Advanced Medical Journal, Vol.11, No.2, P.211-218,2026 https://doi.org/10.56056/amj.2026.477

Relation of Longitudinal Strain to Conventional ECHO in Evaluation of Pediatric Dilated Cardiomyopathy in Children Heart Hospital/ Sulaymaniyah City

Bilal Abdullah Mohammed* Aso Faeq Salih**

Abstract

Background and objectives: While many dilated cardiomyopathy fatalities occur within the first year, patients are often diagnosed at advanced stages. This study evaluates the efficacy of longitudinal strain versus conventional 2D echocardiography for improving early detection and management in pediatric dilated cardiomyopathy.

Methods: This prospective cross-sectional study was conducted from October to September 2024, at the Children Heart Hospital and Jamal Ahmad Rashid Pediatric Hospital ICU in Sulaimani, involving children aged 1 month to 15 years with dilated cardiomyopathy. Echocardiograms were performed using a GE Vivid E9 system by a pediatric cardiologist, assessing left ventricular function through 2D echocardiography, and longitudinal strain. Key parameters included left ventricular volumes, ejection fraction (Simpson's method), mitral valve excursion, and diastolic function (E/A ratio), in line with American Society of Echocardiography guidelines. Data were analyzed using SPSS version 27.0. Descriptive statistics summarized demographic and clinical variables, while t-tests and chi-square tests compared longitudinal strain with conventional 2D echocardiography in assessing pediatric dilated cardiomyopathy. Statistical significance was set at $p<0.05$.

Results: The study involved 17 children (mean age: 7.06±3.11 years; 47.06% male, 52.94% female). Echocardiographic assessments indicated an average Simpson ejection fraction of 38.88% (range: 21.0-58.0), with 29.4% having an ejection fraction <35%, 52.9% between 35-49%, and 17.7% >50%. Simpson ejection fraction, M-mode ejection fraction, and Mitral Annular Plane Systolic Excursion significantly (p-value<0.05) decreased with age.

Conclusion: Our study underscores the utility of longitudinal strain in enhancing the diagnostic accuracy of pediatric dilated cardiomyopathy when used alongside conventional echocardiography.

Keywords: 2D echocardiography, Dilated cardiomyopathy, Longitudinal strain, Relation

*MBChB, Dr. Jamal Ahmad Rashid's Pediatric Teaching Hospital, Qanat Street, Sulaymaniyah, Iraq. Corresponding Author. Email: bilalabdullam@gmail.com.
**MBChB, DCH, FIBMS, Pediatric Cardiology, Pediatrics Department, College of Medicine, University of Sulaymaniyah, Sulaymaniyah, Iraq. Email: aso.salih@univsul.edu.iq

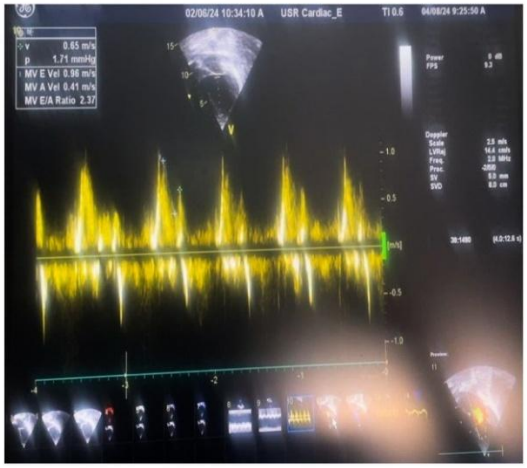
Introduction

Cardiomyopathies are heart diseases affecting systolic and diastolic function, categorized as primary (genetic or acquired) or secondary, with phenotypes including dilated, restrictive, hypertrophic, and arrhythmogenic right ventricular dysplasia.[1,2] The classification of cardiomyopathies is complex, as cases may overlap or transition between types over time.[3] Dilated cardiomyopathy (DCM) is a heart muscle disorder marked by the enlargement of the left ventricle (LV) and a reduction in systolic function, often resulting in heart failure.[4] Often considered an "umbrella" term, DCM encompasses common pathways resulting from various diseases and gene-environment interactions.[5,6] Dilated cardiomyopathy (DCM), primarily linked to left ventricular dilation, affects all demographics, with an incidence of about 0.57 per 100,000 children, predominantly in boys. Approximately 66% of pediatric cases are idiopathic.[7] In children, DCM often arises from myocarditis, neuromuscular diseases (e.g., Duchenne muscular dystrophy), or viral infections such as parvovirus B19 and coxsackievirus. It may also develop after exposure to chemotherapy agents like anthracyclines. Genetic forms of DCM, inherited through autosomal dominant, recessive, X-linked, or mitochondrial patterns, account for 20%-48% of cases.[8] Echocardiography is essential for diagnosing and managing DCM, evolving from M-mode techniques to advanced methods like longitudinal strain.[9] In order for assessing myocardial function longitudinal strain is crucial, which provide valuable insights into regional myocardial velocities that enhance diagnostic accuracy in various cardiac conditions, including pediatric DCM.[10] A significant proportion of fatalities associated with DCM takes place within the first year of diagnosis. Additionally, many patients are often identified only in advanced stages of the disease. Thus, rigorous studies comparing echocardiographic approaches are crucial for improving early detection and management. The current study aims to evaluate the efficacy of longitudinal strain compared to conventional 2D echocardiography in assessing pediatric DCM.

Patients and methods

This prospective cross-sectional study was conducted from October to September 2024, at the Children Heart Hospital and Jamal Ahmad Rashid Pediatric Hospital ICU in Sulaimani. It included children aged 1 month to 15 years diagnosed with DCM by a pediatric cardiologist, excluding those with congenital heart disease or prior surgical interventions. Informed consent was obtained from parents, and demographic and clinical data were collected via a questionnaire. Echocardiograms were performed using a GE Vivid E9 system, assessing left ventricular (LV) function through 2D echocardiography, and longitudinal strain, with all patients showing an ejection fraction under 55% Figure (1) and (2).

A



https://doi.org/10.56056/amj.2026.477

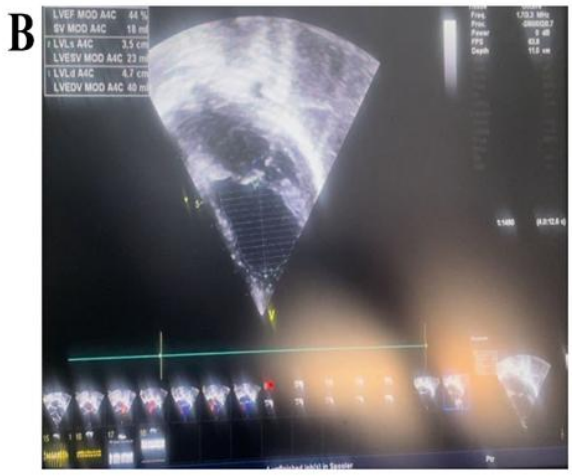


Figure (1): Echocardiographic assessment performed using the GE Vivid 9 system. (A) Evaluation of diastolic dysfunction using 2D echocardiography with mitral valve E/A ratio analysis. (B) Systolic function assessment demonstrated a marked reduction in left ventricular ejection fraction using Simpson's biplane method in 2D echocardiography and M-mode ejection fraction.

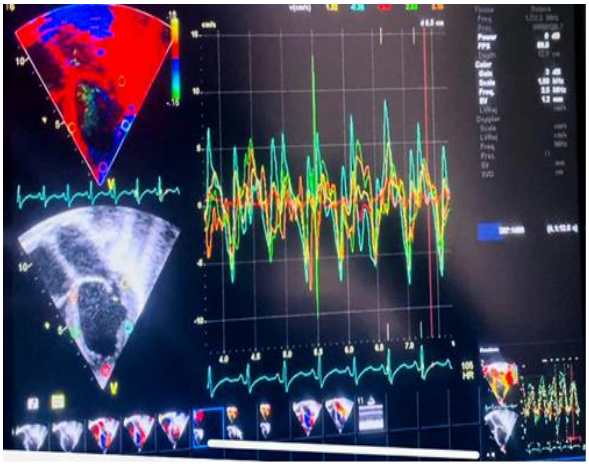


Figure (2): Longitudinal strain echo of L.V function including 5 areas: Baso septal, mid septal, apex, mid lateral, basal lateral.

Data were analyzed using SPSS version 27.0, with descriptive statistics for demographic and clinical variables. Inferential statistics, including t-tests and chi-square tests, compared echocardiographic parameters, with $p<0.05$ deemed significant. Ethical approval was granted by the Sulaimani University review board, and informed consent was obtained from participants' guardians.

Results

The study included 17 children with a mean age of 7.06±3.11 years), ranging from 3 to 13 years. Gender distribution was 47.06% male and 52.94% female. Echocardiographic measurements showed an average Simpson ejection fraction of 38.88% (range: 21.0-58.0), M-mode ejection fraction 42.18% (range: 32.0-55.0), and mitral annular plane systolic excursion (MAPSE) 1.41 cm (range: 0.70-2.20), Table (1). The mean Simpson ejection fraction was 37.0±10.06 in males and 41.0±8.51 in females (p=0.394). Basal lateral measurements were significantly higher in males, averaging 6.02±4.67 compared to 1.0±0.71 in females (p=0.009). Similarly, the mid lateral measurements were 4.01±4.02 in males, significantly higher than 0.24±1.05 in females (p=0.022), Table (2). Although trends were observed, such as lower Simpson ejection fractions in higher weight groups (<20 kg = 43.38±10.34 vs. >40 kg = 33.3±1.53, p=0.314) and increasing lateral wall basal measurements with weight (from 1.86±2.63 in <20 kg to 7.45±5.54 in >40 kg, p=0.220), none of these trends reached statistical significance, Table (3). The Simpson ejection fraction showed a decline from 41.38±12.97 in the 3–6-year group to 33.33±1.53 in the >10-year group, but this change was not statistically significant (p=0.464). Similarly, M-mode ejection fraction measurements demonstrated a decrease from 44.25±7.42 in the 3–6-year group to 37.33±0.58 in the >10-year group, with a p-value of 0.236, Table (4). Echocardiographic parameters showed a significant decrease in Simpson's ejection fraction with age (p<0.001), along with M-

https://doi.org/10.56056/amj.2026.477

mode ejection fraction measurements (p=0.003) and MAPSE values (p<0.001), Table (5).

Table (1): Descriptive Statistics of Demographic, Anthropometric, and Echocardiographic Variables

Variables	Frequency, Mean	Percentage, SD	Mini.	Maxi.
Age (years)	7.06	3.11	3.0	13.0
Gender Male Female	 9 8	 52.94 47.06		
Weight (Kg)	26.76	13.01	14.0	57.0
Height (Cm)	119.47	15.89	95.0	145.0
BMI (Kg/m^2)	17.69	3.97	13.82	27.11
Simpson ejection fraction	38.88	9.31	21.0	58.0
M mode ejection fraction	42.18	5.95	32.0	55.0
MAPSE	1.41	0.45	0.70	2.20
Baso septal	2.01	0.85	0.36	2.95
Mid septal	1.95	0.87	0.36	2.95
Apex	0.89	1.27	-1.59	2.91
Basal lateral	3.66	4.22	-0.37	11.80
Mid lateral	2.24	3.52	-1.22	9.45
MV EA ratio	2.47	0.73	1.10	3.60
Dilated Cardiomyopathy <35 35-49 >50	5 9 3	29.4 52.9 17.7		

*SD: Standard Deviation, BMI: Body Mass Index, MAPSE: Mitral Annular Plane Systolic Excursion, MV EA: Mitral Valve E/A

Table (2): Comparison of Echocardiographic Parameters Between Male and Female Patients

Parameters	Gender		p value
	Male	Female	
Simpson ejection fraction (Mean± SD)	37.0± 10.06	41.0± 8.51	0.394
M. mode ejection fraction (Mean± SD)	41.67± 5.83	42.75± 6.43	0.721
MAPSE (Mean± SD)	1.49± 0.52	1.32± 0.37	0.471
MV EA ratio (Mean± SD)	2.29± 0.65	2.67± 0.81	0.308
Basal lateral (Mean± SD)	6.02± 4.67	1.0± 0.71	0.009
Mid lateral (Mean± SD)	4.01± 4.02	0.24± 1.05	0.022
Apex (Mean± SD)	0.83± 1.35	0.96± 1.27	0.848
Mid septal (Mean± SD)	1.73± 0.92	2.19± 0.79	0.293
Baso septal (Mean± SD)	1.73± 0.92	2.32± 0.70	0.165

*SD: Standard Deviation, MAPSE: Mitral Annular Plane Systolic Excursion, MV EA: Mitral Valve E/A

Table (3): Evaluation of Echocardiographic Parameters Across Different Weight Groups

Parameters	Weight group				p-value
	<20	21-30	31-40	>40	
Simpson ejection fraction	43.38 ± 10.34	35.0± 9.90	37.0± 4.24	33.3 ± 1.53	0.314
M. mode ejection fraction	43.87 ± 7.51	42.75 ± 4.11	41.5± 4.95	37.3 ± 0.58	0.476
MAPSE	1.29± 0.36	1.38± 0.64	1.30± 0.57	1.87 ± 0.06	0.298
MV EA ratio	2.59± 0.74	2.41± 1.05	2.07± 0.52	2.50 ± 0.53	0.861
Basal lateral	1.86± 2.63	3.31± 4.64	5.90± 5.54	7.45 ± 5.54	0.220
Mid lateral	1.45± 3.39	1.82± 3.49	4.53± 3.95	3.38 ± 4.74	0.695
Apex	1.31± 1.38	0.27± 1.03	0.21± 1.73	1.08 ± 1.12	0.522
Mid septal	2.32± 0.69	1.68± 0.78	1.37± 1.34	1.73 ± 1.19	0.439
Baso septal	2.32± 0.69	1.93± 0.78	1.37± 1.34	1.73 ± 1.19	0.513

https://doi.org/10.56056/amj.2026.477

Table (4): Comparison of Echocardiographic Parameters Across Different Age Groups

Parameters	Age group			p-value
	3-6	7-10	>10	
Simpson ejection fraction	41.38± 12.97	38.3± 3.44	33.33± 1.53	0.464
M. mode ejection fraction	44.25± 7.42	41.83± 3.87	37.33± 0.58	0.236
MAPSE	1.44± 0.47	1.15± 0.36	1.87± 0.06	0.067
MV EA ratio	2.44± 0.95	2.50± 0.56	2.50± 0.53	0.990
Basal lateral	1.69± 2.72	4.40± 4.33	7.45± 5.54	0.108
Mid lateral	1.32± 3.47	2.88± 3.32	3.38± 4.74	0.618
Apex	1.22± 1.40	0.36± 1.19	1.08± 1.12	0.466
Mid septal	2.06± 0.78	1.92± 0.97	1.73± 1.19	0.867
Baso septal	2.06± 0.78	2.09± 0.92	1.73± 1.19	0.838

*MAPSE: Mitral Annular Plane Systolic Excursion, MV EA: Mitral Valve E/A

Table (5): Comparison of Clinical and Echocardiographic Parameters among Patients with Dilated Cardiomyopathy

Variables	Dilated Cardiomyopathy			p-value
	<35	35-49	>50	
Simpson ejection fraction	29.6 ± 5.64	38.89 ± 3.37	54.33 ± 3.21	<0.001
M. mode ejection fraction	37.60 ± 4.28	41.89 ± 3.22	50.67 ± 6.66	0.003
MAPSE	1.98 ± 0.16	1.21 ± 0.31	1.07 ± 0.15	<0.001
MV EA ratio	2.09 ± 0.73	2.47 ± 0.64	3.13 ± 0.72	0.143
Baso septal	1.40 ± 0.95	2.29 ± 0.80	2.18 ± 0.39	0.167
Mid septal	1.40 ± 0.95	2.18 ± 0.87	2.18 ± 0.39	0.258
Apex	0.89 ± 0.84	0.77 ± 1.13	1.27 ± 2.49	0.854
Mid lateral	1.57 ± 4.17	2.18 ± 2.89	3.52 ± 5.51	0.771
Basal lateral	4.36 ± 5.77	3.37 ± 3.77	3.38 ± 4.14	0.919

*MAPSE: Mitral Annular Plane Systolic Excursion, MV EA: Mitral Valve E/A

Discussion

Dilated cardiomyopathy (DCM) is a condition affecting the heart muscle, characterized by dilation of the LV and impaired systolic function, which frequently leads to heart failure.[4] Decreased cardiac output can lead to cachexia, fatigue, narrow pulse pressure, renal failure, dyspnea, cognitive dysfunction, and cool extremities.[11] Complications like atrial fibrillation and LV mural thrombosis can result in sudden cardiac failure, making cardiomyopathy critical in pediatric sudden cardiac event diagnosis.[2] Diagnosing DCM requires a multifaceted approach, including family history, clinical assessment, blood tests, and imaging techniques. Screening at-risk family members is essential, necessitating a thorough three-generation family history review.[12,13] Echocardiographic assessments are the most effective method for diagnosing heart diseases in pediatric populations.[14] Deformation imaging is promising for evaluating myocardial function and monitoring patients with heart conditions. However, confusion arises from the lack of comparative efficacy validation against a gold standard and limited information on the feasibility and reproducibility of strain echocardiography measurements. Reliability must be established for routine clinical use.[15] Conventional two-dimensional transthoracic echocardiography in DCM shows left ventricular dilation, reduced wall thickness, and diminished endocardial motion during systole, resulting in decreased systolic indices. While cost-effective and portable, traditional TTE is increasingly insufficient due to DCM's complexity and the need for novel imaging modalities to enhance diagnostic yield and mechanistic understanding.[16] Longitudinal strain is an emerging imaging modality that assesses myocardial deformation as a load-independent indicator of cardiac function. Unlike traditional metrics like ejection

https://doi.org/10.56056/amj.2026.477

fraction, longitudinal strain evaluates global and regional performance, tracking myocardial speckles frame-by-frame throughout the cardiac cycle to provide precise deformation indices for enhanced cardiac imaging diagnostics.[17-20] In a study by Al-Biltagi et al. on the echocardiographic evaluation of left ventricular desynchrony in Egyptian children with congestive heart failure due to DCM, the mean patient age was reported as 3.2 ± 0.6 years. Additionally, 52.7% (17 children) of the cohort were male, with a mean weight of 12.17 ± 1.3 kg and a mean height of 87.1 cm.[21] In comparison, the present study involving 17 pediatric patients showed a mean age of 7.06 ± 3.11 years, with 52.94% (9 children) being male. The mean weight was 26.76 ± 13.01 kg, and the mean height was 119.47 ± 15.89 cm. In this study, the MV E/A ratio was found to be 2.47 ± 0.73, which notably contrasts with the findings of another study that reported a mean E/A ratio of 1.31 ± 0.10.[20] Elevated E/A ratios can indicate enhanced left ventricular filling pressures or altered diastolic function, suggesting a more significant degree of myocardial compliance in our cohort. Conversely, the lower E/A ratio reported in the other study may point to impaired diastolic function or increased myocardial stiffness, aligning with the common observations in patients with more advanced cardiac dysfunction.[22] These discrepancies highlight the importance of considering clinical context and patient characteristics when interpreting E/A ratios, emphasizing the need for further investigation to understand the underlying mechanisms influencing these measurements In this study involving 17 children with a mean age of 7.06 ± 3.11 years, we found that the feasibility of using longitudinal strain echocardiography was consistent with previous finding, which reported high feasibility rates in pediatric populations.[15] The current study found a mean Simpson ejection fraction of 38.88%, with males exhibiting significantly higher lateral wall measurements than females. Furthermore, the current study aligns with existing literature that emphasizes the potential of Speckle TDI for 1st time in detecting early myocardial dysfunction, particularly in male patients, where conventional methods may overlook regional wall abnormalities.[15] Several studies have shown that longitudinal strain, with its ability to assess regional myocardial velocities, can detect early dysfunction even in asymptomatic patients.[23] The present study advocates for broader incorporation of longitudinal strain, as it significantly enhances diagnostic precision, especially in identifying subtle changes in ventricular function that are not apparent with conventional echocardiography. A key limitation of this study is the small sample size, resulting from the limited number of dilated cardiomyopathy cases identified during the research period. This constraint may impact the generalizability of the findings.

Conclusion

Our study supports the use of longitudinal strain as a valuable tool in the assessment of pediatric DCM, complementing conventional 2D echocardiography to improve diagnostic accuracy. Further research is needed to explore the full potential of longitudinal strain in guiding early interventions and improving outcomes.

Acknowledgment

We extend our heartfelt gratitude to all participants for their invaluable contributions to this study and for their unwavering support and assistance.

Conflict of interest

The authors declared no conflicts of interest.

References

1. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, et al.

https://doi.org/10.56056/amj.2026.477

Circulation.2006 Apr;113(14): 1807-16. doi: 10.1161/CIRCULATIONAHA.106.174287/
2. Mallavarapu A, Taksande A. Dilated cardiomyopathy in children: early detection and treatment. Cureus. 2022 Nov;14(11): e31111. doi: 10.7759/cureus.31111. Epub 2022 Nov 4.
3. Yuan SM. Cardiomyopathy in the pediatric patients. Pediatr Neonatol. 2018 Apr;59(2):120-128. doi: 10.1016/j.pedneo.2017.05.003. Epub 2018 Jan 31.
4. Allen HD, Driscoll DJ, Shaddy RE, Feltes TF. Moss & Adams' heart disease in infants, children, and adolescents: including the fetus and young adult. Lippincott Williams & Wilkins; 2013.
5. Sinagra G, Elliott PM, Merlo M. Dilated cardiomyopathy: so many cardiomyopathies! Eur Heart J. 2020 Oct;41(39):3784-6. doi:10.1093/eurheartj/ehz908. Epub 2019 Dec 23.
6. Towbin JA, Lowe AM, Colan SD, Sleeper LA, Orav EJ, Clunie S, et al. Incidence, causes, and outcomes of dilated cardiomyopathy in children. JAMA. 2006 Oct;296(15):1867-76. doi:10.1001/jama.296.15.1867. Epub 2006 Oct 18.
7. Njoroge JN, Mangena JC, Aribeana C, Parikh VN. Emerging Genotype–Phenotype associations in dilated cardiomyopathy. Curr Cardiol Rep. 2022 Sep;24(9):1077-84. doi:10.1007/s11886-022-01727-z. Epub 2022 July 28.
8. Fatema NN, Nazmi NI. Dilated Cardiomyopathy in Paediatric Population: A Review. Cardiovasc J. 2019 Jul;12(1): 64-74. doi:10.3329/cardio. v12i1.43422. Epub 2019 Jul 1.
9. Faggiano A, Avallone C, Gentile D, Provenzale G, Toriello F, Merlo M, et al. Echocardiographic advances in dilated cardiomyopathy. J Clin Med. 2021 Nov;10(23):5518. doi:10.3390/jcm10235518. Epub 2021 Nov 21.
10. Kadappu KK, Thomas L. Tissue Doppler imaging in echocardiography: value and limitations. Heart Lung Circ. 2015 Mar;24(3):224-33. doi: 10.1016/j.hlc.2014.10.003. Epub 2014 Oct 28.
11. Rupp S, Jux C. Advances in heart failure therapy in pediatric patients with dilated cardiomyopathy. Heart Fail Rev. 2018 Jul;23(4):555-62. doi:10.1007/s10741-018-9692-1. Epub 2018 Mar 22.
12. Weintraub RG, Semsarian C, Macdonald P. Dilated cardiomyopathy. Lancet. 2017 Jul;390(10092):400-14. doi:10.1016/S0140-6736(16)31713-5. Epub 2017 Feb 9.
13. Daubeney PE, Nugent AW, Chondros P, Carlin JB, Colan SD, Cheung M, et al. Clinical features and outcomes of childhood dilated cardiomyopathy: results from a national population-based study. Circulation. 2006 Dec;114(24):2671-8. doi:10.1161/CIRCULATIONAHA.106.635128. Epub 2006 Nov 20.
14. Tissot C, Singh Y, Sekarski N. Echocardiographic evaluation of ventricular function—for the neonatologist and pediatric intensivist. Front Pediatr. 2018 Apr; 6:79. doi:10.3389/fped.2018.00079. Epub 2018 Apr 4.
15. Koopman LP, Slorach C, Hui W, Manlhiot C, McCrindle BW, Friedberg MK, et al. Comparison between different speckle tracking and color tissue Doppler techniques to measure global and regional myocardial deformation in children. J Am Soc Echocardiogr. 2010 Sep;23(9):919-28. doi: 10.1016/j.echo.2010.06.014. Epub 2010 July 23.
16. Murtaza G, Virk HU, Khalid M, Rahman Z, Sitwala P, Schoondyke J, et al. Role of speckle tracking echocardiography in dilated cardiomyopathy: a review. Cureus. 2017 Aug;9(6).

doi:10.9734/jpri/2021/v33i39B32206. Epub 2021 Aug 3.
17. Schulz-Menger J. Diagnostic accuracy of CMR in biopsy-proven acute myocarditis. JACC: Cardiovasc Imaging. 2014 Mar;7(3):264-6. doi: 10.1016/j.jcmg.2014.01.005. Epub 2014 Mar.
18. Cameli M, Lisi M, Giacomin E, Caputo M, Navarri R, Malandrino A, et al. Chronic mitral regurgitation: Left atrial deformation analysis by two-dimensional speckle tracking echocardiography. Echocardiography. 2011 Mar;28(3):327-34. doi:10.1111/j.1540-8175.2010.01329. x. Epub 2011 Feb 17.
19. Haugaa KH, Goebel B, Dahlslett T, Meyer K, Jung C, Lauten A, et al. Risk assessment of ventricular arrhythmias in patients with nonischemic dilated cardiomyopathy by strain echocardiography. J Am Soc Echocardiogr. 2012 Jun;25(6):667-73. doi: 10.1016/j.echo.2012.02.004. Epub 2012 Mar 14.
20. D'Ascenzi F, Cameli M, Zacà V, Lisi M, Santoro A, Causarano A, et al. Supernormal diastolic function and role of left atrial myocardial deformation analysis by 2D speckle tracking echocardiography in elite soccer players. Echocardiography. 2011 Mar;28(3):320-6. doi:10.1111/j.1540-8175.2010.01338. x. Epub 2011 Mar 3.
21. Al-Biltagi MA, Tolba OA, El Mahdy H, Donia A, Elbanna S. Echocardiographic assessment of left ventricular dyssynchrony in Egyptian children with congestive heart failure due to dilated cardiomyopathy. Cardiol Young. 2015 Aug;25(6):1173-81. doi:10.1017/S1047951114001863. Epub 2014 Oct 2.
22. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur J Echocardiogr. 2016 Jul;17(12):1321-60. doi:10.1093/ehjci/jew082. Epub 2016 Jul 15.
23. Mahmoud HE, Sabra AM, Awad MS, Hussein A. Value of Pulsed Tissue Doppler Imaging in Predicting the Presence of Significant Coronary Artery Insufficiency. World J Cardiovasc Dis. 2020 Apr;10(5):305-12. doi:10.4236/wjcd.2020.105028. Epub 2020 May 13.