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ORIGINAL ARTICLE

Assessment of subclinical left ventricular systolic function using strain imaging in the follow-up of patients with chronic mitral regurgitation

Kronik mitral yetersizliği olan hastalarda 12. aylık takiplerin sonunda sol ventrikül sistolik fonksiyonlarının subklinik düzeyde strain inceleme ile değerlendirilmesi

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ABSTRACT

Objective: Determining optimal timing for surgery in asymptomatic mitral regurgitation (MR) remains a challenge. The aim of this study was to evaluate subclinical changes in left ventricular (LV) systolic functions using velocity vector imaging (VVI) during follow-up of patients with chronic mitral regurgitation (MR).

Methods: A total of 54 patients (mean age: 57.9±8 years; 55% male) with moderate-to-severe MR and normal LV ejection fraction (EF), and 30 healthy controls (mean age: 56±6.5 years; 55% male) were evaluated using conventional echocardiography and VVI at baseline.

Results: At the end of 12 months, measurements of 45 MR patients were repeated. There was no significant change in LV dimensions or EF on follow-up. LV peak systolic strain and strain rate (SR) were decreased in patients with MR compared with controls (strain: 16.29±3.30 to 23.4±1.9; p=0.0001 and SR: 0.93±0.39 to 4.9±0.6; p=0.0001) at baseline. Impairment was more significant on follow-up. (strain: 13.76±2.68 and SR: 0.27±0.14; p=0.0001).

Conclusion: VVI-derived strain imaging might be used in the assessment of subclinical LV dysfunction and its progression during follow-up of patients with chronic MR especially in the decision of optimal timing for surgery.

ÖZET

Amaç: Semptomsuz mitral yetersizliğinde (MY) en uygun cerrahi zamanı tartışmalı bir konudur. Çalışmamızda kronik MY olan semptomsuz hastaların takibinde sol ventrikül (SV) sistolik fonksiyonlarındaki değişiklikleri. Bir *strain* inceleme yöntemi olan hız vektör görüntüleme (HVG) metodu ile incelemeyi amaçladık.

Yöntemler: Çalışmamıza orta-ileri MY ve SV ejeksiyon fraksiyonu (EF) normal olan 54 hasta (ortalama yaş 57.9±8, %55 erkek) ve 30 sağlıklı gönüllü (ortalama yaş 56±6.5, %55 erkek) ilk değerlendirmede geleneksel ekokardiyografi ve HVG yöntemi ile incelendi.

Bulgular: Takiplerinde, 12. ayın sonunda 45 hastanın klinik ve ekokardiyografik incelemeleri yapıldı. SV boyutlarında ve EF'sinde anlamlı bir değişiklik olmadı. SV *strain* değerleri başlangıçdaki ölçümlere göre önemli derecede azaldı. SV zirve sistolik *strain* (S) ve *strain rate* (SR) değerleri başlangıçta sağlıklı kontrol grubuna göre anlamlı derecede düşük idi (S: 16.29±3.30, 23.4±1.9, p=0.0001 ve SR: 0.93±0.39, 4.9±0.6, p=0.0001). İzlemdeki azalış anlamlı bulundu (S: 13.76±2.68 ve SR: 0.27±0.14, p=0.0001).

Sonuç: Kronik MY olan hastalarda, cerrahi zamanlamanın doğru belirlenmesi ve özellikle SV sistolik fonksiyon bozukluğunun klinik öncesi dönemde değerlendirilmesi için HVG kaynaklı *strain* inceleme kullanılabilir.

Chronic primary mitral regurgitation (MR) is a common and progressive valve disease that is difficult to manage. Due to adaptive remodeling of the left ventricle (LV) and left atrium (LA), patients can remain asymptomatic or minimally symptomatic for a long period of time. However, progressive LV remodeling results in LV systolic failure.[1] In asymptomatic severe MR patients, overt LV dysfunction

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(LV ejection fraction [EF] <60% or LV end-systolic diameter [ESD] ≥4.0 cm) or the development of atrial fibrillation or resting pulmonary arterial hypertension (systolic pulmonary artery pressure ≥50 mmHg) are indications for valve surgery, according to current guidelines.[2] In pre-operative period, LV systolic function is suggested to be most powerful predictor of post-operative LV dysfunction. Therefore, accurate assessment of LV contractile function is crucial in asymptomatic patients with chronic, nonischemic MR in order to prevent irreversible heart failure.[3,4]

Due to limitations of conventional parameters, reliable, new parameters are needed for assessment of LV systolic function in the preclinical phase in order to determine optimal time for surgery.[5] Recently, strain imaging has emerged as reliable method for evaluation of both global and regional ventricular functions.[6] Velocity vector imaging (VVI) is a novel, 2-dimensional strain imaging technique and provides additional data on regional and global cardiac function.[7,8]

In the baseline study, it was demonstrated that VVI-derived LV deformation can determine subclinical LV dysfunction in asymptomatic, chronic MR patients.[9] Outcomes of conservative or surgical approach in patients with moderate-to-severe MR are poorly defined. Thus, present study was designed to evaluate 1-year follow-up changes in LV systolic function using novel strain imaging technique in patients with chronic, moderate-to-severe MR with normal LVEF. Aim was to identify subtle changes that may occur in LV myocardial contractility despite preserved LVEF even in short-term follow-up.

METHODS

Study design and patient population

In the baseline study, 54 asymptomatic, non-ischemic, chronic MR patients with normal LVEF were studied.[9] For the follow-up study, we were able to contact 45 of 54, and re-examined LV systolic functions using both conventional echocardiography and VVI evaluation. Patients were also questioned about their symptoms and functional capacity using New York Heart Association (NYHA) Classification System.[10] Baseline study included 54 patients (mean age: 56.8±9 years; 56% male) with asymptomatic, chronic, non-ischemic MR.[9] Patients had been classified according to degree of MR and mitral regurgitant volume (RV): mild MR (RV: <30 mL; n=7), moderate MR (RV: 30–59 mL; n=29), and severe MR (RV: >60 mL; n=18).[9] In the follow-up study, we examined 45 of the 54 patients with moderate-to-severe MR (mean age: 56.70±16.7 years; 55.5% male) and 30 age- and sex-matched controls (mean age: 56±6.5 years; 55% male). Etiology of MR was: mitral valve prolapse (20 patients), rheumatic changes (15 patients), and degenerative changes (10 patients).

Abbreviations:

CAD	*Coronary artery disease*
CI	*Confidence interval*
EF	*Ejection fraction*
EROA	*Effective regurgitant orifice area*
ESD	*End-systolic diameter*
IVS	*Interventricular septum*
LA	*Left atrium*
LV	*Left ventricle*
LVEDD	*Left ventricular end-diastolic diameter*
LVEDV	*Left ventricular end-diastolic volume*
LVESD	*Left ventricular end-systolic diameter*
LVESV	*Left ventricular end-systolic volumes*
NYHA	*NewYork Heart Association*
MR	*Mitral regurgitation*
PW	*Posterior wall*
RV	*Regurgitant volume*
SI	*Sphericity index*
SR	*Strain rate*
VVI	*Velocity vector imaging*

All 45 patients fulfilled the following inclusion criteria for 12-month follow-up study: (1) presence of MR, (2) functional capacity of Class I according to NHYA,[11] (3) sinus rhythm, (4) normal LVEF (≥60%). Patients with low EF <60%, coexistence of aortic valve disease of more than mild degree, mitral stenosis, known or suspected coronary artery disease (CAD), low-quality echocardiographic image for VVI analysis, with atrioventricular conduction abnormality or atrial fibrillation were excluded from the study. In all, 30 of 54 patients had coronary angiogram with normal coronary arteries. Fifteen patients had negative exercise stress test. None of the patients had any clinical or echocardiographic features of CAD.

Study protocol was approved by local ethics committee of our institute, and detailed written informed consent was obtained from each patient. The study was performed according to the Declaration of Helsinki.

Echocardiographic measurements

Patients underwent transthoracic echocardiography (Acuson Sequoia C256; Siemens, AG, Munich, Germany) using 2.3–3.5 MHz transducer. LV end-diastolic (LVEDD) and end-systolic diameters (LVESD), interventricular septum (IVS) and posterior wall (PW)

thickness were measured from parasternal long-axis view using M-mode.[11] From apical 4-chamber view, LV end-diastolic and end-systolic volumes (LVEDV and LVESV) and LVEF were calculated using modified Simpson's method.[11] Long axis was measured in apical 4-chamber view from apex to mid-point of the mitral valve and short axis length was measured as the axis that perpendicularly intersects the mid-point of the long axis. Sphericity index (SI) of the LV was calculated as ratio of short axis to long axis ratio. Degree of mitral regurgitation was identified using mitral regurgitant volume (RV) and effective regurgitant orifice area (EROA). Mitral RV and EROA were quantified according to previously published guidelines.[12] The area of hemispheric flow through the regurgitant orifice of MR was calculated. Instantaneous flow was calculated as area x flow velocity at aliasing boundary. Effective regurgitant orifice was calculated as flow / maximum velocity of MR jet. RV was calculated as product of EROA x time velocity integral of MR flow as measured with continuous wave Doppler imaging.

Velocity vector imaging

Apical 4-chamber, 2-chamber, and long-axis views were recorded for VVI analysis. High frame rate, acoustic-capture, grayscale-recorded images were analyzed offline using VVI software (Syngo VVI, Siemens Medical Solutions, Malvern, PA, USA). Frame rate was kept between 70 and 100 frame/second. After endocardial border was defined manually by the user, VVI software automatically tracked endocardial borders throughout cardiac cycles, determining sampling points for each segment according to 16 segment-LV model of the American Society of Echocardiography.[13] Resulting velocity vectors in 2-dimensional plane were displayed throughout cardiac cycle. Strain (%) and strain rate (SR; 1/s) were defined as change in relative distance between localized tracked trace points, combined with difference in relative displacement of tissue motion behind tracked points. Strain was defined as instantaneous local trace lengthening or shortening, and SR as the rate of lengthening or shortening.[11] (Figures 1 and 2). Strain and SR values were calculated at aortic valve closure time. Base, mid, and apical segments of the LV were analyzed from apical 4-chamber, 2-chamber, and long axis views; averaged values of strain and SR of each LV wall were taken into consideration for assessment of LV global longitudinal systolic function.

Reproducibility

Intraobserver and interobserver variability for VVI measurements were assessed. For intraobserver variability, sample of 10 VVI measurements was randomly selected and examined by the same observer on 2 different days. For interobserver variability, second observer blinded to clinical information and to the first observer's results, examined the same 10 measurements. Intraclass correlation coefficients for the same observer and different observers were calculated.[14]

Statistical analysis

Statistical data analysis was performed with SPSS for Windows, Version 16.0. (SPSS, Inc., Chicago, IL, USA) program. Results were expressed as mean and standard deviation. Unpaired t-test was used for comparisons between 45 patients who were included in

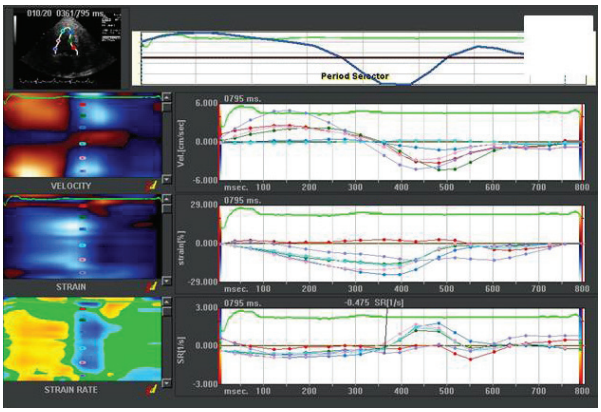

Figure 1. Left ventricular velocity vector imaging-based strain curves of a patient with mitral regurgitation in the baseline examination.

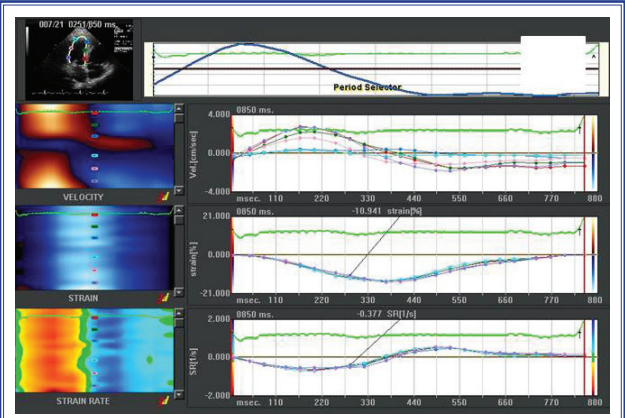

Figure 2. Left ventricular velocity vector imaging-based strain curves of a patient with mitral regurgitation in the follow-up examination.

follow-up evaluation and controls. Paired t-test was used for comparisons between baseline and follow-up examinations. Correlation analyses were derived using Pearson analysis. Results were considered significant when p value was less than 0.05.

RESULTS

Clinical follow-up

Of the 45 patients eligible for follow-up study, none developed manifest symptoms throughout follow-up period, and all patients were under optimal medical treatment. They were alive and had functional capacity I according to NYHA classification at the end of 12 months.

Clinical characteristics and conventional echocardiographic data

There was no significant difference between patients and healthy controls in baseline examination or in follow-up study with respect to age and gender. Mean age was 56.8±9 years in the baseline study, 56.7±16.7 years in follow-up (p=0.85), control group was 55.70±6.30 years (p=0.62). Among patients, 56% were male, while 55.6% of controls were male (p=0.88). At end of follow-up, male gender was 55.5%, when compared to baseline study (p=0.89). Other clinical and demographic characteristics are presented in Table 1. LA diameter was significantly increased in patients with chronic MR; however, it was similar between baseline and follow-up evaluation (p=0.96). In baseline examination, LVEDD (5.38±0.70 to 4.7±0.3; p<0.001), LVESD (3.83±0.65 to 3.2±0.6; p=0.0001), LVEDV (121±32.7 to 95.16±10.44; p<0.001) and LVESV (57.85±26.61 to 34.9±5.9; p<0.001) were significantly greater in MR patients, compared with healthy controls. At conclusion of 12 months, they were slightly greater than baseline evaluation, but difference was not statistically significant. IVS and PW thickness values were similar in each group. No difference between baseline and follow-up evaluations was observed in terms of LV SI (p=0.90). Regarding MR degree quantification, no significant change in mitral RV and EROA parameters was seen at the end of 12-month period. P^1 values included in Table 1 represent significance between basal and follow-up examinations, while p^2 values represent difference between patients and healthy controls (Table 1).

Velocity vector-derived strain imaging

Strain and SR data were obtained and analyzed at baseline and 12-month follow-up. In baseline assessment, LV global longitudinal peak systolic strain (16.29±3.30 to 23.44±1.90; p<0.001) and SR (0.93±0.38 to 4.94±0.55; p<0.001) were significantly decreased in patients with chronic, non-ischemic MR compared with control participants.[9] Impairment of global LV systolic function was more significant at end of 12 months. P values in Table 2 represent significance between basal and follow-up examinations (Table 2).

Correlation analysis of left ventricular deformation

LV deformation parameters were correlated with change in MR degree quantification. It was observed that LV strain value was negatively correlated with mitral RV and EROA (r=-0.391, p<0.001; r=-0.515, p<0.001, respectively). LV SR value was also negatively correlated with EROA (r=-0.300; p=0.006).

Reproducibility

Intraclass correlations for intraobserver variability were good for VVI-derived parameters (longitudinal strain: 0.90, 96% confidence interval [CI] 0.75–0.98; longitudinal SR: 0.76, 95% CI). Intraclass correlations for interobserver variability were also good for VVI-derived measurements (longitudinal strain: 0.89, 95% CI 0.76–0.95; longitudinal SR: 0.90, 96% CI 0.78–0.99).

DISCUSSION

Chronic MR results in hyperkinetic motion of the LV due to volume overload.[15] In the compensated phase of chronic MR, LVEDV increases, representing significant alteration in LV geometry. In order to preserve LV ejection, preload increases while afterload remains unchanged with maintained contractility. After a period of time, LV remodeling develops, with irreversible changes in the myocardium. In this decompensated phase, LVEDV and wall stress increase gradually and LV systolic dysfunction becomes overt as result of failing ventricle. Development of LV systolic dysfunction is a major concern in management of patients with chronic primary MR. Identification of subtle changes in LV contractility in preclinical phase may avoid development of irreversible myocardial damage after surgical

Table 1. Clinical and conventional echocardiographic parameters of the patients in the baseline and the follow-up studies

	MR patients (basal) (n=54)	MR patients (follow-up) (n=45)	*p* value[1]	*p* value [2]	Control group (n=30)
Age (years)	56.8±9	56.70±16.7	0.85	0.62	55.70±6.30
Male (%)	56	55.5	0.89	0.88	55.6
HR (bpm)	74.2±1.8	73.5±1.1	0.95	0.94	75±1.2
SBP (mmHg)	126±5.04	125±4.99	0.39	0.89	125±4.97
DBP (mmHg)	72.81±5.9	73.53±5.51	0.85	0.85	73.56±6.31
Glucose (mg/dL)	77±10.1	75.46±8.30	0.75	0.78	76.1±9.03
Creatinin (mg/dL)	0.86±0.16	0.87±0.15	0.95	0.65	0.91±0.13
Total cholesterol (mg/dL)	161±18.3	167±22.67	0.34	0.45	165±20.3
ACE inhibitors (%)	92.59	91.11			
Diuretics (%)	96.29	100			
Beta blockers (%)	88.89	91.11			
LDL (mg/dL)	83.40±11.70	79.80±15.10	0.48	0.43	79.90±15.36
IVSDD (cm)	1.0±.11	1.1±0.10	0.97	0.98	1.01±0.11
PWDD (cm)	1.1±1.0	0.95±0.08	0.57	0.45	0.97±0.13
LVEDD (cm)	5.38±0.70	5.42±0.34	0.96	<0.001	4.7±0.3
LVESD (cm)	3.83±0.65	3.95±0.33	0.68	<0.001	3.2±0.6
LVEDV (mL)	121±32.7	134±30.6	0.11	<0.001	95.16±10.44
LVESV (mL)	57.85±26.61	60.17±22.3	0.88	<0.001	34.9±5.9
LV EF (%)	60.52±3.99	60.07±2.91	0.85	0.54	62.90±2.09
LV SI	0.82±0.09	0.83±0.10	0.90	<0.001	0.50±0.04
LA (cm)	4.86±0.77	4.90±0.59	0.96	<0.001	3.78±0.30
RV (mL)	52.22±24.27	52.79±18.50	0.92		
EROA (cm^2)	0.32±0.13	0.37±0.009	0.06		

MR: Mitral regurgitation; HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; ACE: Angiotensin converting enzyme; LDL: Low-density lipoprotein; IVSDD: Interventricular septum diastolic diameter; PWDD: Posterior wall diastolic diameter; LVEDD: Left ventricle end diastolic diameter; LVESD: Left ventricle end systolic diameter; LVEDV: Left ventricle end diastolic volume; LVESV: Left ventricle end systolic volume; LV EF: Left ventricle ejection fraction; LV SI: Left ventricle sphericity index; LA: Left atrial horizontal diameter; RV: Regurgitant volume; EROA: Effective regurgitant orifice area.

Table 2. Left ventricular deformation parameters of the patients in the baseline and the follow-up studies

	MR patients (basal) (n=54)	MR patients (follow up) (n=45)	Control group (n=30)	*p*
	Mean±SD	Mean±SD	Mean±SD	
Left ventricular strain (%)	16.29±3.30	13.26±2.68	23.44±1.90	<0.001
Left ventricular strain rate (1/s)	0.93±0.38	0.27±0.14	4.94±0.55	<0.001

MR: Mitral regurgitation; SD: Standard deviation.

correction.[1,16–18] It has been demonstrated in some studies that asymptomatic patients with preserved LVEF develop systolic dysfunction before clinical signs arise.[19] Based on recent data, earlier surgery may be considered in order to preserve LV systolic function and to improve long-term prognosis.[4,16]

Asymptomatic patients with overt LV dysfunction (LVEF <60% or LVESD ≥4.0 cm) are candidates for

valve surgery according to current guidelines;[2] yet there is still high risk of heart failure after surgery. Aggressive attitude toward early surgical intervention is strengthened by results of some studies.[19,20] Watchful waiting for symptoms to develop or for LVEF to decline, as well as for LV to enlarge, is closely related to increased mortality, after surgery.[21] Marciniak et al. investigated LV global systolic function in patients with chronic severe MR before and after mitral valve repair.[22] Based on strain imaging data, patients with significantly impaired LV systolic function in preoperative period developed lower LVEF after the operation. In another study, Kang et al.[21] compared long-term results of early surgery with conventional treatment strategy in asymptomatic patients with severe MR and preserved LVEF. Interventional approach was associated with improved long-term cardiac mortality compared with conservative treatment. Similarly, Ogutu et al.[23] recommended early surgery in order to yield satisfactory peri- and postoperative survival rates in patients with asymptomatic severe MR.

Marciniak et al.[24] demonstrated in their study that most patients with reduced deformation had normal LVEF. Similarly, in our baseline examination, marked impairment in chronic, primary MR patients with normal LVEF was observed using VVI derived strain imaging.[10] At the end of 12 months, present study population presented no significant change in LVESD and EF or MR progression, according to RV and EROA evaluation. However, there was significant deterioration in LV longitudinal systolic function according to novel deformation indices compared to the measurements of baseline study. These results indicate that conventional echocardiographic parameters may not always provide a useful guide to subtle changes in LV contractility. Closer follow-up of chronic MR patients with preserved LVEF will help to identify subclinical changes in LV systolic function in order to prevent irreversible LV systolic dysfunction.

Strain imaging is now considered to be superior to conventional echocardiographic parameters due to its ability to provide quantitative endocardial deformation analysis.[25–27] VVI is an accurate, 2-dimensional strain imaging technique for estimating regional myocardial function and allows for quantification of strain, SR, and velocity.[28] In previous studies, VVI has been used to demonstrate subclinical LV dysfunction.[29,30]

In the present study, we observed subclinical LV damage in patients with chronic, moderate-to-severe MR, despite normal LVEF and dimensions, based on a sensitive method. We suggest that development of LV systolic dysfunction cannot be based only upon progressive changes in conventional measurements like LV dimensions and EF. Among patients with chronic MR, any delay in interventional approach may result in adverse outcomes.

Consequently, we suggest that using VVI-derived strain imaging may be helpful in closer follow-up of patients and identifying optimal timing for surgery before irreversible ventricular dysfunction occurs.

Limitations and strengths

Strength of this manuscript is detailed LV function evaluation using novel imaging technique (VVI), which is known to provide additional data about regional and global myocardial functions. To our knowledge, this study is the first to perform follow-up of chronic MR patients using VVI-derived strain imaging.

In the baseline study, echocardiographic examinations were performed on both the patient groups and control group. At the end of 12 months, we were able to contact 45 patients of the baseline group and all subjects in the control group. We surveyed and performed physical examinations on the patients and the controls. However, we did not perform echocardiography on the control group. Other limitations are small sample size and short-term follow-up of the patient population. Additionally, we were not able to perform coronary angiography on all of our patients. Long-term studies providing more detailed analysis and reliable data for estimation of surgical timing in asymptomatic patients with chronic MR are warranted.

Conflict-of-interest: None.

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