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Effects of Sacubitril/Valsartan treatment on left ventricular myocardial torsion mechanics in heart failure reduced ejection fraction patients,2D speckle tracking imaging.

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Abstract

Background: Left ventricular ejection fraction (LVEF) is calculated from volumetric change without representing true myocardial properties. Strain echocardiography has been used to objectively measure myocardial deformation. Myocardial strain can give accurate information about intrinsic myocardial function, and it can be used to detect early-stage cardiovascular diseases, monitor myocardial changes with specific therapies, differentiate cardiomyopathies, and predict the prognosis of several cardiovascular diseases. Sacubitril/Valsartan has been shown to improve mortality and reduce hospitalizations in patients with heart failure with reduced ejection fraction (HFrEF). The effect of Sacubitril/Valsartan on LV ejection fraction (EF) and torsion dynamics in HFrEF patients have not been previously described. Results: ARNI group of patients showed improvement of symptoms, LVGLS% and diastolic parameters including, E/A, E/e', TV, untwist onset and rate after 6 months of therapy in comparison to the traditionally treated patients. The improvement continued for 11 months with in additional significant improvement of systolic parameters in the form of LVGLS%, EF%, Twist, Apical and basal rotations, main dependent parameters for improvement of EF% was LVGLS% and Apical rotation. Conclusion: To our knowledge this is the first study to demonstrate that therapy with Sacubitril/Valsartan in HFrEF patients could create a state of gradual and chronic LV deloading which cause relieving of myocardial wall tensions and decreasing the LV end diastolic pressure this state could cause cardiac reverse remodeling and reestablishment of starling forces proprieties of LV myocardium, which lead to increase of LV ejection fraction.

Type of manuscript: Research.

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Ethical declaration :

Ethics approval and consent to participate.

Human Institutional Ethics Committee (IEC) of Menoufia University, Shebein el koom, Egypt, approved the study protocol. And was performed in accordance with the Declaration of Helsinki and the code of Good Clinical Practice. All patients provided written informed consent to participate after a full explanation of the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Contributions:

This work was carried out in collaboration between all authors. Author Wassam el din el shafey carried out the data collection and echocardiographic studies, wrote the first draft of the manuscript, and managed the literature searches with the contribution of author Emad Ali Al Khoufi. Authors Wassam el din el shafey did final editing of the manuscript and data analysis. Author Emad Ali Al Khoufi helped in literature retrieval and data analysis. All authors have read and approved the final manuscript.

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Abstract

Background:

Left ventricular ejection fraction (LVEF) is calculated from volumetric change without representing true myocardial properties. Strain echocardiography has been used to objectively measure myocardial deformation. Myocardial strain can give accurate information about intrinsic myocardial function, and it can be used to detect early-stage cardiovascular diseases, monitor myocardial changes with specific therapies, differentiate cardiomyopathies, and predict the prognosis of several cardiovascular diseases. Sacubitril/Valsartan has been shown to improve mortality and reduce hospitalizations in patients with heart failure with reduced ejection fraction (HFrEF). The effect of Sacubitril/Valsartan on LV ejection fraction (EF) and torsion dynamics in HFrEF patients have not been previously described.

Results: ARNI group of patients showed improvement of symptoms, LVGLS% and diastolic parameters including, E/A, E/e', TV, untwist onset and rate after 6 months of therapy in comparison to the traditionally treated patients. The improvement continued for 11 months with in additional significant improvement of systolic parameters in the form of LVGLS%, EF%, Twist, Apical and basal rotations, main dependent parameters for improvement of EF% was LVGLS% and Apical rotation.

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Conclusion: To our knowledge this is the first study to demonstrate that therapy with Sacubitril/Valsartan in HFrEF patients could create a state of gradual and chronic LV deloading which cause relieving of myocardial wall tensions and decreasing the LV end diastolic pressure this state could cause cardiac reverse remodeling and reestablishment of starling forces proprieties of LV myocardium, which lead to increase of LV ejection fraction.

Background:

Left ventricular systolic function assessment is the cornerstone of an echocardiographic examination. LV ejection fraction LVEF is the most commonly employed. It results from the combined action of basal and apical rotation, longitudinal and circumferential contraction and radial thickening. However, LVEF has many limitations; some of them related to the definition itself and others to imaging techniques (1, 2).

The characteristic double helical structure of myocardial fibers results in systolic rotation of the base and apex of the LV in opposite directions along its longitudinal axis, and the algebraic subtraction of this rotation causes LV twist. Due to this muscular movement, the base of the LV moves towards the apex, producing a longitudinal LV shortening (3). Therefore, systolic ventricular contraction results from the combined and simultaneous action of twisting and shortening of LV (Myocardial torsion) which is a fundamental component of cardiac function (4, 5).

Speckle tracking echocardiography (6) (STE) is a useful echocardiographic tool for evaluating myocardial function, due its high spatial and temporal resolution, good intra and interobserver reproducibility (7) , being independent of the insonation angle (8) and it is not affected by translational movements of the heart. It also employed in assessing the torsion mechanics including twist and untwist which has emerged as novel reliable quantitative parameters for the assessment of LV function. Twist and rotational parameters may contribute useful comprehensive information beyond the conventional indices of LV function. (9) Our aim in this study is to assess the effect of Sacubitril/Valsartan on the myocardial mechanics of the left ventricle in HFrEF patients.

2. Methods

2.1. Subjects

The study involved 73 patients with HFrEF where they were randomly assigned into two matched groups. Group (1) including 37 patients with traditional treatment of heart failure and the other group (2) including 36 patients were treated with ARNI plus other evidenced based medical treatments. Along the course of the study, 12 patients failed to be followed up. So the final number of cases in the study who succeeded to be followed up to 11 months were group (1) was 27 cases and group (2) was 34 cases, Full history was taken, and full clinical examination was done. Baseline vital signs, ECG, NYHA classification, conventional echocardiography and STE were done at baseline study and after 6 and 9 months.

Inclusion Criteria:

1. Written informed consent must be obtained before any assessment was performed.
2. Men and women [?] 18 years of age.
3. LVEF [?] 40% subjects who were candidates for on-label sacubitril/valsartan treatment per standard of care.
4. New York Heart Association (NYHA) Functional class II-IV.
5. LVEF [?] 40% via any local measurement within the past 6 months using echocardiography. If a subject was on a loop diuretic, they must be on a stable dose for 2 weeks prior to baseline.

Exclusion Criteria:

1. Pregnant or nursing women.
2. History of hypersensitivity to any of the study drugs.
3. History of angioedema drug related or otherwise.

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4. Subjects with a heart transplant or ventricular assistance device (VAD) or intent to transplant (on transplant list) or implant a VAD.
5. Subjects with a cardio resynchronization therapy device (CRT/CRT-D) implanted within 6 months of screening visit.
6. Subjects who were currently taking inotropic agents.
7. Bile acid sequestering agents such as cholestyramine or colestipol were prohibited to avoid interference with study drug absorption.
8. Any hospital admission/discharge related to heart failure within 2 weeks prior to baseline.
9. The use of outpatient or inpatient i.v. diuretic therapy within 2 weeks prior to baseline.
10. Potassium > 5.2 mEq/L at screening.

2.2. Ethical clearance

The local ethics committee of the hosted University approved the study protocol and written consent was obtained from the patients.

2.3. Study Period

The patients on this study were followed up during the period from February 2019 to the end of December 2019.

2.4. Standard echo-Doppler study:

Standard echo-Doppler was performed using a Vivid E9 ultrasound system (GE Vingmed Ultrasound AS, Horten, Norway). Cine-loops were recorded on DVDs for offline analysis (EchoPAC PC 6.0.0, GE Medical Systems). All the measurements were analysed taking the average of three cardiac cycles. LV diameter and wall thickness were measured according to the criteria of the American Society of Echocardiography. (10)

Left atrium (LA) volume was determined by the biplane-area-length method.(11) Two-dimensional measurements of LV wall thickness were assessed in four segments (anterior and posterior interventricular septum, inferior, and antero-lateral walls) at the mitral valve, papillary muscles and apical levels by parasternal short-axis views. In addition, LV EF was calculated by the Simpson biplane method. (12) As measures of global LV diastolic function peak velocities at the early (peak E) and late (peak A) diastole, their ratio, deceleration time of the E wave and isovolumic relaxation time (IVRT) were assessed by pulsed-Doppler with the sample volume placed at the mitral valve leaflet tips and at the aortic outflow. (13) Finally, by pulsed tissue Doppler, peak early diastolic velocity on the septal part of the mitral annulus was measured (E') and E/E' ratio was calculated.

2.5. Speckle tracking imaging study:

For the STI study, the second-harmonic B-mode images of apical (4-chamber, 2-chamber, and 3-chamber) and short-axis (at the mitral valve and apical level) views were obtained. The LV endocardial border was manually traced at the end-systolic frame and a speckle-tracking region of interest was automatically selected. The width of the region of interest was adjusted as necessary to accommodate the total thickness of the LV wall. The computer automatically tracked stable objects in each frame using the sum of absolute differences algorithm. After these steps, the workstation computed and generated strain curves. For assessment of LV rotational mechanics through scanning and recording from left para-sternal short-axis view of both basal and apical short-axis planes to quantify basal and apical LV rotations using the same probe, with a frequency range 1.7–2.0MHz at a high frame rate (range: 80–115 frame/s).

The basal level was marked as the plane showing the tips of mitral valve leaflets at its center with full-thickness myocardium surrounding the mitral valve. Then the transducer was positioned one or two intercostal spaces more caudal and slightly lateral from the basal site to be perpendicular to the apical imaging plane (14). The apical level was defined just proximal to the level of LV apical luminal obliteration at the end-systole. The cross-section must be as circular as possible. We must pay careful attention to ensure that full thickness of myocardium is imaged throughout the cardiac cycle.

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To analyze twist and untwist parameters, from the basal and apical short axis, data set with a well-defined endo-cardial border and the regions of interest were adjusted to include all myocardial thickness without including the pericardium. The endocardial borders of both basal and short axis planes were manually traced and subsequently tracked by the software. If poor tracking quality was observed, the region of interest was readjusted until acceptable tracking was obtained. After processing, curves of basal and apical LV rotation, twist, twist rate, and untwist rate were automatically generated by the software (Excel; Microsoft Corporation, Redmond, Washington, USA). Twist was calculated as apical rotation relative to the basal rotation, with counterclockwise rotation as viewed from LV apex expressed as positive value and clockwise rotation as a negative value. Peak LV twist, peak LV twist rate (as first positive peak after R wave on ECG), and peak LV untwist rate (as the first negative peak after aortic valve closure) were recorded. Cardiac cycle length was measured as R–R interval. Time to peak twist rate was measured as time from R wave to peak twist rate, and time to peak untwist rate was measured as time from R wave to peak untwist rate.

2.6. Statistical Analysis:

Data were analyzed using Statistical Program for Social Science (SPSS) version 22.0 for windows (SPSS Inc., Chicago, IL, USA). Quantitative data of normal distribution were expressed as mean $\pm$ standard deviation (SD). Qualitative data were expressed as frequency and percentage. Independent-samples t-test of significance was used when comparing between two means of normally distributed data. Pearson correlation was used to measure the association between two quantitative variables. Multivariable regression analysis is used to predict values of one variable based on two or more other variables. The purpose of the test is to determine whether there is statistical evidence that the mean difference between paired observations on a particular outcome is significantly different from zero. Probability (p-value): p-value$<$ 0.05 was considered significant, p-value$<$ 0.001 was considered as highly significant and p-value $>$0.05 was considered insignificant.

Results:

Our prospective study basically included 73 patients diagnosed as HFrEF based on conventional echocardiography study at the outpatient clinic of Menoufia university hospital, a total of 12 cases were excluded during the workflow of the follow ups either because of three cases missed connections, four cases developed severe renal impairment and CKD, three cases were uninterested to continue follow up, and four cases died of sudden cardiac death. Sixty-one patients succeeded to complete the time table of the study, 34 cases were treated by ARNI (ARNI group) and 27 cases were treated by traditional therapy (Traditional group), data reveled that at baseline there were no significant difference in between the traditionally treated and ARNI treated groups regarding basic characteristics, demographic data, symptoms, conventional and STE echocardiographic measurements. (Table.1)

After 6 months, both groups recalled doing the first follow up and there were remarkable differences in symptoms, conventional and STE echocardiography data (Table.2) there were very high statistically significant improvement in diastolic parameters either conventional E/A, E/e', Tricuspid velocity or STE specifically untwist parameters (Untwist onset, and rate).while the ejection fraction and global LV longitudinal strain showed also improvement. For the final recall after 11 months, the data showed exponential improvement for both diastolic and systolic parameters with very high statistically significant improvement of untwist and twist parameters with remarkable improvement of ejection in the ARNI group versus the traditionally treated patients. (Table.3)

On another hand to show the pattern of temporal effect of ARNI therapy among the ARNI group itself we made comparisons between the ARNI group at different follow-ups and it also showed exponential improvement from baseline, 6 months and 11 months follow up with maximal improvement of untwist parameters, twist and ejection fraction after 11 months of follow up. (Table.4, 5)

As regard the ejection fraction of the ARNI group after 11 months it was positively correlated with LV-GLS, Twist, Apical rotation, and negatively correlated with Untwist onset, and rate and basal rotation. (Table.6)(Figures1, 2, 3 and 4)

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From all of these variables the only dependent variables for the improvement of EF% was the LVGLS, and Apical rotation. (Table.7)

As regard the prevalence of systemic hypertension in ARNI group it was (22cases from 34 ARNI treated patients (64%), we did comparison between baseline and 11 months follow up, data showed highly significant improvements in untwist and twist parameters, LVGLS% and EF% in comparison to the weaker however significant improvements in the normotensive group (12 cases).(Table.8,9)

Discussion:

The sound evaluation of cardiac function plays a crucial role in diagnosing cardiovascular diseases, initiating specific therapeutic interventions, monitoring treatment, and determining the prognosis of a variety of cardiovascular conditions. Echocardiography can provide valuable information about the anatomy and function of the heart. (15, 16) Left ventricular ejection fraction (LVEF) provides objective information about left ventricular (LV) systolic function. It has been used to diagnose and classify heart failure (HF),(17,18),determine the suitability of device therapy,(17,19) decide interventions for valvular heart diseases (VHDs),(20,21) determine the need for specific medications,(19) and predict prognosis.(22) However, LVEF is a volumetric parameter with ventricular load-dependence and had limitations such as significant inter- and intra-observer variability and geometric assumptions.(23) Moreover, LVEF does not represent intrinsic myocardial properties.

Strain is a dimensionless index of a change in length between 2 points before and after movement. Strain echocardiography was introduced to the clinical field about 20 years ago, making it a relatively new echocardiographic modality that can measure myocardial deformation. Unlike LVEF, myocardial strain, as calculated by strain echocardiography, can afford indices of regional and global myocardial systolic function noninvasively and objectively. (24)

Strain echocardiography has been used to diagnose subclinical disease states, (25, 26) monitor changes in myocardial function with specific therapies, (27) differentiate cardiomyopathies, (28) and predict the prognosis of several cardiovascular diseases independently of LVEF. (29, 30)

Although the physiological mechanisms of action of Sacubitril/Valsartan are well described, its effects on left ventricular remodeling and left ventricular ejection fraction (LVEF) have not been well studied. Left ventricular remodeling is a major mechanism underlying disease progression in patients with HFrEF (31). The degree of improvement in left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), LV dimensions, and LVEF with therapies are strongly correlated with clinical outcomes, including survival (32).

In the current study, we demonstrated that after 6 months of follow up on the ARNI treated group of patients the symptoms of congestion and dyspnea was remarkably improved this is accompanied with the improvement of diastolic indices that might be explained by a chronic state of LV deloading and reduction of LV end diastolic pressure indexed by the reduction of the tricuspid flow velocity, E/A , E/e' also that could help in the initial improvement of LV global longitudinal strain which indicating that the maximized stretch of LV myocardium and wall tension are reduced with restoration of myocardial starling's forces and this state prepare the LV myocardium recovering the global longitudinal strain. Beta-blockers, ACEi/ARBs, and MRAs have demonstrated potent effects on reverse remodeling and improvement in LVEF in multiple studies (33-36) Animal studies have shown that treatment with Sacubitril/Valsartan compared to Valsartan alone is associated with a statistically significant increase in LVEF and a trend towards improved reverse remodeling (37).

Heart failure has recently been classified according to alterations in the mechanical function of the LV (38). After having observed anomalous specific patterns of ventricular myocardial mechanics in different subsets of patients with heart failure, an alternative approach has been proposed for its characterization (38, 39). Accordingly, heart failure can be classified into three large subgroups: A) Predominant longitudinal dysfunction; B). Transmural dysfunction (longitudinal and circumferential); and C). Predominant circumferential dysfunction. This classification is based on the orientation of the myocardial fibers of the LV, which are arranged obliquely in a double helix shape. Endocardial fibers, which are aligned in a parallel fashion to the LV long axis, are mainly associated with longitudinal mechanics, while transmural fibers are mainly responsible for circumferential mechanics (40). The action of the latter is predominant due to its greater radius of action.

In the case of systolic dysfunction, twist serves as a compensatory mechanism, and the more its reduction the more advanced stage of the disease. In the dilated left ventricle, the fiber muscles in both layers are stretched and oriented more circumferentially, which leads to additional reduction in chamber contractility and torsion (41, 42). Thus, twist and torsion may be a sensitive marker of remodeling of LV wall architecture, useful in the monitoring of disease progression and response to therapy.

The last follow up of our patients groups after eleven months there were a lot of data that strongly supports the idea of the effect of Sacubitril/Valsartan of LV ejection fraction, and reverse myocardial remodeling which might go in agreement with the PROVE-HF trial (43), where the investigators stated that "although improvement in cardiac structure and function was present at six months, at 12 months, further improvement in LVEF and volumes was present, with 25 percent of the study participants experiencing an absolute LVEF increase of more than 13 percent". In that trail they depend on changes in LV end systolic, diastolic and left atrial volumes, but in our study we choose a more precise STE deformational parameters, which had a more sensitive predictive values and accuracy, where we demonstrated that at eleven months most of the torsion mechanics and LV global longitudinal strain consequently LV ejection fraction in addition to the diastolic parameters as untwist rate and onset, that means systolic functional improvement and LV recovery.

Conclusion:

To our knowledge, this is the first study to demonstrate clear recovery of untwist and twist mechanics, global longitudinal strain and LV ejection fraction in HFrEF patients under eleven months therapy of Sacubitril/Valsartan that effect which might be explained by a state of chronic deloading with reduction of LV end diastolic pressure which consequently helps in restoration of starling's forces with recovery of LV geometry that lead finally to the improvement of myocardial performance.

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