Transcatheter mitral valve repair in proportionate and disproportionate functional mitral regurgitation—insights from a small cohort study

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Abstract
Background Functional mitral regurgitation (FMR) can be subclassified based on its proportionality relative to left ventricular function and end-diastolic volume. FMR proportionality could help identify responders to transcatheter edge-to-edge mitral valve repair (MitraClip) in terms of residual FMR and/or clinical improvement.

Methods This single-centre retrospective cohort study evaluated the feasibility of determining FMR proportionality in symptomatic heart failure patients with reduced left ventricular function who were treated with MitraClip for ≥moderate-to-severe FMR. Baseline proportionate (pFMR) and disproportionate FMR (dFMR) were distinguished. Patient characteristics and MitraClip procedural outcomes were described.

Results From an overall cohort of 81 eligible FMR patients, 23/81 (28%) had to be excluded due to missing transthoracic echocardiogram parameters, 22/81 were excluded based on FMR severity. The remaining cohort, of 36/81 patients (44%), could be classified into dFMR (n=26) or pFMR (n=10). Conduction disorders were numerically increased in dFMR. All cases requiring >2 clips were in the dFMR group and absence of FMR reduction occurred more frequently with dFMR. Point of view/Conclusion Important limitations in terms of imaging acquisition affect the translation of the FMR proportionality concept to a real-world data set. We did observe different demographic and FMR response patterns in patients with proportionate and disproportionate FMR that warrant further investigation.

Keywords Mitral valve · Functional mitral valve insufficiency · Valve repair

Introduction
As opposed to degenerative mitral regurgitation, treatment of functional mitral regurgitation (FMR) remains subject to debate [1]. FMR is commonly associated with heart failure and is mainly caused by geometrical or functional abnormalities of structures surrounding the intrinsically normal mitral valve [2]. Currently, FMR therapies—medical or otherwise—are directed at reducing or reversing the remodelling process of the left ventricle [3].

Two randomised controlled trials, COAPT [4] and MITRA-FR [5], investigated percutaneous mitral-valve repair with MitraClip (Abbott, Chicago, IL) in patients with systolic heart failure and >moderate FMR. Conflicting results were reported in terms of mortality and heart failure related hospitalisation [4, 5]. In COAPT, MitraClip treatment improved clinical outcome, while in MITRA-FR, no effect of MitraClip was found [6]. Differences in design and patient characteristics partially explain the discrepancies; in COAPT, patients presented with more severe FMR but less dilated left ventricles compared with patients in MITRA-FR.

Grayburn et al. devised a conceptual framework based on FMR proportionality and disproportional-
Point of View

Proportionality of functional mitral regurgitation in MitraClip therapy

ity to the dimensions and function of the left ventricle [7]. The hypothesis suggested that in a subgroup of FMR patients, the location and damage of affected left ventricular segments is unequally distributed. Consequently, segments involved in leaflet coaptation could be disproportionately affected, causing excessive FMR. Interventions targeting resynchronisation and/or mitral clipping might prove beneficial in the setting of disproportionate FMR (dFMR) [8]. The average COAPT FMR was deemed disproportionate to left ventricular dimensions and function as opposed to the average FMR in MITRA-FR that seemed proportionate (pFMR) [7].

This retrospective study aimed to evaluate the feasibility of the FMR proportionality concept in clinical practice as it has only been scarcely evaluated in a real-world MitraClip context [9, 10]. Furthermore, it describes patient demographics, procedural characteristics and immediate FMR reductions after MitraClip for patients with pFMR or dFMR.

Methods

We retrospectively determined FMR proportionality at baseline in all consecutive heart failure patients with reduced left ventricular ejection fraction (LVEF) who were treated with MitraClip for ≥ moderate-to-severe FMR at the Erasmus University Medical Center. Decision to treat was based on multidisciplinary heart team consensus.

Reasons for excluding patients from analysis were previous mitral valve repair or replacement, heart transplant or untreated significant coronary artery disease requiring revascularisation. Every patient signed informed consent for the clip procedure and use of related data in a dedicated database for study purposes. The study did not fall under the scope of the Medical Research Involving Human Subjects Act per Erasmus Medical Center Institutional Review Board.

The main study objective was to classify baseline FMR as proportionate or disproportionate. Patient and procedure characteristics were described per dFMR and pFMR cohort. Degree of post-procedural FMR reduction (≥1 grade) and residual FMR at discharge were recorded.

Echocardiographic assessment

FMR aetiology and severity were evaluated by transthoracic echocardiogram (TTE) using an integrated approach of multiple qualitative and quantitative parameters including left atrial and ventricular size, jet features, pulmonary artery pressures, effective regurgitant orifice area (using the proximal isovelocity surface area [PISA]), and regurgitant volume (RegVol). RegVol was calculated from the effective regurgitant orifice area or alternatively the volumetric method, if the effective regurgitant orifice area was unavailable and in absence of aortic regurgitation [11, 12]. Reasons for the inability to measure effective regurgitant orifice area and regurgitant volumes were recorded.

Assessment of functional mitral regurgitation proportionality

Severe FMR was considered proportionate when the regurgitation was in line with expected RegVol based on left ventricular size and function derived from the Gorlin hydraulic orifice equation [7]. Using left ventricular end-diastolic volume, LVEF and a set regurgitation fraction of 50% we calculated the expected mitral regurgitation volume (eRegVol) of each individual patient. Similarly, we calculated the upper and lower limits of a grey zone around this value using regurgitation fraction ± 6.6% (Fig. 1, Appendix I in the Electronic Supplementary Material [ESM]). Subsequently, we compared the patient-specific eRegVol with the actual/measured RegVol. A measured RegVol above the eRegVol value was classified as disproportionate, a RegVol within the grey area (approximating the reference line) as proportionate and below as < moderate-to-severe FMR (Fig. 1, Appendix I in the Electronic Supplementary Material [ESM]). Patients with < moderate-to-severe FMR were excluded from the analysis.

Statistical methods

Continuous variables are presented as mean ± standard deviation for normally distributed data, or as median
Fig. 2  Patient identification. Flow chart of the patient identification process showing that only a small percentage of patients in the prospective Mitraclip database was suitable for determination of proportionality. EROA effective regurgitant orifice area, LVEDV left ventricular end-diastolic volume, LVEF left ventricular ejection fraction, RegVol regurgitant volume

Patients who underwent MitraClip at the Erasmus University Medical Center from 2011-2019 (n = 163)

Functional mitral regurgitation (n = 93)

Heart failure with reduced ejection fraction (n = 81)

FMR in which proportionality could be obtained (n = 58)

Final cohort (n = 36)

Exclusion criteria:
LVEF >50% (n = 9)
Previous mitral surgery (n = 3)

Unavailable TTE parameters
Missing EROA+RegVol (n = 20)
Reason:
Poor image quality 40%
PISA not obtained 40%
Eccentric jet 15%
Atrial fibrillation 5%
Missing LVEDV (n = 3)
Reason:
Poor image quality 100%

Non-severe FMR (n = 22)

Fig. 3  Functional mitral regurgitation severity and proportionality. Scatter plot depicting individual values of FMR regurgitant volume vs LVEDV at baseline. FMR proportionality was determined for 3 different groups of LVEF based on LVEF median and interquartile range (bubble size large, medium and small size depict an LVEF of >30%, 21–30% and <21% respectively). Each individual FMR was classified as either disproportionate (red) or proportionate (blue). Patients with FMR reduction are depicted as a dot and patients without reduction are displayed as a cross. Dot/cross size is coded according to LVEF. FMR functional mitral regurgitation, LVEDV left ventricular end-diastolic volume, LVEF left ventricular ejection fraction

Results
We evaluated all patients who received MitraClip in our centre between 2011 and 2019 (Fig. 2). Ninety-three patients were diagnosed with FMR of which 12 were excluded based on exclusion criteria. FMR proportionality could not be determined in 23/81 pa-
Table 1 Baseline clinical characteristics

| Clinical | dFMR (26) | pFMR (10) |
|----------|-----------|-----------|
| Age—yr   | 71.8 ± 10.5 | 66.2 ± 7.6 |
| Male     | 17 (65.4) | 8 (80.0) |
| Hypertension | 18 (69.2) | 7 (70.0) |
| Diabetes mellitus | 8 (30.8) | 5 (50.0) |
| Stroke/TIA | 1 (3.8) | – |
| Peripheral vascular disease | 7 (26.9) | 2 (20.0) |
| COPD     | 3 (11.5) | 2 (20.0) |
| Creatinine clearance—ml/min | 38.2 ± 16.3 | 45.8 ± 11.3 |
| Previous percutaneous coronary intervention | 14 (53.8) | 6 (60.0) |
| Previous coronary artery bypass grafting | 10 (38.5) | 3 (30.0) |
| Ischaemic cardiomyopathy | 20 (76.9) | 8 (80.0) |
| Atrial fibrillation | 14 (56.0) | 5 (50.0) |
| Cardiac resynchronisation therapy | 7 (26.9) | 2 (20.0) |
| Implantable cardioverter defibrillator | 10 (38.5) | 5 (50.0) |
| NYHA functional class | – | – |

| Heart failure medication | – | – |

| Renin-angiotensin system antagonist | 14 (53.8) | 6 (60.0) |
| Beta-blocker | 19 (73.1) | 10 (100.0) |
| Mineralocorticoid antagonist | 19 (73.1) | 8 (80.0) |
| Any diuretic | 26 (100.0) | 10 (100.0) |
| Any inotropes* | – | – |

Data is presented in numbers with (%) unless described otherwise. Plus-minus values are means ± SD. COPD chronic obstructive pulmonary disease, dFMR disproportionate functional mitral regurgitation, NYHA New York Heart Association, pFMR proportionate functional mitral regurgitation, TAVI transcatheter aortic valve replacement, TIA transient ischaemic attack, STS-PROM Society of Thoracic Surgeons predicted risk of mortality. *intravenously administered

Table 2 Baseline ventricular conduction and echocardiographic parameters

| Baseline ECG variable | dFMR (26) | pFMR (10) |
|-----------------------|-----------|-----------|
| ORS duration—ms       | 150 [121–191] | 128 [112–186] |
| ORS duration in non-CRT group—ms | 134 [117–182] | 123 [111–136] |
| CRT or ORS ≥ 150 ms   | 13 (50.0) | 3 (30.0) |
| Left bundle branch block | 16 (61.5) | 6 (60.0) |
| Baseline TTE variable | – | – |
| LVEF—%                | 24.3 ± 1.3 | 30.2 ± 9.3 |
| LVEF—ml               | 150 [129–206] | 142 [95–227] |
| LVEDV—ml              | 200 [175–264] | 219 [167–286] |
| LA volume index—ml/m² | 76.7 ± 17.7 | 61.8 ± 14.5 |
| MR grade—no. (%)      | – Moderate-to-severe | 7 (26.9) | 3 (30.0) |
| – Severe              | 19 (73.1) | 7 (70.0) |
| EROA—mm²              | 34.1 [29–43] | 22.5 [20–27] |
| MR VTI—cm             | 138.9 ± 27.8 | 148.8 ± 11.0 |
| Mitral RegVol—ml      | 43 [40–55] | 32 [25–39] |

Plus-minus values are means ± SD. Other values are median with (interquartile range) or numbers with (%) unless explicitly stated otherwise. CRT cardiac resynchronisation therapy, dFMR disproportionate functional mitral regurgitation, ECG electrocardiogram, EROA effective regurgitant orifice area, LA left atrium, LVEDD left ventricular end-diastolic diameter, LVEDV left ventricular end-diastolic volume, LVEF left ventricular ejection fraction, LVEDS left ventricular end-systolic diameter, LVEF left ventricular end-systolic volume, MR mitral regurgitation, pFMR proportionate functional mitral regurgitation, RegVol regurgitant volume, sPAP systolic pulmonary artery pressure, TR tricuspid regurgitation, TTE transthoracic echocardiography, VTI velocity time integral

dFMR. In dFMR, LVEF and left ventricular end-diastolic volume appeared lower, while total number of clips per procedure and residual FMR severity at discharge were higher (Fig. 3).

Median follow-up was 464 days (IQR 181–935). One year mortality was 26.5% (n = 9). Heart failure related hospitalisation rate within 1 year after MitraClip was 25.7% (n = 8). During follow-up, New York Heart Association (NYHA) class improved in 69% of patients (see Tab. 1 in the Electronic Supplementary Material [ESM]).

Discussion

Our study applied the FMR proportionality concept to heart failure patients who underwent MitraClip therapy in everyday practice and demonstrated that the quality and completeness of echocardiography studies were often suboptimal and lacked essential recordings to determine FMR proportionality. We could categorise only 44% of the overall study cohort into pFMR/dFMR.

Several issues affected the overall sample size of the study. First, methods to determine FMR proportionality rely on effective regurgitant orifice area and RegVol for quantification [9, 10], which may not be straightforward to obtain in FMR [13–15]. In this real-world sample, effective regurgitant orifice area...
interpret FMR in the original framework [10]. We, pFMR and disregards L VEF that seemed essential to lacks established cut-off values to separate dFMR from alternative, simplified method to identify dFMR, yet and left ventricular end-diastolic volume may be an this study.

FMR in heart failure is attractive but not the scope of severe FMR. The application of MitraClip for less severe text of end-stage heart failure with < moderate-to-se grade. This may suggest cause of <moderate-to-severe FMR. This may suggest that the multi-disciplinary heart team may have con- sidered MitraClip as a last resort therapy in the con- text of end-stage heart failure with <moderate-to-severe FMR. The application of MitraClip for less severe FMR in heart failure is attractive but not the scope of this study.

The ratio between effective regurgitant orifice area and left ventricular end-diastolic volume may be an alternative, simplified method to identify dFMR, yet lacks established cut-off values to separate dFMR from pFMR and disregards LVEF that seemed essential to interpret FMR in the original framework [10]. We, therefore, opted to use patient-specific reference lines derived from each individual's RegVol, left ventricular end-diastolic volume and LVEF to determine proportionality. Further validation of this FMR proportionality concept requires larger samples and optimised echocardiography protocols to assure complete mitral regurgitation analysis. Clearly, this framework relies on generally adopted, standardised, echocardiographic acquisition protocols including all required images for quantification.

Although applying the proportionality framework to real-world data proved challenging, some interesting observations were made: 1) dFMR was characterised by conduction disorders and more severe left ventricular dysfunction, 2) dFMR may require more clips, and 3) absence of FMR reduction occurred more frequently with dFMR.

Our data seem to confirm that focal left ventricular remodelling and/or dysynchrony are fundamental mechanisms that underlie dFMR development. There was a higher prevalence of either cardiac resynchronisation therapy implantation or QRS ≥150 ms with dFMR. Prolonged QRS duration marks ventricular dysynchrony [17, 18], while cardiac resynchronisation therapy has been demonstrated to be less efficacious in ischaemic cardiomyopathy [19]. In our dFMR cohort, >75% had ischaemic heart failure, which might explain persistent cardiac dysynchrony, non-response to cardiac resynchronisation therapy, and dFMR.

All cases with >2 clips were in the dFMR group and in spite of using more clips, dFMR reduction appeared less. This finding may result from more extensive mitral regurgitation at baseline. However, clipping does not correct cardiac dysynchrony, which is associated with residual mitral regurgitation after surgical repair [20].

The retrospective nature of our analysis holds inherent selection bias. To determine FMR proportionality, multiple quantitative echocardiographic parameters are required, each associated with measurement inaccuracies. Importantly, FMR severity in clinical practice is graded using a multi-parametric approach including quantitative and qualitative parameters and is often based on multiple echocardiography studies that may reveal dynamic mitral regurgitation. Standardised comprehensive TTE acquisition protocols and experienced imaging specialists seem essential. This study sample was not powered to make any statistical comparison and should be considered as descriptive and hypothesis generating. We believe our study adds perspective to the application of the concept of mitral regurgitation proportionality in clinical practice and warrants further study. A multicentre initiative is ongoing to complement these single-centre observations.

Table 3 Procedural characteristics

| Procedural variable | dFMR (26) | pFMR (10) |
|---------------------|-----------|-----------|
| No. clips           |           |           |
| 1                   | 9 (34.6)  | 5 (50.0)  |
| 2                   | 13 (50.0) | 5 (50.0)  |
| 3                   | 3 (11.5)  | –         |
| 4                   | 1 (3.8)   | –         |
| Technical successa  | 23 (88.5) | 10 (100.0)|

Mitral regurgitation at dischargeb

| Mild                | Moderate            |
|---------------------|---------------------|
| Mild-to-moderate    | Moderate-to-severe  |
| Severe              |                      |
| Trace               | 1 (3.8)             |
| Mild                | 12 (46.1)           |
| Mild-to-moderate    | 2 (7.7)             |
| Moderate            | 5 (19.2)            |
| Moderate-to-severe  | 1 (3.8)             |
| Severe              | 5 (19.2)            |

Discharge MR ≥ moderateb

| None            | 5 (19.2) |
| 1 Grade         | 3 (11.5) |
| ≥ 2 Grades      | 18 (69.2)|
| Mitral mean gradient at dischargeb—mm Hg | 3.7 ± 1.7  |

Data is presented in numbers with (%) unless described otherwise. Plus- minus values are means ± SD dFMR disproportionate functional mitral regurgitation, MR mitral regurgitation, pFMR proportionate functional mitral regurgitation, MVARC Mitral Valve Academic Research Consortium criteria aDefined according to MVARC criteria bObtained with transthoracic echocardiography.
Conclusion

Important limitations in terms of imaging acquisition affected the translation of the FMR proportionality concept to a real-world data set. We did observe different demographic and FMR response patterns in patients with proportionate and disproportionate FMR that warrants further investigation.

Conflict of interest

N.M.D.A. Van Mieghem has received a research grant support from Boston Scientific, Edwards Lifesciences, Abbott Vascular and PulseCath B.V. which were received for activities outside the submitted work. J. Daemen received institutional grant/research support from AstraZeneca, Abbott Vascular, Boston Scientific, ACIST Medical, Medtronic, Pie Medical, ReCor medical and PulseCath, and consultancy and speaker fees from ACIST medical, Boston Scientific, ReCor Medical, Pie Medical, Medtronic and Pulse Cath. J.F. Ooms, M.L. Geleijnse, E. Spitzer, B. Ren, M.P. Van Wiechen, T.W. Hokken and P.T. de Jaegere declare that they have no competing interests.

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