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Impact of Simulated MitraClip on Forward Flow Obstruction in the Setting of Mitral Leaflet Tethering: An In Vitro Investigation

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Abstract

Objectives—We aimed to evaluate diastolic leaflet tethering as a factor that may cause mitral stenosis (MS) after simulated MitraClip implantation, using an in vitro left heart simulator.

Background—Leaflet tethering commonly seen in functional mitral regurgitation may be a significant factor affecting the severity of mitral stenosis (MS) after MitraClip implantation.

Methods—A left heart simulator with excised ovine mitral valves (N=6), and custom edge-to-edge clip devices (GTclip) was used to mimic implantation of MitraClip in a variety of positions. Anterior mitral leaflet (AML) tethering severity was varied for each case (leaflet excursion of 75°, 60°, and 45°, consistent with mild, moderate and severe tethering), and the baseline mitral annular area (MAA) was varied across samples (3.6-4.8cm²). The resulting mitral valve area (MVA), and peak/mean mitral valve gradient (MVG) were measured in each case.

Results—AML tethering severity was a highly significant factor increasing MVG and decreasing MVA(p<0.001). When GTclip placement was simulated with severe AML tethering, mean MVG>5mmHg resulted more frequently than with GTclip placement alone (46% v. 4%, respectively). However, severe AML tethering alone significantly reduced baseline MVA to 3.6±0.2cm², and increased baseline MVG to 3.0±0.4mmHg. At MAA above 4.7cm², severe AML tethering did not cause moderate MS, even with placement of two GTclips (95% confidence).

Conclusions—Our results show that diastolic AML tethering may predispose to MS after clip placement, however, MS was not observed when baseline MVA was above 4.0cm². Severity of AML tethering may be an important criterion in selecting patients for edge-to-edge repair.

Keywords

Transcatheter Mitral Valve Repair; Mitral Stenosis; Edge-to-edge; Alfieri Stitch
Introduction

MitraClip (Abbott Vascular, Santa Clara, California) is currently not approved in the US for treatment of functional mitral regurgitation (FMR), but is widely used off-label for this purpose (1). In many cases, multiple MitraClip devices are used to treat MR (2), though placement of additional devices can further reduce mitral valve area (MVA) and increase of mean mitral valve gradient (MVG), leading to mitral stenosis (MS) (3). Deteriorated long-term outcomes have been recently demonstrated in MitraClip patients with post-procedural moderate MS (mean MVG ≥5mmHg), where the overall rate of moderate MS among patients treated with MitraClip was found to be 25% (4,5). In FMR patients in particular, MS severity after MitraClip may be further exacerbated by diastolic restriction of the anterior mitral leaflet (AML) caused by severe dilatation of the left ventricle (LV) and papillary muscle (PM) displacement (6). However, limited data on the effect of AML tethering on MVA and MVG after MitraClip exists. To date, the majority of experimental studies have focused on the effectiveness of MitraClip in reducing MR, and the loading placed on the leaflets by the device (7). When diastolic MVG has been quantified, MS was not observed, due to the size of the MV under investigation (8). Here, we present a novel study quantifying MVA and MVG resulting from a variety of simulated clip placement locations, in the setting of varied AML tethering severity, and across a range of MV sizes where MS may be a concern. This could provide useful information toward patient selection and procedural optimization for treatment with transcatheter edge-to-edge mitral valve (MV) repair devices.

Methods

Study Overview

The Georgia Tech left heart simulator (GTLHS) and excised ovine MVs (N=6) were used to conduct the following experiment. For each MV sample, AML tethering severity was varied across three levels, and four different configurations of edge-to-edge clip placement were simulated, along with a baseline pre-clip case. These fifteen combinations of AML tether severity and clip placement were simulated on each MV sample. For each combination, resulting mean/peak MVG, and MVA were measured. Baseline mitral annular area (MAA) was varied from sample to sample, and ranged evenly from 3.6cm$^2$ to 4.8cm$^2$, with a mean of 4.15±0.38cm$^2$.

GT Left Heart Simulation Platform

Fresh ovine hearts were procured from an abattoir (Superior Farms, Dixon, CA, USA); their MVs (N=6) were excised and mounted between the left atrium (LA) and LV of the GTLHS (Figure 1). Using an annuloplasty ring sizer set, MVs were initially selected to be in the desired MAA range, and the final annular area was quantified under pulsatile conditions. A piston pump (Vivitro Labs Inc. Victoria, Canada) drove physiological left heart flow within the simulator, while an electromagnetic flow probe (Carolina Medical Electronics, East Bend, NC, USA) measured cardiac output. Wall tapped pressure transducers in the LA and LV were used to measure MVG over the cardiac cycle (Utah Medical Products Inc., Midvale, UT, USA). A Philips iE33 xMatrix echo system and X7-2 transducer (Philips
Healthcare, Andover, MA, USA) were used to acquire 3D gated echo images and measure MVA.

All testing was done at physiological conditions of 120mmHg peak systolic MVG, 5L/min cardiac output, and 70 beats/min heart rate. While typical MitraClip patients may have significantly reduced pre-procedural cardiac output (CO) due to regurgitant fractions exceeding 50%, their post-procedural CO is regularly found to be in the range of 5L/min. Therefore, the mitral inflow volume was held constant at 70mL (5L/min). The baseline MAA was adjusted and set to achieve leaflet coaptation length of >7mm prior to data collection for each experiment. Additional information on GTLHS setup and operation can be found in our previous publications (9,10).

Anterior Leaflet Tethering Method

AML tethering severity was determined by the angle between the AML and the mitral annular plane, with lower excursion angles indicating increasing severity. Severity of AML tethering was controlled by adjusting the position of the papillary muscles (PMs), which were mounted to stainless steel rods, and affixed in ball-in-socket joints, allowing control of PM positioning and displacement within the LV chamber (Figure 1B,C). Standard echo measurement techniques were used to measure the AML tether angle. The echo probe was oriented to simulate the standard 3-chamber view of the MV, and the measurement plane bisected the MV at the A2/P2 line (Figure 2). Next, the angle between the AML and the mitral annular plane was measured. Mild, moderate and severe AML tether angles of 75°, 60°, and 45°, respectively, were based on patient data (11). PMs were displaced laterally and posteriorly in a symmetric manner, and their displacements were empirically adjusted until reaching each target angle, as confirmed by 3D echo. Once a target angle was reached, locations of the PM rods on the exterior of the GTLHS were marked. The recorded markings were used to precisely re-create the AML tether angles in the second phase of each experiment, where MitraClip placement was simulated. A pilot study revealed that the method of leaflet tethering created AML tether angles of 76.5±2.3°, 59.5±2.8°, and 47.6±2.0°. These values were considered substantially similar to published clinical data (see supplementary material) (11).

Prototype Edge-to-Edge Clip Model

Prototype edge-to-edge clips (GTclips) (Figure 3) were designed to replicate the bite profile and dimensions of MitraClip. These GTclips functioned in a similar manner to alligator clips, which allowed them to be quickly deployed and re-positioned without causing damage to the mitral leaflets (Figure 4A). The GTclips were machined from polycarbonate plastic and stainless steel. A cross-hatch pattern was etched into the gripping face of the clip to prevent clip detachment. Over the course of data collection, no instances of clip detachment or leaflet damage were observed. The GTclip leaflet bite profile was compared to that of MitraClip implanted in a patient, showing the width of the GTclip leaflet bite (6.5mm) compared favorably to that of MitraClip (6.8mm)(see supplementary material). Furthermore, MitraClip implantation has previously been successfully simulated by reproducing the rectangular bite profile as shown in the MitraClip indications for use (IFU) (8).
Experimental Conditions and Protocol

The experimental matrix of conditions is shown in (Table 1). For each experiment, PM positions were first determined for each AML tethering angle without GTclips, and corresponding PM rod positions were recorded. Once each desired AML tether angle was reached, a dataset was recorded (pressure and flow waveforms, and 3D gated echo images). Next, the commissural GTclip placement was simulated, and each of the three AML tether angles were sequentially re-created using the recorded PM rod positions, recording a dataset at each AML angle. These steps were repeated for each subsequent GTclip placement strategy (single central, double central, commissural-central).

Data Analysis and Statistical Model

All results are presented as mean±95% confidence interval (95%CI). Mean and peak diastolic MVG were calculated for each condition using the pressure transducer recordings. The change in MVG from pre-GTclip to post-GTclip placement was computed on a pairwise basis for each GTclip condition and for each experiment. Peak diastolic MVA was measured by planimetry on the 3D echo images using Philips QLab 3DQ software following established echocardiographic technique (Figure 4B-D) (12). The change in MVA from pre-clip to post-clip was computed. Measurements on each image were made three separate and independent times, and the intraclass correlation coefficient with 95%CI was found to be 0.983 (0.977-0.989).

Using Minitab 18 statistical software (Minitab Inc., State College, PA, USA), a general linear model (GLM) was fitted to the data for three separate analyses on the resulting MVA, mean MVG, and peak MVG. The AML tether angle and GTclip placement were treated as categorical factors, and the MAA was treated as the continuous covariate. Coefficients can be used to calculate mean and 95%CI values for the measurements. An example calculation for MVA is shown in Equation 1,

\[
MVA = k + (MAA - 4.0)\alpha + \beta + \gamma \quad (1)
\]

where the constant coefficient, \(k\), is summed with the GTclip coefficient, \(\beta\), for the desired clip placement, and the AML coefficient, \(\gamma\), for the desired AML angle. Finally, the product of MAA and the MAA coefficient, \(\alpha\), are added as shown to produce the MVA estimate given the selected inputs.

Bartlett’s test and residual analysis were performed on the measurements, confirming that all data were normally distributed and homoscedastic. Coefficients and overall statistical significance were computed for each factor and level. Percent contribution to total sum of square variance was computed for independent variables, quantifying the portion of variance in the dependent variables that can be attributed to each independent variable. A post-hoc Tukey’s test was performed to compare the mean differences in the dependent variables for each combination of AML tether angle and GTclip placement. Finally, MATLAB (MathWorks, Natick, MA, USA) was used to perform a t-test comparing our averaged results to published clinical MVG and MVA values.
Results

Factors Impacting MV Area and Gradients

Results showed that AML tether angle, GTclip placement, and baseline MAA were highly significant factors impacting the measured mean MVG, peak MVG, and resulting MVA (p<0.001 for each factor and for each measurement) (Table 2).

Effect of Baseline Mitral Annular Area

No significant post-procedural MS (mean MVG≥5mmHg) was observed in the two samples with baseline MAA ≥4.4cm². In contrast, 13 incidents of mean MVG≥5mmHg were observed in the four samples with baseline MAA<4.1cm². Based on the MAA coefficient results shown in Table 2, the minimum MAA that resulted in mean MVG under 5mmHg with 95% certainty was 4.7cm², even in the presence of severe AML tethering and implantation of two GTclips. Baseline MAA of 4.7cm² with severe AML tethering resulted in baseline MVA by planimetry of 3.9±0.3cm².

MV Area and Gradient at the Mean Mitral Annular Area

At the mean MAA (4.15cm²), resulting MVA and MVG for all combinations of AML tether angle and GTclip placement are shown in Figure 5. Groups whose 95% CIs do not overlap are significantly different (p<0.05). The p-values for each possible comparison are tabulated in Tables 1–3 of the supplementary material. In the case of mild AML tether angle without clipping, the mean MVG was found to be 2.4±0.4mmHg, while the mean MVA was 4.0±0.2cm². The severe AML tether angle alone caused an insignificant increase in mean MVG to 3.0±0.4mmHg (p=0.49), but a significant decrease in MVA to 3.6±0.2cm² (p<0.05). No significant differences were detected between the mild and moderate AML tether angles within each GTclip placement group, but significantly larger MVG and smaller MVA was often observed with severe AML tethering. Placement of one and two GTclips had the incrementing effect of increasing MVG and decreasing MVA.

Change in MV Area and Gradient from Baseline

Under mild and moderate tethering, implantation of GTclip caused an increase in mean MVG of 1.2±0.2 and 1.1±0.2mmHg, respectively, while this increase was found to be 1.5±0.2mmHg in the presence of severe AML tethering (p=0.048 for moderate v. severe). This indicates that the increases in MVG post-clip are significantly larger in the presence severe AML tethering (Figure 6).

Rates of MS by GTclip Placement and AML Tether Angle

Moderate MS (mean MVG≥5mmHg) was created in 13 cases, 11 of which were found in the setting of severe AML tethering. Combined, mild and moderate AML tethering created MS at a rate of 4%, while the rate of MS for severe AML tethering was 46%. Clinical reports recommend avoiding placement of additional MitraClips if mean MVG is observed to be >4mmHg (13). Among all single-GTclip experiments, this threshold was exceeded only once (rate of 8%) for each of 75° and 60° AML angles, but five times (rate of 42%) with severe AML tethering (Figure 7).
Comparison of Experimental Findings with MitraClip Clinical Experience

In 12 FMR patients with varying degrees of leaflet tethering, Chan et al report a baseline MVA and mean MVG of 3.6±0.4cm$^2$ and 2.2±0.8mmHg, respectively (6). After implantation of 1.3±0.7 MitraClips per patient, follow-up MVA and mean MVG were found to be 1.5±0.3cm$^2$ and 4.9±1.0mmHg, respectively. Averaged across all AML tether angles, we observed baseline MVA and mean MVG values of 3.8±0.3cm$^2$ and 2.7±1.1mmHg, respectively. Following placement of 1.5±0.5 GTclips, we observed MVA and mean MVG values of 1.9±0.5cm$^2$ and 3.8±1.0mmHg, respectively (Figure 8). None of the experimental results were significantly different from the corresponding clinical values (p>0.05 for all).

Discussion

A potential limitation of the MitraClip device is the creation of MS, which can lead to poorer long-term outcomes (1,4,14–16). However, well-established guidelines and practices are currently in-place to avoid such a result (13,15). For example, as per MitraClip IFU and EVEREST trials, MR patients with baseline MVA<4.0cm$^2$ are contraindicated for MitraClip treatment (17). Per clinical practice, multiple MitraClip devices may be deployed to fully treat MR, but placement of additional devices may further reduce MVA and increase MVG. As a general guideline, additional clips should not be placed if the patient has a mean MVG ≥4mmHg (13).

Clinical evidence has suggested that AML tethering commonly seen in FMR patients may also have an impact on the level of MS resulting from MitraClip implantation, but studies on its effects are limited (6). To investigate this experimentally, we have applied our in vitro left heart model (18,19) to quantify MS severity after MitraClip in the setting of varied levels of AML tethering, showing that AML tethering is, indeed, a significant factor affecting resultant MVG and MVA, as well as the change in those measures relative to pre-clip baseline.

Insights into the Effects of AML Tethering

Within each GTclip group, no differences between AML tether angles of 75° and 60° were observed. However, much larger effects were observed at the severe AML tether angle of 45°. In the presence of severe AML tethering, a higher rate of moderate MS was observed, as compared to that in the presence of mild or moderate AML tethering (46% versus 4%, respectively). However, baseline MVA was significantly lower and baseline MVG was trending higher. When examining the increase in MVG and decrease in MVA after GTclip placement, we found that mean/peak MVG also increased by a significantly larger magnitude in the presence of severe AML tethering, indicating that the AML tether severity may be an important factor to consider when evaluating patients for MitraClip therapy.

Qualitative experimental observations may explain the significantly larger effects in the presence of severe AML tethering. First, severe AML tethering caused a larger jet redirection angle and MVA reduction, which may combine to cause these effects. Second, more manual force was required to displace the PMs and create the severe AML tether angle than that required for either the mild or moderate AML tether angles. These observations
suggest that the AML is under more tension at the most severe tether angles, and could explain the larger increase in MVG and decrease in MVA caused by GTclip placement under this condition. Recent in vitro investigations have shown an increase in force on the edge-to-edge repair with annular dilatation and leaflet flail (18). Repeating these studies while simulating different clip positions and leaflet tethering could shed light on the hypothesized increase in leaflet tension. Furthermore, the newest computational models of the MV, which can simulate the motion of the valve along with the flow of fluid could be used to verify the increased leaflet stress, and quantify at higher fidelity the effect that these factors have on flow through the MV (20).

Effect of GTclip Placement and Positioning

The resulting MS severity largely depended on GTclip number, but was also affected by the positioning of GTclips. For example, resultant MVA after commissural GTclip placement was not significantly different from that after central GTclip placement, but mean MVG was significantly higher after central GTclip placement than after commissural GTclip placement (p<0.05). This could be attributed to the greater resistance to flow in the double-orifice case, despite the total MVA being equal. We also observed differences between the double-clip cases. In the case of a double central GTclip placement, two distinct orifices were made. Placement of commissural and central GTclips created a single larger orifice, a smaller orifice between the GTclips, and a small orifice in the commissure, which caused mean MVG to trend higher than that in the double central GTclip placement.

Among single-GTclip experiments, a higher rate of mean MVG ≥4mmHg was observed in the severe AML tethering group than in the combined mild and moderate group (42% versus 8%, respectively). In these cases, a compromise must be made between further reduction of MR and increase in MVG caused by placing additional GTclips. A similar finding has been reported clinically, with higher rates of compromise due to increased MVG in patients with more severe AML tethering (6).

However, the clinical MVG cutoff of 4mmHg did not always accurately predict presence of MS after placement of additional GTclips. We observed some cases where placement of the second GTclip unexpectedly caused MS, and some cases where this unexpectedly did not cause MS. First, commissural GTclip placement resulted in the lowest mean MVG, and an additional GTclip may often be permitted. However, mean MVG was highest in the central +commissural group. In 4 of 18 cases, we observed mean MVG<4mmHg after commissural GTclip placement, and mean MVG ≥5mmHg after placement of the second central GTclip. This occurred at a rate of 17% for mild and moderate AML tethering, and 33% for severe AML tethering. The larger increase in mean MVG observed with severe AML tethering, and the larger increase observed from single commissural to central+commissural GTclip placement led to a high rate of unexpected MS.

Conversely, central GTclip placement resulted in higher mean MVG, and placement of an additional GTclip often may not be permitted. However, mean MVG was lower after double central GTclip than after central+commissural GTclip. In two of 18 cases, we observed mean MVG ≥4mmHg after the first central GTclip, then mean MVG<5mmHg after the second central GTclip. Both were observed at AML excursion angles of 75° and 60°.
respectively. Here, because of the smaller increase in mean MVG observed with mild and moderate AML tethering, and the smaller increase observed from single central to double central GTclip placement, the second GTclip did not cause MS, even though the MVG cutoff was exceeded after the first GTclip.

Impact of Mitral Valve Area and Mitral Annular Area on Gradients

Several factors make MVA challenging to measure in MitraClip pre-procedural planning and evaluation: the three-dimensional MV orifice, the limited capacity for echocardiographic measurement of areas below 0.5cm$^2$, and the lack of a single, gold-standard measurement approach (12). Nevertheless, MVA by planimetry has been found clinically to correlate with resulting rates of MS better than other methods (Pressure Half-Time MVA and 3D MVA by MVQ) (12). Therefore, all MVA measurements in this study were made by established planimetric guidelines.

The present in vitro investigation was limited by these same challenges. However, our simulator offered precise control of annular area (MAA). Accordingly, within the limitations of this system and the range of tested GTclip configurations, our model identified 4.7cm$^2$ as the MAA above which severe AML tethering did not cause moderate MS (MVG ≥5mmHg), even with placement of two GTclips (95% certainty). At this MAA, our model predicted the mean baseline MVA be 3.9±0.3cm$^2$ (at 45°), showing that, while MS was more frequent with severe AML tethering, the established MVA cutoff of 4.0cm$^2$ was applicable for our findings. Our results showed that MS occurred at the highest rate with severe AML tethering and MVA<4.0cm$^2$.

Limitations

General limitations of the GTLHS have been previously described (10). The rigid GTLHS did not model the compliant chambers of the heart, or the dynamic motion of the heart itself, but rather lumped venous and systemic compliance into discrete chambers, while the programmable pump created a physiological flow waveform through the LA and LV. Thus, the MV samples were subjected to physiological pressure and flow waveforms, but phenomena such as LA dilation, LA fibrosis, and the effects of inter-atrial shunting were not captured. Additionally, MR was not created in our model, as MV samples were sufficiently robust, and coapted even with severe PM displacement. However, all findings were made during the diastolic phase of the cardiac cycle. Though presence of MR in systole may indeed affect the filling dynamics of the LV, LV inflow volume was held constant at 70mL per beat for all experimental cases. Finally, Chan and colleagues did not report tether angle data in the clinical publication used for comparison of with our experimental data (6), however, their cohort of FMR patients had varying degrees of AML restriction. Therefore, the data herein were similarly averaged across AML tethering severities. Thus, on average, the in vitro MVA and MVG results presented here agreed well with those results observed in published clinical data.
Conclusions

These results show that diastolic AML tethering, which may be readily evaluated pre-procedurally with trans-thoracic or trans-esophageal echocardiography, can have a significant impact both on MS severity, as well as the increase in MV gradient after GTclip placement. Moderate MS occurred at a higher rate with severe AML tethering than with mild or moderate tethering (46% versus 4%, respectively). However, our model identified 4.7 cm² as the MAA above which severe AML tethering did not cause moderate MS (placement of up to two GTclips, 95% confidence). At this MAA, the mean baseline MVA was 3.9±0.3 cm² (at 45°), showing that, while MS was more frequent with severe AML tethering, the established MVA cutoff of 4.0 cm² was applicable for our findings. These conclusions are derived from in vitro testing, which compared favorably to baseline and post-clip results in FMR patients undergoing the MitraClip procedure. Severity of AML tethering may be an important criterion in selecting patients and optimizing procedural outcomes for transcatheter edge-to-edge repair.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations and Acronyms

- **AML**: Anterior Mitral Leaflet
- **DMR**: Degenerative Mitral Regurgitation
- **FMR**: Functional Mitral Regurgitation
- **MAA**: Mitral Annular Area
- **MR**: Mitral Regurgitation
- **MS**: Mitral Stenosis
- **MV**: Mitral Valve
- **MVA**: Mitral Valve Area
- **MVG**: Mitral Valve Gradient
- **PM**: Papillary Muscle

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Figure 1.
Georgia Tech Left Heart Simulator (GTLHS) Platform – The GTLHS is shown in (A), where a piston pump drives flow, opening and closing the MV physiologically. The mitral valve (MV) sample is shown in (B), where the papillary muscles (PMs) are tethered. Symmetric PM displacement vectors used to create anterior mitral leaflet (AML) tethering are shown in red (C). LA-Left Atrium; LV-Left Ventricle
Figure 2.
Mild, Moderate and Severe Anterior Mitral Leaflet (AML) Tether Angle – Conventional en face (A) and three-chamber (B) views of the MV in diastole from patients evaluated for MitraClip therapy with mild (left), moderate (center) and severe (right) diastolic AML tethering. Dotted line in (A) indicates position of three-chamber view. Analogous three-chamber view of sample MV within the in vitro Left Heart Simulator (C). AML tether angle was defined as the excursion angle of the AML from the mitral annular plane.
Figure 3.
Custom Edge-to-Edge Clip (GTclip) Design – device dimensions of MitraClip are shown in (A). Dimensions and computer aided design (CAD) of the GTclip are shown in (B), and the final assembled GTclip devices are shown in (C).
Figure 4.
GTclip Placement – Image (A) and 3D echo (B,C) of central GTclip placement on an excised ovine MV sample. A planimetry tracing of one orifice is shown (D). PM–Papillary Muscle; AML–Anterior Mitral Leaflet; PML–Posterior Mitral Leaflet.
Figure 5.
(A) Mean MV Gradient (MVG), (B) Peak MVG, and (C) MV Area (MVA) by GTclip Placement and AML Angle – Mean and 95% confidence interval (95%CI) are shown at a baseline mitral annular area of 4.15cm². The cutoff values for moderate MS are denoted by the red dotted lines. A statistical significance table with p values for all possible comparisons is available in the supplementary material.
Figure 6.
Change from Pre-Clip Baseline in (A) Mean MV Gradient (MVG), (B) Peak MVG, and (C) MV Area (MVA) by Anterior Mitral Leaflet (AML) Tether Angle – Mean values with 95% confidence interval (95%CI) computed at a baseline mitral annular area of 4.15cm². The effect of AML tether angle was significant for the rise both mean and peak MVG(p<0.05), but was not significant for the drop in MVA(p=0.086). *p<0.05
Figure 7.
Incidence of Mitral Stenosis (MS) by GTclip Placement and Anterior Mitral Leaflet (AML) Tether Angle – Incidence of mean MVG $\geq$ 4 mmHg (placement of additional GTclip not suggested) and mean MVG $\geq$ 5mmHg (moderate MS) are indicated by grey and red circles, respectively. Total sample size was N=6 per condition.
Figure 8.
Comparison of MV Area (MVA) Results and Mean MV Gradient (MVG) Results to Clinical Data – Mean±95% confidence interval MVA and MVG are shown for a cohort of 12 FMR patients both pre- and post-clip.(6) The same values computed for the present study are not significantly different(p>0.05 for all).
Table 1

Experimental Matrix – Test conditions simulated on each MV sample for the experiment.

<table>
<thead>
<tr>
<th>Condition No.</th>
<th>GTclip Placement</th>
<th>AML Tether Angle</th>
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<tr>
<td>1</td>
<td>None</td>
<td>75°</td>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
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<td>13</td>
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Table 2

Factors Affecting MV Gradient (MVG) and MV Area (MVA) – All three factors, anterior mitral leaflet (AML) tether angle, GTclip placement, and baseline mitral annular area (MAA), were found to significantly affect mean and peak MVG, and MVA (p.<0.001 for all). The percent contributions show the relative importance of the effect of each factor on the measurement. Contribution of statistical error and small interaction contributions are not shown. Coefficient units are those of the corresponding measurement.

<table>
<thead>
<tr>
<th>Main Factor/Term</th>
<th>Contribution</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean MVG (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant (k)</td>
<td>3.81</td>
<td>(3.71, 3.91)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>MAA − 4.0 cm² (α)</td>
<td>28.24%</td>
<td>−1.55</td>
<td>(−1.80, −1.30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GTclip Placement (β)</td>
<td>39.06%</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>None</td>
<td>−0.99</td>
<td>(−1.19, −0.80)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Single Comm.</td>
<td>−0.43</td>
<td>(−0.61, −0.24)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Single Central</td>
<td>0.01</td>
<td>(−0.17, 0.20)</td>
<td>0.887</td>
<td></td>
</tr>
<tr>
<td>Dual Central</td>
<td>0.54</td>
<td>(0.37, 0.73)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Central+Comm.</td>
<td>0.86</td>
<td>(0.68, 1.05)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>AML Tether Angle (γ)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75 degrees</td>
<td>−0.33</td>
<td>(−0.47, −0.20)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>60 degrees</td>
<td>−0.24</td>
<td>(−0.37, −0.11)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>45 degrees</td>
<td>0.57</td>
<td>(0.44, 0.70)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Peak MVG (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant (k)</td>
<td>6.91</td>
<td>(6.70, 7.12)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>MAA − 4.0 cm² (α)</td>
<td>24.37%</td>
<td>−2.44</td>
<td>(−2.97, −1.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GTclip Placement (β)</td>
<td>36.13%</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>None</td>
<td>−1.50</td>
<td>(−1.92, −1.09)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Single Comm.</td>
<td>−0.78</td>
<td>(−1.18, −0.38)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Single Central</td>
<td>−0.10</td>
<td>(−0.50, 0.30)</td>
<td>0.627</td>
<td></td>
</tr>
<tr>
<td>Dual Central</td>
<td>0.78</td>
<td>(0.38, 1.17)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Main Factor/Term</td>
<td>Contribution</td>
<td>Coefficient</td>
<td>95% CI</td>
<td>P-Value</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------------</td>
<td>-------------</td>
<td>-------------</td>
<td>---------</td>
</tr>
<tr>
<td>Central+Comm.</td>
<td>1.61</td>
<td>(1.21, 2.01)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>AML Tether Angle (γ)</td>
<td><strong>14.04%</strong></td>
<td>-0.54</td>
<td>(-0.82, -0.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>75 degrees</td>
<td>-0.54</td>
<td>(-0.82, -0.25)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>60 degrees</td>
<td>-0.40</td>
<td>(-0.69, -0.12)</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>45 degrees</td>
<td>0.94</td>
<td>(0.66, 1.22)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>MVA (cm²)</strong></td>
<td>(R²=0.95)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant (k)</td>
<td>2.21</td>
<td>(2.16, 2.26)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>MAA - 4.0 m²/α</td>
<td><strong>7.04%</strong></td>
<td>0.65</td>
<td>(0.53, 0.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GTclip Placement (β)</td>
<td><strong>80.65%</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>None</td>
<td>1.53</td>
<td>(1.44, 1.62)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Single Comm.</td>
<td>-0.04</td>
<td>(-0.13, 0.05)</td>
<td>0.402</td>
<td></td>
</tr>
<tr>
<td>Single Central</td>
<td>-0.13</td>
<td>(-0.22, -0.03)</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Dual Central</td>
<td>-0.49</td>
<td>(-0.59, -0.40)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Central+Comm.</td>
<td>-0.87</td>
<td>(-0.97, -0.78)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>AML Tether Angle (γ)</td>
<td><strong>6.85%</strong></td>
<td>0.25</td>
<td>(0.18, 0.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>75 degrees</td>
<td>0.25</td>
<td>(0.18, 0.32)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>60 degrees</td>
<td>0.07</td>
<td>(0.01, 0.14)</td>
<td>0.034</td>
<td></td>
</tr>
<tr>
<td>45 degrees</td>
<td>-0.32</td>
<td>(-0.39, -0.26)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>