Suez Canal University Medical Journal Vol. 27 (10), 2024
Pages 1-7

Role of Speckle Tracking Echocardiography in Early Detection of Left Ventricular Systolic Function Improvement in Heart Failure Patients with Reduced Ejection Fraction Taking Sacubitril/Valsartan.

Mohammed A. El Merry*, Ahmed A. Al Hawary, Khaled Abdelaziz, Mohamed A. Abdel Shafee

Department of Cardiology, Faculty of Medicine, Suez Canal university, Ismailia, Egypt.

Abstract

Background: **We investigated the early improvement signs of LV systolic functions in symptomatic patients with heart failure (HF) with reduced left ventricular ejection fraction (LVEF) at 3 months and 6 months after taking sacubitril/valsartan (S/V) therapy.** ***Materials and Methods*****: Prospective study was done on 51 HFrEF patients receiving S/V. Baseline, 3- and 6-months evaluations were performed with routine 2D echocardiography and STE. LVEF and global longitudinal strain (GLS) were measured. Predictive value of STE was compared with routine echocardiography.** ***Results: After three months, 71.1% of patients revealed LV function improvement by STE, compared to only 56.25% detected by standard 2d echo. 2d speckle tracking detected early improvement in 43.75% of patients who were not yet manifested by conventional 2d Echo. After 6 months, STE continued to identify improvement in 15.6% of patients not detected by standard echocardiography. The agreement between STE and standard echocardiography was very good (k=0.892).*** **Moreover, 28.9% of study population didn't show response to SV by STE, and also none of them showed response by standard echocardiography, indicating that STE has a very good negative predictive value.** ***Conclusion:*** **STE is effective tool in early detection of LV systolic function improvement in comparison to standard 2D echocardiography, among patients with HFrEF receiving Sacubitril/valsartan therapy.**

Keywords: HFrEF, Sacubitril/valsartan, Speckle tracking echocardiography.

Introduction

Globally, heart failure (HF) is a significant clinical and economic burden[1]. Twenty-five years ago, HF was recognized as a worldwide pandemic, and its incidence is still rising. Worldwide, 64.3 million individuals are afflicted with heart failure. According to Groenewegen et al.[2], the prevalence of heart failure in wealthy nations varies from 1% to 2% of the whole population. Regretfully, data about the prevalence of heart failure in Egypt are scarce;

*Corresponding Author: M25merry@gmail.com

yet, indications suggest that around two thirds of HF patients have acute heart failure. Furthermore, 5% was anticipated to be the hospital mortality rate[3]. Many treatment alternatives are now available to lower morbidity and death. The top four medications are mineralocorticoid receptor antagonists (MRA), beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. Recently, it has been demonstrated that a novel family of angiotensin receptor neprilysin inhibitors (ARNIs) significantly improves clinical presentations and prognosis while also reducing morbidity and mortality. One effective example of this type is sacubitril/valsartan (SV)[4]. It is clear that STE plays a significant role in the early detection of left ventricular ejection fraction dysfunction in a large number of patients, including those with diffuse large B cell lymphoma [5], non-ST segment elevation myocardial infarction [6], coronary artery disease [7], and systemic lupus erythematosus[8]. In light of this, this study was conducted with the goal of utilizing the superior characteristics of STE to identify improvements in left ventricular systolic function in HF patients receiving SV and having a reduced ejection fraction (HFrEF).

Materials and Methods

Study population

We prospectively included 51 patients with symptomatic HFrEF who were eligible for sacubitril/valsartan (S/V) treatment between February 2022 and April 2023. Other requirements for participation were not having used S/V treatment in the past and being in NYHA functional class II or III.

The American College of Cardiology/American Heart Association (2017) and the European Society of Cardiology (2016) both suggest optimum heart failure treatment for all patients. Severe decompensated heart failure patients using cardiac inotropes, LV assisted devices, or CRT; patients who were pregnant or nursing; patients who had previously experienced hypersensitivity to SV therapy or intolerance to ACEI/ARB; patients who displayed symptomatic hypotension; patients with a history of angioedema; estimated glomerular filtration rate (eGFR) less than 30 mL/min/m2; potassium concentration greater than 5.5 mmol/L; and poor quality transthoracic echocardiogram images were among the exclusion criteria. The study protocol and the informed consent were in accordance were approved by the Bioethics Committee of Suez Canal University of Medical Sciences. Following the enrollment process, the following factors were evaluated for each patient: Age, sex, BMI, and risk factors (smoking, diabetes, hypertension, dyslipidemia, and chronic kidney disease) are the baseline variables; etiology of heart failure (ischemic or non-ischemic); prior usage of ACE inhibitors or ARBs prior to sacubitril/valsartan administration. Following three and six months, the patients' NYHA class, SV dosage, and kidney function tests (sodium, potassium, urea, and serum sodium levels) were monitored.

Echocardiography

After enrollment, participants underwent 2-dimensional echocardiography at baseline and approximately 3 and 6 months,

according to the study-specific imaging protocol. During the standard transthoracic echocardiography (Philips EPIQ 7C system, USA), cine loops of three cardiac cycles were recorded for the offline analysis with an average frame rate of 56–92 frames/sec and ventricular volumes and diameters were measured according to the American Society of Echocardiography [9]. The average of three cardiac cycles was used to examine all the data. The biplane-area-length approach was utilized to ascertain the left atrium volume. In parasternal long-axis images, two-dimensional measures of the thickness of the LV wall were evaluated. LVEF was computed using the Simpson biplane technique. Peak velocities at the early (peak E) and late (peak A) diastoles, their ratio, and the E wave's deceleration duration were measured using pulsed-Doppler, with the sample volume positioned at the mitral valve leaflet tips and the aortic outflow, as indicators of the overall diastolic function of the ventricle. Ultimately, the peak early diastolic velocity (e′) on the septal portion of the mitral annulus was recorded using pulsed tissue Doppler, and the E/e′ ratio was computed. Speckle tracking echocardiography (STE): The Philips EPIQ 7C aCMQ strain package was used to do 2D speckle tracking echocardiogram. LV GLS measurements were taken from the apical views of the 2, 3, and 4 chambers. At end-systole, the endocardial boundary was manually drawn. The whole myocardial wall, from the endocardium to the myo-epicardial boundary, was tracked using an altered configuration.

Data management:

A Microsoft Excel sheet containing the patient's data was used for data entry, and version 25.0 of the Statistical Package for Social Sciences (SPSS) software was used for analysis. Probability values (P values) of less than or equal to (0.05) were deemed statistically significant (At 95% level of confidence) when statistical significance tests were employed. For quantitative variables, descriptive statistics were shown as (Means ± Standard Deviation), and for qualitative variables, as (Percent). For quantitative variables, the significance of the difference was tested using Student *t* test. The Chi square test was applied to examine relationships between qualitative variables. After gathering information on patients, physicians, and imaging studies, as well as researching the relationships between various aspects, the management outcomes were displayed in tables and graphs. Kendall's coefficient of concordance (W) used ranks to assess agreement between STE and standard Echocardiography and interpreted according to the following results:

- Poor agreement = Less than 0.20
- Fair agreement = 0.21 to 0.40
- Moderate agreement = 0.41 to 0.60
- Good agreement = 0.61 to 0.80
- Very good agreement = 0.81 to 1.00

Results

This study included 51 patients with HFrEF who started Sacubitril/valsartan. From 51 patients included, 6 patients were dropped out, with percent of drop:11.7 % due to the

following causes: one patient died, 2 patients had severe hyperkalemia K > 5.5 mg/dl, 2 patients had severe hypotension and one patient had acute kidney injury, the net number was 45 patients.

Table 1 showed that patients had mean age of (55.6±9.3 years old) ranged from 35 to 74 years old. Most of our population were males (75.6%). They had mean BSA of 1.92±0.2. 35.6% of them were ex-smokers, 33.3% were current smokers and 31.1% were non-smokers. 73.3% of patients were on ACE-I or ARBs before S/V. Most of patients (73.3%) started S/V treatment at a dose of 24/26 mg and 26.7% of patients started at 49 /51 mg. Most of our patients (64.4%) had NYHA class III, 11.2% class II and 24.4% had class IV.

Table 1: Baseline characteristics of the study patients (n=45).

Age (years)	**Mean ±SD**	**55.6±9.3**	
	Range	**35-74**	
Gender	**Male**	**34**	**75.6%**
	Female	**11**	**24.4%**
Smoking status	**Ex-smoker**	**16**	**35.6%**
	Smoker	**15**	**33.3%**
	Non smoker	**14**	**31.1%**
BSA (m2)	**Mean ±SD**	**1.92±0.2**	
	Range	**1.6-2.2**	
ACE-I or ARBs before S/V	**Yes**	**33**	**73.3%**
	No	**12**	**26.7%**
Dose of Sacubtril/Valsartan (mg)	**24 /26**	**33**	**73.3%**
	49 /51	**12**	**26.7%**
NYHA class	**II**	**5**	**11.2%**
	III	**29**	**64.4%**
	IV	**11**	**24.4%**

Quantitative variables were expressed as mean±SD, while qualitative variables were expressed as numbers and percentages

BSA; body surface area, ACE-I; angiotensin-converting enzyme inhibitor, ARBs; Angiotensin receptor blockers, SV; Sacubtril/Valsartan, NYHA; New York Heart Association.

In figure 1, patients had statistically significant increase in LVEF, at 3 and 6 months of follow-up as p<0.001, while had statistically significant decrease in LVESVI, LVEDVI, LA volume, E/A and E/ e' at 3 and 6 months of follow-up as p<0.05.

also, patients had statistically significant increase in LVGLS, at 3 and 6 months of follow-up as p<0.001.

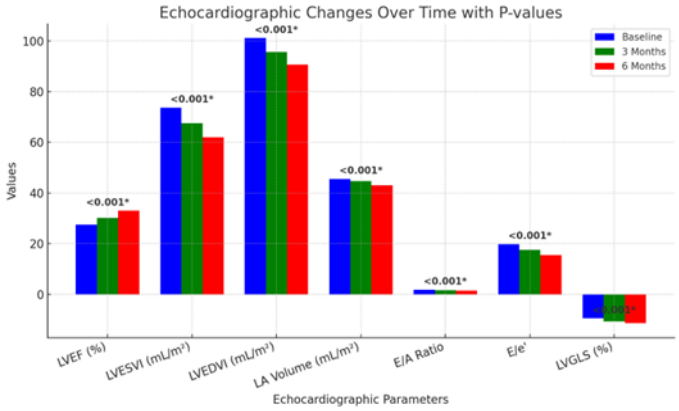

Figure 1: Significant improvements in key echocardiographic parameters over time, indicating reverse cardiac remodeling and improved cardiac function

In table 2, After three months of follow up, 71.1% of all study population showed LV systolic function improvement by STE. From them, only 56.25% showed LV systolic function improvement by Standard echocardiography, while STE detected LV systolic function improvement earlier than Standard Echocardiography in 43.75%. After six months of follow up, STE detected LV systolic function improvement, that was not detected by Standard echocardiography in 15.6% of patients who showed response to SV, with very good agreement between STE and standard echocardiography (k=0.892). 28.9% of study population didn't show response to SV by STE, and also none of them showed response by standard

echocardiography, indicating that STE has a very good negative predictive value.

Table 2: Comparison of LV Function Improvement Detected by Standard 2D Echocardiography and Speckle Tracking Echocardiography (STE) at 3 and 6 Months

Time Point	Method	Responder	Non-Responder	Total	Kendall's Coefficient
At 3 Months	**Standard 2D Echo (LVEF)**	18 (56.25%)	14 (43.75%)	32 (100%)	0.710
	STE (GLS)	32 (71.1%)	13 (28.9%)	45 (100%)	
At 6 Months	**Standard 2D Echo (LVEF)**	27 (84.4%)	5 (15.6%)	32 (100%)	0.892
	STE (GLS)	32 (71.1%)	13 (28.9%)	45 (100%)	

1. **At 3 Months:**
   - **Standard 2D Echo (LVEF):** Detected improvement in **56.25%** of patients.
   - **STE (GLS):** Detected improvement in **71.1%** of patients, including **43.75%** not detected by standard 2D Echo.
   - **Agreement (Kendall's Coefficient):** 0.710, indicating good agreement between methods.
2. **At 6 Months:**
   - **Standard 2D Echo (LVEF):** Detected improvement in **84.4%** of patients.
   - **STE (GLS):** Continued to identify improvement in **15.6%** of patients not detected by standard 2D Echo.
   - **Agreement (Kendall's Coefficient):** 0.892, indicating very good agreement between methods.
3. **Non-Responders:**
   - **28.9%** of patients did not show improvement by STE, and none of these showed improvement by standard 2D Echo, highlighting STE's strong negative predictive value.

Discussion

An objective assessment of left ventricular systolic function and the early identification of improvement with prognostic value in various clinical entities have been made possible by the use of 2D STE in the assessment of patients with HF with reduced ejection fraction (HFrEF)[10]. Therefore, the purpose of this study was to demonstrate the effectiveness of STE in the early identification of improved left ventricular systolic function in HF patients receiving SV and having a decreased ejection fraction (HFrEF). Forty-five HFrEF patients who got sacubitril/valsartan therapy were included in this research. The starting dose of sacubitril/valsartan treatment was 24/26 mg twice day for 33 patients (73.3%), and 49/51 mg twice day for 12 patients (26.7%). At the three-month mark, 97/103 mg were being taken twice daily by 7 patients (15.5%), 24/26 mg by 17 patients (37.8%), and 49/51 mg by 21 patients (46.7%). At the six-month mark, 97/103 mg were being taken twice daily by 14 patients (31.1%), 24/26 mg by 12 patients (26.7%), and 49/51 mg by 19 patients (42.2%). At 3 and 6 months of follow-up, patients in the current research showed a statistically significant rise in LVEF ($p<0.001$), whereas there was a statistically significant decrease in LVESVI, LVEDVI, LA volume, E/A, and E/e' ($p<0.05$). At three and six months of follow-up, patients experienced a statistically significant rise in LVGLS ($p<0.001$). Previous studies have shown that sacubitril/valsartan promotes early LV reversal remodeling in

chronic HFrEF patients using TTE assessment, including GLS, LV twist, and rotation[11,12]. At three months, 32 patients in the current trial demonstrated response by GLS; of them, 18 patients (56.25%) showed improvement by LVEF, and 14 patients (43.75%) had early detection of improvement by STE, with good agreement between STE and standard echo (k=0.710). This study has similarities to another one in that it proposed the use of STE parameters as a useful tool to evaluate the subclinical response to sacubitril/valsartan medication and potentially act as a treatment guide for patients with HFrEF. However, because myocardial strain indices and LVEF are largely load dependent, it may be difficult to consistently use these measurements to assess the improvement in LV contractility after a new HFrEF therapy. Another recently created dynamic STE technique, cardiac work, may also be useful in determining treatment response[13]. According to a different study, GLS is a sensitive technique for evaluating early on how pharmacological therapies, such sacubitril/valsartan, affect favorable left ventricular remodeling. According to Mazzetti et al.[14], the conventional ultrasonography data did not show a statistically significant improvement in GLS until six months following the follow-up. In contrast, the improvement in GLS was statistically significant after three months. We are able to detect modest but meaningful improvements in left ventricular function more quickly after initiating SV treatment. In actuality, GLS improved dramatically after three months, during which time the volumes and LVEF, while showing a positive tendency, only slightly fluctuated. Because of this, there are concerns about the use of strain imaging in relation to its acceptance as a tool for more accurate risk assessment and thorough phenotyping, as well as a crucial component in the staging and phenotyping of HF beyond EF, which can have a positive effect on major cardiovascular outcomes. Notwithstanding the positive outcomes reported, the current investigation is subject to many limitations. Specifically, the study's observational design and absence of a control group preclude a direct comparison of SV's and other medications' effects on left ventricular systolic performance. Moreover, the foregoing issues are particularly addressed in our analysis of GLS at three time periods, and the findings indicate that the improvements observed in GLS are probably caused by SV. On our patient sample, however, we cannot completely exclude out a little Hawthorne effect. These results would need to be confirmed in bigger studies for a detailed head-to-head comparison of the subgroups, notably nonischemic HFrEF patients against ischemic HFrEF patients.

Conclusion

STE demonstrate a potential role in early detection of left ventricular systolic function improvement, in comparison to standard echocardiography, among patients with HF with reduced ejection fraction (HFrEF) who are receiving Sacubitril/valsartan.

References

1. Lippi G, Sanchis-Gomar F. Global epidemiology and future trends of heart failure. AME Med J [Internet]. 2020;5:15.
2. Gregorietti V, Fernandez TL, Costa D, Chahla EO, Daniele AJ. Use of Sacubitril/valsartan in patients with cardio toxicity and heart failure due to chemotherapy. Cardio-oncology (London, England) [Internet]. 2020 Nov 5;6(1):24.
3. Hassanin A, Hassanein M, Bendary A, Maksoud MA. Demographics, clinical characteristics, and outcomes among hospitalized heart failure patients across different regions of Egypt. Egypt Hear J Off Bull Egypt Soc Cardiol [Internet]. 2020 Aug 13;72(1):49.
4. Landolfo M, Piani F, Esposti DD, Cosentino E, Bacchelli S, Dormi A, Borghi C. Effects of sacubitril valsartan on clinical and echocardiographic parameters of outpatients with heart failure and reduced ejection fraction. Int J Cardiol Hear Vasc [Internet]. 2020 Oct 22;31:100656.
5. Wang B, Yu Y, Zhang Y, Hao X, Zhao H, Yang S, et al. Speckle tracking echocardiography in the early detection and prediction of anthracycline cardiotoxicity in diffuse large B-cell lymphoma treated with (R)-CHOP regimen. Echocardiography [Internet]. 2020;37(3):421–8.
6. Keddeas VW, Swelim SM, Selim GK. Role of 2D speckle tracking echocardiography in predicting acute coronary occlusion in patients with non ST-segment elevation myocardial infarction. Egypt Hear J Off Bull Egypt Soc Cardiol [Internet]. 2016/11/01. 2017 Jun;69(2):103–10.
7. Pastore MC, Mandoli GE, Contorni F, Cavigli L, Focardi M, D'Ascenzi F, et al. Speckle Tracking Echocardiography: Early Predictor of Diagnosis and Prognosis in Coronary Artery Disease. Biomed Res Int [Internet]. 2021 Feb 2;2021:6685378.
8. Farag SI, Bastawisy RB, Hamouda MA, Hassib WA, Wahdan HA. Value of Speckle Tracking Echocardiography for Early Detection of Left Ventricular Dysfunction in Patients with Systemic Lupus Erythematosus. J Cardiovasc Echogr [Internet]. 2020/11/09. 2020;30(3):140–5.
9. Doherty JU, Kort S, Mehran R, Schoenhagen P, Soman P. ACC/AATS/AHA/ASE/ASNC/HRS/SCAI/SCCT/ SCMR/STS 2019 Appropriate Use Criteria for Multimodality Imaging in the Assessment of Cardiac Structure and Function in Nonvalvular Heart Disease. J Nucl Cardiol [Internet]. 2019;26(4):1392–413.
10. Desai AS, Solomon SD, Shah AM, Claggett BL, Fang JC, Izzo J, et al. Effect of Sacubitril-Valsartan vs Enalapril on Aortic Stiffness in Patients With Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. JAMA [Internet]. 2019 Sep 17;322(11):1077–84.
11. Januzzi Jr JL, Ahmad T, Mulder H, Coles A, Anstrom KJ, Adams KF, et al. Natriuretic Peptide Response and Outcomes in Chronic Heart Failure With Reduced Ejection Fraction. J Am Coll Cardiol [Internet]. 2019 Sep 3;74(9):1205–17.
12. Januzzi Jr JL, Prescott MF, Butler J, Felker GM, Maisel AS, McCague K, et al. Association of Change in N-Terminal Pro-B-Type Natriuretic Peptide Following Initiation of Sacubitril-Valsartan Treatment With Cardiac Structure and Function in Patients With Heart Failure With Reduced Ejection Fraction. JAMA [Internet]. 2019 Sep 17;322(11):1085–95.
13. Brás PG, Gonçalves AV, Branco LM, Moreira RI, Pereira-da-Silva T, Galrinho A, et al. Sacubitril/Valsartan Improves Left Atrial and Ventricular Strain and Strain Rate in Patients with Heart Failure with Reduced Ejection Fraction. Life. 2023;13(4):995.
14. Mazzetti S, Scifo C, Abete R, Margonato D, Chioffi M, Rossi J, et al. Short-term echocardiographic evaluation by global longitudinal strain in patients with heart failure treated with sacubitril/valsartan. ESC Hear Fail. 2020;7(3):964–72.