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Clinical Use of Doppler Echocardiography in Organic Mitral Regurgitation: From Diagnosis to Patients' Management

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Knowledge of mitral regurgitation (MR) is essential for any care provider, and not only for those directly involved in the management of cardiovascular diseases. This happens because MR is the most frequent valvular lesion in North America and the second most common form of valve disease requiring surgery in Europe. Furthermore, due to the ageing of the general population and the reduced mortality from acute cardiovascular events, the prevalence of MR is expected to increase further. Doppler echocardiography is essential both for the diagnosis and the clinical management of MR. In the present article, we sought to provide a practical step-by-step approach to help either performing a Doppler echocardiography or interpreting its findings in light of contemporary knowledge on organic (but not only) MR.

KEY WORDS: Mitral regurgitation · Heart failure · Mitral repair · Echocardiography.

Understanding the Heterogeneity of Mitral Regurgitation Is Essential for a Correct Diagnosis

Mitral regurgitation is a frequent disease[1-4] diagnosed in the presence of a pathological amount of blood regurgitating from the left ventricle into the left atrium due to mitral valve incompetence usually–but not exclusively–occurring during systole.[5] Mitral regurgitation can occur even in diastole when is present an atrio-ventricular block, pace-makers with short atrio-ventricular delay, and/or significantly elevated left ventricular filling pressures.[6]

Once we have diagnosed the presence of MR we should try to assign it an etiology, which can be either ischemic or non-ischemic. The assessment of the etiology is particularly important, since different etiologies imply different criteria of severity, different prognosis, and may deserve different treatments.[7][8] Multiple etiologies can coexist in the same patient, and in that case it is worth trying to identify the one prevalent. Having established the etiology, the following duty is to recognize the mechanism, which can be either organic or functional. Organic is MR caused by intrinsic anatomic abnormalities affecting the mitral valve itself or its sub-valvular apparatus (for instance myxomatous degeneration, rheumatic disease, aging process, or endocarditis) (Supplementary Fig. 1, 2, and 3). If we exclude an intrinsic lesion, we should than direct our attention to the left ventricle and the mitral annulus, since we are likely facing functional MR. In functional MR, the valve and the sub-valvular apparatus are macroscopically normal, and the incompetence is mainly due to altered geometrical relationships between a diseased ventricle and the mitral valve apparatus (Supplementary Fig. 4).[9] The subsequent diagnostic step is classifying the "type of dysfunction". The type of dysfunction is identified by the systolic position of the margin of the leaflets with respect to the plane of the annulus.[10] Accordingly, we can have three types of dysfunction: Type 1, normal motion of the leaflets with isolated annular dilatation causing poor leaflet coaptation; Type II, excess motion of the margin of a leaflet segment above the annular plane; Type III, restricted motion of the

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leaflets during both diastole and systole (Type IIIa) or during systole only (Type IIIb). The identification of the type of dysfunction is particularly common among surgeons, since it gives insights for selecting specific operative techniques.

How Doppler Echocardiography Relates to Clinical Findings and to Some of the Other Most Commonly Available Diagnostic Techniques of Imaging

Assessment of the severity of any valvular lesion (including MR) is crucial for decision-making and should always be based on the combination of clinical and instrumental findings.[11] No single technique suffices if not integrated by a carefully collected past medical history and combined with an accurate physical examination.[11]

Physical examination represents the first step in the diagnosis of MR severity. Detection of a murmur with a low intensity usually suggests mild MR, whereas a loud murmur usually indicates severe regurgitation.[12] Unfortunately, in many cases the murmur is of a medium intensity, which can be generated either by severe or moderate MR.[12] Cardiac auscultation is even more challenging in functional MR,[13] where severe regurgitation can be completely silent.[14][15] Electrocardiogram (ECG) and the chest X-ray are usually performed alongside clinical examination in almost every patient and may sometimes provide additional information. Cardiac enlargement and/or pulmonary congestion at chest X-ray is consistent with severe regurgitation, as well as the detection of left atrial enlargement or atrial fibrillation at the ECG.

In the past, when non invasive clinical/instrumental assessment was consistent with significant MR, physicians traditionally performed a ventricular angiogram to direct subsequent decision making. This technique is based on the degree of opacification of the left atrium caused by the reurgitant jet, and the degree is generally graded using a scale from 1+ (mild) to 4+ (severe).[16] Although angiography has been considered for many years the gold standard for the assessment of MR, this diagnostic tool is characterized by a significant overlap between grades, particularly in presence of large volumes of regurgitation, when a correct assessment is mandatory to guide surgical indications.[16][17] Furthermore, since the injection of contrast needs to be rapid enough to allow a proper opacification of the left ventricle, such technical requirement may lead to premature ventricular contractions, eventually causing imprecise assessments. Analogously, an improper positioning of the pig tail catheter can interfere with the sub-valvular apparatus causing an overestimation of MR severity.

Moving toward non-invasive assessments of valvular lesions, magnetic resonance imaging (MRI) is emerging as a useful diagnostic tool. The evaluation of the mitral valve from routinely acquired MRI imaging is often inadequate, but the introduction of protocols specifically designed can achieve a notable diagnostic accuracy.[18] In patients with organic MR, MRI can contribute to identify the mechanism of the lesion and the predictability of the repair (recent reports found a sensitivity and specificity of MRI in identifying a flail or prolapsing leaflets approaching 90%).[19] In functional MR, MRI can exclude the presence of coexisting degenerative lesions, assess myocardial viability and analyze regional wall motion abnormalities. The assessment of the amount of regurgitation trough MRI can be achieved through different methods. For instance, we can calculate the regurgitant volume and regurgitant fraction by measuring the left ventricular and aortic stroke volumes. Furthermore, we can search for the presence of systolic reversal in the pulmonary veins, a specific sign of severe MR (see also the following paragraph). Finally, MRI can assess the consequences of volume overload through an accurate evaluation of cardiac volumes and function. Unfortunately, in addition to the limitation due to respiration, MRI is expensive and time consuming, and consequently mostly available in tertiary centers only.

Anatomy and Physiopathology of Mitral Regurgitation by Echocardiography

We believe that Doppler echocardiography represents the gold standard for the diagnosis of MR, providing non-invasively reliable information on the presence of the lesion, its etiology, the mechanism, the dysfunction and the severity of regurgitation. This happens because, two-dimensional (2-D) and three-dimensional (3-D) echocardiography can supply precise details about the functional anatomy of the leaflets, the chordae tendineae, the annulus, the papillary muscle and their supporting walls.

In organic MR, 2-D echocardiography helps to guide diagnosis toward the identification of a specific etiology of regurgitation (degenerative, rheumatic, infective endocarditis etc.). For any given etiology we should than expect a definite group of potential mechanisms. Classic features of Barlow's disease that can be detected by 2-D echocardiography include excess tissue in multiple segments, chordal thickening, annular dilatation and a tendency to calcification (Supplementary Fig. 1). The mechanism of regurgitation usually associated with Barlow' disease lesions is chordal elongation (Type II dysfunction). On the opposite side from Barlow's disease, fibroelastic deficiency is remarkable for chordal thinning, resulting in elongation and rupture. As regards a rheumatic etiology (Supplementary Fig. 2), mitral leaflets commissures and sub valvular apparatus are usually thickened, in association with varying degrees of calcification. In these patients, MR can be combined with stenotic lesions, resulting in the classic hockey stick appearance of the anterior mitral leaflet in diastole and reduced mobility of the posterior leaflet. Concerning endocarditis, the diagnostic clue is represented by the imaging of vegetations appearing as an echogenic mobile masses attached to the valvular leaflets (Supplementary Fig. 3). Usually, vegetations are initially attached to the atrial side, and become identifiable by transthoracic examination only when they reach 3–5 mm in diameter.

The potential mechanisms of the lesion caused by endocarditis include rupture or perforation of the leaflet.

In organic MR, 2-D echocardiography can also support the diagnosis of severity. In long-standing severe regurgitation, left atrial and ventricular volumes need to be dilated; conversely normal cardiac volumes in patients diagnosed as having chronic severe MR should raise concerns regarding the diagnostic accuracy. Similarly, the presence of a prominent flail or a ruptured papillary muscle by 2-D echocardiography (Supplementary Fig. 1) should be interpreted as a specific sign of severe MR. On the other hand, the detection of enlarged cardiac chambers associated with only a mild amount of regurgitation should raise the suspicion of an underestimation of the degree of MR or make us searching for an associated disease resulting in cardiac enlargement.

If segmental analysis by transthoracic study is not diagnostic (Fig. 1-5), trans-esophageal echocardiography (TEE) can help in visualizing the cardiac structures and in delineating more in detail the mechanism of MR (Supplementary Fig. 5).[20] More recently, real time 3-D echocardiography has contributed to further improve the communication between clinicians and surgeons by offering a surgical view of the mitral valve (Fig. 5-8). By 3-D TEE, we can assess diameters and height of the mitral annulus, mitral leaflet surface, the angle between the aortic and the mitral annulus, and the distance between the mitral commissures and the papillary muscles. In selected cases, the measurements of these parameters may enhance the understanding of the mechanism of regurgitation and facilitate the surgical planning.[21]

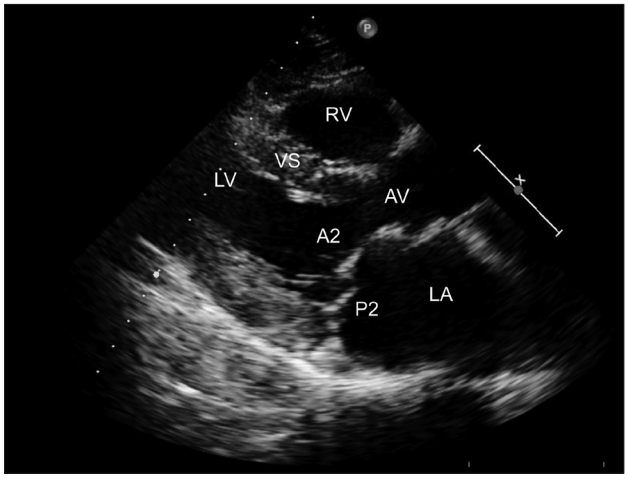

Fig. 1. Parasternal long axis view by transthoracic echocardiography. Segmental analysis of the mitral valve. AV: aortic valve, LA: left atrium, LV: left ventricle, RV: right ventricle, VS: ventricular septum (see also Fig. 5).

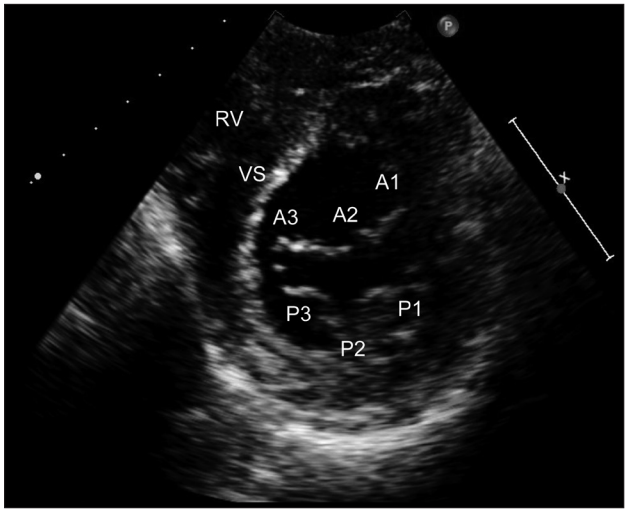

Fig. 2. Parasternal short axis view by transthoracic echocardiography. Segmental analysis of the mitral valve. RV: right ventricle, VS: ventricular septum (see also Fig. 5).

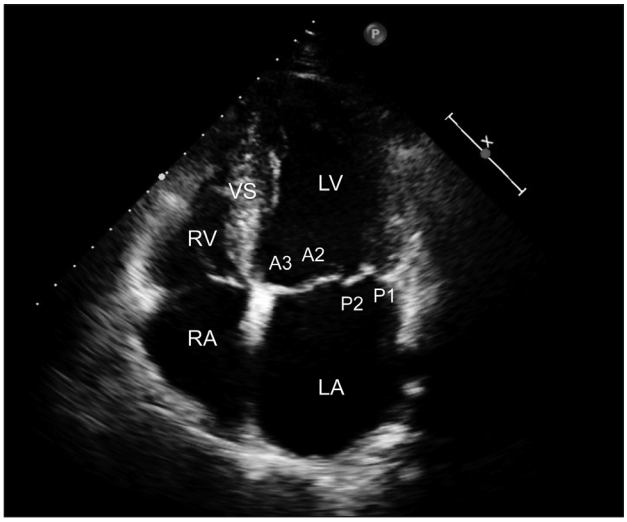

Fig. 3. Four chambers apical view by transthoracic echocardiography. Segmental analysis of the mitral valve. LA: left atrium, LV: left ventricle, RA: right atrium, RV: right ventricle, VS: ventricular septum (see also Fig. 5).

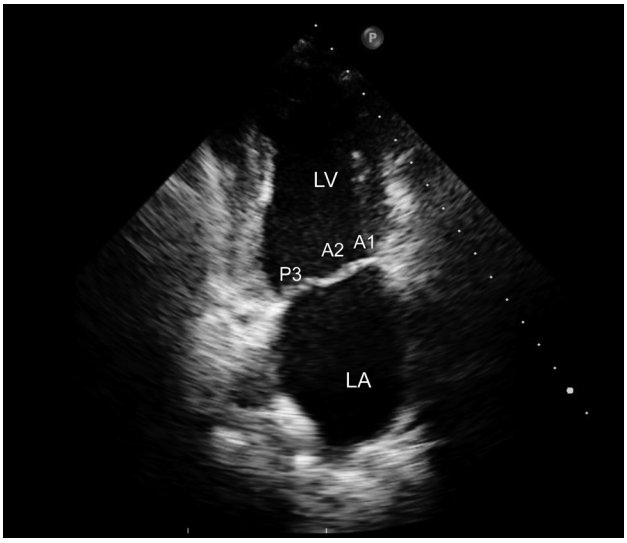

Fig. 4. Two chambers apical view by transthoracic echocardiography. Segmental analysis of the mitral valve. LA: left atrium, LV: left ventricle (see also Fig. 5).

ASSESSMENT OF SEVERITY BY DOPPLER ECHOCARDIOGRAPHY

The visualization of the jet area by color flow imaging provides a rapid screening of the presence and direction of the regurgitant jet. In general, larger jet areas visualized by color flow imaging correspond to larger volumes of regurgitation. Accordingly, a semi quantitative assessment of MR can be obtained trough the assessment of the jet area and of the ratio jet area/left atrium area (Supplementary Fig. 6).[20] Usually this analysis requires an aliasing velocity of 50–60 cm/sec and a color gain set to eliminate random color speckle from the regions without movements. It is also very important to obtain the largest image of the variables of interest (i.e., the left atrium and the jets). This technical tip facilitates tracing and reduce the influence of potential mistakes. The left atrium and the jets are measured by an apical 4-chambers view and long axis view. The thresholds for defining MR severity according to regurgitant jet and jet/atrial area ratio are reported in Supplementary Fig. 6C and D. Unfortunately, color flow imaging underestimates MR in eccentric jets and overestimates central jets. Furthermore, gain and filter setting can additionally interfere with MR assessment performed by color flow imaging.

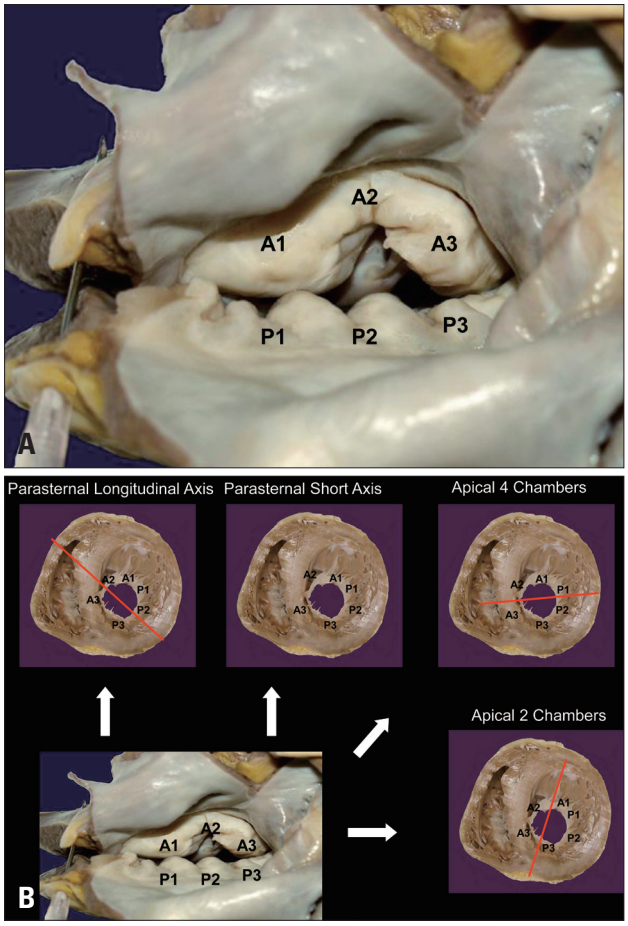

Fig. 5. Surgical view of the mitral valve (A). Spatial orientation of the most commonly used two-dimensional transthoracic echocardiographic views (B). Leaflet segmentation starts with A1-P1 close to the anterolateral commissure, A2-P2 centrally, and A3-P3 close to the posteromedial commissure.

The jet is characterized at its emergence from the leaflets by the presence of a narrow zone corresponding to contraction of the blood flow into the anatomic regurgitant orifice (the narrowest portion of the jet).[22] This "neck" of the jet is defined as vena contracta, and its measurement provides an indirect assessment of the regurgitant orifice (Supplementary Fig. 7). On the clinical field,–due to the physical properties of ultrasounds–the measurement of vena contracta width should be performed using parasternal long-axis views in order to take advantage of the spatial resolution. It is also very important to use the zoom combined with a narrow sector of color flow, in order to obtain the best visualization and high frame rate. The transducer should be positioned trying to visualize the proximal flow acceleration, the vena contracta and the downstream expansion of the jet. In the case of atrial fibrillation, it is important to average the measurements for several cardiac cycles. The thresholds for defining MR severity according to vena contracta is reported in Supplementary Fig. 7B.[20] Although vena contracta width in the context of a fixed orifice is relatively in-

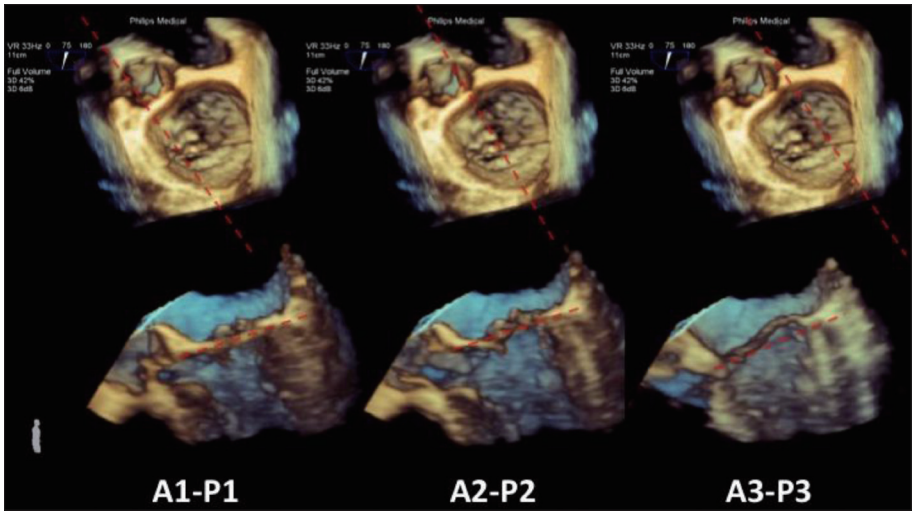

Fig. 6. Three-dimensional trans-esophageal echocardiography facilitates evaluation of mitral valve leaflets. Cross-plane of the surgical view makes easier to measure the prolapse height of every segments. At the bottom in the figure, sagittal view of the valve at different levels. The annular plane is highlighted by the dotted line.

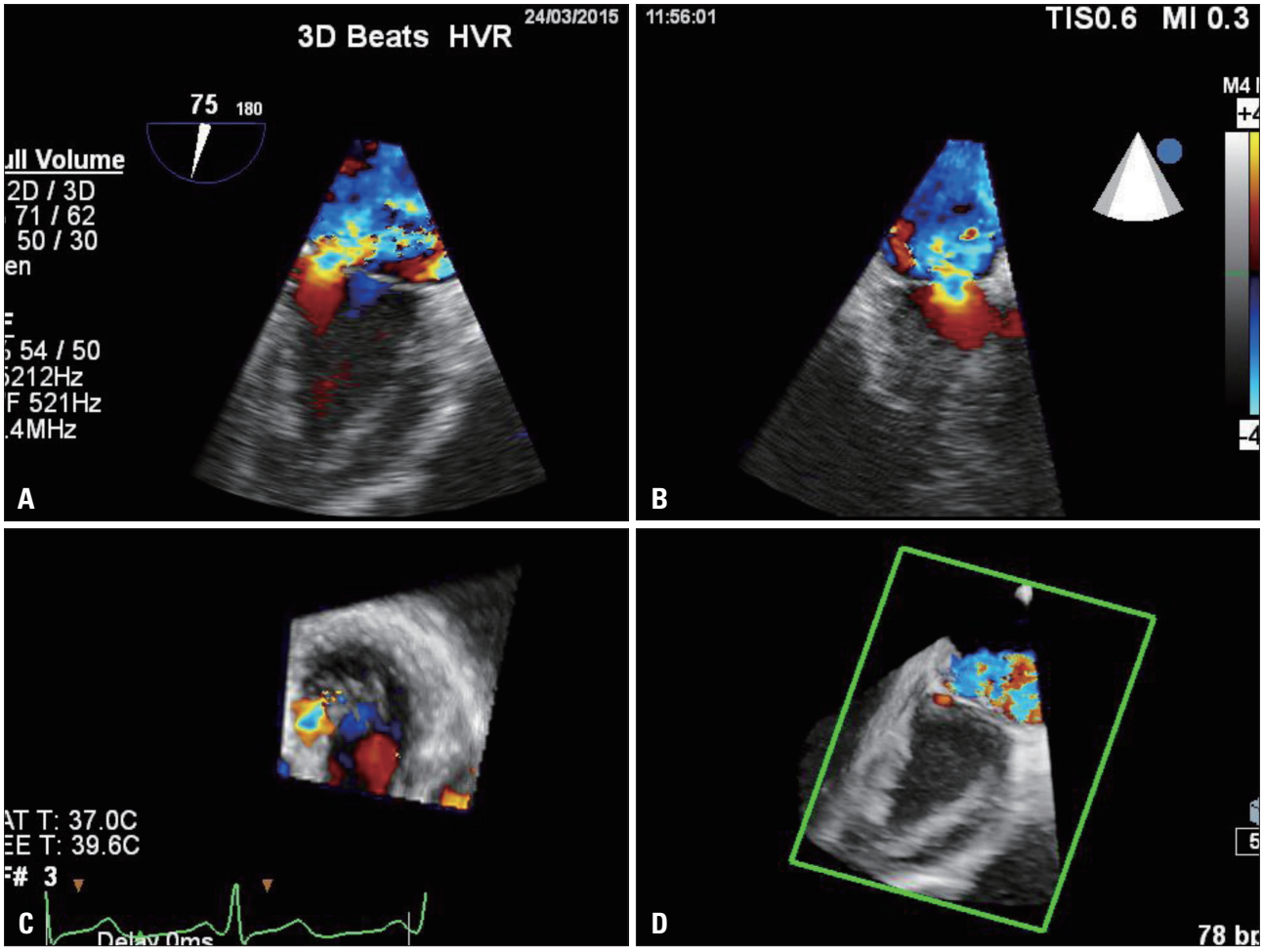

Fig. 7. Multiplanar reconstruction of mitral valve regurgitation using 3-dimensional (3-D) color Doppler full-volume acquisition by transesophageal echocardiography. Multiple simultaneous orthogonal 2-dimensional-like slices are presented in multiplanar reformatting mode, showing the long-axis cut planes (A and B) and the short-axis cut plane parallel to the mitral annulus (C). D: Reformatted 3-D volume illustrating the regurgitant jet. In panel C en face view of the vena contracta area with planimetry is feasible and can be measured (see the text for more explanations).

dependent of flow rate and driving pressures,[23] in dynamic orifices it changes according to hemodynamics and cardiac cycle.[24] The separation of the vena contracta itself from the MR jet, usually obtained in parasternal long axis view, requires considerable practice. Furthermore, since the regurgitant orifice is often elongated along the mitral coaptation line, the views parallel to the line of coaptation tend to show a wide area of vena contracta even in mild MR.[20]

A quantitative assessment of a regurgitant lesion, regardless of the method, imply the calculation of effective regurgitant orifice area (EROA), regurgitant volume (RVol), and regurgitant fraction (RF). The EROA is a measure of the lesion severity. The RVol identifies the volume regurgitated. The RF corresponds to the volume regurgitated in comparison with the total ventricular stroke volume.[21] Quantitative indices should be assessed through different echocardiographic methods in order to provide reliable results. Among the latter, the most commonly used method is proximal isovelocity surface area (PISA) (Supplementary Fig. 8).[25] When blood during the process of regurgitation goes from the left ventricle into the left atrium, on converging toward the mitral valve it gradually accelerates, producing a series of hemisphere-like shells. As we come closer to the orifice of regurgitation, these hemispheres progressively increase in velocity and decrease in surface area. Because of the principle of the conservation of mass, the product of the surface multiplied by the velocity is a constant. Therefore, the product of the surface multiplied by the velocity at the level of any given identified hemisphere in proximity of the regurgitant orifice is equal to the product of the velocity multiplied by the surface at the level of the EROA (the variable of interest). In clinical practice, to use PISA we should image from an apical window. After optimizing the 2-D image, zoom can help improving the detail of the color flow at the level of the flow convergence region. Then, shifting the baseline of the color scale downward (optimal aliasing velocity varies for each patient), we can increase the size of the hemisphere. A small size of the hemisphere amplifies the effects of errors in measurement of the radius. Color baseline adjustment can help to obtain the correct shape,

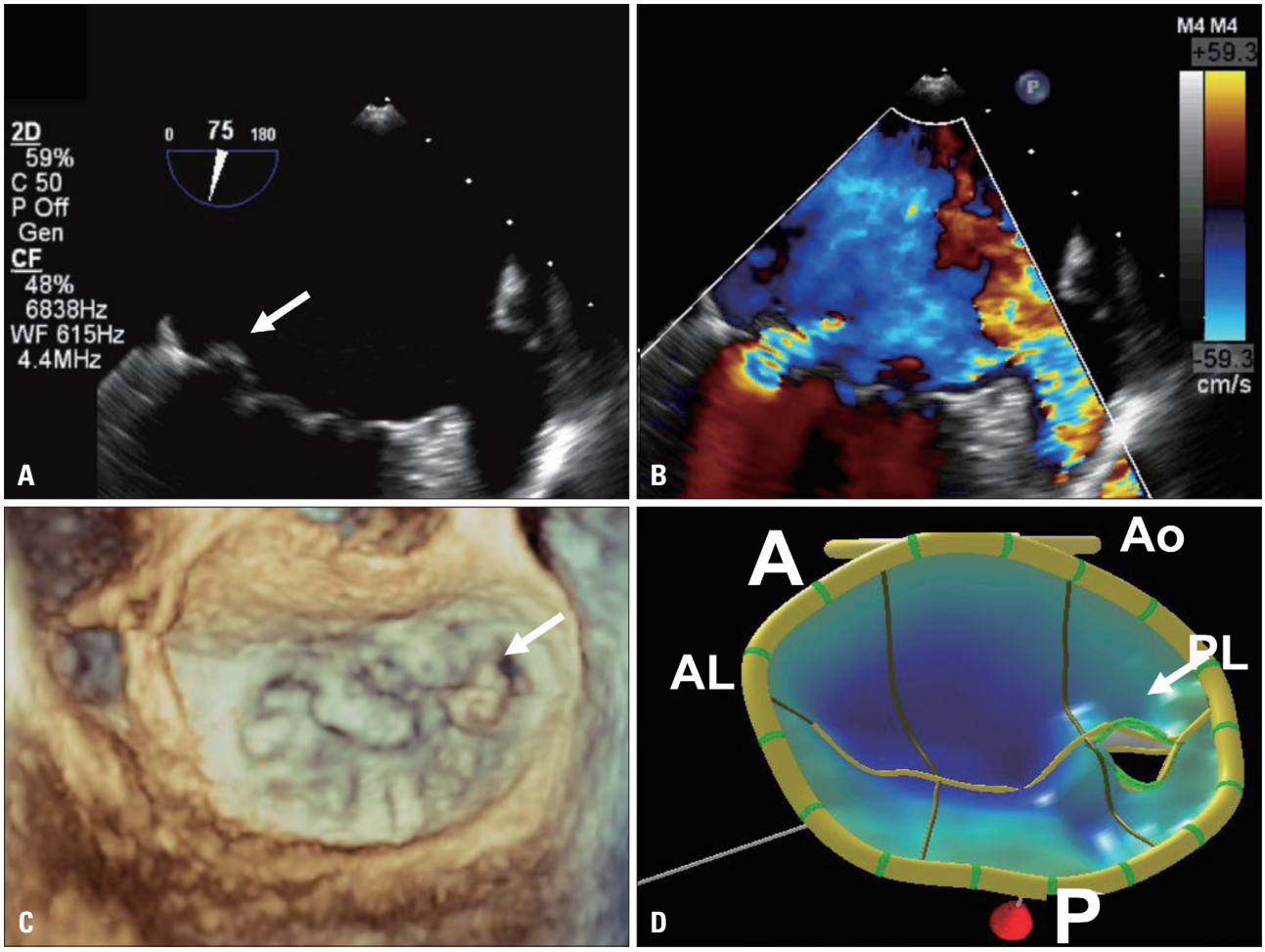

Fig. 8. A and B: Multiplane 2-dimensional transesophageal echocardiogram showing commissural view without (A) and with (B) color Doppler. A: From left to right three scallops of the mitral valve are evident postero-medial commissural scallop (arrow), middle segment of anterior leaflet (A2) and lateral segment of posterior leaflet (P1). B: Mitral regurgitation with eccentric jet from the postero-medial commisure direct toward the left appendage. C and D: Real time 3-dimensional (3-D) transesophageal echocardiography. C: Left atrial view ("en face" surgical view) in zoom 3-D acquisition of the mitral valve. The prolapse of posterio-medial commisural scallop is evident (arrow). D: 3-D transesophageal echocardiography reconstruction of the mitral valve using the mitral valve quantification software. A defect of mitral valve coaptation is present the level of the postero-medial commisure.

which is a portion of a sphere, because lateral flows at angles close to 90° to the ultrasound beam are not visible. We can identify a hemisphere approaching the effective regurgitant orifice and calculate its area as $2\pi r^2$ (where r = radius of the measured shell) and record the velocity of the selected hemisphere (which is given by the machine as aliasing velocity). To proceed further, we can obtain the velocity at the level of the regurgitant orifice (which corresponds to the maximal velocity of the regurgitant jet measured by continuous wave Doppler). At this stage, we have obtained all we need to calculate the EROA. It is worth noticing that the measure of the radius of the hemisphere should be obtained at the same moment of the cardiac cycle when velocity of regurgitation is recorded.

Since:

The area of the hemisphere multiplied by the aliasing velocity = EROA multiplied by peak MR velocity

Consequently:

EROA = ($2\pi r^2$ multiplied by aliasing velocity) divided by peak MR velocity

Regurgitant volume can be obtained by multiplying EROA by regurgitant time velocity integral.

PISA limitations include partial applicability in multiple jets and limited accuracy in eccentric jets, which are characterized by a difficult Doppler alignment.

The rationale of quantitative Doppler in MR is that in the absence of significant aortic regurgitation, the difference between the inflow at the level of the mitral valve and the outflow at the level of the aorta is equal to the RVol. In quantitative 2-D echocardiography, we use the same principle but instead of the mitral valve inflow volume we use the stroke volume of the left ventricle calculated by biapical Simpson rule.[20]

The most common pitfall of quantitative Doppler is the overestimation of mitral valve stroke volume, due to incorrect positioning of the Doppler sample at the level of the mitral leaflets. Concerning 2-D echocardiography, improper MR assessment usually derives from incorrect measurements of ventricular vol-

umes by planimeter.

In the presence of MR, the rise in left atrial pressure produces a reduction of the forward systolic flow at the level of the pulmonary veins. A systolic flow reversal in the pulmonary veins reflects the presence of a significant v-wave and indicates severe MR with high specificity. On the other hand, if systolic reversal is absent, severe MR cannot be excluded, because severe incompetence is not always associated with a prominent v-wave.[20]

Decision Making in Organic MR

Having confirmed the severity of organic MR, indications for surgery become the central argument for the subsequent follow-up and management. This happens because medical treatment in asymptomatic organic MR has not been proved to be beneficial in preventing ventricular dysfunction or any other complication due to volume overload.[11)26)] Nowadays, percutaneous repair is promising but conventional surgery (and particularly mitral repair) remains the gold standard for the treatment of organic MR. Although recently challenged in specific sub groups of patients,[27)28)] the superiority of mitral repair over replacement is due, among various factors, to the better preservation of ventricular function and to the avoidance of prosthetic related complications.[29)30)]

Both American and European guidelines recognize that symptoms are per se an indication for surgery, independently of the presence of additional risk factors and of the type of surgical procedure (repair/replacement). The rationale of waiting for symptoms is based (among other considerations) on the fact that a perioperative death, or even a sub-optimal repair is difficult to accept in an asymptomatic patient. Unfortunately, when surgery is performed in symptomatic patients, surgical risk increases, and post-surgical outcome remains impaired.[31)] Conversely, when a durable mitral repair is performed in patients with no or minimal symptoms, expected survival of operated patients is restored to the their expected outcome.[31)32)] A decision-making driven by symptoms is particularly challenging in the elderly, in those with significant comorbidities, as well as in any patients who do not or who cannot engage in physical activity intense enough to reveal them. These concerns have encouraged the use of exercise test in the setting of valvular heart diseases. For instance, previous studies suggested that asymptomatic patients who were nevertheless unable to exercise for at least 15 minutes on the treadmill, are characterized by an higher incidence of adverse events.[33)] Useful information can also be derived from the more revealing cardiopulmonary exercise test, since a reduced cardiopulmonary capacity has been shown to predict outcome of organic MR.[34)]

Besides symptoms, an indicator for surgery is the development of ventricular dysfunction. While advanced left ventricular dysfunction almost unavoidably causes symptoms, early dysfunction can be asymptomatic due to the reduction of the after load characterizing physiopathology of MR. Scientific guidelines do recommend surgery when left ventricular ejection fraction drops ≤ 60%, even in asymptomatic patients.[11)26)] We recently analyzed the value of left ventricular ejection fraction in patients enrolled in the international MIDA Registry.[35)] We found that ejection fraction is valuable in defining presence and severity of ventricular dysfunction in organic MR. Moreover, our study showed that a large proportion of patients presenting with an ejection fraction between 45% and 60% are rarely symptomatic, but they nevertheless display an higher mortality compared with those who's ejection fraction remain above 60%. The benefits of surgery remain considerable in both these groups, but more favorable in those operated before ventricular dysfunction occurs.[35)36)]

The assumption that the prognostic value of ejection fraction in MR is sub-optimal due to the reduced afterload has encouraged the search for an indicator of ventricular performance of loading dependent. Our group recently showed that irrespective of the presence of symptoms, a left ventricular end-systolic diameter ≥ 40 mm represents an independent risk factor for adverse outcome, not only under medical management but also after mitral surgery.[37)] Our findings not only indicate to consider surgery in patients with left ventricular end-systolic diameter ≥ 40 mm as recommended by the guidelines, but also show that best outcome is achieved in patients operated on before end-systolic diameter reaches 40 mm.[37)]

Concerning an early diagnosis of pre-clinical left ventricular dysfunction, exercise echocardiography is gaining increasing consideration. In asymptomatic MR, the lack of contractile reserve (defined as ≥ 4% increase of left ventricular ejection fraction) has been shown to be a predictor of post-operative ventricular dysfunction;[38)39)]

Other indicators of surgery focus on consequences of volume overload, including pulmonary hypertension and atrial fibrillation. Current guidelines advocate surgery when pulmonary artery systolic pressure is ≥ 60 mm Hg during exercise or > 50 mm Hg at rest.[11)26)] Pulmonary hypertension represents not only a marker of disease severity, but abnormal values of pulmonary artery systolic pressure could independently affect prognosis by inducing right ventricular dysfunction and functional tricuspid regurgitation. Furthermore, elevated pulmonary artery pressure can exert direct unfavorable effects through neurohumoral activation, and/or impairment of pulmonary ventilation. We recently showed that pulmonary hypertension assessed by Doppler echocardiography (i.e., right ventricular systolic pressure > 50 mm Hg) is a strong and independent predictor of adverse outcome.[40)] Furthermore, we found that mitral surgery does not completely abolish the adverse effects of pulmonary hypertension, whereas is particularly beneficial in patients without such complication.

Atrial fibrillation is strictly linked to MR because MR produces left atrial enlargement, a precursor of atrial fibrillation and also because MR is common particularly in the elderly, who are also at high risk for atrial fibrillation.[41)] Our group showed

that the onset of atrial fibrillation is frequent in MR, occurring at a rate of approximately 5% per year.[30)41)] Furthermore, we found that the onset of atrial fibrillation leads to increased cardiac mortality and morbidity.[41)] Previous data showed that when surgery is performed in patients who have already developed atrial fibrillation, post-surgical outcome is less favorable.[31)] Taken together available data on this subject suggest that left atrial protection plays an important role within clinical decision-making. Our group recently showed that in MR, left atrial diameter ≥ 55 mm is associated with increased mortality under medical treatment, irrespective of the presence of symptoms or left ventricular dysfunction.[42)] Similarly, left atrial index (i.e., left atrial volume indexed to body surface area) predicts long-term outcome.[43)]

The brain natriuretic peptide (BNP) and its inactive amino-terminal portion (NT-proBNP) result from the break down of pro-BNP and have vasodilator and diuretic effects. Pizarro et al.[44)] published their prospective experience with asymptomatic patients with organic MR. A cut-off point of 105 pg/mL of BNP has been shown to discriminate patients at higher risk of adverse events.

In conclusions, although debate on early surgery is often attracting the attention of the scientific community, it is worth remembering that current practice is unfortunately too often characterized by an underuse of surgery even in those who have a well-established benefit from it,[1)] and even when surgery is performed, repair (the preferred mode of treatment in the vast majority of patients) is often underuse.[1)]

Taken together, available findings indicate that physicians should refer patients with severe MR and a repairable lesion early to centers able to achieve a durable repair with a low risk of operative mortality. When those requirements cannot be achieved at their local institution, physicians should ask for the help of centers more experienced in the treatment of MR.[26)]

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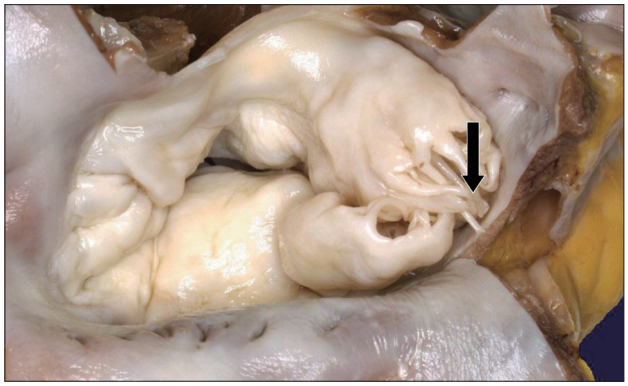
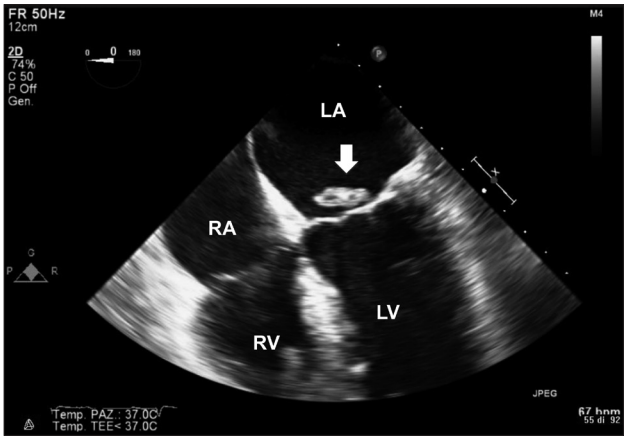
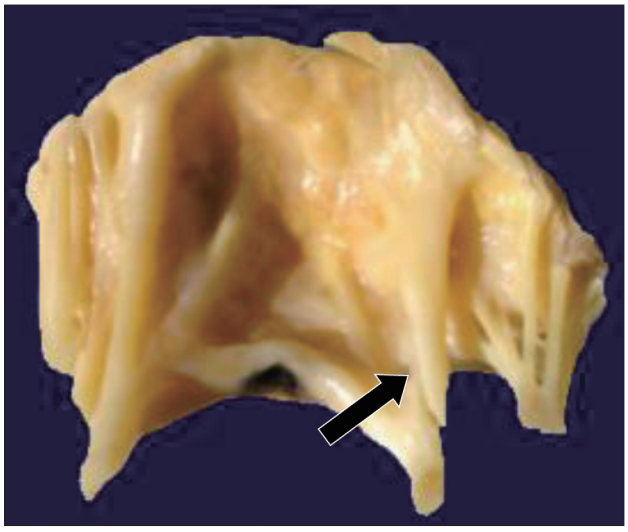


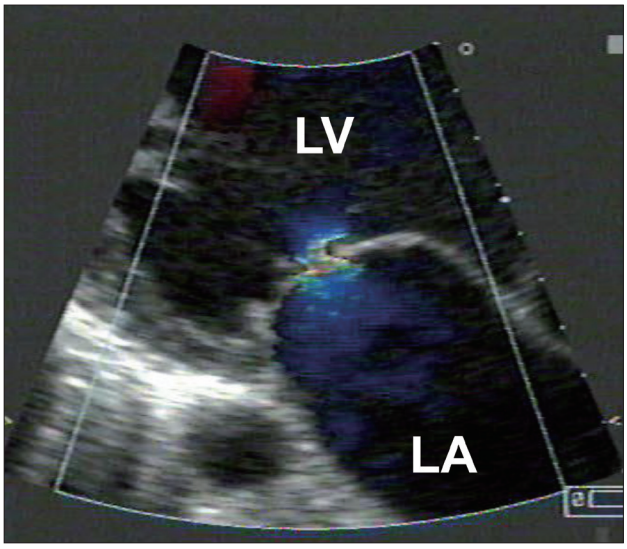
Supplementary Fig. 1. Barlow' disease. In Barlow's disease the most common finding is diffuse excess tissue, the mitral valve size is generally large, and the myxomatous pathological changes usually affects multiple segments, eventually resulting in a "floppy mitral valve". An additional typical finding is diffuse chordal elongation and rupture (arrow) (see the text for more explanations).



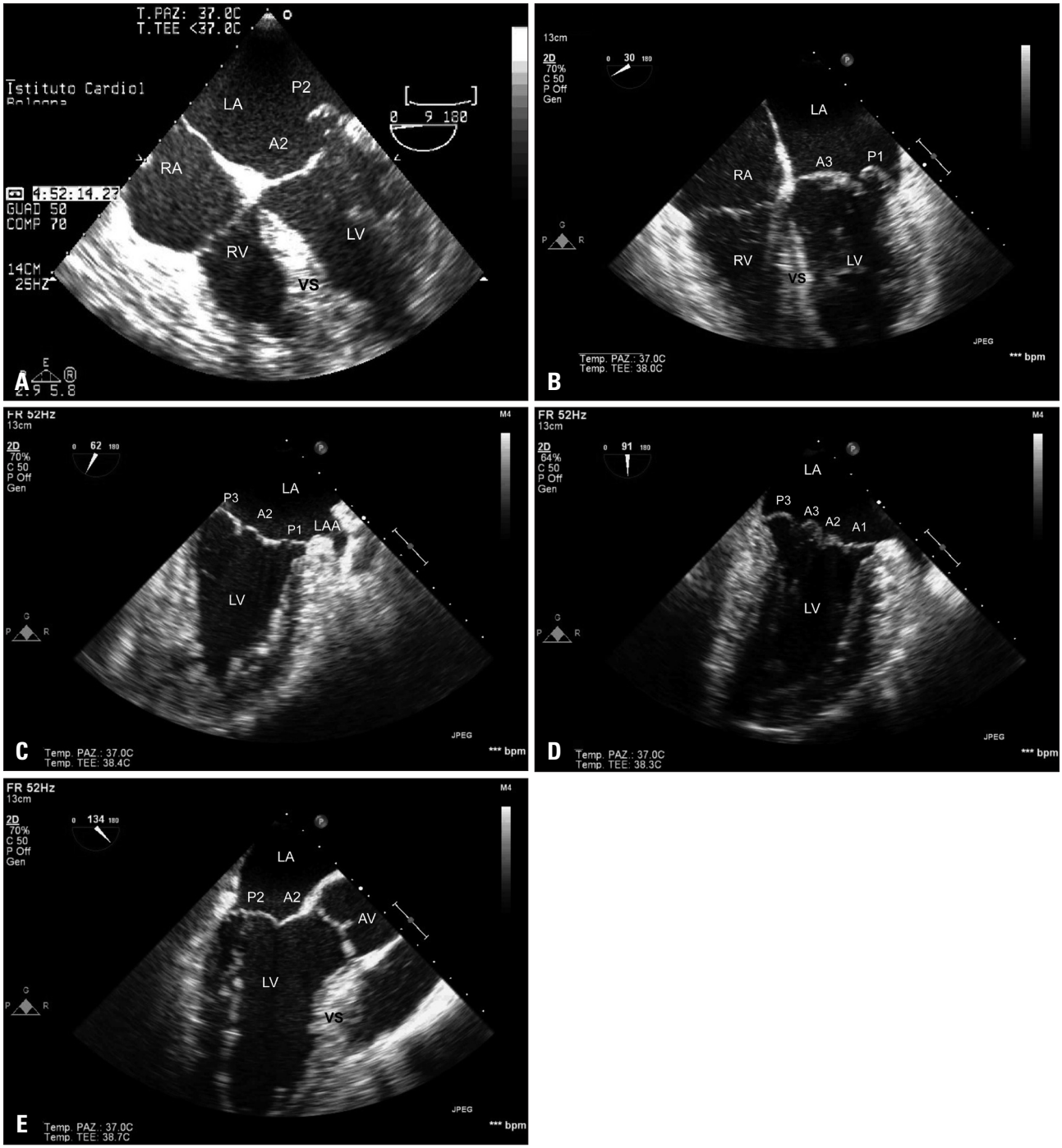
Supplementary Fig. 3. Trans esophageal echocardiography showing a vegetation of the mitral valve (arrow) in a patient presenting with infective endocarditis (see text for the details). LA: left atrium, LV: left ventricle, RA: right atrium, RV: right ventricle.



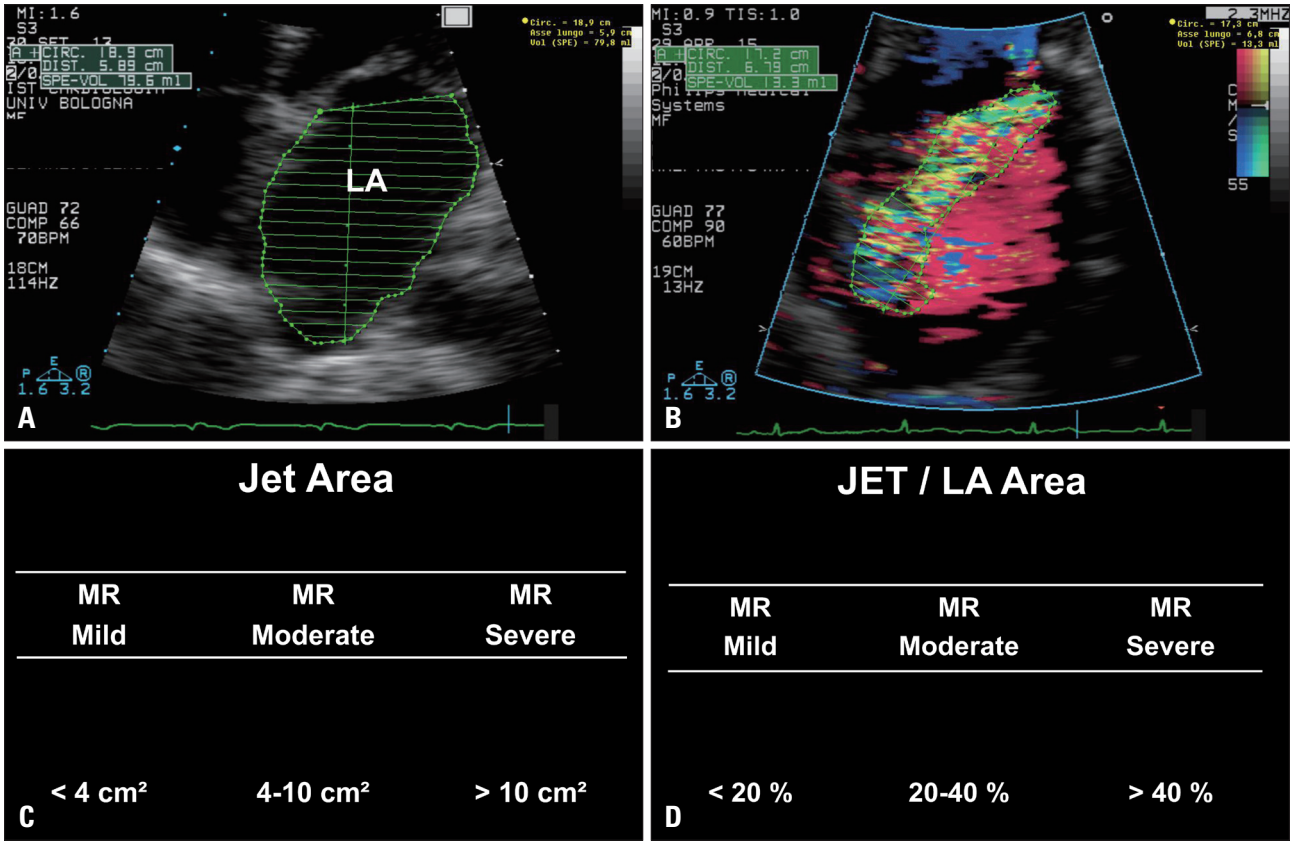
Supplementary Fig. 2. Rheumatic disease. In rheumatic disease the valve leaflets are thickened and sometimes calcified as the commissure. The chordae are invariably thickened, often fused together, and shorten (arrow) (please see the text for more explanation).



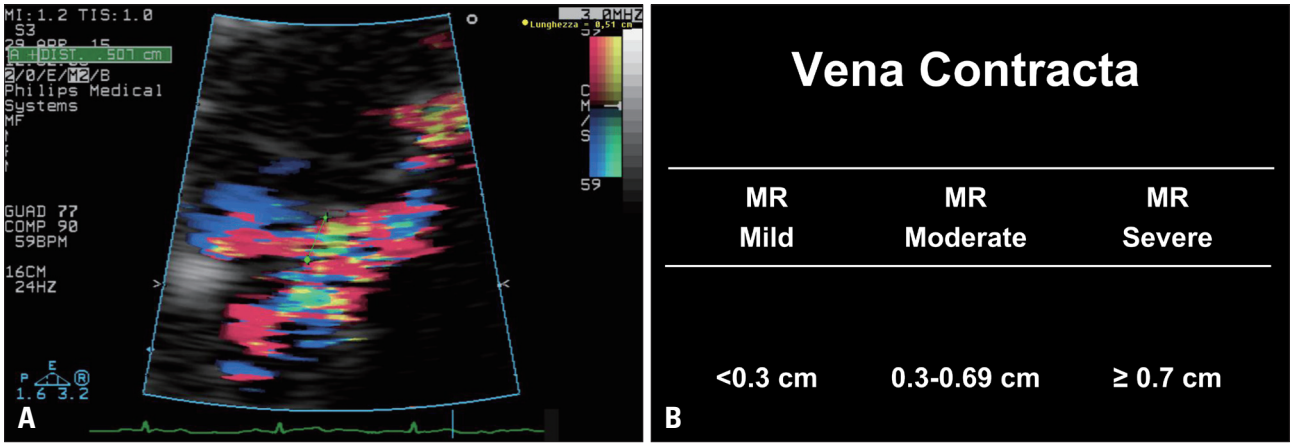
Supplementary Fig. 4. Parasternal long axis view (obtained by transthoracic echocardiography) showing local remodeling at the level of the mitral valve resulting in functional mitral regurgitation from restricted leaflet motion and annular dilatation. LA: left atrium, LV: left ventricle.



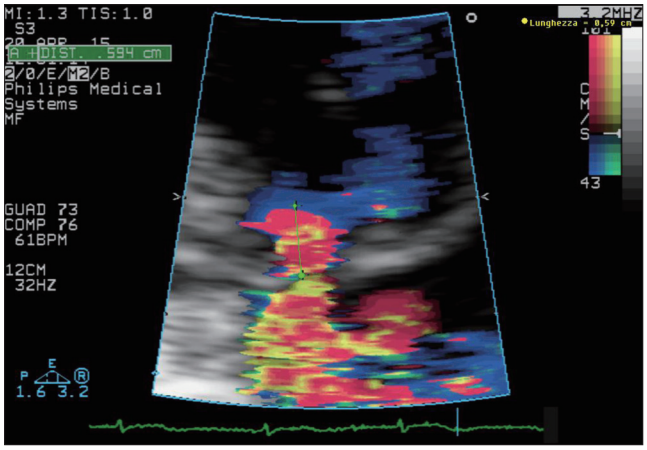
Supplementary Fig. 5. Examination of the mitral valve by transesophageal echocardiography usually implies 4 mid esophageal views (4 chambers A and B; bicommissural C; 2 chambers D; and long axis E) and the trans gastric basal short axis view. AV: aortic valve, LA: left atrium, LAA: left atrial appendage, LV: left ventricle, RA: right atrium, RV: right ventricle, VS: ventricular septum.



Supplementary Fig. 6. Assessment of the severity of mitral regurgitation based on regurgitant jet area (A and B). The regurgitant jet area can be used to assess the severity of MR (C and D, see the text for the explanation). LA: left atrium.



Supplementary Fig. 7. Assessment of the severity of mitral regurgitation based on vena contracta (A and B, see the text for the explanation).



Effective Regurgitant Orifice Area (EROA)

MR Mild	MR Moderate	MR Severe*
<0.20 cm²	0.20-0.39 cm²	≥ 0.40 cm²

*Please note that outcome data suggest that smaller EROA is associated with adverse outcome in functional IMR (≥0.20 cm²).

Regurgitant Volume (RVol)

MR Mild	MR Moderate	MR Severe*
30 ml/beat	30-59 ml/beat	≥ 60 ml/beat

*Please note that outcome data suggest that smaller RVol is associated with adverse outcome in functional IMR (≥30 ml/beat).

Regurgitant Fraction

MR Mild	MR Moderate	MR Severe
<30%	30-49%	≥ 50%

Supplementary Fig. 8. Assessment of the severity of mitral regurgitation based on the proximal isovelocity surface area method (see the text for more explanation).