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Effects of angiotensin receptor-neprilysin inhibitor on exercise capacity in patients with heart failure with reduced ejection fraction

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Abstract. *Angiotensin receptor-neprilysin inhibitor (sacubitril/valsartan) is well known to be superior over angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blockers (ARBs) in terms of reducing cardiovascular mortality in heart failure with reduced ejection fraction (HFrEF). However the impact of sacubitril/valsartan therapy on exercise capacity versus ACEI/ARBs for such patients is less tested.*

Methods. *This non randomized observational study enrolled 100 patients with HFrEF. All participants underwent two sets of cardiopulmonary exercise tests (CPET) at baseline and after 6 months of non interrupted sacubitril/valsartan therapy in addition to optimal anti failure medications. Bridging from ACEI/ARBs to ARNI was done at baseline according to guidelines.*

Results. *After 6 months, patients received sacubitril/valsartan had significant improvement in LVEF from 26 ± 5 to 29.6 ± 8%, peak oxygen consumption (VO_2) improved from 14.6 ± 4 to 17.3 ± 5.2 mL/kg/min, oxygen pulse increased from 11.6 ± 4 to 13.6 ± 5 mL/kg/min and $\Delta VO_2/\Delta$Work increased from 9.1 ± 2.5 to 10.2 ± 1.6 mL/min/watt (p = 0.0001 for all). Conclusion: Sacubitril/valsartan therapy improved exercise tolerance, peak oxygen consumption and LVEF up to 6 months of follow-up.*

Keywords: *heart failure; sacubitril/valsartan; cardiopulmonary exercise test.*

Conflict of interests: none declared.

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Introduction

The **PARADIGM-HF** (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial revealed that sacubitril/valsartan markedly decreased cardiovascular and al-cause mortality in patients with HFrEF compared with the angiotensin-converting enzyme inhibitor (ACEI) enalapril (1). Conversely, only few small trials assessed the improvement in exercise tolerance after initiation of sacubitril/valsartan in patients with HFrEF [2]. Recently in 2019, Palau et al conducted a pilot study demonstrated an increase in peak oxygen consumption (VO_2) after initiation of sacubitril/valsartan, but it was limited by a very short-term follow-up only 1 month with a very limited sample size [3].

Cardiopulmonary exercise test (CPET) is an accurate tool in assessing functional capacity in HFrEF and providing different parameters as peak O_2 consumption (VO_2), oxygen pulse and accelerated rate of O_2 consumption per watt of work ($\Delta VO_2/\Delta Work$) (4). The aim of current study is to evaluate the effects of sacubitril/valsartan therapy on different CPET parameters in a larger sample size and for a longer follow-up period.

Methodology

Study Design and inclusion criteria

A non randomized observational study was conducted at cardiology departments of both Benha university hospital and Benha insurance hospital from February to August 2019. This study included 100 patients with HFrEF with low EF (<35%). Sacubitril/valsartan twice daily was administered for all patients with minimum tolerated dose. Bridging from ACEI/ARBs to sacubitril/valsartan was done at baseline according to guideline recommendations. Patients received sacubitril/valsartan according to recent strategy of national insurance in Egypt. All patients were provided informed consent for participation in this study.

Inclusion criteria:

- Symptomatic heart failure (NYHA) class II–IV, in spite of optimal medical therapy;
- LVEF less than 35%, as measured using 2D echocardiography;
- Previous treatment with maximum tolerated dose of ACEI/ARBs for at least 4 months.

Exclusion criteria:

- Recent hospitalization for HF within 2 months.
- Recent myocardial revascularization within 3 months.
- Concomitant cardiac resynchronization therapy during study follow-up or within 6 months.
- Systolic arterial blood pressure <100 mmHg.
- Estimated glomerular filtration rate <30 mL/min/1.73 m^2 or serum K+ level >5.4 mEq/L.
- Physical inability to perform CPET.

Cardiopulmonary exercise test

Baseline CPET was performed before starting administration of sacubitril/valsartan. Another follow up CPET was performed after 6 months.

All CPETs were performed on a cycle ergo-meter with standard ramp protocol.

Routine warm up was done with a starting work load equal 10 watts with very gradual titration (10 watts every 60 s). Analysis of expiratory oxygen (O_2), carbon dioxide (CO_2), and expired volumes was performed. Twelve lead ECG, pulse oximeter and heart rate monitoring were used during the test. Study end point was limiting dyspnea or fatigue [5].

Switch from aerobic to anaerobic metabolism (anaerobic threshold) was measured using the V-slope analysis and confirmed using ventilatory equivalents and end-tidal pressures of gases (O_2 and CO_2).The relationship between minute ventilation and carbon dioxide production (VE/VCO2 slope) was also used as a measure of ventilatory efficiency. Percent predicted VO_2 represents the achieved peak VO_2 adjusted for age, weight, and height and expressed as a percentage using the equations by Wasserman and Hansen [6].

Statistical Analyses:

P-value <0.05 was considered statistically significant. CPET baseline and follow-up parameters were compared using Mann-Whitney U test for continuous variables and Fisher exact test for categorical variables, respectively.

Results:

Among study population, mean age was 59.8 ± 3 years. Female gender represents 15% of population. According to NYHA classification of HFrEF , Majority of patients were on class II and III (60% and 38%) while only 2 patients (2%) were on class IV. Mean left ventricular ejection fraction (LVEF) was 26 ± 5%. Mean SBP and DBP were 116±13 and 72±2 mmHg respectively. The starting dose of sacubitril/valsartan was (49/51 mg) in 31% of patients while the majority

of patients started with lower doses of sacubitril/valsartan (24/26 mg) (69%) (Table 1).

Table 1. **Baseline demographic data**

Baseline demographic data	
Age, year, mean ± SD	59.8± 3
Female sex, no. (%)	15 (15%)
SBP, mmHg, mean ± SD	116 ± 13
DBP, mmHg, mean ± SD	72 ± 2
Heart rate, beats/min, mean ± SD	66 ± 12
Hypertension, no. (%)	52 (52%)
Diabetes, no. (%)	33 (33%)
eGFR, mL/min/1.73 m^2, mean ± SD	67.5 ± 24.1
LVEF (%), mean ± SD	26 ± 5
NYHA functional class II, no. (%)	60 (60%)
NYHA functional class III, no. (%)	38 (38%)
NYHA functional class IV, no. (%)	2 (2%)
Starting dose of sacubitril/valsartan 24/26 mg	69 patients
Starting dose of sacubitril/valsartan 49/51 mg	31 patients

Cardiopulmonary exercise test and LVEF

The results of CPET showed a significant increase in peak O2 consumption (VO_2) from 14.6 ± 4 to 17.3 ± 5 mL/kg/min (p< 0.0001).We observed a significant increase in percent predicted VO_2 (10.9%) 53.8 ± 14.1 to 64.7 ± 17.8 (p < 0.0001), and a significant increase in O2 pulse from 11.5 ± 3.0 to 13.4 ± 4.3 ml/beat (p < 0.0007). We observed a significant increase in $\Delta VO_2/\Delta$Work slope from 9.2 ± 1.5 to 10.1 ± 1.8 mL/min/watt (p = 0.0001) with increase in peak ventilation from 48.7 ± 12.7 to 59.3 ± 18.9 L/min (p < 0.0001). This improvement in ventilatory response approved with marked reduction in VE/VCO_2 slope from 34.1 ± 6.3 to 31.7 ± 6.1 (p= 0.005). All CPET results are shown in table 2.

At follow-up, systolic blood pressure significantly decreased from 116 ± 13 to109 ± 1 mmHg (p < 0.0001) and this was none limiting for sacubitril/valsartan continuation in any patient. Mean LVEF increased from 26 ± 5 to 29.7 ± 7% (p < 0.0001) and left ventricular end-systolic volume decreased from 152 ± 53 to 146 ± 62 mL (p = 0.002).

CPET and LVEF results stratified by maximum tolerated dose of sacubitril/valsartan

Forty one patients tolerated maximum higher doses of sacubitril/valsartan from 49/51 to 97/103 mg twice daily (group 1). 59 patients tolerated maximum lower doses from 24/26 to 49/51 mg twice daily (group 2).

At follow up, Group 1 had a statistically significant increase in peak VO_2 (15.43 ± 2.2 vs12.34± 2.5 mL/kg/min in group 2; p = 0.0008). Group 1 had a significant increase in LVEF 31.2 ± 2% vs 28.1 ± 3% in group 2 (p <0.001) with non significant decrease in SBP 115 ± 53 vs116 ± 1 mmHg for group 2 (p = 0.07) (Figure 1).

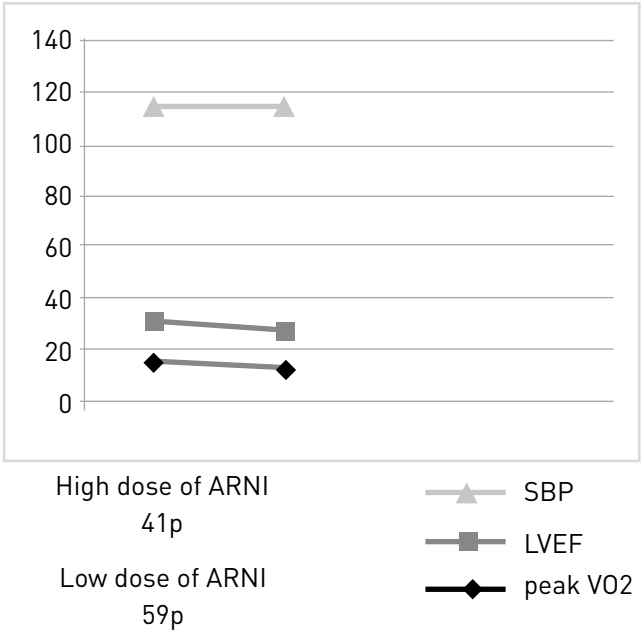

Figure 1. CPET results, LVEF and blood pressure response stratified by maximum tolerated dose of sacubitril/valsartan

Table 2. **Cardiopulmonary exercise test parameters at baseline and after 6 months.**

CPET parameters	Baseline	After 6 months	p value
Peak VO2, mL/kg/min, mean ± SD	14.6 ± 4	17.3 ± 5	<0.0001
Predicted peak VO_2, %, mean ± SD	53.8 ± 14.1	64.7 ± 17.8	<0.0001
O2 pulse (ml/beat)	11.5± 3.0	13.4 ± 4.3	0.0007
Peak RER, mean ± SD	1.12 ± 0.09	1.13 ± 0.09	0.45
Watt (Peak), mean ± SD	70 ± 22	88 ± 29	<0.0001
$\Delta VO_2/\Delta$work, mL/min/watt, mean ± SD	9.2 ± 1.5	10.1 ± 1.8	0.0001
Peak ventilation, L/min, mean ± SD	48.7 ± 12.7	59.3 ± 18.9	<0.0001
Peak tidal volume, L, mean ± SD	1.57 ± 0.43	1.75 ± 0.53	0.009
Peak Respiratory rate, b/m, mean ± SD	30.5 ± 6.7	33.3 ± 7.2	0.006
VE/VCO_2 slope, mean ± SD	34.1 ± 6.3	31.7 ± 6.1	0.005

Discussion

Traditionally, the main indication for cardiopulmonary exercise testing (CPET) in heart failure (HF) was for the selection of candidates to heart transplantation. Recently, CPET is used for risk stratification and evaluation of management strategies [5]. CPET is a valuable tool to guide clinical decision-making and to derive prognostic information in HF patients.(7) In the **PARADIGM-HF** trial, sacubitril/valsartan reduced the risk of death and hospitalization for patients with HFrEF, as compared to enalapril; however, little is known on how sacubitril/valsartan influences cardiopulmonary function [1]. Only few studies showed an improvement in exercise tolerance after initiation of sacubitril/valsartan in patients with HFrEF [2].

In the study of Palau et al, the authors showed an improvement in peak VO_2 in HFrEF patients after sacubitril/valsartan initiation, mostly at low doses. The study was limited by a very short-term follow-up only 1 month with a very limited sample size only 33 patients [3].

In current study, we targeted a larger population (100 patients) and a longer follow-up (6 months) with advanced methodology included higher dosages of sacubitril/valsartan up to 97/103 mg twice daily in 41% of study population. We observed a marked improvement in all CPET parameters with sacubitril/valsartan mainly obtained from an improvement in peak VO_2 (14.6 ± 4 to 17.3 ± 5 mL/kg/min which should be secondary to the improvement of cardiac performance (Table 2). Similar to our results, Vitale G et al. observed an improvement in peak VO_2 (+17% versus baseline) and VE/VCO_2 slope (–7% versus baseline) at follow-up, they conclude in their observational trial that administration of sacubitril/valsartan was associated with a significative improvement in exercise tolerance, peak oxygen consumption, and ventilatory efficiency at 6.2 months follow-up [7].

The prognostic value of CPET in HF with reduced ejection fraction (HFrEF), especially if combined with other key clinical parameters, has been the subject of recent papers.(5) Swank et al. reported in a previous study that for every 6% increase in peak VO_2 there is an 8% reduction in cardiovascular mortality or HF hospitalization (p < 0.001).(8) Arena et al. reported worse 1-year event-free survival from cardiac mortality (83.1% vs. 99.2%; p<0.0001) and worse 1-year event-free survival from cardiac hospitalization (50.6% vs. 84.6%; p < 0.0001) in patients with VE/VCO_2 slope ⩾34. (9)

A **PARADIGM-HF** post-hoc analysis by **Vardeny et al**. demonstrates that lower doses of sacubitril/valsartan confer a similar treatment benefit over enalapril; however, patients taking low doses were associated with a higher risk of the primary events [10].

In current study, patients taking higher doses had better improvement of CPET parameters as compared to patients taking lower doses. Among 41 patients who received sacubitril/valsartan with doses ranged from 49/51 to 97/103 mg, peak VO_2 increased up to15.43 ± 2.2 vs only 12.34± 2.5 mL/kg/min in 59 patients who received a lower doses ranged from 24/26 to 49/51 mg (p = 0.0008). In association, LVEF increased in patients who received higher doses 31.2 ± 2% vs 28.1 ± 3% (p <0.001) with non significant decrease in SBP 115 ± 53 vs116 ± 1 mmHg (p = 0.07) (Figure 1).

Study Limitations

An important limitation of current study is the small sample size; nonetheless, to our knowledge, No other work represents larger sample size of HFrEF patients followed by CPET parameters. This was an observational trial with no control group. Finally, only 2 patients with NYHA class IV were included and the majority of study population had NYHA class II, III on optimized medical therapy.

Further studies are necessary to better clarify underlying mechanisms of this functional improvement.

Conclusions

Sacubitril/valsartan therapy in patients with HFrEF associated with a significant improvement in exercise tolerance up to 6 months follow-up. Higher doses equal better improvement in both exercise tolerance and LVEF.

Conflicts of Interest: The authors declare no conflict of interest.

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