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Three-Dimensional Speckle Echocardiography Versus 2-D Speckle Echocardiography And Conventional Echocardiography For Evaluation Of Subclinical LV Myocardial Dysfunction In Rheumatoid Arthritis Patients

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Abstract

Background: *Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory illness marked by painful, swollen joints which can severely impair physical function and quality of life.*

Aim: *To compare Three-Dimensional Speckle Tracking Echocardiography (3DSTE) Versus 2-D Speckle Tracking Echocardiography (2DSTE) and Conventional Echocardiography for Evaluation of Subclinical LV Myocardial Dysfunction in Rheumatoid Arthritis Cases.*

Patients and methods: *This was a Cross-sectional research in which rheumatoid arthritis cases and matched healthy controls have been evaluated utilizing different types of Echocardiography modalities. The study included cases with rheumatoid arthritis (N = 100) attending the rheumatology clinic, Al-Azhar University Hospital for routine follow up. All the cases selected were known cases of rheumatoid arthritis and none of them in their active episodes. Healthy individual matched to the patients on the basis of age and sex (N = 100) were also included for comparison.*

Results: *Conventional EF showed no difference between groups, but RA patients had larger LV volumes ($p<0.001$) and reduced 2D/3D strains (all $p<0.001$). 3D-LVEF was reduced compared to 2D-LVEF in both groups (p-value below 0.001). 3D volumes exceeded 2D volumes ($p<0.001$). Strong association existed among 2D-GLS and 3D-GLS ($r=0.74$, p-value below 0.001), but weaker for GCS/GRS.*

Conclusion: *3DSTE detects subclinical LV dysfunction in RA more reliably than conventional methods, offering superior sensitivity over 2DSTE for strain assessment.*

Keywords: *Rheumatoid Arthritis, Three-Dimensional Speckle Echocardiography, 2-D Speckle Echocardiography, Conventional Echocardiography*

1. INTRODUCTION

Rheumatoid arthritis is a chronic, systemic autoimmune inflammatory illness marked by painful, swollen joints which can severely impair physical function and quality of life. It is more prevalent in females and can happen at any age; highest frequency is between ages fifty to sixty years (1).

Certain cases with rheumatoid arthritis may present or later develop extra-articular manifestations in other organs (occasionally without clear articular involvement), like pleural effusion, interstitial lung disease, or bronchiectasis. CV manifestations of RA may include coronary and peripheral vascular disease (PVD), pericarditis, premature atherosclerosis, valvular defects, pericardial effusion, conduction defects, myocarditis, arrhythmia, HF especially with preserved ejection fraction (HFrEF), and cardiac nodules. CV manifestations may serve as the initial presentation of a rheumatic condition. Whereas the CV manifestations can be clinically silent, they can substantially elevate morbidity and death, necessitating early identification and management (2,3).

Speckle tracking echocardiography (STE) has been used to evaluate the global longitudinal strain (GLS) of left ventricle (LV), to identify subclinical systolic dysfunction. GLS indicates the average strain of the myocardial segments in a longitudinal direction. It has more reproducibility; can detect subclinical left ventricle dysfunction, and is regarded as a superior predictor of possibility compared to left ventricle ejection fraction. STE has been used for the identification of subtle myocardial damage, obtaining an early diagnosis of cardiac impairment (4).

two-dimensional speckle tracking echocardiography offered a more sensitive instrument for the evaluation of early myocardial dysfunction through assessment of myocardial strain (5). Although global longitudinal strain gives the ideal diagnostic and prognostic data, radial and circumferential strain could also be helpful for assessing global and regional active left ventricle deformation (6).

3DSTE is an advanced imaging method developed for the investigation of LV myocardial deformation utilizing three-dimensional information sets. Three-dimensional speckle tracking echocardiography has the potential to address certain intrinsic restrictions of two-dimensional speckle tracking echocardiography in evaluating complicated left ventricular myocardial mechanics, providing further deformation variables (like area strain) and a complete quantitation of left ventricular geometry and function from a single three-dimensional acquisition. This method has given novel insights into left ventricular mechanics across various clinical fields, like the objective evaluation of global and regional left ventricular function in both non-ischemic and ischemic cardiac illnesses, the assessment of left ventricular mechanical dyssynchrony, and the identification of subclinical cardiac dysfunction in cardiovascular diseases at possibility of development to overt HF. (7,8).

Our research aimed to compare Three-Dimensional Speckle Tracking Echocardiography Versus 2-D Speckle Tracking Echocardiography and Conventional Echocardiography for Evaluation of Subclinical LV Myocardial Dysfunction in Rheumatoid Arthritis Cases.

2. PATIENTS AND METHODS

This was a Cross-sectional research in which rheumatoid arthritis cases and matched healthy controls have been evaluated utilizing different types of Echocardiography modalities. The study included cases with rheumatoid arthritis (N = 100) attending the rheumatology clinic, Al-Azhar University Hospital for routine follow up. All the cases selected were known cases of rheumatoid arthritis and none of them in their active episodes. Rheumatoid arthritis patients were diagnosed according to ACR / EULAR diagnostic criteria for RA classification (9). Healthy individual matched to the patients on the basis of age and sex (N = 100) were also included for comparison.

Exclusion criteria: Patients with Type I and II diabetes, previous history or clinical evidence of cardiovascular diseases, percutaneous coronary intervention (PCI), myocardial infarction (MI) or coronary artery bypass grafting (CABG) and patient with hypertension, patient with heart failure syndromes, cases with severe valvular heart illness and cases with established ischemic heart illness, cases with congenital heart disease, patient with chronic kidney illness, and chronic liver illness, thyroid illness, patient with persistent arrhythmia or frequent extra systole and smoking

Sample size: The sample size has been estimated using the Open-Epi online calculator (version 3.3a, Open-Epi, Atlanta, GA, United States of America). The mean difference equation was used. According to Khana et al. (10) study, the left ventricular global longitudinal strain (LVGLS) was -17.36±1.4 in rheumatoid arthritis patients and -19.96± 2 in controls. Considering a type, I error 5% and power of eighty percent, when the confidence interval was ninety-five percent and when the ratio of Group 1 to Group II was equal to 1, the calculated sample size of 30 in each group has been needed with attrition calculated 10%, we collected 100 persons in each group.

Methods:

All patients have been exposed to the following:

Full history taking: from all cases, involving Age, Name, gender, alcohol intake, smoking, diabetes mellitus, hypertension, cerebrovascular stroke, drugs, peripheral artery disease, cardiac history and family history, **full clinical examination:** with special emphasis on the following information: Pulse: rhythm and rate, neck and head investigation, blood pressure, lower and upper limb investigation, heart and chest investigation and **Twelve-lead electrocardiogram (ECG):** 12-lead ECG were obtained from all participants.

Trans-Thoracic Echocardiography: Echocardiographic and Doppler studies have been conducted for all cases. Cases have been examined at left lateral decubitus position. Full views involving parasternal short axis view (PSAX), parasternal long axis view (PLAX), Apical 2,3,4,5 chambers view, subcostal view were obtained for 2D assessment of LV and ejection fraction has been evaluated using M-Mode of PLAX view and Simpson's method, diastolic function has been evaluated utilizing pulsed wave doppler of mitral flow and tissue doppler imaging.

Two-dimensional Speckle Tracking Echocardiography: for measurement of LV-GLS: Following enhancing image quality, increasing frame rate > 60 fps, and reducing foreshortening, all of which are essential for reducing measurement variability. Global longitudinal strain measurements have been attained in the 3 standard apical views and averaged. Measurements began with the apical long-axis view to observe the closure of the aortic valve, utilizing opening and closing clicks of the aortic valve or aortic valve opening and closing on M-mode imaging (Lang et al., 2015).

Three-dimensional Speckle Tracking Echocardiography: 3D echocardiography was conducted, left ventricle ejection fraction has been determined automatically utilizing 4D Auto LVQ, 4 beats acquisition were obtained for further offline data analysis. Offline analysis was performed by workstation equipped with the 4D Auto LVQ package (Echo PAC v.110.1.3; GE Healthcare). Automatic detection the LV cavity and endocardial border were used unless it has been judged as imprecise by the examiner. In this case, borders have been manually adjusted in multiplanar layout (three apical and three transverse planes) followed by secondary automated refinement. Offline analysis was used to calculate the LV volumes, LVEF and the strain variables as global peak systolic strain, GLS, and GAS of the LV.

Ethical Consideration

The whole procedures of blood sampling, ECG and echocardiography were explained thoroughly to the participants. Written consent has been taken from all patients involved in the research. Aim of the study and any possible risk were discussed with the patients. Patients were assured about the privacy of the collected data.

Statistical Analysis

Statistical analysis has been carried out using SPSS software version 26 (IBM©, Chicago, IL, United States of America). The normality of distribution has been checked utilizing the Shapiro-Wilk test and visual tools like histograms or Q-Q plots. For Continuous variables, the Mann-Whitney U Test has been utilized to compare the 2 groups in the case of non-parametric data, and results were reported primarily as Mean ± SD, Median, and IQR. The Independent Sample T-test was utilized for comparing the parametric data. For Dichotomous parameters, Pearson's Chi-Square or Fisher's Exact test has been utilized. The Chi-square test has been utilized for the comparison of dichotomous variables. The comparison of the paired data was done utilizing the Wilcoxon Signed-Rank test. The correlation of non-parametric data was performed using the Spearman correlation. P-value below 0.05 has been regarded as statistically significant.

3. RESULTS

Table (1): Demographic data of the two groups; cases (RA cases) and controls (Non-RA controls)

Parameters		**Group Ⅰ (RA) Number=100**	**Group Ⅱ (controls) Number=100**	**P value**
Age	Mean ±SD	58.6± 7.4	57.3± 9.2	0.24 *NS
Sex	Male Female	56 (56%) 44(44%)	47 (47%) 53(53%)	0.6 **NS
Height	Mean ±SD	170.4± 5	169.8± 5.3	0.24 *NS
Weight	Mean ±SD	76.4± 5.1	75.9± 5.3	0.5 *NS
Body mass index	Mean ±SD	26.34 ± 1.4	26.38± 2	0.8 *NS

Body surface area	Mean ±SD	1.9± 0.08	1.89± 0.09	0.3 *NS
Systolic blood pressure	Mean ±SD	132± 10.1	129.5± 9.4	0.06*NS
Diastolic blood pressure	Mean ±SD	78.7 ± 6.4	78.1± 6.02	0.4 *NS
Heart rate	Mean ±SD	77.59± 8.8	76.8± 8.7	0.5 *NS

*By the Independent sample t-test **By Chi-square test NS: non-significant P-value below 0.05 is deemed significant

Table 1 demonstrates a statistically insignificant difference has been observed among the RA group and the control group regarding Age, Sex, BMI, SBP, DBP, Height, weight, BSA, and heart rate.

Table (2): Conventional echocardiography results of the RA group and the control group

Parameters	Group Ⅰ (RA) Number=100		Group Ⅱ (controls) Numer=100		P-value
	Mean ±SD	Median (IQR)	Mean ±SD	Median (IQR)	
LVEDD (cm)	5.1±0.4	5.2 (4.7-5.4)	4.8±0.2	4.8 (4.6-5)	<0.001 *HS
LVESD (cm)	3.5± 0.4	3.6 (3.4-3.8)	3.3 ±0.4	3.4 (2.9-3.7)	<0.001 *HS
LVM	150.4±34.4	157(120-180)	150.7 ± 34.8	157(120-180)	0.95 *NS
MEF	63.58±3.4	64 (62.2-67)	63.58 ±3.4	64 (62.2-67)	1.0 *NS
LVEDV [Simpson's]	144.1±20.7	140 (124-160)	124.52±22.3	125(105-145)	<0.001 *HS
LVESV [Simpson's]	61.7±7.4	61 (55-65)	42.6 ±7.9	40 (35-50)	<0.001 *HS
E/A	1.18±0.6	1.05 (0.7-1.4)	1.2 ±0.6	1.2 (0.9-1.4)	0.2 **NS
E/E'	7.7±4.3	7 (6-7.5)	8.2 ±4.3	7 (6-11)	0.6 **NS
TRVel	2±0.2	2 (1.9-2.3)	2 ± 0.2	2 (1.9-2.3)	1.0 **NS

HS: p-value below 0.001

Table 2 shows that there was a statistically significant increase difference between the RA group versus controls regarding LVEDD, LVESD, LVEDV and LVESV. Generally, RA group has a higher value than control group. On the other hand, there were non-significant difference between the two groups regarding MEF, LVM, E/A, E/E' and TRVel.

Table (3): Two-dimensional echocardiography results of the RA group and the control group

Parameters	Group Ⅰ (RA) Number=100		Group Ⅱ (controls) Number=100		P-value
	Mean ±SD	Median (IQR)	Mean ±SD	Median (IQR)	
2DGLS	-17.8 ± 1.4	-18 (-19- -17)	-21 ± 1.4	-21 (-22- -20)	<0.001 HS
2DGCS	-18 ± 0.9	-18 (-19- -17)	-22 ± 2	-23 (-24- -21)	<0.001 HS
2DGRS	38.5 ± 1.2	38 (38-39)	40.4 ± 1.8	40 (39-42)	<0.001 HS

Table 3 shows that Regarding 2D speckle tracking imaging (2DSTE) of the study groups; all parameters of speckle tracking using 2D-STE (2DGLS, 2DGCS, 2DGRS) were found to be significantly various among the 2 groups. The RA group has higher values than control group.

Table (4): Three-dimensional echocardiography results of the RA group and the control group

Parameters	Group Ⅰ (RA) Number=100		Group Ⅱ (controls) Number=100		P-value
	Mean ±SD	Median (IQR)	Mean ±SD	Median (IQR)	

3DLVEDV	147 ± 20.8	145 (130-163)	133.6 ± 22	135 (110-150)	<0.001 HS
3DLVESV	60.4 ± 8.5	60 (55-65)	49.9 ± 8	50 (40-55)	<0.001 HS
3DLVEF	54.7 ± 2.6	55 (53-57)	58.4 ± 2.9	59 (57-60)	<0.001 HS
3DGLS	-16.4 ±1.1	-17 (-17- -16)	-19.1 ± 1.2	-19 (-20- -18)	<0.001 HS
3DGCS	-16.7 ± 1.0	-17.7(-17- -16)	-20.1 ± 1.5	-20 (-21--19)	<0.001 HS
3DGRS	34 ± 4.5	35 (34-35)	39. 1± 1.2	39 (38-40)	<0.001 HS

Table 4 shows that there was a highly significant increase variance of 3D-LV volumes of the patients' group in comparison with the control group. Additionally, a highly significant variance has been observed among the 2 groups regarding 3DEF (mean: 54.7 ± 2.6 for the RA group; mean: 58.4 ± 2.9 for the control group). All 3D speckle tracking parameters (3D-GLS, 3D-GCS, 3D-GRS) demonstrated a greatly significant decrease variance among the two groups.

Table (5): Comparison of 2D conventional LVEF and LV volumes with 3 DEF and 3D LV Volumes

Parameters		**Group I (RA) Number=100**		**Group II (controls) Number=100**		**P-value**
		Mean ±SD	Median (IQR)	Mean ±SD	Median (IQR)	
EF	MEF	63.58±3.4	64(62.2-67)	63.58±3.4	64 (62.2-67)	1.0 NS
	3DLVEF	54.7±2.6	55 (53-57)	58.4±2.9	59 (57-60)	<0.001 HS
LV volumes	LVEDV(Simpson's)	144.1±20.7	140(124-160)	124.52±22.3	125 (105-145)	<0.001 HS
	LVESV(Simpson's)	61.7±7.4	61 (55-65)	42.6±7.9	40 (35-50)	<0.001 HS
	3DLVEDV	147±20.8	145 (130-163)	133.6±22	135 (110-150)	<0.001 HS
	3DLVESV	60.4±8.5	60 (55-65)	49.9±8	50(40-55)	<0.001 HS

Table 5 shows a statistically insignificant variance has been observed among the two groups concerning EF measured using conventional echocardiography, yet a highly significant variance has been observed among the 2 groups when EF is measured using 3D echocardiography (P-value below 0.001). The 3D-LVEF in the patients' group (54.7±2.6) is significantly lower than the 2D-LVEF (63.58±3.4) of the same group. Also, the control group shows similar results where 2D LVEF (63.58±3.4) is significantly higher than the 3D-LVEF (58.4±2.9). There was a greatly significant increase variance of 3D-LV volumes of the patients' group compared to the control group. Also, the 2D-LV volumes (Simpson's) of the patients' group show a highly significant increase difference in comparison with the control group. Generally, the 3D-LV volumes were significantly higher than the 2D-LV volumes (Simpson's).

Table (6): Paired comparison of 2D-STE and 3D-STE derived measurements.

Compared parameters		**Z value**	**p-value**
2D-GLS	3D-GLS	-10.4	0.000* HS
2D-GCS	3D-GCS	-11.1	0.000* HS
2D-GRS	3D-GRS	-11.3	0.000* HS

*Wilcoxon signed rank test

Table 6 shows that all STE measurements showed statistically significant differences between 2D and 3D techniques. 3D-GLS tended to be less negative (more reduced strain) than 2D-GLS. 3D-GCS values also tended to be lower than the 2D-GCS values. Finally, 3D-GRS values were mostly lower than the 2D-GRS values. This suggests that 2D-STE and 3D STE provide significantly different results for strain measurements, particularly for GLS and GRS. This could indicate that the two methods measure strain differently and should not be used interchangeably without consideration of the differences.

Table (7): Correlation of 2D-STE and 3D-STE derived measurements.

Correlated parameters		R	Correlation	p-value
2D-GLS	3D-GLS	0.74	Strong positive	0.000* HS
2D-GCS	3D-GCS	0.45	weak	0.000* HS
2D-GRS	3D-GRS	0.21	Very weak	0.000* HS

*Spearman's rho correlation test

Table 7 shows there was a strong positive association among 2D-GLS and 3D-GLS, which was statistically significant. Also, the correlation between 2D-GCS and 3DGCS revealed a weak positive significant correlation. Finally, the correlation analysis among 2D-GRS and 3D-GRS revealed a very weak significant correlation.

4. DISCUSSION

Conventional echocardiography data revealed insignificant variance among the 2 groups concerning EF. All variables of 2D- STE (2DGLS, 2DGCS, 2DGRS) have been observed to be reduced in the RA group in comparison with control group. There was a greatly significant increase variance of 3D-LV volumes and of the patients' group in comparison with the control group. Additionally, a highly significant variance has been observed among the 2 groups regarding 3DEF (mean: 54.7 ± 2.6 for the RA group; mean: 58.4 ± 2.9 for the control group). All 3D speckle tracking parameters (3D-GLS, 3D-GCS, 3D-GRS) demonstrated a greatly significant decrease variance among the two groups. RA group has reduced strain parameters.

The 3D-LVEF in the patients' group (54.7±2.6) is significantly lower than the 2D-LVEF (63.58±3.4) of the same group. Also, the 3D-LV volumes were significantly higher than the 2D-LV volumes (Simpson's) in the two groups. Although all 2D-STE and 3D-STE parameters were significantly reduced in the RA group, the association among 2D-STE and 3D-STE revealed a strong correlation in the case of GLS only, the correlation was weak in the case of GCS and GRS. The correlation of 2D-- LV volumes (Simpson's method) and 3D-LV volumes revealed a weak positive correlation between them. 3D-derived volumes tended to have higher values for LV volumes than 2D techniques. Also 3D derived EF shows a very weak positive correlation with 2D-derived EF. Moreover, we found the 3D-STE parameters were not significantly correlated with any demographic parameter. Age is the only parameter that shows a significant correlation (p value = 0.01) with 3D GLS.

In agreement with the present research, Ajmi et al. (11) conducted a case-control research with sixty cases with rheumatoid arthritis (mean age 47.7 years) who had no prior history of heart illness, and forty healthy controls (mean age 44.5 years). All participants had tissue Doppler imaging (TDI) and transthoracic echocardiography (TTE) to evaluate mitral annular systolic velocity (S`) and left ventricular GLS utilizing the 2D-speckle tracking echocardiography method. Rheumatoid arthritis cases had a reduced mitral annular velocity S` in comparison with the control group (9.60±1.61 versus 10.72±1.17; p-value below 0.001). Additionally, cases with rheumatoid arthritis demonstrated a reduced negative left ventricular longitudinal strain compared to the control group (-18.74%±1.06 versus -23.11%±1.16; p-value below 0.001). Cases with rheumatoid arthritis exhibit an elevated risk of subclinical left ventricular systolic dysfunction.

Consistent with the present research, Hussaini et al. (12) observed significant variances among the groups concerning global longitudinal strain. Cases with CTDs exhibit a more negative global longitudinal strain and a significant reduction in mitral annular plane systolic excursion (MAPSE) (P-value below 0.001). The evaluation of RV Echocardiography reveals similar results. A positive association existed between LV-GLS and BMI, total cholesterol, and LDL, whereas a negative association was observed among LV-GLS and DBP. The author concluded that global longitudinal strain variables in two-dimensional speckle tracking echocardiography represent a noninvasive, cost-effective instrument of high diagnostic value in cases with connective tissue disease. Global longitudinal strain is a superior noninvasive instrument for the early identification of subclinical left ventricular and right ventricular systolic failure in cases with connective tissue disease.

In line with our outcomes, Bakhoum et al., (13), conventional echocardiography assessment revealed insignificant variance in left ventricular dimensions, ejection fraction (EF) and LA indexed volumes among cases and control. The authors concluded that cases with rheumatoid arthritis had change in left ventricular longitudinal myocardial function and more LA stiffness which is more affected in seropositive cases.

In line with our study, Nikdoust et al. (14) assessed thirty-five cases with active rheumatoid arthritis (mean age = 43.33 ± 22.9 years) and thirty-five healthy controls (mean age = 34.27 ± 9.10 years) for echocardiographic variables. Cases with RA selected were in the active phase throughout the 1st five years of identification. The global longitudinal strain variable was significantly reduced in the rheumatoid arthritis group compared to the healthy group (-19.5 ± 2.34 versus -20.42 ± 3.07; P-value equal to 0.042). Conversely, in contrast to our findings, there was no significant variance in the GCS variable among the two groups (-19.69 ± 3.55 versus -20.49 ± 1.79; P-value equal to 0.566). Additionally, reductions in AO, LA, PWD, IVSD, and RVSm in these cases have been observed when compared to the healthy controls.

Also, Consistent with the study findings, Naseem et al., (15), conventional echocardiography examination revealed that the three groups studied didn't vary regarding left ventricular posterior wall thickness at end diastole, left ventricular septum thickness at end diastole, LVESV, LVEDV, peak mitral E wave velocity, peak mitral A wave velocity, EF%, mitral E/e' ratio and peak S' velocity. The left ventricular and right ventricular GLS value for active rheumatoid arthritis cases has been decreased in comparison with rheumatoid arthritis cases in remission and control group (p-value not more than 0.001). Elevating levels of disease activity has been related to worse left ventricular GLS.

Moreover, Cioffi et al., (16), conventional echocardiography examination demonstrated insignificant variance among the 2 groups regarding LVEDD, left ventricular mass index, E/A ratio, E/E' ratio, and LV ejection fraction. Reduced global longitudinal strain has been identified in fifty-one cases with RA (24%) and in three (5%; P < .001) matched control individuals; reduced GCS has been identified in forty-two rheumatoid arthritis cases (20%) and in 3 (5%; P < .001) control individuals. Combined reduced global longitudinal strain and GCS has been observed in nineteen rheumatoid arthritis cases (nine percent) and not in any control individual (P = 0.03).

In a similar study, Midtbø et al., (17), LVEF was normal in all 3 groups, whereas mean scMWS and global longitudinal strain have been decreased in cases with active rheumatoid arthritis compared to cases with rheumatoid arthritis in remission (95 ±18% versus 105±17% and -18.9±3.1% versus -20.6 ±3.5%, correspondingly, both p-value below 0.01)

5. CONCLUSION

3D-STE is considered a reproducible and reliable method for the detection of subclinical left ventricular dysfunction in RA cases. 3D-STE may be deemed to be a promising instrument in assessing cardiac function and giving precise diagnostic and prognostic data in clinical practice. 3D-STE and 2D-STE were significantly better than conventional echocardiography for detection of subclinical LV dysfunction. All STE measurements showed statistically significant differences between 2D and 3D techniques. 3D-GLS tended to be less negative (more reduced strain) than 2D-GLS. 3D-GCS values also tended to be lower than the 2D-GCS values. Finally, 3D-GRS values were mostly lower than the 2D-GRS values.

LIMITATIONS

The recent research has been restricted by relatively small sample size, being a single center study and no follow up duration. Furthermore, our findings did not take into the potential influences of certain pharmacologic or non-pharmacologic therapies for subclinical LVSD in these cases. However, our outcomes point out that LV dysfunction can be detected at an early stage of the illness. This represents at least a 1st step towards identifying an efficient solution to the issue, and serve as motivation for additional investigations in that direction.

RECOMMENDATION

Additional comparative research with a larger sample size and extended monitor are necessary to validate our findings. Future investigations should be performed utilizing well-designed randomized controlled trials or large comparative observational investigations.

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