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Predictive Value of Fragmented QRS in Response to Levosimendan Therapy in Patients with Heart Failure

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BACKGROUND
Data on the effect on re-hospitalization are limited when levosimendan is added to conventional treatment. We aimed to investigate the role of fragmented QRS (f QRS) on the surface electrocardiogram in predicting the response to levosimendan therapy in patients with acute systolic heart failure.

MATERIAL and METHODS
Patients with a left ventricular ejection fraction of <35% were enrolled in this retrospective observational study. They were administered a levosimendan therapy for 24 h, and the number of re-admissions due to decompensated heart failure annually were recorded. Patients were divided two groups: group I, 0-7 admissions per year and group 2, >7 admissions per year.

RESULTS
There were 42 patients in group I and 24 in group 2. The presence of fragmented QRS was seen in 41% of the patients in group I and in 92% of the patients in group 2 (p<0.001). The presence of fragmented QRS during the hospitalization of patients treated with levosimendan was found to be an independent predictor of the admission of more than 7 patients in the multivariate analysis.

CONCLUSION
The presence of fragmented QRS during hospitalization may predict a lower response to levosimendan therapy in patients with decompensated heart failure.

Key words: Heart failure, electrical heterogeneity, levosimendan

INTRODUCTION

Positive inotropic drugs are necessary in patients with acute decompensated heart failure and systolic dysfunction and having hypotension and/or peripheral hypoperfusion despite vasodilator and diuretic therapy (1). Levosimendan is dissimilar from other positive inotropic remedies in terms of providing increased contractility without enhancing the oxygen consumption of the heart (2). It increases cardiac contractility as a means of enhancing the calcium sensitivity of contractile proteins in the myocardium. Furthermore, it leads to the opening of adenosine triphosphate-sensitive potassium channels in vascular tissues and vasodilatation (3).

The survival benefit of levosimendan is unclear; however, clinical improvement has been demonstrated in various trials. This condition may be due to the heterogeneity of the patient populations in these studies. There are trials specifying patient groups that might further benefit from levosimendan. QRS duration and brain natriuretic peptide (BNP) change have been found to be important for evaluating the response to levosimendan therapy (4, 5). We analyzed patients applying to a hospital with acute decompensated heart failure and who stabilized and were discharged following medical treatment including levosimendan infusion. Parameters affecting annual admission numbers by virtue of decompensated heart failure were investigated. Thus, in our trial, we intended to predict which patients will further benefit from levosimendan therapy.

MATERIAL and METHODS

Study Population

Sixty-six patients under clinical follow-up between 2011 and 2016 were enrolled in this retrospective study; these patients were hospitalized due to acute decompensated heart failure and were administered levosimendan due to the requirement of intravenous inotropic support despite optimal medical therapy.

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Exclusion criteria included permanent atrial fibrillation (AF), paroxysmal AF, systolic blood pressure persistently lower than 85 mmHg or heart rate persistently at 115/min or higher, aortic or mitral valve stenosis, hypertrophic or restrictive cardiomyopathy, second- or third-degree atrioventricular block, severe hepatic dysfunction (liver enzyme levels two times higher than the normal levels), serum creatinine levels higher than 2.5 mg/dL, recent myocardial infarction (within 8 weeks), utilization of an another inotropic drug in the same hospitalization, history of cardiac pacemakers, and sustained or non-sustained ventricular tachycardia. Ethics committee approval and informed consent was obtained.

Study Protocol

Hospitalization data were assessed, where patients were medicated with levosimendan as well as vasodilators and diuretics. All patients received levosimendan with a loading dose of 12 mcg/kg/min over 10 min, followed by an infusion of 0.1 mcg/kg/min for 24 h. The total hospitalization duration was calculated. Moreover, the mean furosemide dose per day was determined. Patients' outpatient follow-up registries were searched in detail. Furthermore, the first re-admission duration and annual admission number due to acute decompensated heart failure despite regular and optimal medical therapy were registered. Patients were divided two groups: group 1, 0-7 admissions per year and group 2, >7 admissions per year. Factors affecting the first admission duration and annual hospitalization rate were investigated.

Patients' electrocardiograms (ECGs) were evaluated prior to initiating levosimendan therapy. The presence of fragmented QRS (fQRS) was investigated in patients'12-lead surface ECGs (Nihon Kohden-Cardiofax S ECG, Japan; 1250 K, 0.5 Hz to 150 Hz filter range, 60 Hz AC filter, 25 mm/s,10 mm/mV) prior to levosimendan infusion. The definition of fQRS was QRS complexes with the presence of an additional R wave or S wave or the presence of <1 R' (fragmentation) in two contiguous leads, corresponding to a major coronary territory [inferior (D2, D3, aVF), lateral (DI, aVL, V6), or anterior (V1-V5) derivations] (6). Additionally, for QRS complexes of a typical right bundle branch block (≥120ms) or left bundle branch block (LBBB; ≥120 ms), fQRS was defined as a QRS complex with >2 R' waves or notches in the R or S waves in two contiguous leads (7).

The relationship between fQRS presence and the annual admission rate and total weight loss was determined. Blood pressure and heart rate on admission were recorded. Transthoracic echocardiography (EPIQ 7 Ultrasound System, PHILIPS, HEIDE, The Netherlands) registries of LVEF, heart chamber diameters, and valvular pathologies were reviewed according to the recommendations of the American Echocardiography Association. Hemogram and biochemistry parameters were noted.

Statistical Analysis

Data were analyzed with Statistical Package for the Social Sciences version 15.0 for Windows (SPSS Inc.; IBM, Los Angeles, USA). Categorical variables were presented as frequency and percentage. The chi-square test and Fisher's exact test were used to compare categorical variables. The Kolmogorov-Smirnov test was used to assess the distribution of continuous variables. Student's t-test was used for variables with normal distribution, and the values were presented as mean±SD. Continuous variables without normal distribution were analyzed using the Mann–Whitney U test and the values are presented as median values (50th persentile) and interquartile ranges (25th and 75th). One-way analysis of variance and the Kruskal-Wallis test were respectively used for parametric and non-parametric variables to compare tertiles. Multivariate logistic regression analysis was used to evaluate the independent associates of the risk of increased re-hospitalization rate. Parameters with a p-value of less than 0.1 in the univariate analysis were included in the model. Odds ratios and 95% confidence intervals were calculated. A two-tailed p-value of <0.05 was considered to be statistically significant.

RESULTS

Sixty-six patients, 54 of whom were males, were included. Forty-two patients were in group 1 and 24 were in group 2. Thirty percent of the patients applied to the hospital in the first month, 55% applied within 2 months, and 92% applied within 6 months because of acute decompensated heart failure. Demographic and clinical characteristics of the patients according to the number of annual applications are listed in Table 1.

The presence of fQRS was found in 41% of the patients in group 1 and in 92% of the patents in group 2 (p<0.001) (Table 2).

Univariate and multivariate logistic regression analyses was performed for factors affecting the number of annual applications. The presence of fQRS during the hospitalization of patients treated with levosimendan was found to be an independent predictor of the admission of more than 7 patients in the multivariate analysis. There was a highly positive significant correlation between the presence of fQRS and re-admission (r=0.555, p<0.001) (Table 3).

DISCUSSION

In our trial, patients with fQRS on their ECGs had more re-admissions to the hospital than those without fQRS on their ECGs, irrespective of the LVEF. This finding may be a subsidiary parameter to the presence of fQRS on ECGs to predict the response to levosimendan therapy in patients with heart failure.

Acute decompensated heart failure is a considerable cause of morbidity and mortality. Such patients are generally treated with diuretics and vasodilators. Positive inotropic drugs are added to the conventional treatment when peripheral hypoperfusion signs are present. Levosimendan does not distinctively potentiate intracellular cyclic adenosine monophosphate and calcium levels; in contrast to other inotropic drugs, levosimendan stabilizes cross-bonds between actin and myosin, leading to enhanced contractility (8-10). Levosimendan stimulates adenosine triphosphate-sensitive potassium channels on vascular smooth muscles, resulting in arterial and venous vasodilatation. Thus, it reduces the preload and afterload (11). Besides these, levosimendan enhances coronary vasodilatation via the nitric oxide-dependent pathway, which inhibits phosphodiesterase-3 and contributes to the protection of the myocardium from ischemia by means of increasing the coronary blood flow (12, 13). It has been demonstrated that levosimendan improves the myocardial systolic function in patients with a stunned myocardium who underwent percutaneous coronary intervention due to acute myocardial infarction (14).

TABLE 1. Patient characteristics according to annual admission number due to decompensated heart failure (which show a normal distribution mean ± SD, not show a normal distribution median (25^{th} vs. 75^{th} percentile)

Variable	0-7 admissions (n=42)	8≤ admissions (n=24)	P value
Age, years	64.5 ±11.9	64.9±15.0	0.626
Male gender, n(%)	34 (81%)	20 (83%)	0.809
Annual readmissions	3.8±1.6	9.5±1.3	<0.001
Systolic BP, mmHg	101±9	102±14	0.859
Diastolic BP, mmHg	63±16	65±10	0.565
Heart rate, beat/min	86±8	90±9	0.101
Serum creatinine	1.2±0.5	1.4± 0.5	0.179
LVEF,%	28.1±7.1	25.6±9.0	0.221
LVEDD, mm	62.6±6.5	65.4±10.0	0.181
LVESD, mm	48.7±8.1	50.8±11.5	0.382
LA diameter, mm	49.0±7.3	51.4±6.4	0.180
DM, n(%)	11 (26%)	10 (42%)	0.194
HT, n(%)	27 (64%)	16 (67%)	0.845
Ischemic cardiomyopathy, n(%)	32 (76%)	17 (71%)	0.632
NYHA functional class 3, n(%)	36 (86%)	6 (14%)	14 (58%)
NYHA functional class 4, n(%)	10 (42%)	0.013	
Mean duration of hospitalization, day	6.7 ± 1.3	7.4 ± 2.0	0.068
History of CABG, n(%)	8 (19%)	3 (13%)	0.492
Mean furosemide dose, mg/day	65±11	77±16	0.001
BB usage, n(%)	30 (71%)	20 (83%)	0.278
ACEI usage, n(%)	30 (71%)	19 (79%)	0.489
ARB usage, n(%)	5 (12%)	1 (4%)	0.293
Spironolactone usage, n(%)	23 (55%)	19 (79%)	0.047
Digoxin usage, n(%)	17 (41%)	11 (46%)	0.672

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BB: beta blocker; BP: blood pressure; CABG: coronary artery bypass grafting; DM: diabetes mellitus; HT: hypertension; LAD: left atrial diameter; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; MPV: mean platelet volume; NYHA: New York Heart Association

TABLE 2. Electrocardiographic characteristics of the groups according to the annual admissions

Variable	0-7 admissions (n=42)	8≤ admissions (n=24)	P value
Presence of LBBB, n(%)	2 (4.8%)	4 (17%)	0.106
Presence of fQRS, n(%)	17 (40.5%)	22 (91.7%)	<0.001
Localization of fQRS, %			
anterior lead	14.3 %	20.8 %	0.001
inferior lead	21.4 %	50.0 %	
lateral lead	4.8 %	20.8 %	

LBBB: left bundle branch block; fQRS: fragmented QRS

TABLE 3. Evaluation of the factors affecting the annual re-admissions>7 by univariate and multivariate logistic regression analysis

	Univariate		Multivariate	
Variable	OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age (years)	1.002 (0.964-1.042)	0.906		
LV diameter (/1mm)	3.000 (0.591-15.226)	0.185		
LA diameter (/1mm)	1.051 (0.976-1.131)	0.110		
fQRS	16.176 (3.355-78.004)	0.001	10.501(1.534 -71.903)	0.017
LBBB	4.000 (0.674-23.725)	0.127		
DM	2.013 (0.695-5.832)	0.197		
HT	1.111 (0.386-3.200)	0.845		
ARB	0.322 (0.035-2.931)	0.314		
LVEF	0.959 (0.898-1.025)	0.220		
Sprinolactone	3.139 (0.987-9.988)	0.053	3.284(0.747-14.439)	0.116
Beta Blocker	2.000 (0.564-7.087)	0.283		
Digoxin	1.244 (0.452-3.424)	0.672		
Furosemide dose	1.071 (1.021-1.123)	0.005	1.017(0.960-1.077)	0.573
Serum creatinine	1.942(0.718-5.257)	0.191		
Heart rate	1.054 (0.988-1.124)	0.108		

ARB: angiotensin receptor blocker; DM: diabetes mellitus; HT: hypertension; fQRS: fragmented QRS; LA: left atrium; LBBB: left bundle branch block; LV: left ventricle; LVEF: left ventricular ejection fraction

Levosimendan also has neurohormonal effects. Thirty to sixty percent reduction of BNP and N terminal-BNP levels has been reported after levosimendan infusion (15). Additionally, it has been stated that levosimendan diminishes the levels of proinflammatory cytokines and apoptosis mediators such as endothelin I, interleukin 6, and tumor necrosis factor-alpha (16-18). It has been demonstrated that this neurohormonal influence continues for at least 7 days (16-18). The prolonged impact of levosimendan may be related to its active metabolite OR-1896, which has an extended half-life of 70-80 h despite the short half-life of 1 h for levosimendan.

Six-month all-cause mortality or re-hospitalization for heart failure significantly decreased in patients with a 58% or more reduction in BNP levels following levosimendan therapy in a study by Farmakis et al. (5) that was performed to predict the response to levosimendan therapy. Another study that searched for the significance of cardiac rhythm to the response to levosimendan therapy showed no difference between the sinus rhythm and AF in terms of the effect on left ventricular systolic and diastolic functions (19). Patients with a basal QRS duration lower than 120 msn had a better outcome in short-term levosimendan therapy in a trial evaluating echocardiographic parameters.

It has been demonstrated in a study assessing ischemic and non-ischemic heart failure patients with an LVEF of <35% that the presence of fQRS on ECGs is correlated with the increased re-hospitalization due to decompensated heart failure and cardiovascular mortality (20). In a trial evaluating patients with post-myocardial infarction heart failure, the presence of fQRS was related to higher cardiac death and hospitalization rates due to heart failure (21). fQRS is more sensitive than the Q wave

in demonstrating myocardial scar tissue in a study by Das et al. (6, 7) fQRS denotes an impairment in signal conduction by virtue of myocardial scarring, fibrosis, and ischemia. In our trial, earlier re-admissions and increased annual re-admissions after levosimendan therapy in patients with fQRS on ECGs may result from a decreased contractile reserve on account of myocardial fibrosis and scarring. This may be a subsidiary parameter to predict a poorer response to levosimendan therapy.

Study Limitations

The number of patients in our trial is insufficient, and the number of patients with non-ischemic dilated cardiomyopathy is particularly insufficient. In our study population, due to the weight of the males, the results may not reflect the findings in females. Moreover, patients with permanent AF and documented paroxysmal AF were not included. However, there is no Holter ECG recording in all patients, and there may be undetectable paroxysmal AF episodes. Furthermore, we could not acquire body mass indexes due to the fact that they were not recorded and our trial is not prospective.

CONCLUSION

The evaluation of the presence of fQRS on ECGs may provide substantial information in patients with decompensated heart failure. The presence of fQRS on ECGs might assist in predicting more frequent re-admissions in patients with heart failure treated with levosimendan.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Antalya Training and Research Hospital (2014).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - Z.E., N.B., Ş.A.; Design - N.B., Z.E.; Supervision - N.B., Ş.A.; Resource - M.E., S.K., R.G.; Materials - Z.E., S.K.; Data Collection and/or Processing - Z.E., M.E.; Analysis and /or Interpretation - N.B., R.G.; Literature Search - N.B., Ş.A.; Writing - N.B., Z.E.; Critical Reviews - Ş.A., M.E., S.K.

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