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Ischemic Mitral Regurgitation: Echocardiographic Algorithm, the Place of Three-Dimensional Transesophageal Echocardiography

Objective	Identify the diagnostic markers of the severe MV changes in patients with ischemic mitral regurgitation (IMR) and suggest a modification of the echocardiography (EchoCG) algorithm.
Materials and Methods	A two-stage examination of 65 patients with mild (n=22), moderate (n=22), and severe (n=21) IMR was performed using two-dimensional (2D) transthoracic EchoCG with dopplerography, 2D and three-dimensional (3D) transesophageal EchoCG (TEE). 4D MV-Assessment in off-line mode was made in TomTec Imaging Systems GmbH, Germany. Statistical analysis (SAS 9.4) included Student's t-test, Kruskal-Wallis method, Pearson correlation, multivariate regression analysis, and ROC-analysis.
Results	According to 3D TEE the significant changes in MV annulus, leaflets and tenting are detected. 3D parameters of MV geometry are related to IMR severity, left ventricle (LV) remodeling (global and regional), and they are different in symmetric and asymmetric variants. In symmetric variant MV reconstruction is correlated with LV dilatation and contractility decrease, in asymmetric variant it's correlated with regional remodeling parameters. Severe IMR is characterized by a decrease in MV annulus displacement (27,0±6,6 mm/s versus 32,4±10,8 mm/s in mild IMR; p<0,05), tenting volume fraction (32,5±14,8% versus 56,2±16,8% in mild IMR; p<0,05), and annulus area fraction (4,7±2,7% versus 6,6±4,5% in mild IMR; p<0,05). Vena contracta width (VCW), Proximal Isovelocity Surface Area (PISA) radius, Effective Regurgitant Orifice Area (EROA), Regurgitant Volume (Rvol), LV end systolic dimension (LV ESD), and central large jet >50% of left atrium (LA) area have a predictive value in the diagnosis of MV geometry severe changes. If thresholds are reached these 2D TTE parameters can be used as indications for the 3D TEE.
Conclusion	3D TEE allows for detailed assessment of MV geometry and function depended on IMR severity and variant. To make decision of MV surgery 3D TEE is recommended if the following indicators are presented: (1) VCW ≥0,7 cm; PISA radius ≥1,0 cm; central large jet >50% of LA area; LV ESD ≥4,0 cm; (2) VCW ≥0,6 cm; PISA radius = 0,6-0,99 cm; EROA ≥0,3 cm2; RVol≥45 cm; IMR eccentric jet + IMR elliptical orifice.

Keywords	Ischemic mitral regurgitation; three-dimensional transesophageal echocardiography
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Ischemic mitral insufficiency as a consequence of myocardial infarction (MI) or chronic myocardial ischemia is one of the most common valvular heart diseases [1, 2]. Its prevalence has increased significantly over the past decades due to the continuing global epidemic of the community diseases (such as, obesity, metabolic syndrome, diabetes mellitus, hypertension), which are the risk factors for cardiovascular complications, as well as better quality of medical care and increased Quality of life for post-MI patients [3, 4]. Severe mitral regurgitation is known to result in chronic heart failure, and it is associated with poor prognosis [5].

Ischemic mitral regurgitation (IMR) develops when mitral valve (MV) leaflets are initially intact. As it progresses, it may results in hemodynamically significant structural and functional remodeling of the MV, which requires surgery [2, 6, 7]. The approach to the surgery of MV failure depends on the preoperative evaluation of the IMRmechanism and severity, as well as the anatomic and functional MV parameters [8–10]. In the context of the growing opportunities of IMR surgical treatment, including a continuing increase in invasive transcatheter interventions for IMR, it is important to identify clear indications for surgery [6, 11].

Conventional diagnostic techniques for IMR are Doppler transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) [11, 12]. TTE makes it possible to better visualize the MV apparatus

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due to its proximity to the MV. The new-generation transducers for three-dimensional (3D) reconstruction of the MV brought the IMR diagnosis to the next level [13]. The advantage of 3DTEE is the possibilityofobtaining detailed information about the morphology of the MV and subvalvular structures, including 3D image of leaflets, chordae, commissures, and the full perimeter ofMVannulus [14].

Progress in IMR studyingis reflected in the guidelines, which were revised in 2017 by all professional societies of cardiology, echocardiography, and cardiovascular tomography [2, 3, 11]. The new guidelines of the American Society of Echocardiography for noninvasive assessment of valvular regurgitation emphasize that 3DTEE should be used in the case of challengingdiagnosis of IMR made through conventional two-dimensional echocardiography (2DTEE). 3DTEE is the preferred diagnosis method due to much more MV parameters information [11].

However, no algorithm exists for the echocardiographic diagnosis of IMR, integrating the indications for 3DTEE. To address this gap, we conducted a comprehensive examinationof patients with IMR, performing TTE and TEE, including three-dimensional modeling of the MV.

The objective of the study was to assess geometrical and functional 3Dparameters of the MV and compare these with 2Ddata of IMR severity and left ventricular (LV) remodeling, and then identify diagnostic markers for the severity of MV insufficiency (or IMR) and develop the echocardiographic algorithm for the examination of patients with IMR.

Materials and Methods

We carried out examination of 65 patients (36 males and 29 females) with the verified diagnosis of coronary artery disease and mild (n=22), moderate (n=22), orsevere (n=21) IMRaccording to TTE [3, 15] without organic lesions of the MV. The study was performed in accordance with Declaration of Helsinki and approved by the ethics committee of the Russian National Cardiology Research Center. All patients provided written informed consent form before their inclusion in the study.

Three groups of patients did not differ in age (mean age 65.4 ± 8.9 years old) and comorbidities, including hypertension (75%), stable angina (80%), and diabetes mellitus (40%). Coronary angiography (CA) found occlusion of one or more coronary arteries (and relevant localization of postinfarction cardiosclerosis, [PICS]) in 71% of patients (n=46), and multivessel disease and chronic myocardial ischemia without PICS in 29% of patients (n=19). One hundred percent of patients with severe IMR had heart failureIII Functional Class according to the New York Heart Association (NYHA). At the time of examination, adequate management of cardiovascular disease was implemented through drug therapy, which was chosen individually for each patient in line with the current standards.

2DTTE was performed at the first stage of the study and 3DTEE at the second stage. The examinations were carried out withthe Vivid E9 ultrasound system using standard procedures with transthoracic (M5S) and transesophageal (6 VT-D) transducers, respectively.

The 2DTTE protocol included assessment of a global (end-diastolic and end-systolic volumes) and regional (apical displacement of posteromedial papillary muscle and interpapillary distance) remodeling of the LV, calculation of ejection fraction (EF), sphericity index, determination of location and extent of regional contractile dysfunction, and the calculation of the asynergia index. To assess the severity of IMR, we used the proximal isovelocity surface area (PISA) method and calculated effective regurgitant orifice area (EROA), regurgitant volume (Rvol), and a semiquantitative parameter of vena contractajet width.

Based on 3DTEE data and subsequent off-line MV modeling using the TomTec software, the following parameters were analyzed:

1) Height, area, and diameters of the annulus (anteroposterior, anterolateral, posteromedial, commissural), annular sphericity index (anteroposterior to anterolateral-posteromedial diameter ratio).
2) Area and length of the MV leafs.
3) Tenting height (distance from the annular plane and the MV leafs), tenting area (area between the annular plane and MV leafs), and tenting volume (volume between the annular plane and MV leafs).
4) Posterolateral angle (PLA, posterior leafangle), nonplanar angle, and mitral-aortic angle.

3D-parameters of MV were estimated using the parameter analysis in different phases of the cardiac cycle:

- Annular displacement and displacement velocity.
- Annular area fraction.
- Tenting volume fraction.

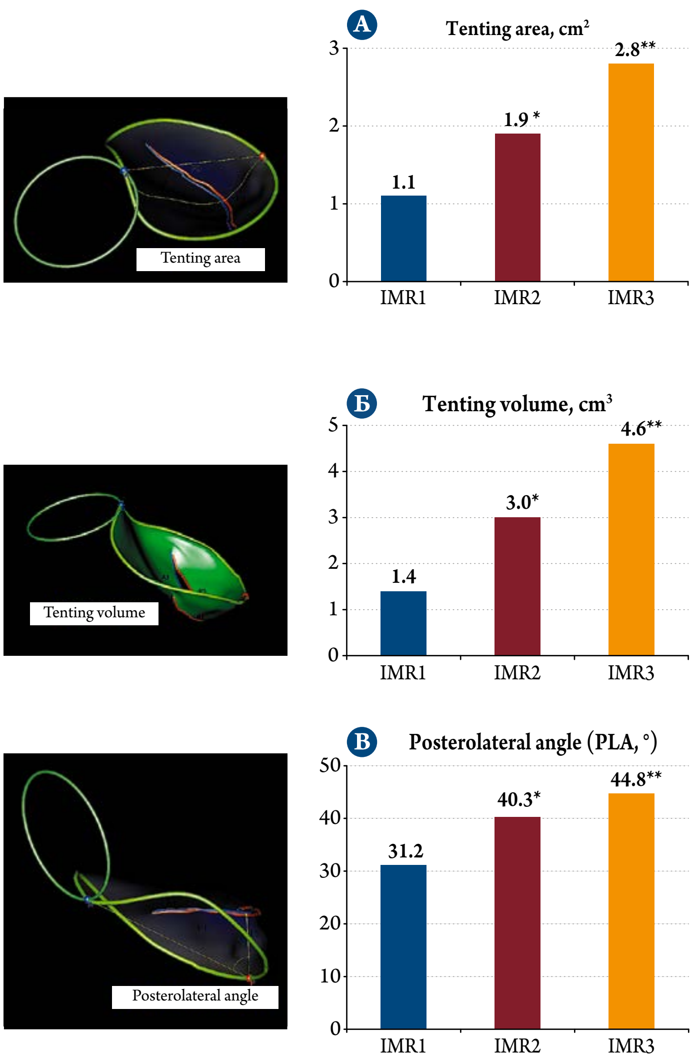
Data obtained were analyzed using the SAS 9.4 statistical package. Student's t-test, Kruskal-Wallis test, Pearson's correlation analysis, multivariate regression analysis, and receiver operating characteristic curve (ROC) analysis were used. Results are presented as the mean and standard deviation (M ± SD);tenting volume is given as the median and interquartile range [Q1; Q3].

Results and discussion

3DTEE found outincrease in the degree of the MV geometrical remodeling due toIMR progressing, which manifested in changes in the annulus, leaflets, and leaflets tenting [16]. The mean values of anterior-posterior, lateral-medial, commissural diameters, the MV annular perimeterand MVarea increased significantly in moderate-to-severe IMR as compared with mild IMR. The annular sphericity index approached 1.0 due to the stretching in the case of severe IMR.

MV 3Dreconstruction allowed estimating MV valvular changes in detail. IMR has long been believed to occur with morphologically intact mitral leaflets, but the 3Dvisualization techniques made it possible to objectively prove otherwise. A significant increase in the length and area of both leaflets were detected according toseverity of IMR, and these data are consistent with those of other studies [8, 17].

Figure 1. Tenting parameters in IMR of different severity according to 3DTEE



A — area; B — volume; C — posterolateral angle of the mitral valve. IMR 1, 2, 3, ischemic mitral regurgitation degree I, II, and III. The differences were significant ($p<0.05$) between * IMR1 and IMR2; ** IMR2 and IMR3. IMR, ischemic mitral regurgitation; 3DTEE, three-dimensional transesophageal echocardiography.

The abnormal typeof leafletclosure/tension resulting from the increased hemodynamic stress and remodeling in severe IMR was accompanied by an approximatelytwofold increase in height (1.07 ± 0.34 cm) and area (2.76 ± 0.98 cm2) of tenting as compared with mild IMR (0.52 ± 0.21 cm2 and 1.10 ± 0.43 cm2, respectively). The increase in the leaflet area resulted in pathological tenting volume: more than 1.0 cm3 in mild IMR (1.35 cm3 [0.98; 2.21 cm3] and more than 4.0 cm3 in severe IMR (4.61 cm3 [3.76; 6.48 cm3]), which was also consistent with the previous studies [8, 17, 18]. The PLA increased from 31.2 ± 12.7° in mild IMR to 44.8 ± 12.9° in severe IMR (Figure 1).A statistically significant decrease in the rate of annular displacement and area fraction was detected in severe IMR (27.0 ± 6.6 mm/sec vs. 32.4 ± 10.8 mm/sec in mild IMR and 4.7 ± 2.7% vs. 6.6 ± 4.5%, respectively; $p<0.05$ for all). Thus, in severe IMRdue to MV dilation and flattening, the annulus becomes adynamic and less able to change its shape depending on the phase of the cardiac cycle. Decreased functionality of the valvular apparatus in severe IMR was confirmed by the reduced tenting volume fraction (to 32% vs. 56% in mild IMR; $p<0.05$).

Correlation analysis showed a significant dependence of geometric and functional changes in MV on the degree of global and regional LV remodeling and IMR severity [19].

In analyzing the results, we noted that the MV geometry and function within each group were heterogeneous due to the differences in the vector of force that affects the MV leaflets and causes the development of different IMR patterns (symmetric and asymmetric) [1, 8, 18]. The asymmetric pattern of IMR was significantly more common in severe IMR (52%; $p<0.05$) (Figure 2) and patients with reduced left ventricle ejection fraction (LVEF) (53% vs. 20% in preserved LVEF; $p<0.05$).

Comparison of echocardiography data with the CA parameters and localization of MI showed that the symmetric pattern of IMR formed as a result of occlusion of the left anterior descending (LAD) artery or LAD + left marginal arteries (LMA) with the development of anterior MI, and in patients with chronic myocardial ischemia (multivessel disease without PICS). The asymmetric pattern of IMR develops in occlusion of the right coronary artery (RCA), circumflex artery (CA) or RCA + CA/LMA with the developmental of inferobasal and lateral or posterolateral MI and impaired regional

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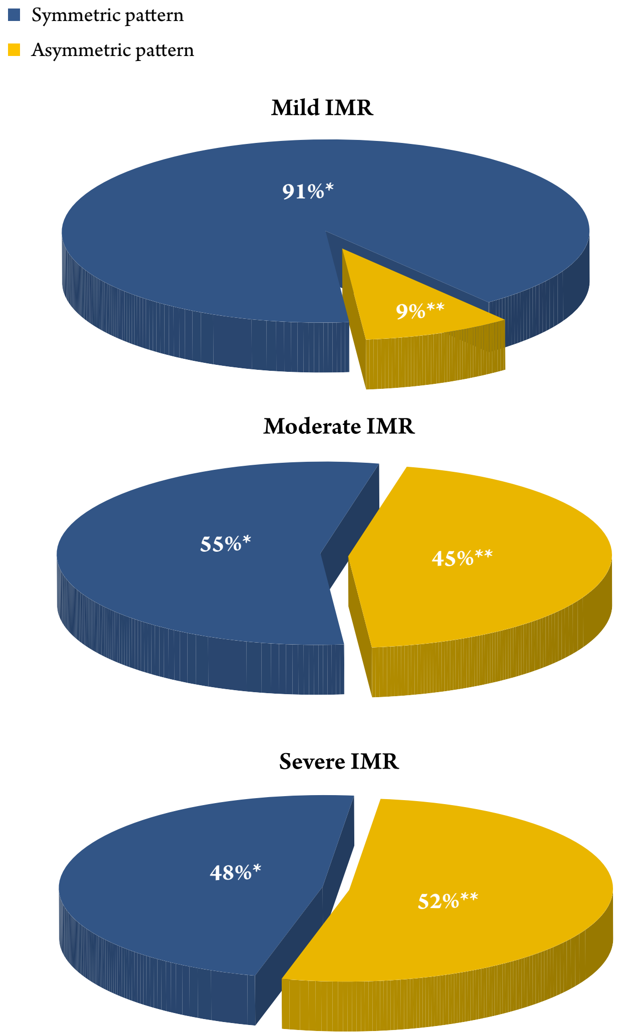
Figure 2. Rate of detection of asymmetric and symmetric patterns of IMR of different severity



The difference in the rate of symmetric (*) and asymmetric (**) IMR patterns in mild and moderate-to-severe MR was significant ($p<0.05$).
IMR, ischemic mitral regurgitation.

contractile function of the inferior and posterior walls of LV (LV lateral wall).

In severe IMR, 3Dparameters of MV geometry differed significantly depending on the pattern: in the asymmetric pattern, tenting height was smaller (0.97 ± 0.11 cm vs. 1.18 ± 0.15 cm), and tenting area, by contrast, was greater than in the symmetric pattern (3.1 ± 0.7 cm2 vs. 2.4 ± 0.4 cm 2 ; $p<0.05$); tenting volume was increased (versus mild IMR), but to a lesser extent than with thesymmetric pattern (4.6 ± 0.7 cm3 vs. 5.5 ± 0.5 cm3; $p<0.05$). Annular area fraction (5.1 ± 0.9% vs. 8.2 ± 1.2%; $p<0.05$) and tenting volume fraction (36.8 ± 4.7% vs. 48.4 ± 3.6% ; $p<0.05$) also differed between two patterns of IMR (Figure 3).

The correlation analysis showed that, in the symmetric pattern, changes in MV geometry significantly depend on the degree of dilation and the decrease in the LV contractile function. In the asymmetric pattern, changes of MV geometry are affected mainly by the severity of regional LV remodeling (increase in the interpupillary distance and apical displacement of the posteromedial papillary muscle), resulting in a higher tension of the posterior Mvleaflet [19, 20].

Based on results of the analysis, cutoff (or threshold) values of the 2DTTE parameters were calculated; thesemay be predictive of significantchanges in 3Dgeometry and function of the MV and, thus, serve as indications for further 3D Echo examination of patients with IMR.

The following parameters of IMR severity are of high diagnostic (informative) significance: vena contracta, PISA radius, EROA, Rvol; LVESD, and central regurgitation jet >50% of LA are also highly informative. Cutoff values depend on the IMR pattern.

After the analysis of data, a modified algorithm of examination in IMR, taking into account the indications for 3DTEE, was suggested (Figure 4).

At the first stage, 2DTTE (or 2DTEE in the case of difficulties of measuring) is performed as recommended by the relevant examination standard (guideline). Restriction of both mitral leafletsor predominantly posterior leaflet is identified, with the respective view of the regurgitation jet (central or eccentric). If a greater jet width is detected, vena contracta width is estimated in the parasternal long-axis view (or apical four-chamber view). PISA (in the apical four-chamber view) is visualized, and the PISA radius is measured at mid-systole.

The second stage (TEE with 3Dreconstruction of the MV) is recommended if the following values were obtained at the first stage:

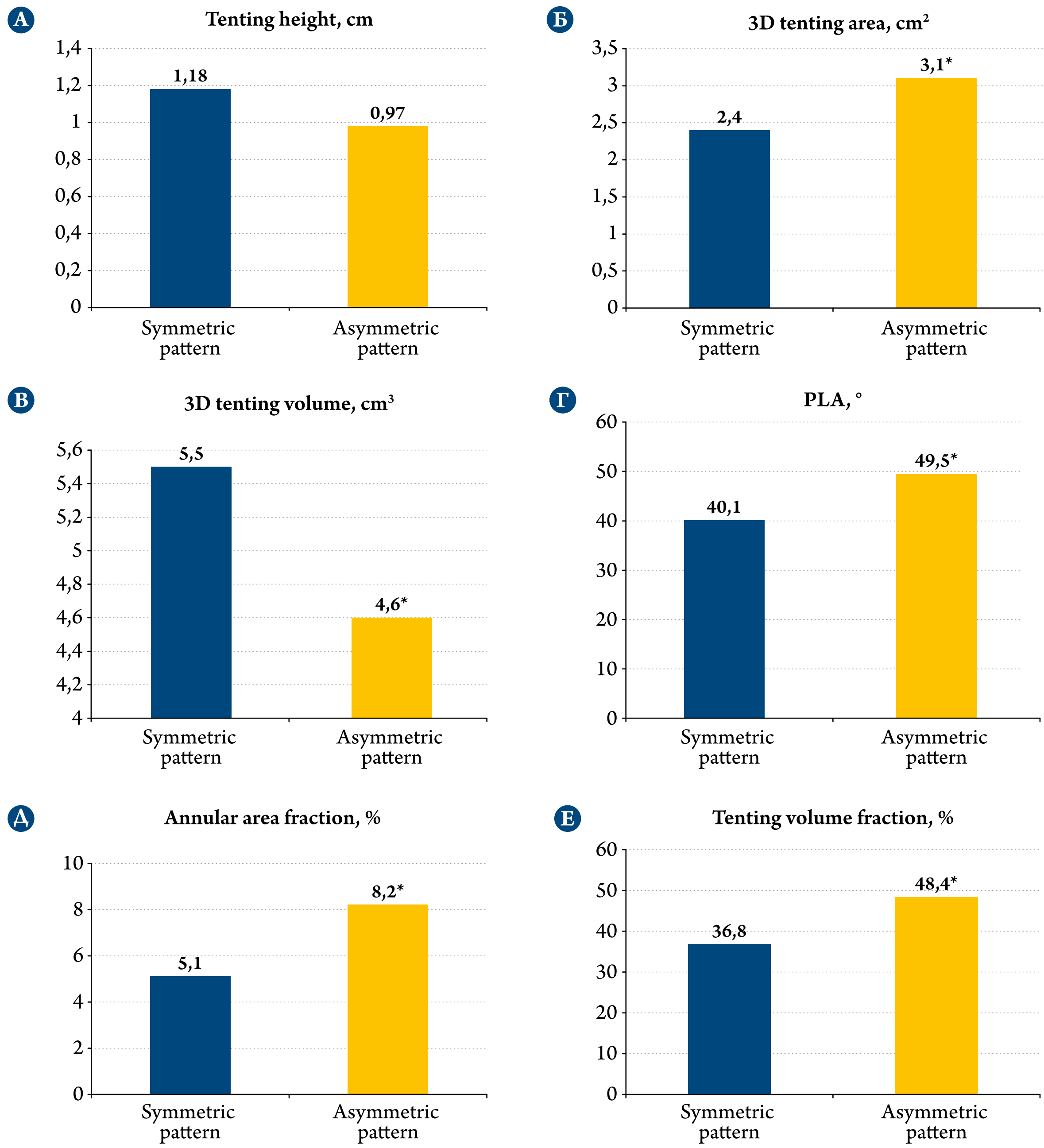
1) Vena contracta width >0.7 cm.
2) PISAradius >1.0 cm.
3) IMR central jet >50% of LA area.
4) LVESD >4.0 cm.

In other cases (see the algorithm shown in Figure 4), indications for 3DTEE depend on the pattern of IMR (symmetric/asymmetric), vena contracta, PISA, EROA, Rvol, and presence/absence of LV dilatation. TEE followed by 3D-reconstruction of the MV may be recommended if these indicators exceed the cutoff values for the particular pattern of IMR.

Conclusion

Three-dimensional transesophageal echocardiography provides a detailed evaluation of the geometrical (including volumetric) and functional parameters of the mitral valve, which very significantly depending on both

Figure 3. 3Dparameters of tenting (A–D) and MV function parameters (E–F) in symmetric and asymmetric patterns of severe IMR according to 3DTEE



A—height; B—area; C—volume; D —posterolateral angle (PLA); E—annular area fraction; F—tenting volume fraction.
*The differences between patient subgroups with the symmetric and asymmetric patterns of IMR were significant ($p<0.05$).
MV, mitral valve; IMR, ischemic mitral regurgitation; 3DTEE, three-dimensional transesophageal echocardiography..

the severity and pattern of ischemic mitral regurgitation. The suggested algorithm based on the standard parameters of two-dimensional and Doppler transthoracic echocardiography allows making decisions concerning the indications for second-stage examination of patients with ischemic mitral regurgitation. The necessity for the three-dimensional visualization of the mitral valve depends on the severity of and the pattern (symmetric/asymmetric) of ischemic mitral regurgitation, and the condition of the left ventricle. Analysis of mitral valve anatomy is a necessary part of the assessment of ischemic mitral regurgitation during preoperative preparation, and allows determining tactics of surgical treatment of patients with severe ischemic mitral regurgitation.

No conflict of interest is reported.

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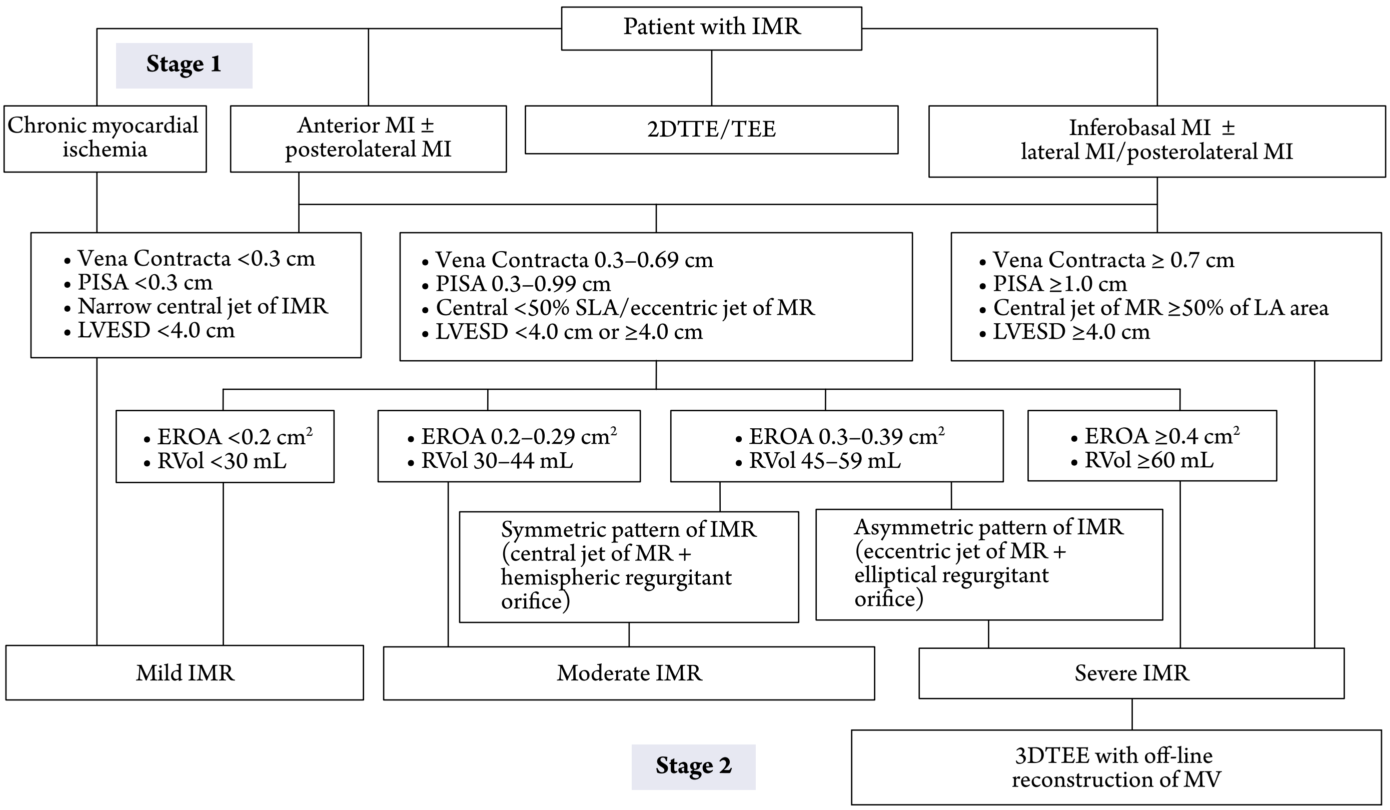
Figure 4. Algorithm for the echocardiographic examination of a patient with IMR



IMR, ischemic mitral regurgitation; MI, myocardial infarction; LVESD, left ventricular end-systolic dimension; LA, left atrium; MV, mitral valve; MR, mitral regurgitation; vena contracta, regurgitation jet width; PISA, proximal isovelocity surface area (radius); EROA, effective regurgitant orifice area, Rvol, regurgitant volume; S, area.

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