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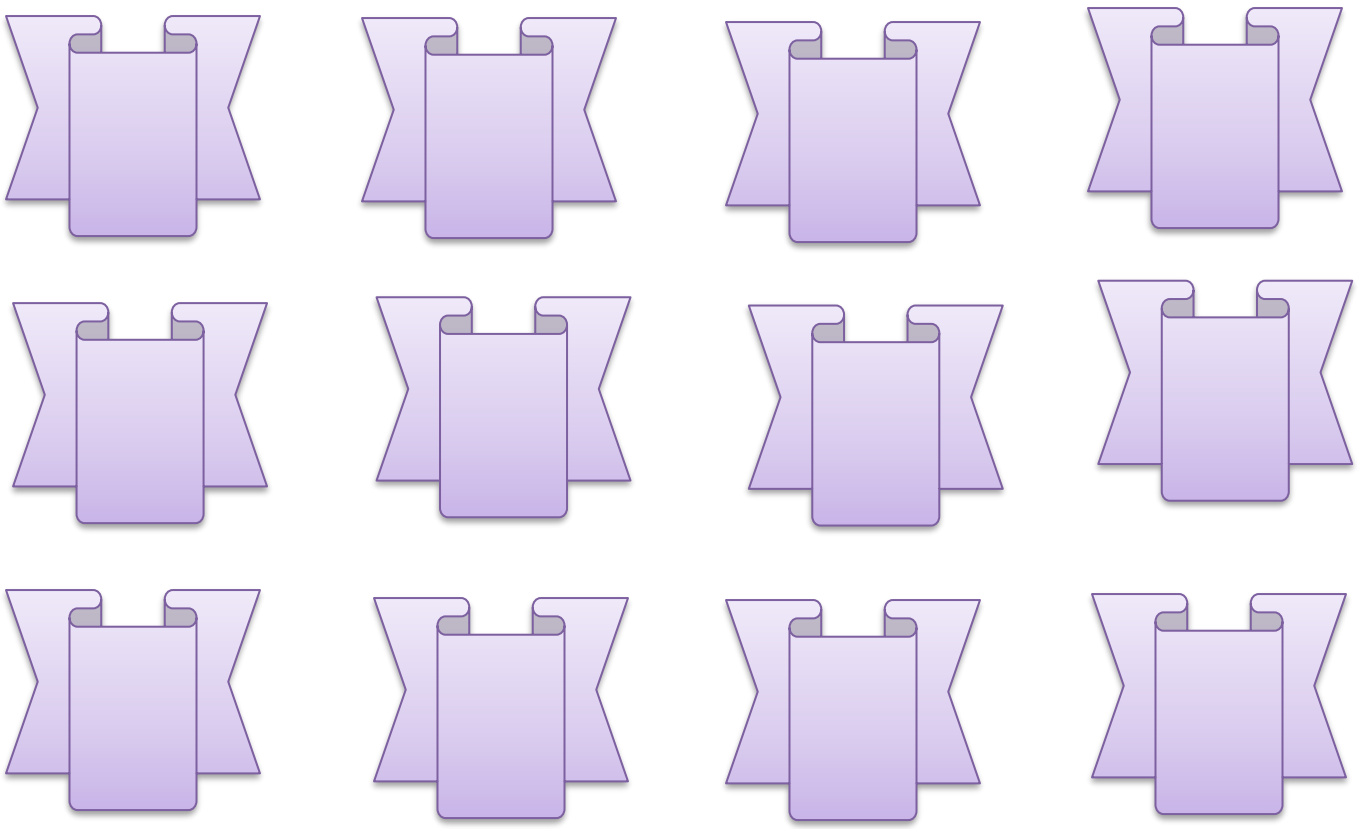

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Original Article

Impact of Sacubitril–Valsartan Treatment on Diastolic Function and Right Ventricular Function in Patient with Heart Failure with Reduced Ejection Fraction

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ABSTRACT

Background: It was proved that sacubitril-valsartan has a major role in ventricular remodeling resulting in improving ejection fraction and ventricular size. Although evaluating the diastolic function in those presenting with Heart failure and reduced ejection fraction [HFrEF] was neglected, the majority of patients with HFrEF also have diastolic dysfunction.

The Aim of the work: In this study, we will focus on studying and explaining the impact of sacubitril–valsartan on diastolic dysfunction and RVD and explaining if the clinical improvement is attributed to improvement in diastolic function and right-side function.

Patients and Methods: Our prospective study enrolled 60 HFrEF patients. All of the included patients were submitted for, ECG, and Standard 2D Doppler transthoracic echocardiography. The following parameters were collected; TAPSE [Tricuspid Annular Plane Systolic Excursion], FAC [fractional area change] 3Systolic pulmonary artery pressure [SPAP], Myocardial performance index [M P I].

Results: According to the percentage of improvement among the studied cases, the majority [80%] of class II cases improved and 20% had no change. Similarly, 82.1% of class III patients saw improvement in NYHA classification. Whereas all cases in class IV were improved [100%]. According to the change of systolic and diastolic blood pressure, the mean Systolic Blood Pressure [mmHg] of subjects before therapy with sacubitril–valsartan was 125.88 ±13.7 and it was 108.8± 11.3 of subjects following therapy with sacubitril –valsartan, and this was statistically substantial [P = 0.001]. The mean of Diastolic Blood Pressure [mmHg] of subjects before therapy with sacubitril –valsartan was 85.25 ± 8.9 and it was 74 ± 11.1 of subjects following therapy with sacubitril –valsartan, and this was statistically substantial [P = 0.001].

Conclusion: The measured parameters of right ventricular function such as TAPSE, MPI, and Fractional area change were all improved significantly indicating a positive effect for sacubitril-valsartan on the right ventricular function.

Keywords: Sacubitril–Valsartan; Right Ventricular Function; Heart failure.

INTRODUCTION

Heart failure [HF] is regarded as a serious global healthcare issue. In 2017, an estimated 64.3 million people worldwide suffered from HF, up from 33.5 million in 1990 [1]. Within the first year after hospitalization, there was a 44% rehospitalization rate and an overall death rate of 17%, according to data from the ESC-HF pilot investigation conducted in Europe [2].

Many factors have contributed to the increased incidence and prevalence of HF. As the population ages and hypertensive and ischemic cardiovascular disease medications improve, mortality is reduced but paradoxically raising the number of cases of chronic HF [3].

The basis of pharmaceutical treatment for those with HF and reduced ejection fraction [rEF] is the modification of the renin-angiotensin-aldosterone system [RAAS] with angiotensin-converting inhibitor [ACE-I], beta-blockers, mineralocorticoids receptor antagonist [MRA], angiotensin receptor neprilysin inhibitor [ARNI], SGlT2 inhibitors dapagliflozin, and empagliflozin [4].

The FDA approved sacubitril/valsartan in 2015 following the PARADIGM-HF trial, which demonstrated a decrease in the paired main result of hospitalization and mortality from cardiovascular-related events among people with HFrEF [rEF = 35% or less and NYHA class II–IV] when contrasted with enalapril [5].

It was proved that sacubitril-valsartan has a major role in ventricular remodeling resulting in improving ejection fraction and ventricular size. Although evaluating the diastolic function in those presenting with HFrEF was neglected, the majority of patients with HFrEF also have diastolic dysfunction. This suggests that assessing diastolic function may offer an extensive framework for understanding its effect on clinical enhancement [6].

Due to the various etiology and patho-physiology, right ventricular dysfunction [RVD] frequently coexists in individuals with HFrEF. Unfavorable alterations in the pulmonary vasculature and right side of the heart are also caused by the passive transfer of higher left-sided filling force in HFrEF patients [7].

Recovery of the right ventricle throughout follow-up investigations was linked to better survival among those with HFrEF. It is widely acknowledged that RVD significantly predicts survival in left-sided HF [8].

In this study, we will focus on studying and explaining the impact of sacubitril–valsartan on diastolic dysfunction and RVD and explaining if the clinical improvement is attributed to improvement in diastolic function and right-side function.

PATIENTS AND METHODS

Our prospective cohort research enrolled 60 HFrEF patients who visited our outpatient center in Sharq-elmadina Hospital [tertiary level hospital specialized in cardiovascular diseases and cardio-thoracic surgery] and International Cardiac Center [ICC] [specialized center in Cardiology in Alexandria government, Egypt]. Our study followed the Helsinki Declaration principles. At the phase of selection, each patient provided written informed permission. We included the patients according to the following criteria:

The Inclusion criteria were: 1] At least 18 years old, 2] NYHA class [II-IV], 3] Left ventricular ejection fraction [LVEF] ≤ 35%, 4] Individuals must have had the best possible HF care for the preceding three months, which may include ACEI or ARBS, 5] The patient needs to be clinically stable, meaning they shouldn't have required hospitalization in the previous month because of HF.

The Exclusion criteria were: 1] To prevent possible disruption in the examination of diastolic function, those with a record of persistent atrial fibrillation, pacemakers, mitral stenosis, prior mitral reconstruction, or prostheses will be eliminated, 2] S-V allergic reactions, angioedema past events, and unacceptably high adverse effects while taking ACEI or ARB, 3] Signs of hypotension and hyperkalemia, and 4] Estimated glomerular filtration rate < 15 mL/ min/1.73 m^2

Data collection: All of the included patients were submitted for, History taking [risk factors for cardiovascular disease, long-term illnesses, the cause of heart failure, and long-term drug use], general and local cardiovascular examinations, routine laboratory investigations, Twelve-lead resting surface ECG, and Standard 2D Doppler transthoracic echocardiography.

Concerning the investigation of the diastolic function, these variables were gathered: 1] Using a pulsed Doppler, the mitral inflow pattern [E

and A], the E/A ratio, and the E deceleration time [DT] were measured, 2] Annular lateral e′ using tissue Doppler imaging. The E/e′ ratio was computed, 3] Both the maximum Systolic pulmonary pressure and the peak tricuspid regurgitant velocity were recorded, 4] The indexed left atrial volume.

In accordance with the ASE's recommendations, all of these characteristics were utilized to categorize patients into three distinct categories of diastolic dysfunction; the measurements were taken in the apical four and two-chamber views [9].

With regards to right ventricle function assessment, these parameters were collected

1] TAPSE [Tricuspid Annular Plane Systolic Excursion]: This is a technique for measuring the distance of systolic excursion of the RV annular segment along its longitudinal plane from a standard apical chamber window to determine right ventricular [RV] function. It is easily obtainable and is a measure of right ventricular longitudinal function. TAPSE < 16 mm indicates RV systolic dysfunction. TAPSE is acquired by placing an M-mode cursor through the tricuspid annulus and measuring the amount of longitudinal motion of the annulus at peak systole [10].

2] FAC [fractional area change]: This gives the RV systolic function estimate. Two-dimensional FAC < 35% indicates RV systolic dysfunction. It is important to make sure that the entire right ventricle is in view, including the apex and the lateral wall in both systole and diastole. Care was taken to exclude trabeculations while tracing the RV area. The endocardial border is traced in apical 4-chamber views from the tricuspid annulus along the free wall to the apex, then back to the annulus, along the inter ventricular septum at end-diastole [ED] and end-systole.

3] Systolic pulmonary artery pressure [SPAP]: This was determined by applying the modified Bernoulli formula to the peak velocity, expressed by the tricuspid regurgitation Doppler signal, and adding the predicted right atrial pressure [RAP] and the maximum pressure gradient separating the peak right ventricle and the right atrium.

4] Myocardial performance index [MPI]: It gives a global RV function index. This is done by obtaining MPI > 0.40, the ejection time [ET], isovolumic contraction time [IVCT], and isovolumic relaxation time [IVRT] indices from the pulsed tissue Doppler to determine RV dysfunction.

The variables must be assessed with a consistent R-R interval to reduce error, but the measurement is still accurate throughout a wide range of heart rates. This method eliminates the geometrical constraints and restrictions of complex RV geometry, which is possible in most individuals with and without TR. Additionally, the MPI is repeatable. Individuals with pulmonary hypertension can use the MPI as a predictive tool at any time, and alterations in the MPI correlate with improvements in clinical condition.

All parameter included in this study was assessed by two certified and experienced cardiologists independent of each other, repeated several times, and compared to each other blindly to confirm the correct result, in case of wide discrepancy between two observers, the study was assessed by a third operator.

Statistical analysis: Data were collected, revised, coded, and entered into the Statistical Package for Social Science [IBM SPSS] version 26. The qualitative data were presented as numbers and percentages while quantitative data were presented as mean, standard deviations, and ranges when their distribution was found parametric. The comparison between two paired groups with qualitative data was done by using Chi-square test and/or Fisher exact test was used instead of Chi-square test when the expected count in any cell was found less than 5. The comparison between two paired groups with quantitative data and parametric distribution were done by using Paired t- test. The comparison between two paired groups with quantitative data and non-parametric distribution was done by using Wilcoxon test.

RESULTS

We included 60 subjects in total for our investigation. As per the participant's demographics, the average age of the patients under study was 57.45 ± 11.79 years, with 32 cases being male and 28 instances being female, and the mean BMI was 26.84 ± 2.72 Kg/m^2.

Among the primary causes of HF identified in this investigation is ischemic heart disease [60%], 31.7% were idiopathic, 5.0% were Postpartum and 3.3% were Post viral.

As regards the risk factors; 63.3% of the cases had obesity, 60.0% of the cases had DM, 55.0% had HTN, 43.3% had smoking, 40.0% had dyslipidemia, 8.3% had COPD, 6.7% had left mastectomy, 5.0% had Old CVS, 5.0% had pulmonary embolism, 3.3% had hypothyroidism and 3.3% had retinopathy.

According to the standard heart failure treatment, all cases had received ACE/ARBS, 76.7% of cases had received Beta-blocker, 75.0% had received MRA, and 70.0% had received SGLT2 Inhibitor and 55.0% had Diuretics.

Table [1] shows that before treatment with sacubitril –valsartan there were no subjects had NYHA classification I, 25 subjects had NYHA classification II, 28 subjects had NYHA classification III and 7 subjects had NYHA class IV. After treatment with sacubitril –valsartan there were 25 subjects had NYHA classification I, 30 subjects had NYHA classification II and 5 subjects had NYHA classification III, which was statistically significant, where major improvement of NYHA classification was encountered in class II, III.

Table [2] demonstrates the frequency and percent of cases in each NYHA class before and after treatment. At the start of the study, 28 cases were classified as class III NYHA, of which, 18 cases changed to class II, 5 cases moved to class I, and 5 remained unchanged. The number of cases in class IV NYHA changed to class II [7 cases, 11.67%]. While 33.3% of class II cases changed to class I [20 cases], and only 5 cases remained the same.

According to the percentage of improvement among the studied cases, the majority [80%] of class II cases improved and 20% had no change. Similarly, 82.1% of class III patients saw improvement in NYHA classification. Whereas all cases in class IV were improved [100%] [Figure 1].

According to the change of systolic and diastolic blood pressure, the mean systolic blood pressure [mmHg] prior to therapy was 125.88 ±13.7 and it was 108.8± 11.3 of subjects following therapy with sacubitril –valsartan, and this was highly statistically substantial [P = 0.001]. The mean of diastolic blood pressure [mmHg] of subjects prior to therapy with sacubitril –valsartan was 85.25 ± 8.9 and it was 74 ± 11.1 of subjects following therapy with sacubitril –valsartan [P = 0.001].

In terms of the echocardiographic changes, the mean of LVEDD [mm] of subjects prior to receiving therapy with sacubitril–valsartan was 67.20 ± 8.06 and it was 65.66 ± 8.23 of subjects following therapy with sacubitril –valsartan, and this was statistically significant. The mean of LVESD [mm] of subjects prior to receiving therapy with sacubitril –valsartan was 58.92 ± 6.74 and it was 56 ± 6.83 of subjects following therapy with sacubitril –valsartan, and this was highly statistically significant [Table 3].

The mean of LVEDV [ml] of subjects prior to receiving therapy with sacubitril –valsartan was 178.85 ± 60.28 and it was 161.8 ± 54 of subjects following therapy with sacubitril –valsartan, this was statistically significant.

The mean of LVESV [ml] of patients before treatment was 135.35 ± 47.8 and it was 117.7 ± 42 of patients after it was highly statistically significant.

The mean of ejection fraction of subjects prior to receiving therapy with sacubitril–valsartan was 24.38% ± 5.2% and it was 27.2% ± 5.7% of subjects following therapy with sacubitril–valsartan, this was statistically significant.

In our investigation, the mean of Mitral E [cm/s] of patients subjects prior to receiving therapy with sacubitril –valsartan was 65.88 ± 14.82 and it was 59.68 ± 14.96 of patients After treatment with sacubitril –valsartan, and this was highly statistically significant. The median of Mitral E/A of patients subjects prior to receiving therapy with sacubitril –valsartan was 1.75 [1.06 – 2.09] and it was 1.34 [0.76 – 1.81] of subjects following therapy with sacubitril –valsartan, and this was statistically significant. The mean of E/ e prime of subjects prior to receiving therapy with sacubitril –valsartan was 11.32 ± 5.04 and it was 9.14 ± 4.67 of subjects following therapy with sacubitril –valsartan, and this was statistically significant [Table 4].

According to the deceleration time [msec], Lateral e prime [cm/s], and Peak TR velocity [m/s]; Table 5 reveals that; the mean of deceleration time [msec] of subjects prior to receiving therapy with sacubitril –valsartan was 190.13 ± 55.97 and it was 201.30 ± 45.02 of subjects following therapy with sacubitril –valsartan, and this was statistically significant. The mean of Lateral e prime [cm/s] of patients subjects prior to receiving therapy with sacubitril –valsartan was 6.74 ± 2.42 and it was

6.94 ± 2.41 of subjects following therapy with sacubitril –valsartan, and this was statistically significant. The mean of peak TR velocity [m/s] of patients subjects prior to receiving therapy with sacubitril –valsartan was 2.41 ± 0.82 and it was 1.99 ± 0.84 of subjects following therapy with sacubitril –valsartan, and this was highly statistically significant.

As regards the Estimated SPAP [mmhg] of subjects prior to receiving therapy with sacubitril –valsartan was 29.8 [19.81 – 41.1] and it was 20 [13 – 36.64] of subjects following therapy with sacubitril –valsartan, and this was highly statistically substantial [P = 0.001]. The median of indexed left atrium volume [ml/m2] of subjects prior to receiving therapy with sacubitril –valsartan was 40.5 [33 – 47.3] and it was 38 [30.5 – 46] of subjects following therapy with sacubitril –valsartan, and this was highly statistically substantial [P = 0.00].

In terms of the diastolic dysfunction grade; before treatment with sacubitril –valsartan there were 24 subjects had diastolic dysfunction grade I, 13 subjects had diastolic dysfunction grade II, and 23 subjects had diastolic dysfunction grade III, while after treatment with sacubitril –valsartan there were 32 subjects had diastolic dysfunction grade I, 20 subjects had diastolic dysfunction grade II and 8 subjects had diastolic dysfunction grade III, and this was statistically substantial [P = 0.007]. In our investigation, the improvement of cases in different grades of diastolic dysfunction, where 38.5% of cases in grade II improved while 61.5% had no change. More than half of grade III cases [65.2%] improved, whereas only 34.8% remained unchanged.

According to the MPI, fractional area changes, and TAPSE [mm], Table 5 reveals that; the median of MPI of subjects prior to receiving therapy with sacubitril –valsartan was 0.79 [0.59 – 1.1] and it was 0.54 [0.37 – 0.89] of subjects following therapy with sacubitril –valsartan, and this was highly statistically significant. The mean of fractional area changes of subjects prior to receiving therapy with sacubitril –valsartan was 33.54% ± 9.52% and it was 37.85% ± 9.75% of subjects following therapy with sacubitril –valsartan, and this was highly statistically significant. The Mean of TAPSE [mm] of subjects prior to receiving therapy with sacubitril –valsartan was 15.1 ± 3.4 and it was 16.9 ± 3.01 of subjects following therapy with sacubitril –valsartan, and this was statistically significant.

Table [1]: Comparison between before and after treatment with sacubitril-valsartan regarding NYHA classification

NYHA classification	Before		After		P-value
	No.	%	No.	%	
I	0	0.0%	25	41.6%	0.000
II	25	41.6%	30	50%	
III	28	46.6%	5	8.3%	
IV	7	11.6%	0	0%	

Table [2]: Categorization of cases according to NYHA classification before and after treatment with sacubitril-valsartan

Treatment	Before			After		
	Grade	Frequency	%	Grade	Frequency	%
NYHA classification	**IV**	7	11.67	**II**	7	11.67
	III	28	46.67	**III**	5	8.3
				II	18	30
				I	5	8.3
	II	25	41.67	**II**	5	8.3
				I	20	33.3
Total		60	100		60	100

Table [3]: Comparison between Before and After regarding LVEDD [mm], LVESD [mm], LVEDV [ml], LVESV [ml] and Ejection fraction

		Before	After	P-value
		No. = 60	**No. = 60**	
LVEDD [mm]	Mean ± SD	67.20 ± 8.06	65.66 ± 8.23	0.000
	Range	48 – 85	47 – 83	
LVESD [mm]	Mean ± SD	58.92 ± 6.74	56 ± 6.83	0.000
	Range	43.9 - 71	40.9 – 68	
LVEDV [ml]	Mean ± SD	178.85 ± 60.28	161.8 ± 54	0.000
	Range	95 - 316	83 – 280	
LVESV [ml]	Mean ± SD	135.35 ± 47.8	117.7 ± 42	0.000
	Range	68.3 – 245	60 – 210	
Ejection fraction	Mean ± SD	24.38%± 5.2%	27.2% ± 5.7%	0.000
	Range	17.0% – 34.8%	17.0% – 39.0%	

Table [4]: Comparison between Before and After regarding Mitral E [cm/s], Mitral E/A and E/ e prime

		Before	After	P-value
		No. = 60	**No. = 60**	
Mitral E [cm/s]	Mean ± SD	65.88 ± 14.82	59.68 ± 14.96	**0.000[a]**
	Range	37 – 99	35 – 96	
Mitral E/A	Median [IQR]	1.75 [1.06 – 2.09]	1.34 [0.76 – 1.81]	**0.000[b]**
	Range	0.65 – 5.98	0.58 – 2.84	
E/ e prime	Mean ± SD	11.32 ± 5.04	9.14 ± 4.67	**0.000[a]**
	Range	5 – 19.8	3.99 – 22.8	

Table [5]: Comparison between before and After regarding Decelerations time [msec], Lateral e prime [cm/s] and Peak TR velocity [m/s]

		Before	After	P-value
		No. = 60	**No. = 60**	
Decelerations time [msec]	Mean ± SD	190.13± 55.97	201.30± 45.02	0.041
	Range	129 – 369	114 – 279	
Lateral e prime [cm/s]	Mean ± SD	6.74 ± 2.42	6.94 ± 2.41	0.000
	Range	3.2 – 11	3.5 – 11.1	
Peak TR velocity [m/s]	Mean ± SD	2.41 ± 0.82	1.99 ± 0.84	0.000
	Range	0.92 – 3.83	0.74 – 3.5	

Table [6]: Comparison between before and after regarding MPI, Fractional area change and TAPSE [mm]

		Before	After	P-value
		No. = 60	**No. = 60**	
MPI	Median [IQR]	0.79 [0.59 – 1.1]	0.54 [0.37 – 0.89]	0.000
	Range	0.36 – 1.4	0.17 – 1	
Fractional area change	Mean ± SD	33.54% ± 9.52%	37.85% ± 9.75%	0.000
	Range	20.9% – 53.0%	22.0% – 53.0%	
TAPSE [mm]	Mean ± SD	15.1 ± 3.4	16.9 ± 3.01	0.000
	Range	9 – 24	11 – 23	

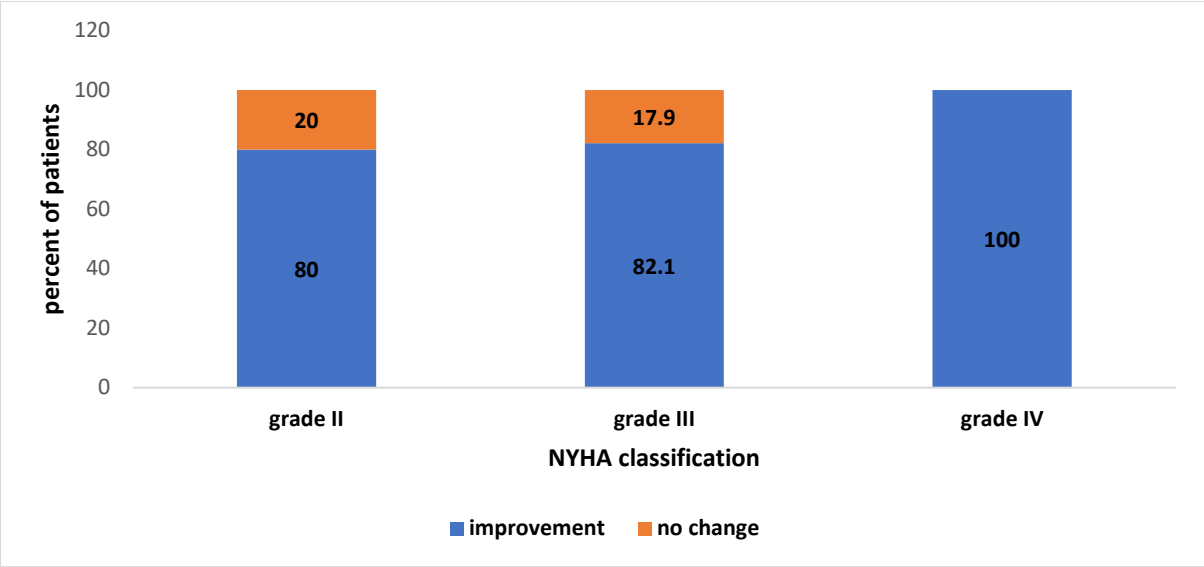

Figure [1]: Degree of improvement in cases according to NYHA classification

DISCUSSION

The current study's findings demonstrated a statistically significant enhancement in the NYHA classification of patients before and after the administration of S-V which is similar to the results reported by other reports [11, 12].

Regarding systolic and diastolic blood pressure, the current study showed a significant distinction between the before and after treatment readings, where they dropped by a range of 15-40 mmHg. These findings agree with those reported by **Romano *et al.*** [12] and **Ledwidge *et al.*** [13] which was explained by the decrease in NT-proBNP concentration, vasodilation, and enhanced diuresis.

In a comparison between the combined effect of S-V and valsartan alone, **Ledwidge *et al.*** [13] reported an improvement in LVEDV of 12.1 ml in S-V group versus 1.6 ml in the valsartan group. Likewise, the LVESV improved by a median of 3.9 ml in the S-V group while those in the valsartan group showed little to no improvement, while the mean absolute increase in LVEF was 2.8%, and nearly half of the patients showed more than 3% improvement in their EF. However, **Pericas *et al.*** [11] reported a slightly lower increase in the ejection fraction [from 29.7% to 34.7%], which was attributed to the low power of the study and the small sample size, subsequently

The reverse remodeling impact on the LVEF, leads to a favorable impact on systolic pulmonary pressure, most likely as a result of the physiological actions of sacubitril [14].

The findings of our investigation showed a statistically substantial improvement [p=0.000] in the mitral valve peak E-wave velocity pre and post-treatment, this finding goes in line with that reported by. Similarly, the mitral E/A ratio was found to improve from a mean of 1.75 to 1.34, with a substantial disparity between the two groupings [p=0.00], which is comparable to that estimated by **Romano *et al.*** [12], who found the E/A ratio improved from 1.67 to 1.42. A similar ratio was reported by **Martens *et al.*** [15] [1.75 to 1.38]. Moreover, the mitral E/ē ratio improved significantly from 11.23 to 9.14 [p=0.00]. Similar ratio was reported by **Pericas *et al.*** [11]. These crucial prognostic indicators show the degree and duration of adverse remodeling of the LV, higher heart-filling pressures, and fluid accumulation.

The findings of our investigation showed a substantial improvement in deceleration time, which agrees with the results of **Pericas *et al.*** [11], who reported a similar improvement in the deceleration time.

Regarding lateral e¯ [cm/s], there was a slight increase in velocity with a substantial variation between the before and after results [p=0.00], from a mean of 6.74 to 6.94. Nearly the same values were reported by **Pericas *et al.*** [11].

Peak tricuspid regurgitation velocity was found to decrease among participants after treatment, from a mean of 2.41 to 1.99 m/sec., [p=0.00]. Similar findings were found by **Brás *et al.*** [16], where the mean tricuspid regurgitation velocity was measured at baseline to be 2.73, and after 6 months to be 2.57. Also, **Romano *et***

al. [12] detected a similar reduction in mean tricuspid regurgitation velocity [from 2.8 to 2.64].

The median estimated SPAP showed a significant reduction after treatment. Consistently, results from a meta-analysis involving 10 primary studies found a significant reduction in SPAP with a mean of 7.21 mm Hg and 95% CI [5.38–9.03 mm Hg] [17]. **Zhang *et al.*** [17] further suggested that the enhancements in LVEDV, or a healthier left ventricle lowering the left-sided filling pressure's backward propagation to the pulmonary circulation and causing a decrease in pulmonary arterial pressure, may be related to the enhancements in SPAP.

The left atrial showed a significant reduction in volume after the treatment period with a median decline from 40.5 to 38 ml/m^2 [p=0.00]. similar findings were reported by **Paolini *et al.*** [18] and **Ledwidge *et al.*** [13].

The current investigation showed significant variation before and after treatment [p=0.007] regarding the diastolic dysfunction grade. This finding coincides with that of **Pericas *et al.*** [11].

TAPSE increased from a mean of 15.1 to 16.9. Similar findings were reported by **Bayard *et al.*** [14] and **Zhang *et al.*** [17] who found that the TAPSE improvement was highly associated with ischemic heart disease patients. Fractional area change increased significantly [p=0.000] from 33.5% to 37.8%. Nearly the same finding was reported by **Yang *et al.*** [19].

Conclusion: The measured parameters of right ventricular function such as TAPSE, MPI, and Fractional area change were all improved significantly indicating a positive effect of sacubitril-valsartan on the right ventricular function.

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