

# Assessment of left ventricular functions with tissue Doppler, strain, and strain rate echocardiography in patients with familial Mediterranean fever

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## ABSTRACT

**Objective:** This study assessed the early changes in regional and global systolic and diastolic myocardial functions in patients with familial Mediterranean fever without any cardiovascular symptoms using tissue Doppler and strain and strain rate echocardiography and compared them to the results of a control group.

**Methods:** This study has a cross-sectional and observational design. FMF patients with normal left ventricular function were included in the study. We excluded patients who had arrhythmia, acquired/congenital heart disease, pericarditis, or acute attack. We compared 45 children with familial Mediterranean fever on colchicine therapy and 45 age- and sex-matched healthy children.

**Results:** The 45 patients with familial Mediterranean fever included 24 (55.3%) girls and 21 (46.7%) boys with a mean age of 11.3±3.7 (range 2-18) years. The mean disease duration was 4.6±2.4 (range 0.5-10) years. In the patient group, the homozygous M694V mutation was the most common (64.4%) mutation. The patients with familial Mediterranean fever had statistically lower longitudinal global strain, radial global strain, and strain rates (-14.44±4.77%, 14.80±6.29%, and 0.59±0.24 s, respectively) than the controls (-17.40±1.79%, 17.53±4.63%, and 0.83±0.51 s) (p<0.05). The circumferential global strain did not differ significantly between the groups.

**Conclusion:** Patients with familial Mediterranean fever who are subclinical from a cardiac aspect might have normal left ventricular function as measured by conventional echocardiography. However, the disease affects their myocardial tissue, and these patients should be followed with conventional, strain, and strain rate echocardiography techniques regularly. (*Anatol J Cardiol* 2015; 15: 663-8)

**Keywords:** familial Mediterranean fever, strain, global strain, strain rate

## Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent fever, peritonitis, pleuritis, arthritis, and erysipelas-like skin lesions. Currently, the Mediterranean fever (MEFV) gene and its product, pyrin, which is expressed by neutrophils, are believed to be responsible for this disease (1-3).

Clinical and subclinical cardiovascular involvement has been reported in a variety of inflammatory rheumatic diseases, including juvenile idiopathic arthritis, ankylosing spondylitis, systemic lupus erythematosus, and Behçet's disease (4, 5). However, evidence of cardiac involvement in FMF patients is limited to pericardial involvement (6, 7).

To assess cardiac involvement and consequently left ventricular function in patients with FMF, conventional echocardiographic methods are used most often. However, subclinical FMF patients are often deemed normal with conventional echocardiography and pulsed-wave Doppler (PWD). Pulsed-wave Doppler tissue imaging evaluates both global and regional myocardial function to reveal subclinical cases and examine left ventricular myocardial segments (8, 9). However, this method can not distinguish between active and passive myocardial movement (such as tethering or translational motion) and is affected by rotational movement of the heart. In addition, because it is limited by image quality and depends on the angle of the apex of the heart, a new technique has been developed: strain (S) and strain rate (SR) echocardiography (10, 11). S and

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**Accepted Date:** 15.07.2014 **Available Online Date:** 19.08.2014

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DOI:10.5152/akd.2014.5544



SR can be determined using two different methods: tissue Doppler and two-dimensional speckle tracking (spot monitor). Tissue Doppler imaging-derived S and SR imaging has been used for measuring mechanical myocardial function for several years (12-14). Nevertheless, tissue Doppler-based S and SR are angle-dependent and subject to sound interference and inter- and intra-user variability; these are important limitations. Speckle-tracking echocardiography is an alternative technique for monitoring the movement of natural acoustic reflections and does not have the limitations associated with tissue Doppler-based S and SR (15-18).

It is known that changes in left ventricular segments in patients with FMF depend on various factors. These factors are fibrous scarring in the cardiac muscle, nodular granulomatous lesions, myocarditis, arteritis, amyloidosis, and agents used in the treatment of FMF. It is reported that increased proinflammatory cytokines cause collagen deposition and fibrosis by activating fibroblast functions in the disease process (4, 5). No study has evaluated myocardial function using S and SR in patients with FMF. Therefore, we evaluated left ventricular function using conventional echocardiography, PWD, and speckle-tracking echocardiography-based S and SR in FMF patients to detect early global and regional changes in systolic and diastolic function in FMF patients and to assess whether myocardial involvement that can not be detected with conventional echocardiography can be identified using S and SR echocardiography.

## Methods

### Study design

This study has a cross-sectional and observational design.

### Study population

This study was performed between May 2012 and September 2012. The study included patients with a diagnosis of FMF followed by the pediatric nephrology clinic of Dr. Sami Ulus Children's Hospital in Ankara. All patients gave written informed consent, and the local Ethics Committee approved the study protocol.

The medical history, physical examination, and laboratory, electrocardiographic, and echocardiographic findings of the FMF patients were obtained from hospital records. After evaluating the patients with standard echocardiographic methods, 45 FMF patients with normal left ventricular function were included in the study. We excluded patients who had arrhythmia, acquired/congenital heart disease, pericarditis, or acute attack. Gene analysis, hemoglobin, white blood cell count (WBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and fibrinogen levels were obtained from the laboratory records. The duration of disease and use of colchicine were determined.

The control group consisted of 45 age- and sex-matched healthy children with normal left ventricular function, admitted to the department of pediatric cardiology for murmur evaluation.

### Study protocol

For all of the study subjects, the echocardiographic recordings were accompanied by monitoring DII derivation with an IE 33 echocardiograph (S5-1 probe, IE33, Philips, Andover, MA, USA) in the back-to-top or left lateral decubitus position by the same pediatric cardiologist (Ö.C.). The left ventricular function of the subjects was evaluated using standard echocardiography, PWD, and S and SR echocardiography.

### Standard echocardiography

Standard two-dimensional, M-mode, and Doppler flow echocardiography measurements were made in accordance with the recommendations of the American Society of Echocardiography (19). All echocardiographic examinations were performed by the same investigator to avoid interobserver variability. M-mode measurements were obtained in the parasternal long-axis position. The shortening fraction (SF), left ventricular posterior wall during diastole, and septum thickness were measured with M-mode echocardiography. The shortening fraction was calculated as the difference between the left ventricular end-diastolic and end-systolic diameters, divided by the left ventricular end-diastolic diameter. The left ventricular end-diastolic and end-systolic volumes were measured using the biplane modified Simpson's method. The mitral valve flow velocity was measured with the conventional PW Doppler technique. In the apical four-chamber view, the sample volume was placed parallel to the tips of the mitral valve and flow. Peak transmitral flow velocity in early diastole (peak E), late diastolic transmitral flow velocity (peak A), the E/A ratio, and E wave deceleration time (the period between the E wave peak and E wave baseline) were obtained from mitral flow tracing.

### Pulsed-wave tissue Doppler echocardiography (PWD)

The best PWD records with the highest amplitude signal were evaluated. Apical four-chamber color tissue Doppler images were obtained while breathing using the activating tissue Doppler image feature on the device. The Nyquist limit was adjusted to the range of -20 to 20 cm/s, and a high frame rate (>100 frames s<sup>-1</sup>) was used. In the apical four-chamber view, a 5-mm tissue Doppler sample volume was placed on the left ventricular septal mitral annulus and lateral mitral annulus, and then, waves representing the systolic and diastolic mitral annular movements were displayed. The peak velocities of waves with a positive S during ventricular systole, a negative Em during early diastolic filling, and negative Am caused by contraction of the left atrium during late diastole were measured throughout the cardiac cycle. The isovolumic relaxation time (the period between the termination of the Sm wave and start of the Em wave), isovolumic contraction time (the period between the termination of the Am wave and start of the Sm wave), ejection time, and myocardial performance index (MPI) were calculated.

### Two-dimensional speckle-tracking echocardiography

Apical four-chamber and parasternal short-axis echocardiographic images of the patients at level of the papillary muscle

were recorded digitally as an average of three beats in cine-loop format for later analysis. Then, the endocardial borders were identified manually with the speckle-tracking software (QLAB ver. 6.0, TMQ, Philips Medical Systems) built into the IE 33 echocardiograph. Then, S and SR were calculated automatically for all myocardial tissue. Because the software does not calculate the peak values of SR automatically, the peak SR of the peak strain and average global rate were calculated manually. The peak longitudinal S and SR of the left ventricular global, basal anterolateral, basal interventricular septal, mid-anterolateral, mid-interventricular septal, apical anterolateral, apical interventricular septal, and apical regions were measured in the apical four-chamber position. In addition, the peak circumferential and radial S and SR values of the global, mid-anteroseptal, mid-inferolateral, mid-anterior, mid-inferior, mid-anterolateral, and mid-inferoseptal regions were measured in the parasternal short-plane position.

### Statistical analysis

The Statistical Package for the Social Sciences for Windows, ver. 11.5 was used for the statistical analysis (SPSS, Chicago, IL, USA). Numerical values are expressed as mean±standard deviation, and categorical data are given as percentages. The Kolmogorov-Smirnov test was used to determine whether the data were distributed normally. The unpaired student's t-test was used to compare the means of normally distributed data, while the Mann-Whitney U test was used for non-normal distributions. Correlations among the quantitative data were analyzed using Pearson's correlation test. The results are given with the 95% confidence interval (CI) and are considered significant at  $p < 0.05$ .

## Results

### General findings

The 45 patients with FMF included 24 (55.3%) girls and 21 (46.7%) boys, with a mean age of  $11.3 \pm 3.7$  (range 2-18) years. There was no significant ( $p > 0.05$ ) difference between the patient and control groups in terms of age, gender, height, and weight. The mean disease duration was  $4.6 \pm 2.4$  (range 0.5-10) years. The homozygous M694V mutation was the most common (64.4%) mutation. All of the patients were on colchicine therapy and were asymptomatic from a cardiovascular standpoint. Table 1 shows the demographic data and laboratory findings of the patient and control groups.

### Standard echocardiographic findings

All standard echocardiographic findings of chamber size and systolic and diastolic function were within normal limits in both groups (Table 2). Ejection fraction (EF) was significantly lower in the patient group than in the control subjects ( $p < 0.05$ ). There was no significant difference between patients and controls in terms of SF, interventricular septum thickness, and left ventricular posterior wall thickness. The mitral valve early

**Table 1. Comparison of demographic and laboratory findings between patients with familial Mediterranean fever and control group**

		Patients	Controls	P
Age, years		$11.3 \pm 3.7$	$11.2 \pm 3.4$	0.868
Gender	F, %	24 (55.3)	21 (46.7)	0.532
	M, %	21 (46.7)	24 (55.3)	
Height, cm		$138 \pm 20.6$	$142 \pm 26.9$	0.416
Weight, kg		$38.5 \pm 13.3$	$38.6 \pm 13.9$	0.468
Colchicine		45% 100		
Duration of disease, years		$4.6 \pm 2.4$ (6 months-10 years)	-	-
WBC, $\times 10^3/\text{mm}^3$		$7.9 \pm 2.7$	-	-
Hb, g/dL		$12.8 \pm 1.2$	-	-
Sedimentation, mm/h		$14.4 \pm 8.7$	-	-
CRP, mg/dL		$5.9 \pm 6.5$	-	-
Fibrinogen, gr/L		$280 \pm 94.9$	-	-

CRP - C-reactive protein; Hb - hemoglobin; WBC - white blood cell

filling velocity wave was significantly higher in patients than in the controls ( $p < 0.05$ ). The peak mitral E-wave, DT, peak A, and E/A ratio were not significantly different between the groups (Table 2).

### Tissue Doppler echocardiographic findings

The Sm wave of the septal mitral annulus was lower in the patient group ( $p < 0.05$ ). The septal MPI was higher in the patients ( $p < 0.05$ ). The septal mitral annular isovolumic contraction time (IVCT) and Am wave were lower in the patient group ( $p < 0.05$ ). There was no difference between the groups in terms of septal mitral annular Em, isovolumic relaxation time (IVRT), ET, E/Em, lateral mitral annulus Am, ET, IVRT, Sm, IVCT, and lateral MPI (Table 2).

### Two-dimensional speckle-tracking strain and strain rate findings

The longitudinal global strain (LGS), basal anterolateral, mid-anterolateral, and apical interventricular septum values were significantly lower in the patient group than in the controls ( $p < 0.05$ ). The circumferential global strain (CGS) and circumferential global strain rate (CGSR) were not found to be different between groups. The radial global strain (RGS) and average radial global strain rate (RGSR) were significantly decreased compared with controls ( $p < 0.05$ ). The radial strain rate (RSR) in the mid-anterior, mid inferior, and mid-inferolateral regions was lower in the patient group ( $p < 0.05$ ). Table 3 shows the longitudinal, circumferential, and radial global strain and strain rate values of familial Mediterranean fever patients and controls.

## Discussion

Conventional echocardiographic EF was lower in patients than in the control group, although it was within normal lim-

**Table 2. The standard echocardiography, pulsed-wave mitral flow velocity, and tissue Doppler values of familial Mediterranean fever patients and controls**

	Patients	Controls	P
EF, %	72.0±5.7	74.4±5.2	0.045
SF, %	40.7±5.2	42.5±5.7	0.136
Septum, mm	7.4±1.5	7.5±1.4	0.717
Posterior wall, mm	7.0±1.3	7.2±1.3	0.653
E, cm/s	99.9±12.1	93.8±14.3	0.035
A, cm/s	52.7±12.6	55.4±12.1	0.305
DT, ms	114.9±24.8	114.5±22.3	0.929
E/A	1.86±0.46	1.86±0.39	0.962
Septum Em, cm/s	13.3±2.3	13.5±1.7	0.728
Septum Am, cm/s	6.7±2.0	7.7±1.1	0.021
Septum Sm, cm/s	7.5±1.1	8.1±1.2	0.027
Septum IVCT, ms	59.5±13.5	53.0±14.4	0.032
Septum IVRT, ms	59.0±15.1	54.9±10.9	0.140
Septum ET, ms	264.7±25.7	272.2±25.1	0.165
Lateral Em, cm/s	15.6±2.7	16.6±2.3	0.074
Lateral Am, cm/s	6.8±2.0	7.5±2.2	0.105
Lateral Sm, cm/s	9.51±2.0	8.8±1.9	0.677
Lateral ICT, ms	60.5±16.2	60.3±14.7	0.939
Lateral IRT, ms	60.4±11.9	56.5±13.7	0.158
Lateral ET, ms	264.9±25.1	272.4±21.5	0.133
Septum MPI	0.44±0.09	0.39±0.07	0.004
Lateral MPI	0.46±0.09	0.42±0.08	0.120
Septum E/Em	7.18±1.44	7.51±1.30	0.258
Lateral E/Em	6.15±1.06	6.11±1.06	0.862

A - late diastole peak transmitral flow velocity; Am - peak late diastolic myocardial velocity; DT - deceleration time; E - peak transmitral flow velocity in early diastole; Em - peak early diastolic myocardial velocity; EF - ejection fraction; ET - ejection time; ICT - isovolumic contraction time; IRT - isovolumic relaxation time; MPI - myocardial performance index; SF - shortening fraction; Sm - myocardial peak systole flow rate

**Table 3. The longitudinal, circumferential, and radial global strain and strain rate values of familial Mediterranean fever patients and controls**

	Patients	Controls	P
Longitudinal global strain	-14.44±4.77	-17.40±1.79	<0.001
Longitudinal global strain rate	-0.38±0.15	-0.42±0.17	0.254
Circumferential global strain	-16.18±3.12	-17.03±2.51	0.157
Circumferential global strain rate	-1.64±0.64	-1.68±0.49	0.804
Radial global strain	14.80±6.29	17.53±4.63	0.022
Radial global strain rate	0.59±0.24	0.83±0.51	0.005

its. In addition, the septal mitral annular Sm and MPI waves measured with PWD were higher, but the strain echocardiographic LGS and RGS findings were lower in the patient group than in the controls. All of these findings are compatible with each other and support each other. These findings

are related to affected left ventricular myocardial tissue in FMF patients.

The aims of this study were to detect early global and regional changes in systolic and diastolic function in FMF patients without cardiac symptoms and assess whether myocardial involvement that can not be detected by conventional echocardiography can be detected with PWD and S and SR echocardiography. Few studies have examined myocardial involvement in FMF patients, and the methods used in these studies were conventional echocardiography and PWD (2, 3). No study has evaluated myocardial involvement with S and SR echocardiography techniques in pediatric FMF patients.

In this study, we observed a weakly significant ( $p<0.05$ ) decrease in EF with conventional echocardiography in the patient group compared to the controls. The SF values were similar for the patients and controls. Note also that although the EF was lower in the patient group, it was still within normal limits.

The EF reflects the radial performance of the myocardium, but it ignores longitudinal contraction and deformation. The systolic mechanics act in the circumferential, longitudinal, and radial directions, due to the complex nature of myocardial fibers. The EF is load-dependent and evaluates the heart globally. In addition, the EF varies across individuals. It gives subjective information for interpreting regional myocardial function (15, 16). The septal mitral annulus IVCT and Sm and Am waves were significantly lower, and the septal MPI was significantly higher in the patient group. The Sm wave velocity, determined by PWD, had a good positive correlation with left ventricular systolic function and was significantly lower in the patient group, showing that systolic function is impaired in these patients. MPI is a parameter that measures left ventricular systolic and diastolic function. Normally, MPI is  $<0.40$ . Progressive deterioration of ventricular function causes MPI to increase (20). In our study, MPI was significantly higher in the patient group, which proves that left ventricular systolic and diastolic function is impaired in FMF patients. Using PWD, Özdemir et al. (4) showed that left ventricular function was preserved, while right ventricular diastolic function was impaired in FMF patients, and reported that this is an early indicator of cardiac involvement. Sarı et al. (7) reported similar findings and showed that right ventricular systolic and diastolic function and left ventricular diastolic function, measured by PWD, were impaired in adult FMF patients. In the present study, we used conventional Doppler echocardiography and PWD and detected systolic and diastolic dysfunction in FMF patients. This result is contrary to Özdemir et al. (4), because they showed that left ventricular function was not affected in their patients. Our results are compatible with Sarı et al. (7), who reported left ventricular diastolic dysfunction in their patients.

To the best of our knowledge, no study has assessed left ventricular function using S and SR echocardiography in pediatric FMF patients. We believe that our study is important, because it is the first such study.

The LGS assesses the longitudinal axis of the left ventricle and was significantly lower in the patient group. This shows that



longitudinal axis left ventricular systolic function and deformation are impaired in pediatric FMF patients. The endocardium of the left ventricle was the region that was affected the most by hypoperfusion, fibrosis, and ischemic changes, probably caused by an increased pro-inflammatory response, the accumulation of amyloid and drugs, and the intensification of the longitudinal muscle fibers in the subendocardial region. Consequently, it is not surprising that the LGS was lower in the patient group. We observed that deformation was decreased in the longitudinal axis, especially in the anterolateral basal, mid- anterolateral, and apical regions of the interventricular septum, and this decrease was significant.

The CGS assesses circumferential left ventricular muscle fibers and was similar in both groups. Therefore, we concluded that the circumferential axis is not affected in patients. CS is more important for distinguishing non-transmural from transmural infarction. If a patient is not affected transmurally, circumferential muscle fibers are rarely affected, and the circumferential strain is usually reported as normal. In this study, we found normal CS and CSR values in the patient group and showed that the circumferential muscle fibers were not affected in FMF patients.

The RGS assesses left ventricular function globally in the radial axis and was significantly lower in the patient group. Therefore, deformation is reduced in the radial axis in FMF patients, and systolic function was impaired for this axis. RGS was also significantly lower in the patient group. The EF reflects the radial force. EF and RGS were lower in the patient group, and these findings support each other.

Myocardial fibers in the heart extend longitudinally, circumferentially and transmurally. Longitudinal fibers are localized in the subendocardial and subepicardial regions, whereas fibers running circumferentially are localized more centrally in the mid-myocardial layer. Because the outer part of the left ventricle generally does not change during the cardiac cycle, the CS can be close to 0 and depends on the area measured; in such cases, the main strains acting on the ventricle are LS and RS. Circumferential fibers are responsible mainly for maintaining the internal pressure (21-24).

Because it is a relatively new technology, in the pediatric age group, there are limited established normal range values for strain and strain rate echocardiography. Marcus et al. (25) presented age-specific reference values for two-dimensional S and SR echocardiography parameters in a large, healthy pediatric and young adult cohort. In our study, the strain measurements in both the patient and control groups were less than the normal ranges reported by Marcus et al. (25). Sims et al. (26) studied S and SR echocardiography in HIV-infected children and young adults and reported that HIV-infected participants demonstrated impaired S and SR findings compared with healthy controls. They also defined that the strain measurements in both the study and control groups were less than the reported normal ranges. This may be due to differences between the various systems that were used to get strain results or due to interobserver variability in the measurement of strain.

## Study limitations

Limitations of the present study included the limited sample size and the relatively wide age range of the patient group. Prospective studies with larger sample sizes are needed to confirm our conclusions. Prior studies have shown some intraobserver and interobserver variability in the measurement of strain. In the present study, only one pediatric cardiologist studied the echocardiographic parameters, but we did not measure intraobserver variability. The exclusion of patients with FMF attack and presence of colchicine as a confounding factor may also be other limitations.

## Conclusion

As a result, we suggest that subtle cardiac functional abnormalities are present in patients with FMF that are demonstrated only on newer, load-independent measures of strain and strain rate echocardiography. Further studies are needed to determine the significance of our findings in patients with FMF, but strain abnormalities, especially LGS and RGS, may be an important preclinical precursor to cardiac disease in this population.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Concept - S.K., Ö.C., S.Ö.; Design - U.A.Ö.; Supervision - Ö.C., Ö.E.; Resource - Ö.C., S.Ö., V.D., O.Y.; Materials - Ö.C., V.D.; Data collection and/or processing - Ö.C., S.Ö., O.Y.; Analysis and/or Interpretation - Ö.C., U.A.Ö.; Literature search - M.E.A., M.K.; Writing - Ö.C., S.K.; Critical review - Ö.C., S.K., Ö.E.

## References

1. Yılmaz E, Özen S, Balcı B, Düzova A, Topaloğlu R, Beşbaş N, et al. Mutation frequency of Familial Mediterranean Fever and evidence for a high carrier rate in the Turkish population. *Eur J Hum Genet* 2001; 9: 553-5. [\[CrossRef\]](#)
2. Tunca M, Akar S, Önen F, Özdoğan H, Kasapçopur O, Yalçinkaya F, et al. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. *Medicine (Baltimore)* 2005; 84: 1-11. [\[CrossRef\]](#)
3. Lidar M, Kedem R, Mor A, Levartovsky D, Langevitz P, Livneh A. Arthritis as the sole episodic manifestation of familial Mediterranean fever. *J Rheumatol* 2005; 32: 859-62.
4. Özdemir O, Agrad P, Aydın Y, Abacı A, Hızlı S, Akkuş H, et al. Assessment of cardiac functions using tissue Doppler imaging in children with familial Mediterranean fever. *Cardiol Young* 2012; 22: 188-93. [\[CrossRef\]](#)
5. Yılmaz O, Ceylan O, Örün UA, Özgür S, Karademir S, Doğan V, et al. Assessment of left ventricular functions with tissue Doppler, strain and strain rate echocardiography in children with juvenile idiopathic arthritis: An observational study. *Anatol J Cardiol* 2012; 12: 339-46.
6. Tutar E, Yalçinkaya F, Özkaya N, Ekim M, Atalay S. Incidence of pericardial effusion during attacks of familial Mediterranean fever. *Heart* 2003; 89: 1257-8. [\[CrossRef\]](#)

7. Sarı I, Arıcan O, Can G, Akdeniz B, Akar S, Birlik M, et al. Assessment of aortic stiffness and ventricular functions in familial Mediterranean fever. *Anatol J Cardiol* 2008; 8: 271-8.
8. Nesbitt GC, Mankad S, Oh JK. Strain imaging in echocardiography: methods and clinical applications. *Int J Cardiovasc Imaging* 2009; 25: 9-22. [\[CrossRef\]](#)
9. Triantafyllou KA, Karabinos E, Kalkandi H, Kranidis AI, Babalis D. Clinical implications of the echocardiographic assessment of left ventricular long-axis function. *Clin Res Cardiol* 2009; 98: 521-32. [\[CrossRef\]](#)
10. Hatle L, Sutherland GR. Regional myocardial function-a new approach. *Eur Heart J* 2000; 21: 1337-57. [\[CrossRef\]](#)
11. Shave R, George K, Whyte G, Middleton N, Hart E, Artis N, et al. A comparison of Doppler, tissue Doppler imaging, and strain rate imaging in the assessment of post-exercise left ventricular function. *Appl Physiol Nutr Metab* 2009; 34: 33-9. [\[CrossRef\]](#)
12. Hoffmann R, Lethen H, Marwick T, Arnese M, Fioretti P, Pingitore A, et al. Analysis of interinstitutional observer agreement in interpretation of dobutamine stress echocardiograms. *J Am Coll Cardiol* 1996; 27: 330-6. [\[CrossRef\]](#)
13. Abraham TP, Nishimura RA. Myocardial strain: can we finally measure contractility? *J Am Coll Cardiol* 2001; 37: 731-4. [\[CrossRef\]](#)
14. Pellikka PA, Nagueh SF, Elhendy AA, Kuehl CA, Sawada SG; American Society of Echocardiography. American Society of Echocardiography recommendations for performance, interpretation, and application of stress echocardiography. *J Am Soc Echocardiogr* 2007; 20: 1021-41. [\[CrossRef\]](#)
15. Koyama J, Ray-Sequin PA, Falk RH. Longitudinal myocardial function assessed by tissue velocity, strain, and strain rate tissue Doppler echocardiography in patients with AL (primary) cardiac amyloidosis. *Circulation* 2003; 107: 2446-52. [\[CrossRef\]](#)
16. Delgado V, Tops LF, van Bommel RJ, van der Kley F, Marsan NA, Klautz RJ, et al. Strain analysis in patients with severe aortic stenosis and preserved left ventricular ejection fraction undergoing surgical valve replacement. *Eur Heart J* 2009; 30: 3037-47. [\[CrossRef\]](#)
17. Isaaz K, Munoz del Romeral L, Lee E, Schiller NB. Quantitation of the motion of the cardiac base in normal subjects by Doppler echocardiography. *J Am Soc Echocardiogr* 1993; 6: 166-76. [\[CrossRef\]](#)
18. McDicken WN, Sutherland GR, Moran CM, Gordon LN. Colour Doppler velocity imaging of the myocardium. *Ultrasound Med Biol* 1992; 18: 651-4. [\[CrossRef\]](#)
19. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; 18: 1440-63. [\[CrossRef\]](#)
20. Feigenbaum H, Armstrong WF, Ryan T. Cardiomyopathies. In: Feigenbaum H, Armstrong WF, Ryan T, editors. *Feigenbaum's Echocardiography*, 6<sup>th</sup> Edition, Lippincott Williams & Wilkins 2005.p.524-58.
21. Doğan V, Öcal B, Örün UA, Özgür S, Yılmaz O, Keskin M, et al. Strain and strain rate echocardiography findings in children with asymptomatic congenital aortic stenosis. *Pediatr Cardiol* 2013; 34: 1152-8. [\[CrossRef\]](#)
22. Pellerin D, Sharma R, Elliott P, Veyrat C. Tissue Doppler, strain, and strain rate echocardiography for the assessment of left and right systolic ventricular function. *Heart* 2003; 89: 9-17. [\[CrossRef\]](#)
23. Mirsky I, Parmley WW. Assessment of passive elastic stiffness for isolated heart muscle and the intact heart. *Circ Res* 1973; 33: 233-43. [\[CrossRef\]](#)
24. Greenbaum RA, Ho SY, Gibson DG, Becker AE, Anderson RH. Left ventricular fibre architecture in man. *Br Heart J* 1981; 45: 248-63. [\[CrossRef\]](#)
25. Marcus KA, Mavinkurve-Groothuis AM, Barends M, van Dijk A, Feuth T, de Korte C, et al. Reference values for myocardial two-dimensional strain echocardiography in a healthy pediatric and young adult cohort. *J Am Soc Echocardiogr* 2011; 24: 625-36. [\[CrossRef\]](#)
26. Sims A, Frank L, Cross R, Clauss S, Dimock D, Purdy J, et al. Abnormal cardiac strain in children and young adults with HIV acquired in early life. *J Am Soc Echocardiogr* 2012; 25: 741-8. [\[CrossRef\]](#)