Relationship Between Changes in Pulse Pressure and Frequency Domain Components of Heart Rate Variability During Short-Term Left Ventricular Pacing in Patients with Cardiac Resynchronization Therapy

Bożena Urbanek 1
Jan Ruta 1
Krzysztof Kudryński 2
Paweł Ptaszyński 1
Artur Klimczak 1
Jerzy Krzysztof Wranicz 1

Background: The aim of the study was to explore the relationship between changes in pulse pressure (PP) and frequency domain heart rate variability (HRV) components caused by left ventricular pacing in patients with implanted cardiac resynchronization therapy (CRT).

Material/Methods: Forty patients (mean age 63±8.5 years) with chronic heart failure (CHF) and implanted CRT were enrolled in the study. The simultaneous 5-minute recording of beat-to-beat arterial systolic and diastolic blood pressure (SBP and DBP) by Finometer and standard electrocardiogram with CRT switched off (CRT/0) and left ventricular pacing (CRT/LV) was performed. PP (PP=SBP-DBP) and low- and high-frequency (LF and HF) HRV components were calculated, and the relationship between these parameters was analyzed.

Results: Short-term CRT/LV in comparison to CRT/0 caused a statistically significant increase in the values of PP (P<0.05), LF (P<0.05), and HF (P<0.05). A statistically significant correlation between ΔPP and ΔHF (R=0.7384, P<0.05) was observed. The ΔHF of 6 ms² during short-term CRT/LV predicted a PP increase of ≥10% with 84.21% sensitivity and 85.71% specificity.

Conclusions: During short-term left ventricular pacing in patients with CRT, a significant correlation between ΔPP and ΔHF was observed. ΔHF ≥6 ms² may serve as a tool in the selection of a suitable site for placement of a left ventricular lead.

MeSH Keywords: Blood Pressure • Cardiac Resynchronization Therapy • Heart Failure

Corresponding Author: Bożena Urbanek, e-mail: bozena_urbanek@op.pl

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Background

Chronic heart failure (CHF) remains a disease associated with an unfavorable prognosis despite developments in pharmacological treatment, particularly in patients with dis-coordinate contraction due to left bundle branch block (LBBB) [1]. Cardiac resynchronization therapy (CRT) applied to enhance synchrony has been beneficial in approximately 60% of patients, who have demonstrated improvement in clinical and hemodynamic parameters and reduced mortality [2–5]. One of the causes of failure of CRT therapy in 40% of cases is suboptimal left ventricular lead placement [6,7]. Its recommended position is lateral or postero-lateral veins, but in individual cases a positive hemodynamic response was observed when stimulation of other sites was performed [8–10]. So far, attempts at intraoperatively reaching the suitable site for epicardiac pacing with an invasive hemodynamic technique or noninvasive echocardiographic methods have not been implemented on a regular basis because they are time-consuming [8,11,12]. Thus, it seems necessary to find new methods in order to assess the hemodynamic immediate response to left ventricular pacing.

The aim of the study was to find the relationship between changes in pulse pressure (PP) and heart rate variability (HRV) components in frequency domain analysis caused by left ventricular pacing in patients with implanted CRT.

Material and Methods

Study population

The study population consisted of patients with non-ischemic and ischemic cardiomyopathy, symptomatic and stable CHF (NYHA III/IV) on optimal medical therapy, with sinus rhythm and QRS duration >120 ms in electrocardiogram (ECG) and left ventricular systolic dysfunction (left ventricular ejection fraction, LVEF) ≤35% who were enrolled into a study with implanted CRT. Exclusion criteria were: atrioventricular II/III° block, sick sinus syndrome, atrial fibrillation, premature ventricular and supraventricular extrasystoles (>1/min), diabetes mellitus, arterial hypertension, and current use of Class III antiarrhythmic drugs. The study was approved by the local Ethics Committee, and all patients gave their written informed consent.

Study protocol

In all the patients, the device was switched off (CRT/0) in the early hours of the morning of the second day following the CRT implantation and programmed in DDD mode with a lower rate limit of 40 ppm with maximal atrioventricular (AV) delay. Patients remained in a silent environment in a supine position for a period of 15 minutes. Their breathing was stable (12 to 16 breaths/min) and individually controlled. Next, finger beat-to-beat arterial systolic blood pressure (SBP) and diastolic blood pressure (DBP) for 5 minutes with a Finometer (Finapres Medical Systems, Amsterdam, The Netherlands) were measured. The technique developed by Peñañ [13] is well validated for measuring instantaneous changes in blood pressure [14,15]. Simultaneously, a standard 12-lead ECG (500 Hz) (MEDEAKardio PC, Gliwice, Poland) was performed to measure frequency domain HRV components using in-house software based on the Matlab Mathematical Language [16]. Then, SBP, DBP, and ECG recordings were repeated with AV delay programmed 100 ms resulting in 100% left ventricular pacing (CRT/LV). The results were used to calculate the mean values of hemodynamic parameters. The mean value of PP during CRT/0 (PP_CRT/0) and CRT/LV (PP_CRT/LV) and CRT/0 (PP_CRT/0) and CRT/LV (PP_CRT/LV) – DBP_CRT/LV) was calculated. Next, the change of PP value was calculated (ΔPP=PP_CRT/0 – PP_CRT/LV) as well as the percentage change of PP (%ΔPP=ΔPP/PP_CRT/0 ×100%). The components of HRV – low-frequency power (LF), high-frequency power (HF), and low-to-high frequency ratio (LF/HF) during CRT/0 (LF_CRT/0, HF_CRT/0, LF/HF_CRT/0), and next during CRT/LV (LF_CRT/LV, HF_CRT/LV, LF/HF_CRT/LV) – were computed. Then, the change of HRV values – ΔLF, ΔHF, and ΔLF/HF – were analyzed. The parameters of blood pressure were expressed in mmHg and the components of HRV in absolute units (ms²).

Statistical analyses

Statistical analyses were performed with STATISTICA PL 9.0 software. The Shapiro-Wilk test was used for measurable variables to verify whether the variable had a normal distribution. For the normal distribution, the results were given as mean and standard deviation (SD) and for the lack of normal distribution measures of position, median (Me), and interquartile range (IQR) (Q25 – quartile I and Q75 – quartile III). The chi square test was used for categorical variables. To compare variable values in the studied groups, we used the Student’s t-test for linked samples if the variable distribution in both cases was normal. For non-normality analysis, we used the Wilcoxon test. Spearman’s rank correlation coefficient was applied to evaluate correlations between the variables. ROC curves (AUC) were used to present measurable variables. The results were considered statistically significant for p<0.05.

Results

Baseline characteristics

The 40 analyzed patients were 63±8.5 years old, 65% were male and 65% had non-ischemic etiology of heart failure,
92.5% were in III class of NYHA, the QRS width was 175±27 ms, and mean LVEF was 25.7±6.6%. All patients had an LBBB configuration on surface ECG. The left ventricular lead was positioned anterior (5%), antero-lateral (15%), lateral (55%), posterior (10%), and poster-lateral (10%). Patient baseline characteristics are summarized in Table 1.

### Influence of short-term left ventricular pacing on pulse pressure and heart rate variability

#### Value of blood pressure and pulse pressure

Short-term CRT/LV caused a statistically significant increase in the values of SBP (P<0.05) and PP (P<0.05). No statistical significance in the DBP value was observed (Table 2).

#### Value of heart rate variability

Short-term CRT/LV caused a statistically significant increase in the LF power (P<0.05) and HF power (P<0.05), but the LF/HF ratio did not change significantly (NS) (Table 3).

Figure 1 presents the example of the measurement of HRV components.

### Relationship between changes of PP and HRV components during short-term CRT/LV

During short-term CRT/LV, a statistically significant correlation between ΔPP and ΔHF (R=0.7384, P<0.05) was observed (Figure 2).

### Table 1. Baseline clinical characteristic in heart failure patients.

| Parameters                     | Value                      |
|--------------------------------|----------------------------|
| Sex: men (n, %)                | 26 (65%)                   |
| Age (y)                        | 63±8.5                     |
| NYHA III class (n, %)*         | 37 (92.5%)                 |
| LVEF (%)**                     | 25.7±6.6                   |
| QRS (ms)                       | 175±27                     |

*NYHA – New York Heart Association; ** LVEF – left ventricular ejection fraction.

### Table 2. Value of blood pressure and pulse pressure (PP) in patients with CRT/0 and CRT/LV.

| Parameters   | CRT/0     | CRT/LV     | P value |
|--------------|-----------|------------|---------|
| SBP (mm Hg)* | 113.9±17  | 118.5±17.4 | <0.05   |
| DBP (mm Hg)**| 68.5±7.1  | 69.6±8.1   | NS      |
| PP (mm Hg)** | 45.5±13.6 | 49±14      | <0.05   |

* SBP – systolic blood pressure; ** DBP – diastolic blood pressure; *** PP – pulse pressure.

### Table 3. Value of components of heart rate variability (HRV) in patients with CRT/0 and CRT/LV.

| Components of HRV | CRT/0       | CRT/LV       | P value |
|-------------------|-------------|--------------|---------|
| LF (ms²)*         | 16.5 (5.5–34.5) | 20.5 (7–45)  | <0.05   |
| HF (ms²)**        | 13 (4–20)   | 22 (7.5–38)  | <0.05   |
| LF/HF***          | 1.5 (0.6–2) | 1.31 (0.6–2) | NS      |

* LF – low frequency power; ** HF – high frequency power; *** LF/HF – low-to-high frequency ratio.
There were no statistically significant correlations between $D_{PP}$ and $D_{LF}$ ($R=0.2821$, NS) or $D_{PP}$ and $D_{LF}/HF$ ($R=0.0711$, NS).

**Percent of change value of pulse pressure (% $D_{PP}$)**

Positive immediate individual hemodynamic response ($D_{PP} \geq 10\%$) was observed in 19 (47.5%) patients, whereas 21 (52.5%) patients did not show such a response. We observed that $D_{HF}$ ($AUC=0.882$, $P<0.05$) is a component which best differentiates changes during short-term CRT/LV in patients who demonstrated $D_{PP} \geq 10\%$ (Figure 3). Thus, the increase in the HF component correlates with increased PP. Table 4 presents the basic values of ROC curves.

Moreover, we determined the referential value for $D_{HF}$, which will allow predicting an increase for $PP \geq 10\%$. $D_{HF} \geq 6$ ms\(^2\) with a sensitivity of 84.21% and specificity of 85.71% implies a possibility of immediate positive hemodynamic response ($D_{PP} \geq 10\%$) during short-term left ventricular pacing (Figure 4).

Of the 19 patients with $D_{PP} \geq 10\%$, 16 (84.21%) demonstrated a change in $HF \geq 6$ ms\(^2\) ($P<0.05$) (Table 5).

**Discussion**

We observed that in patients with implanted CRT, short-term left ventricular pacing can immediately improve left ventricular systolic performance. Based on invasive studies, Dekker et al. observed that biventricular pacing with an optimal left ventricular lead position significantly increased stroke volume (+39%, $P=.01$) and ejection fraction (+30%, $P=.007$) [8]. Nelson et al. confirmed that left ventricular or biventricular pacing strongly enhances systolic function (18±4% rise in arterial pressure and 43±6% increase in $dP/dt_{max}$) [17]. Auricchio et al. observed
that effective left ventricular pacing results in an immediate increase in PP, as evaluated with an invasive method [1]. Other authors confirmed that the increased value of PP positively correlates with improved left ventricular systolic performance, increased stroke volume, and cardiac output [8,17,18]. The method of non-invasive evaluation of changes in PP was used in a study conducted by Butter et al. The authors confirmed that the values of the PP parameter, evaluated with the application of non-invasive photoplethysmography, were correlated with the values of the PP parameter, evaluated with the application of an invasive aortic PP [19].

The results we obtained in our study – increased systolic pressure by 4.6 mmHg and increased PP value by 3.5 mmHg – confirmed the above observations. In the clinical observation, cardiac insufficiency is accompanied by symptoms of a dysfunction of the autonomic nervous system. It is manifested by decreased activity of the parasympathetic system [20,21] and increased sympathetic activity [22,23]. One of the non-invasive markers of the autonomic system is HRV [24]. Patients with cardiac insufficiency demonstrate decreased values of HRV parameters evaluated in both the time domain and frequency analyses, and results of these measurements have high repeatability [24]. In our study, we observed that patients with CRT/0 demonstrated low values of HRV components, which were evaluated with short-term frequency domain analysis, both in the LF and HF spectral components. Casolo et al. observed 10-fold lower values of frequency parameters (LF and HF) in patients with CRT in comparison with healthy subjects. Moreover, the parameters remained stable throughout the day [25].

Values of parameters of the frequency domain analysis are closely related to the progression of the disease. Some authors have noted that in an early stage of a disease, patients demonstrate higher spectral values of the LF component and lower spectral values of the HF component, which confirms a shift in the balance of the autonomic system towards the sympathetic component [26–28]. Other authors have made similar observations while conducting studies on patients with advanced heart failure. It was confirmed that there is a relationship in the long-term improvement in hemodynamic parameters and improvement in decreased HRV parameters.

Table 4. Basic values of ROC curves.

| Components of HRV | AUC**** | **** SE | P value | 95% confidence interval |
|-------------------|---------|---------|---------|------------------------|
| DLF*              | 0.673   | 0.086   | NS      | 0.505                  |
|                   |         |         |         | 0.841                  |
| DHF**             | 0.882   | 0.056   | P <0.05 | 0.773                  |
|                   |         |         |         | 0.991                  |
| DLF/HF***         | 0.548   | 0.093   | NS      | 0.366                  |
|                   |         |         |         | 0.730                  |

* DLF – change of low frequency power; ** DHF – change of high frequency power; *** DLF/HF – change of low-to-high frequency ratio; **** AUC – area under curve ROC; ***** SE – standard error.

Figure 4. Relationship between sensitivity and specificity of the method of forecasting an immediate positive response to short-term left ventricular pacing and ΔHF value.

Table 5. The number of patients with ΔPP ≥10% and ΔHF ≥6 ms².

| GROUP      | ΔPP <10%* | ΔPP ≥10% | ΔHF <6 ms² | ΔHF ≥6 ms² | P value |
|------------|-----------|-----------|-------------|-------------|---------|
| N          | 18        | 3         |             |             | P <0.05 |
| %          | 85.71%    | 14.29%    |             |             |         |
| DPP <10%*  |           |           |             |             |         |
| DPP ≥10%   | N         | 3         | 16          |             |         |
| %          | 15.79%    | 84.21%    |             |             |         |

* ΔPP – change of pulse pressure; ** ΔHF – change of high frequency power.
Auricchio et al. observed patients with implanted CRT within a period of 1 year. They evaluated the impact of the therapy on the tone of the autonomic system by analyzing 5-minute ECG records with the use of the frequency domain method. These authors noted the CRT therapy positively contributed to HRV component values [29]. It positively influenced the ventricular systolic performance, which immediately resulted in a change of PP values [17]. In our study, short-term left ventricular pacing caused a statistically significant increase in the HRV value of LF and HF components.

Percentage change of PP (ΔPP%) was used to evaluate the immediate hemodynamic response to left ventricular pacing. Auricchio et al. noted that a change in PP higher than 5% evaluated by an invasive method proves an immediate positive response to resynchronization therapy [30]. Butter et al. observed that an 8% change in the PP value proves an immediate positive hemodynamic response to effective left ventricular pacing [18]. In the group of patients we studied, an immediate individual positive hemodynamic response to short-term left ventricular pacing was observed in 47.5% of the patients. Vogt et al. noted that a 10% increase in the PP value might facilitate the identification of the suitable site for epicardial pacing, and patients who have had electrodes implanted in this site demonstrate clinical and echocardiographic improvement in long-term observation [31]. Our study confirmed a highly positive, statistically significant correlation between ΔPP and ΔHF. Thus, an increased value of HF might imply the possibility of an immediate individual positive hemodynamic response (ΔPP ≥10%) during short-term left ventricular pacing.

In the literature, there is no thorough analysis of any relationships between ΔPP and ΔHF measured during short-term left ventricular pacing. The results of our study require confirmation in a larger number of patients.

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Conclusions
A significant correlation between ΔPP and ΔHF was observed during short-term left ventricular pacing in patients with CRT. ΔHF ≥6 ms² may serve as a tool in the selection of a suitable site for placement of a left ventricular lead.

What is innovative in the study?
The present study provides important new data that might be useful in a potential application of changes in HF spectral components of HRV. HF power might facilitate the selection of a left ventricular lead placement site when we assume that a positive hemodynamic response (i.e., a change in the PP value) is the evaluation criterion.

Study Limitations
The limitations of the study include the small number of patients because of the exclusion of patients with diabetes, hypertension, a great number of premature ventricular and supraventricular extrasystoles, and disorders of AV conduction of the 2nd and 3rd degree. The obtained HRV results were not verified with any available commercial software. Pressure parameters were evaluated with the use of only one 5-minute non-invasive measurement. With regards to HRV parameters, we used only 1 ECG record. Factors affecting arterial tension and HRV might have affected the obtained results to some extent.

Conflicts of interest
The authors report no conflicts of interest.
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