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EFFECT OF SACUBITRIL/VALSARTAN ON HEART RATE VARIABILITY HRV AND QT DISPERSION IN HEART FAILURE WITH REDUCED EJECTION FRACTION

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ABSTRACT

Background: Treatment of heart failure with reduced ejection fraction(HFrEF) by using Sacubitril/Valsartan reduces sudden cardiac death, but the precise mechanism underlying the beneficial effect on reducing cardiovascular mortality is still not clear. **Objective:** the present study aims to assess effects of Sacubitril/Valsartan on QT dispersion and HR variability in symptomatic patients with HFrEF. **Materials and Methods:** This is prospective study conducted in the department of Cardiology in Tishreen University Hospital-Lattakia -Syria from September 2019 to September 2020. Patients with HFrEF classified according to the NYHA in II-IV who aged 39 to 82 years were enrolled in the study. QT dispersion, SDNN were reordered before starting Sacubitril/Valsartan and after one month of the therapy. **Results:** A total of 22 patients were included, Median age was 50 years, 13 (59.10%) were female, hypertension was present in 15(68.2%) of the patients. Sacubitril/Valsartan reduced QTd (65.09±25.3 vs 51.72±21.7, p:0.004**),** OTc(435.04±27.6 vs 425.40±27.1.p:0.1), QRS(94.54±19.22 vs 93.40±16.39,p:0.6), and increased SDNN(93.22±24.7 vs 111.81±37.2,p:0.01) in the study participants. Spearman's correlation analysis revealed negative correlation between changes in SDNN and dyspnea degree (Spearman's = -0.2, P:0.04**)** and a positive correlation between changes in QTD and dyspnea degree (Spearman's = 0.3, P:0.01**).** Increased dose of drug was correlated with decreased QTd(Spearman's = - 0.1, P:0.5**)** and increased SDNN(Spearman's = 0.1, P:0.4**)**. **Conclusion:** Based on our results, Sacubitril/Valsartan alters ventricular repolarization indices which associated with clinical improvement, so it could be an effective approach in treating patients with HFrEF.

KEYWORDS: Sacubitril/Valsartan, QT dispersion, HR variability, HFrEF.

INTRODUCTION

Heart failure (HF) is a clinical syndrome in which symptoms result from impairment of ventricle filling or ejection of blood or both. HFrEF occurs when the left ventricular ejection fraction (LVEF) is 40% or less and is accompanied by progressive left ventricular dilatation and adverse cardiac remodeling.[1,2]

Worldwide, the burden of heart failure has increased and approximately 50% of cases are HFrEF which represents a major public health concern with substantial morbidity and mortality.[3]

Sacubitril/Valsartan is known as an angiotensin receptor neprilysin inhibitor(ARNI). It blocks harmful effects of renin-angiotensin-aldosterone system(RAAS) activation, and also raising levels of natriuretic peptides that are degraded by neprilysin. Therapy with Sacubitril/ Valsartan successfully improved outcomes in patients with HFrEF.[4,5] The absence of local studies prompted us to carry out this research to assess the effects of Sacubitril/Valsartan on ventricular repolarization parameters in HFrEF patients.

MATERIALS AND METHODS

Study design and data collection

We prospectively studied patients with HFrEF aged 39 to 82 years who presented to the department of Cardiology in Tishreen University Hospital –Lattakia-Syria from September 2019 to September 2020. Patients with one of the following: evidence of presence atrial fibrillation, renal failure stage IV and V, treatment with antiarrhythmic drugs except of beta blockers, and patients with disorders in serum electrolytes (potassium

K, sodium Na, magnesium Mg, calcium Ca)were excluded. Demographic data including age, sex and related to co-morbidities were recorded. All the following measurements were recorded before starting treatment with Sacubitril/Valsartan and after one month: blood glucose, serum electrolytes, QT dispersion, QRS,QTC,SDNN.

Definitions

Heart rate variability (HRV): fluctuations in the RR intervals, can be measured by three methods: time domain measures, frequency domain measures, nonlinear/complexity based measures.[6]

SDNN(ms): The Standard deviation of all normal RR intervals in the entire 24 –hour ECG record, and represents one of HRV indices measured by Time-domain method. It reflects the parasympathetic component of autonomic function, and classified into normal SDNN: above 100 ms, and abnormal SDNN below 100ms.[7]

QT dispersion: defined as the difference between the longest(QT max) and the shorter (QT min) QT intervals within a 12 lead ECG. Patients are classified into three subgroups: normal <40 ms, prolonged:40-80 ms, Very prolonged ≥80ms.[8]

Statistical Analysis

Statistical analysis was performed by using IBM SPSS version 20. Basic Descriptive statistics included means, standard deviations(SD), Frequency and percentages.

Differences of distribution examined by using chi-square test or Fisher exact test as needed. Paired sample t-test was performed to compare indices before and after treatment. Correlations were analysed using Spearman's rank correlation coefficient. Variables with p less than 0.05 were included in the model.

RESULTS

A total of 22 patients with HFrEF (median age: 50 year; 13 females, hypertension in 68.2%) who presented to the department of Cardiology from September 2019 to September 2020were included in the study. The baseline characteristics of patients are as given in table(1).

As shown below, 40.9% of the patients had prolonged QTd, and 50% had abnormal SDNN.

Table 1: Demographic characteristics and electrocardiographic, echocardiographic parameters of the study population.

Variable	
Age (years)	50(39-82)
Sex-n(%)	
Male	9(40.90%)
female	13(59.10%)
Smoking	12(54.5%)
Co=morbidities	
HTN	15(68.2%)
CAD	14(63.6%)
Diabetes mellitus	11(50%)
Dyslipidemia	10(45.5%)
Renal diseases	6(27.3%)
EF	32.7±4.9(20-40%)
QTd(ms)	
Normal	5(22.7%)
Prolonged	9(40.9%)
Very prolonged	8(36.4%)
SDNN(ms)	
Normal	11(50%)
Abnormal	11(50%)

There was a significance decrease in SPB after treatment with Sacubitril/Valsartan(p 0.0001) Fig 1, without any significant difference in laboratory parameters (p>0.05).

Among ventricular repolarization indices, there is a significant reduced in QTd(65.09±25.3 vs51.72±21.7, p=0.004) in particular in Very prolonged QTd subgroup (Fig 2), and significant increased in SDNN without any difference between SDNN subgroups, table(2).

Table 2: Laboratory and electrocardiographic data before and after one month of therapy with Sacubitril/Valsartan.

	Before	After	P-value
SBP	133.2±18.9	122.7±15.2	0.0001
Blood glucose	127.68±47.5	133.59±58.2	0.2
Hemoglobin (Hb)	10.68±1.2	10.49±0.9	0.06
Creatinine (Cr)	1.34±1.06	1.36±0.9	0.6
Serum electrolyte			
Na	134.09±5.2	133.5±3.5	0.3
K	4.27±0.6	4.21±0.1	0.6
Ca	8.9±0.5	9.03±0.5	0.2
Mg	2.09±0.3	2.05±0.2	0.4
QTd	65.09±25.3	51.72±21.7	0.004
Normal	30±7.07	28±14.3	0.7
Prolonged	62±14.1	52.9±17.3	0.09
Very prolonged	90±8.4	65.2±18.6	0.01
QTc	435.04±27.6	425.40±27.1	0.1
QRS(ms)	94.54±19.22	93.40±16.39	0.6
SDNN	93.22±24.7	111.81±37.2	0.01

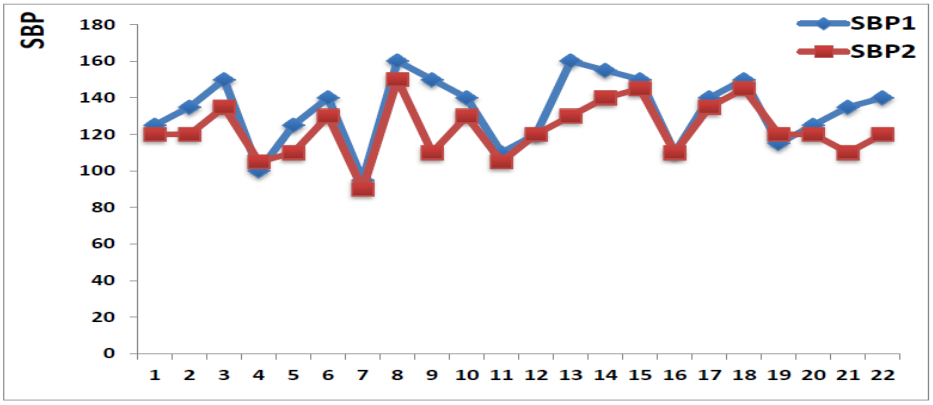
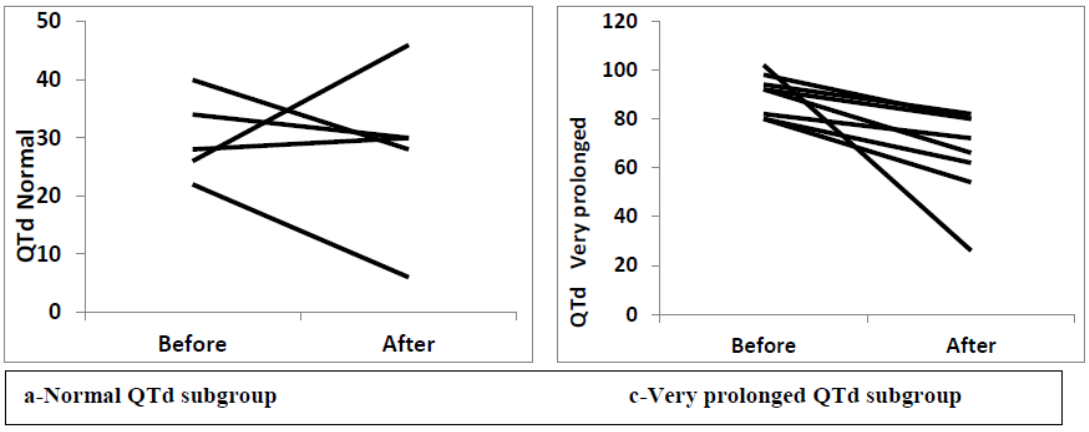


Figure 1: Changes in systolic blood pressure SBP after treatment with Sacubitril/Valsartan,(p 0.0001).



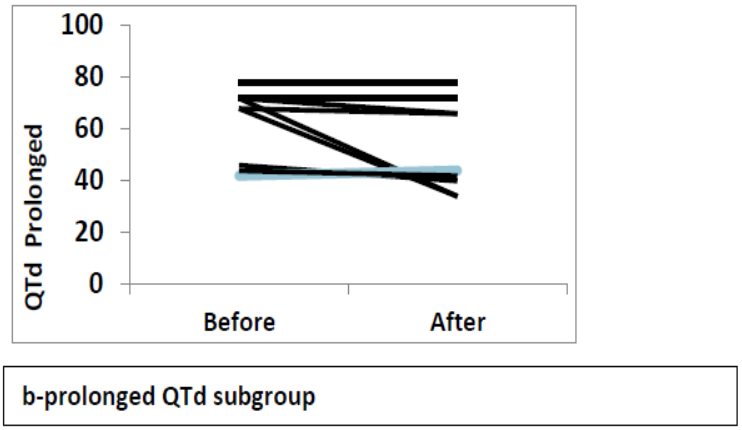


Figure 2: Changes in QTd after administration Sacubitril/Valsartan in the three subgroups of QTd, decreasing average is by 100% in Very prolonged QTd subgroup.

There wasn't relationship between presence of diabetes mellitus DM and changes in QTd, SDNN, table 3.

There wasn't relationship between previous use of Valsartan and changes in QTd, SDNN, table4.

Table 3: Comparison SDNN, QTd according to presence DM.

	Before	After	p-value
Present			
SDNN	89.1±24.4	109±44.2	0.05
QTd	51.6±25.8	44.1±20.9	0.1
Absent			
SDNN	97.2±25.6	114.2±30.8	0.1
QTd	78.5±16.7	59.2±20.8	0.01

Table 4: Comparison SDNN, QTd according to presence of previous use of Valsartan.

	Before	After	p-value
Present			
SDNN	88±30.3	96.5±23.6	0.3
QTd	68±18.4	53±17.2	0.1
Absent			
SDNN	94.4±24.2	115.2±39.3	0.02
QTd	64.4±27.03	51.4±23.09	0.01

There was a negative correlation between changes in SDNN and dyspnea degree (Spearman's = -0.2, P=0.04**)**, and a positive correlation between changes in QTd and dyspnea degree (Spearman's =0.3, P=0.01**),** Fig3**.**

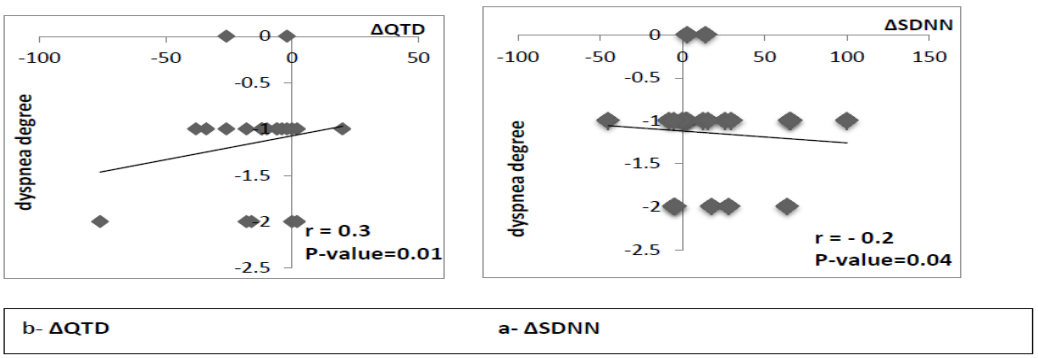


Figure 3: Correlation of dyspnea degree with changes in SDNN (a) and changes in QTd(b).

There was a positive correlation between sacubitril/valsartan dose and changes in SDNN (Spearman's = 0.1, P=0.4**)**. and negative correlation with changes in QTD(Spearman's = -0.1, P=0.5**)**, Fig4.

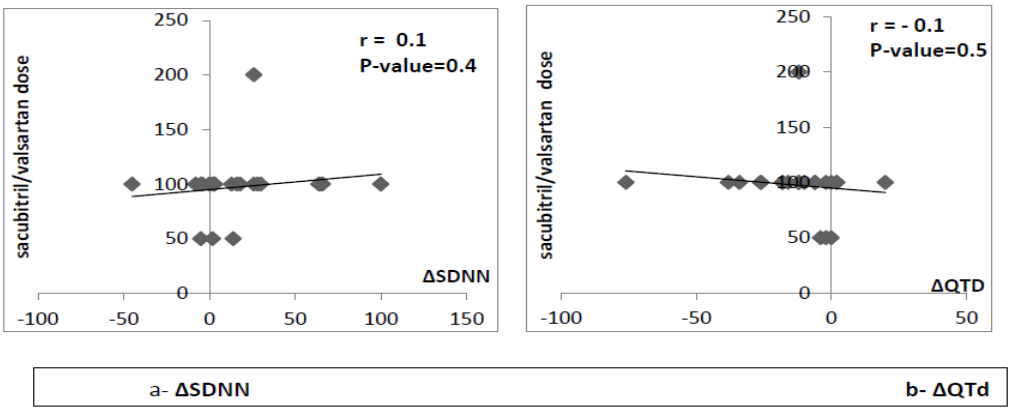


Figure 4: Correlation of sacubitril/valsartan dose with changes in QTD (a) and SDNN(b).

DISCUSSION

This prospective study demonstrated changes in heart rate variability and QT dispersion in patients with HFrEF aged 39 to 82 years after treatment with Sacubitril/Valsartan. This changes include reduction in QTd (more significantly in the very prolonged QTD subgroup) and QTc, increasing in SDNN without significant changes in QRS. Reduction in QTd and increasing in SDNN were correlated with clinical improvement in dyspnea, without any effect of previous use of Valsartan on changes in QTD, SDNN. Increased dose of drug was correlated with decreased QTD and increased SDNN.

Sacubitril/Valsartan drug acts on two pathways activated in HF: it inhibits neprilysin and blocks angiotensin II receptor.[9] Inhibition of neprilysin has a positive impact on heart by a vasodilating action and improvement in the availability of natriuretic peptides which leads to an increase in natriuresis and diuresis, as a result reduction in intravascular volume and BP, in addition to that reduction in left ventricular and vascular remodeling.[10] Blocking angiotensin II receptor reverses unfavorable effects such as: cardiac hypertrophy, fibrosis, cardiomyocyte dysfunction which contributes to proarrhythmic effect. This reduces ventricular premature beats and tachyarrhythmias, consequently reducing sudden cardiac death.[11,12]

The trial that led to approve Sacubitril/Valsartan in patients with HFrEF is PARADIGM-HF which showed reduction in mortality in patients treated with this drug.[13]

A trial by de Diego et al found that adding Sacubitril/Valsartan to the medical therapy for heart failure reduce ventricular tachycardia, increase in biventricular pacing by reduction in premature ventricular contraction.[14]

Sercan et al 2018 showed significant decreasing in QTc after treatment with Sacubitril/Valsartan (415.2±19.7 vs 408.5±20.8,p 0.022)and this consisted with the result of our study.[15]

António et al also found that treatment with Sacubitril/Valsartan reduced QTc interval (451.9 vs. 426.0 ms, p < 0.001), QRS duration (125.1 vs. 120.8 ms, p = 0.033), but decreasing QRS in our study wasn't significant.[16]

Simon et al, 2019 reported a case of 44 old woman with HFrEF showed improvement in SDNN after switching from candesartan to Sacubitril/Valsartan(82 ms to 162 ms).[17] On the contrary, Francisco et al 2018 showed that treatment with Sacubitril/Valsartan was not associated with any improvement in SDNN(42.1±11.5 vs 38.2±12.3, p0.1), and this may be explained by insufficient drug dose that used or period of the therapy is short.[18]

CONCLUSION

The analysis of ECG changes can be used as useful predictor for monitoring effects of the treatment with Sacubitril/Valsartan and its correlation with clinical improvement.

List of abbreviations

HFrEF heart failure with reduced ejection fraction HR: heart rate
NYHA: New York Heart Association SDNN: standard deviation of NN. HTN: hypertension

CAD: Coronary artery disease

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