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Research

The Effect of Various Pacing Modes on Microvolt T-Wave Alternans in Patients Receiving Cardiac Resynchronization Therapy

Kardiyak Resenkronizasyon Tedavisi Alan Hastalarda Çeşitli Kalp Pili Modlarının Mikrovolt T-Dalgası Alternansı Üzerindeki Etkisi

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ABSTRACT

Objective: Microvolt T-wave alternans (MTWA) test is a non-invasive method for risk assessment before sudden cardiac death and malignant ventricular tachycardia. Cardiac resynchronization therapy (CRT) is effective in improving left ventricular (LV) systolic function and cardiac electrical activity. The present study investigates the effect of various pacemaker stimulation modes on MTWA in patients receiving CRT.

Methods: The study included 35 patients who received CRT. MTWA was measured in LV, right ventricular (RV), biventricular (BV), and right atrial (RA) modes at 6±2 months after CRT implementation. MTWA results were classified as negative or non-negative. Positive and indeterminate results were considered non-negative. Continuous variables were expressed as mean±standard deviation, and Cohen's kappa statistic was used to compare various pacing modes, with analyses conducted in SPSS at a significance level of $p<0.05$.

Results: RA pacing was concordant with RV pacing in 27 (76.2%) patients (kappa=0.509; p=0.001); with LV pacing in 23 (65.7%) patients (kappa=0.263; p=0.094); and with BV pacing in 26 (74.3%) patients (kappa=0.463; p=0.003). The positive and negative predictive values of results obtained during RA pacing for predicting similar results obtained during RV pacing were 73.1% and 88.9%, respectively; for LV pacing, 65.4% and 66.7%, respectively; and for BV pacing, 69.2% and 88.9%, respectively. We did not find any differences in non-negative MTWA results across different pacing modes with respect to types of cardiomyopathies, statin or amiodarone treatment, and presence or absence of diabetes mellitus or hypertension.

Conclusion: Similar results are achieved when comparing the MTWA results following RA, LV, RV, and BV pacemaker stimulations in patients receiving CRT.

Keywords: Cardiac resynchronization, biventricular pacemaker, microvolt T-wave alternans

ÖZ

Amaç: Mikrovolt T-dalgası değişim testi (MTDDT) ani kardiyak ölüm ve tehlikeli ventriküler taşikardiden önce risk değerlendirmesi için kullanılan girişimsel olmayan bir yöntemdir. Kardiyak resenkronizasyon tedavisi (KRT) sol ventrikül (SV) sistolik fonksiyonunu iyileştirmede ve kardiyak elektriksel aktivite üzerinde etkilidir. Bu çalışmada yer alan hastalarda çeşitli kalp pili stimülasyon modlarının MTDDT üzerindeki etkisi araştırılmıştır.

Gereç ve Yöntem: Çalışmaya KRT alan 35 hasta dahil edilmiştir. MTDDT, KRT uygulamasından 6±2 ay sonra SV, sağ ventrikül (SaV), biventriküler (BV) ve sağ atriyal (SaA) modları aracılığıyla ölçülmüştür. MTDDT sonuçları negatif ve negatif olmayan olarak değerlendirilmiştir. Pozitif ve belirsiz sonuçlar toplu olarak negatif olmayan olarak değerlendirilmiştir. Sürekli değişkenler ortalama±standart sapma olarak ifade edilmiş ve çeşitli kalp pili modlarını karşılaştırmak için Cohen'in kappa istatistikleri kullanılmış ve analizler SPSS'de $p<0,05$ anlamlılık düzeyinde gerçekleştirilmiştir.

Bulgular: SaA uyarımı 27 (%76,2) hastada SaV uyarımı ile (kappa=0,509; p=0,001), 23 (%65,7) hastada SV uyarımı ile (kappa=0,263; p=0,094) ve 26 (%74,3) hastada BV uyarım ile (kappa=0,463; p=0,003) uyumluydu. SaA uyarımı sırasında elde edilen sonuçların SaV uyarımı sırasında elde edilen benzer sonuçlar için pozitif ve negatif öngörü değerleri sırasıyla %73,1 ve %88,9; SV uyarımı için sırasıyla %65,4 ve %66,7; BV uyarım için

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ÖZ

sırasıyla %69,2 ve %88,9 olarak bulundu. Farklı kalp pili modlarında, kardiyomiyopati tipleri, statin, amiodaron tedavisi, diyabetli ve diyabetsiz veya hipertansiyonlu hastalar açısından negatif olmayan MTDDT sonuçlarında herhangi bir fark bulunmadı.

Sonuç: KRT alan hastalarda SaA, SV, SaV ve BV kalp pili uyarılarını takiben MTDDT sonuçları karşılaştırıldığında benzer sonuçlar elde edilmiştir.

Anahtar Kelimeler: Kardiyak resenkronizasyon, biventriküler kalp pili, mikrovolt T-dalgası alternansı

INTRODUCTION

Cardiac resynchronization therapy (CRT) is recommended as the first choice for patients with severe left ventricular (LV) dysfunction [LV ejection fraction (LVEF) ≤35%] accompanied by interventricular conduction delay and with advanced heart failure (HF) that does not respond to optimal medical treatment (functional capacity III-IV according to the New York Heart Association functional classification) (1-3). CRT improves LV systolic function and cardiac electrical activity. Microvolt T-wave alternans (MTWA) on the electrocardiogram is a prominent non-invasive method for predicting sudden cardiac death and malignant ventricular tachycardia (VT) and for risk assessment (4-8). Positive MTWA is an indicator of poor prognosis in patients with ischemic or dilated cardiomyopathy (CMP) (9,10). The present study aims to assess the effects of various pacemaker stimulation methods [right atrial (RA), right ventricular (RV), LV, and biventricular (BV)] on MTWA in patients receiving CRT.

METHODS

The study included patients with HF who received CRT at our center in accordance with the American College of Cardiology/American Heart Association/European Society of Cardiology 2006 guidelines. A total of 35 consecutive patients who received CRT between 2012 and 2020 were enrolled. Patients who had acute coronary syndrome within the last thirty days, who received coronary revascularization therapy within the last six weeks, and who had a history of prolonged VT were excluded from the study. MTWA was measured in LV, RV, BV, and RA modes 6±2 months after wound healing in patients who received CRT. Patients' medications were not discontinued; medical treatment was continued unchanged.

Ethical approval was obtained from the Demiroğlu Science University Clinical Research Ethics Committee (approval no: 44140529/8737, date: 07.09.2021). The study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent after receiving detailed information.

Microvolt T-Wave Alternans Test

The test was performed, based on the method recommended by Bloomfield et al. (11), using a Heartwave™ system (Cambridge Heart, MA, USA) and high-resolution electrodes (High Res™, Cambridge Heart). To measure MTWA, the patient's skin was prepared, and electrocardiography (ECG) signals comprising at least 128 beats were recorded from three Frank orthogonal leads using specialized electrodes. Alternans voltage (Valt) and alternans rate (K-score) were calculated. If the K-score was ≥3 and Valt was ≥1.9 mV, MTWA was considered significant (10). Suspected or uncertain results were considered indeterminate and could not be classified as positive or negative. The MTWA test was performed using RA pacemaker stimulation first in atrium paced-atrium sensed-inhibited mode, followed by RV, LV, and BV pacemaker stimulation. The MTWA was measured by initiating pacemaker stimulation at 90 pulses/minute and increasing the heart rate every 90 seconds to 100, 110, and 120 pulses/minute. The result was obtained by the device's analysis of the summed pulse counts and was evaluated individually as positive, negative, or indeterminate. Positive and indeterminate results were evaluated collectively and classified as non-negative. This differentiation was made based on previous studies (12,13).

The MTWA results obtained through pacemaker stimulation in four different modes in each patient have been evaluated by comparing the modes with each other using appropriate statistical methods. Various pacing modes were also compared with respect to LVEF; non-ischemic and ischemic CMP; use of statins, angiotensin receptor blockers (ARBs), digoxin, diuretics, angiotensin converting enzyme inhibitors (ACE-Is), and amiodarone; presence of CRT therapy defibrillator (CRT-D); diabetes mellitus (DM); and hypertension. The main data of the article are summarized in the Figure 1.

Statistical Analysis

Continuous variables were expressed as mean±standard deviation; categorical variables were expressed as numbers and percentages. Normality of the data was assessed using the Shapiro-Wilk test. Comparisons of categorical variables were performed using the chi-square test. Various pacing modes were analyzed and compared using Cohen's kappa statistic. Statistical analyses were completed using the SPSS, version 25. A p-value of less than 0.05 was considered significant.

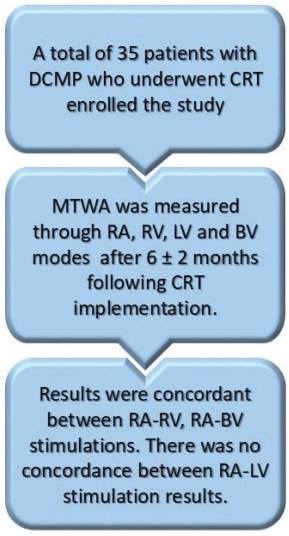

Figure 1. Flow-chart of our study

RESULTS

Characteristics of the Patients

The mean age of the patients included in the study was 67.8±9.6 years. The mean LVEF was 27.0±4.8. Twenty-one (60%) patients had ischemic CMP; 12 (34%) had hypertension; and 6 (17%) had atrial fibrillation. Eleven patients (31%) also received CRT-D. The patients' clinical characteristics are also presented in Table 1. During the evaluation, no patient developed an atrioventricular (A+V) block.

A total of 140 MTWA tests were performed, of which 85 (60.7%) were non-negative. Non-negative tests were observed in 26 patients (74.3%) during RA pacing, 20 (57.1%) during RV pacing, 20 (57.1%) during LV pacing, and 19 (54.3%) during BV pacing. Results were indeterminate in six patients during RA pacing, in two patients during RV pacing, and in two patients during LV pacing. There were no indeterminate results in the BV pacing group. Six patients (17.1%) had negative results at all pacing sites.

Concordance of RA pacing with other sites showed agreement with RV pacing in 27 patients (76.2%; kappa=0.509; p=0.001), with LV pacing in 23 patients (65.7%; kappa=0.263; p=0.094), and with BV pacing in 26 patients (74.3%; kappa=0.463; p=0.003).

The positive and negative predictive values of results obtained during RA pacing for similar results obtained during RV pacing were 73.1% and 88.9%, respectively; for LV pacing 65.4% and 66.7%, respectively; for BV pacing 69.2% and 88.9%, respectively.

Table 1. Patient characteristics

Age (years)	67.8±9.6
Gender (n, %)	
Male	28 (80)
Female	7 (20)
LVEF (%)	27.0±4.8
Ischaemic CMP	21 (60)
PTCA (n)	6 (17.1)
CABG (n)	13 (37.1)
FC	3.07±0.5
QRS time (ms)	144/-19.8
Diabetes	9 (25.7)
Hypertension	12 (34.3)
Atrial fibrillation (paroxysmal)	6 (17.1)
ACE-I therapy	16 (45.7)
ARB therapy	14 (40)
Diuretic therapy	33 (94.3)
Carvedilol therapy	19 (54.3)
Beta-blocker (other) therapy	14 (40)
Amiodarone therapy	6 (17.1)
Digoxin therapy	18 (51.4)
Statin therapy	20 (57.1)
CRT-D therapy	11 (31.4)

LVEF: Left ventricular ejection fraction, CMP: Cardiomyopathy, PTCA: Coronary angioplasty, CABG: Coronary artery bypass surgery, FC: Functional capacity, QRS: Q wave+R wave+S wave, ACE-I: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker, CRT-D: Cardiac resynchronization therapy defibrillator

We did not find any differences in non-negative MTWA results with different pacing modes with respect to types of cardiomyopathies (Table 2), statin, amiodarone, digoxin treatment (Table 3), patients with and without DM or hypertension (Table 4), CRT-D patients (Table 5), LVEF results (Table 6), ACE-I, ARB, diuretic users or non-users (Table 7), of the 35 patients in our study, 33 were receiving beta-blocker therapy, including 19 with carvedilol. Therefore, patients using beta-blockers and those not using them were not analyzed separately.

DISCUSSION

The present study investigates the effect of various pacemaker stimulation methods on MTWA results in patients receiving CRT.

The MTWA test is evaluated by atrial pacemaker stimulation in patients without stimulation-conduction problems in the A+V node, or by submaximal cycling exercise, reflecting technical differences in application (11,14). MTWA test results obtained during exercise are similar to those

obtained during RA pacemaker stimulation (15). The results of both stimulation techniques have recently been shown to be similar when MTWA outcomes from separate RA and RV pacemaker stimulations are compared during an electrophysiological test (12).

The MTWA test detects beat-to-beat T-wave alternans on the ECG that occur at increased heart rates induced by exercise or atrial pacemaker stimulation, to predict sudden cardiac death (8,9). The T-wave alternans measured by the MTWA test reflects intracardiac repolarization alternans.

Table 2. Comparison of pacing modes in patients with ischemic and non-ischemic cardiomyopathy

	Non-ischemic CMP	Ischemic CMP	p
RA pacing (n, %)	12 (85.7)	14 (66.7)	0.262
RV pacing (n, %)	9 (64.3)	11 (52.4)	0.484
LV pacing (n, %)	8 (57.1)	12 (57.1)	1.000
Biventricular pacing (n, %)	9 (64.3)	10 (47.6)	0.330

RA: Right atrium, RV: Right ventricle, LV: Left ventricle, CMP: Cardiomyopathy

Table 3. Comparison of pacing modes with respect to statin, amiodarone and digoxin treatment

	Statin non-users	Statin users	p	Amiodarone non-users	Amiodarone users	p	Digoxin non-users	Digoxin users	p
RA pacing (n, %)	13 (81.3)	13 (68.4)	0.460	13 (81.3)	13 (68.4)	0.460	13 (76.5)	13 (72.2)	0.454
RV pacing (n, %)	9 (56.3)	11 (57.9)	0.922	9 (56.3)	11 (57.9)	0.922	8 (47.1)	12 (66.7)	0.833
LV pacing (n, %)	10 (62.5)	10 (52.6)	0.556	10 (62.5)	10 (52.6)	0.556	8 (47.1)	12 (66.7)	0.833
Biventricular pacing (n, %)	11 (68.8)	8 (42.1)	0.112	11 (68.8)	8 (42.1)	0.112	9 (52.9)	10 (55.6)	0.900

RA: Right atrium, RV: Right ventricle, LV: Left ventricle

Table 4. Comparison of pacing modes in patients with and without diabetes mellitus and hypertension

	Non-diabetic patients	Diabetic patients	p	Hypertension (-)	Hypertension (+)	p
RA pacing (n, %)	19 (73.1)	7 (77.8)	0.781	17 (73.9)	9 (75)	0.781
RV pacing (n, %)	13 (50)	7 (77.8)	0.147	14 (60.9)	6 (50)	0.538
LV pacing (n, %)	15 (57.7)	5 (55.6)	0.911	14 (60.9)	6 (50)	0.538
Biventricular pacing (n, %)	16 (61.5)	3 (33.3)	0.143	13 (56.5)	6 (50)	0.713

RA: Right atrium, RV: Right ventricle, LV: Left ventricle

Table 5. Comparison of pacing modes in patients with and without CRT-D status

	CRT-D negative	CRT-D positive	p
RA pacing (n, %)	18 (75)	8 (72.7)	0.886
RV pacing (n, %)	15 (62.5)	5 (45.5)	0.467
LV pacing (n, %)	15 (62.5)	5 (45.5)	0.467

RA: Right atrium, RV: Right ventricle, LV: Left ventricle, CRT-D: Cardiac resynchronization therapy defibrillator

Table 6. Comparison of pacing modes in patients with LVEF

	RA pacing negative MTWA result	RA pacing positive MTWA result	p
LVEF (%)	27.00±4.71	26.61±4.73	0.753
	RV pacing negative MTWA result	**RV pacing positive MTWA result**	
LVEF (%)	28.73±5.03	25.20±3.81	0.036
	LV pacing negative MTWA result	**LV pacing negative MTWA result**	
LVEF (%)	28.00±4.64	25.75±4.55	0.139
	Biventricular pacing negative MTWA result	**Biventricular pacing positive MTWA result**	
LVEF (%)	26.50±5.40	26.89±4.08	0.481

LVEF: Left ventricular ejection fraction, MTWA: Microvolt T-wave alternans, RA: Right atrium, RV: Right ventricle, LV: Left ventricle

Table 7. Comparison of pacing modes in patients ACE-I, ARB and diuretics non-users/users

	ACE-I non-users	ACE-I users	p	ARB non-users	ARB users	p	Diuretic non-users	Diuretic users	p
RA pacing (n, %)	15 (78.9)	11 (68.8)	0.700	15 (71.4)	11 (78.6)	0.712	1 (50)	25 (75.8)	0.454
RV pacing (n, %)	10 (52.6)	10 (62.5)	0.556	13 (61.9)	7 (50)	0.468	1 (50)	19 (57.6)	0.833
LV pacing (n, %)	11 (57.9)	9 (56.3)	0.922	12 (57.1)	8 (57.1)	1.000	1 (50)	19 (57.6)	0.833
Biventricular pacing (n, %)	10 (52.6)	9 (56.3)	0.830	10 (47.6)	9 (64.3)	0.330	1 (50)	18 (54.5)	0.900

RA: Right atrium, RV: Right ventricle, LV: Left ventricle, ACE-I: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker

The predictive value of T-wave alternans may decline in proportion to the Q wave+R wave+S wave width (14-16).

BV pacemaker stimulation has been shown in several studies to reduce T-wave alternans by decreasing left LV (11,12). Therefore, it is more likely to obtain a negative MTWA result during BV pacemaker stimulation than during RA, LV, or RV pacemaker stimulation. However, some studies suggest that BV pacemaker stimulation may enhance arrhythmogenicity (13). Among other studies similar to the present one, Shalaby et al. (12) studied 42 patients and compared MTWA results by separately analyzing RA and RV pacemaker stimulation during an electrophysiological test. The MTWA test was found to be negative in 47% of patients due to RA pacemaker stimulation. The mean LVEF of the patients was 33±13%. This study concluded that the MTWA results from RA and RV pacemaker stimulation were similar (kappa=0.62; p<0.001) (12). Another study by Raatikainen et al. (16) analyzed MTWA results in 80 post-myocardial infarction patients (mean LVEF 30±7%) and found MTWA positivity rates of 24% with exercise, 45% with atrial pacing, and 50% with ventriculoatrial (V+A) pacing. Similarity rates were 71% between exercise and A+V consecutive pacemaker stimulations; 79% between exercise and RA pacemaker stimulations; and 95% between RA pacemaker stimulations and V+A consecutive pacemaker stimulations. The sympathetic discharge elicited by the cycling exercise test explains the discrepancy between its result and that obtained by electrophysiological testing. The similarity of the test results suggests that the pacemaker stimulation method can also be used in patients who are unable to exercise. This finding supports our use of pacemaker stimulation during the MTWA test, since the patients included in the present study had severely impaired LV function and markedly reduced exercise capacity. The study by Medina-Ravell et al. (17), which included 29 patients with ischemic or dilated cardiomyopathy, suggested that BV pacemaker stimulation CRT may have an arrhythmogenic effect. Another study by Ehrlich et al. (18), which included 30 patients, demonstrated that BV pacemaker stimulation was not arrhythmogenic; MTWA results were similar across different pacemaker stimulation methods and were not affected by BV pacemaker stimulation therapy in HF patients. The study by Anh et al. (19), conducted in 44 patients with implanted intracardiac defibrillators, 27 of whom also received BV pacemaker stimulation CRT therapy, compared the MTWA results from RA, LV, RV, and BV pacemaker stimulations, and observed a significant similarity between the MTWA results from RA pacemaker stimulation and ventricular pacemaker stimulation. This study also demonstrated that such similarity varied among ventricular stimulation sites and that BV pacing reduced MTWA positivity.

The study by Kowal et al. (20) compared BV and RV pacemaker stimulation and showed that BV stimulation reduced the development of arrhythmia compared with RV stimulation. Another study by Anh et al. (21), involving 33 patients who received CRT, analyzed MTWA test results obtained during RA, LV, RV, and BV pacemaker stimulation and demonstrated that BV pacemaker stimulation improved MTWA results. The superiority of the exercise test over the pacemaker stimulation test during the MTWA test has also been demonstrated in a study by Rashba et al. (22).

Consistent with most of these studies, the present study found similar MTWA test results across various pacemaker stimulation modes. A significant similarity has been shown between the results of RA and RV pacemaker stimulation, and between RA and BV pacemaker stimulation. Different from the study by Medina-Ravel et al. (17), 19 the present study did not observe torsade de pointes in any of the patients during the MTWA test and did not find arrhythmogenic potential with BV pacemaker stimulation. Likewise, in contrast to the study by Anh et al. (21), the present study did not observe any significant reduction in MTWA with BV pacemaker stimulation. This may have resulted from differences in patient characteristics, despite the number of patients being approximately the same in the present study. Because we did not discontinue medical treatment during the study, ongoing treatment may have influenced the evaluation results. It should be noted that various medications, which we could not discontinue because of

the clinical status of our patients, have also affected MTWA measurements.

Study Limitation

This may be considered a limitation in our evaluation of the results. A predominance of male patients (n=28; 80%) in our study group of 35 suggests a gender-related imbalance. Contrary to the study by Rashba et al. (22), since the patients included in our study group had extremely impaired LV function and very low functional capacity, and the objective of the present study was to compare various pacemaker stimulation modes, we conducted our examinations using pacemaker stimulation instead of exercise. The study's relatively small sample size is a limitation that may reduce statistical power, particularly for detecting small or subgroup-specific effects. Future studies with larger, multicenter cohorts are needed to confirm and generalize our findings.

CONCLUSION

Similar MTWA results are observed when comparing RA, LV, RV, and BV pacemaker stimulation in patients receiving CRT. The predictive value of data from various pacemaker stimulation modes also differs. Homogeneous studies with larger sample sizes are required to determine the effects of various pacemaker stimulation modes on MTWA. Such studies may explain the relationships between changes in T-wave amplitude and MTWA, and between repolarization dispersion and potential arrhythmogenic effects (23,24). The present study found that, under effective antiarrhythmic medication, various pacemaker stimulation modes did not significantly alter T-wave alternans test results.

ETHICS

Ethics Committee Approval: Ethical approval was obtained from the Demiroğlu Science University Clinical Research Ethics Committee (approval no: 44140529/8737, date: 07.09.2021). The study was conducted in accordance with the Declaration of Helsinki.

Informed Consent: All patients provided written informed consent after receiving detailed information.

FOOTNOTES

Authorship Contributions

Concept: D.E., C.Y., Design: D.E., M.G., N.Y., Data Collection or Processing: D.E., M.G., C.Y., N.Y., Analysis or Interpretation: M.G., C.Y., N.Y., Literature Search: D.E., M.G., C.Y., Writing: D.E.

Conflict of Interest: No conflict of interest was declared by the authors.

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