Analysis of the QRS morphology in lead V1 during 24-hour Holter electrocardiogram monitoring to evaluate function of a cardiac resynchronisation therapy device in patients with sinus rhythm: a pilot study

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Abstract

Background: Cardiac resynchronisation therapy (CRT) is an important advance in the treatment of chronic heart failure. The aim of CRT is biventricular capture in all beats. However, inadequate delivery of biventricular pacing is still seen in about 30% of patients with an implanted CRT device. Device interrogation is a routine approach to assess CRT delivery. However, some reports indicate that analysis of 24-h electrocardiogram (ECG) may provide additional and important information regarding CRT function.

Aim: Assessment of the adequacy of CRT delivery based on device interrogation and analysis of QRS morphology during 24-h ECG recording in patients with preserved sinus rhythm (SR).

Methods: We analysed 24-h Holter ECG recordings and data from device interrogation devices in 43 patients with preserved SR (age 56 ± 23 years, 9 women and 34 men). The obtained results were compared in an independent manner. Assessment of adequacy of CRT delivery by 24-h ECG was based on the occurrence of QRS variability, defined as a change in R wave amplitude in lead V1 by > 3 mm and/or change in QRS duration by > 40 ms and/or change in the R/S ratio. Adequate CRT delivery, i.e. complete resynchronisation, was defined as more than 95% of pacing without the defined QRS variability.

Results: Both methods allowed independent assessment of CRT delivery (p < 0.05 by the Fisher’s exact test). In multivariate analysis, factors that were independently associated with incomplete resynchronisation included ventricular arrhythmias (each 100 ventricular beats per day increased the risk of incomplete resynchronisation 1.14-fold; confidence interval [CI] 1.036–1.25, p = 0.007), maximum heart rate (HR) (each increase by 10 bpm increased the risk 3.3-fold; CI 1.36–7.9, p = 0.008), QRS duration at the minimum HR (each increase by 10 ms increased the risk 1.74-fold; CI 1.075–2.8, p = 0.024), and the programmed atrioventricular delay (each increase by 10 ms increased the risk 2.15-fold, CI 1.18–3.9, p = 0.013).

Conclusions: In patients with preserved SR, device interrogation and evaluation of 24-h ECG are complementary methods to evaluate adequate CRT delivery. Therefore, both methods should be taken into account when assessing CRT function.

Key words: cardiac resynchronisation therapy, inadequate biventricular pacing delivery, QRS complex variability, 24-h ECG, chronic heart failure

INTRODUCTION

Management of chronic heart failure (CHF), regardless of its aetiology, is a major therapeutic challenge. Over the years, development of CHF is associated with left ventricular (LV) remodelling, myocardial dyssynchrony, and subsequently LV systolic and diastolic dysfunction. According to the
2013 guidelines on the management of CHF [1], cardiac resynchronisation therapy (CRT) is a therapeutic option in these patients, but good response to CRT is seen in only 60–70% of patients [2, 3]. A routine approach to evaluate the effectiveness of CRT involves direct device interrogation or remote monitoring at the cardiac electrophoresis device or CRT clinic. A high percentage of biventricular pacing found during standard device interrogation at the CRT clinic is not always associated with an improvement of haemodynamic parameters and clinical condition of the patient.

Evaluation of the electrocardiogram (ECG), including QRS morphology and duration, is important both during patient selection for CRT and when evaluating effectiveness of this therapy. The intended effect of CRT is permanent biventricular pacing which should manifest with stable QRS morphology. Assessment of the effectiveness of CRT by 24-h ambulatory recording of 12-lead ECG (evaluation of paced beat morphology) and device interrogation was evaluated in patients with permanent atrial fibrillation [4]. It was shown that 24-h ECG recording was superior to device interrogation in predicting LV function improvement as evaluated by echocardiography [4]. 24 h ECG recording allows precise evaluation of QRS complexes and identification of fully captured beats, fusion and pseudo-fusion beats, and those resulting from single-chamber (e.g., right ventricle [RV]) ventricular pacing only. This is particularly important as only permanent biventricular pacing (>95% of beats) may be expected to result in a clinical improvement. No reports have been published on the importance of 24-h ECG recording in the evaluation of adequate CRT delivery in patients with sinus rhythm (SR).

The aim of our study was to evaluate the adequacy of biventricular pacing delivery by CRT based on device interrogation and analysis of QRS morphology during 24-h ECG recording in patients with preserved SR.

**METHODS**

**Study group**

For our study, we used forty-three 24-h ECG recordings and data from contemporaneous CRT-D/CRT-P interrogations in 43 patients with preserved SR. The study was performed in patients presenting for a routine CRT device check-up who gave their consent for participation in the study. The patients (9 women and 34 men) were aged 30–78 years, and the mean age was 56 ± 23 years. Reasons for CRT-D device implantation included ischaemic cardiomyopathy (25 patients, 58.2%), inflammatory, dilated, or toxic cardiomyopathy (15 patients, 34.9%), and other (3 patients, 6.9%). Time since CRT device implantation ranged from 3 months to as much as 12 years (mean 1.9 years). CRT device was implanted in 2001–2013, including in 1 patient in 2001, 1 patient in 2008, 2 patients in 2009, 4 patients in 2010, 5 patients in 2011, 16 patients in 2012, and 14 patients in 2013. The mean LV ejection fraction (LVEF) was 31.4% (range 15–50%), and the mean New York Heart Association (NYHA) class was 2.27.

In our study group, all patients received beta-blockers (bisoprolol 51%, carvedilol 28%, metoprolol CR 21%), 41 (95%) patients were treated with angiotensin-converting enzyme inhibitors, and 2 (5%) patients received angiotensin receptor antagonists. Diuretics were used in 90% of patients, and spironolactone or eplerenone were used in 72% of patients. In addition, digoxin was used in 7 (16%) patients, amiodarone in 8 (18%) patients, and ivabradine in 2 (4.6%) patients. Four patients received combined therapy with digoxin and amiodarone (n = 2), digoxin and ivabradine (n = 1), or amiodarone and ivabradine (n = 1).

The study protocol was approved by the Bioethics Committee at the Institute of Cardiology (project No. 1252). The study was supported by institutional statutory funds (No. 2.15/VII/11).

**Evaluation of adequate CRT delivery**

Patients who consented for participation in the study had their device interrogated at the CRT clinic, with a reset of the device pacing counter. A 24-h 12-lead ECG recording was then started, using Lifecard monitors and Ambu Blue Sensor L leads. Twenty-four hour ECG recordings were evaluated when they were technically adequate [5], i.e. included more than 18 h of recording free of artifacts, encompassing morning activity and night-time rest periods. Next day, the pacing counter was read and 24-h ECG recording was terminated. Device interrogation was performed by a technician who did not participate in the evaluation of ECG recordings, and ECG recordings were evaluated by a physician who was unaware of device interrogation findings. Data from device interrogation and ECG recordings were provided to a physician in charge of the study. 24 h ECG monitors were fitted by two technicians with many years of experience in our Holter monitoring laboratory. The monitors were fitted at 9–10 AM, and recording was terminated at 8–9 AM next day. Patients completed diaries, providing data on their activities and the duration of night-time rest.

24 h ECG recordings were analysed interactively using the Impresario system (Spacelabs).

During analysis of 24-h ECG recordings, we evaluated QRS morphology in lead V1 (Fig. 1), QRS duration, R wave amplitude, and the R/S ratio. Beats were considered captured (with complete resynchronisation) if an R wave was seen in lead V1. Beats with a reduction in R wave amplitude by 3 mm, change in the R/S ratio, or QRS duration prolongation by more than 40 ms were categorised as “other” (either incomplete resynchronisation or lack of resynchronisation). Native beats without capture were categorised as “normal”. We also evaluated ventricular and supraventricular arrhythmia (excluding paced beats).
recording. We included the following variables: age, gender, underlying condition (ischaemic vs. dilated cardiomyopathy), minimum and maximum heart rate (HR) during 24-h ECG recording, QRS duration at the time of minimum and maximum HR during 24-h ECG recording, R wave amplitude in V1 at the time of minimum HR, number of ventricular beats, and programmed atrioventricular delay.

In univariate analyses (Table 1), only the presence of ventricular arrhythmia was significantly associated with incomplete resynchronisation (relative risk 1.05). Multivariate analysis identified more variables associated with the risk of incomplete resynchronisation. As shown in Table 2, each 100 ventricular beats per day increased the risk 1.14-fold, each increase in the maximum HR by 10 bpm increased the risk 3.3-fold, each increase in QRS duration at the time of minimum and maximum HR during 24-h ECG recording, R wave amplitude in V1 at the time of minimum HR, number of ventricular beats, and programmed atrioventricular delay increased the risk 1.74-fold, and each increase in programmed atrioventricular delay by 10 ms increased the risk 2.15-fold. This model explained 39% of the overall variance, and the included variables may be considered potential Holter markers of the loss of resynchronisation.

Table 1. Results of univariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.95</td>
<td>0.9–1.01</td>
<td>0.13</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.7</td>
<td>0.2–3.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Ischaemic cardiomyopathy</td>
<td>0.36</td>
<td>0.9–1.4</td>
<td>0.15</td>
</tr>
<tr>
<td>Minimum HR</td>
<td>1.5</td>
<td>0.5–4.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Maximum HR</td>
<td>1.2</td>
<td>0.81–1.7</td>
<td>0.37</td>
</tr>
<tr>
<td>QRS duration at the time of minimum HR</td>
<td>1.2</td>
<td>0.93–1.56</td>
<td>0.14</td>
</tr>
<tr>
<td>QRS duration at the time of maximum HR</td>
<td>0.87</td>
<td>0.63–1.2</td>
<td>0.41</td>
</tr>
<tr>
<td>R wave amplitude at the time of minimum HR</td>
<td>0.99</td>
<td>0.84–1.2</td>
<td>0.99</td>
</tr>
<tr>
<td>Number of ventricular beats</td>
<td>1.05</td>
<td>1.005–1.09</td>
<td>0.03</td>
</tr>
<tr>
<td>Programmed AV delay</td>
<td>1.2</td>
<td>0.9–1.6</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Intervals: HR: 10 bpm; QRS duration, AV delay: 10 ms

Table 2. Results of multivariate analysis (stepwise regression, elimination at p = 0.1)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Maximum HR</td>
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<td>1.36–7.9</td>
<td>0.008</td>
</tr>
<tr>
<td>QRS duration at the time of minimum HR</td>
<td>1.74</td>
<td>1.075–2.8</td>
<td>0.024</td>
</tr>
<tr>
<td>Programmed AV delay</td>
<td>2.15</td>
<td>1.18–3.9</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Intervals: HR: 10 bpm; QRS duration, AV delay: 10 ms

RESULTS

The mean percentage of biventricular pacing was 97.7 ± 3.5% by device interrogation and 91.6 ± 17.6% by 24-h ECG recording (p = 0.001). The percentage of biventricular pacing < 95% was noted in 4 patients by device interrogation and in 12 patients by 24-h ECG recording. In 2 patients, the percentage of biventricular pacing was < 95% by both methods, in 2 patients it was < 95% only by device interrogation, and in 10 patients it was < 95% only by 24-h ECG recording (Fisher test: p < 0.05). Thus, assessment of biventricular pacing by both methods yielded varying estimates.

We also performed univariate (Table 1) and multivariate (Table 2) analyses to identify variables that were significantly associated with incomplete resynchronisation by 24-h ECG recording. We included the following variables: age, gender, underlying condition (ischaemic vs. dilated cardiomyopathy), minimum and maximum heart rate (HR) during 24-h ECG recording, QRS duration at the time of minimum and maximum HR during 24-h ECG recording, R wave amplitude in V1 at the time of minimum HR, number of ventricular beats, and programmed atrioventricular delay.

During patient visits, echocardiography with LVEF measurements by the Simpson method was performed, and the NYHA class was evaluated based on the history, physical examination, and the results of a 6-min walk test.
DISCUSSION

According to our knowledge, our study is the first to show potentially important benefits of routine 24-h ECG recordings in CRT patients with preserved SR. Previously, response to CRT was evaluated using 24-h ECG recordings only in patients with permanent atrial fibrillation [4, 6–8]. Ganesh et al. [4] evaluated 19 patients in whom the threshold of adequate CRT delivery was defined as > 90% of biventricular pacing. In that study, CRT delivery was considered adequate in only 47% of patients. The patients were followed up for 12 months. The authors evaluated NYHA class, echocardiographic parameters including LVEF, and CRT pacing (captured, fusion, and pseudo-fusion beats). The electrocardiographic criterion for CRT device implantation was ventricular dyssynchrony defined as QRS duration ≥ 120 ms, and the remaining criteria were based on NYHA class (III–IV) and LV systolic function (LVEF ≤ 35%).

Our observations indicate that also in patients with preserved SR, 24-h ECG recording provides important additional information on the adequacy of CRT delivery. We showed that in approximately 25% of patients, variable QRS morphology in lead V1 is seen during 24-h ECG recording, corresponding to the percentage of biventricular pacing below 95%. Only in 2 of these patients, incomplete resynchronisation was noted during routine device interrogation. Examples of 24-h ECG recordings with data on percentages of biventricular pacing as read during device interrogation are shown for 2 patients, No. 1 (Figs. 2, 3), and No. 2 (Figs. 4, 5).

Published studies [9–11] indicate an important role of conventional 12-lead ECG in the evaluation of the adequacy of CRT delivery. This evaluation is most commonly based on the assessment of QRS duration and morphology in lead V1, i.e. presence or absence of R wave as a predictor of adequate biventricular pacing. Conventional 12-lead ECG allows evaluation of the morphology of native QRS complexes and QRS morphology during LV, RV, and biventricular pacing [12]. Using this approach, QRS patterns may be defined as corresponding to a better response to CRT. Such information cannot be obtained from averaged, single-channel ECG recorded by the CRT programming device. Mollo et al. [13] showed that reduction of R peak to S peak interval in lead V1, by more than 10 ms is a predictor of a good response to CRT. In the study by Pan et al. [14], good response to CRT was predicted by the presence of QRS notching in lateral wall leads. Algorithms were also proposed to evaluate the effectiveness of biventricular capture based on paced QRS morphology, most commonly in leads I [12, 15] and V1 [15–17].

Taking into account this established utility of conventional 12-lead ECG, and being aware of the fact that recording a short resting ECG strip is not always able to detect ineffective biventricular capture that may occur during usual patient activities, in our study we performed 24-h 12-lead ECG recording.

In our study, we evaluated patients with preserved SR which favours adequate delivery of biventricular pacing. Our observations indicate that also in this group of patients, inadequate CRT delivery may be detected during routine device interrogation. In patients with preserved SR, the presence of fusion and pseudo-fusion beats is of lesser importance, while variation of paced QRS complexes is a more important issue. This variation resulted not only from changes in HR but was also noted following frequent ventricular extrasystoles and during changes of pacing mode (different QRS morphology during atrial sensed, ventricular paced rhythm and atrioventricular sequential pacing). For this reason, 2 or even 3 different paced QRS morphologies were observed in the same patient during 24-h ECG recording. This requires defining a “normal” QRS pattern in lead V1. In case of significant QRS variation, pacing parameters should be optimised under ECG guidance, aiming for stable QRS morphology. Clearly, effects of these interventions may be evaluated using cardiac imaging studies and/or during long-term follow-up which is a subject
Thus, it does not only identify inadequate biventricular capture but also helps evaluate factors that may affect inadequate CRT delivery and determine the most common timing of this problem.

In our study, we found that both approaches to evaluate delivery of CRT pacing are independent from each other. Our observations are substantiated by the results of multivariate analysis of parameters associated with a suspicion of incomplete resynchronisation by 24-h ECG monitoring. They are logically related to the very concept of resynchronisation. The risk of incomplete resynchronisation increased significantly with higher maximum HR (which may by higher than the upper rate limit), longer QRS duration at the time of minimum HR (possible worse resynchronisation at baseline), longer programmed atrioventricular delay (increased likelihood of fusion and pseudo-fusion beats), and a higher number of ventricular beats (reducing the percentage of biventricular pacing).

Figure 3. Patient No. 1, a printout from CRT-P device interrogation at the time of 24-h electrocardiogram recording. The percentage of ventricular pacing: 95%

Figure 4. Patient No. 2, a part of 24-h electrocardiogram recording. Two different paced QRS morphologies depending on the pacing mode: narrower QRS complexes (75%) during atrial pacing and wider QRS complexes (25%)

Figure 5. Patient No. 2, a printout from CRT-P device interrogation at the time of 24-h electrocardiogram recording. The percentage of ventricular pacing: 99.6%.

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Analysis of the QRS morphology in lead V, during 24-hour Holter ECG monitoring

Based on our analyses, 24-h ECG recording may provide important information in addition to data from device interrogation. In a subset of patients, evaluation using both approaches yields significantly different results and these patients may benefit from ECG-guided optimisation of pacing parameters. Both methods are complementary to each other as device interrogation provides important information that is stored in the device memory and may not be obtained from the analysis of 24-h ECG recording. This is particularly the case for all events, e.g. ventricular and supraventricular arrhythmia that occurs during longer periods between subsequent device interrogations (days, weeks, months), and device interventions, both appropriate and inappropriate.

In our opinion, 24-h Holter ECG monitoring should be used to evaluate adequate delivery of CRT pacing, providing both quantitative (percentage of pacing) and qualitative data, as it seems a more precise method in this regard. Taking into account possible time-consuming nature of the assessment of 24-h ECG studies in some patients (particularly those with variable QRS morphology during CRT), screening methods based on assessment of only selected parts of the 24-h ECG recording should be sought for and are a subject of our research.

Limitations of the study

Limitations of the study included small, inhomogeneous patient sample and lacking clinical data from the preimplantation period. This information would allow a broader view of the problem of inadequate CRT delivery in patients with preserved SR, i.e. whether results of the assessment of CRT delivery by 24-h ECG recording are related to clinical outcomes. Does ECG-guided optimisation of CRT parameters lead to a clinical improvement, or is only a “cosmetic” adjustment without clinical significance? A prospective study in a larger patient group and encompassing various stages of therapy would be necessary to solve these issues. We also believe that in patients with noticeable variation of paced QRS complexes, assessment of CRT delivery should be supplemented by resting positional ECG recordings.

CONCLUSIONS

In patients with preserved SR, device interrogation and evaluation of QRS variability in 24-h ECG recording are complementary methods to evaluate adequate CRT delivery. Therefore, both methods should be taken into account when assessing CRT function.

The study protocol was approved by the Bioethics Committee at the Institute of Cardiology (project No. 1252). The study was supported by institutional statutory funds (No. 2.15/VII/11).

Conflict of interest: none declared

References


Analiza QRS w odprowadzeniu V1 w 24-godzinnym elektrokardiogramie w ocenie funkcjonowania rozrusznika z funkcją resynchronizacji u pacjentów z zachowanym rytmem zatokowym: badanie pilotażowe

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Streszczenie
Wstęp: Zgodnie ze standardami w leczeniu przewlekłej niewydolności serca (HF), po uzyskaniu optymalnej farmakoterapii i po spełnieniu określonych kryteriów klinicznych, elektrokardiograficznych i echokardiograficznych należy rozważyć implantację układu resynchronizującego (CRT). Jednak ok. 30% pacjentów z implantowanym CRT nie odnosi korzyści z wszczęcia tego układu. Rutynowa ocena stymulacji resynchronizującej polega na analizie wewnątrzstymulatorowego badania metodą Holtera. Istnieją przesłanki, że analiza 24-godzinnego zapisu elektrokardiograficznego (24-h EKG) może dostarczyć dodatkowych istotnych informacji.

Cel: Celem pracy było porównanie oceny funkcji resynchronizującej CRT uzyskanej na podstawie analizy zapisu wewnątrzstymulatorowego i analizy QRS w 24-h EKG u pacjentów z zachowanym rytmem zatokowym.

Metody: Analizie poddano 43 rejestracje 24-h EKG i równoczesne (z okresu 24 h) wyniki kontroli CRT na podstawie oceny zapisu wewnątrzstymulatorowego, wykonane w grupie 43 chorych z zachowanym rytmem zatokowym (wiek 56 ± 23; 9 kobiet i 34 mężczyzn). Otrzymane wyniki porównywano w sposób niezależny. Na podstawie zmienności morfologii QRS w odprowadzeniu V1 oceniano stymulację w 12-odprowadzeniowym 24-h EKG. Zmienność QRS rozpoznawano na podstawie: zmiany amplitudy R w V1 o > 3 mm i/lub zmiany czasu QRS > 40 ms i/lub zmiany proporcji R/S. Za wynik pełnej resynchronizacji uznano odsetek stymulacji bez zmienności QRS > 95%.

Wyniki: Obie metody oceniały stymulację w sposób niezależny (test Fishera: p < 0,05). W analizie wieloczynnikowej niezależnie związanymi z występowaniem okresowej niepełnej resynchronizacji były: obecność komorowych zaburzeń rytmu (p = 0,007) — każde 100 pobudzeń zwiększało ryzyko utraty resynchronizacji 1,14-krotnie (1,036–1,25), wyższa o 10 udełenek na minutę maksymalna częstotliwość rytmu serca zwiększała ryzyko utraty CRT 3,3-krotnie (p = 0,008), dłuższy czas QRS (o każde 10 ms) podczas minimalnej częstotliwości rytmu serca zwiększał ryzyko utraty resynchronizacji 1,74-krotnie (p = 0,024), każde wydłużenie zaprogramowanego opóźnienia przedświątkowo-komorowego o 10 ms zwiększało ryzyko 2,15-krotnie (p = 0,013).

Wnioski: W grupie pacjentów z zachowanym rytmem zatokowym wyniki oceny efektywności stymulacji resynchronizującej uzyskane podczas kontroli stymulatora i podczas analizy zmienności QRS w badaniu 24-h EKG uzupełniają się, dlatego w standardach oceny prawidłowości resynchronizacji powinny być uwzględnione zawsze obie metody.

Słowa kluczowe: stymulacja resynchronizująca, nieefektywna stymulacja, zmienność morfologii zespołu QRS, 24-h EKG, kontrola stymulatora, przewlekła niewydolność serca

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