by dilation and impaired contraction of the left ventricle or both ventricles [2]. DCM usually occurs with heart failure, which is often progressive. DCM may be idiopathic, familial/genetic, viral and/or immune, alcoholic/toxic or associated with recognised cardiovascular disease in which the degree of myocardial dysfunction is not explained by the abnormal loading conditions or the extent of ischemic damage. Arrhythmias, thromboembolisms and sudden cardiac death are common and may occur at any stage. Nearly 5 – 10 % of patients with dilated cardiomyopathy suffer from sudden cardiac death (SCD). Today, there are no generally accepted indications on clinical findings, identifying DCM patients with an increased risk of sudden cardiac death or malignant ventricular arrhythmias, for prophylactic defibrillator implantation [3].

The aim of this study was to analyse the suitability of blood pressure variability (BPV) as well as heart rate turbulence (HRT), blood pressure turbulence (BPT) and baroreflex sensitivity (BRS) in comparison to heart rate variability (HRV) for a complex and non-invasive risk stratification in patients with dilated cardiomyopathy.

## Materials and Methods

The investigation conforms to the recommendations of the Declaration of Helsinki. The ethical committee of the respective institutions approved the study protocol.

***Patients and data recording:*** The overall study population included 91 gender- and age-matched patients with DCM from the university hospitals in Berlin and Jena (table 1). High-resolution short term ECG (1600 Hz sampling frequency) and continuous non-invasive blood pressure (NIBP, 100 Hz) were recorded over 30 minutes under resting conditions using the Portapres non-invasive blood pressure monitor (TNO Biomedical Instrumentation, Netherlands). Based on volume clamp method [4] and calibration criteria [5] the peripheral arterial blood pressure was measured via finger cuff. Diagnosis of DCM was performed by traditional coronary angiography and echocardiography in all subjects. Patients with chronic renal failure, diabetes mellitus and a permanent pacemaker were excluded from this study. The clinical measures ejection fraction *(EF)* as well as the end-diastolic diameter of the left


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ventricle *(LVEDD)* were registered for every patient. Additionally, the functional and therapeutic classification (*NYHA:* range I – IV) of the New York Heart Association was considered.

Table 1: Characteristics of the study patients

| **Group:** | **$RISK_H$** | **$RISK_L$** |
|---|---|---|
| *N (male / female)* | 14 (11/3) | 73 (59/18) |
| *Age [years]* | 54 ± 11 | 56 ± 10 |
| *EF [%]* | 31 ± 6 | 37 ± 12 |
| *LVEDD [mm]* | 69 ± 10 | 63 ± 7 |
| *NYHA [I – IV]* | 2.8 ± 0.8 | 2.0 ± 0.7 |

During a follow-up period of about 24 months, 14 high-risk DCM patients ($RISK_H$) died due to a cardiac event or needed resuscitation because of a life threatening arrhythmia. 73 low risk patients ($RISK_L$) remained in unchanged state of disease.

***Data pre-processing*** was performed calculating the tachogram (inter beat intervals - IBI), systogram (systolic blood pressure values over time) and diastogram (diastolic blood pressure values over time) from the heart rate and blood pressure time series. Further on, ventricular premature beats and artefacts were removed from the time series to construct the so-called normal-to-normal beat time series (NN). This was performed applying an adaptive variance estimation algorithm, considering the variance within the time series just before and directly after the ectopic beat [6].

***HRV and BPV*** were quantified calculating standard parameters [7] from linear time and frequency domain as well as nonlinear dynamics [8]. Amongst others the following time domain parameters were evaluated from all heart rate and blood pressure time series: the mean IBI (*meanNN*) as well as the mean values of systolic (*sbp_meanNN*) and diastolic blood pressure (*dbp_meanNN*), the standard deviations (*sdNN*, *sbp_sdNN*, *dbp_sdNN*), the square root of the mean squared differences of successive NN intervals (*rmssd*) or of successive blood pressure values (*sbp_rmssd*, *dbp_rmssd*). In addition, parameters from the frequency domain were calculated. *VLF* represents the power of the tachogram, *sbp_VLF* of the systolic blood pressure and *dbp_VLF* of the diastogram in the frequency band 0.0033 to 0.04 Hz, *LF* (*sbp_LF*, *dbp_LF*) is the power within 0.04 to 0.15 Hz, HF (*sbp_HF*, *dbp_HF*) represents the power from 0.15 to 0.4 Hz and XHF (*sbp_XHF*, *dbp_XHF*) is the power from 0.15 to 0.6 Hz. *P* denotes the total spectral power of the tachogram, *sbp_P* and *dbp_P* of the systogram or diastogram. The spectra were estimated using the Fast Fourier transform. To avoid any leakage effect, a Blackman Harris window function was applied. The following ratios were included in the analysis: *VLF/P*, *HF/P*, *LF/HF*, *dbp_VLF/P*, *sbp_HF/P*, *sbp_LF/HF*, *dbp_VLF/P*, *dbp_HF/P*, *dbp_LF/HF*.

To classify dynamic changes within the time series, we developed the following nonlinear concept of symbolic dynamic.

Applying symbolic dynamics [8] the time series of inter beat intervals and blood pressure were transformed into four symbols (0, 1, 2, 3). The transformation into symbols refers to four given levels (see equations 1-4) where μ is the mean IBI or mean blood pressure, a is a special scaling parameter which was set to 0.1 and $bp_n$-$bp_{n-1}$ is the difference between two successive blood pressure maxima or minima or the IBI from ECG at the time point n.

The transformation rules for blood pressure are:

$$0: \quad \mu < bp_n - bp_{n-1} \le (1+a)\cdot\mu \qquad (1)$$

$$1: \quad (1+a)\cdot\mu < bp_n - bp_{n-1} < \infty \qquad (2)$$

$$2: \quad (1-a)\cdot\mu < bp_n - bp_{n-1} \le \mu \qquad (3)$$

$$3: \quad 0 < bp_n - bp_{n-1} \le (1-a)\cdot\mu \qquad (4)$$

After symbol transformation words consisting of three symbols (000,001…333) were defined (figure 1).

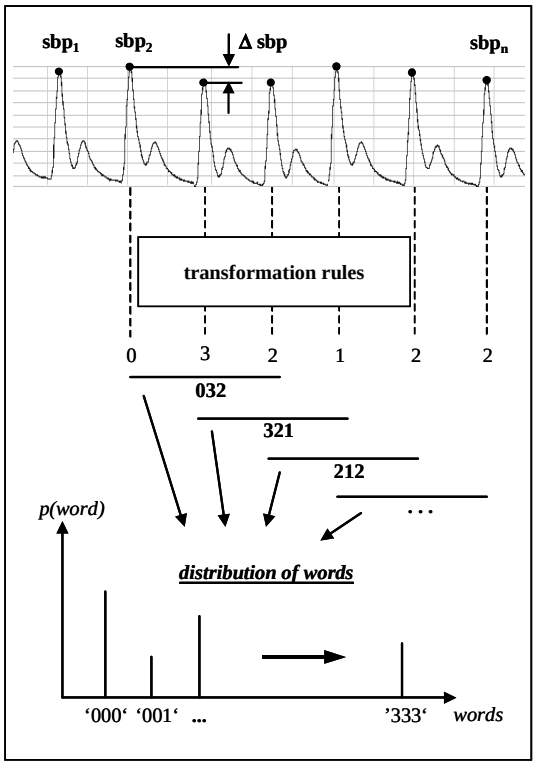


Figure 1: Basic principle of symbol extraction from time series of systolic blood pressure ($sbp_n$).

The Shannon (5) and Renyi entropies (6) calculated from the distribution of words are suitable measures for the complexity of the corresponding tachogram (*wd_shannon*, *wd_renyi*), systogram (*sbp_wd_shannon*, *sbp_wd_renyi*) and diastogram (*dbp_wd_shannon*, *dbp_wd_renyi*). Higher values of these entropies refer to higher complexity within the corresponding time series and lower values to lower ones. The Shannon entropy is


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defined based on the probability distribution p of every single word, whereas k (k = 64) is the total number of words:

$$wd\_shannon = -\sum_{t=1}^{k} p_t \cdot log_2\ p_t \qquad (5)$$

The concept of Renyi entropy was introduced as a generalization of Shannon's approach, where q is a real number and q ≠ 1:

$$wd\_renyi(q) = \frac{1}{1-q} log\left(\sum_{t=1}^{k} {p_t}^q\right) \qquad (6)$$

In an additional mode of symbolic dynamics words consisting of six symbols of a simplified alphabet with only the symbols '0' and '1' were analysed. The symbol '0' stands for a difference between two successive blood pressure maxima or minima lower than a special limit (e.g. 2 mmHg) whereas '1' represents those cases where the difference exceeds this limit. The parameters plvar2 and phvar2 refers to the probability of words consisting only of an unique type of symbols:
plvar2 = p('000000') and phvar2 = p('111111').

***BRS*** was estimated by using the dual sequence method [9]. Therefore, the beat-to-beat series of systolic blood pressure was scanned to identify a 'sequence', that is a series of three heart beats in which a monotonic increase (or decrease) of systolic pressure is followed by a monotonic increase (or decrease) of IBI. The slope of the regression line between IBI and systolic blood pressure values of each sequence gives a local estimate of the BRS. Two kinds of IBI responses were analysed: bradycardiac fluctuations (an increase in systolic blood pressure causes an increase in IBI – *brady_slope*) and tachycardiac fluctuations (a decrease in systolic blood pressure causes a decrease in BBI – t*achy_slope*). Both parameters *n_tachy* and *n_brady* refer to the number of tachycardiac and bradycardiac fluctuations.

***HRT and BPT*** were estimated from ECG and NIBP in 65 patients with single premature ventricular contraction (PVC) followed by a compensatory pause [10, 11]. The turbulence onset *(HR-TO)* was defined as the difference between the first two IBI after PVC and the two IBIs immediately prior to the PVC. Turbulence slope *(HR-TS)* was the slope of the steepest regression line over any sequence of five consecutive IBIs within the first 15 sinus rhythm intervals after PVC. For blood pressure analysis we calculated *MBP-TS* representing the maximum positive slope of a regression line fitted to five consecutive mean blood pressure values within the first 15 sinus rhythm intervals after a PVC (see figure 2). The postextrasystolic amplitude potentiation *(PEAP)* is defined as the quotient of the difference between the first normal amplitude PVC ($BP_{+1}$) after a PVC and the last normal blood pressure amplitude ($BP_{REF}$) before a PVC ($BP_{REF}$) in percent (7).

$$PEAP\,[\%] = \frac{BP_{+1} - BP_{REF}}{BP_{REF}} \cdot 100 \qquad (7)$$

Furthermore, we calculated BRS from the ratio of heart rate *HR-TS* to blood pressure *MBP-TS* turbulence slope *(Turb-BRS)* [11].

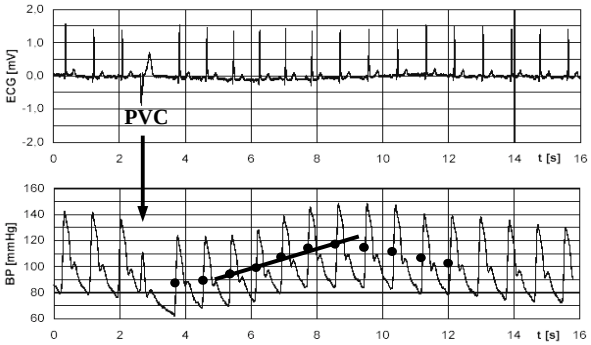


Figure 2: Basic principle of calculation of *MBP-TS* after a PVC

***Statistical analyses*** for evaluating the differences in HRV and BPV as well as HRT, BPT and BRT between low risk DCM patients ($RISK_L$) and high risk DCM patients ($RISK_H$) were performed using the Mann-Whitney u test to get the univariate significances. Considering the Bonferroni criterion for multiple statistical comparisons the univariate significances (p<0.05) had to be corrected to p<0.0003.

The COX regression model was applied to determine how effectively the two groups could be discriminated by the significant univariate parameters.

## Results

Both groups, $RISK_H$ and $RISK_L$, were age-matched (p=0.628), gender-matched (p=1.0) and could not be discriminated by the clinical parameter *EF* (p=0.082). However, the clinical measures *LVEDD* and *NYHA* were different in both groups (*LVEDD*: p = 0.033; *NYHA*: p = 0.001), but regarding to the Bonferroni criterion (p < 0.0003) not univariate significant.

Table 2: HRV - significances (p) for discrimination between $RISK_H$ and $RISK_L$ (* p<0.05; ** p<0.0003 - fulfilling Bonferroni criterion)

| **parameter** | **p** | **$RISK_H$** mean ± std | **$RISK_L$** mean ± std |
|---|---|---|---|
| *meanNN* | 0.070 | 828.9 ± 112.6 | 907.0 ± 145.7 |
| *sdNN* | 0.715 | 35.6 ± 19.1 | 38.1 ± 22.2 |
| *rmssd* | 0.996 | 22.7 ± 15.7 | 22.8 ± 14.3 |
| *LF* | 0.267 | 57.5 ± 69.7 | 89.7 ± 147.4 |
| *HF* | 0.510 | 42.2 ± 67.9 | 41.5 ± 59.5 |
| *XHF* | 0.538 | 45.7 ± 71.4 | 44.9 ± 62.4 |
| *wd_shannon* | 0.935 | 2.4 ± 0.7 | 2.5 ± 0.5 |

Neither short-term HRV (table 2) nor baroreflex analysis (table 3) revealed significant differences be-


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tween $RISK_H$ and $RISK_L$. The number of all spontaneous tachycardiac (*n_tachy*: p=0.630) and bradycardiac events (*n_brady*: p=0.278) were comparable in both patient groups. Compared to patients with low risk DCM patients with a high risk showed decreased but not significant bradycardiac (p=0.110) and tachycardiac baroreflex slopes (p=0.075).

Table 3: BRS - significances (p) for discrimination between $RISK_H$ and $RISK_L$ (* p<0.05; ** p<0.0003 - fulfilling Bonferroni criterion)

| parameter | p | $RISK_H$ mean ± std | $RISK_L$ mean ± std |
|---|---|---|---|
| *n_tachy* | 0.630 | 27.7 ± 31.8 | 29.6 ± 28.2 |
| *n_brady* | 0.278 | 33.5 ± 50.1 | 33.8 ± 30.9 |
| *tachy_slope* | 0.075 | 5.6 ± 3.9 | 8.2 ± 4.8 |
| *brady_slope* | 0.110 | 5.3 ± 4.0 | 7.6 ± 5.0 |

Heart rate turbulence and blood pressure turbulence parameters did not contribute to risk stratification in DCM patients (table 4). The parameters describing the cardiovascular regulation after a PVC revealed no significant differences between high risk and low risk patients. Compared to low risk patients (*PEAP*: 30.5% ± 21.5%) postextrasystolic regulation is decreased in high-risk patient (*PEAP*: 37.8% ± 14.6%) but not univariate significant (p=0.091).

Table 4: HRT and BPT - significances (p) for discrimination between $RISK_H$ and $RISK_L$
(*p<0.05; ** p<0.0003 - fulfilling Bonferroni criterion)

| parameter | p | $RISK_H$ mean ± std | $RISK_L$ mean ± std |
|---|---|---|---|
| *HR-TO (%)* | 0.373 | 0.7 ± 3.7 | -0.4 ± 3.4 |
| *HR-TS (ms/IBI)* | 0.249 | 8.0 ± 5.9 | 11.9 ± 8.7 |
| *MBP-TS (mmHg/IBI)* | 0.245 | 1.4 ± 0.9 | 1.1 ± 0.7 |
| *Turb_BRS (ms/mmHg)* | 0.170 | 10.0 ± 11.7 | 17.3 ± 16.6 |
| *PEAP (%)* | 0.091 | 37.8 ± 14.6 | 30.5 ± 21.5 |

Several parameters of systolic and diastolic BPV show high significant (p<0.0003) differences between $RISK_H$ and $RISK_L$ (table 5). Especially measures from nonlinear dynamics (Shannon and Renyi entropy) of diastolic as well as systolic blood pressure variability revealed high significant differences between the two groups. In comparison to systolic blood pressure the standard deviation of the differences between successive diastolic blood pressure amplitudes (*dbp_rmssd*) and the spectral power from 0.15 – 0.6 Hz (*dbp_XHF*) of diastolic blood pressure time series are highly significant (both p<0.0003).

The COX regression model was applied to the univariate significant parameters of blood pressure variability as well as clinical data. Figure 4 shows the Receiver Operator Curve (ROC) of the parameter *dbp_wd_shannon* of the diastolic blood pressure in comparison to the ROC of the clinical measures *NYHA* and *EF*. The ROC of *NYHA* and *EF* cover an area of 76.6% and 65.4% (*NYHA*: specificity 69.7%; sensitivity 64.3%; *EF*: specificity 60.5%, sensitivity 64.3%) whereas the parameter *dbp_wd_shannon* of the symbolic dynamics covers an area of 87.8% (specificity: 85.7%; sensitivity: 77.9%).

Table 5: systolic (sbp) and diastolic (dbp) blood pressure variability - significances (p) for discrimination between $RISK_H$ and $RISK_L$ (* p<0.05; ** p<0.0003)

| parameter | p | $RISK_H$ mean ± std | $RISK_L$ mean ± std |
|---|---|---|---|
| *sbp_rmssd* | 0.0372* | 3.38 ± 1.18 | 2.91 ± 2.08 |
| *sbp_XHF* | 0.0793 | 0.97 ± 0.87 | 0.68 ± 1.34 |
| *sbp_wd_shannon* | 0.0005* | 2.96 ± 0.32 | 2.62 ± 0.36 |
| *sbp_plvar2* | 0.4487 | 0.09 ± 0.09 | 0.17 ± 0.20 |
| *sbp_wd_renyi025* | 0.0008* | 3.52 ± 0.25 | 3.26 ± 0.25 |
| *sbp_wd_renyi4* | 0.0098* | 2.20 ± 0.41 | 1.88 ± 0.44 |
| *dbp_rmssd* | 0.0001** | 1.90 ± 0.59 | 1.39 ± 0.61 |
| *dbp_XHF* | 0.0002** | 0.27 ± 0.20 | 0.13 ± 0.15 |
| *dbp_wd_shannon* | 0.0000** | 3.08 ± 0.28 | 2.59 ± 0.36 |
| *dbp_plvar2* | 0.0002** | 0.32 ± 0.24 | 0.62 ± 0.26 |
| *dbp_wd_renyi025* | 0.0000** | 3.58 ± 0.20 | 3.29 ± 0.23 |
| *dbp_wd_renyi4* | 0.0000** | 2.39 ± 0.33 | 1.80 ± 0.39 |

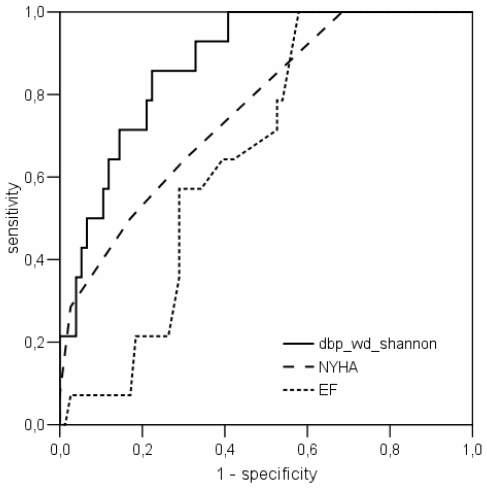


Figure 4: Receiver Operator Curve of the clinical measures *NYHA* and *EF* as well as the nonlinear parameter *dbp_wd_shannon*

**Discussion**

In this study we analysed the suitability of blood pressure variability as well as heart rate turbulence,


ISSN: 1727-1983 

blood pressure turbulence and baroreflex sensitivity in comparison to heart rate variability for risk stratification in patients with DCM. According to the MACAS study [12] the analyses of short term HRV and baroreflex sensitivity did not contribute to risk stratification. Likewise, the application of heart rate turbulence and blood pressure turbulence do not lead to an enhanced risk stratification. Analysing blood pressure time series with linear time and frequency domain as well as nonlinear dynamics reveals significant differences between survivors and cardiac deaths. Considering especially the transformed diastolic blood pressure time series the entropy of word distribution is increasing with progression of disease. Furthermore, the spectral power from 0.15-0.6 Hz *(XHF)* as well as the parameter *rmssd* is more increased in diastolic than in systolic blood pressure within the group of high risk patients. Compared to *NYHA* (specificity: 69.7%, sensitivity 64.3%) and *EF* (specificity: 60.5%; sensitivity: 64.3%) the application of the parameter *dbp_wd_shannon* improves considerably the classification of the DCM patients (specificity: 85.7%; sensitivity: 77.9%). These results suggest to initialize a further study developing an optimal (multivariate) parameter set for identification DCM patients with an increased risk for sudden cardiac death .

## Conclusions

The analysis of short term HRV and baroreflex sensitivity as well as heart rate and blood pressure turbulence is not suitable to improve risk stratification in DCM. However, measures from systolic and especially diastolic BPV enhance the separation between high and low risk and could contribute to an early non-invasive prediction of sudden cardiac death in patients with dilated cardiomyopathy.

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