R/S Ratio Variability in Lead V₁ Observed between Selected Four 1-Minute ECG Fragments of 24-Hour ECG as a Predictor of Incomplete Resynchronization during Full 24-Hour ECG: Pilot Study

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Background: About 30% of patients do not have an effective cardiac resynchronization therapy (CRT). Routine assessment of CRT by devices interrogation (DI) is not entirely reliable. Additional information provide detailed QRS analysis in 24-hour ECG, however it is time-consuming. The aim of the study was the assessment of R/S ratio variability in lead V₁ between selected fragments of 24-hour ECG as a predictor of incomplete biventricular pacing (BIVP) during full 24-hour ECG.

Methods: The 12-lead 24-hour ECGs of 43 patients with sinus rhythm were studied. During 24-hour ECG the 6-minute walk test (6MWT) was performed. The CRT was assessed by analyzing DI and full 24-hour ECG and four 1-minute fragments of these ECG recordings: during the minimum and the maximum heart rate and at the 1st and last minute of 6MWT.

Results: During DI the effective (>95%) BIVP was present in 36 patients (83.7%). Analysis of full 24-hour ECG confirmed appropriate BIVP in 31 patients (72%) and suspected incomplete BIVP ($\leq 95\%$) in 12 patients (28%). In 9/12 patients the R/S ratio variability in lead V₁ was visible between selected ECG fragments of 24-hour ECG. These results were not associated with the results of DI but were significantly associated with full 24-hour analysis of QRS.

Conclusions: R/S variability in lead V₁ between selected fragments of 24-hour ECG can be considered a predictor of potentially incomplete BIVP confirmed by further complete 24-hour ECG analysis in patients with appropriate pacing reported during DI.

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cardiac resynchronization pacing; the QRS-variability; 24-hour ECG; 6-minute walk test

The treatment of chronic heart failure (CHF) is based primarily on pharmacotherapy but in some cases electrotherapy is necessary. The development of CHF for many years can lead to remodeling of the left ventricular (LV) and intraventricular conduction disturbances. This leads to systolic and diastolic dysfunction of LV. According to the guidelines,¹ in patients with CHF, one of the meth-

ods of treatment is the cardiac resynchronization therapy (CRT). However, only 60–70% of patients have an effective biventricular pacing (BIVP).^{2,3} Routinely the BIVP is analyzed during the device interrogation (DI). Presence of BIVP >95% during DI is not always associated with the improvement in hemodynamic and clinical status of the patients. One of the simple methods that may verify the

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presence/absence of BIVP is electrocardiogram (ECG) in which we analyze QRS duration and morphology. Usually in cases with effective BIVP we observe a stable QRS morphology in the ECG. The QRS complexes should have a shorter duration than the QRS complexes before the CRT implantation and smaller or greater R wave in lead V₁. There are two studies that compare the evaluation of the effectiveness of CRT pacing using the 24-hour electrocardiogram (the analysis of the morphology of paced beats) and the analysis of the functions of the CRT in DI.^{4,5} The results indicate that these two methods of assessing CRT stimulation are complementary. Unfortunately the exact and detailed analysis of QRS morphology in 24-hour electrocardiogram (24-hour ECG) can be sometimes difficult and time-consuming. The aim of the study was the analysis of the usefulness of the assessment of R/S ratio variability in lead V₁ between selected fragments of 24-hour ECG as a predictor of incomplete (<95%) BIVP in full 24-hour ECG.

METHODS

Study Group

The study used 43 recordings of 24-hour Holter ECG which were performed in 43 patients with sinus rhythm who came for a routine DI and who agreed to participate in the study. Mean age was 56 ± 23 years (9 women and 34 men). Mean NYHA class was 2.27. Table 1 summarizes the demographics and the clinical characteristics of the patients.

CRT Control

In patients who agreed to participate in the study after routine device interrogation the device counter was reset and at the same time the monitoring of the 24-hour ECG (12-lead 24-hour ECG) was started.

Recording and Analysis of the 24-hour ECG

The Lifecard recorder was used to register 12-lead 24-hour ECG. Recordings were analyzed interactively with the Spacelabs software by one physician. During the analysis of QRS morphology in lead V₁ the QRS duration, the R wave amplitude and R/S ratio were observed and analyzed. The

variability of the QRS morphology was diagnosed as follows:

- the R wave amplitude in V₁ changed more than 3 mm
- and / or
- the QRS duration changed more than 40 ms
- and / or
- the R/S ratio changed from positive to negative.

The main criterion for the recognition of effective BIVP among the observed QRS complexes was the shortest duration of the QRS. According to the above rules, paced QRS were annotated as "paced" (those with effective BIVP) or "others" (those with suspected not fully effective BIVP). The evolutions of sinus rhythm without pacing were counted as "normal." Supraventricular and ventricular arrhythmias were evaluated too. The supraventricular evolutions conducted by the pacemaker were analyzed as "paced" or "others" depending on QRS morphology.

The percentage of CRT pacing was determined by the following formula:

$$\frac{\text{"paced"}}{\text{"paced"} + \text{"other"} + \text{"normal"} + \text{"ventricular"} + \text{"supraventricular"}}$$

Analysis of the Selected ECG Fragments

Realizing the purpose of the study, another independent physician assessed the variability of R/S ratio waves in four 1-minute 24-hour ECG fragments: during the minimum and the maximum heart rate and during the 6MWT (at the first minute and at the last minute of the 6MWT). According to the above described scheme, the variability of QRS complexes between the compared fragments was treated as a highlight of possible incomplete BIVP in 24-hour ECG.

The Figures 1–3 show the QRS variability in selected fragments of 24-hour ECG.

The 6-Minute Walk Test

6MWT was done during the registration of the 24-hour ECG. The start and the end time of the 6MWT was recorded by a physiotherapist. The 6MWT was performed according to the established rules.⁶ The patients marched alone, at their own pace, on a flat surface of an empty corridor in the hospital and the distance in meters was evaluated. For the purposes of the study we took into account the 1-minute ECG fragments at the beginning and end of the test.

Table 1. The Demographics and the Clinical Characteristics of the Patients (n = 43)

Variable	
Clinical Characteristics	
Age (years)	56 ± 23 (30–78)
Gender (females /males)	9 / 34
Ischemic/nonischemic cardiomyopathy	25/18
NYHA class	2.27 ± 0.45
Left ventricular ejection fraction (%)	31 ± 10 (15–50)
NTproBNP (ug/L)	1887 ± 2772 (47.46–14,378)
24-hour ECG	
Mean HR (bpm)	70 ± 7 (60–86)
Min HR (bpm)	58 ± 6 (49–70)
Max HR (bpm)	109 ± 18 (69–150)
Ventricular extrasystoles /24 hour	1099 ± 1578 (4–5435)
Percentage of CRT pacing in 24-hour EKG (%)	91.6 ± 17.6 (50–100)
HR during 6MWT, 1st min (bpm)	72 ± 15 (55–110)
HR during 6MWT, 6th min (bpm)	98 ± 17 (65–123)
6-Minute Walk Test	
Distance in the 6MWT (m)	398 ± 132 (58–575)
Interrogation Devices	
Percentage of CRT pacing during 24 hours in ID (%)	98 ± 3 (91–100)
Medicines	
Beta-blockers	43 pts (100%)
ACE-I	41 pts (95%)
ARB	2 pts (5%)
Spironolacton/eplerenon	31 pts (72%)
Digoxin	7 pts (16%)
Amiodarone	8 pts (18%)
Ivabradine	2 pts (4,6%)
Diuretic	39 pts (90%)

ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CHR = chronic heart failure; CRT = cardiac resynchronization therapy; ECG = electrocardiogram; EF = the left ventricular ejection fraction; HR = heart rate beats per 1 minute; ID = interrogation devices; max HR 24-hour ECG = the maximum heart rate in the 24-hour ECG; mean HR 24-hour ECG = mean heart rate in the 24-hour ECG; min HR 24-hour ECG = the minimum heart rate in the 24-hour ECG; NS = not statistically significant; NYHA = New York Heart Association –functional classification of heart failure; P = probability value; n = the number of the respondents; SD = standard deviation; 6MWT = 6-minute walk test; 24-hour ECG = 24-hour electrocardiogram; 1st min = in the first minute of the 6-minute walk test; 6th min = in the sixth minute of the 6-minute walk test.

Statistical Analysis

All continuous variables are expressed as mean ± SD. Categorical variables are summarized as absolute number and relative frequencies. The chi-square test was used to compare the incidence of specific QRS variability in the 24-hour ECG in groups of CRT pacing ≤95% and >95%. Fisher's Exact Test was used to assess the independence of variables. P value <0.05 was considered as statistically significant.

RESULTS

Variability of R/S Ratio in the Selected Fragments of the 24-Hour ECG and the Results of DI

During DI in 7 of 43 patients (16.3%) the estimated BIVP was ≤95% (average 93.2 ± 2.1%),

in 36 of 43 patients (83.7%) the BIVP was >95% (mean 98.7 ± 1.3%). We checked the association between the observed variability of the R/S ratio between the four selected fragments of the 24-hour ECG and the CRT pacing in the DI (Table 2). In this analysis, the variability of the R/S ratio was observed in both groups of patients: with the BIVP >95% and with the BIVP ≤95% in DI. It is important that in the group of patients with effective BIVP in DI 8 patients (22%) showed the R/S variability between at least one of the combinations of the selected and compared ECG fragments.

Based on the data presented in Table 2, there was no significant association between the calculated BIVP in DI (≤95% vs >95%) and the R/S ratio variability among at least one of the combinations of the four compared fragments of 24-hour ECG. However, the variability of the R/S ratio between

Figure 1. The QRS variability in V₁ of the minimum (A) and the maximum (B) heart rate (25 mm/s, voltage 0.1 mV).

Table 2. The Comparison of the Prevalence of the R/S Ratio Variability between Selected Fragments of the 24-Hour ECG with the Results of CRT Pacing Evaluated in Interrogation Devices

R/S Ratio Variability between Compared Fragments of the R/S24-Hour ECG	CRT >95% in ID n = 36 (83.7 %)	CRT ≤95% in ID n = 7 (16.3%)	P
Min HR vs the max HR	4 Patients	3 Patients	0.0374
The beginning vs at the end of the 6MWT	4 Patients	2 Patients	0.2225
At least one pair of all compared combinations	8 Patients	4 Patients	0.0595

CRT = cardiac resynchronization therapy; CRT pacing ≤95% in the ID = pacing assessed in interrogation devices ≤95%; CRT pacing >95% in ID = pacing assessed in the interrogation devices >95%; ECG = electrocardiogram; HR = heart rate; n = number of the patients; P = probability value; vs = versus; 6MWT = the 6-minute walk test; 24-Hour ECG = 24-hour electrocardiogram.

the fragments during the minimum HR and maximum HR showed a significant association to the calculated BIVP in ID. It seems that the assessment of the selected four 1-minute ECG fragments taken from 24-hour ECG can provide us with additional information about BIVP.

Variability of R/S Ratio in the Selected Fragments of the 24-Hour ECG and the QRS Variability in Complete 24-Hour ECG Analysis

The average percentage of BIVP during the 24-hour ECG was 91.6 ± 17.6%. The presence of the QRS complex variability which could indicate an incomplete BIVP (≤95%) was observed in 12 patients (28%). Five of those patients demonstrated the R/S ratio variability

between QRS recorded at the minimum and maximum HR during the 24-hour ECG. Additionally, if we also take into account the ECG fragments from the beginning and the end of the 6MWT, we find the R/S ratio variability between these four 1-minute ECG fragments in nine patients (Table 3). Summarizing the data in Table 3, we observed a statistically significant association in the study group between the presence of incomplete BIVP in the 24-hour ECG and the appearance of the R/S ratio variability between the selected four 1-minute fragments of the 24-hour ECG.

6-Minute Walk Test

All patients performed the 6MWT correctly (Table 1). The presentation of clinical results of this test (distance covered, symptoms) is not the subject of the analysis in this work. For the realization of

Table 3. The Comparison of the Prevalence of the R/S Ratio Variability between Selected Fragments of the 24-Hour ECG with the Results of CRT Pacing Evaluated in 24-Hour ECG

R/S Ratio Variability between Compared Fragments of the 24-Hour ECG	CRT >95% in 24-Hour ECG n = 31 (72 %)	CRT ≤95% in 24-Hour ECG n = 12 (28 %)	P
Min HR vs the max HR	2 Patients	5 Patients	0.0050
The beginning vs at the end of the 6MWT	1 Patients	5 Patients	0.0011
At least one pair of all compared combinations	3 Patients	9 Patients	<0.0001

CRT = cardiac resynchronization therapy; CRT pacing ≤95% in the 24-hour ECG = resynchronization pacing assessed in the 24-hour ECG ≤95%; CRT pacing >95% in the 24-hour ECG = resynchronization pacing assessed in the 24-hour ECG >95%; ECG = electrocardiogram; HR = heart rate; n = number of the patients; P = probability value; vs = versus; 6MWT = the 6 minute walk test; 24-hour ECG = 24-hour electrocardiogram.

Figure 2. The variation of the QRS morphology in V₁ recorded during the 6-minute walk test (25 mm/s, voltage 0.1 mV).

the objectives of this study, 1-minute fragments of ECG were selected: the first minute at the beginning of the test and the last minute of the test (Table 1). In the study group all patients had a higher HR at the beginning of the 6MWT [71 ± 11 (57–110)] in comparison to the minimum HR in the full 24-hour ECG [58 ± 6 (49–70)], (Table 1). In 8 patients (18%) the maximum HR for the 24-hour ECG was achieved at the last minute of the 6MWT and 35 patients achieved the maximum HR in other activities during the 24-hour ECG recording. The variability of R/S ratio between two selected fragments during the 6MWT was evaluated. It was

Figure 3. The R/S ratio variability in V₁ of the minimum (A) and the maximum (B) heart rate (25 mm/s, voltage 0.1 mV).

found in 6 patients. In 5 of the 6 patients the analysis of the full 24-hour ECG demonstrated the incomplete resynchronization <95% (statistically significant correlation).

DISCUSSION

In patients with BIVP >95% assessed in usual device interrogation and with the absence of clinical improvement, the incomplete BIVP should be suspected. In this case, the 24-hour ECG with the analysis of the morphology of paced QRS may add some important data and present for example QRS variability that is related with BIVP problems. A detailed analysis of around 100 000 evolutions may be sometimes difficult and time-consuming. Our work is the first study which proposes to assess the BIVP effectiveness by evaluation of the R/S ratio variability between selected 1-minute ECG fragments of the 24-hour ECG both at rest and during exercise (6MTW) to be used as a screening

method before the decision on the assessment of the full 24-hour ECG.

Two Methods of CRT Control and Two Views at the Function of the Pacemaker

The usual care of the patients with CRT includes periodic device interrogation. Apart from routine checking of sensing and pacing of all three leads we analyze the percentage of BIVP. Having good results (>95%) we should remember that the device counts "the spikes" and the effect of pacing is unknown. The electrical effect of pacing can be followed electrocardiographically. Sometimes even in standard ECG we may observe the QRS variability due to different reasons—fusion and pseudo-fusion (too long AV delay), variable QRS in V₁ with different amplitude (or disappearance) of R wave. Long-term ECG monitoring may express this variability even more deeply. The assessment of the effectiveness of CRT pacing using the 24-hour ECG and the analysis of the pacemaker's function during DI and the comparison of the two controls were the subject of two studies.^{4,5} Referring to previous observation of the authors,⁵ it can be concluded that in patients with sinus rhythm both methods (the 24-hour ECG and the DI) estimate the CRT function independently. Each of these methods provides different information about the functions of the device. Therefore, it can be concluded that both methods of CRT control complement each other.

The Importance of 6-Minute Walk Test

A routine DI is performed in a sitting position in stable rest conditions. During the 24-hour ECG we may observe how the CRT works in different conditions. 6MWT is a kind of standard, safe exercise to increase heart rate giving chance to present CRT performance but on the other hand gives us information about the exercise capacity of the patients (very useful for clinical follow up). During the test, the heart rate is accelerated, ventricular and supraventricular arrhythmia may be increased, which may disrupt the functioning of the pacemaker. In our opinion, the 24-hour ECG enriched with the 6MTW should be helpful in revising CRT functions in the patients. Our results show that the ECG fragments at the beginning and end of the 6MWT may help in detection of

incomplete BIVP in the 24-hour ECG in patients with appropriate pacing in DI.

Analysis of the Selected ECG Fragments

Considering the time-consumption of the analysis of the full 24-hour ECG (especially in patients with a variable QRS morphology during CRT pacing) screening methods before deciding of the full 24-hour ECG analysis should be sought. We proposed a simple analysis of selected fragments of the 24-hour ECG. The question was which fragments to choose. The easiest way was to select a minimum and maximum HR. In considering this issue we also took into account the diagnostic and prognostic significance of the 6MWT in patients with heart failure. Finally, we chose four 1-minute fragments of the 24-hour ECG—in the maximum HR, the minimum HR, at the beginning of the 6MWT and at the end of the 6MWT. The next simplification of the screening analysis was the assessment of only R/S ratio in lead V₁ in the selected fragments of the 24-hour ECG. Our results indicate that such a choice seems to be justified since the analysis of all the combinations of selected ECG fragments gave the results that firstly, did not significantly associate with the results of ID and secondly, significantly associated with the analysis of the full 24-hour ECG. If we take into account only minimum and maximum HR during the 24-hour ECG, we get results of a much lower value.

CRT Assessment in the 24-Hour ECG and Clinical Practice

It is an open question if the 24-hour ECG should be done routinely in patients with CRT. No such recommendation has been proposed. Our previous study demonstrated that the analysis of the 24-hour ECG gave additional information about CRT functioning. In our opinion a long-term ECG recording may be necessary in cases with appropriate BIVP during DI but with no clinical improvement (or worsening). We also state that the 24-hour ECG (with the 6MWT) may be performed as a part of routine examination 6 months after CRT implantation. In this case, it may present the pacing during clinical improvement (for possible further comparison when patients' condition worsens) or suggests the pacing optimization in cases without clinical improvement.

Limitations of the Study

A limitation of the study was a small group of patients, a lack of randomization and a lack of data from the period prior to the implantation of the CRT system that we could compare with the results obtained at the time of our observation of the patients (for example the distance covered by the patients in the 6MTW before and after the implantation of the CRT). We also believe that in patients with noticeable variation of paced QRS complexes, the assessment of the CRT delivery should be supplemented by resting positional ECG recordings. In our study we evaluated the QRS morphology in lead V₁ in which the QRS variability related to the patient's position should be theoretically the smallest. We also could not verify the results from DI and the 24-hour ECG beat by beat because it was impossible. Hence, we did not know how the beats that were counted by us as possible with incomplete BIVP were counted by device. We compared only two 24-hour summaries—from ECG and DI.

CONCLUSIONS

The R/S variability in lead V₁ in selected fragments of the 24-hour ECG can be considered a predictor of potentially incomplete BIVP confirmed by a further full 24-hour ECG analysis in patients with appropriate pacing reported during DI.

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