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ÖZGÜN ARAŞTIRMA/ORIGINAL ARTICLE

The Relationship Between Narrowing of the QRS Duration and Improvement in the 6-Minute Walking Distance After Cardiac Resynchronization Therapy

Kardiyak Resenkronizasyon Tedavisi Sonrası 6 Dakikalık Yürüme Mesafesinde İyileşme ile QRS Süresindeki Daralma Arasındaki İlişki

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Anahtar Sözcükler:
Altı dakikalık yürüme testi
Kardiyak resenkronizasyon tedavisi
Kronik kalp yetmezliği

Key Words:
Cardiac resynchronization therapy
Chronic heart failure
Six-minute walking test

ÖZ

Amaç: Kardiyak resenkronizasyon tedavisinin, elektriksel dissenkroniye bağlı azalmış ejeksiyon fraksiyonlu kalp yetmezliği olan hastalarda etkili olduğu kanıtlanmıştır. Bu çalışmanın amacı, kardiyak resenkronizasyon tedavisi sonrası QRS süresindeki daralma ile fonksiyonel kapasitenin bir göstergesi olan 6 dakikalık yürüme mesafesi ile arasındaki ilişkiyi incelemektir.

Gereç ve Yöntem: Çalışmaya sol ventrikül ejeksiyon fraksiyonu ≤%35 olan kronik kalp yetmezliği ile takip edilen (%38 iskemik, %62 iskemik olmayan) toplam 39 semptomatik (New York Heart Association sınıf II-IV) hasta (20 kadın, 19 erkek) dahil edildi.

Bulgular: Kardiyak resenkronizasyon tedavisi öncesine kıyasla, kardiyak resenkronizasyon tedavisi sonrası değerlendirmede QRS süresinde istatistiksel olarak anlamlı azalma (153.62 ± 8.49 ve 131.44 ± 9.86 msn, p <0.001) ve 6 dakikalık yürüme mesafesinde artış (247.77 ± 52.93 vs. 361.15 ± 66.17 m, p <0.001). QRS süresindeki daralma ile kardiyak resenkronizasyon tedavisi sonrası 6 dakikalık yürüme mesafesi arasında orta derecede negatif korelasyon (r = -0.52, p <0.001) tespit edildi.

Sonuç: Çalışmamız, azalmış ejeksiyon fraksiyonlu kalp yetmezliği ve kardiyak resenkronizasyon tedavisi hastalarında, kardiyak resenkronizasyon tedavisi implantasyonu sonrası QRS süresindeki daralmanın 6 dakikalık yürüme mesafesindeki artış ile ilişkili olduğunu göstermiştir.

ABSTRACT

Objective: Cardiac resynchronization therapy has been proved to be effective in patients suffering from reduced ejection fraction heart failure related to electrical dyssynchrony. The aim of this study was to investigate the relationship among narrowing of the QRS duration after cardiac resynchronization therapy and the evaluation of functional capacity by 6-minute walking test.

Material and Method: A total of 39 symptomatic (NYHA class II-IV) patients (20 females, 19 males) with chronic heart failure (38% ischemic, 62% non-ischemic) who had left ventricle ejection fraction ≤ 35% were included into the study.

Results: The evaluation after cardiac resynchronization therapy revealed statistically significant decrease in QRS duration (153.62 ± 8.49 vs. 131.44 ± 9.86 msec, p < 0.001) and increase in 6-minute walking distance (247.77 ± 52.93 vs. 361.15 ± 66.17 m, p < 0.001) compared to before cardiac resynchronization therapy. It was detected moderate negative correlation (r = -0.52, p < 0.001) between narrowing of the QRS duration and 6-minute walking distance after cardiac resynchronization therapy.

Conclusion: In patients with reduced ejection fraction heart failure and cardiac resynchronization therapy, our study has shown that increase in narrowing QRS duration after cardiac resynchronization therapy implantation is associated with development in 6-minute walking distance.

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Introduction

Heart failure (HF) which is the most common clinic discharge diagnosis in patients <65 years of age, still remains to be an important cause of mortality and morbidity despite the better understanding pathophysiology and advances in therapy (1). Improvement of heart failure is characterized by progressive left ventricular (LV) remodeling and deteriorating feature.

Biventricular pacemaker therapy (BiV), which is also known as cardiac resynchronization therapy (CRT), is one of the most significant development in the management of heart failure with a wide QRS complex during the last decade. CRT, delivered via atrial-synchronous biventricular pacing, has emerged as an powerful treatment for moderate-to-severe HF patients with ventricular dyssynchrony. In particular, CRT via simultaneous or sequential biventricular stimulation alleviates signs and symptoms, improves cardiac function, and prolongs survival in a high percentage of sufferers who present with drug-refractory chronic congestive heart failure, LV systolic dysfunction, and a wide QRS complex (2-5).

Evaluation of functional capacity is traditionally done by simply asking patients some questions. “How many flights of stairs can you climb or how many blocks can you walk?” However, patients vary in their recollection and might record overestimations or underestimations of their real functional capacity. Objective measurements are generally better than self-reviews.

The 6-minute walking test (6MWT), which is a practical simple test that requires a hundred feet hallway, however no exercising equipment or advanced education for technicians, measures the distance that a patient can quickly walk on a flat, hard floor in a period of six minutes. The 6MWT appraises the integrated and global responses of all systems involved during exercise, including the pulmonary and cardiovascular systems, and so forth. The self-paced 6MWT assesses the submaximal stage of functional capacity. Most patients do not achieve maximal exercise capacity in the course of the 6MWT; as an alternative, they choose their own depth of exercising and are allowed to stop and rest throughout the test. However, because most activities of daily living are carried out at submaximal stages of exertion, the 6-minute walking distance (6MWD) might better reflect the functional exercising stage for daily physical activities.

Moderate to severe heart failure is one of the most powerful indications for the 6MWT to measure the response to clinical interventions. The 6MWT has additionally been used as a one-time measure of functional status of patients, as well as a predictor of mortality and morbidity (6-7).

The 6MWT is a submaximal exercise test that can be carried out by a patient not tolerating maximal exercise tests (8).

The test is quite simple, requires cheap equipment, and is reproducible. In addition, it is taken into consideration secure because patients are self-limited during exercise. Recently, because the 6MWD has been proven to correlate substantially with peak oxygen consumption (VO2) and Ve-VCO2 slope in sufferers with advanced chronic heart failure, it serves as a prognostic indicator in HF (9-10).

The 6MWT does not determine peak oxygen uptake, diagnose the reason of dyspnea on exertion, or examine the causes or mechanisms of exercise limitation (6-7). The data provided by a 6MWT should be taken into consideration complementary to cardiopulmonary exercise testing, no longer a substitute for it. In spite of the distinction between these two functional exams, some good correlations have been reported between them.

In the present study, we aimed to assess the relation between the distance walked during the 6MWT and narrowing of the QRS duration after cardiac resynchronization therapy.

Material and Method

Study Population

We carried out a retrospective evaluation of a prospective register of patients referred to CRT. Consecutive patients with moderate to severe reduced ejection fraction heart failure (HF-REF) [New York Heart Association (NYHA) functional class II–IV] receiving optimal medical treatment and referred to CRT were evaluated. The indication for CRT was symptomatic HF patients (NYHA class III–IV) despite drug therapy, left ventricle ejection fraction (LVEF) ≤ 35%, LV end-diastolic diameter> 55 millimeters(mm), left bundle branch block (LBBB) and sinus rhythm and QRS period >130 milliseconds(msec). Patients with cardiac or non-cardiac disease that limited their ability to perform 6-MWT and patients with atrial fibrillation, QRS duration <130 msec, non-LBBB, and patients with a recent history of myocardial infarction and unstable angina were excluded. The study protocol was approved by the institutional review board at Lutfi Kırdar Kartal Training and Research Hospital (Date: 29.01.2016 - Decision number:

2016/514/76/9). Detailed informed consent was obtained from all patients.

Study Design

All patients (n = 39) who had a device successfully implanted were evaluated with the 6MWD, NYHA functional class, body-weight, 12-lead surface electrocardiogram (ECG), a comprehensive transthoracic echocardiogram at baseline and after 6 months. Heart rate (HR) was calculated from the ECG. The diastolic and systolic BPs were measured by a cuff manometer after 10 minutes of supine rest.

Each patient received a three-chamber pacemaker without or with defibrillator consistent with the clinical indication according to the contemporary guidelines. The BiV pacing leads were inserted transvenously through the subclavian route, First electrode was positioned within the right atrium if the patient was in sinus rhythm, second electrode at the apex of the right ventricle, and third electrode in a posterolateral branch (whenever possible) through the coronary sinus. If transvenous implant was not possible, the LV electrode (third electrode) was implanted epicardially. The remaining leads (first-second electrode) were positioned conventionally, in the right atrium appendage (patients in sinus rhythm) and the right ventricle apex. In those CRT devices permitting sequential pacing, settings were optimized with the aid of echocardiography as described previously (11).

Electrocardiographic examinations of all the patients were performed by digital electrocardiograph (Cardiofax, Nihon Kohden Co. Ltd, Japan). QRS duration was measured by a single heart specialist who was blinded to the clinical details and outcomes of the study.

Echocardiographic parameters blanketed left atrial and LV dimensions, as measured by M-mode echocardiography in the parasternal long-axis view. LVEF were quantified by the Simpson's method in the four- and two-chamber views on a Vivid 7 Pro (GE Vingmed Ultrasound AS N-3190 Horten, Norway) workstation. Mitral regurgitation was measured using the flow convergence method with a hemispheric assumption (12). All echocardiographic measurements were carried out according to the criteria of American Society of Echocardiography (13). Echocardiographic parameters were analyzed in a core laboratory by a single heart specialist who was blinded to the clinical details and outcomes of the study. Even though ventricular pacing pulses were frequently observed on the simultaneously recorded ECG, each study was analyzed individually and without reference to echocardiographic pics or measurements from other visits.

The six-minute walking test was performed indoors, along a flat, enclosed 30 meters(m) (about 100 feet) corridor with a hard surface, according to American Thoracic Society guideline (14). All the measurements were repeated in all the patients after 3 months. The QRS duration and the 6MWT were analyzed at baseline and 3 months after CRT. The correlations between the changes in electrocardiographic QRS duration and the changes in 6MWD were assessed.

Statistical Methods

All statistical analyses were conducted using software from IBM SPSS statistics version 20. All data were expressed as mean values ± standard deviation (mean±SD). Comparisons between two groups were made by unpaired Student's t test. The baseline characteristics of the 2 groups (3-months after CRT versus baseline) were compared using a paired t test for continuous variables and a x^2 test for discrete variables. Doppler echocardiographic measurements are summarized as medians along with the 95% confidence interval for the median. Nonparametric tests were used to assess the differences of the changes in measurements from baseline to the 3-month follow-up. The relationship between the changes in electrocardiographic QRS duration and the changes in 6MWD was assessed by bivariate correlation analysis. A p value <0.05 was considered significant.

Results

The mean age of the 39 patients (24 females, 39 males) originally included in the study was 61.1 ± 11.4 years and mean LVEF was 27.5 ± 3.7%; 15 (38.5%) patients suffered from ischemic heart disease. Additional baseline demographic and clinical characteristics of the study population are listed in Table 1.

The systolic and diastolic BP and pulse pressure remained unchanged over time. Body weight did not change. The LV echocardiographic data, the results of the 6MWD and the QRS duration during BiV pacing and during spontaneous rhythm is presented in Table 2.

There was statistically significant decrease in QRS duration (131.5 ± 9.9 vs. 153.6 ± 8.5 msec, p <0.001) in 3 month after CRT (during BiV pacing) compared to baseline (during spontaneous rhythm) (Figure 1a). The duration of the spontaneous QRS remained unchanged in 3 month

Table 1. Baseline demographic and clinical characteristics

Parameters		Values
Age, year		61.0 ± 11.4
Gender, male, n (%)		19 (49)
HF causes	İschemic, n (%)	15 (38.5)
	Non-ischemic, n (%)	24 (61.5)
NYHA class	II, n (%)	6 (15.3)
	III, n (%)	30 (77)
	IV, n (%)	3 (7.5)
Diabetes mellitus, n (%)		8 (20.5)
Hypertension, n (%)		10 (25.6)
Dyslipidemia, n (%)		15 (38.5)
Chronic kidney disease, n (%)		2 (5.4)
Current smoking, n (%)		15 (38.5)
Alcohol Consumption, n (%)		11 (28)
Body mass index, kg/m^2		23.18 ± 3.52
Diuretic use, %		100
ACE inhibitor use, %		76
Angiotensin receptor blocker use, %		15
Aldosterone antagonist use, %		90
Beta-blocker use, %		97
Ivabradine use, %		5

after CRT (BiV pacing turned off) compared to baseline (during spontaneous rhythm before CRT).

Distance walked in 6 minute was significantly higher in 3-month after CRT compared to baseline (361.2 ± 66.2 m vs 247.8 ± 52.9, p <0.001) (Figure 1b). In 3-month follow-up after CRT, a mean improvement in 6MWD of 113 m, or 45 % compared with baseline, was found with highly statistically significant improvements. The NYHA class improved by 0.9. Furthermore, increase in left ventricular ejection fraction (33.2 ± 3.4 vs. 27.5 ± 3.7%, p<0.001), decrease in left ventricular end diastolic diameter (65.2 ± 7.4 vs. 71.1 ± 8.3 mm, p <0.001) and left ventricular end systolic diameter (61.8 ± 8 vs. 65.5±7.9 mm, p<0.001) were found statistically significant in patients assessed by echocardiography in 3 month after CRT compared to baseline. Left ventricular end systolic diameter had decreased markedly by 8.1 % at 3 months. Left ventricular end diastolic diameter had decreased markedly by 10.6 % at 3 months. Left ventricular ejection fraction had decreased markedly by 21% (relatively) at 3 months.

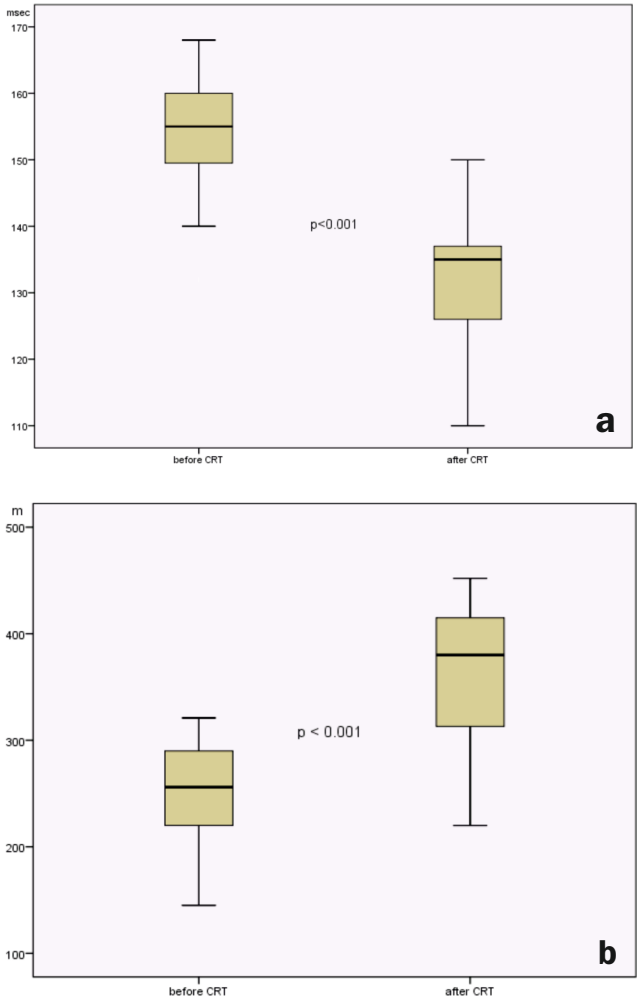

Figure 1. Distribution plot of the QRS duration (a) and the 6-minute walking distance (b) before and after CRT. CRT: cardiac resynchronization therapy, m: meter, msec: millisecond

Table 2. The results of the QRS duration, the 6-minute walked distance, and the echocardiographic data at 3-month after CRT (during BiV pacing) compared to baseline.

Parameters	Baseline	3-month after CRT	p value
Six minute walk distance, m	247.77 ± 52.93	361.15 ± 66.17	p < 0.001
QRS duration, msec	153.62 ± 8.49	131.44 ± 9.86	p < 0.001
LV EDD, mm	71.05 ± 8.31	65.15 ± 7.35	p < 0.001
LV ESD, mm	61.82 ± 8.6	55.13 ± 7.91	p < 0.001
LV ejection fraction, %	27.53 ± 3.74	33.15 ± 3.38	p < 0.001

LV: left ventricle, EDD: End-diastolic diameter, ESD: End-systolic diameter

It was detected moderate negative correlation (r =-0.52, p <0.001) between narrowing of the QRS duration and improvement in 6MWD at 3-month after CRT compared to baseline (Figure 2).

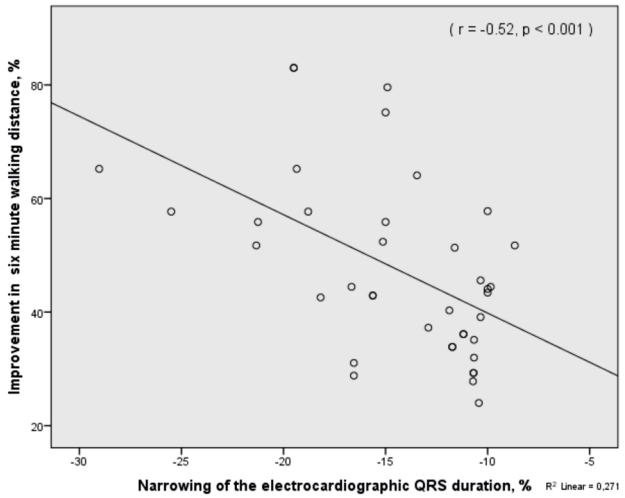

Figure 2. The correlation between narrowing of the QRS duration and improvement in the 6-minute walking distance in patients implanted CRT. CRT: cardiac resynchronization therapy

Discussion

CRT is a cost-effective and efficacious therapy for patients with NYHA class III-IV heart failure despite optimal medical management, sinus rhythm, an LVEF of 35% or less, and prolonged QRS duration. CRT improves HF symptoms and signs, exercise capacity, left ventricular remodelling and function, while also reducing frequency of HF hospitalizations and death. CRT at optimized AV delay results in improvement in functional capacity, which is associated with improved systolic and diastolic LV function, a decrease in mitral regurgitation during shortterm and long-term follow-up (15).

Recent studies show the clear clinical benefits of treating patients with CRT. It also points to the reverse ventricular modeling that occurs with this therapy, with a progressive and sustained increase in LVEF, decrease of the severity of mitral regurgitation and decrease in LV size.

Exercise capacity provides a beneficial prognosis in patients with low EF. In a multivariate evaluation, the observed effect of a good exercise capacity was independent of LVEF. These information indicated that in patients with a low LVEF after myocardial infarction, bene-ficial prognostic information can be obtained from exercise testing (16).

A 6MWT, NYHA class, and VO_2 are broadly accepted prognosis indicators for evaluating clinical and functional aspects in HF patients who have not received CRT (17-20). VO_2 is used to grade the severity of HF (21).

Both exercise heart rate and cardiac index were correlated significantly with VO2 by Szlachcic et al. They reported its effectiveness as an independent prognosis index of survival in patients suffering from HF (22). However, this test is difficult to assess and is not available at every hospital.

The 6MWT is a safe, simple, inexpensive, and reproducible test for evaluating submaximum exercise capacity, and offers some measure of a patient's ability to perform daily activities (14, 23). This test has a significant correlation with functional class and peak VO_2.

The distance walked during the 6-MWT (mean, 418 ± 20 m) significantly correlated with 6-MWT VO_2 (r= 0.71) and peak $V o_2$ (r = 0.63); the 6-MWT VO_2 also showed a high correlation with peak $V o_2$ (r = 0.86) (24).

The 6-MWT correlated well with the cycle ergometer (r = 0.579) and almost as well with the four functional status questionnaires (r = 0.473–0.590) as the questionnaires did with one another (0.423–0.729) in patients with heart and lung disease. These results suggest that exercise capacity in the laboratory can be differentiated from functional exercise capacity (the ability to undertake physically demanding activities of daily living) and that the walk test provides a good measure of function in patients with heart and lung disease (25).

Baseline functional capacity, measured by the 6MWT distance, and LV ejection fraction are independent predictors of mortality in moderate to severe HF patients, despite CRT. A 6MWT distance walked of <225 m identifies patients at high risk of cardiovascular death at midlong term (26).

Linde et al. found a significant sustained benefit in exercise tolerance quality of life from BiV over a 12-month follow-up period. They reported that a mean improvement in 6MWD of 70 m (20%) compared with baseline, was found with highly statistically significant improvements between baseline and the 12-month follow-up. At the same time, they reported that the peak VO2 had increased by 1.7 ml/min/kg (11%), and the NYHA class improved by 0.7. However, there was no evidence of an incremental improvement over the 12-month follow-up period (27).

In the literature, there are no studies examining the correlation between the distance walked during the 6MWT and narrowing of the QRS duration after CRT compared to baseline. Previous studies generally point out the improvement of 6MWD after CRT.

In our study, between the distance walked during the 6MWT and narrowing of the QRS duration were found to be significantly correlated after CRT compared to baseline.

Functional exercise capacity and narrowing of the QRS duration were found to be significantly correlated after CRT compared to baseline.

These results suggest that exercise capacity in the laboratory can be differentiated from functional exercise capacity (the ability to undertake physically demanding activities of daily living) and that the 6-MWT provides a good measure of function in patients with chronic heart failure implanted biventricular pacemaker.

The exclusion of patients with HF with wide QRS complex with AF or non-LBBB is one of the major limitations of our study. The moderate negative correlation between narrowing of the QRS duration and 6MWD after CRT should be followed in terms of clinical outcomes in the longer term. Moreover, this relationship should be supported by more long-term, more comprehensive and multicenter studies.

Conclusion

In the patients with reduced ejection fraction heart failure implanted biventricular pacemaker, our study has shown that increase in narrowing QRS duration after CRT implantation is associated with an obvious improvement in 6MWD according to functional exercise capacity.

Yazarlık Katkısı: Fikir/Hipotez: ME,MA, Tasarım: MA, Veri toplama/Veri işleme: ME, Veri analizi: ME, Makalenin hazırlanması: ME,MA

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