Alternans of Blood Pressure and Heart Rate in Patients with Dilated Cardiomyopathy

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Abstract

Alternans is characterized by changes of interbeat intervals (IBI) and blood pressure amplitudes (BPA) on a beat-to-beat basis. We hypothesize that an impaired myocardial performance influences the duration and amplitude of the alternans and could enhance the diagnostics in patients with dilated cardiomyopathy (DCM). ECG and non-invasive blood pressure were recorded from 91 DCM patients and 45 healthy controls. Alternans phenomena were detected as a beat preceded and followed by beats that had higher or lower values in the respective modality. Mean duration of IBI alternans ($p=0.032$) as well as BPA alternans (systolic: $p<0.001$; diastolic: $p=0.021$) and maximum alternans durations (IBI: $p=0.003$; systolic BPA: $p<0.001$; diastolic BPA: $p=0.004$) were significantly enlarged in DCM. Alternans analysis seems to be useful for an enhanced classification and functional assessment of DCM patients.

1. Introduction

Electrical and hemodynamical alternans are symptoms of limited cardiac output. Thereby, the incidence of occurred alternans phenomena is associated with the severity of the impaired cardiac performance [1]. Several studies proved the occurrence of alternans in patients with abnormal left-ventricular function [2] and directly after ventricular premature complexes [3,4] triggered by postextrasystolic potentiation [5,6]. Hemodynamical alternans is characterized by regular alterations between a high and a low blood pressure amplitude and can result in a beat-to-beat alternation of the heart rate (electrical alternans) [1,7].

The hypothesis of this study was that an impaired myocardial performance influences the duration and amplitude of the alternans phenomena. Therefore, the objective was to investigate whether an extended analysis of alternans contributes to an enhanced characterization of patients with dilated cardiomyopathy (DCM). For this purpose the frequency, amplitude and duration of alternans patterns from blood pressure and beat-to-beat interval time series were determined and analyzed in DCM patients and heart healthy subjects (REF).

2. Methods

From 91 DCM patients (ejection fraction 35±12, left ventricular diameter of 63±8 mm) with sinus rhythm and 45 REF age matched subjects thirty minutes of high-resolution ECG (orthogonal corrected Frank lead ECG with 22 bit resolution) and synchronized continuous non-invasive blood pressure (NIBP) were recorded (Figure 1) at the university hospitals of Berlin and Jena. All recordings were performed under standardized resting conditions (supine position, quiet environment, same day time). NIBP was measured on the left middle finger applying the Portapres M2 blood pressure monitor (TNO-TPD, Amsterdam, Netherlands) [8] based on the volume clamp method [9] and the calibration criteria [10]. Using a commercially available amplifier system (Twente Medical Systems, Netherlands) ECG and NIBP were discretized (sampling frequency: ECG=1600Hz and NIBP=500Hz) and stored in a database together with the patient data.

DCM was diagnosed by experienced cardiologists via angiography and echocardiography. From every patient the clinical measures ejection fraction (EF), end-diastolic diameter of the left ventricle (LVEDD) as well as the functional and therapeutic classification of the New York Heart Association (NYHA: range I – IV) to quantify the status of heart failure were registered. Patients with atrial fibrillation or flutter, permanent pacemaker or defibrillator, chronic renal failure and diabetes mellitus were excluded from this study. All DCM patients got a comparable treatment with drugs as ACE inhibitors, beta blockers, diuretics and digitalis.

Heart rate time series (tachogram) consisting of interbeat intervals (IBI) and blood pressure amplitude time series (systogram and diastogram) consisting of systolic maxima (SYS) as well as enddiastolic minima (DIA) were extracted from the raw data. Calibration intervals in the blood pressure that occur approximately all 60 heartbeats as a result of the adaptation of the Portapres as well as disturbances or artifacts were replaced by interpolated beats applying an adaptive variance estimation algorithm [11].

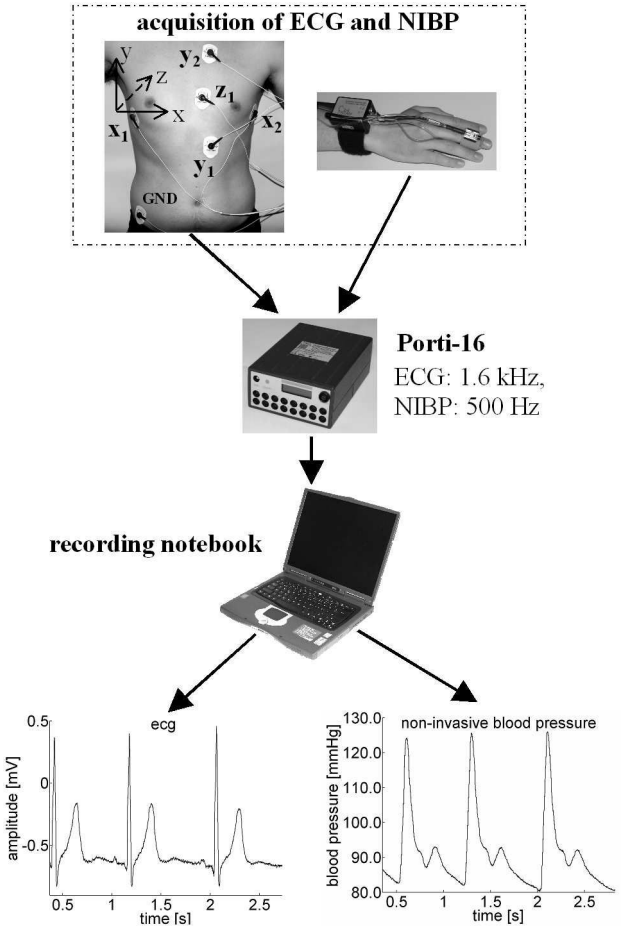

Figure 1: Measuring system for acquisition of ECG and non-invasive blood pressure.

From the extracted normal-to-normal beat time series heart rate and blood pressure alternans phenomena were estimated. The detection of the electrical alternans was carried out on the basis of at least four consecutive IBIs. Thereby, alternans phenomena were detected if a short or a long IBI_n was followed by at least three intervals with the sequence long-short-long:

$(IBI_n < IBI_{n+1} > IBI_{n+2} < IBI_{n+3})$

or short-long-short

$(IBI_n > IBI_{n+1} < IBI_{n+2} > IBI_{n+3})$.

Hemodynamical alternans was defined as alternate fluctuation of the blood pressure of at least four consecutive systoles

$(SYS_n < SYS_{n+1} > SYS_{n+2} < SYS_{n+3})$ or

$(SYS_n > SYS_{n+1} < SYS_{n+2} > SYS_{n+3})$

and diastoles

$(DIA_n < DIA_{n+1} > DIA_{n+2} < DIA_{n+3})$ or

$(DIA_n > DIA_{n+1} < DIA_{n+2} > DIA_{n+3})$

respectively.

The duration of a alternans pattern was defined as 2 if the IBI sequence showed the character “long-short-long” or “short-long-short”. The number of further alternating IBIs following this sequence was added to the alternans duration (Figure 2). Two examples of alternans in heart rate and blood pressure time series are shown in Figure 3 and Figure 4. Considering four IBIs or blood pressure amplitudes as the minimum alternans sequence the duration of an alternans is limited to at least 2.

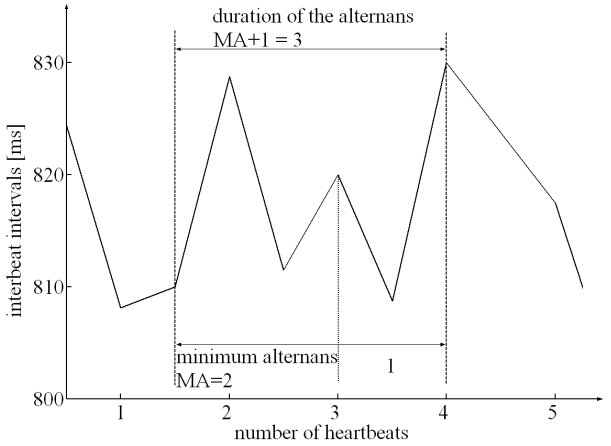

Figure 2: Determination of the alternans duration.

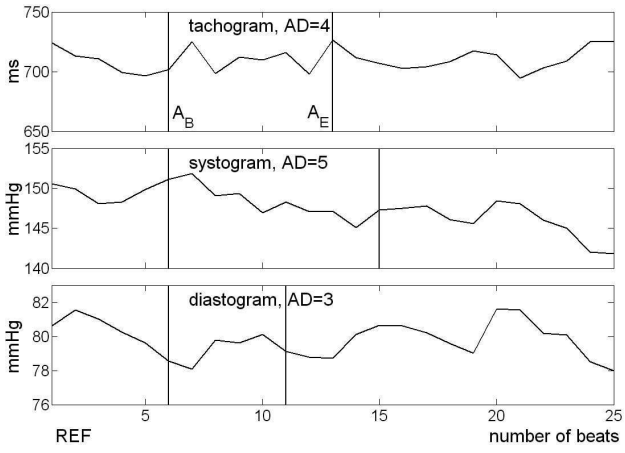

Figure 3: Examples of alternans in heart rate and blood pressure time series (REF)
(AD - alternans duration, A_B - alternans begin, A_E - alternans end).

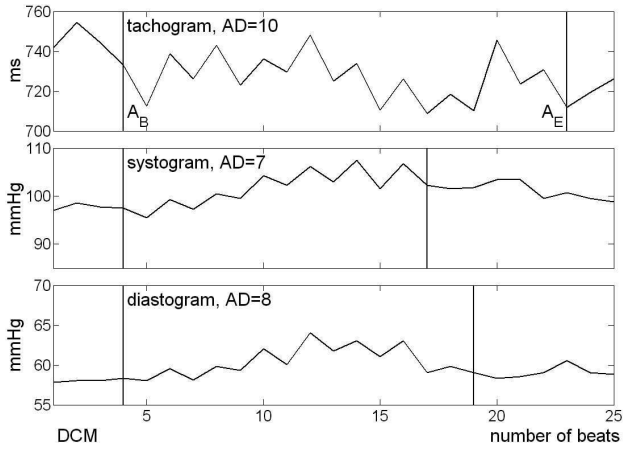

Figure 4: Examples of alternans in heart rate and blood pressure time series (DCM)
(AD - alternans duration, A_B - alternans begin, A_E - alternans end).

Subgroups consisting of 53 DCM patients and 39 REF subjects were matched for age, gender, heart rate and blood pressure (Table 1). For each DCM patient and REF within these subgroups the minimum, maximum and mean values of duration, amplitude as well as the total number of occurred alternans patterns within the IBI and blood pressure time series were calculated to quantify the alternans sequences. Mean values and standard deviations were estimated for all alternans parameters using the SPSS 13.0 software. Using Mann-Whitney U-test with a significance level of $p<0.05$ univariate significance values describing the possibility to classify DCM and REF were estimated.

3. Results

The highest significant values ($p<0.001$) in differentiating between DCM and REF were obtained considering the systolic and diastolic hemodynamical alternans parameters (Table 2). The mean duration (MeanAD) of the systolic (DCM: 3.05±3.22 periods, REF: 2.08±0.07 periods; $p<5.7E-08$) as well as the diastolic (DCM: 2.68±1.92 periods, REF: 2.24±0.13 periods; $p<0.021$) alternans patterns was significantly enlarged in patients with DCM compared to REF. Furthermore, the maximum alternans durations (MaxAD) within the blood pressure amplitude time series were enlarged in DCM (systolic: 10.25±14.54 vs. 3.82±0.91 periods, $p<6.3E-08$; diastolic: 8.40±8.57 vs. 5.51±2.05 periods, $p<0.004$). Previous studies [1,2] could show an increased occurrence of alternans patterns within the blood pressure amplitude series in DCM. The same result was proven in this study and showed an increased total number of diastolic alternans patterns (TotA: 229.15±71.78 vs. 203.21±77.83, $p<0.042$) in DCM patients. Considering the IBI alternans, the mean (2.46±0.97 vs. 2.21±0.19 periods, $p<0.032$) and the maximum duration (7.43±6.37 vs. 4.97±1.72 periods, $p<0.003$) of the alternans patterns were also enlarged in DCM in contrast to REF. The amplitude of the alternans patterns could not differentiate between DCM and REF.

Table 1: Matched DCM and REF subgroups;
NYHA - New York Heart Association, LVEDD - left ventricular end-diastolic diameter, meanIBI - mean interbeat interval, meanSYS - mean systolic value, meanDIA - mean diastolic value, mean value ± standard deviation, p - significance value.

parameter	DCM	REF	p
number of patients (♂/♀)	53 (42/11)	39 (25/14)	0.15
age [years]	53 ± 11	52 ± 10	0.95
ejection fraction [%]	35 ± 12	/	/
NYHA index	2.3 ± 0.7	/	/
LVEDD [mm]	63 ± 8	/	/
meanIBI[ms]	857 ± 137	862 ± 129	0.66
meanSYS [mmHg]	118 ± 16	120 ± 16	0.49
meanDIA [mmHg]	65 ± 8	66 ± 8	0.26

Table 2: Results of the alternans analysis for the group test REF vs. DCM; IBI - interbeat interval time series, SYS and DIA - systolic and diastolic blood pressure time series, MeanAD and MaxAD [periods] - mean and maximum alternans duration within a time series, TotA - total number of alternans patterns within a time series, mean value ± standard deviation, p - significance value.

signal	parameter	DCM	REF	p
IBI	*MeanAD*	2.46 ± 0.97	2.21 ± 0.19	0.032
	MaxAD	7.43 ± 6.37	4.97 ± 1.72	0.003
SYS	*MeanAD*	3.05 ± 3.22	2.08 ± 0.07	5.7E-08
	MaxAD	10.25 ± 14.54	3.82 ± 0.91	6.3E-08
DIA	*TotA*	229.15 ± 71.78	203.21 ± 77.83	0.042
	MeanAD	2.68 ± 1.92	2.24 ± 0.13	0.021
	MaxAD	8.40 ± 8.57	5.51 ± 2.05	0.004

4. Discussion and conclusions

The results of this study permit the conclusion that a detailed investigation of both electrical and hemodynamical alternans phenomenon contributes to an enhanced characterization of DCM patients. We could demonstrate that the mean and maximum duration of the alternans patterns was significantly enlarged in patients with DCM particularly in the systolic blood pressure time series. Interestingly, the standard deviation of the alternans durations was very high within the DCM group. This could be an effect of the group composition that

includes both low risk patients with a slight impaired left ventricular function and high risk patients mostly with a dramatically declined ventricular function. Considering the original patient groups (93 DCM, 45 REF) nearly the same results were obtained with one exception: the alternans amplitudes differed significantly. These differences between DCM and REF are closely related to the mean systolic and diastolic blood pressure and disappear if the groups are blood pressure matched.

Leder et al. showed in a small number of patients with dilated cardiomyopathy (n=22) vs. REF (n=21) that the amount of alternans patterns indicates the stage of the disease and observed significantly more singular and repetitive alternans patterns in patients compared to a control group within the IBI time series and the blood pressure amplitude series [1]. This study, however, was limited to the investigation of the mean blood pressure alternans, and therefore, no information about the detailed diastolic and systolic alternans behavior were available.

Several studies could show that pulsus alternans is triggered by postextrasystolic potentiation in patients with impaired left ventricular function [5,6]. Voss et al. [6] found slight beat-to-beat fluctuations within the blood pressure time series and less influenced IBI time series after ectopic beats in patients with idiopathic dilated cardiomyopathy. Davies et al. [5] presented an incidence of postectopic alternans in 29% of all investigated patients with chronic congestive heart failure. Thereby, the patients with postectopic pulsus alternans had have a significantly lower heart rate turbulence slope as well as ventricular ejection fraction and a trend toward a lower baroreflex sensitivity than those without postectopic alternans patterns.

The reason for hemodynamical alternans is a combination of alternations in hemodynamic variables and inotropic state and might be associated with electrical alternans [12].

Pulsus alternans is related to the end-diastolic volume which is altered presumably due to the Frank-Starling mechanism [13] or an increased availability of intracellular calcium that causes a varying contractility of the ventricle [14].

In a further study we will investigate if the introduced and promising analysis method is suitable to differentiate between low and high risk in DCM patients, and consequently, if it could be useful for an enhanced risk stratification in DCM.

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