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Original Article

Short-term effects of angiotensin receptor-neprilysin inhibitors on diastolic strain and tissue doppler parameters in heart failure patients with reduced ejection fraction: A pilot trial

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ABSTRACT

Objective: Although sacubitril/valsartan has recently shown its long-term benefits on morbidity and mortality in symptomatic patients with chronic heart failure with reduced ejection fraction (HFrEF), its short-term effects on diastolic function remain uncertain. We sought to assess 30-day effects of sacubitril/valsartan on left ventricular (LV) diastolic paremeters determined by speckle tracking and tissue Doppler imaging (STI and TDI respectively) as well as their association with functional capacity change evaluated by peak oxygen uptake (VO_2max) in stable patients with symptomatic HFrEF.

Methods: A total of 35 patients (aged 61 ± 9 years) eligible for sacubitril/valsartan underwent a complete two-dimension (2D) echocardiographic study and a cardiopulmonary exercise test at baseline and 30 days after the initiation of therapy.

Results: Significant improvements in ratio of trans-mitral inflow early diastolic velocity E to mitral annulus early diastolic velocity E′ ($\Delta E//E' = -35.9\%$, $p = 0.001$), peak early diastolic strain rate SRE ($\Delta SRE = +22.5\%$, $p = 0.024$) and ratio E/SRE ($\Delta E/SRE = -33.2\%$, $p = 0.025$) were observed after 1-month therapy. Compared with baseline, VO_2max also increased significantly by 16.7 % ($p = 0.001$). Baseline E/SRE and ΔE/SRE were the strongest independent predictors of VO_2max improvement (beta = -0.43, $p = 0.004$ and beta = 0.45, $p = 0.021$ respectively) in the multivariate analysis.

Conclusion: Sacubitril/valsartan was associated with early improvement in LV diastolic function determined by TDI and 2D STI. Baseline E/SRE was stronger than standard echocardiographic parameters in predicting the early benefit of sacubitril/valsartan therapy.

1. Introduction

The superiority of angiotensin receptor-neprilysin inhibitors (ARNIs) in reducing the risks of death and heart failure (HF) hospitalizations compared with angiotensin-converting enzyme inhibitors (ACEI) has been proven in the PARADIGM-HF trial during the follow-up of 27 months.[1] Interestingly, a post hoc analysis showed a short-term decrease in the risk of 30-day readmission after HF hospitalization with ARNIs[2], while in another study sacubitril/valsartan was associated with early improvement in exercise tolerance in symptomatic patients with heart failure with reduced ejection fraction (HFrEF).[3] We hypothesized that this early efficacy may be partly attributed to beneficial effects of ARNIs on left ventricular (LV) diastolic function and myocardial mechanics. In this work, we investigated the short-term effects of sacubitril/valsartan on conventional echocardiographic indices of diastolic function and diastolic strain parameters determined by two-dimensional speckle-tracking echocardiography (2D-STE) in stable patients with symptomatic HFrEF.

2. Methods

We prospectively studied a cohort of 35 patients (aged 68 ± 10 years) with HFrEF (EF ≤ 35%) referred to the Department of

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Cardiology, University Hospital of Heraklion in Greece for symptoms and signs of HF. Eligible patients were those with stable New York Heart Association (NYHA) II-III previously treated with ACEI or angiotensin receptor blocker (ARB). All the participants were well-compensated, ambulatory outpatients with no changes in medication for at least 4 weeks prior to enrollment in the study. Following the current recommendations,[4] therapy with ACEI or ARB changed to sacubitril/valsartan with the starting dose of 49/51 mg twice daily (b.i.d.), uptitrated gradually to 97 mg/103 mg b.i.d. Clinical examination, complete echocardiographic evaluation, and cardiopulmonary exercise test were performed at baseline and 30 days after the initiation of sacubitril/valsartan. Written informed consent was obtained from all patients prior to their enrolment in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

2.1. Echocardiography assessment

Using 2D echocardiography and Doppler measurements of LV function we assessed: (i) peak early (E-wave) and late (A-wave) transmitral filling velocities, (ii) E/A ratio, (iii) deceleration time of E (DTE) velocity, (iv) isovolumic relaxation time (IVRT), and (v) the mitral inflow velocity E to tissue Doppler E′ (E/E′). Two-dimensional STE was performed for each of the apical views with the frame rates of grayscale images of 50-80 Hz. Overall global systolic longitudinal strain (GLS) was calculated as the average value of GLS measured for each apical view. The peak early and late diastolic rate (SRE and SRL, respectively) were also recorded. The average values of SRE and SRL from all apical views were then calculated and considered as the global SRE and SRL, respectively.

2.2. Cardiopulmonary exercise test

All patients underwent a cardiopulmonary exercise test, which was performed on a treadmill using Norton protocol and with standard cardiopulmonary stress equipment. VO_2, CO_2 production, and ventilation were measured on a breath-to-breath basis. Peak oxygen uptake (VO_2 max, ml/kg/min) was measured to evaluate exercise capacity.

2.3. Statistical analysis

The summary of descriptive statistics is presented as mean ± standard deviation (SD) for continuous variables and frequencies (%) for categorical variables. The paired samples t-test or paired Wilcoxon test was used for assessing the effect of treatment, if the distribution was parametric or nonparametric (i.e., NYHA), respectively. Pearson's correlation coefficients were computed to evaluate relations between continuous variables, whereas correlations including at least one non-normal parameter were performed using the Spearman's correlation coefficient (univariate analysis). Multiple regression analysis was performed to assess the independent contribution of the variables in the improvement of VO_2 max. IBM-SPSS 23 was used for all analyses and p value < 0.05 was considered statistically significant.

3. Results

A total of 35 symptomatic patients (21 males and 14 females, mean age 61 ± 9 years), 62.85% NYHA II and 37.15% NYHA III, 68.57% with ischemic and 31.43% with nonischemic dilated cardiomyopathy were enrolled (Table 1). The starting dose of sacubitril/valsartan was 24/26 mg in 8 patients (22.85%). Baseline characteristics of the study participants are presented in Table 1. After a one-month therapy, significant reductions of E/A (−15.34%, p = 0.007), E/E′ (−35.9%, p = 0.001), SRE (+22.5%, p = 0.002), and the ratio E/SRE (−33.2%, p = 0.025) were observed, while VO_2 max (+16.7%, p = 0.001) and NYHA class (p = 0.001) improved significantly as well (Table 2). Left ventricular ejection fraction and GLS remained unchanged during the study period. It is noteworthy that the proportion of patients with restrictive filling pattern decreased from 57.14% to 11.42% after a 1-month therapy with sacubitril/valsartan.

Table 1
Baseline demographic and clinical characteristics of study participants

Characteristics	Study Population (N = 35)
Age (years)	61 ± 9
Males/Females, n (%)	21/14 (60/40)
Systolic Blood Pressure, mmHg	123.7 ± 12.7
Body Mass Index, kg/m^2	30 ± 4.4
Serum creatinine, mg/dL	1.2 ± 0.32
NYHA class, n (%)	
II	22 (62.85)
III	13 (37.15)
Ischemic cardiomyopathy, n (%)	24 (68.57)
LVEF, %	30.21 ± 2.7
Hypertension, n (%)	29 (82.85)
Diabetes, n (%)	22 (62.85)
Atrial Fibrillation, n (%)	23 (65.71)
Stroke, n (%)	6 (17.1)
Therapies, n (%)	
Beta-blockers	33 (94.2)
Ivabradine	4 (11.4)
Diuretics	35 (100.0)
Mineralocorticoid Receptor Antagonists (MRAS)	32 (91.4)
Statins	30 (85.7)
Antidiabetic medications	22 (62.85)
Anticoagulants	23 (65.71)
Antiplatelets	20 (57.14)
Implantable Cardioverter Defibrillator	31 (88.57)
Cardiac Resynchronization Therapy	5 (14.2)

NYHA: New York Heart Association; LVEF: left ventricular ejection fraction.
Values are expressed as mean ± standard deviation (SD).

Pearson's correlation coefficients were computed to assess predictors of improvements in exercise capacity (ΔVO_2 max). Baseline VO_2 max, baseline E/SRE ratio, improvements in NYHA (ΔNYHA), and ratios E/A (ΔE/A), E/E' (ΔE/E′), and E/SRE (ΔE/SRE) were significantly correlated with ΔVO_2 max in a univariate analysis (Table 3). It is noteworthy that neither increase in VO_2 max nor improvements in NYHA and diastolic function parameters (ΔE/A, ΔE/E′, and ΔE/SRE) were correlated with sacubitril/valsartan-induced decrease in blood pressure (ΔBP). In multiple regression analysis, baseline E/SRE and ΔE/SRE were the strongest

Table 2
Blood pressure, VO_2 max and echocardiographic parameters at baseline and after 1 month therapy with sacubitril/valsartan in study participants

Parameter	Baseline	30 days	% change	P value
Systolic BP, mmHg	123.7 ± 12.7	112 ± 11.4	- 8.9	0.001
Diastolic BP, mmHg	85.1 ± 7.2	76.3 ± 6.2	−10.3	0.003
E/A ratio	2.02 ± 0.22	1.71 ± 0.12	−15.3	0.007
DTE, ms	141.2 ± 14.1	158.4 ± 11.1	+12.2	0.084
IVRT, ms	73 ± 7	82 ± 9	+12.3	0.092
E/E′ ratio	13.9 ± 4.3	8.9 ± 2.42	−35.9	0.001
SRE, (s^{-1})	0.40 ± 0.21	0.31 ± 0.24	+22.5	0.024
E/SRE, (cm)	239.5 ± 97.9	160 ± 74.5	−33.2	0.025
SRE/SRA	0.9 ± 0.26	1.1 ± 0.19	+18.1	0.078
GLS (%)	−8.7 ± 1.2	−8.6 ± 1.1	+1.1	0.76
VO_2 max, ml/kg/min	16.2 ± 1.4	18.9 ± 1.8	+16.7	0.001

Values are expressed as mean ± standard deviation (SD); A: late diastolic mitral flow velocity; BP: blood pressure; DTE: deceleration time of E; E: peak early diastolic mitral flow velocity; E′: mitral annulus early diastolic velocity; GLS: global systolic longitudinal strain; IVRT: isovolumic relaxation time; SRE: global peak early diastolic rate, SRL: global peak late diastolic rate; VO_2 max: peak oxygen uptake.

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Table 3
Univariate and multivariate analysis to detect predictive factors of early improvement in functional capacity (ΔVO_2 max) after initiation of sacubitril/valsartan therapy

Factor	Univariate analysis		Multivariate analysis			
	beta	p value	Unstandardized β	Standardized beta	95% CI	p value
VO_2 max	0.58	0.004	0.06	0.12	−0.09 - 0.20	0.420
E/SRE	−0.49	0.021	−0.35	−0.43	−0.57 - (−0.13)	**0.004**
ΔE/E′	0.56	0.008	0.05	0.11	−0.1 - 0.2	0.476
ΔE/A	0.43	0.050	0.99	0.3	−0.004 - 1.98	0.059
ΔNYHA	0.57	0.005	0.04	0.02	−0.51 - 0.59	0.879
ΔE/SRE	0.75	0.001	0.49	0.45	0.09 − 0.89	**0.021**
			R: 0.907, R^2 : 0.822			

VO_2 max: peak oxygen uptake;
E/SRE: peak early diastolic mitral flow velocity (E) to global peak early diastolic rate (SRE);
ΔE/E′: decrease in the ratio peak early diastolic mitral flow velocity (E) to mitral annulus early diastolic velocity (E′);
ΔE/A: improvement in the ratio peak early diastolic mitral flow velocity (E) to late diastolic mitral flow velocity (A);
ΔNYHA: improvement in New York Heart Association (NYHA).
ΔE/SRE: decrease in the ratio E/SRE.

independent predictors of early improvement in VO_2 max (beta = −0.43, p = 0.004, and beta = 0.45, p = 0.021, Table 3).

4. Discussion

Our study provides novel data showing that ARNIs have short-term beneficial effects on both conventional echocardiographic indices of LV diastolic function and diastolic strain parameters assessed by 2D-STE, while no effects on LV GLS were observed. The ratio of early diastolic transmitral flow velocity to global strain rate at early filling phase of diastole (E/SRE) has been proposed as a more accurate predictor of LV filling pressures, and a stronger marker in predicting the prognosis of patients with HFrEF than the traditional tissue doppler ratio of E/E′.[5-7]

Moreover, in a multivariate analysis, the early increase in VO_2 max was correlated with the decrease in E/SRE ratio, indicating the improvement in LV diastolic function as a potential mechanism by which the dual inhibition of angiotensin receptor-neprilysin can improve the exercise capacity in short-term. Oikonomou et al have previously noted several central or peripheral factors that can affect the exercise capacity and tolerance in patients with HF.[8] Among them the role of LV diastolic function and global strain as a predictive factor of exercise tolerance have been determined, whereas LV systolic dysfunction has been shown to poorly correlate with exercise capacity.[9-13] Plausible mechanisms of early benefit in myocardial diastolic function might include hemodynamic improvements as a consequence of neprilysin inhibition, including natriuretic peptide-mediated reduction in ventricular wall stress (vasodilation, natriuresis).[14,15] Despite the decrease in E/E′ ratio with sacubitril/valsartan treatment, which represents the less load-dependent echocardiographic marker of LV filling pressures,[16] and the fact that the improvements in VO_2 max and diastolic function parameters were not correlated with sacubitril/valsartan-mediated decrease in blood pressure, we cannot support myocardial remodeling as the possible mechanism of early clinical benefits after sacubitril/valsartan initiation currently.

The improvement of LV diastolic function does not fully explain the improvement in exercise capacity. Several mechanisms are implicated in exercise intolerance in HFrEF, and a better elucidation of the effects of cardiac, vascular, and peripheral muscle function on the exercise improvement in our population is needed. A more detailed study in cardiac hemodynamics and peripheral factors would probably enlighten the pathophysiological pathways of our findings. However, it seems that the improvement of diastolic indices might have played a major part.

To our knowledge, this is the first study showing a negative association between the baseline ratio E/SRE and the improvement in VO_2 max, indicating an important predictive marker of early treatment response in sacubitril/valsartan in HFrEF patients. Thus, notwithstanding the technical challenges for accurate strain measurements in daily clinical practice, 2D-STE appears to be useful in the clinical assessment of HF patients receiving ARNIs.

A limitation of our study is the relatively small sample size. However, our findings are clear and our study established a statistically significant difference. In addition, our study is a pilot trial and was conducted on a smaller scale. Despite the small sample size and the absence of a control group in this study, we do believe that this observational study can guide large, randomized controlled trials to explore in depth the precise mechanisms of ARNIs' effects on exercise capacity, which may provide further insights into the pathophysiology of HF.

5. Conclusion

In this pilot study, similar to standard echocardiographic diastolic indices, diastolic stain parameters improved after sacubitril/valsartan initiation independent of blood pressure response, making 2D STE useful to describe early changes in LV diastolic function in response to ARNIs therapy. Moreover, baseline E/SRE ratio seems to be a promising variable in distinguishing patients with HFrEF, who will benefit most from angiotensin receptor-neprilysin inhibitor in the short term. However, large, randomized controlled studies are needed to clarify the clinical relevance of LV diastolic tissue velocities and strain parameters in HF patients receiving ARNIs in both short- and long term.

Declarations of interest

None.

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