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ORIGINAL RESEARCH

VALVULAR HEART DISEASE

A Simulation Study of the Effects of Number and Location of MitraClips on Mitral Regurgitation

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ABSTRACT

BACKGROUND MitraClip (MC) is a device that is implanted on the mitral valve (MV) percutaneously to treat severe mitral regurgitation (MR). It is common practice to place the MCs at the site of the most significant MR jets identified by echocardiography.

OBJECTIVES We used computational modeling to examine changes in MR after MC placement.

METHODS Echocardiographic images from 29 patients with MR were analyzed to reconstruct geometries for finite element simulations and created fluid structure interaction models of the MV with deformable hyperelastic material, the left ventricle as the surrounding geometry, and blood flow. Blood flow was modelled with smoothed particle hydrodynamics. The number of blood particles on the atrial side of MV was used to estimate MR. MC placement was based on the MR jets (jet-based strategy using primary and secondary jets) and simulation models using various MCs locations.

RESULTS Computational modelling was able to quantitate reductions in MR after MC placement. Reduction in MR was related to the number of MCs used: 42% reduction with 1 MC, 62% with 2 MCs, and 88% with 3 MCs. Using 2 MCs did not always result in an MR reduction greater than with a single MC. In 31% (9 of 29) of patients, the jet-based strategy did not lead to maximum MR reduction. The majority of patients (89%) who did not have maximal MR reduction with the MC placement using the jet-based strategy, had wide jets, and/or had multiple jets.

CONCLUSIONS Subject-specific simulation models may be helpful to identify optimal locations for MC placement in patients with MR. (JACC Adv 2022;1:100015) © 2022 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Mitral valve (MV) regurgitation is the most prevalent cardiac valve disease in the United States. Severe mitral regurgitation (MR) is present in nearly 4 million patients, and each year 250,000 new patients are added to the MR population.[1,2] Although surgery can be an option for patients with severe MR, nearly one-half of the patients with MR are not eligible for surgery because of poor cardiac health conditions.[3] For these patients, MitraClip (MC) may be an indicated therapy. Improvements in current MC therapy can have an important impact on patients' health conditions and

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ABBREVIATIONS AND ACRONYMS

FE = finite element

ID = identifier

LV = left ventricle

MC = MitraClip

MR = mitral regurgitation

MV = mitral valve

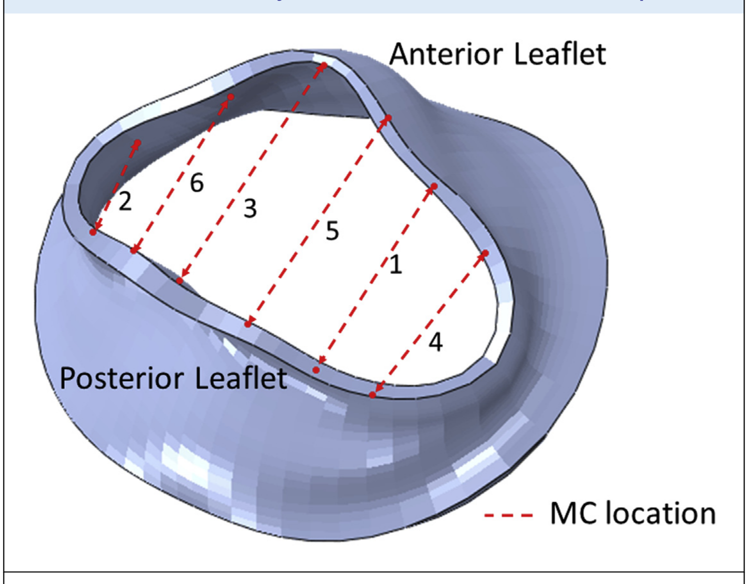
SPH = smoothed particle hydrodynamics

quality of life. Currently, the MCs are implanted based on location of the MR jets. One, 2 or more MCs can be used, and their location may vary. The indication for more MCs is the degree and width of leakage flow jets.[4] The common practice is to place the MC where the largest and most significant MR jet is observed, and if additional jets are observed, more MCs are placed at the respective locations.

It is important to investigate the role of number of MCs because the implants remain in the heart permanently. Several studies have simulated MC therapy on MR,[5-8] but we know of no systematic study on the alterations in MV regurgitation caused by different number of MCs in a group of patients. Because access to the implantation site of the MC is limited, the interventionalist may place 1 or more MCs in locations that may not be optimal and lead to repeat MC procedure or surgery.[9-12] Likewise, because of difficulties in MC implantation, the interventionalist may implant 2 MCs nonoptimally, although the outcome could be similar with just 1 MC implant. Nonoptimal MC interventions can place additional burden on the patient and health care system because of repeat interventions and unwanted effects of MC intervention such as leaflet damage.[13-16]

The goal of our study was to investigate changes in MR after MC placement. Our approach was based on computational modeling, because it is challenging to conduct such analysis experimentally. We modeled various scenarios for MC implantation, including placement of 1, 2, or 3 MCs. Because MC locations also vary, we simulated the MR for different numbers of MCs and their locations. Finally, we examined MR changes after MC placement using a jet-based approach to MC placement and a simulation model, which identified the MC locations associated with the maximal MR reduction (optimal MR reduction).

FIGURE 1 **The Valve Geometry and the 6 Locations Where an MC can be Implanted**



Four landmark points were used to morph the mitral valve geometry based on 3-dimensional echo images. Clip placement location is defined as C1-6. MC = MitraClip.

METHODS

MV SIMULATION. Finite element (FE) fluid structure interaction models were created using the Abaqus software package. The main features of the model have been described previously.[17-19] The model consists of the MV, including the leaflets and the chords, and the left ventricle (LV). For computational efficiency, the LV was modeled as a rigid material, and the surrounding geometry for the blood. Because the MV and LV did not match in the annulus, a deformable surface that had no effects on the MV deformations was used to seal the gap between them. The leaflet material was modeled by a hyperelastic fiber-reinforced material.[17,18]

PATIENT IMAGES. The MV geometry was reconstructed from 3-dimensional echocardiography images from 29 patients. All patients included in this study had degenerative or mixed degenerative/functional MR. None of the patients included in this study had pure functional MR and none of the patients had severe LV dysfunction or LV end-diastolic diameter ≥7.0 cm. The images pertain to a retrospective patient database from the University of California-San Francisco Medical Center. All patients' data were obtained in accordance with IRB number 19-27738. The workflow to reconstruct FE models from images in described in another report.[19]

BLOOD FLOW SIMULATION AND QUANTIFICATION OF MR. To model blood flow, we used smoothed particle hydrodynamics (SPH), a meshless FE method in which the blood was simulated using particles, each of which is in contact with surrounding particles and surfaces. The method was used for the fluid structure interaction for computational efficiency. The number of blood particles in the atrial side of MV was used to estimate MR.

MC SIMULATION SCENARIOS: JET-BASED AND MAXIMAL MR REDUCTION MODEL. The MC body was not simulated, but its effects on MV structure were considered. Connectors between 2 nodes from each leaflet were created while each node was linked to its surrounding nodes. We considered 6 locations along leaflet edges where the MC can be implanted

(Figure 1). We assumed 1, 2, or 3 MCs could be implanted. The single MC scenarios included a single MC at each location, which means for each patient geometry, there can be 7 single MC scenarios. The double MC scenarios included 8 possibilities, whereby the MCs can be located at the following locations: 1 and 6; 2 and 4; 3 and 4; 3 and 5; 3 and 6; 4 and 6; and 5 and 6 (Figure 1). We also considered a triple MC scenario where the MC was placed at locations 1, 3, and 4 (Figure 1).

The current clinical practice is to implant MCs based on the regurgitation jets observed using echocardiography. The interventionalist first places a MC in the location of the largest and most significant jet, and then if there is a second jet, the second MC is placed in the respective location (jet-based approach). We simulated this jet-based procedure in our FE models within our available options for MC locations. For the first MC, we placed the MCs in the closest location to sites 1-6 in Figure 1. For the second MC, if the respective location was available in our data set, the MC was placed there. If the second location was not simulated in our data set, the MC was placed in the closest available site. For example, if the combination of the first and second MCs led to locations 1 and 3, this set is not available in the data set, but the combination 3 and 5 is close to 1 and 3. As such, we used a simulation for MCs at locations 3 and 5 for that patient. In addition to examining MR reduction using the jet-based approach, we created simulation models that identified the MC locations associated with maximal MR reduction (maximal MR reduction simulation models; optimal locations).

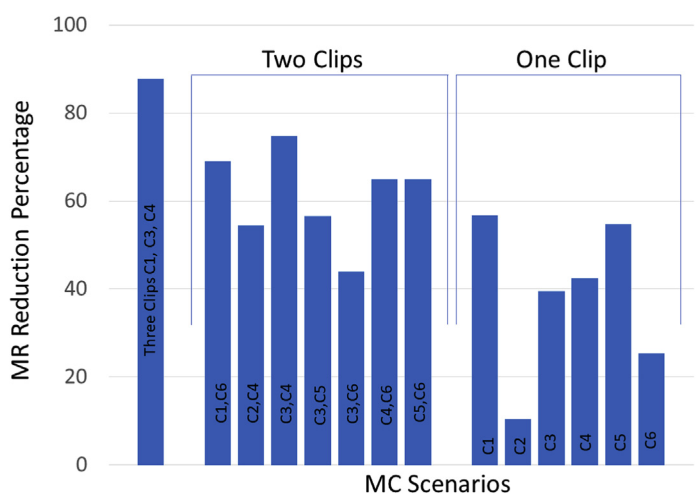
MV ORIFICE AREA. The MV orifice area was computed using ImageJ software version 1.53e (National Institutes of Health). A 2-dimensional projection of the MV approximately perpendicular to a plate passing through the annulus was used (viewed from the atrium). The edges of the leaflets were approximated with polygons, and the respective areas was computed by ImageJ.

STATISTICAL ANALYSIS. To examine the difference between a single MC and 2 MCs, we calculated the percentage reduction in blood leakage flow in a treated mitral valve compared with the same valve but untreated. To compare the 2 scenarios, we used a paired, 2-tailed Student's *t*-test. A 5% significance level was used.

RESULTS

NUMBER OF MCs AND REDUCTION OF MR. On average, the 3 MCs scenario had the biggest effect on the reduction in MR. With a 3 MC scenario the average decrease in MR was 88%, with the 2 MC scenario it was 62%, and with the 1 MC scenario it was 42%. In other words, the average MR reduction with 3 MCs was nearly 26% larger than with 2 MCs, and the average MR reduction with 2 MCs was nearly 20% larger than the single MC scenarios (Figure 2). There was a significant difference in the reduction in MR between 1 and 2 MCs (42% for 1 MC and 62% for 2 MCs; $P < 0.05$).

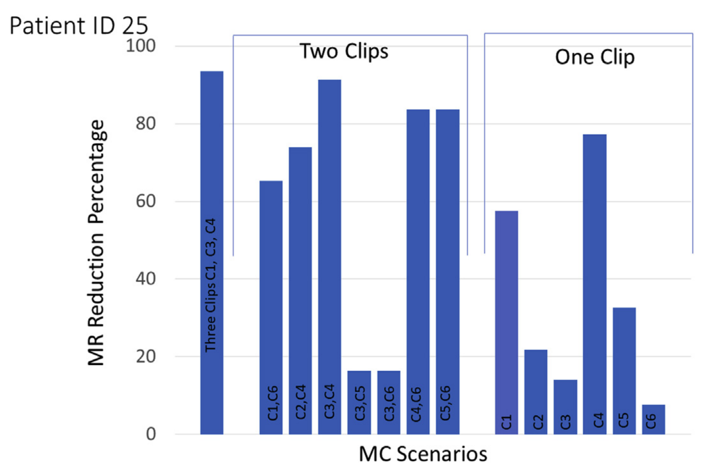
FIGURE 2 The Average Percentage MR Reduction for 1-, 2-, and 3-Clip Scenarios



The MR reduction is relative to no clip condition (baseline MR). Clip placement location is defined as C 1-6 based on Figure 1. MC = MitraClip; MR = mitral regurgitation.

Although on average 3 MCs led to the largest reduction in MR, there was individual variability. There were cases (patient identifiers [IDs] 9 and 28) where the maximal MR reduction (100%) could be achieved with 3, 2, or 1 MC. Notably, for patient ID 9, the MR was relatively low even when there was no MC. For this patient, 100% MR reduction was achieved with 2 clips located at "3, 4" or "3, 5" or "3, 6" or "4, 6" or "5, 6", as well as with one clip located at 3, or 5 or 6. In some patients, a 1-clip scenario achieved an MR reduction comparable to a 2-clip scenario. For example, for patient ID 25, a 2-clip scenario with MC located at sites 2 and 4 led to a 74% reduction in MR, and a single MC at site 4 led to 77% MR reduction (Figure 3). For patient ID 26, 2 MCs at locations 3 and 6 (in Figure 1) resulted in an MR reduction of 50%, and a single MC located at site 1 led to a 50% reduction in MR (Figure 4). In patient ID 26, having a single MC and 2 MCs provided 217% and 102% greater average orifice area than 3 MCs, respectively (the orifice area for 3 MCs was approximately 37.2 mm^2).

FIGURE 3 MR Reduction by 1, 2, and 3 Clips (Patient ID 25)



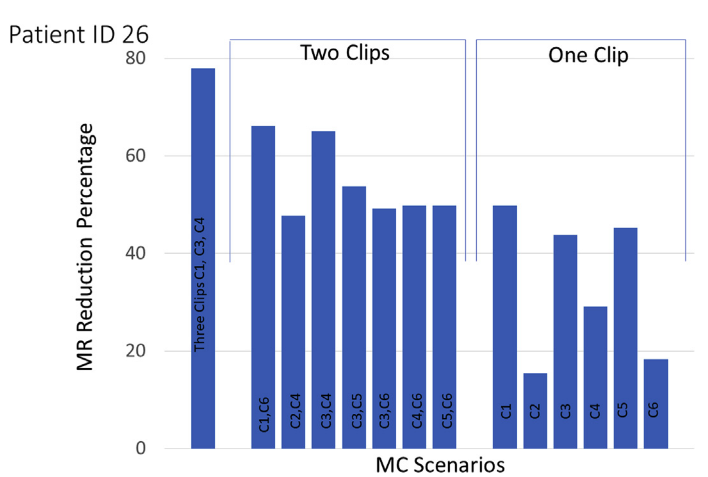
The MR reduction is relative to no clip condition (baseline MR). Abbreviations as in Figure 2.

MC PLACEMENT AND MR REDUCTION. In some patients, jet-based placement of the MC resulted in optimal MR reduction, similar to the maximal MR reduction simulation model. For sample patient ID 1, a strong jet (most significant jet) was not detectable. Instead, there was a wide jet (Figure 5). Placement of the MC in approximately the center of the wide jet caused a secondary jet (Figure 5). The approach of placing the second MC in the location of the secondary jet was the optimal 2 MC scenario, as indicted by simulation results. Specifically, the optimal 2-clip scenario was related to having the MC at locations 3 and 4, and when the MC were located at the center and close to the secondary jet, the MR reduction was 85% and the MR reduction at locations 3 and 4 was optimal (Table 1, Figure 5). Similarly, for patient ID 5, placing the MCs based on jet locations provided optimal results (Table 1, Figure 5).

In other patients, a 2-clip scenario with MC locations based on the primary and secondary jets did not provide optimal MR reduction (Table 1, Figure 5). For patient ID 64, there were multiple jets initially. The first MC was placed in location 3, corresponding to the strongest jet. Accordingly, the second jet occurred at a location closest to site 5, resulting in an MR reduction of 72%. Based on the maximal MR reduction simulation model, the best MR reduction for this case was with MCs at locations 3 and 4, which resulted in an MR reduction of 85%.

For patient ID 66, there were 2 prominent jets (Figure 5). The first MC was placed at the location of the strongest jet, which corresponded to site number 3 in Figure 1. The second MC was placed at the location of the other jet, which was close to site number 5 in Figure 1. The resulting double MC configuration led to a 62% MR reduction, which was less than that seen in the maximal MR reduction model at 66% (MCs at locations 3 and 4) (Figure 5).

FIGURE 4 MR Reduction by 1, 2, and 3 Clips (Patient ID 26)

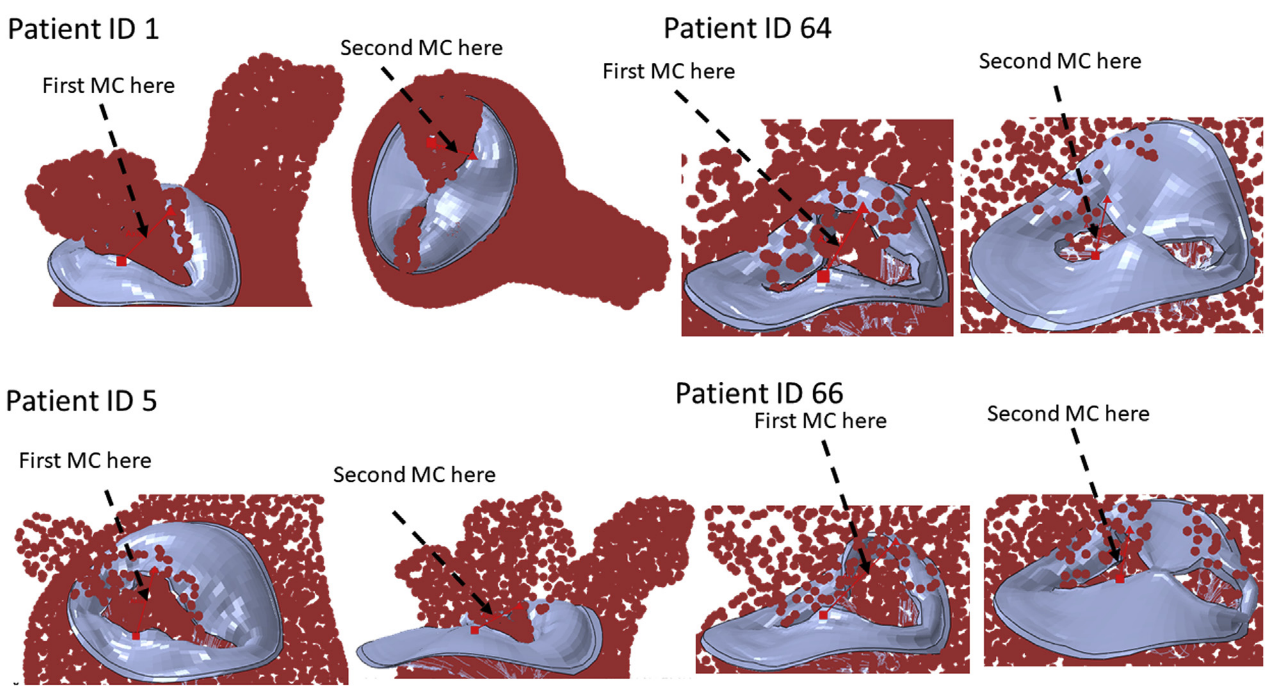


The MR reduction is relative to no clip condition (baseline MR). Abbreviations as in Figure 2.

JET-BASED MC PLACEMENT. In 14 of the 29 patients (48%), the jet-based approach produced optimal MR results, similar to the maximal MR reduction model. In 9 of the 29 patients (31%; 95% CI: 14%-48%), the optimal MR (maximal MR reduction model) results were different from jet-based locations, and in 6 of the 29 patients (21%), the FE simulation did not converge or the baseline MR was negligible. In those patients in whom clips placed at the location of jets led to maximum MR reduction, 85% had a noticeable strong jet. On the other hand, in 89% of patients in whom jet-based MC placement did not lead to maximum MR reduction, there was either a wide jet or there were multiple jets (Figure 6).

The simulation results show that the locations of the MCs in the maximal MR reduction simulation model can be different than that seen with the jet-based strategy (Central Illustration). For patient ID 5, the MC locations in the simulation model were similar to jet-based MC locations. For patient ID 43, the locations of the MC in the simulation model and jet-based MCs were relatively close. However, for patient ID 46, the locations of the MCs in the simulation model were noticeably different from jet-based MCs.

FIGURE 5 Implanting the MCs by Following Regurgitation Jets



The first MC was placed at the location of the strongest jet. Then, the second MC was placed at the location of the secondary jet. Four sample patients are shown here. Clip placement location is defined as C 1-6 based on **Figure 1**. MC = MitraClip.

DISCUSSION

Currently, interventional cardiologists do not use systematic optimization tools to select the locations of MC implantation. Instead, their approach to implant the MCs is based on echocardiographic identification of jets and experience. This study adds to our understanding of MC interventions by using computational models to investigate changes in MR after MC procedure. The effects of MC on MR are not straightforward. First, there is no general rule that can simply determine the optimal location of MC(s). The locations that led to maximum MR reduction for some patients were not optimal for others. Yet, some rules can be derived from our study: 1) the more MCs implanted, the more reduction in MR that is achieved; 2) placement of the first MC in the location of the strongest jet and the second MC in the location of the secondary jet is often a good strategy, but it does not always guarantee maximal MR with 2 MCs; and 3) placing 2 MCs does not guarantee that MR will be less than MR achieved with 1 MC.

In general, our results support the current clinical approach for selecting the location of the MCs using the primary (strong) jet. We found that in almost one-half of cases, the jet-based approach produced optimal MR results, similar to the maximal MR reduction model. Some patients who require MC therapy have complex MV anatomy, which includes the presence of a wide jet and/or multiple jets. For those patients, implantation of the MC is more challenging.[20] In line with clinical data, we found that using the location of the strongest jet for MC implantation is not optimal when the jet is wide or there are multiple jets (**Figure 6**).

Overall, the MR reduction that can be achieved by 3 MCs cannot be achieved with 2 MCs, and similarly, the MR reduction that can be achieved with 2 MCs cannot be achieved with 1 MC. Therefore, so far as the MR reduction is considered, using 3 MCs is preferred to 2 MCs or 1 MC, provided they are placed in optimal locations. However, using more MCs is likely associated with other MC-related side effects, such as a higher pressure gradient across the MV (mitral stenosis) and higher likelihood of leaflet injuries.[9,21] Results for orifice area, based on fluid dynamics principles, implies that a single MC can lead to a lower pressure gradient than 2 MCs, and 2 MCs can lead to a lower pressure gradient than 3 MCs.[22] As such, in clinical practice, 3 MCs are not necessarily better than

TABLE 1 MR Reduction and MC Placement Location: Jet-Based vs Maximal MR Reduction Simulation Model

Patient ID	Jet-Based MR Reduction (%)	Maximal MR Reduction Simulation Model: MR Reduction (%)	Jet-Based MC Locations	Maximal MR Reduction Simulation Model: MC Locations
1	85	85	3, 4	3, 4
5	100	100	3, 4	3, 4
64	72	85	3, 5	3, 4
66	62	66	3, 5	3, 4

MC = MitraClip; MR = mitral regurgitation.

2, and 2 MCs are not necessarily better than 1. Importantly, using 1 MC can lead to an MR close to that obtained with 2 clips (provided the locations of 2 MCs are not optimal). Given that implantation of 1 MC may have fewer potential complications, 1 MC can be optimal.

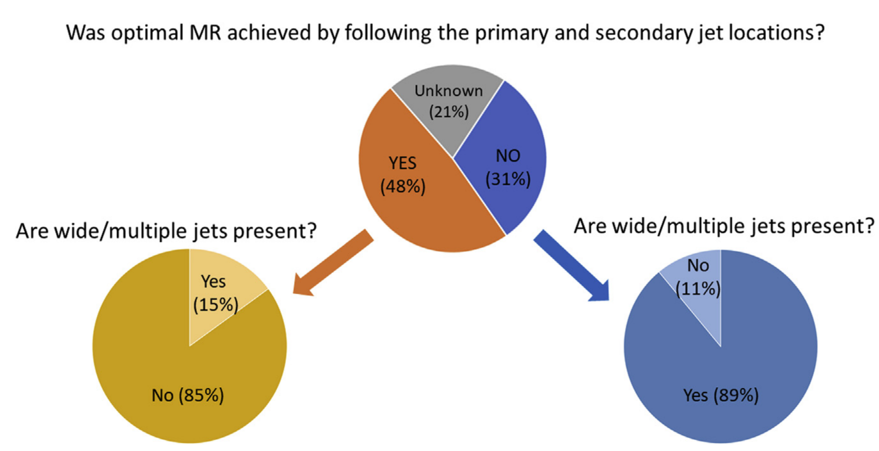
Our results underline the importance of personalized strategies for optimal MC intervention. Given that physics-based models simulate personalized strategies, the patient-specific simulations can inform clinicians of optimal decisions. Because MV physics-based models can become time-consuming, an appropriate approach can integrate physics-based models with artificial intelligence, including machine learning methods, to provide simulation results in real-time, suitable for clinical use.[19]

The etiology of MR also plays an import role in MC outcomes. In this study, we did not investigate the relations between MR etiology and MC outcomes. Notably, the number of MCs and the MC procedure influence the MV annulus diameter and shape, which changes across MR etiologies. Future work could explore possible relations between MC parameters, including number of the clips and clip locations, and MC outcomes for specific MR etiologies. Because MV shape is affected by MR etiology, etiology-based MC studies can provide more generalizable results for clinical applications.

STUDY LIMITATIONS. A caveat of our study was that we simulated the effects of MC implantation, but the MC body was not considered. The outcome of MC therapy could have important correlations with MC structure.[20,23,24] Future work should include simulations with the MC bodies and their interaction with the leaflets.

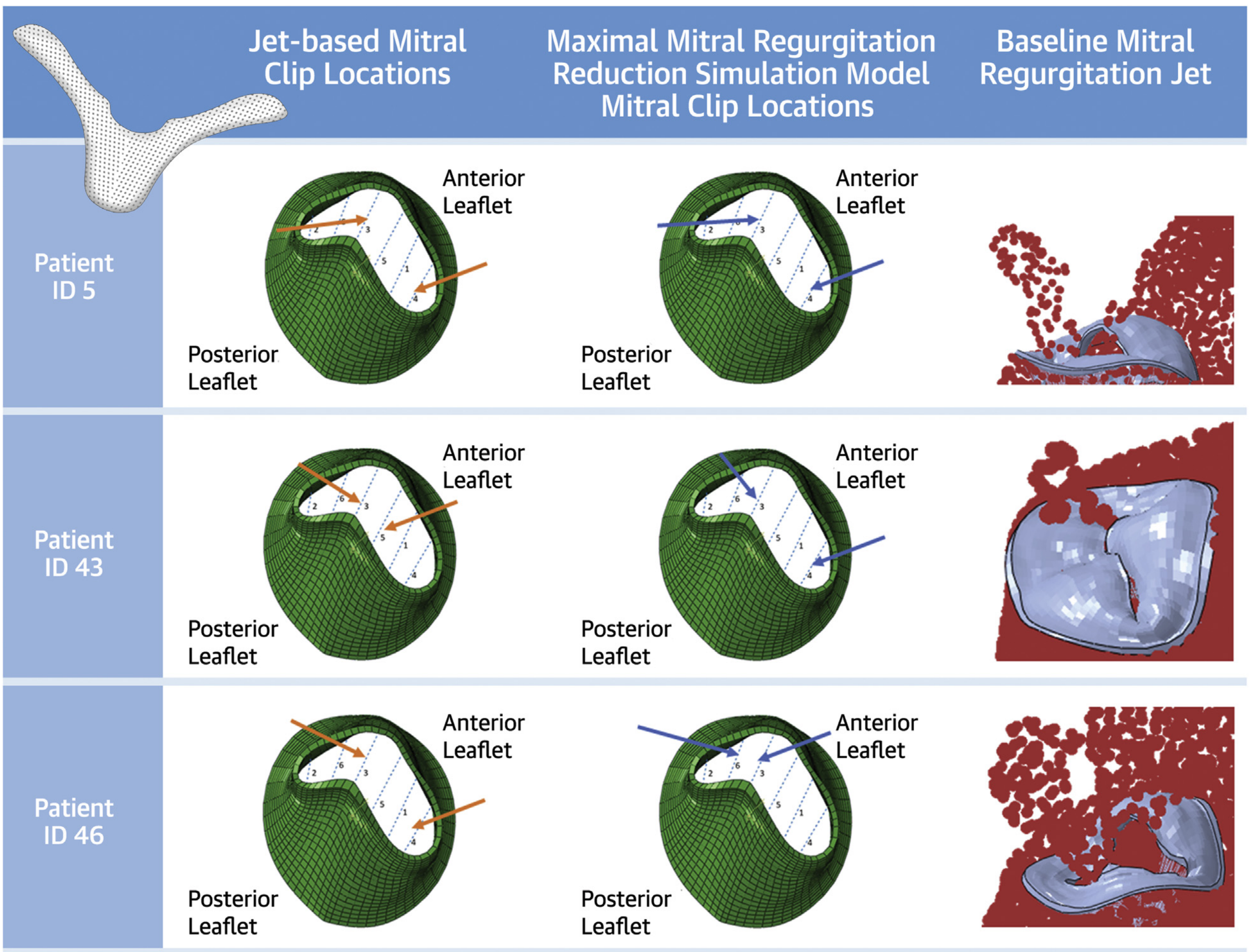
Our simulation workflow did not include some aspects of MC interventions that may have an important role in the suboptimal MC outcomes and changing MC strategy. The MV functions in synchrony with the LV and left atrium. It should be noted that inclusion of these aspects will demand more computational expenses, however, including software, hardware, time, and technical expertise costs. Moreover, the presence of indentations in the MV leaflets are lacking in our simulation workflow because of limitations in shape reconstruction from the echo images used.[19] Although changes in MV orifice were not a focus of this study, we have provided one example to

FIGURE 6 Analysis of MC Procedure Outcomes Based on Regurgitation Jets



In 31% of cases in this series, using the location of the MR jets (jet-based strategy) for MC placement did not lead to an optimal MR reduction. In cases without optimal MR reduction, 89% had either a wide jet or multiple jets. "Unknown" refers to simulations that did not converge or baseline MR was negligible. MR = mitral regurgitation.

CENTRAL ILLUSTRATION **The Locations of Mitral Clips According to the Jet-Based Strategy and the Maximal Mitral Regurgitation Reduction Simulation Model for 3 Sample Patients**



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The locations of mitral clips according to the jet-based strategy **(orange arrows)** and the maximal mitral regurgitation reduction simulation model **(blue arrows)** for 3 sample patients. The respective baseline mitral regurgitation jets are shown on the **right**.

highlight this clinically important issue. Further studies are needed to focus on changes in MV orifice after MC procedures.

Finally, our blood flow modeling had limitations. We used SPH to model blood flow because of its computational efficiency.[19] Computation of flow volume, pressure gradient, and shear rates is not as straightforward using SPH, however, compared with other methods that consider blood as a continuum media, and solve 3-dimensional Navier-Stokes equations.[22,25] Because the main goal of our study was to compare different scenarios of MC intervention rather than values of blood flow characteristics, using SPH was appropriate for our goals. If an analysis needs fluid characteristics of blood flow, methods that solve 3-dimesional Navier-Stokes equations might be more appropriate.

CONCLUSIONS

An optimal MC intervention strategy is subject-specific, and there are many factors that affect the outcomes of this intervention including the MV anatomical specifications, the interactions among the MV and LV, the MC device dimensions, and the number and locations of MCs. Using the location of the most significant jets can be a good strategy for optimal MC interventions; however, this strategy can fail because of subject-specific parameters. Computational simulations can provide virtual experiments to guide the cardiologists before they do the actual interventions. Given the costs associated with computational models, artificial intelligence can help utilize computational models more efficiently.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Severe MR is the most common valvular problem, and it can have serious consequences. The MC intervention is one of the possible solutions for this disease, but this intervention does not always lead to optimal outcomes. The number of implanted MCs and their locations are important factors that can alter MC intervention outcomes. It is not possible to investigate the effect of these factors experimentally. In this paper, we used computational simulations to describe the effects of number and locations of MCs on the MR.

TRANSLATIONAL OUTLOOK: Our in-silico experiments can be used to inform the cardiologist for optimal MC specifications. These experiments, however, are time-consuming. To overcome this limitation, artificial intelligence can be used to replicate the in-silico results in a matter of seconds.

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KEY WORDS intervention, MitraClip, mitral regurgitation, mitral valve, simulation