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**ORIGINAL ARTICLE**
**TMVR**

# Impact of Percutaneous Edge-to-Edge Repair in Patients With Atrial Functional Mitral Regurgitation

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***Background:*** The aim of this study was to clarify the clinical outcomes of patients with atrial functional mitral regurgitation (FMR) who underwent the MitraClip procedure compared with those with conventional FMR and sinus rhythm (SR).

***Methods and Results:*** Of 303 patients with FMR who underwent the MitraClip procedure, 40 with "atrial-FMR" defined as FMR with permanent atrial fibrillation and normal left ventricular (LV) function/size and 115 with "sinus-FMR" defined as FMR with SR and LV dysfunction were reviewed. Transthoracic and 3D transesophageal echocardiography, and the cardiac complication rate (composite of all-cause death, heart failure admission, mitral valve (MV) surgery, and redo MitraClip procedure) during the 12-month follow-up were compared between the groups. After the MitraClip procedure, reductions in the mitral annular area and its anteroposterior dimension and in the leaflet closure area were observed in both groups. MV orifice area was smaller with greater transmitral pressure gradient ($P<0.05$) after the procedure in atrial-FMR patients than in those with sinus-FMR. The prevalence of residual MR was similar, but significant tricuspid regurgitation (TR) was more prevalent in the atrial-FMR group at follow-up. Cardiac complication rate was comparable between groups (20% vs. 25%, $P=0.63$).

***Conclusions:*** Reduction of MR occurred in atrial-FMR probably because of the increase in leaflet coaptation area. Significant TR was more common after the MitraClip procedure in patients with atrial-FMR than with sinus-FMR. However, mid-term outcomes were comparable between patients with atrial-FMR and sinus-FMR.

**Key Words:** 3D transesophageal echocardiography; Atrial fibrillation; Functional mitral regurgitation; MitraClip procedure

Recently, functional mitral regurgitation (FMR) caused by left atrial (LA) enlargement and mitral annular dilation in patients with atrial fibrillation (AF), despite normal left ventricular (LV) function and size and also normal mitral valve (MV) leaflets, has been reported as "atrial-FMR".[1,2] This subtype of FMR should be clearly distinguished from conventional ventricular FMR in terms of its different mechanism (**Supplementary Figure 1**). In 2019, Nagaura et al reported differences between atrial-FMR and ventricular FMR with AF in the geometric change of the MV apparatus after the MitraClip procedure.[3] However, atrial-FMR patients may develop LV dysfunction or dilation as a result of MR-induced volume overload. In other words, ventricular FMR with AF, such as in the previous report, may potentially include atrial-FMR patients who develop LV dysfunction. In the setting of FMR with LV dysfunction and AF, we are unable to determine the temporal sequence of AF and MR, so in order to characterize atrial-FMR, we excluded ventricular FMR with AF in this study. The clinical outcomes of patients with atrial-FMR after the MitraClip procedure have not been studied previously.[3] Therefore, the aims of this study were to (1) determine the structural differences using 3D transesophageal echocardiography (TEE) before and after the MitraClip procedure, and (2) compare the clinical outcomes of patients with atrial-FMR as opposed to those with ventricular FMR with sinus rhythm (SR), which is defined as "sinus-FMR".

## Methods

We retrospectively reviewed 651 consecutive patients who underwent percutaneous MV repair with the MitraClip system at Cedars-Sinai Medical Center from January 2010 to December 2018. The study flow chart is shown in **Figure 1**. Exclusion criteria were (1) degenerative MR, (2)

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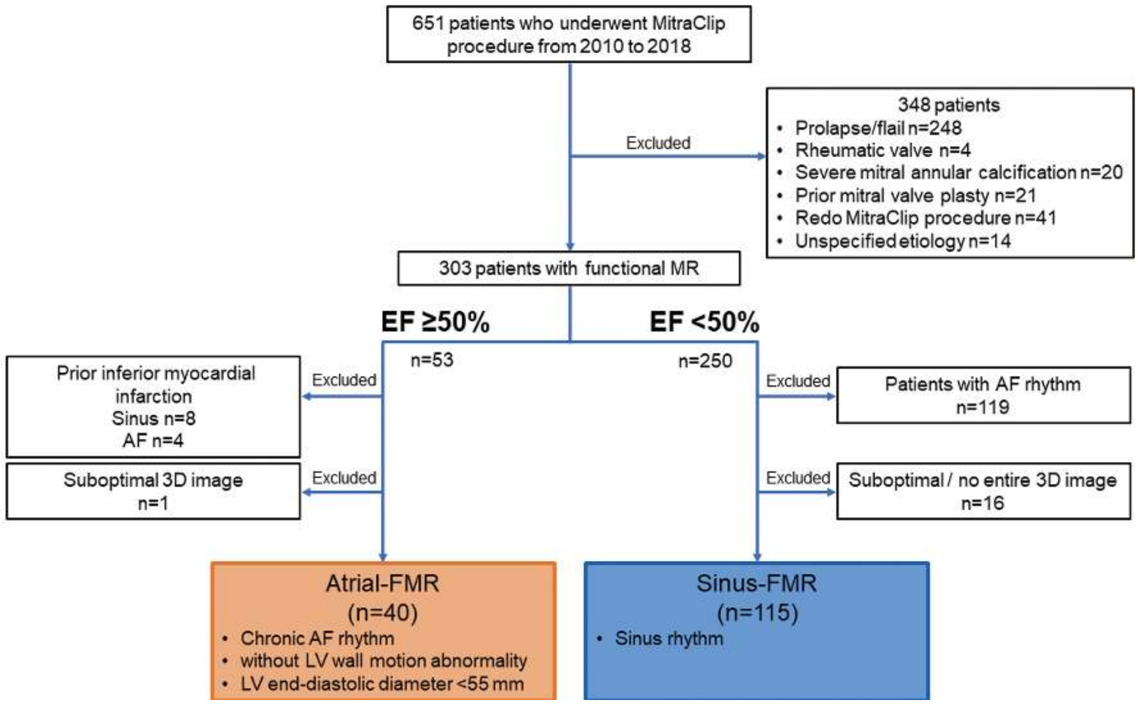


**Figure 1.** Study flow chart. AF, atrial fibrillation; LV, left ventricle; MR, mitral regurgitation.

severe mitral annular calcification, (3) prior MV surgery, (4) redo MitraClip procedure, and (5) unspecified etiology. After exclusion, 303 patients with FMR who had normal MV leaflets regardless of LV function were identified. Patients with FMR were divided into atrial-FMR and sinus-FMR groups; atrial-FMR was defined as patients with (1) LV ejection fraction (EF) ≥50% without LV wall motion abnormality, (2) LV end-diastolic diameter <55 mm,[4] and (3) permanent AF rhythm. Sinus-FMR was defined as patients with (1) LVEF <50%, and (2) SR. Permanent AF or SR was determined according to the predominant rhythm on ECG at both clinical visit and TEE before the MitraClip procedure. All the patients were symptomatic with grade 3/4+ MR and considered appropriate to undergo the MitraClip procedure by our heart team, which included electrophysiologists. Specifically, in patients with atrial-FMR, the decision for the MitraClip procedure as the therapeutic strategy was made under consideration of the chronicity of AF with regard to both LA size and duration of AF. All patients underwent the MitraClip procedure as previously described.[5] This observational study was approved by the Cedars-Sinai Institutional Review Board and in concordance with the Declaration of Helsinki.

All invasive hemodynamic measurements were performed while the patients were under general anesthesia in the cardiac catheterization laboratory, as previously described.[6] Cardiac output index and pulmonary artery pressure were measured using a balloon-tipped Swan-Ganz catheter. Direct LA pressure was obtained from the transseptal catheter positioned in the LA.

Comprehensive 2D transthoracic echocardiography (TTE) at baseline and follow-up (1 day and 12 months after the MitraClip procedure) was performed using a commercially available ultrasound system (iE33, Philips Healthcare, Best, The Netherlands). All measurements were made according to current guidelines.[7] LVEF was calculated using the biplane discs method. LA volume index was calculated using the biplane area length method during systole. The severity of MR was graded as mild (1+), moderate (2+), moderate to severe (3+), or severe (4+) using the criteria of the American Society of Echocardiography.[8] The severity of tricuspid regurgitation (TR) was graded as mild, moderate, and severe by the integrative method according to current guidelines.[8] MR 3/4+ after the MitraClip procedure was defined as residual MR. Moderate or severe TR was defined as significant TR.

Intraprocedural TEE was performed under sedation using a fully sampled matrix-array transducer that can display both 2D and 3D images (X7-2t or X8-2 Live 3D transducer; Philips). The probe was positioned to acquire volume datasets focused on the entire MV before and immediately after the MitraClip procedure using the live 3D zoom mode or 4-beat full-volume mode. The acquisition was ECG-gated, with sector setting optimized for resolution. In patients with AF, we chose the live 3D zoom mode and performed 1-beat volume acquisition to avoid stitch artifacts. All 3D TEE data were digitally stored for off-line analysis.

For the 3D MV measurements obtained before and immediately after the MitraClip procedure, the acquired datasets were analyzed off-line using commercial software MVN (Mitral Valve Navigation, QLAB version 10.7; Philips). The 3D MV annulus and leaflets were measured by MVN at mid-systole as follows (**Figure 2**, **Upper panels**): (1) 4 reference points of the annulus (e.g., anterior, posterior, anterolateral, and posteromedial points) were marked on

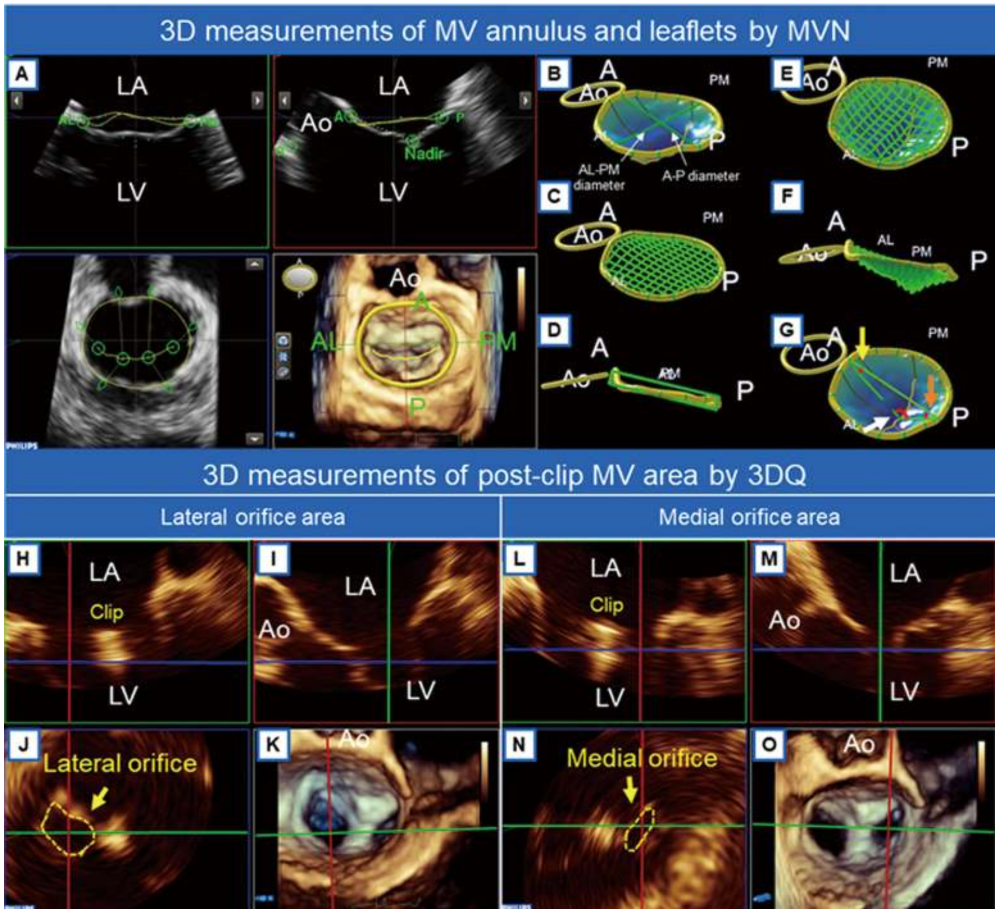


**Figure 2.** 3D mitral valve (MV) quantitative analysis. (**Upper**) Mitral Valve Navigation (MVN) analysis. (**A**) 3D MV annulus and leaflets measured at mid-systole showing 4 reference points of the annulus (A, P, AL, and PM) marked on 2 cut planes representing the long-axis view and an orthogonal plane, following the outlined annulus and traced MV leaflets to obtain a 3D reconstruction model and MV geometric parameters, including (**B**) A-P and AL-PM diameters, (**C**) annular area, (**D**) height, (**E**) leaflet closure area, (**F**) tenting volume, (**G**) non-planarity angle (white arrow) and angles of anterior (yellow arrow) and posterior mitral leaflets (orange arrow). (**Lower**) 3D Quantification (3DQ) analysis. 3D MV orifice area after the MitraClip procedure measured in diastole at the time of peak valve opening. The lateral (**H**–**J**) and medial (**L**–**N**) sides of the MV are displayed using 3 orthogonally oriented planes. Direct planimetry was performed separately in the plane orientated perpendicularly to the orifices (**J**,**N**). Both orifice areas were then summed to determine the MV orifice area immediately after the MitraClip procedure (yellow arrows in **J** and **N**). A, anterior; Ao, aortic valve; AL, anterolateral; LA, left atrium; LV, left ventricle; P, posterior; PM, posteromedial.

2 cut planes representing the long-axis view and an orthogonal plane; (2) the annulus was outlined by marking a total of 20 annular points on 8 equiangular image planes intersecting at the center of the mitral annulus; (3) the closed MV leaflets were traced on successive 17 long-axis planes equidistant parallel to the anteroposterior direction; (4) the MV apparatus was reconstructed by QLAB, generating 3D geometric parameters, including MV annular anteroposterior diameter, anterolateral-posteromedial diameter, mitral annular area, height, leaflet closure area, tenting volume, leaflet tethering angles of the anterior and posterior mitral leaflets, and the non-planarity angle, which represents the saddle shape of the annulus.[9]

The leaflet closure area represents the minimal area that needs to be covered by the leaflets to occlude the mitral orifice.[9] Additionally, the following parameters of the mitral annulus and leaflet were calculated. (1) Ellipticity: anterolateral-posteromedial diameter/anteroposterior diameter×100, which represents the ellipsoid shape of annulus. (2) Acquired coaptation area after the MitraClip procedure: leaflet closure area before procedure−leaflet closure area after procedure.

The 3D MV orifice area immediately after the MitraClip procedure was measured using QLAB 3DQ software (**Figure 2**, **Lower panels**), which is widely used for MV orifice area quantification.[10] In diastole at the time of the peak valve opening, each lateral and medial side of the MV can be displayed using 3 orthogonally oriented planes. Direct planimetry was performed separately in the plane orientated perpendicularly to the orifice. Lateral and medial orifice areas were then summed up to determine the MV orifice area immediately after the MitraClip procedure. In patients with AF, 3 measurements from 3 different volume data sets were averaged. All the values except for angles were indexed to body surface area.

All clinical and laboratory data were collected from the

**Table 1. Baseline Clinical Characteristics and Transthoracic Echocardiographic Findings**

| | Atrial-FMR (n=40) | Sinus-FMR (n=115) | P value |
|---|---|---|---|
| **Clinical characteristics** | | | |
| Age, years | 83 (76–87) | 72 (65–79) | <0.001* |
| Male | 19 (48) | 76 (66) | 0.038* |
| Body surface area, $m^2$ | 1.84 (1.70–2.02) | 1.85 (1.68–2.00) | 0.91 |
| Systolic blood pressure, mmHg | 117 (106–132) | 107 (99–120) | 0.003* |
| Diastolic blood pressure, mmHg | 64 (56–75) | 65 (58–71) | 0.87 |
| Heart rate, beats/min | 71 (64–85) | 78 (69–86) | 0.12 |
| Society of Thoracic Surgery score | 7.8 (4.0–12.8) | 6.6 (2.7–10.5) | 0.08 |
| NYHA functional class III/IV | 39 (98) | 106 (92) | 0.46 |
| B-type natriuretic peptide, pg/mL | 364 (270–482) | 971 (463–2,290) | <0.001* |
| eGFR, mL/min/1.73 $m^2$ | 52 (38–61) | 40 (26–65) | 0.25 |
| Arterial hypertension | 31 (78) | 90 (78) | 0.92 |
| Diabetes mellitus | 13 (33) | 38 (33) | 0.95 |
| Coronary artery disease | 11 (27) | 71 (62) | <0.001* |
| Chronic obstructive pulmonary disease | 12 (30) | 14 (12) | 0.009* |
| History of stroke | 7 (18) | 17 (15) | 0.68 |
| Lead insertion in right ventricle | 13 (33) | 47 (41) | 0.35 |
| Diuretics | 32 (80) | 99 (86) | 0.36 |
| $\beta$-blocker | 21 (53) | 81 (70) | 0.039* |
| ACE-I or ARB | 13 (33) | 52 (45) | 0.16 |
| Amiodarone | 2 (5) | 25 (22) | 0.015* |
| **TTE findings at baseline** | | | |
| LV end-diastolic diameter, mm | 50 (44–54) | 60 (54–68) | <0.001* |
| LV end-systolic diameter, mm | 33 (28–38) | 51 (45–61) | <0.001* |
| LV end-diastolic volume index, mL/$m^2$ | 62 (50–72) | 138 (119–176) | <0.001* |
| LV end-systolic volume index, mL/$m^2$ | 25 (19–30) | 105 (82–134) | <0.001* |
| LV ejection fraction, % | 58 (54–62) | 25 (19–33) | <0.001* |
| Stroke volume index, mL/$m^2$ | 25 (20–30) | 23 (16–28) | 0.09 |
| Left atrial volume index, mL/$m^2$ | 87 (69–117) | 57 (47–67) | <0.001* |
| Effective regurgitant orifice, $cm^2$ | 0.30 (0.22–0.43) | 0.30 (0.22–0.41) | 0.87 |
| Regurgitant volume, mL | 46 (31–63) | 44 (34–59) | 0.94 |
| Vena contracta, mm | 6.4 (5.1–7.8) | 6.4 (5.2–8.1) | 0.47 |
| Mitral regurgitation severity 3+ | 22 (55) | 49 (43) | |
| Mitral regurgitation severity 4+ | 18 (45) | 66 (57) | 0.18 |
| Systolic PA pressure, mmHg | 47 (38–57) | 46 (35–59) | 0.53 |
| TAPSE, mm | 12.2 (10.1–14.6) | 15.0 (12.0–19.0) | 0.002* |
| Right atrial area, $cm^2$ | 30 (23–36) | 21 (17–25) | <0.001* |
| Tricuspid regurgitation severity ≥moderate | 26 (65) | 61 (53) | 0.19 |

Values are expressed as median (interquartile range) or n (%). *P<0.05, Atrial-FMR vs. Sinus-FMR. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; FMR, functional mitral regurgitation; LV, left ventricle; NYHA, New York Heart Association; PA, pulmonary artery; SR, sinus rhythm; TAPSE, tricuspid annular plane systolic excursion.

medical records. In-hospital complications were assessed according to the Valve Academic Research Consortium 2 criteria.[11]

TTE and New York Heart Association functional class, as well as B-type natriuretic peptide levels, were assessed at 12-month clinic visit after the procedure. The clinical endpoint was a composite of the following cardiovascular complications during 12-month follow-up: all-cause death, rehospitalization for heart failure, MV surgery, and redo MitraClip procedure.

Categorical variables are presented as numbers and relative percentages, and compared with the chi-square test or the Fisher exact test, and continuous variables are presented as mean±SD or median (interquartile range) and compared with unpaired Student's t-tests or Wilcoxon rank sum tests as appropriate. Paired Student's t-tests or Wilcoxon signed rank tests were applied to compare hemodynamic parameters and 3D TEE variables before and after the MitraClip procedure. Friedman test with post-hoc Bonferroni multiple comparison was applied to compare repeated measurements at each time point in the serial TTE findings. Event-free survival curves up to 12 months after the MitraClip procedure for patients with atrial-FMR and those with sinus-FMR were constructed using the Kaplan-Meier method and compared using the log-rank test. Multivariate Cox proportional hazard ratio

**Table 2. 3D Transesophageal Echocardiographic and Hemodynamic Data During the MitraClip Procedure**

| | Atrial-FMR (n=40) | | | Sinus-FMR (n=115) | | |
|---|---|---|---|---|---|---|
| | Before MitraClip | After MitraClip | P value | Before MitraClip | After MitraClip | P value |
| **3D TEE variables** | | | | | | |
| AL-PM diameter, mm/m² | 21.6 (19.8–23.6)* | 21.7 (19.5–24.8)† | 0.22 | 19.6 (17.8–21.7)* | 20.0 (18.0–22.1)† | 0.005‡ |
| A-P diameter, mm/m² | 19.7 (17.7–21.0)* | 18.1 (16.6–19.1)† | <0.001‡ | 17.3 (15.6–18.5)* | 15.6 (14.1–17.0)† | <0.001‡ |
| Ellipticity, % | 111 (100–118)* | 120 (115–129)† | <0.001‡ | 115 (108–123)* | 127 (119–137)† | <0.001‡ |
| Mitral annular area, mm²/m² | 618 (540–709)* | 579 (512–689)† | <0.001‡ | 519 (447–595)* | 489 (420–553)† | <0.001‡ |
| Annular height, mm/m² | 2.6 (2.1–4.0) | 2.7 (2.0–3.3) | 0.90 | 2.9 (2.2–3.6) | 3.0 (2.4–3.7) | 0.06 |
| Non-planarity angle, ° | 145 (134–156)* | 148 (137–161)† | 0.43 | 105 (93–116)* | 117 (107–129)† | <0.001‡ |
| Leaflet closure area, mm²/m² | 680 (585–777) | 615 (563–736)† | <0.001‡ | 643 (563–736) | 594 (501–657)† | <0.001‡ |
| Tenting volume, mL/m² | 0.6 (0.2–1.0)* | 0.6 (0.3–0.8)† | 0.51 | 1.7 (1.2–2.3)* | 1.4 (0.9–1.9)† | <0.001‡ |
| AML length, mm/m² | 14 (12–17) | 13 (11–15) | <0.001‡ | 15 (13–16) | 13 (11–14) | <0.001‡ |
| PML length, mm/m² | 7 (5–8) | 6 (5–7) | <0.001‡ | 7 (5–8) | 5 (4–7) | <0.001‡ |
| AML angle, ° | 10 (7–14)* | 10 (5–13)† | 0.18 | 23 (19–26)* | 18 (14–23)† | <0.001‡ |
| PML angle, ° | 23 (14–31)* | 19 (15–30)† | 0.29 | 52 (43–60)* | 44 (36–54)† | <0.001‡ |
| Acquired coaptation area, mm²/m² | – | 42 (21–70) | – | – | 54 (23–94) | – |
| MV orifice area after MitraClip, mm²/m² | – | 111 (83–121)† | – | – | 114 (96–140)† | – |
| **Immediate invasive hemodynamic variables** | | | | | | |
| Cardiac index, L/min/m² | 2.6±0.8* | 2.8±0.9 | 0.015‡ | 2.1±0.7* | 2.6±1.3 | <0.001‡ |
| Mean PA pressure, mmHg | 28±11 | 29±10 | 1.0 | 32±11 | 29±8 | 0.002‡ |
| LA pressure V-wave, mmHg | 33±14 | 25±7 | <0.001‡ | 36±20 | 22±10 | <0.001‡ |
| Mean LA pressure, mmHg | 21±8 | 18±6 | 0.007‡ | 23±10 | 17±7 | <0.001‡ |

Values are expressed as median (interquartile range) or mean±SD. *P<0.05, Atrial-FMR vs. Sinus-FMR before MitraClip. †P<0.05, Atrial-FMR vs. Sinus-FMR after MitraClip. ‡P<0.05, before vs. after in each groups. AL-PM, anterolateral-posteromedial; AML, anterior mitral leaflet; A-P, anteroposterior; LA, left atrium; MV, mitral valve; PML, posterior mitral leaflet. Other abbreviations as in Table 1.

analysis for time-to-event outcome between the 2 groups was performed adjusted by age as a covariate. Reproducibility of the 3D measurements, as described by absolute difference±SD and intraclass correlations, was evaluated in 20 datasets per month after the initial measurement (in a blinded fashion) by J.Y. for intraobserver variability and by a second trained echocardiographer (T.N.) blinded to the initial measurements for interobserver variability using the same datasets. All 2-sided P values <0.05 were considered statistically significant. All data were statistically analyzed using the SPSS software package, version 23.0 (SPSS, Chicago, IL, USA).

## Results

The 303 patients with FMR were divided into 53 and 250 patients on the basis of LVEF ≥50% or <50%. Among them, 40 patients with atrial-FMR and 115 patients with sinus-FMR were eligible for analysis; the excluded patients were as follows: 12 with LVEF ≥50% and prior inferior myocardial infarction, 119 with LVEF <50% and AF, and 17 with suboptimal or no entire 3D images (**Figure 1**). Baseline characteristics and TTE findings of the 2 groups are shown in **Table 1**. Patients in the atrial-FMR group were older and more likely to be female compared with the sinus-FMR group. Systolic blood pressure and the prevalence of chronic obstructive pulmonary disease were higher, and B-type natriuretic peptide, the prevalence of coronary artery disease, and use of $\beta$-blockers and amiodarone were lower in the atrial-FMR group than in the sinus-FMR group. As expected, patients in the atrial-FMR group had larger LA volume index and right atrial area, smaller LV cavity size, and greater LVEF (all P<0.05) compared with the sinus-FMR group. There were no significant differences between the groups in the severity of MR, systolic pulmonary artery pressure, and prevalence of significant TR before the MitraClip procedure.

Baseline 3D TEE findings of the 2 groups are shown in **Table 2**. The anterolateral-posteromedial diameter, anteroposterior diameter, and mitral annular area were larger in the atrial-FMR group than in the sinus-FMR group (all P<0.05). The atrial-FMR group also had smaller ellipticity (P=0.02), indicative of a more circular annulus, and had a greater non-planarity angle (P<0.001), which represented a more flattened annulus, compared with the sinus-FMR group. As for the MV leaflet parameters, the tenting volume and anterior and posterior mitral leaflet angles were smaller in the atrial-FMR group than in the sinus-FMR group (all P<0.05). There were no significant differences in leaflet closure area between groups before the MitraClip procedure.

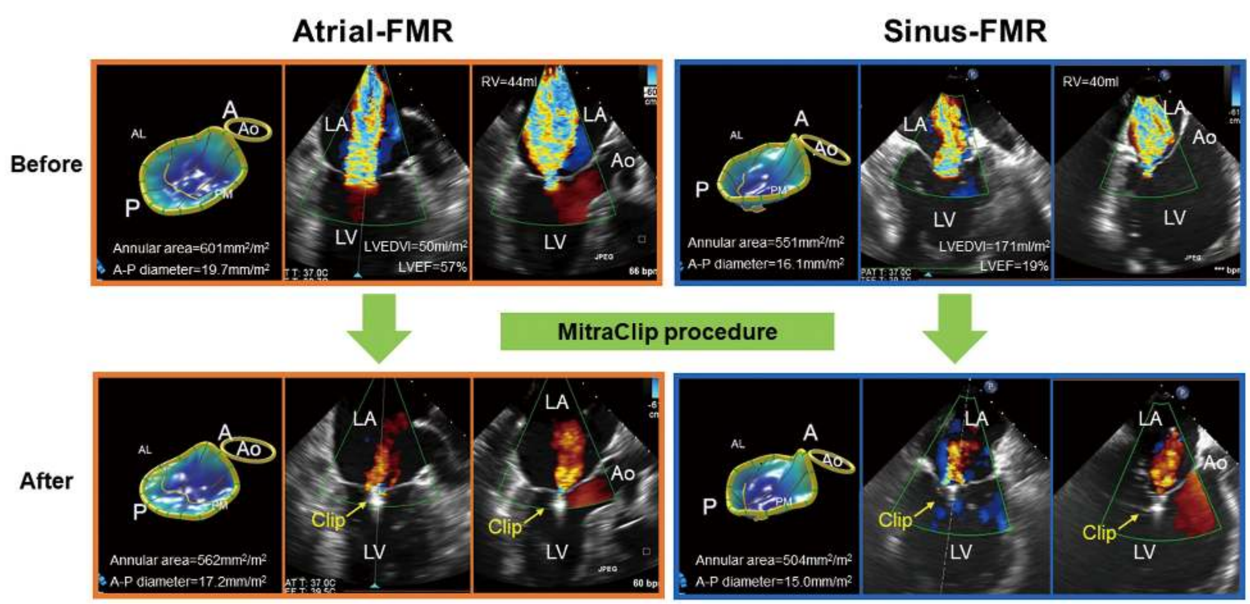


**Figure 3.** Representative cases of patients with atrial-FMR and sinus-FMR before (**Upper**) and after (**Lower**) the MitraClip procedure. MR was significantly reduced after the procedure with a reduction in the A-P diameter, and annulus area without reduction in tenting volume in the atrial-FMR group. On the other hand, MR was significantly reduced after the procedure with a reduction in the A-P diameter and annulus area with reduction in tenting volume in the sinus-FMR group. A, anterior; Ao, aortic valve; AL, anterolateral; FMR, functional mitral regurgitation; LA, left atrium; LV, left ventricle; P, posterior; PM, posteromedial; SR, sinus rhythm.

**Table 3. Serial Transthoracic Echocardiographic Findings and Clinical Assessment**

| | Atrial-FMR (n=40) | | | Sinus-FMR (n=115) | | |
|---|---|---|---|---|---|---|
| | Baseline (n=40) | 1-day (n=40) | 12-month (n=19) | Baseline (n=115) | 1-day (n=115) | 12-month (n=62) |
| **TTE variables** | | | | | | |
| LV end-diastolic volume index, mL/m² | 62 (50–72)* | 60 (47–68)* | 53 (50–69)* | 138 (119–177)*,†,‡ | 135 (113–159)*,† | 132 (114–170)*,‡ |
| LV end-systolic volume index, mL/m² | 25 (19–30)* | 26 (19–30)* | 24 (19–30)* | 105 (82–134)* | 100 (80–126)* | 97 (79–144)* |
| LV ejection fraction, % | 58 (54–62)* | 56 (53–60)* | 59 (54–62)* | 25 (19–33)* | 22 (17–30)* | 23 (17–31)* |
| Stroke volume index, mL/m² | 25 (20–30) | 29 (23–38)* | 33 (25–36)* | 23 (16–28) | 22 (17–31)* | 23 (19–33)* |
| Left atrial volume index, mL/m² | 87 (69–117)* | 82 (66–108)* | 69 (50–133)* | 57 (47–67)* | 52 (46–64)* | 56 (46–66)* |
| Right atrial area, cm² | 30 (23–36)* | 30 (24–38)* | 28 (21–34)* | 21 (17–25)* | 22 (18–25)* | 21 (17–26)* |
| TAPSE, mm | 12.2 (10.1–14.6)* | 12.0 (10.0–16.2)* | 13.2 (10.0–15.0) | 15.0 (12.0–19.0)* | 15.7 (13.0–19)* | 14.1 (11.9–17.9) |
| Systolic PA pressure, mmHg | 47 (38–57) | 45 (36–53)* | 45 (36–53) | 46 (35–59)†,‡ | 38 (30–47)*,† | 40 (27–48)‡ |
| Mean TMPG, mmHg | – | 5.0 (3.4–6.0)* | 5.0 (3.0–6.0)* | – | 3.5 (2.7–5.0)* | 3.0 (2.0–5.0)* |
| Mitral regurgitation ≥3/4+ | 40/40 (100)†,‡ | 6/40 (15)† | 3/19 (16)‡ | 115/115 (100)†,‡ | 9/115 (8)† | 11/115 (18)‡ |
| Tricuspid regurgitation ≥moderate | 26/40 (65) | 23/40 (58)* | 11/19 (58)* | 61/115 (53)†,‡ | 41/111 (37)*,† | 19/62 (30)*,‡ |
| **Clinical follow-up variables** | | | | | | |
| NYHA III/IV | 39/40 (98)‡ | – | 6/21 (29)‡ | 106/115 (92)‡ | – | 18/62 (29)‡ |
| B-type natriuretic peptide, pg/mL | 364 (270–482)* | – | 295 (243–425) | 971 (463–2,290)*,‡ | – | 465 (213–1,299)‡ |

Values are expressed as median (interquartile range) or n (%). *P<0.05, Atrial-FMR vs. Sinus-FMR at same follow-up point. †P<0.05, baseline vs. 1 day. ‡P<0.05, baseline vs. 12 months. §P<0.05, 1 day vs. 12 months. TMPG, trans-mitral pressure gradient. Other abbreviations as in Table 1.

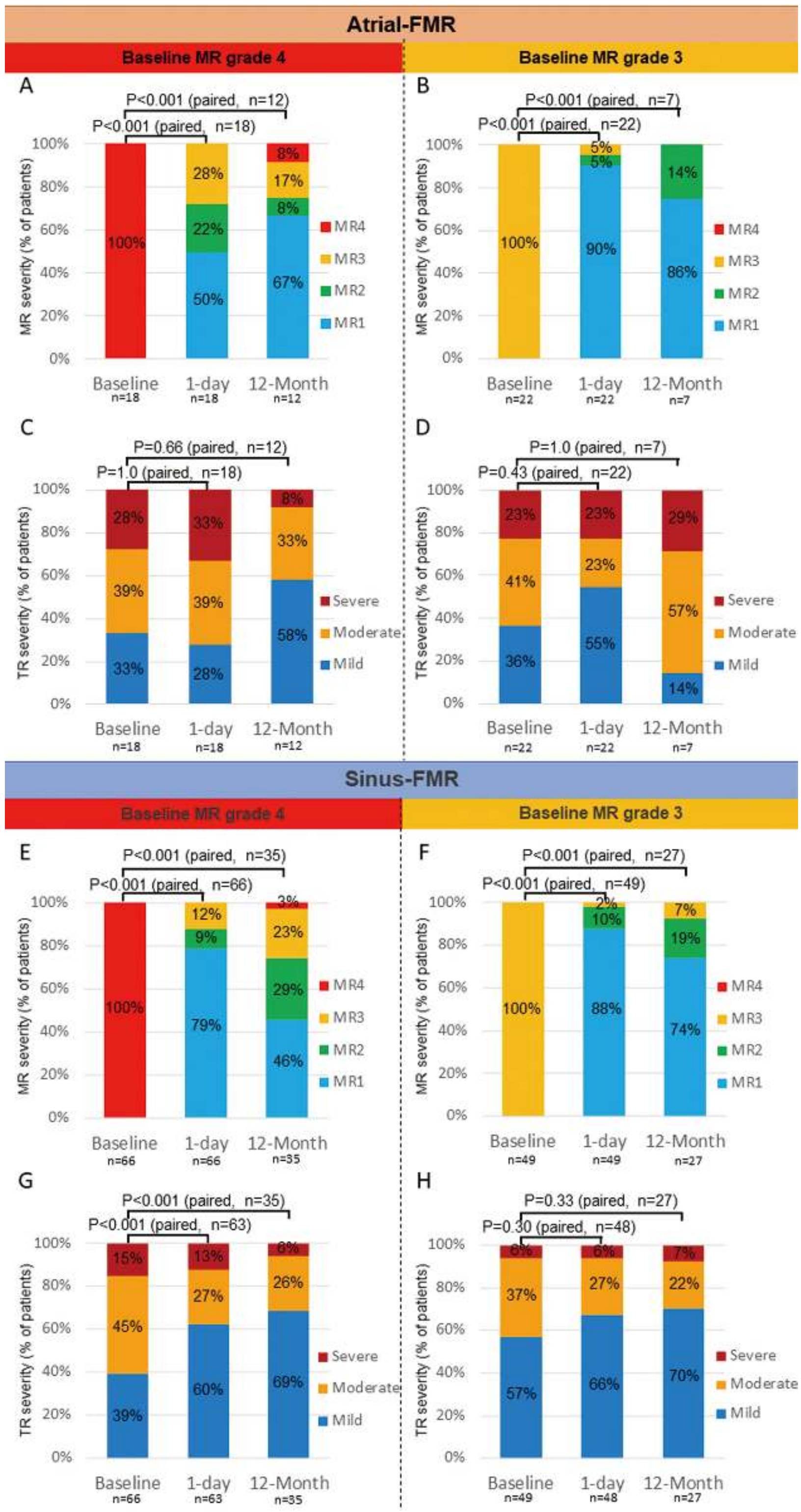


**Figure 4.** Intra-individual changes in severity of MR and TR from baseline to follow-up after the MitraClip procedure dividing the patients into those with grade 4 MR and those with grade 3 MR. In the atrial-FMR group with both grade 4 and 3 MR, MR severity was significantly reduced after the procedure (**A**,**B**) but TR severity was not significantly reduced (**C**,**D**). In the sinus-FMR group with both grade 4 and 3 MR, MR severity was significantly reduced after the procedure (**E**,**F**). TR severity was significantly reduced in sinus-FMR patients with grade 4 MR (**G**) but there was no significant change in TR severity in those with grade 3 MR (**H**). FMR, functional mitral regurgitation; TR, tricuspid regurgitation.

Geometric changes by 3D TEE are shown in **Table 2**. In both groups the anteroposterior diameter, mitral annular area, leaflet closure area, and length decreased after the MitraClip procedure (all P<0.05). Significant reductions were found in tenting volume and leaflet angles in the sinus-FMR group after the procedure whereas these parameters did not change in the atrial-FMR group. The non-planarity angle only increased in the sinus-FMR group after the procedure. There was no significant difference in acquired coaptation area between the 2 groups

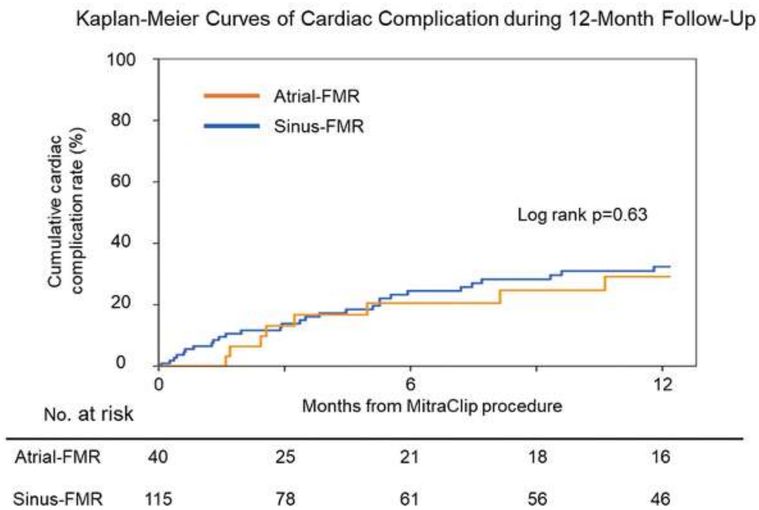


**Figure 5.** Kaplan-Meier curves of cardiac complications during 12-month follow-up. The main composite outcome of cardiovascular complications during 12-month follow-up was comparable between the atrial-FMR and sinus-FMR groups (20% vs. 25%, P=0.63). FMR, functional mitral regurgitation; SR, sinus rhythm; TR, tricuspid regurgitation.

after the procedure. Representative cases before and after the MitraClip procedure are shown in **Figure 3**.

Before the MitraClip procedure, only the cardiac index was significantly higher in the atrial-FMR group and the remaining hemodynamic data did not show differences between the 2 groups (**Table 2**). After the MitraClip procedure, the cardiac index increased and the LA pressure V-wave and mean LA pressure significantly decreased in both groups. Mean pulmonary artery pressure also decreased in the sinus-FMR group (P=0.002) but did not change in the atrial-FMR group. After the MitraClip procedure, there were no significant differences in all hemodynamic variables between the 2 groups.

There were no significant differences in procedural characteristics or in-hospital complications between the 2 groups (**Supplementary Table 1**).

Serial TTE findings are shown in **Table 3**. The median 12-month TTE follow-up period was 367 [interquartile range: 272–395] days. In the sinus-FMR group, the LV end-diastolic volume index (138 vs. 135 mL/m$^2$, P<0.05) and systolic pulmonary artery pressure (46 vs. 38 mmHg, P<0.05) significantly decreased from baseline to 1-day follow-up and did not change from 1-day to 12-month follow-up. Any other TTE parameters such as LVEF (25% vs. 22%) and LA volume index (57 vs. 52 mL/m$^2$) in the sinus-FMR group did not show significant differences during follow-up. On the other hand, in the atrial-FMR group there were no significant differences in TTE parameters such as LV end-diastolic volume index (62 vs. 60 mL/m$^2$), LA volume index (87 vs. 82 mL/m$^2$), and systolic pulmonary artery pressure (47 vs. 45 mmHg) during follow-up. Intra-individual changes in MR severity and TR severity from baseline to follow-up after the MitraClip procedure, dividing the patients into those with grade 4 MR and those with grade 3 MR, are shown in **Figure 4**. In the atrial-FMR group with both grade 4 and 3 MR, MR severity was significantly reduced after the procedure (**Figure 4A**,**B**), whereas TR severity was not significantly reduced (**Figure 4C**,**D**). In the sinus-FMR group with both grade 4 and 3 MR, MR severity was significantly reduced after the procedure (**Figure 4E**,**F**). TR severity was significantly reduced in sinus-FMR patients with grade 4 MR (**Figure 4G**), but there was no significant change in TR severity in the sinus-FMR patients with grade 3 MR (**Figure 4H**). There were no significant differences in the prevalence of residual MR (MR ≥3/4+) between the atrial-FMR and sinus-FMR groups at 1-day (15% vs. 8%, P=0.19) and 12-month follow-up (16% vs. 18%, P=1.0) (**Table 3**). However, the prevalence of significant TR (TR ≥moderate) was higher in the atrial-FMR group both at 1-day (58% vs. 37%, P=0.024) and slightly more so at 12-month follow-up (58% vs. 30%, P=0.031) (**Table 3**).

Median transmitral pressure gradient at 1-day follow-up was significantly higher in the atrial-FMR group compared with the sinus-FMR group (**Table 3**). 3D TEE analysis showed that the MV orifice area immediately after the MitraClip procedure was significantly smaller in the atrial-FMR group than in the sinus-FMR group (111 [83–121] vs. 114 [96–140] mm$^2$/m$^2$, P=0.039) (**Table 2**). The significant difference in the median transmitral pressure gradient between the 2 groups continued until 12-month follow-up (**Table 3**).

The median clinical follow-up of patients studied was 326 [interquartile range: 62–685] days. The prevalence of New York Heart Association functional class III/IV decreased from baseline to 12-month follow-up in both the atrial-MR group (98% vs. 29%, P<0.01) and sinus-FMR group (92% vs. 29%, P<0.01). There was no significant difference between the 2 groups in the prevalence of New York Heart Association functional class III/IV at 12-month follow-up (29% vs. 29%, P=0.97). B-type natriuretic peptide level significantly decreased from baseline to 12-month follow-up in the sinus-FMR group but not in the atrial-FMR group (**Table 3**).

Kaplan-Meier analysis showed no significant difference between groups in the rate of the main composite outcome of cardiovascular complications during 12-month follow-up (20% vs. 25%, P=0.63) (**Figure 5**). In the multivariate Cox proportional hazard ratio analysis adjusted by age as a covariate, no significant difference in the rate of the main composite outcome of cardiovascular complications during 12-month follow-up was found between the 2 groups (adjusted hazard ratio 0.79, confidence interval [0.35–1.77], P=0.57). Additionally, there were no significant differences between groups in the individual components of the composite outcome (**Supplementary Table 1**). The prognosis analysis was also tested between patients with ischemic cardiovascular myopathy (ICM) and non-ICM among the sinus-FMR group (**Supplementary Figure 2**), and showed no statistically significant difference between ICM and non-ICM patients.

The intra- and interobserver variability of the 3D measurements is shown in **Supplementary Table 2**.

## Discussion

In the real world, there are many patients who have both MR and AF and undergo MV repair with a MitraClip.[12] The MR usually develops prior to AF in degenerative MR. As for FMR, in the setting of LV dysfunction and AF, patients in whom AF predates the development of FMR may be indistinguishable from those who develop MR prior to AF. In order to characterize atrial-FMR and separate it from ventricular FMR with AF, we excluded the latter group in this study (**Supplementary Figure 1**). Pure atrial-FMR may not be as common as ventricular FMR with or without AF.[1] However, in clinical practice, it is important to recognize this subtype of FMR and understand its underlying mechanism. In addition, it is crucial to understand both the effects and the effectiveness of MV repair with the MitraClip.

Arora et al reported the effect of AF during 1-year follow-up in a large number of patients with degenerative MR who underwent the MitraClip procedure.[12] Patients with degenerative MR and AF had a higher rate of mortality (25.9%) or heart failure admission (22.1%) after the MitraClip procedure compared with patients with degenerative MR but without AF. In contrast, in our study, patients with atrial-FMR appeared to have much lower mortality (7.5%) and rate of heart failure admission (15%) during 1-year follow-up after the MitraClip procedure. The better outcomes can be explained by the fact that LV function and size were normal in the present study's patients with atrial-FMR. Atrial-FMR reportedly improves when SR is restored after catheter ablation,[2] but the present study is the first to report mid-term clinical outcomes of patients with atrial-FMR who underwent the MitraClip procedure.

In comparison with the sinus-FMR group, the mitral annular area was larger in the atrial-FMR group. However, leaflet area was similar between groups. Atrial-FMR is thought to be caused by insufficient increase in leaflet area to cover the mitral annular area.[4] In our study, the MitraClip procedure increased the leaflet coaptation area to reduce MR in patients with atrial-FMR.

After the MitraClip procedure, we found a greater transmitral pressure gradient in the atrial-FMR group than in the sinus-FMR group. We also found a smaller MV orifice area in the atrial-FMR group than in the sinus-FMR group on 3D TEE. However, there were no differences in clinical outcomes between the 2 groups. Cheng et al reported that patients with residual mild MR, but increased transmitral pressure gradient, had better outcome than those with residual moderate MR and normal gradient after the MitraClip procedure.[13] Although their study population differed from ours, their results are consistent with ours.

In the sinus-FMR group, decreased LV volume after the MitraClip procedure was observed in concordance with previous reports of a reduction in B-type natriuretic peptide level.[14] On the other hand, we could not discern improvement of left heart cavity size in the atrial-FMR patients with no improvement of B-type natriuretic peptide level over time. This can be explained by the baseline LV cavity size being within normal range before the procedure in the atrial-FMR group. B-type natriuretic peptide levels remained elevated probably because permanent AF itself can elevate the B-type natriuretic peptide level in this patient group.[15] The prevalence of significant TR after the procedure was higher in the atrial-FMR group, which was finding is consistent with our previous finding of a relationship between functional TR with tricuspid annular dilation and AF.[16]

Abe et al reported that the combination of significant MR and TR predicted poor outcome for patients with AF.[17] Persistent TR after the MitraClip procedure, which was commonly seen in patients with atrial-FMR, may be one of the determinants of cardiac complication during follow-up. Therefore, concomitant intervention for significant TR with the mitral procedure may improve the prognosis for the AF patients with both MR and TR.

There are conceivable therapeutic options for patients with atrial-FMR, including restoration of SR and surgical mitral annuloplasty. The present patients with atrial-FMR had a markedly enlarged LA (87 mL/m$^2$) as compared with those who were treated by catheter ablation (LA size: 31.8 mL/m$^2$) in the previous report.[2] Therefore, restoration of SR with improvement of MR by catheter ablation cannot be expected. On the other hand, isolated surgical mitral annuloplasty is more invasive and rarely chosen for high-surgical risk patients. Therefore, at present the MitraClip procedure may be considered as a potential therapeutic option for atrial-FMR in patients with a prominently large LA and high-surgical risk.

### Study Limitations

First, this was a retrospective, observational, single-center study. Second, our patient sample with atrial-FMR was relatively small, limiting the statistical power of the event rate during follow-up. However, this series is the largest to date of atrial-FMR patients undergoing the MitraClip procedure. Third, only tricuspid annular plane systolic excursion was measured as a parameter of RV systolic function, but it may not represent the entire RV function, especially in AF patients.[7,16,18]

In conclusion, reduction of MR after the MitraClip procedure in patients with atrial-FMR probably occurred because of the increase in leaflet coaptation area. Significant TR was more common after the MitraClip procedure in patients with atrial-FMR than with sinus-FMR. However, mid-term outcomes were comparable between patients with atrial-FMR and sinus-FMR.

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## Supplementary Files

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-20-0971