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EDITORIAL VIEWPOINT

Echocardiographic assessment of functional mitral regurgitation: opening Pandora's box?

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Abstract

Two recent trials of transcatheter mitral-valve repair in patients with functional mitral regurgitation (FMR) presented opposing results for the MitraClip® compared to medical therapy alone. The conflicting results gave rise to intensive discussions about assessment of mitral valve regurgitation (MR). A recent editorial viewpoint provided a potential explanation presenting a new pathophysiologic concept. However, the echocardiographic characterization of both trials' patients is inconsistent and the discussed concepts appear to suffer from plausibility weaknesses. It is well conceivable that limitations in the echocardiographic assessment of the trial patients introduced a bias regarding the selection of patients with severe (or less severe) MR that may be a more plausible explanation for the differences in outcome. We here illustrate our viewpoint regarding the two MitraClip trials and also illustrate the difficulties in assessing functional MR properly. It may indeed be "opening Pandora's box", but we will also make an attempt to provide a solution.

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Introduction

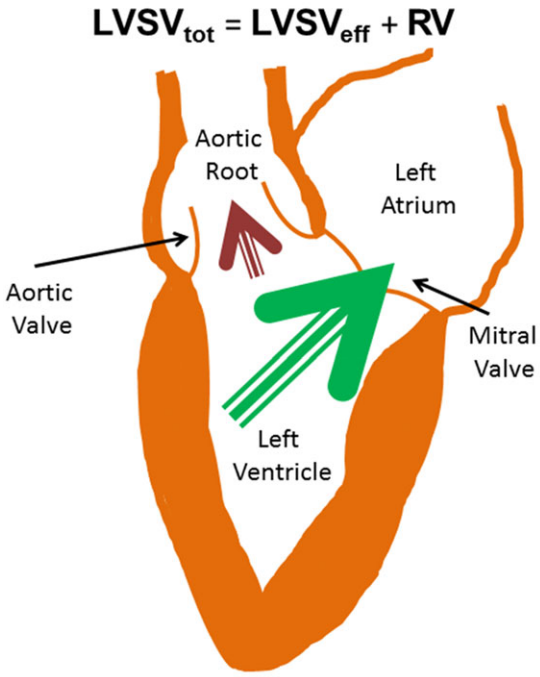
Two recent trials of transcatheter mitral valve repair in patients with functional mitral regurgitation (FMR) presented different results for the MitraClip® compared with medical therapy alone with respect to all-cause mortality and the rate of hospitalization for heart failure.[1,2] While the MITRA-FR investigators did not observe an effect on death and hospitalization within 12 month follow-up,[1] the COAPT investigators documented a 29% reduction of death and a 46% reduction of hospitalization within a 24 month follow-up.[2] These conflicting results gave rise to intensive discussions about assessment of mitral valve regurgitation (MR) summarized and addressed in several papers including a recent editorial viewpoint.[3–6] Because the echocardiographic characterization of the patients in both trials is inconsistent, the assessment of MR severity by semiquantitative parameters has to be reconsidered.[7–9] The different results of MITRA-FR and COAPT need to be interpreted in the context of previous surgical trials using the Alfieri procedure.[10–14] It is unclear why therapies using nearly the same principle—Alfieri suture vs. MitraClip®—will have different prognostic implications, if patient cohorts of the recent trials are comparable.

Echocardiographic measurements in MITRA-FR and COAPT

As illustrated in *Figure 1*, in the MITRA-FR trial (in both control and treatment groups), the mean values of left ventricular end-diastolic volume (LVEDV) were about 245 mL (indexed LVEDV—135 mL/m^2), the left ventricular ejection fraction (LVEF) 31%, the effective regurgitant orifice area (EROA) 0.3 cm^2, and the regurgitant volume (RV) 45 mL. Based on these data, the calculated total left ventricular stroke volume ($LVSV_{tot}$) is about 76 mL, left ventricular effective forward stroke ($LVSV_{eff}$) volume is about 31 mL, and regurgitant fraction (RF) is about 59%.

In the COAPT trial (control and treatment groups), the mean values for LVEDV were about 195 mL, the LVEF was 31%, the EROA about 0.4cm^2, and RV were not presented

Figure 1 Scheme of left ventricular long-axis view illustrating forward stroke volume and regurgitant volume in patients with FMR. The table summarizes the haemodynamic parameters presented and calculated from the data of the MITRA-FR and COAPT trial. EROA, effective regurgitant orifice area; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVSV, left ventricular stroke volume; RF, regurgitant fraction; RV, regurgitant volume.



	MITRA FR	COAPT
LVEDV	245ml estimated from 135ml/m²	193ml
LVEF	31%	31%
$LVSV_{tot}$	76ml calculated from LVEDV and LVEF	51ml
EROA	0.3cm²	0.4cm²
RV ⇒	45ml	60ml
$LVSV_{eff}$ ⇒	31ml calculated from $LVSV_{tot}$ - RV	-9ml calculated from $LVSV_{tot}$ - RV
RF	59% calculated	118% calculated
Heart rate	73/min	?
Cardiac Output	2.2 l/min calculated	?
Reference	1	2,15

in the primary outcome publication but presented by the COAPT investigators at the recent meeting of the American College of Cardiology.[15] $LVSV_{tot}$ was reported as 51 mL and the RV as 60 mL. Thus, calculated RF would exceed 100%. These inconsistencies make the trial result difficult to interpret.

Attempted explanation for the conflicting echocardiographic results

It is accepted that using the popular proximal isovelocity surface area (PISA) approach for quantification of MR severity, the calculation of the EROA and consecutively also of RV determined by the PISA method is highly prone to methodological errors.[4,7–9,16,17] The centre of the orifice area and the maximum PISAs have to be correctly visualized in a representative sectional plane. Mathematical assumptions of a round office area, a central jet formation, and symmetric sphere-shaped PISAs are rarely present in reality. In addition, mitral regurgitation is dynamic, which can hardly be fully characterized by single snapshot during the cardiac cycle. Despite these limitations, the PISA method was used in the recent two trials for MR quantification. Not surprisingly, MITRA-FR presents conclusive data of RV, while the COAPT trial was not able to provide conclusive data using the PISA method.

Because characterization of MR severity in the COAPT trial is inconclusive, it is not appropriate to conclude per se that all patients had moderate-to-severe or severe MR. Selection or sampling bias towards moderate and mild FMR may have induced inaccurate quantification.[18–20]

A second attempt to explain the different results of MITRA-FR and COAPT is the relation of EROA and RV to LVEDV and to distinguish between proportionate and disproportionate FMR according to LV size.[4,21] The more enlarged LV dimensions, the less reverse remodelling can be presumed after treatment. However, the mean difference of LVEDV between the two trials is 'only' 45 mL, and the mean LVEF in the COAPT trial cohorts is practically the same than in the MITRA-FR cohort suggesting that LV remodelling of all cohorts in both trials is in the same range considering the measuring error of LV planimetry using the Simpson's method within the range of ±20% using transthoracic 2D echocardiography due to foreshortening views. Thus, conclusions based on LVEDV and LVEF in FMR patients in MITRA-FR and COAPT should be drawn with care. To analyse LV remodelling and reverse LV remodelling after therapy in more detail, additional

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parameters describing the LV geometry and LV function should be presented such as sphericity ratio and index, lateral and posterior dislocation of the papillary muscle, interpapillary muscle distance, tenting area and tethering angles, and LV contractility parameters such as peak power index and global longitudinal peak systolic strain.[22–28] However, LV contractility parameters should only be determined in patients with regular sinus rhythm. Both trials have not presented any of these assessments. This lack of information substantially limits the interpretation of the results.

Can a 'teleological approach' to characterize functional mitral regurgitation be accepted?

Addressing the described inconsistencies and the potential of reverse LV remodelling in FMR, Grayburn *et al*. proposed a new conceptional framework.[4,22] For clinical decision making, 'the principal reason to fully characterize and quantify the determinants of functional MR is to determine if an intervention directed at the mitral valve is capable of changing the clinical course of the disease'[4] and 'viewed through this lens, the precise sequence of events that may have led to the clinical presentation of the patient becomes irrelevant. If an intervention directed at the mitral valve changes the natural history of the disease, then the MR should be considered a target for therapy, even if it is "secondary" to LV dysfunction'.[4] While these statements sound convincing, this rather teleological approach to FMR should at least be based on an accurate characterization of the patients' haemodynamic state. However, this characterization is not convincing in both trials based on inconclusive data. As presented for COAPT, the mean $LVSV_{tot}$ is about 50 mL. A 50% RF representing severe FMR would correspond to an RV of 25 mL. Thus, the mean measuring error of RV in COAPT is about 35 mL (RV was reported to be 59 mL, *Figure 1*) corresponding to a 140% difference of the presumably correct RV. Considering such an enormous measuring error, it has to be assumed that patients with mild or moderate MR were also included into the cohorts of COAPT, significantly influencing and improving the overall prognosis per se. The assumed forward stroke volume of 25 mL in the COAPT trial in the presence of a 50% RF and an assumed heart rate of 100/min implies a cardiac index in the range of 1.5 L/min m^2 (which is probably overestimated based on the assumptions made), which meets criteria for cardiogenic shock. In addition, the forward stroke volume of 31 mL at a heart rate of 73 bpm in the MITRA-FR trial results in a cardiac output of 2.2 L/min and an estimated cardiac index of 1.2 L/min m^2, describing similar haemodynamics as in COAPT.

If patients with mild and moderate FMR, who will have a better prognosis per se, were included in the trials, the impact of percutaneous mitral valve therapy in FMR has to be reevaluated from a different point of view. The positive outcome data from COAPT (improvement in symptoms and survival in the MitraClip group) suggest a prognostic impact of this intervention in patients with heart failure. It therefore has to be compared with new options of conservative heart failure therapy.[29,30] Regarding this issue, it is extremely important that prior to inclusion into the trials, conservative medical heart failure therapy was optimized. Unfortunately, both trials do not provide clinical and echocardiographic data of the patients prior to inclusion—especially prior to intervention—to prove the optimization of baseline medical therapy and to document exclusion of FMR due to potential acute ischaemia-induced or inflammation-induced heart failure or partial cardiac decompensation due to hypertension or arrhythmias.

The PRIME investigators recently reported in a patient cohort with a mean LVEDV of 202 mL, a mean LVEF of 34%, and (in contrast to MITRA-FR and COAPT) a mean EROA of only 0.2 cm^2, significant changes in mitral valve function as a consequence of medical treatment. Sacubitril/valsartan led to a 30% reduction of the EROA (primary end point vs. 9% with valsartan alone) as well as a significant decrease of the secondary end point RV by 33% with sacubitril/valsartan and 12% with valsartan alone, documenting that optimizing medical therapy has a substantial ability to reduce MR severity in heart failure patients (presumably if reverse LV remodelling is present).[31,32]

With respect to an optimized baseline medical therapy prior to inclusion into the trial and the potential influence of optimized medical therapy on the trial end point, Grayburn *et al*. comment the COAPT data as follows: 'the authors of the COAPT trial have not explained why a difference in background drug treatment would explain the discordant results across the two studies. Interestingly, in the COAPT trial—even though medical therapy was supposed to have been maximized prior to randomization—drug treatments were intensified to a greater degree in the device than in the control arms during the follow-up period'.[4] Considering the PRIME data, the discrepancy of baseline medical therapy casts doubt on comparable optimization of medical therapy at inclusion and during follow-up due to a relevant confounding bias.[33,34] It would therefore be important to get insights into the clinical and echocardiographic data of the pre-inclusion period of both trials.

In addition, the potential long-term side effects of induced mitral valve stenosis after Mitra-clipping have to be considered. Assuming a circular mitral valve orifice area, central clipping and a clipping bridge of 4 mm after clipping an orifice area of 4 cm^2 ($\pi \times r[cm]^2 = 4[cm^2] = 3.14 \times 1{,}13[cm]^2 = 4[cm^2]$) will result in two orifice areas after clipping ($3.14 \times 0.57[cm]^2 + 3.14 \times 0.57[cm]^2 = 2.05[cm^2]$). Based on the recommendations of echocardiographic assessment of valve stenosis, the range of mild mitral valve stenosis is between 1.5 and

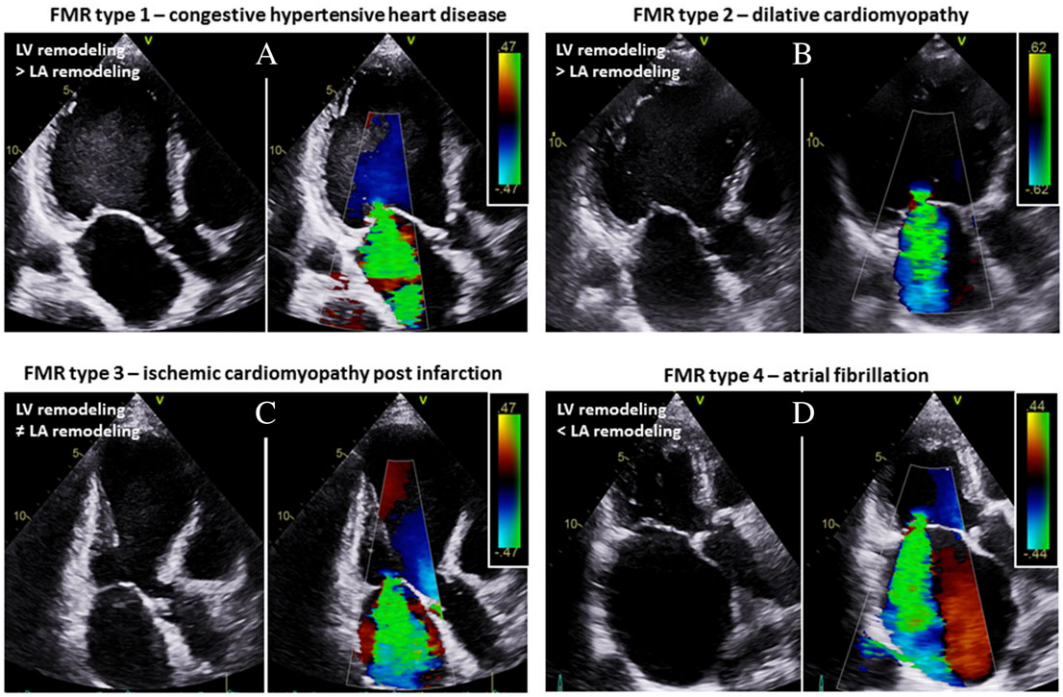
2.5 cm^2. With respect to the impact of the MitraClip® procedure on the generation of mitral stenosis, in theory, a mitral valve orifice area should be larger than 4.5 cm^2 prior to intervention. Otherwise, one would risk inducing functional mild or mild-to-moderate mitral stenosis. Thus, in future trials of percutaneous mitral valve therapy, the mitral valve orifice area prior and after therapy as well as echocardiographic parameters characterizing the pulmonary circulation should be provided to be able to analyse potential long-term effects of restrictive LV filling patterns after intervention potentially influencing outcome.

Proposal of a new echocardiographic approach classifying and analysing functional mitral regurgitation

Because of the uncertainty in characterization of FMR patients, a more detailed echocardiographic assessment with respect to the underlying pathophysiology would be helpful. Four types of FMR may be differentiated and analysed according to the stage of the disease (echocardiographic examples are shown in *Figure 2*): first, FMR induced by non-ischaemic LV remodelling due to congestive heart failure in hypertensive heart disease (FMR type 1); second, non-ischaemic LV remodelling in dilated or toxic cardiomyopathy or post-myocarditis (FMR type 2); third, ischaemic FMR induced by territorial myocardial infarction and LV remodelling of the viable myocardium (FMR type 3); and fourth, FMR induced by left atrial (LA) remodelling, most often due to chronic atrial fibrillation (FMR type 4).

(1) FMR type 1: The echocardiographic characterization of the disease stages in FMR type 1 due to hypertensive heart disease is relatively easy. As an example, the echocardiographic assessment in a patient with untreated hypertensive heart disease is shortly described focusing on the parameters LVEF, LVEDV (both determined by LV planimetry), and left ventricular end-diastolic pressure (LVEDP) determined by the surrogate parameter E/E′. The first stage of mild MR is characterized by a regurgitant jet into the left atrium in the presence of normal values of LVEF, LVEDV, and E/E′ determined by echocardiography. An increasing amount of regurgitation resulting in mild-to-moderate MR is compensated just by an increase in LVEF to ranges >55% to maintain cardiac output. Thus, $LVSV_{tot}$ increases due to the RV increase and $LVSV_{eff}$ remains constant in the presence of normal values of LVEDV and E/E′. A further increase of regurgitation results in dilatation and an excentric LV hypertrophy described by echocardiography by an increased LVEF and an increased

Figure 2 Illustration of different types of FMR: (A) FMR type 1 due to congestive hypertensive heart disease, (B) FMR type 2 due to dilated cardiomyopathy, (C) FMR type 3 due to extended anterior myocardial infarction, and (D) FMR type 4 with mitral annulus dilatation due to chronic atrial fibrillation. Each example is presented in the apical long-axis view at systole by grey scale imaging and by colour-coded Doppler imaging including scale with Nyquist limit. FMR, functional mitral regurgitation; LA, left atrial; LV, left ventricular.



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LVEDV in the presence of a normal E/E′. With further increasing MR, e-velocity will significantly increase resulting in a significant increase of E/E′, which is in parallel documented by an increase in systolic pulmonic arterial pressure. Beside medical therapy, interventional or surgical therapy may be an option, presumably most effective if LVEDP is increased. The last stage of FMR type 1 is characterized by contractile insufficiency resulting in decreasing LVEF in the presence of increased LVEDV and increased E/E′. Deformation of the left ventricle and the mitral valve in FMR type 1 is characterized among other parameters by a large tenting area and the seagull sign.[7,24,25]

(2) FMR type 2: FMR in dilated or toxic cardiomyopathy is also due to LV remodelling causing retraction and tethering of the mitral leaflets with consecutive FMR. In contrast to hypertensive heart disease, LVEF decrease in the presence of LVEDV increase will be primarily observed. Thus, the sequelae of LVEDV and LVEDP increase can vary.

(3) FMR type 3: The scenario in ischaemic FMR varies between different conditions depending on location and extension of myocardial ischaemia. The echocardiographic evaluation is more complex. For example, a patient with mild regurgitation may exhibit an RV of 25 mL and an $LVSV_{tot}$ of 100 mL in a normal LV prior to infarction. The RF is 25%. If an acute myocardial infarction occurs, contractile function usually acutely decreases. Assume $LVSV_{tot}$ is reduced to 50 mL. Because in the acute stage, LV dimensions are normal, LVEDP is increased, RV is unchanged with 25 mL, resulting at once in a 50% RF representing severe MR according to current definitions. Depending on revascularization success, LV remodelling, concomitant medical therapy, and the tethering forces to the mitral valve, different sequelae may occur. In the presence of optimal circumstances with predominant closing forces to the mitral valve, ischaemic myocardium recovers and LV remodelling can be nearly completely avoided resulting in restoration of mild MR. If myocardial infarction and scar formation occurs without tethering of the mitral valve under optimal therapy, LV remodelling within at least borderline increases of LV dimension will cause borderline increase of LVEDV and E/E′ in the presence of reduced LVEF and a mild-to-moderate or moderate MR. If scar formation affects papillary muscles and the mitral integrity of the chords and LV remodelling as well as aneurysm formation occurs, the severity of MR will increase and the constellation of reduced LVEF, increased LVEDV, and increased E/E′ can be assessed. Deformation of the mitral valve at this stage of FMR type 3 is also characterized among other parameters by a large tenting area, an increased vena contracta, and mostly by excentric jet formation.

(4) FMR type 4: The echocardiographic scenario in FMR type 4 may again be different—mainly with respect to the differences in LV size due to concomitant myocardial ischaemia and old infarcted areas as well as due to arrhythmia-induced tachy-cardiomyopathy. If LV function is normal, the mitral annulus is dilated due to the LA remodelling resulting in insufficient coaptation of the mitral leaflets. The deformation of the mitral valve in FMR type 4 is characterized by nearly zero tenting area. In patients with FMR type 4, echocardiographic assessment by semiquantitative MR parameters is highly prone to error. Vena contracta and RV determination by PISA method is misleading due to the variability of LV contraction during atrial fibrillation, analysis of jet area and its relation to the LA is generally misleading and should not be used, and reversal of pulmonary vein flow is misleading due to the large LA dimensions. Thus, a quantitative assessment of RF can be proposed—of course with respect to all their limitations. The echocardiographic constellations of a relevant FMR type 4 vary between normal and reduced LVEF due to concomitant diseases, normal LVEDV or mildly increased LVEDV in the presence of markedly increased LA volume, and increased E/E′, which is, however, per se increased in patients with atrial fibrillation.

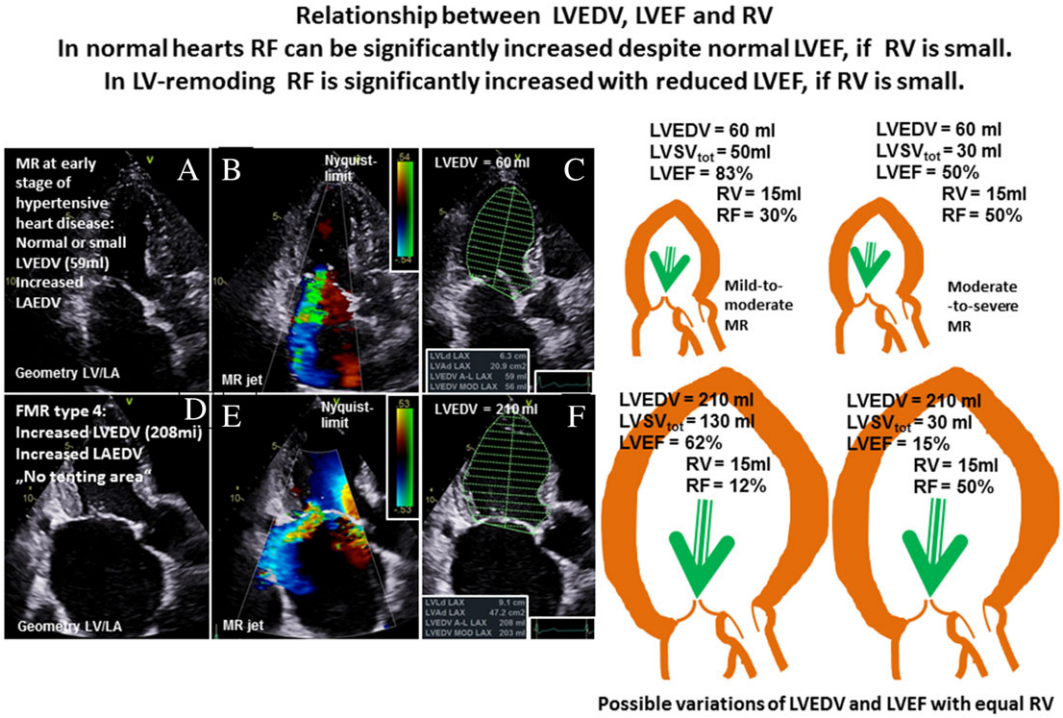
It has to be discussed whether or not this proposal of FMR classification can be more differentiated into additional types. However, this proposal sets the stage to determine the prognostic importance of these echocardiographic subgrouping in FMR.

Echocardiographic assessment of functional mitral regurgitation focusing on regurgitant fraction as target parameter

The inconsistencies of echocardiographic assessment of MR severity by semiquantitative parameters support a quantitative approach to determine MR severity by echocardiography.[35,36] Thus, we suggest that RF may be the only reliable parameter to quantify the severity of valvular regurgitation. Parameters such as EROA or RV are as semiquantitative as vena contracta or reversal of pulmonary vein flow. It is easy to understand that RV is semiquantitative despite declaring a true number because a fixed RV (e.g. 30 mL) may exhibit substantially different effects in relation to potentially significantly different related volumes (such as end-diastolic volume, EF, stroke volume, and cardiac output.)

In conclusion, the relationship between $LVSV_{tot}$ and RV is relevant in humans with significantly varying cardiac outputs. Thus, MR severity can only be depicted by the parameter RF as illustrated in *Figure 3*. Attempts to characterize FMR by PISA radius without information about the Nyquist limit

Figure 3 Illustration of the impact of LV size, LV ejection fraction, and regurgitant volume (RV) on regurgitant fraction (RF): a case of mitral regurgitation at early stage of hypertensive heart disease with normal sized LV (LVEDV about 60 mL) is shown in the apical long-axis view by grey scale imaging (A) and by colour-coded Doppler imaging including scale with Nyquist limit (B). In addition, the volume measurement of LVEDV is presented (C). A case of FMR type 4 with increased sized LV (LVEDV about 210 mL) is shown by representative images in (D–F). The schemes on the right side illustrate the relationship between LV size and LVEF on RF in the presence of equal RV. FMR, functional mitral regurgitation; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVSV, left ventricular stroke volume; MR, mitral valve regurgitation; RF, regurgitant fraction; RV, regurgitant volume.



cannot be precise and the determination of an RV, which is greater than $LVSV_{tot}$, is implausible. Finally, describing vena contracta in other sectional planes than the parasternal long-axis view, in which the vena contracta was defined, is not yielding valid numbers. The most reliable and most robust semiquantitative parameter to estimate MR severity appears to be the ratio of VTI_{MV} (where VTI_{MV} is the transmitral velocity time integral) and VTI_{LVOT} (where VTI_{LVOT} is the velocity time integral of the left ventricular outflow tract), which is unfortunately not provided in the MITRA-FR and in the COAPT trial.[7–9]

If we focus on RF, it is necessary to determine $LVSV_{tot}$ and $LVSV_{eff}$, using all options provided by conventional echocardiography and cardiac magnetic resonance tomography.[8,35–41] 3D echocardiography can additionally improve the assessment of RF in patients with FMR by planimetry of the cross-sectional areas of the left and right ventricular outflow tracts in 3D data sets and by 3D volumetry of the left and right ventricle using transthoracic or transesophageal 3D data sets to determine $LVSV_{tot}$ and $LVSV_{eff}$ as a countercheck of the conventional 2D Doppler echocardiographic measurements. In case echocardiography does not provide reliable data, cardiac magnetic resonance tomography can be used for a quantitative approach to determine RF in FMR patients.[8,40,41] It should be highlighted and pointed out that quantitative echocardiographic assessment of RF in FMR is a challenge, because it is depending on a comprehensive echocardiographic investigation consisting in a complete documentation to perform a conclusive, objective, and transparent analysis.

Implications and conclusions

Our current understanding of assessing and treating patients with FMR is still limited. The available diagnostic tools lack clear-cut thresholds to determine the severity of secondary mitral regurgitation and for guiding intervention. Multimodal imaging and a comprehensive disease-based approach provide the best strategy to treat heart failure patients with FMR. After two large prospective randomized trials, it seems that a

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therapeutic intervention may have a prognostic impact and can improve symptoms in selected patients, but uncertainty still exists with regard to the appropriate indication. After MITRA-FR and COAPT assessing FMR based on echocardiography still appears like opening Pandora's box. However, we believe that the following conclusions can be drawn and should be considered in the future:

(1) A precise quantitative approach to determine MR severity is possible by comprehensive and standardized 2D and 3D echocardiography, focusing on RF as key parameter.
(2) A pathomechanism-oriented classification of FMR by echocardiography may be considered.
(3) The echocardiographic assessment of FMR severity as performed in COAPT and MITRA-FR does not appear to be appropriate for identification of patients deriving a therapeutic effect of percutaneous mitral valve therapy (a substantial selection bias appears likely). The calculated RV in the FMR patients in COAPT appears to be higher than the total stroke volume. With respect to the limitations of semiquantitative grading of the MR severity including the 2D-PISA method, future trials analysing therapeutical effects in FMR should provide a quantitative assessment of the individual RF.
(4) An additional image library should be considered in future trials on FMR to illustrate echocardiographic documentation quality.
(5) Differences in baseline medical therapy between control and treatment groups should be reason enough to provide additional clinical and echocardiographic follow-up data prior to inclusion into future FMR trials and follow-up after inclusion.
(6) The significant treatment effect in PRIME and the potential differences in baseline medical therapy in MITRA-FR and COAPT should cause attention, because they suggest a potential confounding bias.
(7) Echocardiographic analysis of LV filling properties and right ventricular geometry and function should be included into future FMR trials.

Conflict of interest

None declared.

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