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ORIGINAL ARTICLE

The Feasibility of 3D Echocardiography Examination for Determining the Left Ventricular Dyssynchrony Index: A Pilot Study

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Abstract

Purpose: Three-Dimensional Echocardiography (3DE) allows simultaneous evaluation of the entire Left Ventricular (LV) volume, motion, and mechanical dyssynchrony. This study aimed to provide valuable data on the feasibility and reliability of 3DE in assessing LV dyssynchrony in healthy individuals.

Materials and Methods: One hundred healthy volunteers, including both male and female genders, with a mean age, weight, and Body Mass Index (BMI) of 39.64±10.21 years, 76.57±14.65 kg, and 27.59±4.3 kg.m-2, respectively, without evidence of structural heart or chronic disease, were included in this study. 3DE examinations were conducted using a 4-chamber view and the full-volume method for all volunteers. Dyssynchrony was automatically quantified as the Systolic Dyssynchrony Index (SDI) for selected LV segments using Q-lab software. The standard deviation of the time to attain minimum systolic volume was considered SDI, expressed in percent RR duration. Consequently, a single SDI (global SDI), which could provide more reliable information, was used for quantifying the degree of LV dyssynchrony by comparing all segments.

Results: According to echocardiographic findings, the mean global LV-SDI, apical SDI, basal SDI, and mid SDI were 28.68±15.48, 26.16±27.47, 24.41±14.35, and 22.07±18.24 msec, respectively. After correction for RR intervals, these values were 3.49±1.97%, 3.21±3.58%, 2.97±1.82%, and 2.68±2.19%, in that order.

Conclusion: 3DE proves to be a useful tool for evaluating LV dyssynchrony. The data provided include age- and sex-related changes in total and regional SDI in healthy volunteers, serving as a suitable reference for further investigations into LV dyssynchrony changes.

Keywords: Echocardiography; Three-Dimensional; Ventricle; Heart Failure.

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1. Introduction

Cardiovascular Diseases (CVD) stand as the primary reason for mortality worldwide, placing a significant burden on healthcare organizations. Among various types of CVD, congestive heart failure stands out as a major contributor to mortality [1–3]. Consequently, the improvement of diagnosis, prognosis, and treatment decisions heavily relies on the evaluation of ventricular performance [4]. Therefore, the application of a feasible and noninvasive method, particularly for the estimation of Left Ventricular (LV) size and function, proves beneficial in developing more appropriate treatment strategies [5–7].

In this context, echocardiography emerges as an excellent choice for ventricular evaluation due to its advantageous characteristics, including availability, non-invasiveness, and cost-effectiveness [8, 9]. Among the three types of cardiac dyssynchrony-atrioventricular dyssynchrony, interventricular dyssynchrony, and intraventricular or LV mechanical dyssynchrony-patients with heart failure solely attributed to intraventricular or LV mechanical dyssynchrony exhibit an appropriate response to Cardiac Resynchronization Therapy (CRT) and experience improved long-term survival. The synchronous contraction of the LV is crucial for maintaining overall cardiac performance, and LV dyssynchrony can impact cardiac morphology and function. CRT, as an established therapy, specifically targets LV dyssynchrony, aiming to enhance LV function in patients with end-stage heart failure [10].

Clinically, a commonly utilized marker for intraventricular dyssynchrony is the wide QRS (Q, R, and S waves) duration on Electrocardiography (ECG) [11, 12]. However, in some cases, there is no evidence of electrical conduction delay in the ECG, despite the occurrence of mechanical dyssynchrony in the patient [13]. Conversely, in approximately 30-40 percent of patients with a wide QRS, clinical improvement cannot be achieved following CRT treatments. Therefore, various echocardiographic methods have been explored to study intraventricular dyssynchrony and response to CRT. Several previous studies have investigated better indices of mechanical dyssynchrony compared to QRS as predictors of response to CRT [14, 15].

Presently, several available echocardiographic imaging methods are used for measuring mechanical dyssynchrony, such as tissue Doppler imaging (TDI), 2-dimensional Speckle-Tracking Echocardiography (STE), three-Dimensional Echocardiography (3DE), and 3D-STE [16, 17]. However, most of these methods have several limitations (inherent technical and physiologic limitations). For instance, the dependence on ultrasound beam angle, translational cardiac motion, the limited study of myocardial velocities in one dimension, and the lack of reproducibility restrict the extensive utilization of TDI for assessing LV mechanical dyssynchrony in clinical settings [18]. Two-dimensional strain imaging has addressed some of the challenges of TDI by being unaffected by ultrasound beam angle and by examining various directions of motion. However, it is a time-consuming process that necessitates multiple acquisitions and comprehensive analysis [19].

3DE can address these limitations and provide more reliable and reproducible results for LV function, as well as offer visual estimates of ejection fraction [17]. The potentialities provided by 3DE as a unique imaging technique include the evaluation of whole LV volumes, LV regional systolic motion, and global LV mechanical dyssynchrony [20, 21]. Regional function analysis in the specific time domain is particularly important for patients with potential LV dyssynchrony and heart failure. 3DE can help predict eligible patients for CRT. Generally, the Systolic Dyssynchrony Index (SDI) has a reverse relationship with ejection fraction while no definite relation with QRS. 3DE proposes a new group of eligible patients for CRT who may be overlooked due to a normal QRS duration. Overall, using 3D LV dyssynchrony enables the identification of patients who can or cannot benefit from CRT. 3DE appears useful as it provides the distribution map of regional contraction times [21].

This investigation aimed to establish a comprehensive dataset assessing the feasibility and reliability of 3DE in evaluating global and regional LV dyssynchrony in healthy adults. The study aimed to introduce a cutoff value for the global LV mechanical dyssynchrony index using 3DE. Additionally, the assessment of regional LV wall motion, specifically in the basal, apical, and mid segments of the myocardium, was performed. The segmental SDI was quantified using this diagnostic technique to provide data specific to healthy adults.

2. Materials and Methods

2.1. Study Design

This cross-sectional single-center pilot study was designed to assess the spatial pattern of LV synchrony using 3DE. A total of 100 healthy adult volunteers, aged 20 years and older, representing both genders and without evidence of structural heart and chronic disease, were included in this study. Before participation, individuals were provided with the necessary information, and informed consent was obtained.

The research protocol and methodology of this study were approved by the National Ethical Committee. Comprehensive demographic, clinical, biochemical, and 2D echocardiographic characteristics were collected and recorded for all participants. The initial assessment involved a 2D echocardiogram. Participants with an LV Ejection Fraction (LVEF) greater than 50% and no other abnormalities on 2D echocardiography underwent further evaluation with 3DE, performed by an experienced operator using the Philips echocardiography system (Philips Medical Systems, Andover, MA, USA).

2.2. 3D Echocardiography

3DE was conducted in an apical 4-chamber view and four-beat mode for the LV, employing an EPIQ7 ultrasound machine (Philips Medical Systems, Andover, MA, USA) and the X5-1 Xmatrix-array transducer. The ECG-gated acquisition technique was utilized during the 4 sequential cardiac cycles, obtaining LV-focused 4 wedge-shaped sub-volumes during a single breath-hold from the apical window. Adjustments of lateral width were made to encompass the entire LV. A 3DE image with clear visualization of all 16 segments of the endocardium in both end-diastolic and end-systolic frames was deemed suitable. Parameters such as LV End-Diastolic Volume (LVEDV), LV end-Systolic Volume (LVESV), and LVEF (Simpson’s rule) were estimated from 3DE.

Offline analysis using Q-lab software (version 6. Philips) was conducted to calculate ventricular volume throughout the cardiac cycle at different points. The mitral valve annulus and LV apex were identified using five points (anterior, inferior, septal, lateral, and apical) during the end-diastolic and end-systolic frames. These points were employed for the automatic detection of endocardial borders. A 3D mathematical model was utilized to calculate time-volume in the cardiac cycle, automatically detecting 16-segment models based on the American Heart Association (AHA). Plots were generated to illustrate changes in the volume of each segment throughout the entire cardiac cycle. Parameters such as total myocardial volume in systole and diastole, segmental minimal volume, and the time to reach minimal volume were measured using Q-lab software.

Dyssynchrony was automatically quantified for the selected LV segments, and the standard deviation of the time to attain the minimum systolic volume of these segments was indicated as SDI. Both global and regional SDI were acquired and corrected for RR intervals, expressed as a percentage of the cardiac cycle. This corrected SDI was presented as a percentage to compensate for the variability of heart rate between individuals and enhance reproducibility. A single SDI value was obtained for quantifying the degree of LV dyssynchrony from a comparison of all segments. It's important to note that all measurements with 3DE were repeated for each volunteer to ensure more reliable and reproducible results.

2.3. Statistical Analysis

The normality of the data was evaluated utilizing the Kolmogorov-Smirnov statistical test. The independent t-test was used for comparing normally distributed parameters, while the Mann-Whitney test was employed for non-normally distributed parameters. The correlation of the evaluated 3DE parameters with age was assessed using Pearson and Spearman's correlations. All analyses were conducted using SPSS version 23. A significance level of less than 0.05 was deemed statistically significant for all analyses.

3. Results

The descriptive analysis of demographic and cardiac function diagnostic parameters is presented in Table 1. The mean age of the individuals involved was 39.64±10.2 years. The Kolmogorov-Smirnov test

Table1. Indicators of descriptive statistics for the examined variables

Variable	Mean±SD	Minimum	Maximum
Demographic characteristics			
Age (y)	39.64±10.21	21	62
Weight (kg)	76.57±14.65	45	125
Height (cm)	166.34±9.55	150	192
BMI (kg/m^2)	27.59±4.3	18.49	41.29
Parameters of echocardiography			
End diastolic volume	73.45±18.34	32.50	129.90
End systolic volume	29.11±7.42	13.80	55.70
LVEF	60.73±2.35	54.20	66.10
Storke volume	45.03±10.89	24	77.70
SDI (msec)	28.68±15.48	9	98
SDI basal (msec)	24.41±14.35	3	70
SDI mid (msec)	22.07±18.24	3	127
SDI apical (msec)	26.16±27.47	1	193
SDI (%)	3.49±1.97	1.13	12.78
SDI basal (%)	2.97±1.82	0.39	9.35
SDI mid (%)	2.68±2.19	0.38	14.43
SDI apical (%)	3.21±3.58	0.20	26.30

indicated that age (p=0.186), weight (p=0.054), height (0.152), ESV (p=0.07), and LVEF (p=0.2) exhibited a normal distribution. Consequently, parametric tests were applied for these parameters. The data distribution of other parameters was non-normal and assessed using non-parametric statistical tests.

According to echocardiographic findings, the mean (±SD) values of global LV-SDI, apical SDI, basal SDI, and mid SDI were 28.68±15.48, 26.16±27.47, 24.41±14.35, and 22.07±18.24 milliseconds, respectively. Both global and regional SDI were corrected for RR intervals, expressed as a percentage of the cardiac cycle, and displayed as a percentage. The obtained corrected mean (±SD) values of global LV-SDI, apical SDI, basal SDI, and mid SDI were 3.49±1.97%, 3.21±3.58%, 2.97±1.82%, and 2.68±2.19%, respectively. The minimum (1 millisecond) and maximum (193 milliseconds) times of SDI were both obtained from apical SDI.

Echocardiographic indices were compared between genders, as shown in Table 2. Among the demographic parameters, height, weight, body mass index (BMI), and echocardiographic parameters including ESV, EDV, stroke volume, and apical SDI were found to be significantly higher in men.

The correlation coefficient values of the evaluated parameters with age are presented in Table 3, indicating no significant strong correlation between age and the parameters.

4. Discussion

A fundamental strategy for diagnosing, prognosticating, and treating structural heart diseases involves the accurate and reproducible quantitative assessment of LV size and function. In this context, various applications of 3DE highlight the pivotal role of LV quantification. The application of real-time 3DE, through the analysis of 17-segment time–volume curves to evaluate mechanical dyssynchrony, has yielded promising results across a diverse spectrum of patients [22]. However, despite the potential advantages of mechanical dyssynchrony as a guide for CRT, LV electrical dyssynchrony is currently more commonly utilized. It is crucial to note that 3DE results strongly hinge on mechanical delay [21]. In this context, data derived from the 3DE technique indicate that the most frequently delayed segments in infarcted myocardium are located at the apical and mid segments of the LV, correlating with segmental wall motion abnormalities. Conversely, in cases of dilated cardiomyopathy, the most frequently delayed LV segments are found at the basal and mid-levels in patients with a more globally hypokinetic LV, exhibiting abnormalities in diffuse motion [23, 24].

Recently, clinicians have incorporated 3DE as a supplementary technique to 2D echocardiography due to the additional volumetric information it offers, despite the existence of untapped potential applications of 3DE [25].

Table 2. Comparison of echocardiographic indicators between men and women

Variable	Male	Female	P-value
Demographic characteristics			
Age (y)	39.60±10.76	39.67±9.86	0.973
Weight (kg)	85.76±14.05	69.37±10.59	<0.001*
Height (cm)	173.05±7.99	161.07±7.07	<0.001*
BMI (kg/m^2)	28.67±4.59	26.75±3.89	0.035*
Parameters of echocardiography			
End diastolic volume	84.33±19.28	65.07±12.32	<0.001*
End systolic volume	33.72±7.5	25.56±5.07	<0.001*
LVEF	60.77±2.18	60.71±2.49	0.904
Stroke volume	51.63±10.69	39.85±7.87	<0.001*
SDI (msec)	32.7±19.42	25.52±10.67	0.11
SDI basal (msec)	22.62±12.28	25.76±15.75	0.363
SDI mid (msec)	27.55±24.08	17.86±10.42	0.101
SDI apical (msec)	33.97±36.16	20.15±16.19	0.033*
SDI (%)	3.98±2.48	3.11±1.38	0.241
SDI basal (%)	2.81±1.64	3.11±1.95	0.417
SDI mid (%)	3.34±2.87	2.18±1.29	0.12
SDI apical (%)	4.16±4.79	2.46±2.01	0.052

SD: Standard Deviation, BMI: Body Mass Index, LVEF: Left Ventricular Ejection Fraction, SDI: Systolic Dyssynchrony Index

Table 3. Correlation between age and echocardiographic indicators

Variable	r	P-value
Demographic characteristics		
Weight (kg)	0.042	0.690
Height (cm)	-0.155	0.141
BMI (kg/m^2)	0.2	0.058
End diastolic volume	0	0.996
End systolic volume	0.043	0.685
LVEF	-0.071	0.499
Stroke volume	-0.001	0.992
SDI (msec)	0.096	0.366
SDI basal (msec)	0.147	0.162
SDI mid (msec)	0.140	0.183
SDI apical (msec)	0.028	0.794
SDI (%)	0.104	0.325
SDI basal (%)	0.148	0.159
SDI mid (%)	0.134	0.202
SDI apical (%)	0.031	0.767

It serves as a noninvasive, reproducible, fast, and feasible method for patients with preserved LV function, facilitating the identification and quantification of LV dyssynchrony [26]. However, prior to widespread adoption of this promising technology, accurate validation and the establishment of appropriate cut-off values are deemed essential.

In a study by Kapetanakis *et al.* [27], LV synchrony was analyzed in a large population with varying degrees of LV systolic function using a different 4-dimensional LV post-processing software. Their results demonstrated a significant correlation between SDI and LVEF, while a weak relation was reported between QRS duration and SDI. Additionally, Park *et al.* [28] evaluated LV mechanical parameters using real-time 3DE in 23 patients with advanced heart failure compared to 16 normal individuals. Results revealed a higher mean value of SDI in the patient group compared to the normal individuals. Marsan *et al.* [29] assessed LV mechanical dyssynchrony in a group of heart failure patients scheduled for CRT. Utilizing real-time 3DE, the baseline SDI mean value observed by them was 7.3%, with an SDI cut-off value of 5.6% to define LV mechanical dyssynchrony. Our present study, designed as a pilot study, was initiated due to the absence of available data on 3DE indices in our population. Within this study, global and regional dyssynchrony was evaluated using SDI in 100 healthy individuals. Echocardiographic results indicated a higher mean value in global SDI compared to regional SDI values. A meta-analysis of 73 studies reported a 94% feasibility of real-time 3DE for assessing ventricular dyssynchrony. The meta-analysis also highlighted that SDI provides a good predictive response to CRT [30].

Previous researchers have employed different software packages for quantifying LV mechanical dyssynchrony using 3DE, leading to potential variations in SDI values. Notably, Q-lab is a software that calculates the SDI index by utilizing an LV model derived in two orthogonal planes representing the standard apical four and two-chamber views as guides. Straka *et al.* [31] utilized the Q-lab software to analyze mean SDI values for a 16-segment model. In another study, Kapetanakis *et al.* [27] used Tom Tec software (Tom Tec Imaging Systems GmbH, Germany) and a 16-segment model in a large patient sample with refractory congestive heart failure to analyze LV synchrony. Their findings revealed a significant relationship between SDI and LVEF. Mehrotra [32] also provided additional confirmation of the benefits of real-time 3DE, mentioning that mechanical dyssynchrony can occur between two or more of the 16 myocardial regions described by the American Society of Echocardiography from the base to the apex.

It's important to note that the LV is divided into 17 segments, excluding the apical segment to yield SDI-16, although it actually encompasses 17 segments. Discrepancies in SDI values across previous studies may arise from differences in the number of segments (16 or 17-segment model) and the use of different software for analysis. The generated SDI values from different software are not necessarily directly comparable due to variations in segmentation, the definition of the center of gravity, and edge-detection algorithms of the LV endocardium. To explore normal values for SDI, Sachpekidis *et al.* [33] compiled reported values from previous studies involving healthy volunteers. They noted that regardless of the type of software and number of segments, previous studies obtained similar mean SDI values. In our present study, consistent with prior research, Q-lab analysis software and the 16-segment model were employed in healthy individuals. Unlike global SDI, there is limited data about regional SDI limits. Interestingly, in our study, similar to the data reported by Kapetanakis *et al.* [27] (SDI, 3.5+/-1.8% and 4.5+/-2.4%; P=0.7), a highly synchronized segmental function (SDI, 3.49±1.97%) was observed. It is important to highlight that the 16-segment model is more commonly used for calculating the SDI than the 17-segment model and has been employed in the majority of previous studies [34]. Preliminary data suggests that SDI-16 may offer better differentiation between patients with dyssynchrony and normal individuals compared to SDI-17. Additionally, it has been demonstrated that various factors such as sex, weight, age, and BMI do not seem to affect normal SDI values, although exceptions may exist for children with lower dyssynchrony.

Achieving a consensus in SDI results requires further accumulation of experimental data. However, it is advisable to gather locally accepted data from each institution, despite the obvious importance of widely accepted cut-off values. The establishment of more definitive normal values is facilitated by improved standardization of the method. In our study, we focused on normal subjects from our local population to obtain locally specific cut-off values. Ultimately, our study found that normal SDI values do not appear to be significantly affected by sex and age. The study's main limitations include a small sample size and the exclusion of patients with heart diseases, necessitating future research addressing a broader range of cardiac conditions.

5. Conclusion

The use of 3DE proves to be a viable technique for assessing LV dyssynchrony. Our investigation focused on estimating age and sex-related variations in both total and regional SDI among healthy volunteers. In our study, the mean global LV-SDI and mean corrected global SDI (corrected for RR intervals) were determined to be 28.68±15.48 and 3.49±1.97% msec, respectively. These findings serve as valuable reference values, offering a foundation for subsequent research endeavors aiming to explore alterations in LV dyssynchrony among individuals afflicted with diverse cardiovascular diseases.

References

1- Theresa A McDonagh *et al.*, "2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC." *European heart journal,* Vol. 42 (No. 36), pp. 3599-726, (2021).

2- Islam Y Elgendy, Dhruv Mahtta, and Carl J Pepine, "Medical therapy for heart failure caused by ischemic heart disease." *Circulation research,* Vol. 124 (No. 11), pp. 1520-35, (2019).

3- Ali Tarighatnia, Asghar Mesbahi, Amir Hossein Mohammad Alian, Evin Koleini, and Nader Nader, "An analysis of operating physician and patient radiation exposure during radial coronary angioplasties." *Radiation protection dosimetry,* Vol. 182 (No. 2), pp. 200-07, (2018).

4- Sherif F Nagueh, "Left ventricular diastolic function: understanding pathophysiology, diagnosis, and prognosis with echocardiography." *JACC: Cardiovascular Imaging,* Vol. 13 (No. 1 Part 2), pp. 228-44, (2020).

5- Dawud Abawi *et al.*, "The non-invasive assessment of myocardial work by pressure-strain analysis: clinical applications." *Heart Failure Reviews,* Vol. 27 (No. 4), pp. 1261-79, (2022).

6- Sherif F Nagueh, "Non-invasive assessment of left ventricular filling pressure." *European journal of heart failure,* Vol. 20 (No. 1), pp. 38-48, (2018).

7- Ali Tarighatnia, Gurkaran Johal, Ayuob Aghanejad, Hossein Ghadiri, and Nader D Nader, "Tips and tricks in molecular imaging: a practical approach." *Frontiers in Biomedical Technologies,* Vol. 8 (No. 3), pp. 226-35, (2021).

8- Lars Gunnar Klaeboe and Thor Edvardsen, "Echocardiographic assessment of left ventricular systolic function." *Journal of echocardiography,* Vol. 17pp. 10-16, (2019).

9- Maria Concetta Pastore *et al.*, "Basic and advanced echocardiography in advanced heart failure: an overview." *Heart Failure Reviews,* Vol. 25pp. 937-48, (2020).

10- Ziyu Wang, Yongquan Wu, and Junmeng Zhang, "Cardiac resynchronization therapy in heart failure patients: tough road but clear future." *Heart Failure Reviews,* Vol. 26 (No. 3), pp. 735-45, (2021).

11- Laura R Bear, Peter R Huntjens, Richard D Walton, Olivier Bernus, Ruben Coronel, and Rémi Dubois, "Cardiac electrical dyssynchrony is accurately detected by noninvasive electrocardiographic imaging." *Heart rhythm,* Vol. 15 (No. 7), pp. 1058-69, (2018).

12- Raymond Pranata, Emir Yonas, Rachel Vania, Alexander Edo Tondas, and Yoga Yuniadi, "Fragmented QRS is associated with intraventricular dyssynchrony and independently predicts nonresponse to cardiac resynchronization therapy—systematic review and meta-analysis." *Annals of Noninvasive Electrocardiology,* Vol. 25 (No. 4), p. e12750, (2020).

13- Amit Noheria, Sandeep Sodhi, and G Joseph Orme, "The evolving role of electrocardiography in cardiac resynchronization therapy." *Current Treatment Options in Cardiovascular Medicine,* Vol. 21pp. 1-14, (2019).

14- George Bazoukis *et al.*, "Association of QRS narrowing with response to cardiac resynchronization therapy—A systematic review and meta-analysis of observational studies." *Heart Failure Reviews,* Vol. 25pp. 745-56, (2020).

15- VA Kuznetsov, AM Soldatova, JD Kasprzak, DV Krinochkin, and NN Melnikov, "Echocardiographic markers of dyssynchrony as predictors of super-response to cardiac resynchronisation therapy–a pilot study." *Cardiovascular ultrasound,* Vol. 16pp. 1-7, (2018).

16- Lang Gao *et al.*, "Clinical utility of three-dimensional speckle-tracking echocardiography in heart failure." *Journal of Clinical Medicine,* Vol. 11 (No. 21), p. 6307, (2022).

17- WN Lee, Y Zhang, and H Li, "A novel high quality ultrafast ultrasound imaging method for mapping heart dynamics." *Abstracts--Poster Session--Poster session,* Vol. 6p. i1211, (2019).

18- Jens-Uwe Voigt and Marta Cvijic, "2-and 3-dimensional myocardial strain in cardiac health and disease." *JACC: Cardiovascular Imaging,* Vol. 12 (No. 9), pp. 1849-63, (2019).

19- Osama II Soliman *et al.*, "Quantification of left ventricular systolic dyssynchrony by real-time three-dimensional echocardiography." *Journal of the American Society of Echocardiography,* Vol. 22 (No. 3), pp. 232-39, (2009).

20- Andrada C Guta *et al.*, "Three-dimensional echocardiography to assess left ventricular geometry and function." *Expert Review of Cardiovascular Therapy,* Vol. 17 (No. 11), pp. 801-15, (2019).

21- Denisa Muraru, Alice Niero, Hugo Rodriguez-Zanella, Diana Cherata, and Luigi Badano, "Three-dimensional speckle-tracking echocardiography: benefits and limitations of integrating myocardial mechanics with three-dimensional imaging." *Cardiovascular diagnosis and therapy,* Vol. 8 (No. 1), p. 101, (2018).

22- Masaaki Takeuchi, Karima Addetia, and Roberto M Lang, "Advanced Assessment of the Left Ventricle." *Textbook of Three-Dimensional Echocardiography,* pp. 73-86, (2019).

23- Victoria Delgado *et al.*, "Assessment of left ventricular dyssynchrony by real-time three-dimensional echocardiography." *Revista Española de Cardiología (English Edition),* Vol. 61 (No. 8), pp. 825-34, (2008).

24- Bing Xing, Ailin Cao, Wei Sun, and Xiyan Hou, "Relationship between left ventricular diastolic dyssynchrony and systolic dyssynchrony in hypertrophic cardiomyopathy by single-cardiac real-time three-dimensional ultrasonography." *Experimental and Therapeutic Medicine,* Vol. 15 (No. 4), pp. 3769-74, (2018).

25- Roberto M Lang *et al.*, "EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography." *European Heart Journal–Cardiovascular Imaging,* Vol. 13 (No. 1), pp. 1-46, (2012).

26- Victor Mor-Avi *et al.*, "Real-time 3-dimensional echocardiographic quantification of left ventricular volumes: multicenter study for validation with magnetic resonance imaging and investigation of sources of error." *JACC: Cardiovascular Imaging,* Vol. 1 (No. 4), pp. 413-23, (2008).

27- S Kapetanakis, MT Kearney, A Siva, N Gall, M Cooklin, and MJ Monaghan, "Real-time three-dimensional echocardiography: a novel technique to quantify global left ventricular mechanical dyssynchrony." *Circulation,* Vol. 112 (No. 7), pp. 992-1000, (2005).

28- Jae-Hyeong Park, "Two-dimensional echocardiographic assessment of myocardial strain: important echocardiographic parameter readily useful in clinical field." *Korean Circulation Journal,* Vol. 49 (No. 10), p. 908, (2019).

29- Nina Ajmone Marsan *et al.*, "Real-time three-dimensional echocardiography permits quantification of left ventricular mechanical dyssynchrony and predicts acute response to cardiac resynchronization therapy." *Journal of cardiovascular electrophysiology,* Vol. 19 (No. 4), pp. 392-99, (2008).

30- Sebastiaan A Kleijn *et al.*, "A meta-analysis of left ventricular dyssynchrony assessment and prediction of response to cardiac resynchronization therapy by three-dimensional echocardiography." *European Heart Journal–Cardiovascular Imaging,* Vol. 13 (No. 9), pp. 763-75, (2012).

31- Frantisek Straka *et al.*, "A Pilot Study of Systolic Dyssynchrony Index by Real Time Three-Dimensional Echocardiography and Doppler Tissue Imaging Parameters Predicting the Hemodynamic Response to Biventricular Pacing in the Early Postoperative Period after Cardiac Surgery." *Echocardiography,* Vol. 29 (No. 7), pp. 827-39, (2012).

32- Rahul Mehrotra, "Three-dimensional echocardiographic systolic dyssynchrony index-what is the correct cut-off?" *Indian Heart Journal,* Vol. 70 (No. 5), p. 765, (2018).

33- Vasileios Sachpekidis, Amit Bhan, and Mark J Monaghan, "Three Dimensional Echocardiographic Evaluation of LV Dyssynchrony and Stress Testing." in *Textbook of Real-Time Three Dimensional Echocardiography*: *Springer*, (2010), pp. 63-80.

34- Haiyong Wang, Yan Song, Jingjing Mu, Jing Shang, Jiabing Wang, and Litao Ruan, "Left ventricular systolic dyssynchrony in patients with Kawasaki disease: a real-time three-dimensional echocardiography study." *The International Journal of Cardiovascular Imaging,* Vol. 36pp. 1941-51, (2020).