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RESEARCH

Effect of sacubutril/valsartan on Tp-e, QT, QTc, Tp-e/QTc parameters in heart failure with reduced ejection fraction

Düşük ejeksiyon fraksiyonlu kalp yetersizliğinde sakubutril/valsartan'ın Tp-e, QT, QTc, Tp-e/QTc parametreleri üzerine etkisi

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Abstract

Purpose: The purpose of this study is to evaluate ventricular repolarization before, at the first month, and sixth month after Sacubutril/Valsartan, an angiotensin receptor neprilysin inhibitor (ARNI) treatment in heart failure patients with reduced ejection fraction (HFrEF).

Materials and Methods: We included 49 patients with HFrEF who switched to ARNI therapy. The 12-lead electrocardiography (ECG) was evaluated before ARNI therapy and also during the first and sixth months of the therapy. We evaluated demographic, clinical, and laboratory parameters, as well as medications and ECG data, including heart rate. Additionally, we examined QT, QTc, Tp-e, Tp-e calculated (Tp-ec), Tp-ec/QTc, Tp-e/QT, and Tp-e/QTc.

Results: After receiving ARNI treatment, ventricular repolarization indices were significantly reduced in the first and sixth months compared to before treatment. Specifically, the QTc values decreased from 457.6 ms to 443.8 ms, and the Tp-e/QT ratio decreased from 0.21±0.03 to 0.19±0.03. Additionally, the QTc values decreased from 457.6 ms to 444.9 ms, and the Tp-e/QT ratio decreased from 0.21±0.03 to 0.18±0.03. However, when the first and sixth months under ARNI treatment were compared, no significant difference was found (QTc: 443.8 ms vs. 444.9 ms, Tp-e/QT: 0.19±0.03 vs. 0.18±0.003).

Conclusion: ARNI treatment in HFrEF positively affected QTc, Tp-e, and Tp-ec intervals and Tp-e/QT, Tp-e/QTc, and Tp-ec/QTc ratios, which are indicators of ventricular repolarization. Moreover, this effect started in the first month and continued in the sixth month.

Keywords: Angiotensin receptor neprilysin inhibitor; Tp-e; Tp-e/QTc ratio; QTc; Sudden cardiac death; Ventricular repolarization.

Öz

Amaç: Bu çalışmada, düşük ejeksiyon fraksiyonlu kalp yetersizliği (HFrEF) hastalarında Sakubutril/Valsartan-Anjiyotensin reseptör neprilisin inhibitörünün (ARNI) tedavisi öncesi, tedavi sonrası birinci ve altıncı aylarda ventriküler repolarizasyonu değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışmaya anjiyotensin dönüştürücü enzim inhibitörlerinden veya anjiyotensin reseptör blokerlerinden (ACE-I/ARB) ARNI tedavisine geçen 49 HFrEF hastası dahil edildi. ARNI tedavisi öncesinde, birinci ve altıncı aylarda 12 derivasyonlu elektrokardiyografi (EKG) değerlendirildi. Demografik, klinik ve laboratuvar parametrelerinin yanı sıra ilaçlar ve EKG verileri, kalp atış hızı, QT, QTc, Tp-e, hesaplanan Tp-e (Tp-ec), Tp-ec/QTc, Tp-e/QT ve Tp-e/QTc değerlendirildi.

Bulgular: ARNI tedavisi aldıktan sonra ventriküler repolarizasyon indekslerinde tedavi öncesine göre birinci ve altıncı ayda anlamlı azalma görüldü. Spesifik olarak QTc değerleri 457.6 ms'den 443.8 ms'ye, Tp-e/QT oranı ise 0.21±0,03'ten 0.19±0.03'e düştü. Ayrıca QTc değerleri 457.6 ms'den 444.9 ms'ye, Tp-e/QT oranı ise 0.21±0.03'ten 0.18±0.03'e düştü. Ancak ARNI tedavisi altında birinci ve altıncı aylar karşılaştırıldığında anlamlı fark saptanmadı (QTc: 443.8 ms vs. 444.9 ms, Tp-e/QT: 0.19±0.03 vs. 0.18±0.003).

Sonuç: HFrEF'de ARNI tedavisi ile ventriküler repolarizasyonun göstergeleri olan QTc, Tp-e ve Tp-ec aralıklarında ve Tp-e/QT, Tp-e/QTc ve Tp-ec/QTc oranlarında olumlu etkilendi. Üstelik bu etki 1. ayda başlayıp 6. ayda da devam etti.

Anahtar kelimeler: Ani kardiyak ölüm, Anjiyotensin reseptörü neprilisin inhibitörü, Tp-e; Tp-e/QTc oranı; QTc, Ventriküler repolarizasyon.

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INTRODUCTION

Heart failure (HF) is an increasingly prevalent condition, affecting 1-2% of the world's population. Key pathologies in HF include decreased cardiac output, elevated intracardiac filling pressures, pathophysiologically excessive adrenergic activity, and activation of the renin-angiotensin-aldosterone system (RAAS)[1,2]. Patient outcomes are improved with the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ACE-I/ARB). Sacubutril/Valsartan, an angiotensin receptor neprilysin inhibitor (ARNI), also demonstrates efficacy. Mineralocorticoid receptor antagonists (MRA), beta-blockers, and cardiac devices are additional therapeutic options [1,2]. Nevertheless, sudden cardiac death (SCD) remains a significant cause of mortality in individuals with low ejection fraction (HFrEF)[3].

The initial study on sacubitril/valsartan, the pioneering ARNI, showed superior outcomes by reducing both mortality and morbidity compared to enalapril [4]. In addition, a significant decrease in SCD has been reported as an important cause of low mortality due to ARNI[4,5]. A recent study showed that ARNI reduces ventricular arrhythmias effectively. It also reduces appropriate ICD shocks more effectively than RAAS inhibition[6]. ARNI's precise mechanism for reducing SCD, ICD shocks, and cardiovascular mortality remains unclear[5,6].

An increase in ventricular depolarization dispersion, as measured by the QT interval (QT), QT dispersion (QTd), and overall myocardial repolarization dispersion, is associated with susceptibility to ventricular arrhythmias[7,8]. Additionally, the prolongation of the T wave peak-to-T wave end interval (Tp-e interval), considered a parameter of total repolarization distribution, may be valuable in predicting increased cardiovascular mortality and ventricular arrhythmias[9-13]. Abnormally prolonged or shortened QT intervals predispose individuals to the development of ventricular tachycardia and sudden cardiac death (SCD)[14,15]. The Tp-e/QT ratio appears to be more reliable than the QT and Tp-e intervals as an indicator of ventricular repolarization distribution[11]. Increased Tp-e and Tp-e/QT ratios have been reported to predict appropriate ICD shocks as well as indicate an increased risk of ventricular arrhythmia in HF patients with ICDs for primary prevention[16,17]. The addition of SGLT2 inhibitors to optimal medical therapy has been shown to positively affect ventricular repolarization markers[18]. Reports indicate that switching from ramipril to ARNI positively affects QTc, Tp-e, and Tp-e/QTc in HFrEF and reduces symptoms within the first month [19]. However, it remains unclear whether the effects on ventricular repolarization persist in the long term.

Our aim is to examine the effect of switching from ACE-I/ARB to ARNI on ventricular repolarization in HFrEF by measuring Tp-e, QTc, and Tp-e/QTc in a six-month long-term follow-up.

MATERIALS AND METHODS

Study population

The study followed the principles of the Declaration of Helsinki (2013). Approval was obtained from the Antalya Training and Research Hospital Ethical Committee (Date: 03/07/2020, Decision No. 10/26). The study was planned to be conducted on patients with medical records who were regularly followed up in our clinic's HF outpatient clinic. Between January 2019 and July 2020, we screened 998 HFrEF patients. Inclusion criteria were age ≥ 18 years, left ventricular ejection fraction (LVEF) ≤ 35%, switching from ACE-I/ARB to ARNI, having an artifact-free electrocardiography (ECG), and a six-month follow-up. Ventricular preexcitation and atrioventricular conduction abnormalities were excluded. Patients with baseline or follow-up electrolyte disturbances, thyroid dysfunction, and medications causing QT prolongation were excluded from the study. In the follow-up, 56 patients switched from ACE-I/ARB to ARNI use. The study included 49 individuals who were monitored for six months. Their ECG assessments were conducted without any artifacts. The medical records evaluated the ECG recording, medications, demographics, and laboratory parameters. We increased the doses of ARNI, beta-blockers, and spironolactone to their maximum levels. This was done according to the guidelines for HF. We evaluated LVEF using the biplane Simpson method[20]. During ACE-I/ARB therapy and at the first and sixth months after ARNI therapy, we analyzed a 12-lead ECG. The baseline ECG recorded the rhythm (atrial fibrillation or sinus rhythm). Heart rate (HR), QT, QTc, Tp-e, Tp-e calculated (Tp-ec), Tp-ec/QTc, Tp-e/QT, and Tp-e/QTc were also calculated and recorded.

Electrocardiography

ECGs were evaluated using 12 leads at a paper speed of 25 mm/sec (Nihon Kohden, Tokyo, Japan). The evaluations occurred before starting ARNI, after one month, and after six months of treatment. ECGs were electronically recorded in the PACS system (Sectra Work Station IDS7, Sectra AB Teknikringen 20 SE-58330 Linköping, Sweden). Two cardiologists, who were unaware of the patient's identity, measured all ECG parameters. Both cardiologists made 6 measurements, each with 3 different parameters. These measurements calculated the average value. We measured the resting HR and all the intervals in milliseconds. The QT interval was computed by measuring from the onset of the QRS complex to the intersection point where the steepest downward slope of the T wave met the isoelectric baseline. The corrected QT interval (QTc) was determined using the formula QT divided by the square root of the RR interval [21]. The time between the peak and end of the T wave was defined as the Tp-e interval in the precordial leads [12,22] (Figure 1). Also, the corrected Tp-e interval was calculated with the following formula: Tp-ec= Tp-e/ √R_R interval. Tp-e/QT, Tp-ec/QTc, and Tp-e/QTc ratios were measured.

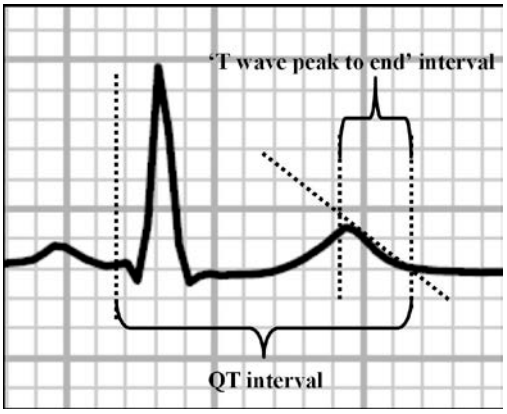

Figure 1. T wave peak to end (Tp-e) and QT intervals on electrocardiography.

Statistical analysis

The Kolmogorov-Smirnov test and Q-Q plot were used for normality. Descriptive statistics for normally distributed data are given as the mean ± standard deviation. The Chi-square test was used for categorical data to compare groups. Numerical variables in dependent groups were analyzed using the Paired samples t-test or Wilcoxon's signed rank test. Data were analyzed with SPSS version 21.0 for Windows. (SPSS, Chicago, IL, USA). A p-value of 0.05 was considered significant.

RESULTS

The age of the cohort was 61.3±13.6 years. Among the study population, 67.3% were male. Ischemic etiology was present in 55.1% of the patients, and the mean LVEF was 25.6% ±6.9%. All patients used ACE-I/ARB. Spironolactone use was 85.8%. Beta-blocker use was 98%. Table 1 shows the baseline characteristics. After switching from ACE-I/ARB to ARNI, all patients were taking 100 mg bid at one month and 200 mg bid at six month.

Table 2 displays the measurements taken during ARNI treatment, including electrocardiographic, laboratory, and clinical parameters. These measurements were assessed before treatment, at the first month, and sixth month of treatment. After receiving ARNI treatment, the indices for ventricular repolarization decreased significantly. At one month of treatment, a decrease was observed compared to before starting ARNI treatment. Specifically, the QTc values decreased from 457.6 ms to 443.8 ms ($p=0.015$). Additionally, the Tp-e/QT ratio decreased from 0.21±0.03 to 0.19±0.03 ($p<0.001$). The decrease continued when compared to the baseline at six months. The measurements were QTc: 457.6 ms vs. 444.9 ms ($p=0.024$) and Tp-e/QT: 0.21±0.03 vs. 0.18±0.03 ($p<0.001$). There was no significant difference when ARNI treatment was continued. When comparing the first and sixth months, there was no difference in QTc measurements (443.8 ms vs. 444.9 ms, $p=0.794$). Additionally, there was no difference in Tp-e/QT values (0.19±0.03 vs. 0.18±0.003, $p=0.063$) (Table 2). The HR was significantly reduced at both the first and sixth months compared to before ARNI treatment ($p=0.034$, $p=0.009$, respectively). While ARNI treatment was continued, no difference was detected between the first and sixth months ($p=0.457$).

ARNI treatment was associated with lower NYHA levels. While the rate of NYHA III and IV patients was 57.2%, it decreased to 12.2% in the first month and 10.2% in the sixth month ($p<0.001$). With ARNI treatment, NT-proBNP levels consistently decreased at one month and six months compared to baseline. The levels were 4514 pg/ml, 3296 pg/ml, and 2456 pg/ml, respectively ($p < 0.001$).

Table 1. Baseline clinical parameters of the study population.

Parameters	
Age (years)	61.3±13.6
Male, n (%)	33 (67.3)
Hypertension, n (%)	26 (53.1)
Heart failure etiology, n (%) Ischemic Non-ischemic	 27 (55.1) 22 (44.9)
Diabetes mellitus, n (%)	21 (42.9)
Hyperlipidemia, n (%)	15 (30.6)
Systolic blood pressure (mm Hg)	106.3±20.2
Diastolic blood pressure (mm Hg)	63.7±11.2
Left ventricular ejection fraction (%)	25.6±6.9
ACEI/ARB use,n (%)	49 (100)
Beta-blocker use, n (%)	48 (98)
Spironolactone use, n (%)	42 (85.8)
Diuretic use, n (%)	43 (87.8)
Digoxin use, n (%)	9 (18.4)
Ivabradine use, n (%)	9 (18.4)
SGLT2 inhibitors, n (%)	0 (0)
Cardiac resynchronization therapy/implantable cardioverter defibrillator, n (%)	17 (34.6)
Rhythm: sinus rhythm, n (%)	37 (75.5)

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; SGLT2, Sodium-glucose Cotransporter-2. Numerical variables were presented as the mean ± SD and categorical variables presented as percentages.

Table 2. Electrocardiographic indices, laboratory and clinical parameters before ARNI treatment, 1. and 6. months after ARNI treatment

Parameter	**Before**	**1. month**	**6. month**	**p^1-value**	**p^2-value**	**p^3-value**
Heart rate, bpm	*78.3* ± 18	73.1 ± 13.8	71.9 ± 14	**0.034**	**0.009**	0.457
QT, ms	405.5 ± 41.6	406.2 ± 44.7	411.1 ± 46.4	0.892	0.311	0.294
QTc, ms	457.6 ± 43.7	443.8 ± 41.2	444.9 ± 37.7	**0.015**	**0.024**	0.794
Tp-e, ms	85 ± 9.5	76.7 ± 10.5	74.1 ± 10.2	**<0.001**	**<0.001**	0.106
Tp-ec, ms	96.6 ± 16	84.3 ± 13.8	80.8 ± 13.8	**<0.001**	**<0.001**	0.092
Tp-e/QT	0.21 ± 0.03	0.19 ± 0.03	0.18 ± 0.03	**<0.001**	**<0.001**	0.063
Tp-e/QTc	*0.19 ± 0.02*	0.17 ± 0.02	0.17 ± 0.02	**<0.001**	**<0.001**	0.081
Tp-ec/QTc	0.21 ± 0.03	0.19 ± 0.03	0.18 ± 0.03	**<0.001**	**<0.001**	0.063
NT-proBNP, pg/ml	4514 ± 5616	3296 ± 2971	2456 ± 2307	**<0.001**	**<0.001**	**<0.001**
NYHA, % I II III / IV	 0 42.9 57.2	 24.5 63.3 12.2	 40.8 49 10.2	<0.001	0.052	<0.001

ARNI, angiotensin receptor neprilysin inhibitor; NYHA, New York Heart Association; NT-proBNP, N terminal-pro brain natriuretic peptide. Numerical variables were presented as the mean ± SD.

[1] P value between before and after 1 month

[2] P value between before and after 6 months

[3] P value between after 1 month and after 6 months

DISCUSSION

In this study, we observed an improvement in repolarization dispersion parameters in patients with HFrEF with ARNI treatment. Positive improvement was observed in all analyzed parameters: QTc, Tp-e, and Tp-ec intervals, Tp-e/QT, Tp-e/QTc, and Tp-ec/QTc ratios. Moreover, this positive effect begins

early with ARNI treatment and continues for six months.

The PARADIGM-HF trial included 8399 HF patients in NYHA classes II, III, and IV with LVEF ≤ 40%. The trial reported a lower occurrence of cardiovascular mortality or initial hospitalization for HF with ARNI compared to ACE-I[4,5]. ARNI treatment reduces sudden cardiac death and death from worsening HF by 20% compared to enalapril[5]. No pathophysiological mechanism to explain SCD was reported in the PARADIGM-HF study. A prior investigation in patients with HFrEF documented a 14% rise in the likelihood of ventricular arrhythmia associated with elevated Tp-Te intervals and a 19% elevation in the risk of mortality linked to increased Tpe_c[23].

The Tp-e/QTc ratio is a new indicator of ventricular repolarization dispersion. It predicts arrhythmias better than Tp-e or QTc intervals alone. The sensitivity of the Tp-e/QTc ratio is increased. Notably, this ratio remains unaffected by variations in body weight and HR[11]. When SGLT2 inhibitors were added to HF treatment, the ventricular repolarization markers QT, QTc, QTd, Tp-e, and Tp-e/QTc were observed to improve positively in the first month[18]. In another study, an improvement in the Tp-e interval and Tp-e / QT and Tp-e / QTc ratios was observed in the third month with intravenous iron treatment in HF patients with iron deficiency[24]. While QTc, Tp-e, and Tp-e/QTc had positive effects, a decrease in NT-proBNP and improvement in symptoms were detected in patients who were switched from ramipril to ARNI, in the first month[23]. Similarly, in our study, it was observed that the improvement in QTc, Tp-e, and Tp-ec intervals and Tp-e/QT, Tp-e/QTc, and Tp-ec/QTc ratios continued in the sixth month. These positive effects on ventricular repolarization in patients with HFrEF may be predictive of reducing the arrhythmogenic effect in the long term.

The ventricular myocardium is not electrically homogeneous, and M cells located in the deep subepicardial layer have longer action potential durations compared to endocardial and epicardial cells[25]. Myocardial remodeling and fibrosis are hallmarks of arrhythmogenic structural remodeling, creating a gradient across myocardial layers that contributes to ventricular dispersion. Remodeling and fibrosis may damage the myocardium. Previous studies have shown that ARNI reduces ventricular fibrosis and remodeling, compared favorably to RAAS blockers[26,27]. ARNI induces positive changes in the electrophysiological and anatomical structure of the myocardium, predisposing it to ventricular arrhythmias[26-28].

Recent studies indicate that switching to ARNI therapy reduces ventricular tachycardia/fibrillation and related ICD shocks in HFrEF patients. Following ARNI treatment, a significant decrease in non-sustained ventricular tachycardia and premature ventricular contractions has been observed[6,29]. Prior research has shown that sympathetic stimulation increases the Tp-e interval and myocardial repolarization dispersion[30]. In our study, a significant decrease in HR was observed, consistent with previous findings, indicating an improvement in sympathetic tone after ARNI treatment[6,19].

The potential antiarrhythmic effects of ARNI may be attributed to modulating the RAAS, increasing natriuresis and diuresis, decreasing sympathetic tone, reducing cardiac fibrosis, enhancing reverse remodeling, and positive electrophysiological improvements[5,6,31]. In addition to modulating the RAAS, ARNI potentiates the action of natriuretic peptides. Elevated NT-proBNP levels, associated with heightened wall stress, serve as an independent prognostic factor for ventricular arrhythmias in HF[32]. Our study observed a significant decrease in NT-proBNP values during the first and sixth months of ARNI treatment. Heightened wall tension increases the function of stretch-sensitive sodium, potassium, and calcium channels, contributing to ventricular arrhythmias[33]. ARNI demonstrates clear effects, including a reduction in sudden cardiac death, decreased overall mortality, and a lower incidence of ICD shocks. Furthermore, there is an improvement in ventricular repolarization. However, the precise mechanism behind these effects remains unknown. Therefore, additional studies are needed.

Our study had some limitations. Most importantly, the number of patients was limited because it was planned retrospectively. The data on arrhythmias, ventricular arrhythmias, and ICD shock after ARNI treatment were insufficient. We evaluated only the arrhythmogenic parameters in the ECG in previous studies. The study population was small, and the follow-up was short. It was insufficient to evaluate cardiovascular outcomes.

In conclusion, switching from ACE-I/ARB to ARNI improved NYHA class in HFrEF and decreased NT-proBNP levels, as well as improved ventricular

repolarization parameters both at one month and six months. These positive effects on ventricular repolarization in patients with HFrEF may be important in predicting the reduction of the arrhythmogenic effect in the long term. However, the positive effects of ARNI on cardiac electrophysiology are not fully understood, and there is much more to be learned and clarified.

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