ORIGINAL ARTICLE

# The Effect of Sacubitril / Valsartan on Diastolic function of HFmrEF patients by Tissue Doppler

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Abstract

*Background:* ***The left ventricular ejection fraction (EF) plays a critical role in diagnosing heart failure, determining its characteristics, predicting its outcome, and making decisions about treatment.***

*Aim of the work:* ***To examine the impact of Sacubitril / Valsartan on the diastolic function of patients with heart failure and mildly reduced ejection fraction (HFmrEF).***

*Patients and methods:* ***An interventional study targeting patients with HFmrEF for 90 days of follow-up after initiating Sacubitril/Valsartan as part of their standard care was conducted at Suez Health Insurance Cardiology Clinic and Helwan Insurance Hospital.***

*Results:* ***94 patients (62% males; 60.9 ± 8.84 years) with HFmrEF in NYHA class II–IV were evaluated. A significant improvement in the NYHA class and diastolic function after treatment with standard doses (P<0.001). 63% of the patients had diastolic dysfunction grade 3, and 2% had better grades after 3 months of S–V treatment. Moreover, there was a reduction in E/e' ratio from (11.8) to (9.9) with non-significant changes in systolic function.***

*Conclusion:* ***In addition to an improvement in NYHA class and symptoms in patients with HFmrEF Sacubitril/Valsartan significantly improved diastolic parameters, This echocardiographic improvement is particularly relevant in those patients with better NYHA class at 3-month follow-up.***

*Keywords:* Sacubitril; Valsartan; Diastolic; HFmrEF; Doppler

## 1. Introduction

Heart failure (HF) is a serious condition that occurs in patients with acquired abnormalities in the structure and function of the heart and is usually caused by coronary artery disease (CAD), hypertension, or cardiomyopathy.[1]

Over the past three decades, the use of evidence-based pharmacological and non-pharmacological therapies for heart failure has increased, largely due to a better understanding of its pathophysiology.[2]

The first-line ARNI is sacubitril-valsartan (S-V), which has recently been shown to be effective in reducing mortality and hospitalizations due to heart failure compared to enalapril in the HFpEF population.[3]

Heart failure with mildly reduced ejection fraction (HFmrEF) has become a distinct condition that includes patients with an ejection fraction between 40% and 49%. This patient group often presents with symptoms similar to heart failure with reduced ejection fraction (HFrEF) and is at increased risk of morbidity and mortality.[4]

Therefore, it is important to find treatment options for people with HFpEF. There is strong evidence that angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs) can partially reduce left ventricular dilation and remodeling in HF. However, morbidity and mortality in patients with HF remain unacceptably high.[5]

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In recent years, the angiotensin receptor neprilysin inhibitor (ARNI) sacubitril-valsartan has been shown to reduce the risk of death in patients with HF with HFrEF.[6]

TDI Ea is a more accurate method for assessing HFpEF than routine Doppler evaluation (E/A). In heart failure, measuring left ventricular diastolic function can provide more information about TDI than measuring left ventricular systolic function. TDI is a simple, non-invasive alternative technique for assessing left ventricular diastolic function. This offers an additional advantage in patients with pseudonormalization compared to conventional Doppler E/A.[7]

The current study aimed to examine the impact of Sacubitril / Valsartan, a medication that inhibits angiotensin receptors and neprilysin, on the diastolic function of patients with heart failure and mildly reduced ejection fraction (HFmrEF).

## 2. Patients and methods

In the current interventional study that enrolled 100 ambulatory patients with HFmrEF for follow-up after Sacubitril / Valsartan by experienced echocardiographers using a standard protocol and a commercially available ultrasound system with a phased-array transducer from September 2023 to April 2024, the study was conducted at Suez Health Insurance cardiology Clinics and Helwan Insurance clinics.

This study follows certain inclusion parameters including 1) Studied patients had to be at least 18 years old, 2) Participants had to be classified as NYHA class II- IV, and 3) Participants had to have LVEF between 41% up to 49%, with informed written consent taken from all studied participants before enrollment into the study, 4) Participants must have been hemodynamically stable. While 1] a significant history of permanent atrial arrhythmia, 2] individuals with pacemakers, 3] patients with Primary mitral valve diseases, and 4] patients with previous mitral-repair or mitral-prosthesis were excluded.

ACEI or ARB medication was substituted with sacubitril–valsartan (S–V) in suitable patients, following clinical practice recommendations. (8) A 36-hour wash-out time was implemented after the last dose of ACEI before starting sacubitril–valsartan (S–V), to minimize the likelihood of angioedema. A dosage of sacubitril–valsartan (S–V), at a low level (24/26 mg per 12 hours), was provided to the patients and then uptitrated to (49/51 mg per 12 hours) after 4 weeks according to blood pressure and renal function tests. The patients underwent reassessment every 4 weeks to confirm that they were receiving the prescribed dosage of sacubitril–valsartan, provided that there were no contraindications present.

The study recorded demographic information, somato-metric measures, cardiovascular risk factors, HF etiology, and chronic medicines. The trial methodology involved conducting clinical evaluations, electrocardiograms (EKG), echocardiograms, and blood tests prior to the commencement of S–V treatment. A 2D Doppler transthoracic echocardiogram was conducted using the guidelines provided by the American Society of Echocardiography (ASE)[8] before starting S-V treatment and again after 3 months of follow-up.

The left ventricle end-diastolic volumes (LVEDV) and end-systolic volumes (LVESV) were measured, obtaining LVEF with Simpson's biplane method.[9]

Regarding the investigations of diastolic function, we calculated these parameters: E/A Ratio (>0.8 and ≤2.0). An E/A ratio of <0.8 indicates Grade I diastolic dysfunction, while a ratio of≥2 suggests a restrictive filling pattern. E/e' Ratio (≤14) Lateral e' velocity (≥10 cm/sec) Left Atrial (LA) Volume Index (≤34 mL/m²) Peak Tricuspid Regurgitation (TR) Velocity (<2.8 m/s).[10]

The primary objective of this study was to assess alterations in traditional diastolic function parameters prior to and during the initiation of S-V therapy. The main objective was to assess the DD grade with time, as described in Figure 1. The secondary outcomes measured in this study included the improvement of diastolic and systolic echocardiography parameters, clinical improvement measured according to NYHA class, at the conclusion of the follow-up period.

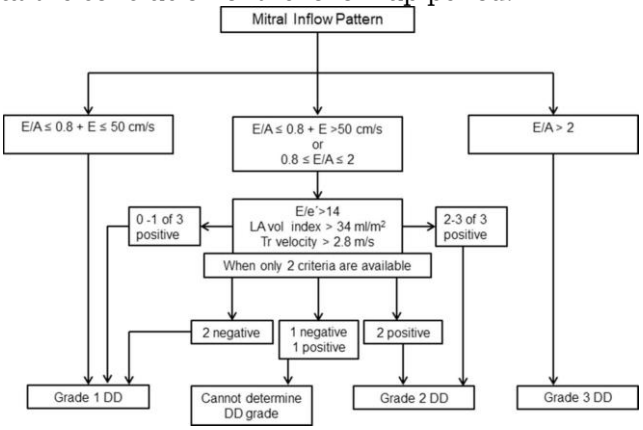


Figure 1. Algorithm for estimating grade diastolic function in patients with reduced LVEF. Adapted from the American Society of Echocardiography (ASE) 2016 Grading of diastolic dysfunction.

Statistical design:

The statistical analysis was conducted using SPSS 23 computer software. Qualitative information is expressed numerically and as percentages (N.% %), and quantitative information, after undergoing normality testing using the Shapiro-Wilk test, is represented with mean ±

standard deviation (SD) and (range) if it was normally distributed. Inferential statistics: The P value, also known as the significance level, is utilized to ascertain the statistical significance of a given outcome. If the P value is greater than 0.05, the result is considered non-significant. If the p-value is less than or equal to 0.05, the result is considered significant.

## 3. Results

In this study, 100 patients with heart failure and mildly reduced ejection fraction were selected to be treated with Sacubitril/Valsartan as part of their standard care.

Six patients were excluded from the follow-up as two patients died, three were non-compliant with the drug, and one patient refused the follow-up.

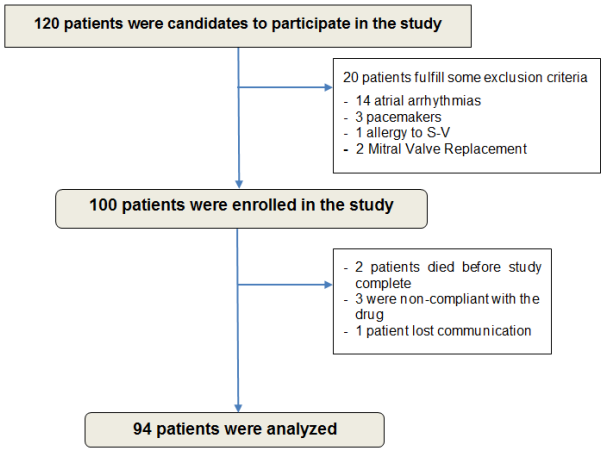


Figure 2. Flow chart. Selection process of patients included in the final analysis.

The patients studied age ranged from 38 to 85 years with a mean ± SD of 60.9

± 8.84, (62%) of the patients were males and (38%) were females, (52%) were active smokers and (10%) were ex-smokers. Also, (19%) had a previous heart failure hospitalization, (63%) had a previous PCI and (5%) had a previous CABG. (Table 1)

*Table 1. Baseline data among studied patients*

| VARIABLES | | ALL PATIENTS (N=100) |
|---|---|---|
| AGE (YEARS) | Mean ± SD | 60.9 ± 8.84 |
| | Range | (38 – 85) |
| SEX (N. %) | Male | 62(62%) |
| | Female | 38 (38%) |
| SMOKING STATUS (N. %) | Ex Smokers | 10 (10%) |
| | Active smokers | 52 (52%) |
| PAST HISTORY (N. %) | Heart failure hospitalization | 19 (19%) |
| | PCI | 63 (63%) |
| | S/P CABG | 5 (5%) |
| ASSOCIATED COMORBIDITIES (N. %) | Diabetes mellitus | 61 (61%) |
| | Hypertension | 70 (70%) |
| | Myocardial infarction | 58 (58%) |
| | Stroke | 8 (8%) |
| | COPD | 27 (27%) |
| | Angina | 77 (77%) |
| DRUG HISTORY (N. %) | BB | 89 (89%) |
| | MRA | 25 (25%) |
| | ACEIs | 87 (87%) |
| | Diuretics | 57 (57%) |
| | SGLT2i | 100 (100%) |
| SBP (MMHG) | Mean ± SD | 130.4 ± 14.94 |
| | Range | (100 – 180) |
| DBP (MMHG) | Mean ± SD | 82.1 ± 9.84 |
| | Range | (60 – 100) |
| SERUM CREATININE (MG/DL) | Mean ± SD | 0.96 ± 0.26 |
| | Range | (0.4 – 1.5) |
| SERUM NA (MEQ/L) | Mean ± SD Range | 138.7 ± 4.24 (131 – 148) |
| SERUM K (MMOL/L) | Mean ± SD | 4.2 ± 0.43 |
| | Range | (3.4 – 5.5) |
| HEMOGLOBIN (G/DL) | Mean ± SD | 13.08 ± 1.42 |
| | Range | (10.2 – 17) |
| EGFR (ML/MIN/1.73 M2) | Mean ± SD | 58.5 ± 20.2 |

*PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft,

*NYHA=New York heart association class, SBP=systolic blood pressure, DBP=diastolic blood pressure

There was a significant improvement in the NYHA class as (10.6%) of the patients were class Ⅳ , about 6 patients out of 10 improved to class III , Also (53.2%) were NYHA class III but after 3 months only these patients became in higher classes which indicates improvement in the clinical status. (P<0.001). Table (2)

*Table 2. Categorization of cases according to NYHA classification before and after treatment with sacubitril-valsartan.*

| TREATMENT | BEFORE | | | AFTER | | |
|---|---|---|---|---|---|---|
| | Grade | Freq | % | Grade | Freq | % |
| NYHA CLASSIFICATION | IV | 10 | 10.6 | III | 6 | 6 |
| | | | | IV | 4 | 4.2 |
| | III | 50 | 53.2 | III | 8 | 8.5 |
| | | | | II | 22 | 23.7 |
| | | | | I | 20 | 21.2 |
| | II | 34 | 36.2 | III | 2 | 2.1 |
| | | | | II | 22 | 23.7 |
| | | | | I | 10 | 10.6 |
| TOTAL | | 94 | 100 | | 94 | 100 |

DD grade before and after treatment, 10 out of 13 grade III cases (77%) improved to grade II, while 3 cases (23%) remained unchanged. Regarding grade II, 28 out of 46 cases (60%) improved to grade I, while 15 out of 46 cases did not change (33%). In grade I most of cases remained in the same grade (30 cases) only 4 cases improved and 1 case deteriorated to Grade II.

Regarding Diastolic Dysfunction grade before and after treatment, 10 out of 13 grade III cases (77%) improved to grade II, while 3 cases (23%) remained unchanged. Regarding grade II, 28 out of 46 cases (60%) improved to grade I, while 15 out of 46 cases did not change (33%). In grade I most of cases remained in the same grade (30 cases) 1 case deteriorated to Grade II.

*Table 3. Comparison between the diastolic dysfunction grade before and after treatment with sacubitril-valsartan*

| TREATMENT | BEFORE | | | AFTER | | |
|---|---|---|---|---|---|---|
| | Grade | Freq | % | Grade | Freq | % |
| DIASTOLIC DYSFUNCTION CLASSIFICATION | III | 13 | 14% | III | 3 | 3.1% |
| | | | | II | 10 | 10.6% |
| | II | 46 | 49% | III | 3 | 3.1% |
| | | | | II | 15 | 15.9% |
| | | | | I | 28 | 30% |
| | I | 35 | 37% | I | 34 | 36.2% |
| | | | | II | 1 | 1.1% |
| TOTAL | | 94 | 100% | | 94 | 100% |

Also, there was a significant reduction in SBP, DBP and HR after 3 months of follow-up; as mean of SBP was 130.4 ± 14.94 and became 123.7 ± 11.7 after 3 months (P<0.001), while the mean of DBP was 82.1 ± 9.84 and become 74.1 ± 10.3 after 3 months (P<0.001) and mean of HR was 74 ± 9.43 and become 72.8 ± 10.5 after 3 months (P=0.03).

Table (4) - Clinical classification at baseline and after 3 months

| VARIABLES | | BASELINE (N=94) | AFTER 3 MONTHS (N=94) | P VALUE |
|---|---|---|---|---|
| SYSTOLIC | Mean ± SD | 130.4 ± 14.94 | 123.7 ± 11.7 | <0.001 |
| | Range | (100 – 180) | (100 – 150) | |
| DIASTOLIC | Mean ± SD | 82.1 ± 9.84 | 74.1 ± 10.3 | |
| PRESSURE (MMHG) | Range | (60 – 100) | (60 – 90) | <0.001 |
| HEART RATE (BEAT/M) | Mean ± SD | 74 ± 9.43 | 72.8 ± 10.5 | 0.03 |
| | Range | (58 – 93) | (53 – 93) | |

*NYHA=New York heart association class, SBP=systolic blood pressure, DBP=diastolic blood pressure

We also reported a significant improvement in LVEDV as the mean of LVEDV was 134 ± 17.3 and reduced to 128 ± 17.4 after 3 months follow-up (P<0.001), while the EF and LVESD showed non-significant improvement after 3 months follow-up (P>0.05). While Diastolic Parameters measured by TDI showed significant improvement of e`(Lateral), E/e' ratio as the mean of e`(Lateral) was 5.79 ± 1.01 and increased to 7.2 ± 0.79 at 3 months follow up (P<0.001), And significant reduction in the median of E/e` ratio from 11.82 (3) to 9.95 (4.77) at follow up (P<0.001). LAD showed a significant reduction from 3.9 ± 0.57 to 3.55 ± 0.28 at follow-up (P<0.001). Also, LAVI showed significant improvement as the median of LAVI was 36.3 (5.7) and reduced to 32.95 (5.4) at follow-up (P<0.001). Other parameters of the Diastolic function showed variable response as the mean of TR Velocity was 2.13 ± 0.6 and reduced to 1.98 ± 0.38 at follow-up (P=0.04). (Table 5)

*Table 5. Baseline and follow up echocardiographic findings among studied patients.*

| VARIABLES | | BASELINE (N=94) | AFTER 3 MONTHS (N=94) | P VALUE |
|---|---|---|---|---|
| EF (%) | Mean ± SD | 44.3 ± 2.38 | 44.8 ± 1.91 | 0.09 |
| | Range | (40 – 49) | (41 – 50) | |
| LVEDD (CM) | Mean ± SD | 5.31 ± 0.42 | 5.1 ± 0.45 | <0.001 |
| | Range | (3.9 – 6) | (4.25 – 5.75) | |
| LVESD (CM) | Mean ± SD | 4.07 ± 0.43 | 4.2 ± 0.46 | 0.07 |
| | Range | (2.7 – 4.9) | (3.1 – 5.2) | |
| LVEDV (ML) | Mean ± SD | 134 ± 17.3 | 128 ± 17.4 | <0.001 |
| | Range | (104 – 166) | (102 – 165) | |
| PWD (CM) | Mean ± SD | 1.01 ± 0.23 | 1.01 ± 0.22 | 0.79 |
| | Range | (0.4 – 1.6) | (0.4 – 1.6) | |
| IVSD (CM) | Mean ± SD | 0.98 ± 0.25 | 0.96 ± 0.24 | 0.74 |
| | Range | (0.5 – 1.8) | (0.5 – 1.8) | |
| LA (CM) | Mean ± SD | 3.9 ± 0.57 | 3.55 ± 0.28 | <0.001 |
| | Range | (3.2 – 4.5) | (2.8 – 4.2) | |
| AOV (CM) | Mean ± SD | 2.59 ± 0.32 | 2.58 ± 0.32 | 0.35 |
| | Range | (2.1 – 3.3) | (2.1 – 3.3) | |
| E'(LATERAL) (CM/S) | Mean ± SD | 5.79 ± 1.01 | 7.2 ± 0.79 | <0.001 |
| | Range | (4.3 – 7.9) | (5.6 – 9.2) | |
| E/A | Median (IQR) | 1.1 (0.51) | 0.9 (0.37) | <0.001 |
| | Range | (0.42 – 2.5) | (0.4 – 2.2) | |
| E/E' RATIO | Median (IQR) | 11.82 (3) | 9.95 (4.77) | <0.001 |
| | Range | (6.1 – 18.7) | (3.2 – 19.5) | |
| TR V (M/S) | Mean ± SD | 2.13 ± 0.6 | 1.99 ± 0.38 | 0.04 |
| | Range | (1.01 – 4.6) | (1.1 – 2.9) | |
| LAVI (ML/M²) | Median (IQR) | 36.3(5.7) | 32.95(5.4) | <0.001 |
| | Range | (27.6 – 43.6) | (23.6 – 40.3) | |

*EF=ejection fraction, LVEDD=left ventricular end diastolic diameter, LVESD=left ventricular end systolic diameter, LVEDV=left ventricular end diastolic volume, PWd=posterior wall diameter, IVSd=interventricular septal diameter, LA=left atrium diameter, AoV=Aortic valve diameter, e'=mitral annulus early diastolic velocity, E/A=the ratio of early to late ventricular filling velocity, TR V=Tricuspid regurgitation velocity, LAVI=left atrial volume index.

## 4. Discussion

Cardiologists may have regarded individuals with a higher degree of sickness severity, in which case the use of Sacubitril/Valsartan (S-V) may be more suitable. (9) Therefore, this study assessed the alterations in traditional diastolic function parameters prior to and during the initiation of S-V therapy.

Currently, Lakhani et al.,[11] found that the majority of previous studies on heart failure has been focused on HF with HFrEF and HF with preserved ejection fraction (HFpEF), but HFmrEF has received less attention.

Although Solomon et al.[12] concluded that the

current understanding of HFmrEF treatment primarily relies on the findings of subgroup analysis in clinical studies.

Furthermore, Pericas et al.[13] observed that the majority of patients observed a steady enhancement in their diastolic parameters, including the E/e' ratio and left ventricular end-diastolic volume (LVEDV). Our study demonstrated a considerable improvement in NYHA class, with only 4.3% of patients classified as class Ⅳ after 3 months, compared to the initial 10.6%. A total of 42 out of 50 patients (84%) demonstrated improvement from class III, which was statistically significant (P<0.001). These findings are consistent with previous data.

Regarding systolic and diastolic blood pressure, our study showed a significant distinction between the before and after treatment readings, as the mean of SBP was 130.4 ± 14.94 and became 123.7 ± 11.7 after 3 months (P<0.001), while the

mean of DBP was 82.1 ± 9.84 and became 74.1 ± 10.3 after 3 months (P<0.001). These findings agree with those reported by Romano et al.[14], which were explained by the decrease in NT-proBNP concentration, vasodilation, and enhanced diuresis.

Our study discovered that the implementation of S-V alters LV diastolic values in a positive direction. Conversely, no significant changes in left ventricular Ejection Fraction after three months of treatment, aligning with Qin et al.[15]. However, it is noteworthy that LVEF levels were significantly higher in the ARNI group at the six-month follow-up (p < 0.001),

The findings of our investigation showed the mitral E/A ratio was found to change from 1.1 to 0.9, which is comparable to that estimated by Romano et al. (14) who found the E/A ratio improved from 1.67 to 1.42. A similar ratio was reported by Martens et al.[16] [1.75 to 1.38] [18].

Moreover, the mitral E/$\bar{e}$ ratio improved significantly from (11.82) to (9.95) [p

<0.001]. A similar ratio was reported by Shah et al.[17]. These crucial prognostic indicators show the degree and duration of adverse remodeling of the LV, higher heart-filling pressures, and fluid accumulation. There was a significant increase in velocity with a substantial variation between the before and after results [p<0.001], from a mean of 5.79 to 7.2.

Regarding left-atrial-volume index as a parameter of diastolic function assessment, our study showed a significant decrease in volume post-treatment period (3 months) with a median decline from 36.3 to 32.95 ml/m2 [p= 0.48]. In line with our findings, Ledwidge et al.[19], who observed a decrease in atrial volume from 56.5 ± 32.8 to 48.8 ± 9.1 mL after 24 months of treatment, which is considered part of the reverse remodeling process.

### *4. Conclusion*

Sacubitril/valsartan has been shown to be a promising therapy for improving diastolic function and clinical outcomes in patients with heart failure, particularly those with HFrEF. Notably, patients with a better NYHA functional class showed the most significant improvements in diastolic echocardiographic parameters after three months of follow-up, while there was no improvement in systolic parameters during the first three months of treatment. The decrease in LV volume despite the lack of significant changes in LVEF implies that sacubitril/valsartan primarily affects LV filling pressure rather than systolic function.

## Disclosure

The authors have no financial interest to declare in relation to the content of this article.

## Authorship

All authors have a substantial contribution to the article

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## Conflicts of interest

There are no conflicts of interest.

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