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JOURNAL OF PACING AND CLINICAL ELECTROPHYSIOLOGY, Volume 25, No. 9, September 2002

Alternans of Blood Pressure and Heart Rate in Dilated Cardiomyopathy

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LEDER, U., ET AL.: Alternans of Blood Pressure and Heart Rate in Dilated Cardiomyopathy. *Impaired myocardial performance is known to be associated with electrical and mechanical beat-to-beat alternans phenomena. The alternans in blood pressure and heart rate and their interdependency in idiopathic dilated cardiomyopathy (IDC) were studied. The arterial blood pressure and the electrocardiograph (ECG) were continuously recorded in 22 patients suffering from IDC (age 49 ± 13 years, ejection fraction 0.33 ± 0.13, left ventricular diameter of 67 ± 8 mm) and in 21 healthy controls (age 52 ± 15 years). The beat-to-beat variations of the interbeat intervals (IBI) and of the blood pressure amplitudes (AMP) were measured. An alternans beat was defined as a beat preceded and followed by beats that had higher or lower values in the respective modality. The percentages of singular and repetitive alternans patterns, and the interdependency of the alternans patterns in AMP and IBI were assessed. The study found significantly more singular and repetitive alternans patterns in the IDC group compared to the control group both in the analysis of AMP and IBI (singular alternans in IBI: 55 ± 11 vs 47 ± 7%, $P < 0.01$; singular alternans in AMP: 61 ± 15 vs 45 ± 6%, $P < 0.01$; triple alternans in IBI: 29 ± 18 vs 16 ± 9%, $P < 0.01$; triple alternans in AMP: 34 ± 24 vs 12 ± 7%, $P < 0.01$). The amplitudes of the AMP alternans patterns were higher in IDC compared to controls (9 ± 7 vs 4 ± 2% of AMP, $P = 0.01$) whereas they did not differ in IBI. The correlation analysis revealed a significant interdependency of the alternans pattern in IBI and AMP in 18 of 22 IDC patients and in 12 of 21 controls ($r = 0.50 \pm 0.21$ [IDC]; $r = 0.26 \pm 0.05$ [controls]). The slope of the linear regression (ΔAMP vs ΔIBI) was steeper in the IDC group compared to the control group (62 ± 50 vs 20 ± 22 mmHg/s, $P < 0.01$). The percentages of alternans patterns appearing in IBI and AMP were positively correlated to the left ventricular diameter ($r = 0.70$ in the IBI, and $r = 0.30$ in the AMP). The blood pressure amplitude and the heart rate did not differ between the two groups. Patients suffering from IDC have a higher prevalence, stability, amplitude, and interdependency of alternans patterns in IBI and AMP compared to the control group. The amount of alternans patterns indicates the stage of disease. The alternans analysis may have impact on the functional assessment of patients suffering from heart failure. (PACE 2002; 25:1307–1314)*

alternans, dilated cardiomyopathy, heart failure, heart rate variability, blood pressure variability

Introduction

The beat of the heart varies as a result of different factors, including the myocardial, respiratory, hemodynamic, circadian, nervous, and mental status. Time-domain values of heart rate variability (HRV) can be derived from simple statistical calculations performed on the set of interbeat intervals (IBIs), and the frequency-domain analysis addresses the underlying rhythms.[1] Most of the methods, however, do not consider the beat-to-beat context of the variability.

The most noticeable finding in the beat-to-beat cardiac variability is the alternans phenomenon. The alternans is a special case of beat-to-beat variation with a characteristic repetitive alternation of measurement parameters. Pulsus alternans can be found in some patients with abnormal left ventricular function and can also develop after spontaneous premature beats.[2,3] Its permanent appearance is a significant sign of severe cardiac impairment. Nevertheless, the diagnostic impact of neither the blood pressure alternans nor the heart rate alternans has been systematically studied in heart failure patients.

Blood pressure alternans and heart rate alternans are expected to be of value in the functional assessment of patients suffering from idiopathic dilated cardiomyopathy (IDC). This pilot study measured frequency, stability, amplitude, and interdependency of alternans patterns in blood pres-

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Received January 16, 2001; revised August 6, 2001; accepted September 26, 2001.

sure and heart rate in IDC patients and in healthy controls.

Methods

Subjects and Noninvasive Blood Pressure Recording

Twenty-two patients suffering from IDC with a left ventricular ejection fraction (LVEF) (measured by means of biplane ventriculography) of 0.33 ± 0.13 and a left ventricular end-diastolic diameter of 67 ± 8 mm (measured by means of two-dimensional echocardiography) were studied. The mean age of the IDC was 49 ± 13 years. The diagnosis was confirmed by coronary angiography. IDC patients received the optimum medical treatment including angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and nitrates. The data from the IDC group were compared to 21 healthy controls (controls, mean age of 52 ± 15 years). The healthy status of the control group was confirmed by history, physical examination, 12-lead ECG, and echocardiography. The study was approved by the ethics committee of the Friedrich-Schiller-University Jena.

The finger blood pressure (left middle finger) and the orthogonal ECG were noninvasively recorded at rest in the supine position with the Portapres device (TNO Medical, Amsterdam, NL) for 200 seconds. The recording principle and the measurement device (Fig. 1) have been described in detail elsewhere.[4]

The blood pressure and the ECG were digitized at 0.2 and 1 kHz, respectively. The IBI and the amplitudes of the blood pressure (AMP) were measured automatically, and the results of the automatic measurements were checked visually beat-by-beat afterwards. Data segments with poor quality and calibration intervals of the Portapres device were rejected. Extrasystolic and postextrasystolic beats were also excluded from the analysis.

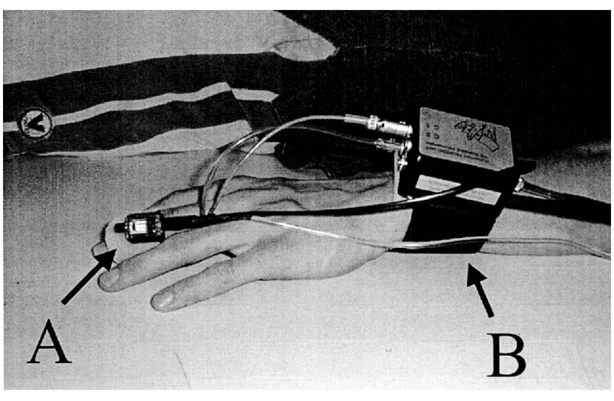

Figure 1. *Noninvasive continuous recording of the arterial finger blood pressure with the Portapres device. The pressure of a finger cuff (A) is regulated by servo pumps (B) which use a photoelectric transmission signal for the input.*

The IBIs were measured as the intervals between the peaks of the R waves, and the AMPs were measured as the difference of the maximum systolic pressure and the end-diastolic pressure at the onset of the systolic wave. The resulting data (Fig. 2) were analyzed for alternans patterns.

Definition of Alternans Patterns

Each beat was classified whether it belonged to an alternans pattern or not and with respect to the number of beats belonging to the respective sequence of alternating beats. An alternans beat was defined as a beat preceded and followed by beats that had higher or lower values in the respective modality. For that purpose the value of the index beat (n) to the values of the respective predecessor (n-1) and successor values (n+1) were compared. The index beat qualified for an alternans beat if the following two conditions were fulfilled: (1) IBI alternans: ($IBI_{n-1} < IBI_n$ and $IBI_{n+1} < IBI_n$) or ($IBI_{n-1} > IBI_n$ and $IBI_{n+1} > IBI_n$), and (2) AMP alternans: ($AMP_{n-1} < AMP_n$ and $AMP_{n+1} < AMP_n$) or ($AMP_{n-1} > AMP_n$ and $AMP_{n+1} > AMP_n$).

A threshold was not applied when comparing the values. Double alternans was defined as two consecutive alternans beats, triple alternans was defined as three consecutive alternans beats, and quadruple alternans was defined as four consecutive alternans beats. Figure 3 displays a classification example.

This classification procedure was performed for the IBI and the AMP. The percentages of the beats belonging to the alternans phenomena of different minimum durations (single, double, triple, and quadruple) were calculated. Please note that in this analysis the index beat may belong to different alternans series (e.g., a quadruple alternans series consists of four consecutive alternans beats, and each of these beats again constitutes a single alternans phenomenon).

To assess the interdependency between the beat-to-beat variations of the different modalities (IBI and AMP) a linear regression analysis was performed and linear correlation coefficients were calculated for the beat-to-beat differences ΔIBI versus ΔAMP. The beat-to-beat differences (ΔIBI, ΔAMP) of the series of IBI and AMP values were calculated by subtracting the respective predecessor values from the actual ones:

$$\Delta AMPn = Amp_n - Amp_{n-1}, \text{ and}$$
$$\Delta IBI_N = IBI_n - Amp_{n-1};$$
n: number of the beat.

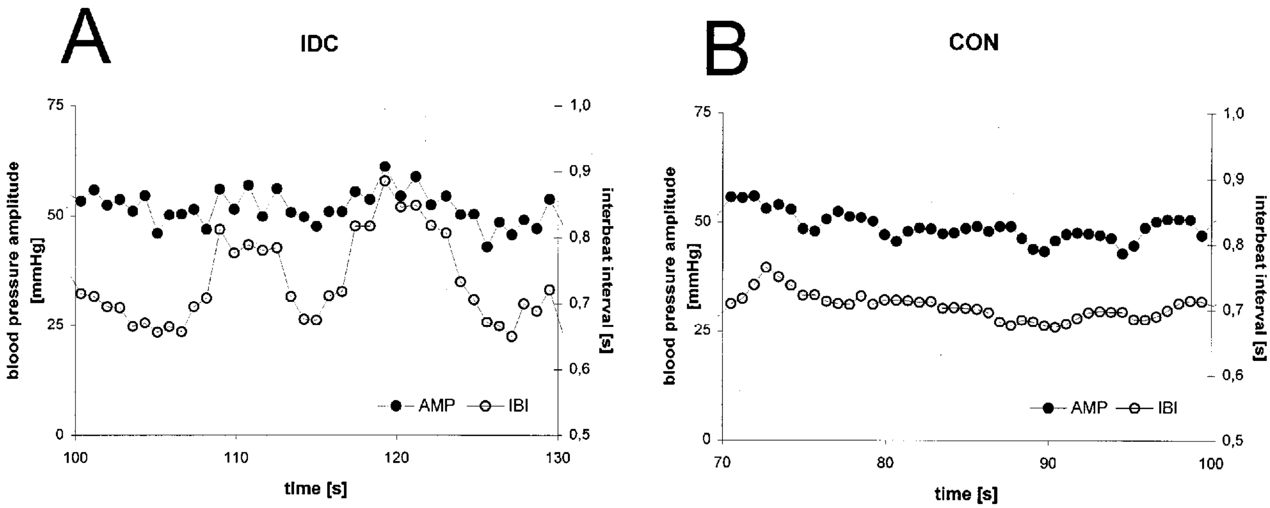

Figure 2. *Examples of the sequences of blood pressure amplitudes (AMP) and interbeat intervals (IBI) in a patient with idiopathic dilated cardiomyopathy (ICD) (A) and a control (CON) (B). These sequences were analyzed for alternans patterns (see Fig. 3).*

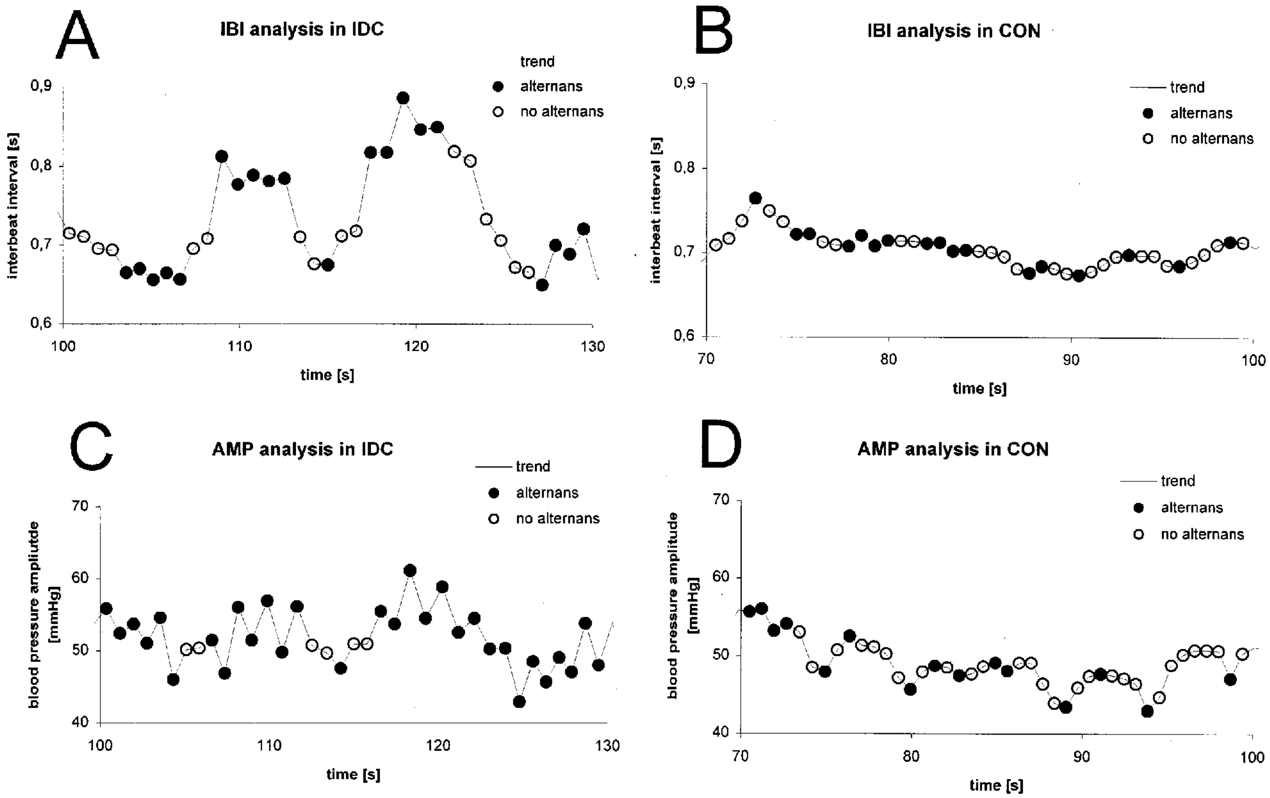

Figure 3. *Alternans classification of the interbeat intervals (IBI) (A, B) and blood pressure amplitudes (AMP) (C, D) in an idiopathic dilated cardiomyopathy (IDC) patient (left) and in a control (CON) (right) calculated from the data displayed in Figure 2. The beats were classified for alternans patterns. In the AMP sequence of the IDC (C) has a prominent alternans pattern.*

Examples of the resulting sequences of beat-to-beat differences are depicted in Figure 4 (upper row).

A linear regression analysis (ΔAMP vs ΔIBI) was performed (Fig. 4C and D). The qualitative analysis of the interdependency of IBI and AMP was done by means of a crosstabulation of the beat classifications (alternans vs no alternans for each of the modalities IBI and AMP, respectively).

The magnitude of an alternans was defined as the absolute value of the mean of the ΔAMP (or ΔIBI) of the respective single alternans sequence.

Statistical Analysis

The mean and the standard deviation were calculated for each of the parameters. Pearson's method was applied to correlate the ΔIBI with the ΔAMP. The least square linear regression was performed to calculate the slope of the ΔAMP versus the ΔIBI. The two-sided *t*-test for unequal variances was performed to compare the mean values of the IDC group versus the control group. The equality of the variances was tested with the Kolmogorov-Smirnov method. The chi-square test was applied to analyze the coincidence of alternans phenomena occurring in AMP and IBI.

Results

The age (49 ± 13 vs 52 ± 15 years), the heart rate (79 ± 11 vs 76 ± 10 beats/min), and the blood pressure amplitude (47 ± 15 vs 48 ± 13 mmHg) did not differ between the IDC and the control groups (Table I).

The magnitude of the IBI alternans was not different between the IDC and the control groups (2.9 ± 2.1 vs 2.7 ± 2.7% of the IBI), whereas the magnitude of the AMP alternans was higher in the IDC group than in the control group (8.9 ± 7.1 vs 4.5 ± 2.3% of AMP, P = 0.01).

Frequency of the Alternans Patterns

The percentage of the alternans patterns in the AMP was significantly higher in the IDC group compared to the control group (61 ± 15 vs 45 ±

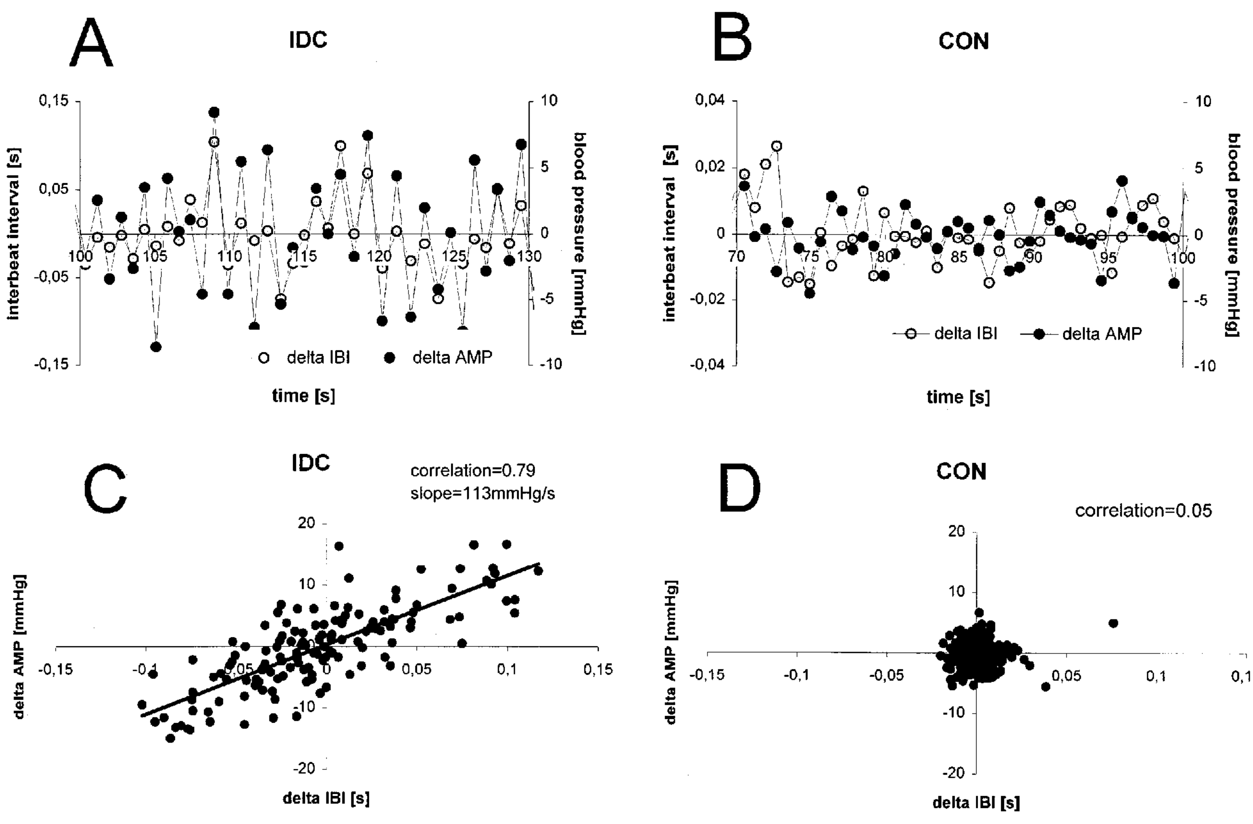

Figure 4. *Beat-to-beat differences (ΔAMP, ΔIBI) in an IDC (A) and in a CON (B) calculated from the data in Figure 2. The time sequences (cutout) are displayed in the upper row, and the correlation plots are displayed in the lower row. In the IDC patient a marked correlation between ΔIBI and ΔAMP was found © which was not observed in the CON group (D). ΔAMP = change in blood pressure amplitudes; ΔIBI = change in interbeat intervals; IDC = idiopathic dilated cardiomyopathy; CON = control.*

Table I.

Blood Pressure, Heart Rate, and Percentages of Alternans Phenomena Appearing in Heart Rate and Blood Pressure in the IDC and CON

Parameters	Unit	IDC Mean	IDC SD*	CON Mean	CON SD*	*t*-test
SBP	mmHg	105.8	22.5	113.7	21.0	0.23
DBP	mmHg	59.0	15.7	65.7	11.5	0.11
AMP	mmHg	46.8	14.9	47.9	12.8	0.79
HR	min^{-1}	79.1	11.0	75.9	10.2	0.32
SDNN	ms	30.5	11.1	30.2	17.2	0.96
IBI Alternans						
Singular	%	54.8	10.7	47.1	6.7	0.006*
Double	%	41.2	16.6	28.5	9.8	0.003*
Triple	%	29.2	17.6	16.3	9.2	0.004*
Quadruple	%	21.5	17.0	10.1	8.3	0.007*
Magnitude	ms	24	18	23	24	0.91
Magnitude	%	2.9	2.1	2.7	2.7	0.80
AMP Alternans						
Singular	%	61.2	15.3	45.5	6.0	< 0.001*
Double	%	46.3	22.6	25.4	7.3	< 0.001*
Triple	%	33.8	23.8	12.1	7.3	< 0.001*
Quadruple	%	26.2	24.0	7.9	5.3	< 0.001*
Magnitude	mmHg	3.9	2.7	2.1	0.9	0.005*
Magnitude	%	8.9	7.1	4.5	2.3	0.010*
Slope (ΔAMP *vs* ΔIBI)	mmHg/s	62.2	50.2	20.5	22.5	0.002*
Correlation (ΔAMP *vs* ΔIBI)		0.50	0.21	0.26	0.05	0.001*

CON = control group; IDC = idiopathic dilated cardiomyopathy; IBI = interbeat intervals; SBP = systolic blood pressure; DBP = diastolic blood pressure; AMP = blood pressure amplitude; HR = heart rate; SDNN = standard deviation of the IBI; SD = standard deviation; *t* = test significance < 5%.

6%, P < 0.01) (Table I). In none of the controls but in 13 of 22 IDC patients, the percentage of beats with an AMP alternans pattern exceeded 60%.

Somewhat lower, but nevertheless significant differences were observed between the IDC and the control groups in the IBI alternans analysis (55 ± 11 vs 47 ± 76%, P < 0.01). In 9 of the 22 IDC patients and in none of the controls, > 60% of beats having an alternans pattern was observed.

Stability of the Alternans Patterns

The duration of the alternans patterns significantly differed between the IDC and the control groups. The prevalence of double, triple, and quadruple alternans phenomena was significantly higher in the IDC patients (Table I). These differences were more striking in AMP analysis compared to the IBI analysis. For instance, in the IBI analysis a quadruple alternans was observed in 22 ± 17% of the beats of the IDC group and in 10 ± 8% of the beats of the Control group (P < 0.01), whereas in the AMP analysis a quadruple alternans was observed in 26 ± 24% of the beats of the IDC group and in 8 ± 5% of the beats of the Control group (P < 0.01).

Interdependency Between the Alternans in the IBI and the AMP

In the IDC group a significant correlation (P < 0.05) was found between the ΔIBI and ΔAMP in 18 of 22 patients, whereas in the Control group a significant correlation was found in 12 of 21 subjects. The mean linear correlation coefficients were 0.50 ± 0.21 in the IDC group and 0.26 ± 0.05 in the Control group, respectively (P < 0.01). The slope of the linear regression analysis (ΔAMP/ΔIBI) was higher in the IDC group than in the Control group (62 ± 50 vs 20 ± 22 mmHg/s, P < 0.01) (Fig. 4).

Figure 5 displays the percentages of single alternans phenomena observed in IBI and AMP.

A high amount of alternans phenomena in IBI was associated with a high amount of alternans phenomena in AMP in the IDC group (Fig. 5).

The crosstabulations (Tables II and III) revealed that the interdependencies between the alternans in IBI and AMP were not caused by a di-

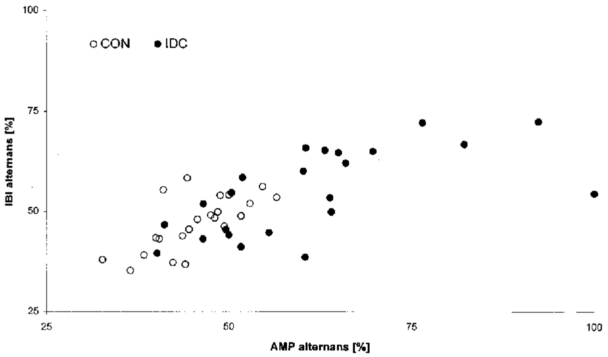

Figure 5. *Scatter plot of the percentage of single alternans phenomena in AMP and IBI in the two groups. AMP = blood pressure amplitudes; IBI = interbeat intervals.*

Table III.

Beat Classification Table of the Control Group

CON	IBI Alternans Yes	No	Sum
AMP alternans			
Yes	988 (22.2%)	1026 (23.1%)	2014 (45.3%)
No	1071 (24.1%)	1360 (30.6%)	2431 (54.7%)
Sum	2059 (46.3%)	2386 (35.7%)	4445 (100%)

The beats of the study group were pooled (n = 4445) and classified for the criteria IBI alternans and AMP alternans, respectively (chi-square 11.1, $p = 0.001$). CON = control group; IBI = interbeat intervals; AMP = blood pressure amplitude.

rect beat related coincidence of the two phenomena. In the IDC and in the Control groups, the number of beats with matching alternans classifications was only 44%. Nevertheless, the chi-square test was significant for both the IDC and the Control alternans crosstable (P < 0.01).

Alternans and Clinical Parameters

Figure 6 displays the percentage of single alternans phenomena as a function of the left ventricular diameter.

The left ventricular end-diastolic diameter positively correlated with the percentage of alternans pattern (r = 0.61 in AMP, r = 0.70 in IBI), with the magnitude of the alternans (r = 0.51 in AMP, r = 0.35 in IBI), and with the slope of the regression of the ΔAMP versus ΔIBI (r = 0.49).

No significant correlation was found between the alternans parameters and the left ventricular ejection fraction and the QRS duration, respectively.

Table II.

Beat Classification Table of the IDC Group

IDC	IBI Alternans Yes	No	Sum
AMP alternans			
Yes	1178 (33.7%)	893 (25.6%)	2071 (59.3%)
No	698 (20.0%)	724 (20.7%)	1422 (40.7%)
Sum	1876 (53.7%)	1617 (46.0%)	3493 (100%)

The beats of the study group were pooled (n = 3493) and classified for the criteria IBI alternans and AMP alternans, respectively (chi-square 20.6, $p < 0.001$). IDC = idiopathic dilated cardiomyopathy; IBI = interbeat intervals; AMP = blood pressure amplitude.

Discussion

The amount of beat-to-beat alternans phenomena occurring in blood pressure and heart rate were quantified, and significant differences were demonstrated between patients suffering from IDC and healthy control subjects.

In the case of randomly varying AMP and IBI, the percentage of single alternans beats among the entire number of beats would be expected to be 50%; a decrease of a parameter value can be followed by an increase or a further decrease. The same occurs with an increase of a parameter value. The overrepresentation of alternans patterns in diseased hearts (55% and 61%, respectively) arises from the disturbance of short-term fluctuations of heart rate and blood pressure like respiratory sinus arrhythmia. In the healthy hearts, the percentage of alternans patterns was < 50%. This indicates the presence of systematic short-term fluctuations of the blood pressure and the heart rate.

This study demonstrated that in patients suffering from dilated cardiomyopathy, the amount and the stability of alternans phenomena in the blood pressure and the heart rate was significantly higher compared to healthy controls. The pulsus alternans, a condition in which the arterial pressure oscillates between a lower level and a higher level on a beat-to-beat basis, is a fundamental finding in the variability of blood pressure. It had been initially described by the German physiologist, L. Traube, as early as in 1872.[5] It can be observed in clinical states of heart failure, valvular heart diseases, and during rapid tachycardias.[6]

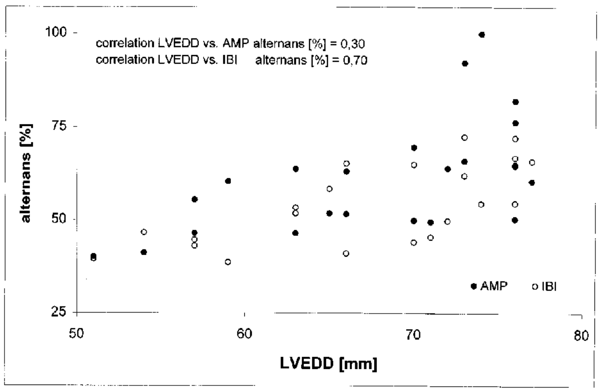

Figure 6. *Correlation analysis of the left ventricular end-diastolic diameter (LVEDD) and the percentage of alternans phenomena.*

The mechanism of pulsus alternans has not been fully understood. A beat-to-beat variation of the left ventricular volume[7,8] has been discussed. This hypothesis suggests that weak beats leave larger end-systolic volumes, and the respective subsequent beats have larger end-diastolic volumes. This improves the ventricular performance, and the appearing decrease of the filling volume in the next beat results in an opposite contractility effect. The second hypothesis refers to an alternating myocardial contractility that was reported to exceed the variations in the filling volumes.[9,10] Variations in intracellular calcium handling by the sarcoplasmatic reticulum[11] and consecutive oscillations in the left ventricular relaxation[12] have also been suggested as causes for this phenomenon. The calcium released during the systole enters an uptake pool and is not available for re-release in the next beat.[13] In addition, the presence of sympathetic alternans in heart failure with pulsus alternans was demonstrated in an experimental setup.[14] There may be an interaction between hemodynamic alternans, heart rate alternans, and electrical alternans phenomena such as T wave alternans.

In contrast to the beat-to-beat variability in blood pressure that occurs with pulsus alternans, rapid beat-to-beat variations in heart rate were thought to be absent in the setting of ventricular failure. This was explained by an attenuation of parasympathetic tone in congestive heart failure. The heart rate alternans in dilated cardiomyopathy was first described in a case report by Binkley et al.[15] During a short period before the onset of a ventricular tachycardia, periods of alternating sinus intervals were observed,[16] suggesting a possible relationship between the alternating beat-to-beat interval dynamics and the onset of life-threatening arrhythmias.

The magnitude of the IBI alternans was as low as 3% of the interval duration. Supposing a mean heart rate of 75 beats (i.e., an interbeat interval of 800 ms), a continuous alternans phenomenon of 3% (24 ms) would entail a standard deviation of the time series (SDNN) of 12 ms. This calculation example illustrates that the presence of an alternans in heart rate does not substantially increase the standard deviation measures in the analyses of the HRV. Therefore, the alternans of the IBI remains completely concealed from considerably larger dynamic changes in the heart rate. Our method completes the statistical analysis of HRV and blood pressure variability by analyzing a specific pattern (i.e., a beat-to-beat alternation of the measurement values).

An interdependency of the alternans appearing in blood pressure and heart rate was found. A high number of alternans phenomena in the heart rate was associated with a high number of alternans phenomena in the blood pressure in the patient group, and vice versa. However, it was not caused by a direct coincidence of blood pressure alternans and heart rate alternans in the individual beats. The latter conclusion can be drawn from the coincidence tables (Tables II and III). This may indicate that here is not a direct coupling but an interdependency between the alternans in heart rate and blood pressure which is mediated by the underlying disease. The blood pressure alternans, therefore, can not be simply explained by the interval-force relationship of the left ventricular contractility analogous to one of the theories of postextrasystolic potentiation.

Functional impairment of the left ventricle as it is in IDC is associated with alternans patterns in the heart rate and the blood pressure. The incidence, the amplitude, the stability, and the interdependencies of alternans phenomena seem to be associated to the stage of the disease. Studies are necessary to comprehensively assess the prognostic impact of these findings.

Study Limitations

To avoid risk of an arterial puncture, the blood pressure was recorded noninvasively using the Penaz method.[17] This may adversely affect the accuracy of the blood pressure recordings. However, the accuracy of the Penaz method and the device used have been proven to reflect the correct intraarterial pressure.[18,19] The reproducibility of the alternans analysis was not tested.

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